FLUORINE INTOXICATION

A Clinical-Hygienic Study

WITH A REVIEW OF
THE LITERATURE AND SOME EXPERIMENTAL
INVESTIGATIONS

BY

KAJ ROHOLM

1937

PREFACE

Cryolite intoxication, a hitherto unknown disease among the workers at the Øresund Chemical Works, Copenhagen, was found in November, 1932, as a result of a profitable collaboration between the Industrial-hygienic Researches of the Inspectorate of Factories and Workshops and the X-ray Department of the Rigshospital. Professor P. Flemming Møller, the leader of that department, interested me in the disease and suggested that I should go more deeply into the problems of fluorine intoxication. Through the medium of an appointment at private expense as Assistant Physician under the Inspectorate of Factories and Workshops, I was enabled to complete the principal part of the investigations which form the foundation of the present work. The material from the first investigation was placed at my disposal, including the blocks for the illustrations Figg. 16, 19—26, 28 and 29.

I wish to thank Professor Flemming Møller for inducing me to embark on the subject, for kind permission to examine my material by X-ray at the Rigshospital, for passing judgment on the radiographs of cryolite workers' lungs, and for unflagging interest in my efforts. To the Director of the Inspectorate of Factories and Workshops, Mr. E. Dreyer, and its Chief Physician, Dr. Sk. V. Gudjonsson, I tender my best thanks for their confiding the task to me and allowing me a free hand to complete it as well as for their interest and support. By his energetic labours for industrial hygiene in Denmark Dr. Gudjonsson laid the foundation on which this work was started.

A great deal of the work was done at the Copenhagen University Institute of Hygiene and the Budde Laboratory, to whose Director, Professor L. S. Fridericia, I am greatly indebted for hospitality, the best of facilities, and friendly interest. I am obliged to the staff of workers at the Institute for help and encouragement in the daily work. Miss Kirsten Becker and Miss Lotte Holm assisted me in tending the experimental animals and with the preparation of microscopic slides. Preparations were photographed in collaboration with Messrs. Henrik Jensen and E. D. Lange. Some of the microphotographs are

the work of Miss Margrete Falck, of the Copenhagen University Institute of Pathological Anatomy.

It would not have been possible to carry on the work without help and kindness from many quarters. Dr. O. Brinch discussed problems of bone pathology with me and gave me valuable guidance. Dr. J. Engelbreth-Holm assisted me in judging the microscopic organ changes. Mr. R. Bøgvad, M. Sc., examined bone slides in the polarization microscope. Mr. H. Buchwald, the Chief Chemist, analyzed fluorine preparations for me and helped with the analytical part. Mr. C. J. Howitz, of Viborggaard Farm, Herlufmagle, and Mr. S. Hjortlund, the Veterinary Surgeon, Copenhagen, assisted me to tend and slaughter the large experimental animals.

Materials of many kinds, comprising case-records, radiographs, autopsy material and statistics, were entrusted to me by Professors H. M. Hou-Jensen, Poul Møller, K. Sand, Erik Warburg, and J. Collin, all in the Copenhagen University; Professor J. J. Holst, School of Dental Surgery; Dr. M. Degerbøl, Zoological Museum; the Chief Chemist H. H. Stevenius-Nielsen, of the Danish Fertilizer Company, Ltd.; Chief Physician G. Biering, Kommunehospitalet; Chief Physician Chr. I. Baastrup, Bispebjerg Hospital, and the Cryolite Mining and Trading Co. Ltd., Copenhagen.

The sending out of an international questionnaire was made possible through the kind assistance of Dr. Johs. Frandsen, Director of the Danish National Health Service, and the Ministry of Foreign Affairs. With financial assistance from the Dano-Icelandic Union-Foundation I was able to undertake a journey to Iceland in the autumn of 1935 to investigate conditions connected with the sheep disease *gaddur*. When collecting literature I was given excellent help by many Danish and foreign libraries, but especially by the University Library in Copenhagen, where the officials were indefatigable in their readiness to assist. By means of a grant from the Budde Foundation I was able to make library studies in Berlin in the summer of 1934.

A number of investigators abroad very kindly placed materials of various descriptions at my disposal: Professor E. W. Baader, Berlin; Dr. M. Bonjean, Rabat; Professor J. Casares Gil, Madrid; Dr. Juan Chaneles, Buenos Aires; Mr. H. T. Dean, D. S., Washington; Professor Niels Dungal, Reykjavik; Dr. León Goldemberg, Buenos Aires; Dr. F. S. McKay, New York; Professor L. Slagsvold, Oslo; Dr. Margaret C. Smith, Tucson, Arizona; Dr. H. Velu, Casablanca.

It was possible to accomplish the work in its present form through considerable financial support from the Øresund Chemical Works, Copenhagen. Mr. H. Tuxen, the Manager, Dr. A. Westergaard, the Secretary, as well as the

employees and officials have displayed great interest in it and helped me in the course of my daily collaboration with them. So did Mr. C. F. Jarl, C. B. E., the Proprietor of the Works, who induced me to extend my investigations as far as possible in order to find out available prophylactic measures. The translation of the book is the work of Mr. W. E. Calvert, Copenhagen.

I tender my most cordial thanks to all who in any way have aided me in my work.

Blegdamshospitalet, Copenhagen N.   *Kaj Roholm.*
February 1937

TABLE OF CONTENTS

PART I

A REVIEW OF THE RÔLE PLAYED BY
FLUORINE IN BIOLOGY

Chapter

PART II

TECHNIQUE EMPLOYED IN OWN INVESTIGATIONS

PART III

INVESTIGATIONS INTO SPONTANEOUS
CRYOLITE POISONING

PART IV

OWN EXPERIMENTAL INVESTIGATIONS

PART V

DISCUSSION AND GENERAL CONCLUSIONS

ILLUSTRATIONS

INTRODUCTION

The basis of the present work will be better understood if an introduction is given in the form of a brief description of the chemistry of fluorine compounds, a historical review of research work on fluorine in biology, and finally, an account of the extent of my own investigations.

The Chemistry of Fluorine Compounds

In the Periodic System fluorine is placed at the head of the halogen group; in many ways, however, its position is a special one as compared with the other halogens. Several aspects of the chemistry of the fluorine compounds have been studied only to a small degree. The element fluorine is the most electro-negative of all elements; its affinity to a number of elements is very considerable. Free fluorine plays no part in toxicology, as it immediately reacts with water, forming hydrogen fluoride.

A non-silicic fluorine compound treated with a strong, non-volatile acid will by heating and distilling produce *hydrogen fluoride* (HF), a colourless liquid (b. p. 19.4°) readily soluble in water, forming *hydrofluoric acid*. Hydrogen fluoride is a rather weak acid; its degree of dissociation is low compared with the strong mineral acids. In its various forms hydrogen fluoride displays considerable chemical affinity, especially to silicic acid compounds. When hydrogen fluoride attacks quartz, the result is *silicon tetrafluoride* (SiF_4) a colourless gas hydrolyzable by water to *hydrofluosilicic acid* (H_2SiF_6)

$$3\,SiF_4 + 4\,H_2O \rightarrow 2\,H_2SiF_6 + Si(OH)_4$$
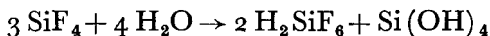
Fluorides are salts of hydrogen fluoride, represented by the general formulæ of MF, MF_2, MF_3 ..., where M indicates mono-, di- and trivalens elements respectively. At lower temperatures hydrogen fluoride occurs in the form of

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H_2F_2 and forms acid salts, for example MHF_2, which under heating break down to the corresponding normal salt and (anhydrous) hydrogen fluorine. The properties of the fluorides often differ from those of the corresponding salts of other halogens. Silver fluoride, for instance, is soluble in water. Calcium fluoride is almost insoluble, a fact of essential importance to the pharmacological mode of action of fluorine. Another point of importance is the great tendency of the fluorides to form complex compounds. The solubility of the most common fluorides is given in Table 1; as a rule the solutions react neutrally.

Silicofluorides or fluosilicates are salts of hydrofluosilicic acid, of the formulæ M_2SiF_6, $MSiF_6$, $M_2(SiF_6)_3$... Generally they are more readily soluble than the corresponding fluorides (Table 1), and in solution they give an acid reaction, as there occurs a hydrolysis according to the equation:

$$3\,M_2SiF_6 + 4\,H_2O \rightleftarrows 6\,MF + 2\,H_2SiF_6 + Si(OH)_4$$

Fluoraluminates are also of toxicological interest — salts of the hypothetical acid H_3AlF_6; they are stable, sparingly soluble and are not hydrolizable in aqueous solution. *Organic fluorine compounds* are only of slight interest to toxicology; the introduction of fluorine in an organic compound may increase its toxicity (499).

In commerce we find hydrofluoric acid and hydrofluosilicic acid, the minerals fluorspar (CaF_2) and cryolite (Na_3AlF_6), silicofluorides, which are a by-product of superphosphate manufacturing, and divers synthetically made fluorides. The solid fluorine compounds are usually colourless, crystalline or amorphous substances; usually they are very pure products.

TABLE 1.

The Water Solubility of Some Fluorine Compounds.)*

Compound	Fluorine content	Solubility at 25° C. and per 100 c.c.
	%	g.
NaF...............................	45.46	4.210
CaF$_2$.............................	48.63	0.0017
Na$_2$SiF$_6$...........................	60.57	0.759
K$_2$SiF$_6$............................	51.70	0.176
BaSiF$_6$............................	40.68	0.024
Na$_3$AlF$_6$ (cryolite).................	54.26	0.039
Na$_3$AlF$_6$ (synthetic)................	52.50	0.063

*) Unpublished investigations by Buchwald.

History

Fluorine minerals have been known since the Middle Ages. The name is derived from their characteristic property of acting as a *flux*, i. e. to promote the fusion of other minerals. The Nuremberg artist Schwanhard (1670) is credited with the first attempts at etching glass by means of the vapours that are generated when fluorspar is treated with sulphuric acid (353). In 1771 Scheele produced the aqueous solution of hydrogen fluoride. Gay-Lussac and Thénard described the corrosive effect of the acid on the skin (1809). The element fluorine was first isolated in 1886 by Moissan (589).

An Italian chemist Dominico Morichini in 1803 demonstrated the presence of fluorine in a fossil elephant-tooth found outside the city of Rome. Together with Gay-Lussac he showed later that fluorine is also present in fresh teeth, of both animals and man. The discovery made quite a stir and was the cause of a protracted controversy. About the year 1846 George Wilson, the Scottish chemist, made investigations on a broader basis and showed that fluorine is widespread in nature, in springs and sea-water, in vegetable ash, in blood and milk of animals. The French chemist Nicklès formed similar conclusions.

The toxic properties of fluorine compounds were studied for the first time in animal experiments, by Rabuteau in 1867. Round about 1890 Tappeiner and Schulz published more detailed records of investigations on acute experimental poisoning, and Brandl and Tappeiner attempted to produce chronic poisoning in a dog. Waddel made certain interesting but not very well known clinical observations. In the period from 1890 to 1920 the interest in the toxicology of fluorine was limited and kept alive solely by sporadic cases of acute poisoning and by the occasional employment of the fluorine compounds in the conserving of foods and in therapy. During the past ten or fifteen years, however, the question has been studied with steadily increasing zeal, for several reasons.

In 1912 Bartolucci observed a cattle disease resembling osteomalacia round about an Italian superphosphate factory, and he expressed the opinion that its ætiology might be connected with the fluorine content in the waste products from the factory. His observations attracted no great attention. It was only when a similar cattle disease broke out endemically in the neighbourhood of a Swiss aluminium factory during the Great War that the incentive was given to a series of investigations into fluorine poisoning by Cristiani and co-workers. The cattle disease, however, continued to be a riddle. But in 1934 important observations were published. Slagsvold described chronic fluorine intoxication among herbivora in the vicinity of Norwegian aluminium fact-

ories, and Roholm was able to identify a domestic animal disease (*gaddur*), long known in Iceland, as a poisoning by fluorine compounds.

McCollum, Simmonds, Becker and Bunting showed in 1925 that rats fed on a diet containing fluorine display peculiar degenerative dental changes. A dental disease in man, *mottled enamel*, which Black and McKay described in 1916 as occurring in Colorado, has proved to be rather widely distributed in several parts of the world. The ætiology was unknown until 1931, when Smith, Lantz and Smith demonstrated by means of animal experiments that the disease was caused by a relatively high fluorine content in the drinking water. Independently of their work, Velu proved that a common dental ailment in North Africa among animals and man, *darmous*, was of the same origin.

Since the close of last century there are records of a number of cases of acute poisoning in man by various fluorine compounds. Chronic human poisoning with bone symptoms was described for the first time in 1932, by Flemming Møller and Gudjonsson, in cryolite workers. In the last decades two uses for fluorine substances especially have given rise to investigations into its toxicology, particularly in U. S. A.: that of native phosphorite containing fluorine as a source of calcium and phosphorus in the rearing of domestic animals, and that of fluorine compounds for combating plant parasites. Many works have appeared in the last few years; those of Margaret C. Smith and co-workers and of Phillips and co-workers may especially be mentioned.

Own Investigations

Above all the present work is a hygienic investigation, arriving out of Flemming Møller and Gudjonsson's observation of cryolite poisoning, which previously had been unknown. In June 1932 the writer was entrusted by the Inspectorate of Factories and Workshops with the task of investigating the effects of cryolite on man, but with a free hand as to how the investigation was to be carried out. In order to determine if cryolite poisoning was an intoxication by fluorine, the effects of cryolite and fluoride had to be investigated in animal experiments. It was necessary to examine the affected workers in order to obtain, if possible, more complete knowledge than had been feasible at the first preliminary examination. For throwing light on the significance of cryolite poisoning it was considered desirable, partly to make comparisons with any other forms of fluorine intoxication described in the literature, partly to endeavour to produce similar conditions in animals. Consequently the plan of the work was as follows:

(1) *A critical-synthetic exposition of fluorine intoxication on the basis of the literature,* there being no collective work on the subject*). This proved to be a comprehensive task, for there were many individual works of interest to the subject, especially dating from recent years. These works are spread over all kinds of spheres, often difficult of access and not uncommonly contradictory. Furthermore, during the time it took to collect the literature, a considerable number of investigations were published, and these had also to be taken into consideration. This exposition, necessary as it was on account of the wide scope of the task, forms Part I. A practically complete bibliography on the subject concludes the work.

(2) An *investigation on human cryolite intoxication,* as extensive as possible under the prevailing circumstances. This means a clinical examination of the workers, one that had to be carried out at the factory and in working hours, as well as an investigation on morbidity, fate after discharge and other matters connected therewith. Quite unexpectedly, two workers died of intercurrent disease and this gave an opportunity for patho-anatomical examinations (Part III).

(3) A series of *intoxication experiments on animals,* intended for widening present knowledge. This work was planned and carried through without knowledge of a large part of the literature referred to in Part I. As, judging by the preliminary perusal of the literature, the various animals differed in their reaction, several kinds of animals were used. Relatively large animals were chosen in order to be able to demonstrate bone changes by X-ray examination. Considerations of economy, space, and the compass of the work made it possible to use only a limited number of animals of each kind. Of necessity the intoxication symptoms had to be studied in broad outlines and the description had to be concise. For this reason the value of the experimental investigations must particularly be appraised in the light of the fact that they confirm and supplement works then available or published afterwards (Part IV).

(4) By means of *putting the results of the literature studies and those of own investigations together,* it now proved possible to obtain an idea of the various forms of fluorine intoxication and their mutual relationship. This exposition has been made in systematic, but brief form, taking due regard to the phenomena that may be regarded as certain or probable. By this means it was possible to throw light on important points connected with human cryolite intoxication. As the fluorine problem proved to be a

*) In 1933 DeEds (228) and McClure (535) published review works on fluorine intoxication, but only briefly and without going into important aspects.

very wide one, and of considerable actual interest, an account of intox-
ication possibilities and a review of the prophylactic problems, based on
an international inquiry, has been added. A summary concludes this
section (Part V).

A work of this kind suffers from conspicuous weaknesses. Of necessity it
is extensive, burdened by the literature apparatus and yet showing the un-
certainty arising from the fact that the problem is new and far reaching.
On the other hand, the time had arrived for the first systematic examina-
tion of the question, and it was necessary in the present case to take it up
on a broad basis. The author hopes to have contributed something towards
consolidating and to some degree increasing present knowledge, and to
have indicated domains where further research is desirable. Fluorine in-
toxication is of considerable interest. Michaëlis (581) recently, without know-
ing the modern works on the subject, uttered the following prophetic words:

"Mit grosser Wahrscheinlichkeit sind bei der Erforschung des Fluorstoff-
wechsels theoretisch und praktisch neue, wichtige Ergebnisse zu erwarten.
Zahlreiche und mühevolle Untersuchungen werden notwendig sein, um auf
die gestellten Fragen klare Antworten zu erhalten. Nicht nur die Besonder-
heiten der chemischen Bestimmung des Fluorgehalts, sondern die enge Ver-
knüpfung des Fluorstoffwechsels mit zahlreichen anderen physiologischen
Faktoren anorganischer und organischer Natur werden die Lösung der Auf-
gabe erschweren. Sicher ist es, dass hier ein grosses, teils unbekanntes, teils
übergangenes Material sich darbietet, das wert ist, gründlich und mit Aus-
dauer bearbeitet zu werden."

PART I

A REVIEW OF THE RÔLE PLAYED
BY FLUORINE IN BIOLOGY

FLUORINE INTOXICATION IN MAN

1. Local Effect

A number of fluorine compounds have a corroding effect on the skin. The active agent seems to be the undissociated HF-molecule, which is capable [1] of penetrating intact epidermis. Consequently, local action is not confined to hydrofluoric and hydrofluosilicic acids alone, it being shared by all acid-reacting solutions of fluorides, especially bifluorides and fluosilicates. Gaseous silicon tetrafluoride is hydrolyzed by the moisture of the air into hydrofluosilicic acid. Slightly soluble fluorides also have a corrosive effect on mucous membranes. The ordinary skin lesions scarcely provide the possibility of any absorption of importance. Poisoning may arise through absorption from the mucous membranes.

The local effect of hydrofluoric acid is well known in manufacturing and in the laboratory. In practice it is assumed that highly diluted solutions of [1] hydrofluoric acid are not dangerous; this, however, to a great extent depends upon how long the influence is allowed to act. Slight exposure causes redness and a sustained burning sensation. Stronger action produces yellowish, leathery changes in the epidermis, developing into painful and slow-healing ulcerations. Blisters and pustules are common, as are painful suppuration under the finger nails, which may become loose. Cases of this kind are not rare in the reports from various countries on occupational diseases (111). Usually the injury is transient, though protracted, but a few cases have been observed with secondary fatal termination without any evidence of an absorption. In Prussia a workman in 1927 sustained such severe corrosion when opening a vessel containing hydrofluoric acid that he afterwards died (28). A French chemist [1] Lerroux died in 1866 after hydrofluoric acid corrosion (663).

In the gaseous state hydrogen fluoride also has a marked effect upon conjunctivæ and mucous membranes in the respiratory passages: irritation, developing into inflammatory changes. Chemists having to do with fluorine

know these effects. Some investigators have suffered from protracted diseases in the air passages, for instance the Knox brothers; the Belgian chemist Loyet, who himself mentions his ailment (524), died when 32 years old of a pulmonary affection which was probably connected with his dangerous work (468). A similar account is given about Nicklès (19). Under certain circumstances the teeth of glass-blowers working with glass containing fluorine are said to be attacked by hydrofluoric vapour (449, 410). The conditions have not been deeply investigated, however; other acids may produce a similar decalcification of the enamel.

Certain cases are known of workers contracting acute pulmonary symptoms after inhaling fluoric dust. In a German plant for electrolytic manufacturing of beryllium, dyspnoea, cyanosis and general debility developed among the workers (848). Stethoscopic signs were found of bronchitis; X-ray examination revealed disseminated, blurred, partly confluating patches in the lungs, indicating a bronchiolitis. Baader*) found in one of the workers a transitory paresis of the diaphragm. Simultaneously there were severe conjunctivitis and eczema of the uncovered areas of the skin. The workers were exposed to dust of sodium silicofluoride and sodium berylliumfluoride, but also to active gaseous fluorine compounds (HF, SiF_4). Frostad (293) describes fluorine intoxication among the workers at an old-established Norwegian aluminium works. It sometimes happens that considerable quantities of dust and gases are developed in the furnace room. The workers suffer from chronic bronchitis and attacks of dyspnoea resembling bronchial asthma. Other symptoms are acute abdominalia, sudden gastric pains and vomiting, sometimes with blood. As cryolite (which is used at these works) in dust form does not cause such violent acute symptoms, the probability is that they are the effect of more active fluorine compounds (HF, NaF?).

2. Acute Poisoning

a. Frequency and Form

Scattered about in the literature there are records of cases of acute poisoning by fluorine compounds. The first to be described was published in 1873 by King (457), concerning a man who died 35 minutes after having taken half an ounce (about 14 g.) of a solution of hydrofluoric acid. In the period 1873—1935 a total of 60 fatal cases has been published. In the same period 52 persons survived the poisoning; in other words, the mortality is high. Several of the cases are only incompletely described. As the material is not available in col-

*) Personal communication.

lective form, all cases have been put together in Tables 2 and 3, containing the fatal and the non-fatal cases respectively*).

The frequency of acute poisonings is rising: Whereas up to 1918 the number of deaths was only 6, the figure for the period 1918—35 rose to 53. The greater part (43) were accidents (taken by mistake), 15 were suicides and 2 were murders. The two sexes are equally represented, and the age of those who died varies from 2½ to 76 years. The preparations responsible for the poisonings comprise only few easily obtainable categories used in the household or in industry; they were:

Insecticides .... 15 cases
Rat or mouse poison .... 14 cases
Disinfectants .... 6 cases
Corrosives .... 3 cases
Preservatives .... 1 case
Unstated .... 21 cases

Regarding the compounds employed there are definite or fairly definite particulars in 52 cases. In 27 it was sodium fluoride (NaF), in 15 cases it was sodium fluosilicate (Na_2SiF_6); solutions of hydrofluoric acid or hydrofluosilicic acid were the cause in 8 instances**). The non-fatal cases do not alter this picture: They were mostly accidents, especially mistakes made when cooking food. Here again rat poison and insect powder, i. e. sodium fluoride and sodium fluosilicate, predominate. There are no cases of suicide in this group, which indicates pronounced toxicity and little effect from treatment.

*) Most probably the real number of poisonings is greater, but they have not been diagnosed or published. According to Sharkey and Simpson (735) the Reports of the Chief Medical Examiner of the City of New York contain records of three accidental deaths from sodium fluoride poisoning in 1918—20, two accidental deaths in 1925, one accidental and one suicidal death in 1926, one accidental death in 1927, three in 1928, one in 1929, and six in 1930. These to a total of 18 fatal cases have been included in the figure given above.

**) In the literature I have found only two cases of acute poisoning from inhaling *gaseous fluorine compounds*, possibly due to absorption. Both concerned workers in a superphosphate factory in Dublin and were published in 1887 by Cameron (123). In one case the workman felt unwell after having been for a moment in the chamber where the crude phosphate treated with sulphuric acid is stored after mixing (*the den*). He complained of difficulty in breathing and died that evening. In the other and better investigated case a workman died 8—10 hours after having, no doubt being unfamiliar with the premises, been inside the den. The only symptoms were marked respiration difficulty and a vomition. He was conscious till the last. Necropsy revealed oedema and hyperæmia of the lungs. In the lung Cameron discovered the presence of fluorine and large quantities of SiO_2 (presumably deposited on the mucous membranes by the decomposition of SiF_4).

There is also a case of horse poisoning with hydrofluosilicic acid vapour (29).

TABLE 2.

Acute, Fatal Fluoxications 1873—

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age *)	Preparation used	Fluorine compound	Dose	Duration	Clinic
1873	King (457)	S	♂ 46	Corrosive	HF	1/2 oz. (ca. 14 g.)	35 minu	Violent vomitin motoric restlessn pupils contracte ed a while after ceased.
1899	Anonymous (21)	A	♂ 51	Corrosive	HF	1/2—2 oz. of 9.2% sol. = 1.3—5.2 g. HF	1 hou	Pale and clamm
1899	Baldwin (46)	A	♂	Insecticide	NaF	ca. 10 g.	10—12 h	Vomiting; diarr
1908	Rosner (691)	A	♂ 37	Disinfectant (Montanin)	H_2SiF_6	ca. 27.5 g.	15 minu	Vomiting with b pain when swal ion; dyspnoea;
1911	Hickey (413)	A	♀ 10	Insecticide (Roach Death)	NaF	1 tea-spoonful	1 hou	Vomiting; diarr pains in extrem blue; uncoordina ncoherent speec
1917	Spaeth (763)	A	Boy	Disinfectant (Montanin)	H_2SiF_6			

*) Where nothing else is indicated the individuals are adults of no specified age.

TABLE TABLE 2.

Acute, Fatal Fluor intoxications *1873—1935.*

	Duration	Clinical symptoms	Necropsy results
4 g.)	35 minute	Violent vomiting; cold sweat; great motoric restlessness; pulse small, rapid; pupils contracted; respiration continued a while after the heart action had ceased.	Corrosion of *mouth, throat* and *oesophagus). Gastric* mucous membrane black on the prominent folds, otherwise hyperæmic and with numerous small erosions. *Duodenum* hyperæmic. *Liver* large, *kidneys* and *spleen* hyperæmic. *Blood* in heart semi-fluid, gives strong acid reaction.
of = HF	1 hour	Pale and clammy; vomiting.	*Lips* much burned. *Tongue:* dorsum brown, but not much corroded. Back part — with *epiglottis* and *fauces* — dark red, hyperæmic and ecchymosed. *Pharynx:* mucous membrane dark purple, swollen and ecchymosed. *Oesophagus:* marked hyperæmia, colour slate-blue, with dark red patches. *Stomach:* wide-spread ecchymoses in cardiac region, small in pyloric region. *Blood* tarry-coloured, fluid. *Lungs:* hyperæmic, black.
.	10—12 hour	Vomiting; diarrhoea; pains in limbs.	*Stomach:* mucous membrane inflamed.
g.	15 minute	Vomiting with blood; stomach pains; pain when swallowing; thirst; salivation; dyspnoea; convulsions.	Superficial corrosion on *tongue,* in *throat* and *oesophagus. Gastric* contents pulpy, acid, with brownish-grey-white shreds of mucous membrane. Mucous membrane stiffer at cardia, pylorus and long lesser curvature, is grey-white in colour and distinctly corroded; also corrosion on mucous membrane folds. Vascular network brownish. Otherwise the mucous membrane is swollen, pale rose in colour. Similar changes in *duodenum. Kidneys* hyperæmic, but no microscopic inflammatory changes. *Liver and spleen:* greyish-white corrosions on the gastric surfaces.
nful	1 hour	Vomiting; diarrhoea; stomach pains; pains in extremities; face pale, lips blue; uncoordinated eye movements; incoherent speech.	

TABLE 2.

(Continued).

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age	Preparation used	Fluorine compound	Dose	Duration	Clinical
1920	Kockel & Zimmermann (465)	S	♀ 16	Rat poison (Orwin)	Na_2SiF_6		Some ho (10—12	omiting; weakne
1920	Kockel & Zimmermann (465)	M	♀ 63	Probably rat poison (Orwin ?)			2 days multane severe tr ma of he	omiting.
1920	Kockel & Zimmermann (465)	M	♀ 68	Probably rat poison (Orwin ?)			6—10 ho	omiting; diarrho
1921	Krause (479)	A	♂ 13	Disinfectant (Montanin)	H_2SiF_6	ca. 10 g.	rapid	tomach pains; vo
1921	Berg (56)	A	♀ 35	Preservative ("Buttersalz")	Na_2SiF_6	1 tea-spoonful	9—10 ho	tomach pains; col
1922	Fischer (271)	A	♀		Na_2SiF_6	11 g.	10 (8 ? hours	omiting with bloo nsation; pains hoea; tetany spas nt paralysis of e ntraction; paraly nsors; bad pulse;
1922	Riechen (676)	A	♂	Insecticide	Na_2SiF_6		Died same	
1923	Kurtzahn (485)	S	♀	Mouse poison (Orwin)	Na_2SiF_6			eadache; vomitin eat weakness; sa fficulty in swall eech; deficient c

TABLE 2.
(Continued).

Duration	Clinical symptoms	Necropsy results
Some hours (10—12 ?)	Vomiting; weakness; perspiration.	*Gastric contents* blood-red-chocolate coloured. *Gastric mucous membrane* swollen, blood-saturated, numerous small hæmorrhages on longitudinal folds. *Small intestine:* contents hæmorrhagic; mucous membrane swollen, blood-saturated.
2 days (simultaneous severe trauma of head)	Vomiting.	In *stomach* bloody liquid. Mucous membrane deeply folded longitudinally, slimy, diffuse red with few dotted bleedings. Redness sharply delimited at pylorus. *Duodenum* pale. *Small intestine:* slight redness in proximal part.
6—10 hours	Vomiting; diarrhoea.	Body exhumed after just under two months. In *stomach* red mass. Mucous membrane smooth, red in patches.
rapid	Stomach pains; vomiting.	
9—10 hours	Stomach pains; cold shivers; vomiting.	*Gastric contents* very acid. Mucous membrane dark, greyish-yellow, vessels dilated; small blood extravasations.
10 (8 ?) hours	Vomiting with blood; urticaria; choking sensation; pains in abdomen; diarrhoea; tetany spasms in hands; transient paralysis of eye muscles; ulnaris contraction; paralysation of hand extensors; bad pulse; dyspnoea.	*Gastric contents* dirty grey, rather thin, turbid. *Gastric mucous membrane* swollen, decomposed, red; near pylorus some superficial loss of substance. *Kidneys* full of blood; microscopic inflammatory phenomena.
Died same day		Signs of corrosion.
	Headache; vomiting with blood; thirst: great weakness; salivation; dyspnoea; difficulty in swallowing; inarticulate speech; deficient circulation.	

TABLE 2.
(Continued).

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age	Preparation used	Fluorine compound	Dose	Duration	Clinical sy
1923	McNally (549)	A	♀ 59	Insecticide	NaF		$3^1/_2$ ho	disposition; weak testinal symptoms)
1923	McNally (549)	A	♀ 45	Insecticide ?	NaF	4—4.5 g.	4 hou	ausea; convulsion uscular weakness ood; diarrhoea; fa ed; difficulties of s
1923	McNally (549)	A	♀ 36	Insecticide ?	NaF	15—16 g.	$^3/_4$ ho	rning sensation; vo ffuse abdominal pa rple-red patches; tremities paralyse eech; profuse pers
1923	McNally (549)	S	♂ 19	Rat poison		2 tea-spoonfuls		rning pains in ab arrhoea; muscular ies of speech.
1923	Sommelet (760)	A	♂	Insecticide	Na_2SiF_6		rapi	
1924	Bizot (79)	A	♂		NaF	1 tea-spoonful	9 ho	vere epigastric pai rhoea; prostration ic contractions of t
1924	Kipper (458)	S	♀ 23	Rat poison (Rawatol)	NaF Na_2SiF_6		From noon same n	
1924	Lührig (525)	A	♂ 57	Insecticide	Na_2SiF_6		6—7 h	miting.
1924	Lührig (526)	A	♂ $2^1/_2$	Disinfectant (Kerman)	H_2SiF_6		5 min	
1925	Lührig (528)	A	♂	Insecticide	Na_2SiF_6	$^1/_2$ tea-spoonful	10 ho	

TABLE 2.
(Continued).

	Duration	Clinical symptoms	Necropsy results
	3½ hours	Indisposition; weakness; (no gastro-intestinal symptoms).	*Stomach swollen*, hyperæmic areas with small hæmorrhages. Mucous membrane of *small intestine* hyperaemic and swollen.
g.	4 hours	Nausea; convulsions; severe thirst; muscular weakness; vomiting with blood; diarrhoea; facial muscles paralysed; difficulties of speech.	
g.	¾ hour	Burning sensation; vomiting with blood; diffuse abdominal pains; face pale with purple-red patches; salivation; lower extremities paralysed; difficulties of speech; profuse perspiration; thirst.	In the *stomach* turbid, hæmorrhagic fluid of alkaline reaction. Mucous membrane oedematous, hæmorrhagic, partly necrotic. *Duodenum* and *jejenum*: mucous membrane swollen. Acute *pulmonary oedema*.
onfuls		Burning pains in abdomen; vomiting; diarrhoea; muscular paralysis; difficulties of speech.	*Stomach* swollen with few diffuse bleedings. Congestion of chest and abdominal organs.
	rapid		
onful	9 hours	Severe epigastric pains; vomiting; diarrhoea; prostration; painful spasmodic contractions of the arms and legs.	
	From after noon till same night		*Stomach and duodenum*: mucous membrane rosy red, detached. Microscopy: necroses reaching middle of tunica propria. *Kidneys*: slight signs of acute toxic nephritis. *Spleen* enlarged, much blood.
	6—7 hours	Vomiting.	In *stomach* slimy hæmorrhagic-brown contents. Mucous membrane in stomach and *intestine* swollen, hyperæmic, with small bleedings.
	5 minutes		Grey-white corrosion of *lips, tongue, gullet, larynx*. *Stomach* hyperæmic, but without swelling or hæmorrage.
oonful	10 hours		No definite changes.

2

TABLE 2.
(Continued).

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age	Preparation used	Fluorine compound	Dose	Durat	Clinical s
1925	Dyrenfurth & Kipper (237)	A	♀		Na_2SiF_6	less than a knife pointful	abou hou	omiting; stomach feet.
1925	Raestrup (666)	A	♂ 42	Mouse poison (Mausex)?			10 h	omiting; violent s
1925	Raestrup (666)	A	♂ 44	Mouse poison (Mausex)?			6 h	omiting; violent st
1926	Huppert (427)	S	♂ 57	Corrosive	HF		1 h	
1926	Lührig (529)	S	♂	Insecticide	Na_2SiF_6		8 h	
1930	Bochkor (84)	S	♀ 15	Corrosive?	NH_4F (in solution)		½ h	ollapse; hiccough; domen.

TABLE 2.

(Continued).

e	Duration	Clinical symptoms	Necropsy results
un a intful	about hours	Vomiting; stomach pains; thirst; cramp in feet.	*Tongue* dry, greyish-red. Mucous membrane in *larynx-trachea* bright red, in *oesophagus* swollen in lower two-thirds. In *stomach* greyish-red, acid reacting fluid. Mucous membrane swollen, greyish white-red, slime coated. Similar changes of mucous membrane in *duodenum* and *jejenum*.
	10 hour	Vomiting; violent stomach pains.	*Stomach:* mucous membrane swollen and dark-red, but brownish-red on the folds. In *duodenum* and proximal part of *small intestine* slight swelling and redness of mucous membrane. *Large intestine* slightly swollen and coated with mucus.
	6 hour	Vomiting; violent stomach pains.	*Stomach contents* brownish-red, reacting slightly acid. Mucous membrane swollen, dark red, decomposed in patches. Mucous membrane in *small intestine* swollen.
	1 hour		Light grey crust on mucous membrane in *mouth, pharynx, larynx, trachea, oesophagus.* In *stomach* and *small intestine* similar changes on swollen and soft mucous membrane. Gastric mucous membrane greyish-brown, detached in large areas; microscopic cell infiltration, with blood extravasation. *Kidneys:* microscopic signs of acute toxic nephritis. *Liver:* degenerative fatty liver with increase of connective tissue.
	8 hour		
	$1/_2$ hour	Collapse; hiccough; pains in neck and abdomen.	*Pharynx, soft palate, oesophagus:* mucous membrane faded, greyish-white and somewhat tanned; detached in oesophagus. In *stomach* most of mucous membrane missing, tissue greyish-green with prominent, blackened vessels. In depressions between folds remains of greyish-white tanned mucous membrane. Microscopic blurring of structure in all tissue and poor nucleus staining. In proximal part of *small intestine:* slight greyish colouring. Corrosion of gastric surfaces of liver, spleen and left lung. *Heart:* small bleedings in left ventricle.

TABLE 2.
(Continued).

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age	Preparation used	Fluorine compound	Dose	Durati	Clinical sy
1930	Fullerton (295)	A	♂ 76	Insecticide	NaF	1 tea-spoonful	12 ho	ausea; vomiting; c ne legs and finge vallowing; coma.
1930	Pietrusky (653)	S	♀ 19	Rat poison (Orwin?)			6 ho	ndisposition; vomit stlessness; dyspnoe
1931	Zeynek & Stary (893)	S?	♀	Rat poison (Orwin)	Na_2SiF_6		less t 24 ho	omiting.
1931	Sedlmayer (730)	S	♀ 21	Mouse poison	Na_2SiF_6		3 ho	omiting; diarrhoea ll of temperature;
1932	Gellerstedt (327)	S	♂ 49	Rat poison (Rattoxin)	Na_2SiF_6	0.7—1 g.	3½ h	iolent stomach pair rrhoea; attacks of clo ainful spasms.
1932	Jeckeln (439)	S	♂ 59	Insecticide (Tanatol)	Na_2SiF_6		4½ h	omiting; convulsive ains in legs; uncons

TABLE 2.

(Continued).

e	Duration	Clinical symptoms	Necropsy results
onful	12 hour	Nausea; vomiting; cramp-like pains in the legs and fingers; difficulty in swallowing; coma.	
	6 hour	Indisposition; vomiting; diarrhoea; restlessness; dyspnoea.	In *stomach* alkaline reacting fluid. Mucous membrane much swollen, red, with pin-head bleedings at pylorus, in *duodenum* and proximal part of *small intestine*. *Kidneys* hyperæmic with microscopic signs of toxic nephritis. Small sub-pleural and sub-pericardial hæmorrhages.
	less than 24 hour	Vomiting.	
	3 hour	Vomiting; diarrhoea; violent spasms; fall of temperature; unconsciousness.	*Stomach contents* dark red, bloody, slimy, very acid. Mucous membrane swollen with small bleedings on folds. Similar changes in *intestine*. Hæmorrhage in both *lungs*. Moderate hyperæmia of the *brain*.
g.	$3^1/_2$ hour	Violent stomach pains; vomiting; diarrhoea; attacks of clonic, later tetanic, painful spasms.	*Oesophagus:* mucous membrane greyish-white with pin-point hæmorrhages. *Stomach:* contents grey-red, slimy, semi-fluid. Mucous membrane hyperæmic, studded everywhere with small hæmorrhages, especially on ridges of folds and in pylorus and at cardia. Microscopy: acute superficial gastritis with hyperæmia, hæmorrhage and oedema. *Duodenum:* similar but less pronounced changes. Cellular fatty degeneration in *heart, liver* and *kidneys*. Diffuse *organoleucocytosis*, with degenerative changes in leucocyte protoplasm. Hæmolysis of erythrocytes.
	$4^1/_2$ hour	Vomiting; convulsive stomach pains; pains in legs; unconsciousness.	*Stomach:* severe hæmorrhagic gastritis; mucous membrane turbid, swollen, diffuse, dark red with pin-point blood extravasations, fresh defects at cardia. *Small intestine:* mucous membrane swollen, red, turbid, with slimy, yellowish, flocculent coating. Microscopy: enteritis.

TABLE 2.
(Continued).

Year	Author	Accident (A), suicide (S) or murder (M)	Sex and age	Preparation used	Fluorine compound	Dose	Durati	Clinical sy
1933	Flamm (274)	A	♂ 22	Disinfectant	H_2SiF_6		98 ho	urning sensation in odominal pains; dia se of temperature; nic and clonic c ranosis; superficial ration; bad pulse.
1933	Kraul (477)	A	♂	Insecticide (Albatol)	Na_2SiF_6	ca. 6—8 g.	12 ho	omiting; dizziness ch pains; high t uish; paræsthesiæ
1933	Sharkey & Simpson (735)	A	♀ 39	Roach powder	NaF	ca. 18 g.	7 ho	urning, bitter tast ausea; violent vomi tarrhoea; prostratio nosis of skin and m uddenly generalize ratory paralysis.
1933	Weidemann (850)	A	♀ 71	Rat poison ?	NaF		22 ho	omiting with blood ch pains; pains ramp in calves; par
1935	Maletz (555)	A	♂ 41	Roach powder	Na_2SiF_6		6—7 h	eakness; nausea; ng; profuse perspi uscular cramps, i ly the facial mus reath; cardial failu
1935	Neugebauer (665)	S	♀ 24	Rat poison	NaF?		6 ho	omiting; severe sto ess.

TABLE 2.
(Continued).

	Duration	Clinical symptoms	Necropsy results
	98 hours	Burning sensation in throat; vomiting; abdominal pains; diarrhoea; dyspnoea; rise of temperature; painful universal tonic and clonic convulsions; sopor; cyanosis; superficial, accelerated respiration; bad pulse.	Dark violet patches on the *skin*, hyperæmia of mucous membranes. Defects of epithelium in *throat* and *oesophagus*. *Gastric* mucous membrane inflamed, with blood extravasations and limited necroses. Similar changes in *duodenum* and proximal part of *jejunum*. *Lungs* oedematous. *Kidneys:* acute toxic, hæmorrhagic nephritis. *Brain:* oedema and hyperæmia.
3 g.	12 hours	Vomiting; dizziness; diarrhoea; stomach pains; high temperature; face bluish; paræsthesiæ in hands and feet.	
g.	7 hours	Burning, bitter taste in the mouth; nausea; violent vomiting and retching; diarrhoea; prostration; greyish blue cyanosis of skin and mucous membranes; suddenly generalized convulsion; respiratory paralysis.	Greyish blue cyanosis of *skin*; extreme passive congestion with greyish blue discoloration of buccopharyngeal and vaginal *mucous membranes* and skin of inner aspect of thighs. Extreme acute passive congestion of all organs. Petechial hæmorrhages of *gastric, duodenal* and *jejunal* mucous membranes. Advanced cloudy swelling of *liver* and *kidneys*. Terminal *pulmonary* oedema.
	22 hours	Vomiting with blood; diarrhoea; stomach pains; pains in sacral region; cramp in calves; paræsthesiæ in hands.	In *stomach* copious bloody slime. Mucous membrane swollen with fine blood extravasations. *Small intestine* bluish red, full of fluid, mucous membrane swollen.
	6—7 hours	Weakness; nausea; retching and vomiting; profuse perspiration; generalized muscular cramps, involving particularly the facial muscles; shortness of breath; cardial failure.	Petechial epichordal and subpleural hæmorrhages. Mucosa of small and large *intestine* somewhat swollen and creamy white in color; the *duodenal* mucous membrane showed a few reddened patches. *Kidneys* congested and slightly swelled.
	6 hours	Vomiting; severe stomach pains; weakness.	Hyperæmia of mucous membranes in *mouth, throat* and *oesophagus*. *Gastric* contents bloody; the mucous membrane swollen, with blood extravasations, partly detached. Microscopy: acute gastritis with cell degenerations. Similar changes in small *intestine*. *Kidney* hyperæmic, oedematous with exudate and erythrocytes in tubuli contorti. *Lungs:* acute emphysema, hyperæmia and oedema; degeneration of alveolar epithelium.

TABLE 3.

Acute, Non-fatal Fluorine Poisonings 1873—1935.

Year	Author	Accident (A) or attempted murder (M)	Number poisoned	Preparation	Fluorine compound	Dose	Symptoms	Course
		A	6—7	Insecticide	NaF		Vomiting; diarrhoea; pains in limbs.	
1899	Baldwin (46)	A	4	Insecticide	NaF	Up to 9 g.	Vomiting; diarrhoea; painful spasms.	Woman, 69, recovered only after 4 weeks.
		A	3	Insecticide	NaF		Vomiting	
1908	Rosner (691)	A	1	Disinfectant (Montanin)	H_2SiF_6	ca. 3.3 g.	Vomiting; gastric pains; pains on swallowing; thirst; salivation	Urine for several days contained albumin, erythrocytes, casts.
1911	Hickey (413)	A	2	Insecticide (Roach Death)	NaF	2 teaspoonfuls	Vomiting; diarrhoea; weakness.	Symptom-free in two days.
1915	Stanton & Kahn (766)	A	1	Insecticide	NaF			Child 19 months. Well on 8th day.
1920	Valée (814)	A	8		NaF	0.228— 0.456 g.	Stomach pains; dizziness; vomiting.	Pains lasted 12 hours.
1922	Hillenberg (415) Lüning (531)	M ?	1	Rat poison (Erun)	Na_2SiF_6		Nausea; vomiting; salivation; diarrhoea.	
1925	Raestrup (666)	A	4	Rat poison (Mausex)			Vomiting; stomach pains.	

TABLE 3.

(Continued).

Year	Author	Accident (A) or attempted murder (M)	Number poisoned	Preparation	Fluorine compound	Dose	Symptoms	Course
1931	Sedlmeyer (729)	M?	1	Insecticide	Na_2SiF_6		Vomiting; muscular stiffness, cramp, especially in extremities; fever, anuria; hands in peculiar position (bent, turned inward); albuminuria, hæmaturia.	2nd day still albuminuria, whereafter symptoms subsided.
1933	Kraul (477)	A	10	Insecticide (Albatol)	Na_2SiF_6	6—8 g.	Nausea; vomiting; dizziness; diarrhoea; stomach pains; headache; high temp.; face bluish; paræsthesiæ.	
1933	Weidemann (850)	A	2	Rat poison ?			Vomiting; diarrhoea; stomach pains, pains in sacral region; cramp in calves; paræsthesiæ in hands.	During convalescence headache and no appetite.
1933	Sharkey and Simpson (735)	A	7	Roach powder	NaF		Nausea; vomiting; cramplike pains in the abdomen.	

b. Clinical Symptoms

The clinical picture of the intoxication is best demonstrated by an example. Fischer (271) in 1922 described a well-observed case. A nurse by mistake took about 11 g. sodium fluosilicate. She vomited at once, but afterwards felt relatively well. After three hours a universal, urticarial eruption appeared, accompanied by continuous vomiting with some blood, a feeling of suffocation, abdominal pains and diarrhoea. Vomiting ceased seven hours after the commencement of the intoxication. Then in succession she had tetany-like convulsions of both hands, brief spasms in the eye muscles, severe bilateral ulnaris contraction and paresis of the extensor muscles of the hand. Death occurred after 10 hours under weakening pulse, dyspnoea and convulsions.

In the published casuistics the clinical observation is often defective, which makes it difficult to judge of the sequence and relative frequency of the various symptoms. In Table 4 I have summarized the various symptoms in 34 cases of fatal poisoning. Broadly speaking the symptoms may be gathered into two groups, one expressing an acute local irritation of the gastro-intestinal canal, the other indicating both an irritating and a paralysing effect on the central nervous system or musculature.

The acute gastro-intestinal symptoms: *vomiting*, often hæmorrhagic, diffuse *abdominal pains*, and *diarrhoea*, introduce the intoxication and occur with very great constancy. Convulsions and pareses, often alternating, are a characteristic but by no means constant phenomenon, which occurs after a certain (varying) time has elapsed and may continue until death occurs. Besides universal *convulsions*, tonic or clonic, *spasms* may be confined to certain groups of muscles, especially those of the extremities. They are often painful. It is natural to regard certain other symptoms as expressing a hyperfunction of the musculature: Motoric restlessness, hiccough, contraction of the pupils and pains and paræsthesiæ in the extremities. The *pareses* usually are localised to certain groups of muscles (eye muscles, facial muscles, hand extensors, and those of the lower-extremities). In several cases mention is made of a *general weakness* or inertness, which may be interpreted as a universal hypofunction of the musculature. As regards some symptoms it is difficult to decide whether they are caused by an increased or decreased muscular activity; this applies to the difficulty with speech, which may increase to dumbness, trouble with swallowing, uncoordinated eye movements. Of the other symptoms only *thirst*, salivation and *perspiration* occur with fair frequency. The skin of the face may be pale or cyanotic. Prior to exitus there are dyspnoea and weakened pulse; usually the sensorium is unaffected to the last.

A numerical evaluation of the symptoms in the non-fatal cases is not feasible.

TABLE 4.

Frequency of Each Symptom in 34 Cases of Acute Fatal Fluorine Poisoning.

Vomiting	31	cases
Pains in abdomen	17	,,
Diarrhoea	13	,,
Convulsions, spasms	11	,,
General weakness, muscular weakness, collapse	8	,,
Dyspnoea	7	,,
Pains or paræsthesiæ in extremities	6	,,
Paresis, paralysis	5	,,
Difficulties with speech, inarticulation	5	,,
Thirst	5	,,
Perspiration	5	,,
Weak pulse	5	,,
Change in facial colour	5	,,
Nausea	4	,,
Unconsciousness	4	,,
Salivation	3	,,
Impaired swallowing	3	,,
Motoric restlessness	2	,,
High temperature	2	,,
Dizziness; headache; hiccough; urticaria; cold shivers; choking sensation; pupil contraction; uncoordinated eye movements; pains in sacral region; low temperature	1	case

The intoxication presents the same picture in reduced form. In the ten cases reported on by Kraul (477) he observed a considerable rise of temperature. In other cases (691, 729) there were transitory signs of toxic nephritis. Usually the symptoms died away in the course of a few days, without permanent consequences.

There is some considerable variation in the time which elapses before death occurs; most frequently it is from 6 to 10 hours, but two hours is not rare. More than 12 hours, however, is very uncommon. Hydrofluoric acid and hydrofluosilicic acid are extremely toxic: they have caused death after 15 and 35 minutes; a child $2^1/_2$ years old in fact died in the course of five minutes (526).

c. Morbid Anatomy

In many cases the post-mortem investigations available are of little value; in Table 5 I have summarized the particulars regarding the 32 cases in which necropsy was performed. With one exception there were acute inflammatory or corrosion phenomena in the stomach, more or less marked. In about half

of the cases changes of a similar nature were found in the small intestine; in about one-fourth in mouth and oesophagus. The only organic change occurring next after these with anything like frequency is signs of acute toxic nephritis.

Changes in the *mouth, throat and oesophagus*, and at times in the lips, the soft palate and in the larynx, are observed only when the toxic substance is hydrofluoric acid or hydrofluosilicic acid. They are rather superficial corrosions of the mucous membrane, which turns greyish-white, as if tanned or coated with a thin crust.

The reaction of the *stomach contents* may be acid, but alkaline too; as a rule the records state nothing as to this. Frequently the colour indicates the presence of blood. The most frequent changes in the *gastric mucous membrane* are swellings, hyperæmia and sporadic bleedings, especially in the pyloric region. The colour of the mucous membrane may vary, although a diffuse red, lighter or darker, occurs rather often. Especially along the lesser curvature and on the top of the folds of the mucous membrane there are sometimes greyish corrosions. The formation of an actual crust seems to be rare, though the membrane may seem to be tanned (84) and have a stiff feeling (691). There is commonly a loss of substance in the form of scattered necroses or more diffuse detached

TABLE 5.

Pathologico-Anatomical Changes in 32 Cases of Acute Fluorine Intoxication.

Corrosion phenomena in mouth, throat and oesophagus........	8 cases
Inflammatory or corrosion phenomena in stomach.............	30 ,,
Hæmorrhagic stomach contents	10 ,,
Changes in { duodenum	11 ,,
small intestine*)	16 ,,
large intestine	2 ,,
Corrosion of neighbouring organs to stomach	2 ,,
Hyperæmia of abdominal organs	6 ,,
Acute nephritis	8 ,,
Degenerative changes in liver	3 ,,
Hæmorrhage or oedema in lungs...........................	5 ,,
Sub-endocardial hæmorrhage	2 ,,
Discoloration of skin or mucous membranes	2 ,,
Sub-pleural hæmorrhage; brain hyperæmia or oedema; acid reaction of blood; degenerative changes in heart, lungs and blood	1 case
No definite changes..	1 ,,

*) In several cases duodenum is not mentioned separately. Two cases, where the intestinal changes are referred to summarily and together, are not included.

patches of the mucous membrane, more rarely in the form of small scattered erosions. The histological examination reveals an acute severe gastritis with cell infiltration, bleedings, oedema and necroses.

In the *intestine* the changes are both rarer and less pronounced. The picture is inflammatory in character, with swellings, hyperæmia and slight bleedings in the mucous membrane. The changes decrease in strength anally, duodenum is most often affected, the large intestine as a rule not.

The *kidneys* are attacked rather frequently. In 8 cases signs were found of acute toxic nephritis with hyperæmia and fatty degeneration of the epithelium in the convoluted tubules. In the other organs there are no changes that are to be regarded as particularly characteristic. The gastric surfaces of liver, spleen and lungs are sometimes the seat of corrosions. The abdominal organs are often hyperæmic. In a few cases there is cell degeneration in heart, liver and other organs. It is probable that a systematic examination of the cases of acute poisoning will reveal other signs of the protoplasmic effect of fluorine than those now known.

It is an interesting circumstance that the changes in the organs *may* be very slight. In one of Lührig's cases (528) there was nothing definitely pathological at all, in another merely hyperæmia of the gastric mucous membrane, but no swelling or bleeding (526). In conclusion it may be mentioned that on necropsy the body is often found to be surprisingly well preserved and that in a large number of cases it has been possible to find fluorine in the stomach contents or the organs.

d. Toxic and Lethal Dose

Unfortunately, the available data for judging of the toxicity of fluorine compounds are few and often unprecise; they are given in Table 6, a distinction being made between toxic dose and lethal dose. In several cases *dosis letalis* is considerable, 8 to 18 g. sodium fluoride or sodium fluosilicate. The smallest quantity of sodium fluoride that has caused death in an adult individual is about 4 g. (549). For sodium fluosilicate the dose is much lower: 0.7 to 1 g. (327, 237). On the other hand the toxic doses are surprising, in that up to 9 g. of sodium fluoride has been tolerated, of sodium fluosilicate 6 to 8 g., whereas so relatively small a dose as 0.228 g. sodium fluoride gave distinct symptoms of poisoning (gastralgia, faintness and vomiting).

There is not sufficient material to enable us to decide whether there is any difference in the toxicity of sodium fluoride and sodium fluosilicate, though there is a difference in solubility and fluorine content; practical experience seems to indicate that there is not. Hydrofluoric acid and hydrofluosilicic acid

TABLE 6.

Approximate Toxic and Lethal Dose in Acute Fluorine Poisoning in Man.

Fluorine compound	Toxic dose	Lethal dose	Death occurred after	Author
	g.	g.	hours	
*HF (hydrofluoric acid)	..	14	$1/2$	King (457)
*NaF	..	10	10—12	Baldwin (46)
*NaF	up to 9	..	..	do.
*NaF	4—10	..	..	Hickey (413)
*NaF	..	2—5	1	do. (child)
NaF	0.228—0.456	..	..	Vallée (814)
NaF	..	4—4.5	4	McNally (549)
NaF	..	15—16	$3/4$	do.
*NaF	..	4—10	..	do.
NaF	..	2—5	9	Bizot (79)
NaF	..	2—5	12	Fullerton (295)
*NaF	..	18	7	Sharkey and Simpson (735)
H_2SiF_6 (hydrofluo-silicic acid)	..	27.5	$1/4$	Rosner (691)
H_2SiF_6	3.3	..	..	do.
*Na_2SiF_6	..	2—6	9—10	Berg (56)
*Na_2SiF_6	..	11	10	Fischer (271)
Na_2SiF_6	..	1—3	10	Lührig (528)
Na_2SiF_6	..	0.2—0.6	8	Dyrenfurth and Kipper (237)
*Na_2SiF_6	..	0.7—1	$3^1/_2$	Gellerstedt (327)
*Na_2SiF_6	..	6—8	12	Kraul (477)
Na_2SiF_6	6—8	..	..	do.

*) Composition of preparation not stated, but almost pure NaF or Na_2SiF_6 is often used as rat poison and insecticide. Technical hydrofluoric acid contains about 70 per cent. HF, in earlier times about 30 per cent. The same commercial preparation is indicated in varying compositions (for instance *Montanin*). A teaspoonful of NaF corresponds to 2—5 g.; for Na_2SiF_6 the same measure is 2—6 g. Sufficient to lie on a knife-point may vary considerably, but may be estimated approximately at 0.2—0.6 g.

must be assumed to have the highest degree of toxicity. We know of too few cases to enable us to determine the *dosis minima letalis*. In a case described by Rosner (691) about 3.3 g. hydrofluosilicic acid caused merely a transitory intoxication.

3. Chronic Poisoning

a. Sporadic Cases

In 1901 Schwyzer (723) published a case of presumed chronic fluorine poisoning in a man who for a long time had drunk large quantities of beer

to which fluorine had been added as a preservative. The case scarcely has anything to do with fluorine. It will suffice to show the manner in which the presence of fluorine was demonstrated: (1) A glass plate was found to be corroded after vaporizing blood on it. (2) The addition of distilled water to an incinerated blood sample caused an odour which was identified as the smell of hydrogen fluoride, etc. None of the tests recorded prove or even show the probability of the presence of fluorine. Schwyzer's case does not seem to require any unusual explanation with regard to the ætiology.

Sauer's case is dubious. A twenty-year old man engaged in exterminating cockroaches, etc., when preparing sodium fluosilicate contracted acute gastric symptoms and inflammation of conjunctivæ and the mucous membranes of the air passages. The X-ray examination showed multiple demarcated areas of lesser density in various bones close to the joints. Clinically there were articular swelling and tenderness. Sauer concluded by regarding the bone changes as tuberculous (704). An actual though somewhat complicated case of chronic fluorine poisoning was published in 1930 by Sedlmeyer (728). The agreement with the symptoms familiar from acute poisoning is considerable.

A 41-year old man died after several months' illness with the following symptoms: gastro-intestinal pains, vomiting, sanguinolent diarrhoea and intermittent albumin-uria. Under loss of weight and general weakness there developed palpitations and dyspnoea, motoric uncertainty, pains in the legs, motoric paralysis and at last para-lysis of respiration and heart. Murder being suspected, the body was exhumed after twelve months, and the chemical analysis revealed the presence of arsenic in excess of the so-called natural quantity. It was only cleared up by the confession of the murderess that death probably was due to protracted ingestion of fluorine compounds. From spring to autumn the wife had wilfully strewn rat-poison on her husband's food almost daily. The preparation used (Orwin) consisted of sodium fluosilicate containing very small quantities of arsenic. Nothing could be said as to the dosage. The dead man having been an alcoholist, the possibility was naturally considered whether the widespread paralysis might be due to alcoholic neuritis or Landry's paralysis.

b. Poisoning with Cryolite

In the winter of 1931—32 Flemming Møller and Gudjonsson (591) examined a number of Copenhagen workers for silicosis. In a factory where cryolite (Na_3AlF_6) is cleansed and ground, filling the air with dust, 30 out of 78 workers, male as well as female, had a peculiar sclerotic bone affection not previously described but now revealed under X-ray examination. In pronounced cases the affection had attacked all the bones of the organism, but the vertebral column and pelvis in particular.

On the Röntgen plate the shadow of the bones revealed abnormal density. The structure was altered, from thickening and blurring of the various trabeculæ to a

complete extinction of all structure. The bone contours were indistinct, the normal cristæ prominent and the muscle attachments often calcified. The ligaments of columna to a great extent were calcified too. In the long tubular bones compacta was thickened and the marrow cavity narrowed. In about half of the workers attacked certain blood changes were observed, a reduction of the hæmoglobin percentage and number of erythrocytes, and an increase of the number of juvenile, staff-nucleated leucocytes. In addition, a common feature at the factory while working in dust was an acute but transitory gastro-intestinal affection manifested by loss of appetite, nausea, vomiting and irregular defæcation. In 39 of the workers, silicosis of up to 2nd stage was also found. The clinical symptoms were surprisingly few; but among those most affected the vertebral column was stiff and rigid, and there were complaints of dyspnoea and indefinite pains in the body.

Flemming Møller and Gudjonsson assumed the affection to be a fluorine poisoning caused by the cryolite dust. The acute gastric symptoms were considered to be the outcome of a slight corrosion of the mucous membrane of the stomach, arising from the fact that the hydrochloric acid of the stomach liberates hydrofluoric acid from the dust swallowed. The bone changes were considered due to absorption and, presumably, the result of a deposition of calcium fluoride in the bones. By means of experiments on rats it was demonstrated that cryolite is toxic, but no symptoms identifiable with either the acute or the chronic poisoning were observed.

c. Mottled Enamel

Though in the earlier literature there are scattered reports of a dental disease with the characteristic symptom of dark patches on the enamel, the works of Black and McKay in 1916 must be regarded as fundamental (86, 548). They studied the disease in Colorado, U. S. A., where it is widespread and has been known for many years.

Symptoms. The disease or anomaly is localised to small, restricted geographical regions and solely affects children who have grown up on the spot; but a high percentage of them are attacked. Only the permanent teeth are affected, the deciduous teeth very rarely. In the main the teeth retain their shape. The changes are of two kinds, which must be kept quite separate. In the first place the enamel in spots or more diffusely loses its normal translucence and becomes turbid, whitish, with a tone that recalls chalk or unglazed paper (*mottled*). This change is already observable at the eruption of the tooth. In the second place, after eruption a dark, pigmentary substance is deposited in the defective enamel (*stained*). The colour may vary in intensity, from yellow via brown to black. The coloured areas are arranged in irregular patches or more regular transversal bands, and are mostly localised to the labial surfaces of incisors and canines, that is to say the areas exposed to the light (Fig. 1).
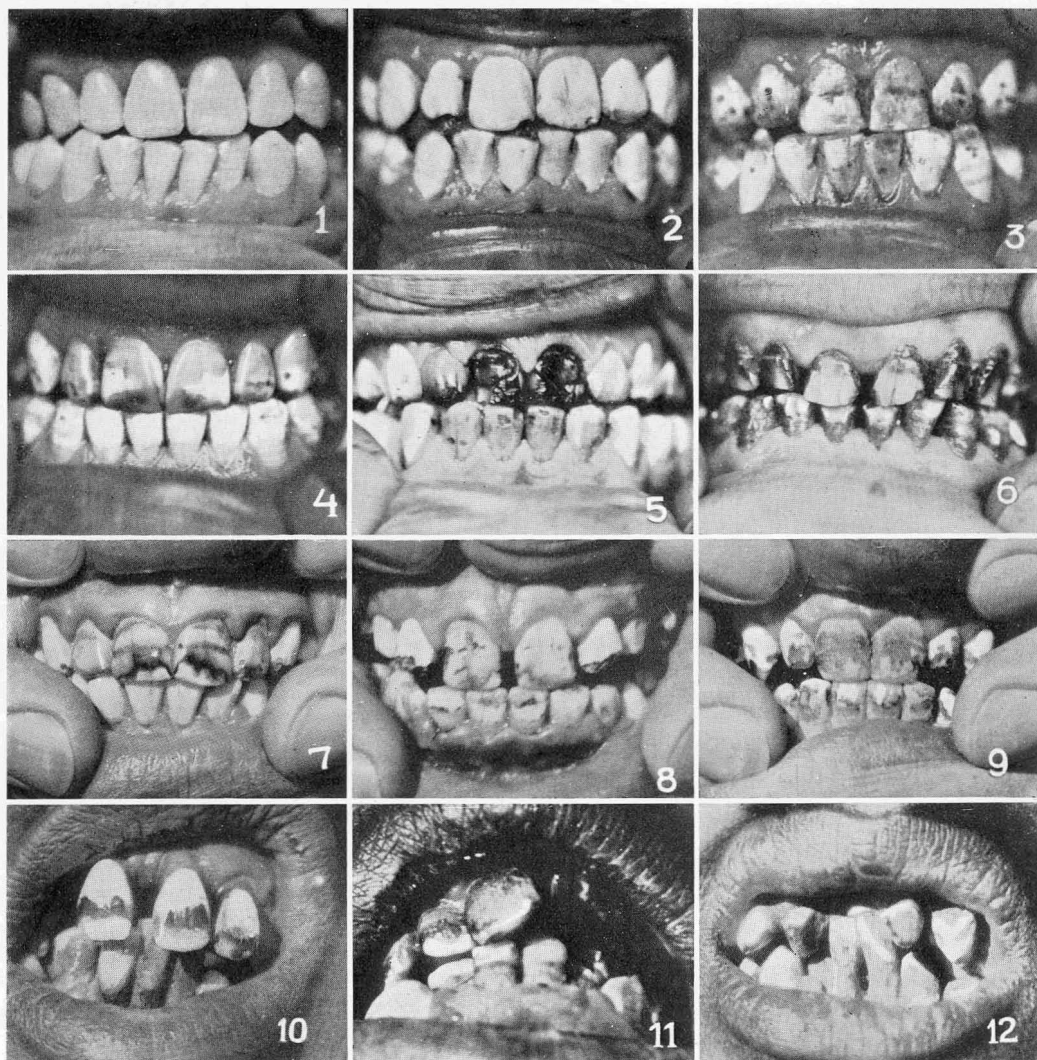
Fig. I. Various types of *mottled teeth*. *1* Normal dentition. *2* Enamel dull, chalky-white, without pigmentation. *3—7* and *10* Pigmentation of various degrees, punctiform, patchy or diffuse. *8* and *9* Enamel corroded. *11* and *12* Anomalies of size, form and position.

2—6 Dientes veteados (Argentina). *7—9* Mottled teeth (U. S. of America). *10—12* Darmous (North Africa). [Reprinted by permission of Dr. Chaneles from *Revista Odontológica* 1932 (*1—6*), of Dr. McKay from *Public Health Reports* 1930 (*7—9*), and of Drs. Gaud, Charnot and Langlais from *Bulletin de l'Institut d'Hygiène de Maroc* 1934 (*10—12*)].

To a certain degree the extent of the changes in the same set of teeth depends upon the length of the period in which the injurious factor has worked. As the permanent teeth calcify in a certain order in the period from about birth to the age af 12 or 14, the spread of the anomaly enables us to judge of how long the injurious influence has lasted. Caries does not seem to be especially frequent in the moderately attacked teeth. Still, the enamel is more brittle than normally, is inclined to chip off, and fillings do not hold well. The surface of the enamel may show irregularities, partly due to restricted areas of hypoplasia (*pitted*), partly due to real corrosion of the enamel. In North Africa, where Velu (824) has described an identical state (*darmous*), which is frequent in certain areas, especially among natives, the changes often are more severe (307). Shedding may be delayed and the permanent teeth sometimes deviate considerably from the normal in size, shape and position (Fig. 1). The teeth are not very resistant and wear down at an abnormal rate, often irregularly. Chewing and cold sometimes cause pain. Tartar accretions and inflammation of gingiva often develop.

Histopathology. According to researches by Black (80) the unclear, chalky colour is the result of a defective deposition of interprismatic substance in the outer third or fourth of the enamel. Williams (864) has shown that in more severe cases the enamel prisms change their form, and both prisms and interprismatic substance calcify imperfectly. The dentine is likewise affected (73, 5). The dark pigment deposited in the defective enamel is of unknown nature. McKay (543) demonstrated the presence of manganese. Montelius, McIntosh and Ma (594) analysed the enamel and found values inside the normal boundaries for organic tissue, calcium, phosphorus and iron. It is therefore probable that the pigment does not originate from bleedings as Wofford (880) assumed, or from infiltration of serum derivatives at all. Nor is there any perceptible decalcification. The behaviour of the pigment during calcination indicates that it is of an organic nature (594). It can be bleached with various oxidizing media, but not permanently; no effective treatment is known.

Ætiology. At the time of Black and McKay's investigations it was the popular belief that the anomaly was associated with drinking water, especially from artesian wells. Where the water supply was changed it was possible to stop the development of the anomaly in an affected region. Analyses of the water showed nothing abnormal, however. McKay has occupied himself with these matters in a number of works (544), but the cause remained unclear and led to several untenable hypotheses (302, 73, 283, 652).

Research during the past few years has solved the riddle. By means of spectrographic investigations Petrey observed the presence of fluorides in the drinking water at Bauxite, Arkansas, where mottled enamel is endemic. With this as his incentive Churchill (166) in 1931 examined a series of drinking-water samples from various parts of U. S. A. and was able to show that to a certain extent the fluorine content was parallel with the occurrence of the tooth anomaly. In drinking water from five areas where mottled enamel was endemic, he found from 2 to 13.7 mg. fluorine per litre*). In ignorance of this find, Smith, Lantz and Smith (753) at the same time were experimenting with a condition which, feature for feature, resembled mottled enamel, by giving rats concentrated drinking water from an affected area. They also drew attention to the fact that the dental changes were the same as those found by McCollum and collaborators (538) in 1925 in incisors of rats on a diet containing sodium fluoride. Later experiments on rats, dogs and guinea pigs (751) confirmed the correctness of this observation, which has since been further confirmed in other quarters. For the dental disease occurring in North Africa Velu (823) had already arrived at the same results.

We may now regard it as an established fact that mottled enamel is caused by a relatively high fluorine content in drinking water. On the basis of experience in Arizona Smith and Smith (746) showed that the drinking water does not contain more than 2 mg. of fluorine per litre in localities that are free of mottled enamel. The threshold value lies at 2—3 mg. At this concentration about half the people have sound teeth, half have slight degrees of the anomaly. The concentration of 3—5 mg. gives slight to moderate degrees, over 5 mg. fluorine gives moderate to severe degrees of mottled enamel. Munoz (599) arrived at similar threshold values by analysing the drinking water from 150 different localities in Argentina. In later works Smith and collaborators (754, 748) state that improved analysis technique has shown that *the threshold concentration is 1 mg. fluorine per litre.*

Occurrence. Since mottled enamel was described in 1916 this disease has been recognised in many parts; it is also called *mottled teeth* or simply *mottling*. In North Africa the term *darmous* is employed, in Argentina the name *dientes veteados*. In U. S. A. Dean (222) in a work dated 1933 collected the reports in the U. S. literature and supplemented them with a questionnaire to the dental organizations. By this means, in addition to the 125 already known localities in many

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*) In U. S. A. the fluorine content of drinking water is given as *parts per million* (p. p. m.). In the present work all results of water analyses are given as mg. per litre, which practically is the same.

states, he registered other 75 definite areas, villages, larger towns, rural districts, Texas, Arizona and Colorado being the states most affected. In *America* the disease has also been reported from Mexico, especially the town of Durango*) Argentina (158), Barbados and the Bahama Islands.

On the occurrence in *Europe* we have only sparse accounts. Gasparrini and Piergili (302) described an identical affection in 1916, *denti scritti*, in the environs of Rome. In Spain and England, and probably Holland, the disease has been recognized in limited areas. In *Africa* the disease is widespread in Algeria, Tunisia and Morocco, where the large phosphorite deposits are. It is also known on the Sinai Peninsula and in certain parts of South Africa, as well as in the Azores and the Cape Verde Islands. Our knowledge of some of these occurrences is due to private information to McKay (544). In *Asia* the affection has been described from several places in North China (14, 15) and Japan (564).

*) There are one or two early descriptions of tooth anomalies that are identifiable as mottled enamel. In the work of the German dentist Kühns (483) I have found the earliest mention of it (1888). He briefly describes the dental state of a family which had come from the town of Durango in Mexico. All the members of the family born in that town had, all according to the duration of their sojourn there, black spots on, or rather *in* the teeth, as the spots could not be removed. The affection was stated to be known throughout Mexico. Kühns considered that the black colour was possibly produced by manganoxydes emanating from the action of the sun on manganese salts, thought to have been deposited in the tooth substance by means of the drinking water.

In 1901 the American physician Eager (238), who examined emigrants in Naples, reported the characteristic dark colour of the enamel among the population from certain quarters of the town. The anomaly was called *denti di Chiaie*, after a part of the town where there were many mineral springs. Eager connected this disease with volcanic emanations which either contaminated the atmosphere or dissolved in the drinking water. An investigation by McKay in 1927 showed that the disease had disappeared in Naples after the water supply had been changed.

From Colorado, where mottled enamel is widespread, Fynn (297) gave a description in 1910.

CHAPTER II

INTOXICATION OF PLANTS AND ANIMALS

1. Injuries to Plants

In the course of time injuries to plants have been observed round about various factories, and these have been traced to a fluorine content in the waste gases from these places. Where a factory's raw materials contain fluorine, the smoke gas may under certain circumstances contain hydrogen fluoride (HF); if silicates or quartz are present as well, which very often is the case in practice, silicion tetrafluoride (SiF_4) may also be given off. With the humidity of the atmosphere there is a partial hydrolysis of SiF_4 to hydrofluosilicic acid (H_2SiF_6). Consequently, the active compounds are hydrofluoric acid and hydrofluosilicic acid in finely atomized form with a large surface. Their ability to form *fog* is shared with sulphuric acid and hydrochloric acid, but their toxicity is much greater. The heavy fogs are slow to disperse and therefore may do great damage under circumstances where it is difficult to renew the air.

The damaged plants present no characteristic picture but general signs of acid corrosion, depending upon the concentration and the duration of the influence (grey or brown spots or borders, early leaf fall, stunted growth, badly formed fruit, etc.). Damage has been reported to all kinds of forest trees, fruit trees, cereals and grasses. Only little light has been thrown on the question of the significance of gaseous fluorine compounds in the industrial smoke problem. In his great monograph of 1923 on smoke damage Stoklasa (774) says scarcely anything about fluorine. Our knowledge comes mostly from earlier works by Ost (621, 622) and Wislicenus (875, 876, 877). The cases of damage that are known shall be briefly referred to.

Round about *superphosphate factories* injurious effects upon the vegetation were described 1891—96 by Mayrhofer (571), Rhode (675) and Ost (621). The latter calculates that with an annual handling of 10 million kg. of phosphorite with a content of 2.5 per cent. fluorine the factory put 170,000 kg. fluorine into the atmosphere in the form of hydrogen fluoride and silicon tetrafluoride. The raw products of *brickworks* may contain fluorine. Wislicenus (877) in 1913 examined a brickworks that was damaging a wood; the clay contained 0.16 per cent. fluorine and the waste gas 0.6 g. per cbm. Damage to the vegetation round about *chemical works* producing

hydrofluoric acid has been observed repeatedly (621, 289, 425), last in 1931. Schröder and Reuss (716) described plant damage in 1883 round a *copper works*. A special position is occupied by *aluminium works*, inasmuch as the damaged vegetation especially has caused secondary animal diseases which shall be referred to in a later chapter. Wilczek (856) and Faes (263) have in late years occupied themselves with conditions round a certain factory, and later Cristiani (190). Measured by the spread of the cattle disease the effects of the fluoric gases were traced as far as 5 km. from the factory; as a rule the distances are shorter. It is possible that a number of cases of plant damage round about brickworks, *glass and enamel works* and various *metal works*, described at the beginning of the present century, may have been caused by fluorine compounds (389, 31).

Some of the cases are not fully elucidated, as the analyses which alone can settle the question were not made. Quantitative determination of fluorine in vegetable ash is difficult. Nevertheless, it has been shown that the slight normal content of fluorine increases when the plants are exposed to fluoric smoke (571, 620, 289). The fluorine content may possibly be increased before the damage is visible to the naked eye. The question of whether plants under similar circumstances can take up fluorine from the soil has not yet been handled; nor whether fluoric smoke can change the biology of the soil.

We must assume that when *volcanoes* containing fluorine erupt, the vegetation is damaged in exactly the same way; this has happened repeatedly in Iceland (687). Localised corrosion can also be observed after *spraying plants* with fluorine compounds for parasites.

2. Acute Poisoning of Animals

As in human medicine, veterinary medicine reports a number of scattered cases of poisoning which confirm the picture given of the acute human poisoning, as to both symptomatology and pathological anatomy. In almost every case there were inflammatory changes in the kidneys, which would indicate that this organ has not been examined with sufficient thoroughness in the human cases. The uncertain question of the lethal dose remains unsettled.

In 1902 Emmerling (254) issued a warning against the use of phosphate of lime as a supplement to pig feed. In connection with this Damman and Manegold (215) described poisoning among *pigs* which had received phosphate of lime with up to 8.4 per cent. content of sodium fluoride (perhaps in the form of calcium fluoride). The symptoms, which were gone into more closely in experiments, were loss of appetite, weakness, paralysation of the hindquarters, and death in the course of a few days. Necropsy revealed inflammation in the gastro-intestinal tract and in the kidneys. An unusual case of poisoning was that of a *horse*, which accidentally remained ten minutes in an outlet canal used for the condensation of hydrofluosilicic vapour. Death occurred after four hours under restlessness, dyspnoea and paralysation of the hindquarters. Necropsy gave a negative result (29). Another horse died after

eating rat-poison (Na_2SiF_6) mixed with maize meal (99). Another case was that of 18 *dairy cows* which, instead of residual meal, were given almost pure sodium fluosilicate (482). Death occurred 12—14 hours afterwards, with convulsions, increased chewing motions and frothing at the mouth. Hyperæmia of the abomasum, small intestine and kidneys was found; fluorine was traced in the organs. Freund and Wieden (296) in 1928 observed a number of cases of poisoning at a *mink* farm, the animals having been given adulterated bone meal with up to 0.43 per cent. fluorine. The symptoms were loss of appetite, thirst, diarrhoea, vomition, salivation, universal trembling, convulsions and paralysis. The unweaned young also died. In addition to the usual changes in the gastro-intestinal tract, necropsy revealed dystrophic calcification and degeneration of the epithelium in the kidneys. There was also fatty degeneration of the liver cells. Hedström (398) in 1932 reported on three cases of acute poisoning of *dogs* which had eaten rat-poison (Rattoxin, NaF). The pathologico-anatomical finds were hyperæmia of the gastro-intestinal tract, liver and kidneys.

3. Chronic Poisoning of Animals

a. Enzootics round Factories

In 1912 Bartolucci (48) described some cases of a strange disease among the cattle on a farm close to a superphosphate factory in *Italy*. After two or three months there the cattle went thin and the coat became coarse and lifeless. Difficulty of movement set in: The animals lay down and got up with difficulty, they limped, and adopted a characteristic pose when standing, with curved, stiff back, belly drawn in and stiff hind-quarters. Widespread, tender swellings appeared at the joints, and after four or five months thickening of the ribs and of the bones of head and shoulders. Although the appetite was fairly good and ruminating was unimpaired, a cachectic condition finally developed and necessitated slaughtering. No post-mortem examination could be made.

Bartolucci described the disease as osteitis, conforming clinically with the classical osteomalacia. Ætiologically he associated the disease with the content of fluorine compounds in the waste gases from the works. In that case the poisoning was communicated through the medium of the drinking water or the vegetation. A point in favour of the former pathogenesis was the fact that water from a well close to the ditch leading off the factory's waste water contained fluorine, and that the affection ceased when the animals were given water from the town mains. A few years later Bartolucci saw the same sickness in another place under similar circumstances (49).

In *Switzerland*, in the years 1911—1918, a disease like osteomalacia appeared among the cattle in the vicinity of an aluminium works, and for a long time its ætiology was unclear. After long litigation the works had to compensate for certain smoke damages to the vegetation, but were declared not liable for the

cattle disease. The majority of the expert witnesses considered the affection to be an ordinary osteomalacia, which is endemic in Switzerland. Cristiani (267), who was called in as an expert at a time when the disease had almost disappeared, gives the following description of the clinical symptoms: In contrast to osteomalacia, the disease attacked not only dairy cows but all kinds of ruminants in the area concerned; the cows were most frequently seized, however. There was first emaciation, succeeded by cachexia; the hide became dry and hard. The animals had difficulty in getting up owing to stiffness in the limbs and rump. When standing they shivered and transferred the body weight first to one then to another leg; the gait was laboured and painful. In addition there was an important symptom: swelling of the extremities and spontaneous fractures. The disease sometimes ended with death in the course of months. Of 450 head of cattle about one-third were attacked.

On the basis of a series of researches Cristiani and Gautier set up the hypothesis (266) that the affection was a chronic fluorine poisoning, produced by an abnormally high fluorine content in the plants. The origin was, they believed, the corrosion of the vegetation close to the works, caused by the emanation of gaseous fluorine compounds (HF, H_2SiF_6). The disease occurred within a distance of 4—5 km. from the works. The localisation depended upon the wind, and the frequency of the disease ran parallel with the productive activity of the works.

Cristiani and collaborators (269, 210) were able experimentally to produce a chronic, often fatal intoxication of guinea pigs by means of ingested fluorine compounds. The same picture was secured when using fodder reaped near the factory on the windward side and fodder which had experimentally been exposed to hydrofluoric vapour (211, 212). On some points the symptoms of the experimental fluorine intoxication agreed with those of the cattle disease, on others they did not. In particular, there were lacking the characteristic thickening of the bones and the spontaneous fractures, although it was possible to demonstrate a certain increase in the fragility of tibia (265). Histological examination of the guinea-pig bones showed no osteoid tissue, though this phenomenon was very characteristic of the cattle disease. Cristiani pointed out the cachexia in both instances as the essential feature of the picture and did not consider the affection to be osteomalacia.

The results arrived at by the other experts in their investigations had the effect that Cristiani's opinion was not supported. Treadwell was unable to trace fluorine over the cryolite melting bath in which aluminium is made. Analyses of bone ash from diseased animals gave 3.1 and 3.4 $^0/_{00}$ fluorine. In contrast, Treadwell in healthy cattle from various rural districts in Switzerland found 0.26—0.67 $^0/_{00}$ and in really osteomalacic cattle from other places 0.43 $^0/_{00}$. Apparently healthy cattle in the district near the aluminium works had 2.16—4.18 $^0/_{00}$ fluorine in the bone ash. Bone ash from cattle at a slaughtery in Zurich revealed varying quantities of fluorine, up to 2.1 $^0/_{00}$. The considerable normal variations were therefore taken into account and the Court could not regard the fluorine found in the bones as a sign of poisoning.

There is no thorough pathologico-anatomical investigation on this cattle disease. Askanazy (40) made a histological examination of various bone slices from four attacked cows whose organs had presented nothing of interest. Microscopy revealed a very typical osteomalacia: bone emaciation and osteoid borders, up to $100\,\mu$ wide, round the Haversian canals. In some places (ribs, pelvis, vertebræ, skull) there were subperiosteal growths of osteoid tissue with partial calcification. In one case the marrow revealed a gelatinous atrophy. Scarcely any osteoclasts were observed and no outstanding signs of osteoplastic activity.

Further light has been thrown upon this mysterious cattle disease by scattered observations in later years. In *France*, Sette (734) in 1928 observed similar cases among cattle in a byre close to a superphosphate works. He assumed, however, that gaseous fluorine compounds caused the disease in conjunction with other acid waste products, and that the symptoms were to be taken as a general sign of acid poisoning. From *Germany* came a communication in 1931 from Hupka and Götze (425) regarding osteodystrophic symptoms in cattle in the vicinity of both a chemical works and a superphosphate works. Dairy cows especially were attacked and yielded less milk. There were also difficult and painful gait, emaciation, and solid growths on the ribs, of sizes up to that of two fists, as well as more or less pronounced thickening of the bones and joints of the foot. Hupka described actual paralysis of the fore legs, Götze pains in the joints. In the byre the affected animals recovered rather quickly. The connection between the disease and the activities of the factories was beyond doubt. Damage to vegetation was established as well as a high fluorine content in hay from some of the fields concerned. As feeding experiments on cattle with fluorine compounds (114, 408) did not give bone symptoms, it was thought that the affection was not a direct poisoning with fluorine, but that the effects must be indirect through influence on the plants*).

A weighty contribution to the study of these matters came from *Norway* in 1934. Slagsvold (742) reported that for several years disease had appeared among sheep and cattle grazing round Norwegian aluminium works. The symptoms are loss of appetite, emaciation and anæmia. Conjunctival irritation occurs with photophobia. The gait becomes stiff and painful, the animals lie

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*) Haubner (390) in 1878 described a disease which for many years had visited cattle round about the metal works in Freiberg (Saxony). The symptoms were not unlike those described above (i. e. gait difficulties, thickening of extremities, spontaneous fractures). The affection was taken to be a combined sulphuric-acid and arsenic poisoning. Ost (622) afterwards criticised the analyses and considered that the disease had nothing to do with the smoke from the metal works. The possibility of a fluorine intoxication was not ventilated, and it cannot be ruled out as a possibility; fluorspar is employed in ore smelting, and certain kinds of ore frequently contain the same mineral.

down a lot and are strikingly tender and stiff in back and limbs. Bone fractures are common; on the other hand it is doubtful if there is thickening of the bones. The hooves are hard, and, despite outdoor grazing, they continue to be long. Sheep have thin, stiff wool which falls off considerably in winter. Cows are apt to have diarrhoea and yield only little milk. In both animals, but in sheep especially, chewing becomes impaired. The grinding surfaces of the molars wear irregularly and form sharp points corresponding to hollows in the opposite teeth (Fig. 2). In air-dried hay from the district as much as 25 mg. fluorine per 100 g. was found. It was possible to show experimentally that the affection was a fluorine poisoning (5ſ6). The author had an opportunity of examining the skull of a young sheep from the neighbourhood of a Norwegian aluminium factory. The central incisors had white, opaque, corroded enamel with brownish pigmentation. The ash of the mandible contained 4.5 $^0/_{00}$ fluorine, and of the incisors and molars 4.5 and 4.9 $^0/_{00}$ respectively.*)

b. Darmous

In certain parts of North Africa (Algeria, Tunisia, Morocco) there occurs a disease, *darmous* or *dermes***), which attacks the permanent teeth, of animals especially, but also of human beings. The first description was published in 1922 by Velu (817), but it was known before that. We have clinical works by Compain (174) and Claudon (168), but in particular a series of experimental and clinical works in the past few years by Velu (818—836), which have cleared up the ætiology and pathogenesis of the disease.

The disease attacks the permanent teeth only, and only of individuals who are in the affected area during the period in which those teeth calcify. Only in horses are typical changes in the first dentition sometimes observed (828). Adults, man or animal, coming to the area escape the disease. The reports mainly concern sheep, which are particularly exposed. The characteristics are that the enamel becomes milky and studded with more or less confluent brown and black patches and bands (Fig. 3). The surface of the enamel is uneven and rough, as if corroded in limited areas. The teeth wear down at an abnormal rate, often unevenly, so that ruminating becomes difficult. The more resistant parts of the teeth may meet the corresponding gingiva. Often the

*) Bardelli and Menzani (47a) reported recently that since 1929 damage to vegetation, failure in the cultivation of silkworms and disease among herbivora of the same character as that described above, had been observed round about an aluminium factory in North Italy. Air-dried hay from the neighbourhood contained an average of 59.3 mg. fluorine per 100 g. as compared with 14 mg. in control hay. The bone ash of diseased animals contained 2.1— 8 $^0/_{00}$ fluorine, as against an average of 1.2 $^0/_{00}$ for normal animals. By means of administering fluorine compounds it was possible to produce similar symptoms among cows and goats.

**) These terms are of Arabic origin; their meaning is not known with certainty.

teeth are smaller, especially the incisors, which sometimes loose their spatula form, become more cylindrical and turn on their longitudinal axis.

In 1926 Compain drew attention to the fact that this tooth affection is often accompanied by a thickening of the mandible, sometimes more diffuse, in other cases in the form of exostoses. The bone thickening, a very bad prognostic sign, is due to newly-formed tissue. The surface of the bone is uneven and porous, but cannot be cut with a knife. The marrow is reddish. Histological examination proved the bone to be spongious and the marrow fibrous, deficient in cells. The changes seemed to be indolent, but the animals were unwilling to take hard feed. Except for the mandible, the osseous system apparently was not attacked (174, 367). Velu (824), however, states that the horses in a certain region often sustain fractures, and he reproduces the picture of a rib with multiple fractures, taken from a mule attacked by darmous.

The ætiology was obscure for a long time, although it was realised that the noxious agent was probably to be found in the drinking water. Compain pointed out that the disease occurs only in those parts of North Africa that have deposits of phosphorite. By means of protracted experiments, including some with sheep, Velu showed in 1931 that it was no localised dental disease, but a general chronic intoxication with fluorine, communicated through the drinking water which passes through beds of phosphorite with a high fluorine content*). In a work published in 1934 Gaud, Charnot and Langlais went more deeply into the pathogenesis (367). Filtered drinking water contains relatively insignificant quantities of fluorine; in water from six springs and wells they found 0.14—2.25 mg. fluorine per litre. Much more significant is the fluorine content of suspended material in the water, of the plants and especially of the dust on the plants. Sometimes the dust was found to contain up to 600 mg. fluorine per 100 g.; darmous did not occur in places where the fluorine content of the soil was lower than 20 mg. per 100 g. In the ash of the mandibles of sound but young sheep they found up to 0.32 $^0/_{00}$ fluorine, in tooth ash up to 0.40 $^0/_{00}$. The corresponding figures for animals attacked by darmous were 3.2 and 4.6 $^0/_{00}$ respectively**). The fluorine content in the organs was low, as a rule lower than 1 mg. per 100 g. fresh organ.

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*) Dean found mottled enamel in cattle in South Carolina, where there are large phosphorite deposits, and in Texas (224). Neff points out that there seems to be a relationship between the amount of fluorine in natural waters and the condition of the teeth of the fish living therein (604).

**) Dr. Velu has kindly given the writer various materials for analysis. In 7 water samples I found 0.26—1.03 mg. fluorine per litre. Incisors and mandible of an apparently normal, adult sheep contained respectively 4.7 and 5 $^0/_{00}$ fluorine in the ash; for an animal attacked by darmous the figures were 6 and 7 $^0/_{00}$ respectively.
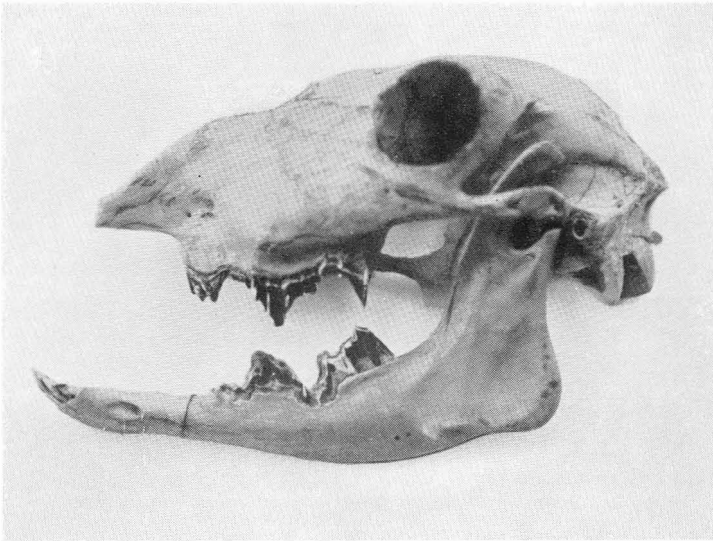
FIG. 2. Skull of young sheep from the vicinity of a Norwegian aluminium factory, attacked by fluorine intoxication. Pronounced changes in premolars and molars, injury to edge of mandible. (Reproduced by permission of Dr. L. Slagsvold from *Norsk Veterinær-Tidsskrift*, 1934).
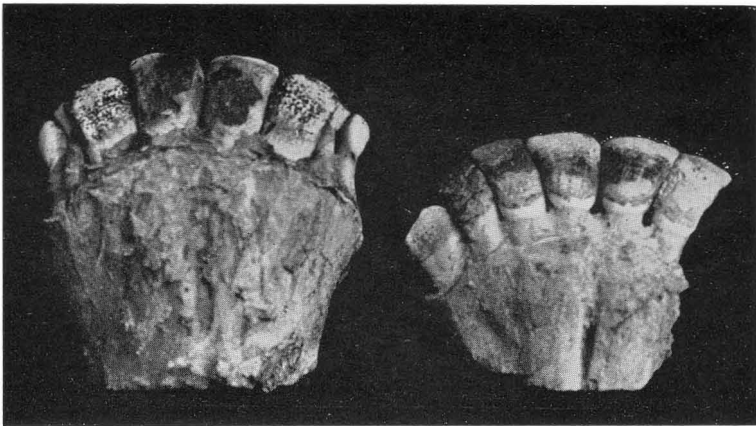
FIG. 3. Incisors of sheep attacked by *darmous*. Enamel dull, pigmented and corroded. (Reproduced by permission of Dr. H. Velu from *Archives de l'Institut Pasteur d'Algérie*, 1932).
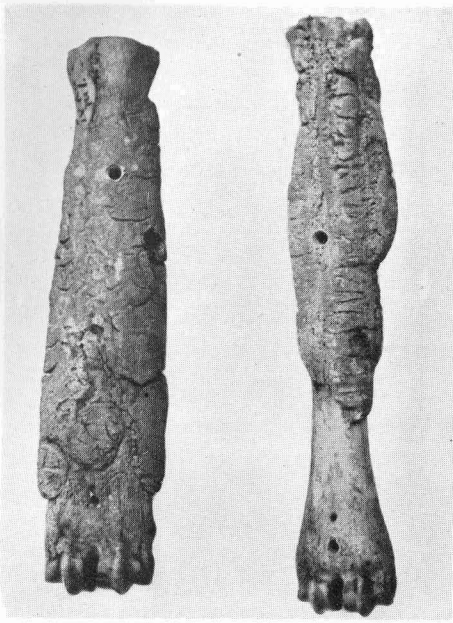
FIG. 4. (a) Metacarpus. (b) Metatarsus. Diffuse periosteal deposits.
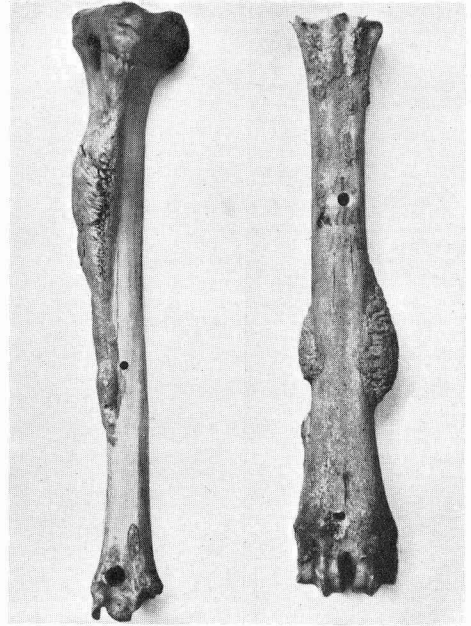
FIG. 5. (a) Tibia. (b) Metatarsus. Insular deposits.
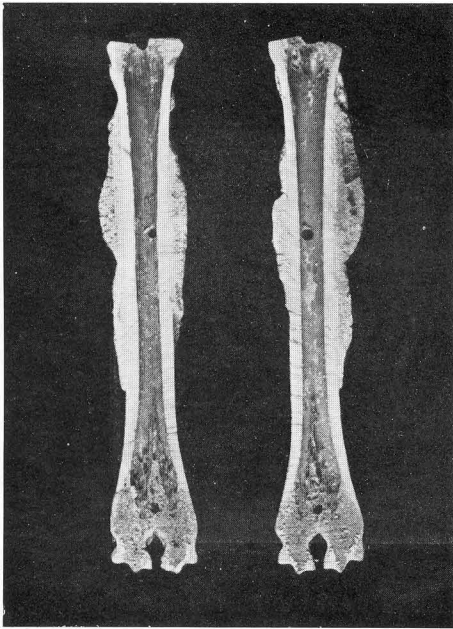
FIG. 6. (a) Divided metatarsus, with diffuse deposits. (b) Röntgen picture of divided metatarsus. No definite halisteresis.
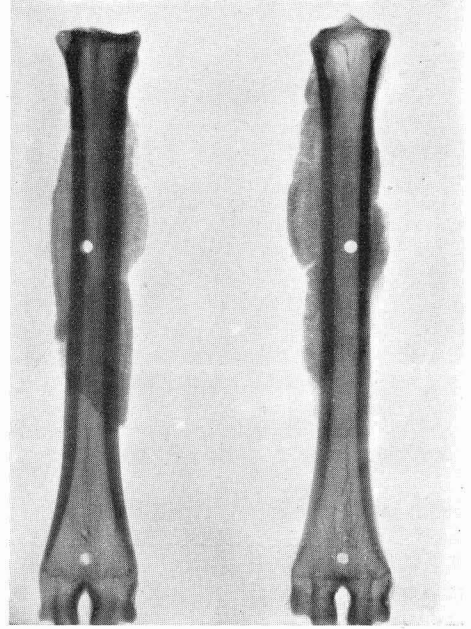
FIGG. 4—6. Bones of Icelandic sheep, died in conjunction with the eruption of *Hekla* in 1845. (Reproduced from *Nordisk Medicinsk Tidsskrift* and *Archiv für Tierheilkunde*, 1934).
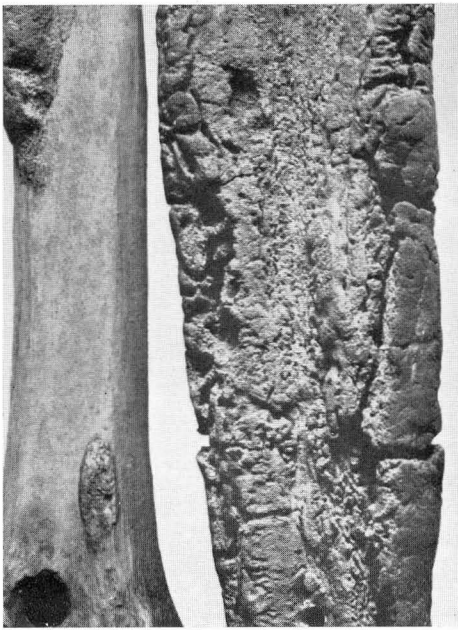
(a)   (b)

FIG. 7. (a) Tibia with sporadic deposits.
(b) Metacarpus with diffuse deposits. Magni-
fied with hand-glass.
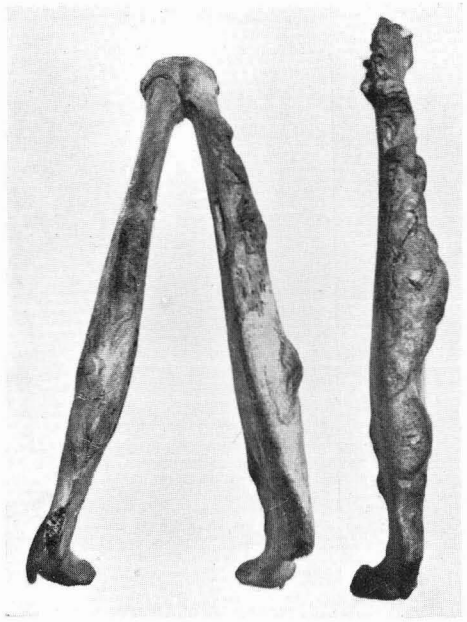
FIG. 8. Mandibles, from below. Nodular
deposits.
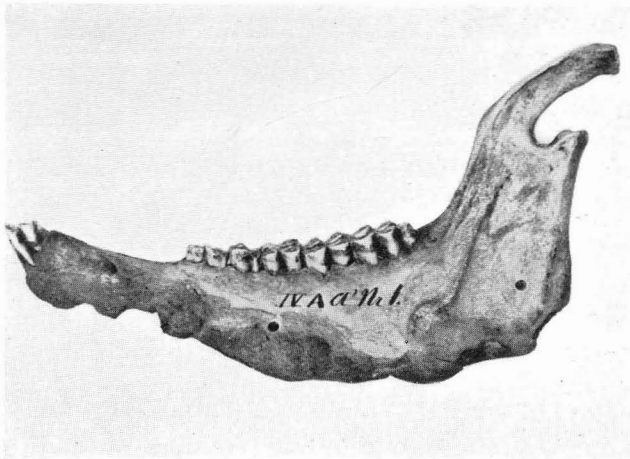
FIG. 9. Mandible, lateral view. Deposits, but no dental changes.

FIGG. 7—9. Bones of Icelandic sheep, died in conjunction with the eruption of *Hekla* in 1845.
(Reproduced from *Nordisk Medicinsk Tidsskrift* and *Archiv für Tierheilkunde*, 1934).

c. Domestic Animal Disease in Iceland after Volcanic Eruption

In the Icelandic literature from round about the year 1000 up to recent times we find accounts of how the domestic animals turned sick and died when there were volcanic eruptions (270). The earliest attempt to describe the symptoms dates from the year 1694. Later and more comprehensive accounts are due to Magnus Stephensen (769), Hannes Finsen (269), and especially Schyte (726), who gave a good description of the disease which broke out in conjunction with *Hekla*'s last eruption in 1845. The disease, which has played a great rôle in Iceland's economy, has since been observed in 1875 after the eruption of *Askja,* and probably in 1918 in connection with the eruption of *Katla.*

The disease attacked animals which ate the grass contaminated with the fallen ash, which means sheep especially, as cattle and horses were kept stabled as much as possible and so escaped. Many animals died acutely, in the course of days or weeks. Chronic changes developed in the course of months and were observable in the year after the eruption. There were emaciation, increased diuresis, decrease of milk yield, loss of strength, and impairment in the use of the limbs. The bones, especially those of the extremities and the jaws, were thickened by growths which could be cut with a knife. No mention is made of spontaneous fractures. It was characteristic that young animals especially were attacked. The disease was not infectious. The symptoms disappeared when the animals were taken indoors and fed on hay mown before the eruption. Later symptoms, which could be traced up to ten or twelve years after an eruption, were a variety of dental affections attacking only the permanent teeth of animals which had not shed their milk teeth prior to the eruption. The incisors, which in some cases were smaller and more pointed than normally, were studded with yellow and black spots; they decayed quickly (*ashtooth*). The molars underwent the greater changes, however, being deformed so that the row became irregular, making cud-chewing difficult. Sharp prominences would gnaw holes in the opposite jaw. This dental disease has the ancient Icelandic name of *gaddur* or *gaddjaxl* (gaddur, spike; jaxl, jaw-tooth).

At the Royal Agricultural and Veterinary College in Copenhagen there is a collection of bones (mandibles, extremities) of adult sheep which grazed on fields in the vicinity of Hekla during the eruption of 1845 (Figs. 4—9). The teeth seem to be normal. All the bones are covered with general or more scattered coatings of a characteristic, porous and brittle, osseous tissue. In severe cases the thickness of the bone may be twice the normal (Fig. 4). The articular surfaces are normal. Röntgen examination of the bones reveals no definite

halisteresis (Fig. 6). On analysing material from the Icelandic sheep bones the following fluorine content was found in the ash:

Metatarsus, refuse from sawing............................... 5.6 $^0/_{00}$
Metatarsus, compacta .... 4.4 ,,
Metatarsus, exostosis .... 20.6 ,,
Mandible... 16.7 ,,
Incisors, apparently normal................................. 2.8 ,,

No fluorine has ever been found in the ejecta of the Icelandic volcanoes, but the sheep disease represents a biological proof. No doubt there are gaseous fluorine compounds (HF, SiF_4) in the volcanic exhalations. That the ash apparently is toxic is doubtless due to the fact that the fluorine compounds condense round the fine particles of ash together with the moisture of the atmosphere. Mention is often made of corrosion phenomena on the vegetation, even at long distances from the active volcano. Roholm showed that similar bone changes can be induced in sheep in the course of two months or so by means of ingested sodium fluoride (687).

d. Feeding on Fluoric Forage

Fluoric Lees. The addition of hydrofluoric acid or alkaline fluorides to the mash was formerly of importance in the manufacturing of spirits. The method, which owes its origin to Effront (239—248), has the advantage of restraining deleterious fermentations, especially those caused by bacteria, while at the same time the production of alcohol proceeds uninterruptedly, and in fact is increased. The addition amounts to 6—10 g. ammonium fluoride or hydrofluoric acid per hl. of mash. As the total fluorine quantity probably passes into the lees, there is a possibility of intoxication when the lees are used as cattle feed.

Maercker (551), who introduced the method into Germany, declined to accept the possibility of an intoxication, especially on account of Tappeiner's works (786, 787). In the first reports on the use of the method we find hidden among the many enthusiastic opinions a few statements that the cattle were reluctant to take the fluoric lees, and that diarrhoea, reduced milk yield and even pareses were observable at times. Kötz (473) in 1913 states as the experience of farmers that fluoric refuse as cattle feed causes thickening of the leg and foot joints of the cattle. Ullmann (811) in 1930 says that the method has not been used much in Germany, for one reason because the farmers will not have the lees as they are injurious to the animals. In other reports the method is described as being harmless to cattle (368).

Thus there is not much definite information, but the conclusion seems to be permissable that the fluorine added in practice represents a threshold value

which under some circumstances causes intoxication, under others it does not. The figures vary quite a lot; we may take as the average value the maximum figure originally given by Effront: 6 g. fluoride (NaF, NH₄F) per hl. mash and probably in the lees too. A cow of 500 kg. can consume up to 70 litres of lees a day, which corresponds to about 4 mg. fluorine per kg. body weight.

Fluoric Mineral Mixtures. As the growing use of mineral mixtures as a fodder supplement in animal husbandry has raised the price of bone products, experiments have been made with various calcium phosphates occurring in nature and much cheaper to buy, the so-called *phosphorites*. The calcium and phosphorus content of these products is about the same as in bone meal, but they all contain fluorine, often in considerable quantities (3—4 per cent.). Their effects have been investigated, especially in America.

In the first but not very comprehensive experiments of Hart, McCollum and Fuller (384) in 1909 and Hart, Steenbock and Fuller (386) in 1914, the investigators considered they had seen favourable effects on the osseous system. In 1921 a series of experiments by Forbes et al. (277, 278, 279) showed that a daily supplement of 9—18 g. *rock phosphate**) given to growing pigs gave a poor calcium and phosphorus retention as compared with bone meal, chalk and calcium carbonate precipitate. The quantity of ash from the bones was smaller, the ratio of P:Ca relatively high and the fragility greater than in the controls. There was a relative increase of the magnesium content. Buckner, Martin and Peter (117) observed that hens given rock phosphate ad libitum had diarrhoea and laid fewer eggs than the controls, which received no mineral supplement. In 1927 Hart, Steenbock and Morrison (387) advised against giving rock phosphate as a mineral supplement; a cow that had received a 3 per cent. supplement to its feed had a prematurely born calf which died in convulsions a few days later.

It was gradually realised that these unfortunate effects were the result of the fluorine content, and this provided the impulse to a number of investigations into the toxicology of fluorine, partly in the form of phosphorite, partly as well-defined fluorine compounds. The results of these investigations are dealt with in Chapter VIII.

*) *Rock phosphate* and *phosphatic limestone* are terms for different kinds of phosphorites extracted in U. S. A. The calcium and phosphorus content varies, as the names indicate.

CHAPTER III

OCCURRENCE OF FLUORINE IN INANIMATE NATURE

As will have appeared from the foregoing chapters, the occurrence and distribution of fluorine in nature are of great importance in the development of certain forms of chronic poisoning. According to Washington (845), who embarked on a calculation of the chemical composition of the earth's crust, fluorine stands thirteenth among the elements in order of importance, before the other halogens and far ahead of toxic elements like lead, arsenic and mercury. Phosphorus occupies the tenth place with 0.13 per cent.; fluorine is at 0.077 per cent. Thus there is ample opportunity for the occurrence of fluorine in soils derived from the eruptive rocks.

1. Minerals and Rocks

A number of minerals containing fluorine have a rather considerable distribution, some of them in the form of large deposits. First in order of importance is fluorspar or *fluorite* (CaF_2), which occurs all over the world; the largest and best-known deposits are in U. S. A., England and Germany. One rare mineral is *cryolite* (Na_3AlF_6), found only at Ivigtut in Greenland in any large quantity. Fluorspar and cryolite contain 48.67 and 54.30 per cent. fluorine respectively. *Apatite*, which may contain up to 3.8 per cent. fluorine ($3 Ca_3(PO_4)_2 \cdot CaF_2$), occurs in almost all eruptive rocks. A number of more or less widely distributed minerals (*topaz, tourmaline, lepidolite,* etc.) have a varying, usually small, content of fluorine.

Of particular importance is the rich occurrence of native phosphate or *phosphorite*, deposits of calcium phosphate in amorphous form, the raw material in the manufacture of superphosphate. In almost every case they contain fluorine, most frequently 2 to 5 per cent., varying in the different deposits. Phosphorite is regarded as a weathering product of apatite, but some content of organic origin is usual. Fluorine is assumed to be present in the same form as in apatite, but the question has not been settled definitely. There are deposits,

often of great thickness, in U. S. A. (Florida, Tennessee, South Carolina), North Africa (Tunisia, Morocco, Algeria), West Indies, and on several islands in the South Seas. Most countries in Europe have deposits, and some of them are utilized. Occurrences more or less known are common in all parts of the world (780).

2. Soil

Fluorine is communicated to the soil by the weathering of the rocks containing the element. McCaughey and Frey (533) very frequently ascertained the presence of fluoric minerals in samples of American soils. Steinkoenig (768) analysed 9 soil samples and in 8 of them found between 0.01 and 0.15 per cent., on an average 0.03 per cent. In North Africa Gaud, Charnot and Langlais (367) investigated the fluorine content of the soil in the regions of the great phosphorite deposits. The fluorine quantity was high (up to 0.06 per cent.) in the vicinity of places where the deposits reached up to the surface, but considerable quantities could be demonstrated far beyond these areas. The fluorine-containing compounds are mostly spread in the form of dust, which deposits its fluorine content on the top soils. Only small quantities of fluorine were found in the groundwater. The fluorine contained in dust and soil plays a dominating part in the occurrence of *darmous*. The threshold concentration in the soil seemed to be about 0.02 per cent. fluorine, at which and lower concentrations darmous did not occur.

3. Water

Compared with the water analyses that have been made the number of fluorine determinations is very modest. In Table 7 I have collected from the literature the available quantitative analyses of fluorine in drinking water; the earliest was made in 1822 by Berzelius (66). A number of early qualitative determinations have not been included in the table.*) The latest analyses (from and including 1931) were made with reference to the occurrence of *mottled enamel*.

Mineral springs are relatively rich in fluorine, as Gautier has pointed out (308). Water from 39 French mineral springs contained from 0.15 to 6.32 mg. fluorine per litre. The fluorine content increased as the temperature of the spring rose. After earthquakes Gautier and Clausmann were able to show a

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*) The waters were from the following localities: *France*: Bussang, Vosges (863); Plombieres, Vichy, Contrexeville (609). *Germany*: Burtscheid near Aachen (857); Ems, Schlangenbad, Weilbach, Gneilau, Fachingen (288). *Italy*: Vall dell' Irno, Fratte, Salerno (152); Val Secchia (654). *U. S. A.*: The geyser "Old Faithful", Yellowstone Park, Wyoming (149).

TABLE 7.

Fluorine Content in Natural Waters.

Year	Investigator	Locality	mg. fluorine per litre or kg.
1822	Berzelius (66)	Sprudel, Carlsbad; Czechoslovakia	1.61
1873	de Gouvenain (362)	Vichy, Bourbon-⎱ l'Archambault ⎰ France ...... Néris (Allier)	7.6 2.68 6.14
1875	Husemann (428)	Eisensäuerling, St. Moritz; Switzerland	0.285 0.787
1885– 87	v. Than (791)	Szliácser-Quellen ⎱ Felsö-Alaper ⎰ Hungary Tata-Tóváros (Totis)	0.74 1.82 0.22
1888	Treadwell (866)	Neue Säuerling, St. Moritz; Switzerland	0.088
1892	Bosshard (102)	Sauerquellen, St. Moritz; Switzerland	0.239 1.691
1893	Hillebrand (414)	Ojo caliente, New Mexico; U. S. A.	5.2
1895, 1905	Casares (148 ,149)	9 mineral waters from Pyrenees .. Lugo ⎱ Guitiriz ⎰ Galicia; Spain	4.0—13.6 11.3 12.8 (max.)
1899	Lepierre (504)	Gerez; Portugal	10—12
1899	Ferreira da Silva and d'Aguiar (268)	Gerez ⎱ Vidago ⎰ Portugal	10.4 0.43
1907	Carles (129)	86 French mineral waters, ⎱ of which 65 .... ⎰	0.45—8.19*) 2.26 or more
1911	Gautier and Moureu (324)	Source Lanternier, Nancy; France	1.14
1914	Gautier and Clausmann (320)	39 French mineral waters........ Hunyadi—Janos; Hungary .... Korbous; Tunisia .... Geres ⎱ Celorico da Beira ⎰ Portugal.... Agnano; Italy	0.15—6.32 1.04 2.53 2.50 (max.) 4.47 2.50 (max.)
1929	Stuber and Lang (778)	Tap water ⎰Freiburg⎱ Germany ⎰Kiel⎱	0.028 0.165
1931	Churchill (166)	5 water samples from different places in U. S. A..............	2—13.7
1932	Smith and Smith (746)	45 water samples from Arizona, U. S. A......................	0—12.6
1932	Smith and Lantz (750)	Divers water samples from U. S. A.	0—17
1933	Ainsworth (5)	Maldon, Essex; England	4.5—5.5
1934	Munoz (599)	30 water samples from Argentina..	2.4—15
1934	Charonnat and Roche (160)	150 French mineral waters.......	0.5—15.5

*) Result stated as 1—18 mg. *fluorures*, presumably NaF.

transitory increase of the fluorine content of the water (321). Water from lakes and rivers, mostly French, contained from 0.01 to 0.6 mg. fluorine per litre. In calcareous areas the fluorine content of the water was relatively low (319, 320). In sea water fluorine was first found by Wilson (865) and Forchhammer (280). Quantitative analyses were made by Carnot (140), who in 1896 found 0.822 mg. fluorine per litre in the ocean, and by Gautier and Clausmann (320), who report 0.3 mg. By modern colorimetric methods Thompson and Taylor (754) found that the fluorine content of sea water varies with the time of the year, the distance from the shore and the depth in the sea; the values varied between 1 and 1.4 mg. per litre.

In the question of the fluorine content of drinking water the solubility of the native calcium fluoride is of particular interest; other fluorine compounds on the whole are more readily soluble. One litre of water can dissolve 16 mg. calcium fluoride or about 8 mg. fluorine. Wilson (866) has shown that its solubility increases with rising temperature and increasing content of carbon dioxide in the water; these are matters of importance especially to the ability of mineral springs to take up fluorine. It may also be that the pronounced disposition of the fluorine compounds to form complexes plays some rôle. The highest fluorine content observed is 15—20 mg. per litre.

4. Volcanoes

Fluorine-containing products may be given off by volcanic eruptions; our knowledge of such matters is, however, rather limited. As the fluorine content of soil in volcanic regions seems to be especially high, and as at any rate the Icelandic volcanoes have caused fluorine intoxication in animals, it becomes a matter of interest to know the fluorine-ejecting volcanoes. In Table 8 is summarized what I have been able to find in the literature on the subject; the list makes no pretence of being complete. The gaseous volcanic emanations may contain fluorine in the form of hydrogen fluoride (HF) and silicon tetrafluoride (SiF_4), or in the form of salts (especially NH_4F, NaF, KF, MgF_2, CaF_2). Different fluorine compounds may be formed during an eruption by the chemical conversions that take place, most frequently silico-fluorides, which may occur in more or less pure form in deposits, or mixed with the various volcanic products: ash, lapilli, lava, etc. Only rarely has it been possible to judge of the quantitative proportions. Day and Shepherd (220) collected the gases evolved during the 1912 eruption of *Kilauea* and found that the fluorine content in the condensate exceeded the quantity of the other compounds. Shipley (759) states that the fluorine content in the

TABLE 8.

Volcanoes Emitting Fluorine.

Situation	Date of volcanic activity or collection of sample	Analyses published, year	Investigator	Fluorine compound (F = simple qualitative determination)	Nature of volcanic emission
Vesuvius, Italy	1850	1855	Scacchi (705)	HF	Exhalation
	1855	1855	do.	HF	do.
	1870, 1872	1875	do.	HF	do.
	1872	1875	do.	$(NH_4)_2SiF_6$ (Cryptohalite)	Deposition at fumarole
	1872	1887	Scacchi (708)	SiF_4	Exhalation
	1895	1899	Matteucci (565)	HF	do.
	1906	1906	Brauns (110)	Na_2SiF_6	Lava
	1906	1906	Stoklasa (773)	HF; F	Exhalation; lapilli
	1913	1913	Gautier (310)	HF?	Exhalation
	1895	1910	Zambonini (888)	K_2SiF_6 (Hieratite)	Deposition at fumarole
	..	1926	Zambonini and Carobbi (850)	Na_2SiF_6 (Malladrite)	do.
	..	1926	Zambonini (889)	KBF_4 (Avogadrite)	Sublimation product
Nocera, Sarno Italy	..	1882	Scacchi (706)	$2(CaMg)F_2 + (Ca,Mg)O$ (Nocerine)	Deposit from earlier volcanic activity
Suffioni at Lardarello, Toscana, Italy	1913	1913	Gautier (310)	F	Exhalation
Etna, Italy	1908?	1908	Lacroix (486)	F	Deposition at fumarole
Vulcano, Italy	..	1882	Cossa (178)	K_2SiF_6 (Hieratite)	Deposition at fumarole
	..	1914 —15	Koenigsberger and Müller (466)	$F(K_2SiF_6?)$	Deposition at fumarole
	..	1925	Roccati (685)	HF	Exhalation
Chinyero, Canary Isl.	1909	1912	del Campo (124)	NH_4F	Sublimation product
Mt. Pelé, Martinique	1902	1927	Shepherd and Mervin (738)	F	Lava

TABLE 8.

(Continued.)

Situation	Date of volcanic activity or collection of sample	Analyses published, year	Investigator	Fluorine compound (F = simple qualitative determination)	Nature of volcanic emission
Kilauea, Hawaii	1912	1913	Day and Shepherd (220)	F	Exhalation
Katmai, Alaska	1917	1920	Shipley (739)	HF; F	Exhalation; deposition at fumaroles
	1919	1923	Allen and Zies (8)	HF; F	do.
Barari, India	1926	1926	Christie (165)	$(NH_4)_2SiF_6$ (Cryptohalite)	Deposition from earlier volcanic activity

fumaroles at *Katmai* was so considerable that the glass containers in which the gas was condensed were corroded. Analyses by Allen and Zies (8) showed up to 0.099 volume per cent. hydrogen fluoride in the same fumaroles. Gautier (310) found 0.11 mg. fluorine, presumably in the form of hydrogen fluoride, per litre air at the *Vesuvius* eruption in 1913.

The scattered distribution of the fluorine-ejecting volcanoes over the globe (Italy, Canary Islands, Martinique, Hawaii, Alaska, Iceland) indicates that the ability to give off fluorine is general. Of particular toxicological interest is the frequent occurrence of the very toxic, volatile compounds hydrogen fluoride and silicon tetrafluoride. Most volcanoes have been investigated only little, or not at all, for the occurrence of fluorine in the products, but a negative result after an examination seems to be a rare phenomenon.

CHAPTER IV

DISTRIBUTION OF FLUORINE IN ANIMATE NATURE

1. Plants

Müller and Blake (860) seem to have been the first — in 1845 — to demonstrate the presence of fluorine in vegetable tissue (barley). Wilson (866) believed that fluorine occurred widespread in the vegetable kingdom, but in small and varying quantities; the element came from the fluorine-containing weathered minerals in the soil, was taken up in dissolved form, and presumably converted in the plant to silicofluorides. Wilson (870) demonstrated fluorine especially in the siliceous stems of Gramineæ and Equisetaceæ. In the course of time a number of qualitative tests have been made. Woelcker (883) found fluorine in the ash of *Armeria maritima*, Salm-Horstmar (761) in *Lycopodium clavatim*, Alvisi (16) in ripe, but not in unripe grain. There is a long number of investigations on the normal occurrence of fluorine in grapes, some with a positive, others with a negative result (page 303). The quantitative analyses made are likewise few in number and the results varying, presumably due partly to analytical difficulties, partly to actual variations in the fluorine content of soil and plants.

In order to establish whether or not there had been damage from factory emanations Ost (621) set the normal content of fluorine in the ash of healthy plants at about 0.1 per cent. In barley and malt Woodman and Talbot (884) found from 0.04 to 10 mg. fluorine per kg. In North Africa Gaud, Charnot and Langlais (367) showed recently that the fluorine content of the plants depends upon the fluorine concentration in the soil. In a region where there was no *darmous*, wheat straw contained 7.42 mg. fluorine per 100 g. dry substance; in a region with darmous, 20.9 mg. Soil samples from the two localities had a fluorine content of 0.016 and 0.060 per cent. respectively. A long series of investigations has been made by Gautier and Clausmann (322) who, employing a method of their own, analysed 64 samples of vegetable tissue, especially from food plants. They found fluorine in all of them, but in greatly varying quantities; no plant group was especially rich in the element. The highest fluorine content was in leaves (3—14 mg. per 100 g. dry substance), the lowest in stems, wood and bark (0.36—1.7 mg.). In seeds and fruit-meat the quantity was of medium value and fairly equal everywhere; the skins of fruit were always very much richer in fluorine. In banana pulp they found 0.38, in the skin 5.10 mg. per 100 g. dry substance. Mayrhofer, Schneider and Wasitzky (573), who

also used their own method, in 1932 found fluorine in most cultivated plants, but not in tomatoes, potatoes and tobacco. The quantity varied between 0.006 and 0.048 mg. per 100 g. fresh plant. Expressed in the same way, Gautier and Claus-mann's figures fluctuate between 0.01 and 5.90 mg. Thus there is a considerable difference, and the same applies to the various analyses that are directly comparable.

2. Bones and Teeth

The organic tissues that are richest in fluorine are the bones and teeth, and they are the first in which the presence of the element was demonstrated. Although numerous analyses have been made, some uncertainty still prevails, not only as to the normal quantity, but also whether the teeth normally contain fluorine at all.

a. Presence of Fluorine

In 1803 Morichini (595) observed the evolution of hydrofluoric acid vapours when treating a fossil elephant tooth with sulphuric acid. There was fluorine in both the osseous substance and the enamel, more in the latter. The find caused a stir and called forth opposition, though Klaproth (460) confirmed it with material sent to him. Together with Gay-Lussac (326), Morichini (596) undertook new investigations, which in part confirmed the first results and in part established the presence of fluorine in fresh ivory and dental enamel of man and animals. The discovery was immediately contested by Brande (167) and Fourcroy and Vauquelin (284), who, though able to show traces of fluorine in fossil bones, were unable to do so in recent bones. After Berzelius (65) in 1807 had demonstrated fluorine in human and animal bones and attempted a quantitative analysis, the discovery was generally acknowledged. Berzelius (68) later on realized that his analyses had given exaggerated values (up to 9.3 per cent. calcium fluoride in ox bones).

Round about 1840 came another group of investigations, some of them denying the presence of the element in fresh bones (671, 672, 332), others confirming it (259, 556, 583, 218, 76). There was general agreement that fluorine is constantly present in fossil bones, often in considerable quantities (163, 444). In 1844 Middleton (584) set up the theory that the fluorine content in fossil bones increases with their age and actually permits of a geological dating. In 1846 George Wilson took the question up on a broader basis and, in a series of excellent works (865—870), proved that in addition to being present in bone tissue, fluorine was to be found in many other animal tissues, in plants, in springs and in sea water. Subsequent investigators have mostly confirmed the presence of fluorine in bones and teeth. Still, among modern

investigators there is disagreement; for instance Gassmann (305, 306) and Beretta (55) have denied the presence of fluorine in the teeth.

b. Quantity

In Table 9 I have summarized the results of most of the available analyses. I have omitted the earlier investigations (404, 858, 852, 416, 717), in which the fluorine content was *calculated* on the basis of the quantity of acid equivalent to the surplus of basic elements in bone ash. The use of this method leads to fantastically high values (as much as 8 per cent. fluorine). The value of several early investigations is small owing to the analytical method employed; as a rule there are only few analyses from each investigator.

According to Table 9, with especial reference to the results of recent years, the fluorine content of bones and teeth seems to be more or less the same in man and in animals. The quantity most frequently stated is $0.1—1.5 \, ^0/_{00}$ fluorine, calculated on the ash, but there is quite a number of values that fall outside these limits; for example, Salinas y Ferrer (699) found a value as high as $11.8 \, ^0/_{00}$ fluorine in the mandible of a man 45 years of age. Klement (462), employing good analytical technique, showed that the bones and teeth of marine animals contain about ten times the quantities of fluorine given above as the average quantities. According to a few older analyses of isolated dentine and enamel (441, 317), the fluorine content is almost the same as in bone, higher if anything in enamel than in dentine. Boissevain and Drea (90) spectrographically found $0—0.65 \, ^0/_{00}$ fluorine in the enamel of normal human teeth. Normal enamel and dentine from cattle contain, according to Chang et al. (159), $0.266 \, ^0/_{00}$ and $0.625 \, ^0/_{00}$ fluorine, respectively, expressed on dry weight.

c. Origin

The fact that fossil bones usually contain much more fluorine[*] than recent bones led first to the assumption that hydrofluoric acid is formed by the metamorphosis of the phosphoric acid in the bone (460, 671), or that the prehistoric organisms actually contained the very considerable quantities of fluorine found in their bones (569). After Wilson's investigations the phenomenon was capable of a more simple explanation: Fluorine compounds

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[*] There are a number of analyses, mostly old, of fossil bones (Baumert (50), Claus (169), Greene (364), Wicke (854), Aeby (3), Wilson (871), and so on). There is a good deal of difference in the fluorine content indicated (about 1 to 16 per cent. CaF_2). It is particularly interesting that Scacchi (709) found 6.2 per cent. CaF_2 in a fossil stag bone discovered near Vesuvius. In human bones from Pompeii Liebig (509) demonstrated a considerable fluorine content. Fossil plant remains, too, sometimes contain large quantities of fluorine (650).

TABLE 9.

Analyses of Normal Fluorine Content in Bones and Teeth.

Investigator	Year	Result expressed in $^0/_{00}$ fluorine of fresh bones (F), dry substance (D) or ash (A)	Material		Method
Zalesky (887)	1866	F*) 2.29 3.0	Homo Ox	} bones	Glass etching
Carnot (137)	1892	A 1.6—3.1	Homo Ox	} femur	Carnot
Wrampelmeyer (885)	1893	F 6.5—15.5	Homo:	teeth	Carnot
Gabriel (298)	1894	A $\overline{\overline{<}}$ 0.5 $\overline{\overline{<}}$ 1.0	Homo Ox:	{ bones, { teeth bones	Glass etching
Kühns (484)	1895	A 2.9 2.5	Homo	{ enamel { dentine	Carnot
Michel (582)	1897	F 5.6—6.7	Homo:	teeth	Fresenius
Bertz (64)	1898	A 11.70 6.66 9.25	Homo Calf:	{ enamel { dentine enamel	Fresenius
Harms (382)	1899	A 0.06 0.05—0.22 0.05—0.18	Homo: Various animals	teeth { bones { teeth	Precipitation of silicic acid (estimated)
Hempel and Schefler (467)	1899	A 1.9—5.2 2.0—3.9	Homo Horse	} teeth	Hempel
Jodlbauer (441)	1903	A 0.4 1.2—2.7 2.7—2.8 0.5—3.2	Homo Various animals	{ mandible { teeth { enamel } bones	Hempel
Zdarek (892)	1910	F 0.29—0.45	Homo:	bones	Gravimetric
Renner (674)	1912	A 0.7—1.6 1.0—1.3	Homo: Ox:	teeth bones	Hempel
Gautier and Clausmann (317)	1913	A D	0.524-0.929 0.306-1.23 0.369 1.72 0.615	Homo Ox Dog	} femur { os frontis { enamel { dentine	Gautier and Clausmann
Sonntag (761)	1917	F ca. 0.4-1.5	Dog	{ bones { teeth	Glass etching

*) Expressed on non-fatty material.

TABLE 9.

(Continued).

Investigator	Year	Result expressed in $^0/_{00}$ fluorine of fresh bones (F), dry substance (D) or ash (A)		Material		Method (mod. = modification)
Trebitsch (807)	1927	D	2.9—5.9	Homo:	teeth	Gravimetric as lanthan-fluoride after Meyer and Schulz
Bethke et al. (69)	1929	D*)	0.231-0.409	Pig:	femur	Reynold, Ross and Jacob
Lang (488)	1930	D	0.276-0.45	Rabbit:	bones	Steiger (mod.)
Kick et al. (454)	1933	D*)	0.36—0.57 0.43—0.92	Pig	{ femur { teeth	Reynold, Ross and Jacob
Sharpless and McCollum (736)	1933	A	0.1—0.75 0.06—0.21	Rats	{ bones { teeth	(Steiger mod.)
Boissevain and Drea (90)	1933	A	7.0 0.65 1.12 1.3 0 0.68	Homo (Colorado) Homo (New York)	} bones } enamel } dentine } bones } enamel } dentine	Specto-graphic
Klement (462)	1933	?	0.59 0.30 0.38—0.65 8.0—16.2 6.9—7.4	Homo Various animals Marine animals	{ cranial bones { tooth } bones } bones } teeth	Willard and Winter (mod. Armstrong)
Salinas y Ferrer (699)	1934	A	0—11.8 0—0.6 0—1.7 0—0.65 0.55—0.95 0—1.5	Homo Various mammals Birds: Fish:	{ bones { teeth } bones } teeth bones bones	Offermann (mod.); Colorimetry after de Boer
Chang, Phillips et al. (159)		D*)	0.5376 0.6225 0.2666 0.5840	Cow	{ molar dentine { enamel { bone	Willard and Winter (mod. Armstrong)

*) Expressed on non-fatty material.

are widespread in nature; calcium fluoride to a certain low degree is soluble in water, especially water containing carbon dioxide. This explains why fluorine can be deposited in bones in the ground and taken up by plants and animals. The relation between the content of fluorine in water and soil and its presence in living beings, which Wilson demonstrated in 1846, has only been taken up for examination in recent years. Boissevain and Drea (96) were able to show in 1933 that in individuals who always had lived in Colorado Springs, where the water contains 2 mg. fluorine per litre, the average fluorine content of enamel and dentine was 0.65 and 1.12 $^0/_{00}$; in bone ash they found on an average 7 $^0/_{00}$ fluorine. For inhabitants of New York, where the water does not contain demonstrable quantities of fluorine, the corresponding figures were: enamel 0, dentine 0.65 $^0/_{00}$; bone (from the region east of the Appalachian Mountains), 1.3 $^0/_{00}$ fluorine. In North Africa, extensive investigations in 1934 by Gaud, Charnot and Langlais (307) showed that the fluorine content of plants varies with the fluorine concentration in the soil. A high fluorine content in the soil with secondary accumulation of fluorine in the plants is a factor in producing *darmous* in herbivora, biochemically characterized by an increase of the fluorine content of the bones up to 40-fold.

d. Form

There is a certain affinity between calcium phosphate and fluorine; this is indicated, for example, by the frequent occurrence of fluorine in the native phosphates. Carnot (139) showed experimentally in 1893 that bone also possesses a marked ability to absorb and fix fluorides in dissolved form. In fossil bones the fluorine content increases with age; the ratio fluorine: phosphoric acid for bones dating from the earliest geological periods is the same as for apatite. Carnot accepted Middleton's theory and considered it possible to utilize the fluorine content of a fossil bone for an approximation of its age, especially where bones of various origins are found at the same place. The theory has met with criticism (53) and on the whole is scarcely tenable. The fluorine in the surrounding earth strata is of decisive significance.

Gabriel (298), one of the first modern investigators, put the simplest composition of the inorganic substance of bone at $Ca_3(PO_4)_2 + Ca_5HP_3O_{13} +$ aq. Of this, 4 to 6 per cent. phosphoric acid should be substitutable with CO_3, Cl or F; nevertheless, he found the normal fluorine content of bone ash to be no higher than 0.5—1 $^0/_{00}$. One of the latest works is by Klement and Trömel (464), who state that the main component of the inorganic substance is hydroxylapatite $Ca_{10}(PO_4)_6 \cdot (OH)_2$. In theory there is the possibility that fluorine is present in bone as fluorapatite, $Ca_{10}(PO_4)_6 \cdot F_2$ or $3 [Ca_3(PO_4)_2] \cdot CaF_2$. Pure fluorapatite contains 3.77 per cent. fluorine, and as the fluorine content in bone ash is probably less than 1 $^0/_{00}$, there can at the most be a mixed form of crystal between hydroxylapatite

and fluorapatite. Tooth ash, heated to 800°, gave exactly the same Röntgen diagram as hydroxylapatite, which means the fluorapatite and hydroxylapatite have identical crystal structure, and that F^- and OH^- can replace each other isomorphously.

3. Other Animal Tissues

In 1805 Gay-Lussac (326) suggested that fluorine was probably to be found in urine like other ossifying substances. Berzelius (65) was successful in demonstrating the fact, but it was necessary to work on large quantities of urine. Round about 1850 Wilson (868) found the element in ox blood, cow milk, cheese and whey, Nicklès (608) in the blood of man, mammals and birds, and in urine, gall, saliva and hair. Horsford (424) in 1869 proved the presence of fluorine in the human brain, Tamman (785) in the hen's egg — shell, white and yolk, most in the latter.

Analyses of certain normal organs have been published by Zdarek (892), Gautier and Clausmann (316, 318), Lang (488) and Chang et al. (159). Some of the results are shown in Table 10. The agreement is rather slight,

TABLE 10.

Fluorine Content of Normal Organs.

Investigator	Gautier & Clausmann (1913)	Lang (1928)	Zdarek (1910)	Chang, Phillips and co-workers (1934)
Method	Own	Steiger (mod.)	Gravimetric	Willard & Winter (mod. Armstrong)
Material	Man	Rabbit (6 individuals)	Man (2 adult males)	Dairy cow (3 individuals)
	mg. F per 100 g. dry substance			
Brain	3.07	—	0.23—0.27	—
Heart	—	8.1—30.1	0.45—0.46	0.23—0.27
Lungs	2.44	3.0—12.9	0.22—0.70	—
Liver	2.13	10.1—18.4	0.68—0.80	0.52—0.56
Spleen	—	—	0.82—2.35	—
Kidneys	0.95	7.1—14.8	1.34—1.54	0.69—1.01
Muscle	0.57	8.9—20	—	—
Blood	0.46*)	0.75**)	0.35*)	—

*) Expressed per 100 g. fresh blood.
**) Expressed per 100 c. c. blood.

and the material small; one cannot say more than that the normal fluorine content of the organs seems to vary from tenths of mg. to a few mg. per 100 g. dry substance. There is not sufficient evidence to show that some organs (except bones and teeth) are especially rich in fluorine, nor especially poor.

Gautier and Clausmann, whose investigations are rather comprehensive, found that the fluorine quantity was least in the vital organs, greater in the connective and supporting tissues, but higher in epidermis and its derivatives. Epidermis contained 16.4, hair up to 17.2, enamel up to 181 mg. fluorine per 100 g. dry substance. Chang et al. (159) were unable to demonstrate larger amounts of fluorine in tendon, hair and hoof than in parenchymatous organs of dairy cattle. In 1933 Boissevain and Drea (96) could not substantiate the presence of fluorine by means of spectrographic examination of organs from individuals in Colorado, where the water is particularly high in fluorine content.

According to Stuber and Lang's theory (777, 778) the fluorine content of the blood is of importance to coagulation and therefore has been the subject of some research. In various German towns Stuber and Lang found blood fluorine varying between 0 and 0.85 mg. per 100 c.c.; the variations were attributed to the varying fluorine content of the drinking water. Blood of hæmophiles contained 3—4 mg. fluorine per 100 c.c.; in animal blood, the fluorine content on the whole varied parallel with the bleeding time from 0 (dog, cat) to 1.5 mg. per 100 c.c. (goose). In contrast, Hoff and May (419) and Feissly, Fried and Oehrli (266), in both normals and hæmophiles, could only find traces of fluorine which were indeterminable quantitatively, or at any rate were lower than 0.5—1 mg. per 100 c.c.

In a number of lower animals Middleton (583) has demonstrated the presence of fluorine. Silliman *junr.* (741) found fluorine in several corals. According to results obtained by Carles (131, 132), marine mollusc shells contain about ten times as much fluorine as the corresponding organs of non-marine molluscs. Oyster shells contain 0.01—0.02 per cent. fluorine (131, 161).

EFFECTS OF FLUORINE ON PROTOPLASM AND ENZYMES

1. Protoplasm. Lower Organisms

The deleterious effect on protoplasm, familiar from practical experience with hydrogen fluoride, is also characteristic of most of the simply composed fluorine compounds. Subcutaneous injection of a soluble fluoride (3—4 per cent.) kills the tissue around the place of injection under inflammatory phenomena; a crusty necrosis forms, which falls off and leaves a slowly healing ulceration. Isolated cells or tissue placed in a solution of sodium fluoride are destroyed quickly as compared with equimolecular solutions of the sodium salts of the other halogens. In this respect fluorine stands out from the group (602, 851, 214). Prior to the destruction of nerve or muscular tissue there is a severe but brief irritation (370, 786). Experimenting with isolated dog intestine Heidenhain (462) showed that the addition of 0.04—0.05 per cent. sodium fluoride to a solution of sodium chloride inhibited both water and salt resorption, though no changes could be observed in the cells. A 1 per cent. solution of sodium fluoride produced enormous hyperæmia and destruction of the mucous membrane. Vernon (837) found that the perfusion of the isolated rabbit kidney with 0.1—1 per cent. sodium fluoride produced a temporary reduction of respiration; the effect only became permanent at 1.5 per cent. Kisch (459) found recently that sodium fluoride in weak solution $\left(\dfrac{m}{700} - \dfrac{m}{500}\right)$ may have a stimulating effect upon the respiration of the rat kidney. The tissue-destroying effect of 1 per cent. sodium fluoride has been applied in investigating the function of the kidneys: Injection of a few c. c. in ureter electively destroys the epithelium in the tubule system and provides a possibility of studying the isolated function of glomeruli (163, 96).

Algæ placed in a 0.5 per cent. solution of sodium fluoride displayed morphological changes in the nucleus within an hour (517). Growth experiments with higher plants showed inhibition after the addition of 0.025 per cent. sodium fluoride; 0.1 per cent. was very toxic. Hydrofluoric acid had still stronger effects (95). For bacteria and lower fungi the fluorine compounds are very toxic. The antiseptic effect of sodium fluoride was first demonstrated by Kolipinski (467) in 1886. Tap-

peiner (786) found that 0.5—1 per cent. sodium fluoride suppressed all growth of bacteria, 2 per cent. killed after 1—6 days. Even a concentration as low as 0.03—0.04 per cent. inhibited the growth of a number of bacteria (563). Spores, on the other hand, are highly insensible; d'Herelle (409) states that sporulating bacteria which had lain several weeks in 2.5 per cent. sodium fluoride grew out when grown on a suitable medium. As Effront (239—248) showed, yeast cells by cultivating in fluoric medium may become inured to fluorine to a degree that inhibits all activity in non-inured strains. During the inuring process there is a change in the appearance, growth and ferment-production of the cells. The exact mechanism of this peculiar inuring process, which has been of importance to industry, is not known (261). A similar phenomenon is observable in bacteria: Dysentery and coli bacteria can gradually be inured to sodium fluoride in a concentration of 1.2 per cent. (409).

2. Effect on Blood in vitro

In 1890 Arthus and Pagés (38) discovered that the addition of 0.15 per cent. alkaline fluoride inhibits coagulation of the blood. The effect cannot be due to a simple precipitation of calcium, as the addition of a soluble calcium salt to fluoride plasma does not produce coagulation, which in fact occurs under the same conditions in oxalate plasma. The addition of sodium fluoride simultaneously inhibits the glycolysis (34) and oxygen consumption (37) of the blood.

Bordet and Gengou (98) explained the inhibition of coagulation by assuming that the precipitated calcium fluoride binds the enzymes that are active in the coagulation process. There is more probability in a contemporaneous explanation by Calugareanu: Sodium fluoride inhibits blood coagulation by a special effect upon the cells, whereby the emission of the fibrine ferment is inhibited (122). In conformity with this Foit (276) found in 1931 that recalcified fluoride plasma coagulates on the addition of non-cellular tissue extracts. Foit also showed that the fluorine concentration in the blood must be rather high (about 45 mg. per cent. or about 0.1 per cent. sodium fluoride) before the inhibition of coagulation is evident. According to Portier and Duval (658), 1 per cent. sodium fluoride affects the erythrocytes in such a manner that they cannot increase in volume without bursting in a hypotonic solution of sodium fluoride; on the other hand the ability to shrink in a hypertonic solution is retained. Presumably, sodium fluoride fixes the cell membrane and the outer layers of protoplasm (*fixateur physiologique*). If 1—4 per cent. sodium fluoride is added to the blood it becomes viscid, jellied. This phenomenon, which must be taken to be a kind of coagulation, is perhaps the result of a combination between fluorine and the protein substances of the blood. Oxalic acid has not this effect (804).

3. Effect on Various Enzymatic Processes

As will already appear from the above, the fluorine compounds, like certain other antiseptica, have a pronounced influence upon enzymatic processes. Arthus and Huber (37) considered it possible to make a general division

of the enzymes into two groups according to their reaction to 1 per cent. sodium fluoride. All fermentations due to vital processes (*ferments figurés*) should be capable of being stopped, i. e. decomposition of organic substances, the conversion of milk sugar to lactic acid by microorganisms, and so on. The soluble enzymes (*ferments solubles*) on the other hand should not be inhibitable, i. e. the enzymes of the digestive secretions, the invertin of yeast, the diastase of malt, etc. The inhibitory effect could not be the result of a precipitation of calcium, as sodium oxalate lacks it, but substrates rich in calcium required relatively large quantities of fluorine. Arthus and Huber's division is not practicable; the position is not so clear. The most usual effect of fluorides is an inhibition of the enzymatic process; sometimes, however, a stimulation is observed. As to the exact mechanism of the influence there is an absence of unanimity; some investigations (635, 600) would indicate that an inactive combination is formed between the NaF molecule and the enzyme, others do not (694, 432). As a rule the process seems to be reversible.

Proteolytic Enzymes. According to Treyer (808), 1 per cent. sodium fluoride has an inhibitory effect on trypsin and pepsin; according to Hehner and Hehner (461), even 0.04 per cent. inhibits the action of pepsin. Vandervelde and Poppe (816) observed no effect of sodium fluoride in various concentrations (maximum 0.12 per cent.) on the breaking down of certain proteins by trypsin and pepsin. By investigating the clotting effect of pepsin on milk Clifford (170) has shown that the concentration is of great importance. When the concentration of sodium fluoride exceeded 0.0144 molarity, the process was inhibited; with a sufficiently weak concentration there was even stimulation. The gelatinase formed by *Bacillus prodigiosus* is inhibited in its action by 1 per cent. sodium fluoride (367).

Lipases of varying origins seem to be very sensitive to fluorides; as a rule the effect is an inhibition (451, 35, 694). Loewenhart and Peirce (516) showed that even in a concentration of 1 : 5 millions sodium fluoride reduces the effect of liver extract on ethylacetate by 50 per cent. This extraordinary sensitivity might even be employed for the detection of very small quantities of fluorine, for instance in food (11). As regards pancreatic lipase Terroine (790) has shown that varying concentration can govern both inhibition and stimulation.

Urease. Investigations by Jacoby (431, 433) showed that the bacterial splitting of urea is inhibited by sodium fluoride. The effect developed first in neutral or acid milieu and grew with increasing acidity. Oxalic acid and citric acid had not this effect.

Glycolytic Enzymes. Inhibition of the blood glycolysis (34, 777), and Effront's showing that the starch-splitting action of yeast can be preserved, despite the addition of fluorine compounds, have already been referred to. The same applies to malt diastase, a circumstance that has been of some importance in practice, because unwanted fermentations can be suppressed simultaneously. It seems as if the different glycolytic enzymes behave quite variously under the influence of fluorides; the conclusions of the available investigations do not lend themselves to expression in brief form. An inhibitory effect on ptyalin or pancreatic diastase differing from that of the other halogens is reported by several investigators (634, 461, 881,

686). A stimulating effect on the same enzyme has been observed by Wachsmann and Grützner (841), even with a saturated solution of sodium fluoride. Doby (234) found that the amylase of the potato was powerfully stimulated; in a 2.5 per cent. solution of sodium fluoride the effect was trebled. Taka-diastase behaves differently according to the concentration of the fluoride (882). Lang and Lang (489) showed that the effect on pancreatic diastase is complicated. The fluor-ion is inhibitory to the formation of maltose, but at the same time stimulating on the conversion of maltose to glucose. The total effect is an inhibition of the diastatic process. Clifford (170) states that the influence of the various fluor salts on starch digestion varies: some inhibit, others are inactive. Ewig (262) has shown that in isolated tissue both anaerobic and aerobic glycolysis is greatly inhibited by sodium fluoride $\left(\dfrac{m}{100}\right)$. The fluoride effect is associated with F^- and is reversible. The glycolysis in the carcinoma cell is inhibited under the influence of fluorine, whereby it approaches the glycolysis in normal tissue.

Glycolysis in muscle. Fluorine has an inhibitory effect on the lactic acid synthesis occurring during muscle metabolism. DeEds (228) gives the following description: "Normally, muscular activity is accompanied by an increase in the amount of lactic and phosphoric acids as compared with the resting muscle. A portion of this lactic acid, about one fifth, is normally burned to carbon dioxide and water. Embden and Lange and Embden and Hentschel regarded lactocidogen as the precursor of lactic and phosphoric acids, and believed that these three substances exist in muscle in a state of dynamic equilibrium:

$$\text{Lactocidogen} \rightleftharpoons \text{Lactic Acid} + \text{Phosphoric Acid}$$

They showed that this reversible reaction could be shifted by the sodium salts of various anions, and that, if the anions were arranged in the order of their ability to shift the equilibrium, the arrangement of the anions was that of the Hofmeister series. Salts at the sodium iodide end of the series facilitated hydrolysis of the lactocidogen, while salts at the other end showed little of this effect, or even favoured resynthesis of lactocidogen. Interestingly enough, sodium fluoride was most effective in favouring synthesis. These observations of Embden and his co-workers are in agreement with the results obtained by Lipmann. Lipmann found that fluoride decreased the respiration of excised muscle directly by a decreased oxygen consumption and indirectly by a lessened lactic acid production, i. e., an inhibitory action on the splitting of lactocidogen". Embden's view of fluorine's mode of operation must probably be modified. Recent investigations (Meyerhof, Lundsgaard, etc.) have shown that "the immediate precursor of lactic acid in muscle is a labile hexose monophosphate. Fluorides interfere with the formation of lactic acid by converting this labile ester to a stable form, the Robison ester, glucose-6-phosphate, which in turn is changed to an even more stable diphosphate. Neither of these latter substances serve as lactic acid precursors under ordinary conditions. These equilibria are modified by the salts of the Hofmeister series in the same manner as the lactocidogen-lactic equilibrium of Embden and co-workers".

CHAPTER VI

EXPERIMENTAL INVESTIGATIONS INTO THE EFFECTS OF GASEOUS FLUORINE COMPOUNDS

1. Effect on Plants

The damage observed on vegetation in the neighbourhood of factories whose waste gases contain fluorine compounds has led to a number of experimental investigations. *Acute* or *chronic* injury can be produced all according to the concentration of the toxic compound and the duration of its action. The very important practical question of the possibility of *invisible* injury, i. e. an increase of the fluorine content of the plants without other macroscopically recognizable changes than, perhaps, a stunting of growth, has not been studied.

Schmitz-Dumont (713) in 1896 instituted the first experiments on the effects of hydrogen fluoride on fir, oak and maple in a closed room. At a concentration of 0.01 per cent. (1 : 10000) there was a discolouration already after one or a few days, commencing on the leaves as a yellowish border and gradually turning into a darker, brownish shade. With an exposure of 3—4 weeks the concentration 0.00033 per cent. gave the same effect. Sertz (732) arrived at similar results later. Fir and pine displayed a browning of the needles even after one hour's exposure to hydrogen fluoride or silicon tetrafluoride in a concentration of 0.01 per cent. With a daily exposure of up to 3 hours both compounds in a concentration of 0.0004 per cent. produced visible damage in the course of a period varying from one week to one month. Cristiani and Gautier (206) have also verified the injurious effect of hydrogen fluoride.

By spraying pine and fir Wislicenus (876) found that fluorine compounds are much more toxic than the other compounds that are of significance in the industrial smoke problem. A $\frac{n}{200}$ solution of hydrofluosilicic acid gave visible damage after repeating the spraying 17 times; chlorine and sulphurous acids only after 200—350 times. The following series gives increasing effect:

HCl, SO_2*), H_2SO_4, Cl, HF, SiF_4 and H_2SiF_6. Wislicenus points out that presumably the most toxic gaseous fluorine compounds always occur in dissolved and finely atomized form on account of the humidity of the atmosphere.

2. Effects on Animals

The former inhalation therapy with hydrofluoric acid for pulmonary tuberculosis has given rise to a number of experimental investigations. According to Ronzani (689) the usual therapeutic concentration was 0.004 per cent. hydrogen fluoride. Chevy (164) records the apparently erroneous observation that guinea pigs can respire hydrogen fluoride in a concentration of 1 : 1500 (about 0.07 per cent.) with impunity. Comprehensive investigations by Ronzani (689) and later by Machle et al. (541, 539, 540) show that *hydrogen fluoride* is a harmful agent, not only as a pulmonary irritant, but also as a volatile poison with a systemic effect due to absorption.

Ronzani (689) used rabbits and guinea pigs. In a concentration of 0.066 per cent. (about 0.6 mg./l.) hydrogen fluoride caused restlessness, secretion from nose and lachrymatory glands, dyspnoea and spasms of varying intensity with subsequent muscular flaccidity; death occurred after 30 to 90 minutes. The lowest lethal concentration was 0.003 per cent. (about 0.03 mg./l.); under these conditions guinea pigs died after one day's inspiration. Common necropsy findings were catarrhal bronchopneumonia, interstitial pneumonia and pulmonary oedema. There were also dimness of cornea and ulcerations of the freely accessible mucous membranes. Where the action had been more protracted (0.001 per cent. for three hours twice daily for a month) there were anæmia, emaciation and reduced resistance to infection. Of 36 rabbits and guinea pigs, 10 died before the end of the experiment. There were considerable changes of cornea, nasal mucous membrane and lungs. In 1934—35 Machle and workers with exact technique repeated Ronzani's experiment with hydrogen fluoride on rabbits and guinea pigs. The concentration of 1.5 mg./l. caused death after five minutes; 1 mg./l. was tolerated for 30 minutes without death, but the lesions were considerable. The animals also survived about 0.1 mg./l. for 5 hours and 0.025 mg./l. for 41 hours, but pathologico-anatomical changes were found in them all, especially in the lungs (congestion, hæmorrhage, emphysema, oedema, bronchopneumonia). There were congestion and parenchymatous changes of other organs too, but similar phenomena were also observed in many of the controls. After a single exposure to a toxic concentration it was long before the changes disappeared. The toxic symptoms were those usually accompanying the breathing of acid, locally irritating gases: sneezing, coughing, hæmorrhagic vomition, slow respiration; corrosion of corneæ and conchæ. No mention is made of convulsions. In an experiment on man the concentration of 0.026 mg./l. was disagreeable but tolerable for several minutes. Inuring was not observed (541). On subjecting rabbits to protracted exposure to sub-lethal concentrations of hydrogen fluoride (0.0152—0.053 mg./l.) a storage of fluorine was

*) Stoklasa (774, 775) observed the effect on vegetation at the following concentrations: 0.05 per cent. SO_2 (acute injury); 0.0008 per cent. SO_3 (chronic injury).

found in the organism. The fluorine content of bones and teeth amounted to as much as ten times that normally found. With these doses no irritation symptoms from corneæ or conchæ were observed, and no marked influence on the general condition, but necropsy revealed degenerative changes in lungs, liver and kidneys (539, 540).

Only little light has been thrown upon the effects of *silicon tetrafluoride*. Flury and Zernik (275) report, on the basis of unpublished experiments, that mice and cats can without injury tolerate inspiration of 0.1 mg./l. (0.025 per cent.) for 15 minutes. Cameron (123), who in 1887 published two unique fatal cases of poisoning with SiF_4, experimented with two animals. A guinea pig died after 15 minutes in an atmosphere with 0.5 per cent. silicon tetrafluoride. Transient irritation symptoms were observed, but no convulsions. The lungs were hyperæmic, and the respiratory passages as far as alveoli coated and partly blocked with precipitated silicic acid. A rat, which died four hours after 20 minutes' exposure to about 0.5 per cent. SiF_4, had intermittent spasms of the extremity muscles.

The effects of certain gaseous *organic fluorine compounds* have been studied in animal experiments. Moissan (588) showed that ethyl and methyl fluoride (C_2H_5F, CH_3F) have very slightly pronounced narcotic properties compared with ethyl chloride. Whereas 8 per cent. ethyl chloride produced a harmless narcosis on guinea pigs, ethyl fluoride produced irritation symptoms immediately: hurried respiration and bristling fur. At the concentration of 3.3 per cent. strong motor restlessness was observed; with rising concentration there occurred convulsive twitchings, jerky respiration and paralysis of the hind extremities. Respiration ceased at the concentration 6—7 per cent.; there were still movements in the heart for 90 minutes. Methyl fluoride was much less poisonous; a rabbit breathed 14 per cent. without symptoms of intoxication. Yant (886) studied the effects on dogs and monkeys of various compounds employed in recent years in the refrigerating industry, compounds which are gases at ordinary temperature and pressure. The toxicity is moderate or low. Dichlordifluorætan (CCl_2F_2) was fairly well tolerated in a concentration of 20 per cent. for 8 days, 7—8 hours per day. Consciousness was retained; tremor and staggering gait were observed, but they quickly disappeared when the action ceased. Dichlortetrafluorætan ($C_2Cl_2F_4$) was much more toxic; exposure to the concentration of 20 per cent. caused death after 16 hours, under tremors and convulsions. Necropsy showed congestion of all organs and hæmorrhage in lungs and the gastro-intestinal tract.

EXPERIMENTAL ACUTE AND SUBACUTE FLUORINE INTOXICATION

1. Experiments on Man

Scattered about in earlier literature are reports on the effects of small quantities of fluorine compounds on man. The experiments were made particularly for therapeutic purposes and provide a picture of slight acute poisoning. Krimer (481) was the first to examine the effects of fluorine compounds taken per os (1820); he considered that hydrofluoric acid could be used for dissolving foreign bodies of glass in the stomach. One of his experiments was to observe the effects of hydrofluoric acid on himself; 10 drops of a 7—8 per cent. solution caused immediate burning in the throat, a choking sensation, abdominal disturbance, pressure and burning, eructation, and finally vomiting, followed by constipation for two days. Round about 1880—1890 there was a period of experimenting with fluorides or hydrofluoric acid against various affections (878, 179, 842, 467).

Even quantities as small as 0.05 g. sodium fluosilicate caused dizziness, nausea, eructation and weak pulse (91). In children 0.012 g. sodium fluoride caused gastric pains. Bloxam (82) ate a piece of salmon which had been kept for two months in a solution of 5 per cent. sodium fluoride, the result being salivation, vomiting, diarrhoea and weak pulse. He calculated the ingested quantity at 5.5 g. sodium fluoride; a friend who took 1 g. mixed in food had identical symptoms. Rabuteau (665) and Baldwin (46) both had distinct intoxication symptoms after ingesting 0.25 g. sodium fluoride per os. In 1883 Waddel (842, 843) gave a comprehensive survey of the physiological and pathological effects of the fluorine compounds, supplemented with a number of experiments on both animals and man. He observed several interesting phenomena. In four healthy men, who in the course of 5 days in succession ingested a total of 36 grains of potassium fluoride (or on an average 0.46 g. daily), the hæmoglobin percentage fell during the experiment by 5 to 10 per cent. and the number of erythrocytes by almost 25 per cent. There were also transient polyuria and a marked increase of the urea excretion (19—59 per cent.). The composition of the blood became normal after 12—14 days.

There are also some experiences in therapy with intravenous injection of sodium fluoride. Casares (146) reports that injection of 0.035—0.07 g. intravenously (in a 3.5 per cent. solution) causes violent but brief abdominal pains. After 0.20—0.26 g. sodium fluoride there were thirst, anorexia, vomiting, slight rise of temperature, shivering and transient restlessness; the symptoms lasted 20 hours at the most. Goldemberg (345), who has resumed the use of fluorine in therapy in recent years, states that intravenous injection of up to 0.35 g. sodium fluoride (2.5 per cent. solution) is tolerated without other inconvenience than intense pain with a sensation of heat, localized either to the lumbar region or the abdomen. The phenomenon occurs 5—10 minutes after the injection and lasts some minutes. After 10—15 injections of 0.10 g. sodium fluoride (daily or every other day), goitre patients had polyuria, thirst, nycturia and pollachiuria, a syndrome which Goldemberg names *diabète insipide fluorique*. The symptoms disappeared rapidly when the treatment was discontinued; albuminuria or glycosuria were not observed.

A comparison of all these observations with the symptoms in acute, spontaneous poisoning reveals distinct agreement: the gastro-intestinal irritation, salivation, thirst, and motor restlessness. Other symptoms, to which the rapidly progressing acute poisoning does not give rise, present themselves more clearly: polyuria, reduction of the number of red blood corpuscles, increased urea excretion. It is an interesting observation that intravenous injection of toxic doses produces symptoms from the gastro-intestinal tract, and that even doses as small as 0.05 g. sodium fluoride or sodium fluosilicate may have a toxic action, administered both per os and intravenously.

2. Intoxication Symptoms in Animals

Several of the earlier investigations offer no guarantee as to the purity of the preparations employed. The dosages recorded must be seen in that light. The remark applies for instance to Rabuteau (665), the first to investigate the toxicity of various fluorine compounds, particularly sodium fluoride (1867). Dogs given 0.25 g. sodium fluoride per os presented no symptoms of intoxication; with the same dose rabbits reacted with indisposition and salivation. Dose 0.5 g. rapidly caused vomiting in dogs, but no other symptom; the same quantity given a dog in its food several days in succession produced nothing abnormal. Intravenous injection of 1 g. sodium fluoride in a dog resulted merely in salivation and high temperature. Tappeiner (786, 787), who together with Schulz (719) published the first systematic investigation (1889), summarized the results of his experiments on warm-blooded animals (rabbits, guinea pigs, mice, cats, dogs) as follows: In a dose of 0.5 g. per os or 0.15 g. subcutaneously or intravenously, expressed per kg. body weight, sodium fluoride gives:

(1) Sopor and weakness.
(2) Convulsions, partly attacking one or other extremity, partly in seizures all over the body, in some animals assuming epileptiform character. They may predominate the intoxication or merely be indicated, especially after oral ingestion.
(3) Paralysation of the vasomotor centre.
(4) Increase of respiration frequency and depth, followed by paralysis.
(5) Vomiting.
(6) Salivation and lachrymation unchecked by atropin.
(7) Premature *rigor mortis*.

As the only symptom in the frog, sodium fluoride in non-lethal doses produced strong fibrillation of the whole striated musculature, lasting up to 24 hours. If the dose was increased to any great extent the muscles lost their irritability and became rigid.

TABLE II.

Dosis minima letalis of various Fluorine Compounds.

Investigator	Year	Fluorine compound	Animal	Method of administration	Dose in g./kg. of compound used		Dose in g./kg. calculated as fluorine*)	
					tolerata	minima letalis	tolerata	minima letalis
uzot (81)	1893	NaF	Rabbit	Intraven.	0.08	0.10	0.036	0.045
ret (636)	1898	NaF	Dog	Intraven.	..	0.08	..	0.036
eland and rtzahn (855)	1923	NaF	Rabbit	Orally	..	0.1—0.2	..	0.045—0.090
		Na_2SiF_6	Rabbit	Orally	..	0.074—0.149	..	0.045—0.090
		NaF	Frog	Parenteral.	..	0.474	..	0.214
		NaF	Toad	Parenteral.	..	0.428	..	0.194
genta (552)	1928	NaF	Dog	Intraven.	..	0.05	..	0.023
ake (494)	1928	NaF	Rabbit	Intraven.	0.075	0.0875	0.034	0.040
		NaF	Dog	Orally	..	0.05—0.1	..	0.023—0.045
Nito (614)	1928	NaF	Dog	Intramuscul.	..	0.031—0.05	..	0.014—0.023
		NaF	Frog	Parenteral.	..	2—3	..	0.90—1.36
ldemberg (344)	1930	NaF	Rat	Intraperitoneal.	..	0.028—0.035	..	0.013—0.016
		NaF	Rabbit	Orally	0.147	0.200	0.054	0.073
		Na_2SiF_6	Rabbit	Orally	0.100	0.125	0.061	0.076
ehlberger (597)	1930	Na_2SiF_6	Rabbit	Orally	0.150	0.175	0.061	0.071
		NaF	Rat	Subcutan.	0.094	0.125	0.034	0.046
		Na_2SiF_6	Rat	Subcutan.	0.050	0.070	0.031	0.042

*) The theoretical fluorine content of the particular compound was used in this calculation. Muehlberger alone gives the analyses of the preparations employed.

Contemporaneous investigations by Blaizot (81), Müller (598) and Frese (287) on the whole confirmed the description of the intoxication symptoms. Müller was able to supplement the picture, inasmuch as in dogs he observed increased output of urine, thirst and albuminuria. The few later investigations into acute poisoning convey little that is really new. Janaud (435) found fluorine in the saliva and urine of a dog that died after intravenous injection of about 0.14 g. sodium fluoride per kg. body weight. In rabbits that were given various fluorine compounds by stomach tube Muehlberger (597) observed salivation, diarrhoea, tremor, sometimes terminal clonic and tonic spasms. Animals given lethal or sub-lethal doses became cachectic and in some cases died 5—7 days afterwards. Albuminuria was frequent.

The results of a series of experiments to determine *dosis minima letalis* are given in Table 11. Agreement on the whole is good. A number of circumstances make it difficult to fix definite values. It is not an easy matter to make and stock preparations containing the theoretical quantity of fluorine. This has not been taken into consideration as a rule. One important factor is the difference in the technique of administering. Friedenthal (291) has shown with regard to the Ca-precipitating compounds that the tolerance increases considerably with intravenous injection when the operation proceeds slowly. As there is no information as to the speed of injection, the results of the various investigators strictly speaking are not directly comparable. Importance may also be attached to the concentration of the solution employed, varying conditions in administering per os (tube), etc.

The apparent difference in the toxicity of sodium fluoride and sodium fluosilicate lies in the different fluorine content (NaF: 45.24 per cent. F; Na_2SiF_6: 60.54 per cent. F). Allowance being made for this, the two compounds are equally toxic, even with parenteral administration. This fact, which was first established by Wieland and Kurtzahn (855) and afterwards verified by Muehlberger (597), also applies to the relatively insoluble barium fluosilicate ($BaSiF_6$). There has been no determination of the acute toxicity of cryolite on higher animals; in experiments with insects, which seem to be sensible to fluorine compounds, Shepard and Carter (757) showed that the low-soluble compounds ($BaSiF_6$, K_2SiF_6, Na_3AlF_6) are just as toxic as sodium fluoride, or rather, more so. Their solubility in water is not directly proportional to their toxicity. The insects consume the leaves powdered with the poison, or with their mouths clean their legs and antennæ when they have been in contact with it.

With intravenous administration, *dosis minima letalis* for dogs and rabbits varies between 0.023 and 0.045 g. fluorine per kg. body weight; taken by

the mouth the dose is 0.023—0.090 g. Subcutaneous, intramuscular or intra-peritoneal administration seems to be just as effective as intravenous; in several cases there is only a slight difference in the dose between administration per os and intravenously, which is a sign of rapid absorption from the gastro-intestinal tract.

3. Morbid Anatomy

Rabuteau's (665) records of necropsy results are fairly worthless; Tappeiner (787) was unable to find constant changes. On the foundation of older observations by Schulz (719), Müller (598), Frese (287), Crzellitzer (214) and Heidenhain (462) it is possible to state that changes in the organs after toxic or fatal doses comprise two systems: the gastro-intestinal tract and the kidney. In the mucous membranes of the digestive tract there are signs of acute inflammation, hyperæmia, swelling, bleeding and epithelial degeneration. The changes are most pronounced in the stomach (sometimes mention is made of actual corrosion), but are also observable in the intestine. It is very characteristic that these changes occur just as frequently and pronouncedly after intravenous injection as after ingestion of fluorine compounds by mouth. In dogs and rabbits Schulz and Müller saw hyperæmia of the kidneys and degeneration of the epithelium of the urinary passages. Siegfrid (740) records very full post-mortem examinations of rabbit and hedgehog. Besides the inflammatory changes already mentioned, he occasionally found in the stomach multiple ulcerations, hæmorrhages in the kidneys and exudations in the Bowman capsules, as well as degeneration of the epithelium of the tubules, with formation of casts. In the liver he also observed scattered islands with incipient necrosis, especially after ingestion of sodium fluosilicate.

Sporadic investigations in recent years have verified this picture. Dalla Volta (839) has published a microscopic examination of the hæmorrhagic gastritis (and duodenitis) occurring in cats and rabbits after ingestion through stomach tube of a 2 per cent. solution of sodium fluoride (0.1—0.25 g. NaF per kg.). The same hæmorrhagic gastroenteritis was seen by Larsson (492) and Hedström (398) in intoxications of various animals with the rat poison Rattoxin (NaF or $NaHF_2$). In addition to the usual changes in the kidney, which are also mentioned by Dalla Volta and Larsson, Hedström saw hyperæmia and oedema of the liver. Muehlberger (597), too, found a similar action on liver and kidneys of rabbits after lethal intoxication with sodium fluoride by mouth. Two more recent observations are due to Foit (276), who describes hæmorrhage in thymus of rabbits which died from acute poisoning, and to Pavlovic and Tihomirov (633), who report hyperæmia of

the parathyroid glands — also in rabbits killed two days after intravenous injection of 0.06 g. sodium fluoride per kg. The microscopic examination revealed numerous hæmorrhages and parenchymatous degeneration of the cells.

4. Effects on Various Tissues or Functions

With regard to certain organs or functions there have been investigations into the effects of a single ingestion of a fluorine compound. These investigations are scattered, not very comprehensive, and often are lacking in confirmation by other investigators. Yet the multiple biological effects of fluorine are beyond doubt.

The Blood

In 1898 Perret (636) stated that the blood of a dog which died 35 minutes after an intravenous injection of 0.10 g. sodium fluoride per kg. did not coagulate spontaneously when collected in a vessel. Similar observations were made by Stuber and Sano (779), supporting the theory set up later by Stuber and Lang (778) as to the significance of fluorine to the coagulation process of the blood. In their opinion there is no specific coagulation ferment, but the *causa movens* in the process of coagulation is the lactic acid formed by the glycolysis. It is thus assumed that fluorine increases the time of coagulation by inhibiting the glycolysis of the blood. In blood of hæmophiles Stuber and Lang (777) found up to 3—4 mg. per cent. fluorine; in blood from normal individuals the fluorine content varied between 0 and 0.85 mg. per cent. Other investigators (419, 266, 276) have been unable to verify that the fluorine content in hæmophile blood is higher than normally. Foit (276) has shown by experiments on rabbits that the coagulation of the blood does not proceed parallel with glycolysis and that the coagulation time is not changed much when blood fluorine is increased to about 3 mg. per cent. by intravenous injection of sodium fluoride.

After giving sodium fluoride per os to dogs in doses of 0.001—0.002 g. per kg., Risi (681) observed a reduction of from 1 to 3 million erythrocytes (from normally 7—8 millions), and a fall of leucocytes amounting to 2—3000. The changes were distinct even after 5 minutes, and were maximal in the course of 1—5 hours. Simultaneously a displacement to the left of the Arneth blood picture was found, an increase of the osmotic pressure of the total blood, increase of the surface tension and of the albumin content of the serum. Viscosity and specific conductivity were reduced. In the acute sodium fluoride poisoning of rabbits Foit (276) observed a fall in the number of lymphocytes and basophile leucocytes. There was an indefinite increase of neutrophile leucocytes, a moderate one of eosinophile leucocytes; the monocytes disappeared entirely. After intravenous injection of 0.05—0.06 g./kg. sodium fluoride on rabbits Valjavec (813) found that the hæmoglobin percentage and number of erythrocytes had a tendency to diminish, but not constantly. The number of leucocytes was constantly increased, with a relative diminution of lymphocytes and a relative increase of the number of polymorphonuclear leucocytes. There was also a displacement to the left of the Arneth blood picture.

The Circulatory System

According to Crzellitzer (214) intravenous injection of 0.05 g. sodium fluoride per kg. in dogs gives an incomplete and shortened diastole; the systole is also diminished. De Nito (614) on the isolated dog heart saw a reduction of frequency and beat volume at the concentration of 1 : 100000 (NaF). The effect is stated to be partly on the depressing centres in the heart, partly direct upon the musculature. In the frog the effect is almost exclusively through the depressing centres. Blood pressure is only slightly affected (Crzellitzer, de Nito). Paralysation of the vaso-motor centre as assumed by Tappeiner (787) does not seem to be an early phe-nomenon. Recent works by Gottdenker and Rothberger (359, 360) show that toxic doses of sodium fluoride cause serious irregularities in the heart functions of the frog and the dog.   .

Musculature

In both frogs and mammalia a characteristic symptom in the poisoning is the inability to perform voluntary movements and a universal fibrillation. Earlier investigators like Schulz (719), Crzellitzer (214) and, to some extent, Tappeiner (787), thought the fibrillation was a manifestation of some central irritation. Ac-cording to investigations by Garrey (361) it is presumable that the effect is peripheral; it was observed both in the isolated muscle and after destruction of the central nervous system, nerve division and after the administration of curare. As is the case *in vitro* (page 63), fluorine also influences the phosphate metabolism in the muscle under acute intoxication (587).

The Central Nervous System

The prostration observed under acute poisoning was considered by Tappeiner (787) to be due to a paralysation of the vasomotor centre, but by Schulz (719) to a particular depressive action of the brain. Among these earlier investigators there seems to be agreement that while the effect on the central nervous system is temporarily an irritation, it is mostly a paralysation. The phenomena observed in respiration are ascribed to a depressive action on the respiratory centre. Small doses produce quicker and deeper, larger doses superficial and irregular respiration (614, 214). Respiration ceases before the heart function.

Glands

Salivation was observed by Tappeiner (787) even after division of the nerves and after administration of atropine; thus the point of attack must be peripheral, in the gland cells themselves or in the nerve ends. In the dog Crzellitzer (214) saw constantly increased secretion from the lachrymatory glands and nostrils.

Renal Function. N-Metabolism

The toxic damage to kidneys observed by several investigators, with secondary changes of the urine, has already been referred to. Hewelke (412) in 1890 determined the nitrogen excretion in urine and fæces of a dog which was given 0.025 g. sodium fluoride per kg. by the mouth every day for 18 days. Compared with the periods before and after ingestion he observed a hundred per cent. increase of the urine quantity and a doubtful reduction of the N-excretion. In experiments (1931—1932), likewise with dogs, Gottlieb and Grant (361) observed increased excretion of water, chlorine and nitrogen after intravenous injection of 0.005—0.020 g. sodium fluoride per kg. The urine was alkaline on litmus up to one week after the injection, whereas

the control animals had acid urine. No pathological components were found in the urine and the kidneys remained normal when examined microscopically, even after repeated injections. Gautrelet and Mallié (3²5) state in 1906 that the total N-excretion was unchanged in the urine of a rabbit which had been given a sub-cutaneous injection of 0.03 g. sodium fluoride per kg., but that the nitrogen was excreted solely in the form of ammonia. It was thought that this effect, which ceased after 48 hours, was due to an inhibitory effect on the urea-forming ferment of the liver.

Sugar Metabolism

In the experiment just referred to, Gautrelet and Mallié also observed a transient glycosuria. Goldemberg (3⁴3) announced in 1928 that oral ingestion of 0.06 g. sodium fluoride per kg. caused transitory hyperglycæmia and glycosuria in a kid. Investigations by Magenta (55²) showed that intravenous injection of sodium fluoride in dogs gave a moderate rise of the blood sugar; only with lethal doses (0.05 g./kg.) was glycosuria observed. Under acute intoxication of rabbits Foit (2⁷6), too, saw hyperglycæmia, which reached the maximum one hour after intravenous injection; simultaneously the lactic acid content of the blood rose. Suekawa (781) has shown that there is no increase of blood sugar in splanchnectomized rabbits after injection of sodium fluoride. The influence of fluorine on the intermediate sugar metabolism in muscle is previously referred to (page 73).

Mineral Metabolism

More recent investigations show that the calcium content of the blood may be reduced after injection of sodium fluoride. The phenomenon seems to have been observed first in 1930 by Rebeca Gerschmann (3³0), who in dogs saw a fall of blood-Ca averaging 3.3 mg. per cent. (from normally about 11 mg. per cent.) after intravenous injection of 0.03 g. sodium fluoride per kg. The fall reached the maximum 2 hours after the injection; a rise began after three hours, but normal values had not been reached again after 24 hours. At the same time the inorganic phosphates increased from 3.2 to 5 mg. per cent. Jodlbauer (4⁴3) gave rabbits subcutaneous injection of 0.05 g. sodium fluoride per kg. on three successive days and observed a fall of serum-Ca that was most pronounced one hour after the injection and began to be equalized after four hours. The heaviest fall observed was from 17.4 to 8.8 mg. per cent. (determined as CaO according to de Waard's method). After the third injection the animals began to tremble universally. Foit (2⁷6) also saw a fall in serum-Ca in acutely intoxicated rabbits, but without observing symptoms from the musculature. The lowest values (7.6—8 mg. per cent.) were recorded one to three hours after the injection; after 24 hours the calcium level returned to its original height. Pavlovic and Bogdanovic (6³2) found a reduction of blood-Ca in dogs (averaging from 16.6 to 14.7 mg. per cent.) two days after intravenous injection of 0.06 g. sodium fluoride per kg.; at the same time the inorganic phosphorus content of the blood had fallen from 7.3 to 5.5 mg. per cent. (average).

Total Metabolism

In 1930 Goldemberg (3⁴4) determined the basal metabolism of rats after intraperitoneal injection of 0.015—0.018 g. sodium fluoride per kg. and constantly found a reduction varying from 12 to 63 per cent. The effect began 15 minutes after the injection and lasted from some hours to several days. The dose employed was about half the minimum lethal dose. Görlitzer (356) saw a very considerable

reduction of the metabolism in mice after administration of hydrofluoric acid in toxic doses, both percutaneously and subcutaneously. It was possible to show that the effect was not the result of reduced food ingestion or the introduction of hydrogen-ions, but was to be regarded as a specific effect of fluorine. In the same concentration the other halogen hydrogens were without influence upon the metabolism, or they caused an increase. Tadpoles placed in a hydrofluoric solution of the concentration 1 : 25000 were pronouncedly inhibited in their development.

Dental Tissue

Schour and Smith (715) in 1934 showed that a single subcutaneous injection of sodium fluoride (0.3 c.c. of 2.5 per cent. solution) in the rat produces disturbances in tooth development, appearing macroscopically on the incisors after about 4 weeks in the form of a circular, sharply delimited band of white, non-pigmented enamel. By means of histological examination changes could be seen in the posterior part of the incisor 12—24 hours after the injection, viz. (a) an irregular incremental surface of the organic enamel matrix covered with deeply staining hemispherical globules, and (b) an abnormal character and distribution of globules within the ameloblast layer. After 24—48 hours both enamel and dentine presented two incremental layers, one a light coloured, consisting of hypoplastic and deficiently calcified tissue, the other a dark one, normal in structure and normally or excessively calcified. The former layer represents the immediate response to the injection, the latter a subsequent restitution. With repeated injections a similar pair of layers, light and dark, forms for each one. In very oblique sections the light layers of poor enamel present themselves later (as the tooth grows) as the macroscopically recognizable bands. This pattern, however, became blurred, if either the dose or the number of injections was increased beyond a certain limit. The effect on tooth development by a single fluorine dose on rats has also been studied by Loewe and Salfeld (521).

CHAPTER VIII

CHRONIC EXPERIMENTAL FLUORINE INTOXICATION

From the point of view of hygiene, chronic fluorine intoxication is much more interesting than acute intoxication. Most investigations date from the last four or five years and have been undertaken especially for the purpose of throwing light upon the dental affection *mottled enamel*, and for studying the effect of fluoric mineral supplements on the rearing of pigs or cattle. Other lessons have been learned in the course of experiments carried out in order to find the ætiology of spontaneous chronic fluorosis*) in domestic animals. Accordingly, the available material is very scattered and has been treated from very different angles. Only gradually have the various symptoms of the chronic intoxication been recognized; but in many respects our knowledge is still defective.

An earlier investigation, one that has had some bearing on the conception of chronic intoxication, is Brandl and Tappeiner's (108) lengthy experiment with a full-grown dog (1891). In the course of about 22 months (648 days) the dog received in all 402.9 g. sodium fluoride perorally, or on an average about 22 mg. fluorine daily per kg. body weight. The symptoms were strikingly few. Necropsy revealed certain changes in the osseous tissue, but the other organs were normal. Attention was thus called especially to the bones, and also to some extent to the gastro-intestinal tract. The general view was accordingly that fluorine is an element of low toxicity. Investigations by Hewelke (412), Carlau (126), Schwyzer (724) and Rost (692) were the outcome of the interest taken in the toxicology of fluorine at the beginning of the present century; on the whole they are not very comprehensive, nor do they go very deeply into the subject, but they direct attention to the effects of fluorine both on the general condition and on various systems of organs. About 1920—25 the modern works begin to appear: Goldemberg (337), Sollman, Schettler and Wetzel (759), Cristiani and Gautier (205—212), McCollum and co-workers (538).

*) This etymologically unfortunate term for chronic fluorine intoxication was introduced 1912 by Bartolucci (49) and has come into general use.

Since the ætiology of mottled enamel was established in 1931, the number of works appearing on chronic fluorine poisoning has steadily increased.

In the following is a brief report on the experience hitherto gained, arranged according to systems of organs. Several works that are difficult of access are, however, referred to in greater detail. For practical reasons discussion of the results has been left till Chapter XXVII. For handy reference the investigations in which the daily intake of fluorine is expressed in relation to body weight, or where a calculation of this sort has been possible on the basis of details given of weight and food intake, are listed in Table 12. In several experiments with rats the necessary data are missing, but in such cases the average daily intake of fluorine per kg. has been calculated on the fluorine concentration in the food by assuming that a rat weighs 100 g. and consumes 8 g. of food mixture daily. It is obvious that this method of calculation is rather unreliable, and is especially applicable to the short experiments (a rat of 50—60 g. normally trebles its weight in the course of 8—9 weeks). The average daily intake of food also varies a good deal according to the food mixture employed. In Table 12 the results of these calculations are marked with an asterisk. Apart from rats, the animals mostly used were cattle and pigs.

1. Growth. General Condition. Reproduction

Body weight, which is a readily comprehensible reflection of the condition of the entire organism, is a good measure of the existence and degree of a chronic intoxication. Loss of weight, absolute or relative, is the commonest and first symptom in chronic intoxication from fluorine compounds. All depending on the dose, one observes all degrees from a slight inhibition of growth, compared with control animals, to a rapid loss of weight, which continues until death occurs. Simultaneously with loss of weight there is a lack of appetite, often very pronounced. Where the food consumed is determined it is found to decrease regularly; parallel with this there is a relatively high food consumption in comparison with the increase of weight. Reduced vitality is characteristic of all the kinds of animals employed; the animal moves about less and seems drowsy. Large animals (such as cattle) lie about a good deal.

In appearance they become unthrifty. The coat loses its normal softness and gloss. The hairs seem coarser and stiffer. These phenomena have been seen on rats, guinea pigs, cattle and sheep. Cristiani (197) observed that the skin of a goat became dry and scurfy. Hauck, Steenbock and Parsons (393) describe increased growth of the claws of rats which had been given 0.15 per

TAB BL.

Experimental rin

Investigator	Year	Animal (y = young, growing animal; a = adult)	Duration of experiment	Fluorine compound used	Fluorine in %	ppr aily of fl ng. ody
Brandl and Tappeiner (108)	1891	Dog (a)	648 days	NaF		
Sollman, Schettler and Wetzel (759)	1921	Rats (y)	5—24 weeks	NaF	0.00009—0.0 0.009—0.0 0.0226—0.1	.06 6.8 8.9
McCollum et al. (538)	1925	Rats (y)	77—338 days	NaF	0.0226	1
Schulz and Lamb (721)	1925	Rats (y)	up to 9 mths.	NaF	0.0113—0.0 0.0452—0.0 0.113	9 36 9
Bergara (57)	1927	Rats (y)	up to 5 mths.	NaF		2 1 2
Bethke, Kick, Edgington and Wilder (69)	1929	Pigs (y)	144 days	NaF	0.029 0.058 0.097	1 2 3
Chaneles (155)	1929	Rats (y)	3—6 mths.	NaF		22
Taylor (789) Reed and Huffman (670)	1929, 1930	Cattle (y)	up to 5 years	R. Ph.***)	ca. 0.0525*)	3
McClure and Mitchell (537)	1931	Rats (y)	78—95 days	NaF " " CaF$_2$ "	0.0106 0.0313 0.0623 0.0313 0.0623	8 2 5 2 5

*) Calculated on the basis of the fluorine concentration in the diet, it being assumed that a rat g. ar
**) Expressed in % of the basal ration (grain mixture).
***) R.Ph. = Rock phosphate, usual fluorine content 3.5 %.

TABLE 12.

Experimental Chronic Fluorine Intoxication.

Fluorine in diet %	Approximate daily intake of fluorine mg. per kg. body weight	Symptoms of Intoxication
	22	Transient vomiting and diarrhoea; stiffness of columna in movement. *Necropsy:* changes in teeth and bones; considerable deposition of fluorine in all organs.
0.00009—0.0045	0.068—3.6	None.
0.009—0.018	6.8—9	Growth retardation; incomplete restitution.
0.0226—0.104	18.9—68.3	Growth retardation; increased mortality.
0.0226	18*)	Growth retardation; reduced lifetime; typical dental changes; cranial bones white and porous.
0.0113—0.0226	9—18*)	Growth normal; reduced reproduction.
0.0452—0.0678	36—54	Growth retardation; reduced reproduction. } dental changes, unthrifty
0.113	90	Death after 8—14 weeks. } appearance.
	283	Loss of weight; death after 10 days. } Yellowish, untidy coat; drowsy; laborious gait; eye symptoms;
	129	Growth retardation; death after 55 days. } typical dental changes; retarded enchondral ossification; bone
	29	Growth retardation. } density reduced under X-rays; no reproduction.
0.029	11	Growth, utilization of food and bone strength normal. } F-content of bones
0.058	21	Growth normal or slightly reduced. } increased.
0.097	37	Growth, utilization of food and bone strength reduced. }
	22.6	Growth retardation; poor reproduction; untidy coat; typical dental changes; hæmorrhage from vagina and nares; no changes in bones under X-ray.
ca. 0.0525**)	3	Reduced growth, appetite and milk yield; coat coarse and rough; salivation; unable to drink cold water; teeth worn down irregularly. *Necropsy:* thickening of mandible, exostoses on metatarsals.
0.0106	8*)	None.
0.0313	25	Growth retardation; changes in bone ash.
0.0623	50	Growth retardation; reduced food intake; reduced Ca-retention; changes in bone ash. } Typical dental changes.
0.0313	25	Growth retardation; doubtful changes in bone ash. }
0.0623	50	Growth retardation; reduced Ca-retention; doubtful changes in bone ash. }

ed that a rat weigh and consumes 8 g. food mixture daily.

Investigator	Year	Animal (y = young, growing animal; a = adult)	Duration of experiment	Fluorine compound used	Fluorine in %|
McClure and Mitchell (536) (McClure (535))	1931	Pigs (y)	3 × 2 weeks	CaF_2 + R. Ph.	0.013 0.017 0.026	
Velu (821)	1931	Rats (a)	96—298 days	CaF_2		
Du Toit et al. (800)	1932	Cattle (a)	8—12 mths.	NaF		6
Smyth and Smyth (758)	1932	Rats (y)	16 weeks	$BaSiF_6$		
				Na_3AlF_6 (synthetic ?)		
Hauck, Steenbock and Parsons (393, 394)	1933	Rats (y)	4—40 weeks	NaF	0.0678	
Bethke et al. (71)	1933	Pigs (y)	23 weeks {	NaF R. Ph.	0.01—0.0 3 0.017—0.0 6	
			up to 26 mths.	R. Ph.	0.034—0.0	
		Rats	19 weeks	NaF { CaF_2	0.0045 0.009—0.02 0.0049—0.0	7.
Kick, Bethke and Edgington (454)	1933	Pigs (y)	144—160 days	NaF R. Ph. NaF R. Ph.	0.010 0.016 0.029—0.0 0.032—0.0	10 12
Lamb, Phillips et al. (487, 647)	1933	Rats	Several generations	NaF	0.018	18

*) Calculated on the basis of the fluorine concentration in the diet, it being assumed that a ra

TABLE 12.

(Continued).

Fluorine in diet %	Approximate daily intake of fluorine mg. per kg. body weight	Symptoms of Intoxication
0.013 0.017 0.026	3.2 3.5 5.5	Reduced growth and food intake. } Doubtfully reduced Ca-retention.
	33	Typical changes in teeth; increased curvature of vertebral column; cachexia; death.
	6.2—6.9	Loss of weight; poor milk yield; gait impaired; paralysis; calf dies just after birth. Exostoses of extremity bones; swollen joints.
	5.3 11.5 20.6 6.3 11.8 23.1	None Doubtful Distinct toxic effect None Doubtful Distinct toxic effect } Toxic symptoms: reduced appetite, growth retardation; poor appearance; reduced reproduction; typical dental changes. *Necropsy:* degeneration of liver and kidneys.
0.0678	54*)	Growth retardation; reduced food intake; typical dental changes; increased growth of claws; linear metaphyses; slight thickening of costochondral connection; reduction of bone and tooth ash. *Necropsy:* hæmorrhage in pyloric mucous membrane; kidneys pale and granulated; atrophy of testes.
0.01—0.06 0.017—0.034	3.5—20 6—12	Mandibles thickened, surface uneven with exostoses. Increased breadth of dental arch.
0.034—0.07		Mandibles thicker and higher, surface uneven with exostoses. Compacta thickened: marrow cavity increased. Typical dental changes.
0.0045 0.009—0.0226 0.0049—0.0097	3.6*) 7.2—18 3.9—7.8	Incipient typical dental changes. Pronounced dental changes. Incipient typical dental changes.
0.010 0.016	3.5	No symptoms (increased F-content in bones and teeth).
0.029—0.097 0.032—0.070	10—37 12—29	Growth retardation; reduced food intake; poor utilization of food; thirst. Bones (mandible, femur): white, uneven, with exostoses; strength reduced; ash content partly reduced, F-content increased. Kidneys (with R. Ph. alone): chronic, granular nephritis.
0.018	8—20 25	Growth retardation; reduced weight of offspring (threshold value). Oestrus ceases; milk secretion ceases (threshold value).

ned that a rat we and consumes 8 g. food mixture daily.

Investigator	Year	Animal (y = young, growing animal; a = adult)	Duration of experiment	Fluorine compound used	Fluorine in %	[approximate]ly int[ake] fluor[ine] per [bod]y wei[ght]
DeEds and Thomas (229)	1933—34	Rats (y)		NaF Na_2SiF_6 $BaSiF_6$ Na_3AlF_6	0.0012 0.0015 0.0019 0.0024	0.5— 1—2
Gaud, Charnot and Langlais (307)	1934	Guinea pigs (y)	$3\frac{1}{2}$ mths.	NaF CaF_2		10 10
Phillips and Lamb (646)	1934	Rats		NaF R. Ph.		20—3
Roholm (687)	1934	Lamb, sheep	51—71 days	NaF		15
Smith and Leverton (756)	1934	Rats	up to 20 weeks	All comp. NaF (and other comp.) $BaSiF_6$ Na_3AlF_6 CaF_2 NaF nat.Na_3AlF_6 CaF_2	0.001 0.011 0.022 0.045 0.022 0.226 0.455 0.000 3.6 54	1 13 24 36 27 250 475 40 1900 3400
Phillips, Hart and Bohstedt (644)	1934	Cattle (y)	$4\frac{1}{2}$ years	R. Ph.	0.022—0.?	72—9
Sutro (783)	1935	Rats (y)	up to 1 year	NaF		1.3—3

**) Expressed in % of the basal ration (grain mixture).

TABLE 12.

(Continued).

Fluorine in diet %	Approximately daily intake of fluorine mg. per kg. body weight	Symptoms of Intoxication
0.0012 0.0015 0.00137 0.00243	0.5—1 1—2	Incipient typical dental changes.
	10 10	Increased curvature of vertebral column. Reduced shadow of bone tissue under X-rays. Rachitic hypertrophy of sundry osseous parts. *Necropsy:* hypertrophy of thyroid and parathyroids; 0.14 % fluorine in total ash (control 0.01 %). Increased stiffness and curvature of vertebral column. Bone density increased under X-rays; 0.12 % fluorine in total ash.
	20—30	Changes in incisors, thyroid and kidneys; less constant changes in liver and suprarenals.
	15	Slight appetite; disposed to diarrhoea; loss of weight; thickening of mandible; gait impaired; death under muscular restlessness, and dyspnoea. *Necropsy:* periosteal growths on mandible, skull and long bones.
0.0014	1	Incipient dental changes (threshold value).
0.0113	13	None, except for dental changes.
0.0226	24	Growth retardation, poor utilization of food; offspring poor (threshold value).
0.0452	36	No reproduction.
0.0226 0.2260 0.4520	27 250 475	Growth retardation; poor utilization of food (threshold values).
0.0904 3.6 5.4	40 1900 3400	Death after 9—11 days.
0.022—0.088	2—9.00	Threshold value for toxic effect 2—3 mg. fluorine daily per kg. body weight. Intoxication symptoms: anorexia, inanition; reduced milk production; molar abrasion; exostoses of the long bones and mandibles, increased breaking strength of metacarpals; ankylosis; increased fluorine content of teeth, bones and thyroid; degeneration of parenchymatous organs.
	3—33.9	Typical dental changes. Effect on bones depending on dose, time of ingestion and calcium content of diet. Both osteosclerosis and osteoporosis observed. Darkstaining granules in irregular matrix.

cent. sodium fluoride in their food. In some experiments changes in the eyes were observed. Bergara (57) says of his rats that the eye was less brilliant on account of a certain dullness of the cornea; secretion collected on the edge of the eyelids. In one case, again a rat, in which the diet seemed adequate, Chaneles (155) saw xerophthalmia. In sheep Slagsvold (742) observed photo-phobia and serous secretion from the conjunctivæ. The wool was refractory and thin.

Together with a poor general condition there is an unfavourable effect on reproduction and milk secretion.

A series of rat experiments at Iowa Agricultural Experimental Station (25) showed that on a diet containing fluorine the succeeding generations were less prolific than the first generation; with 0.05 per cent. calcium fluoride in the diet three generations were secured, with 0.005 per cent. four or more, and on a non-fluoric basal diet seven generations. A content of 2.5 per cent. rock phosphate in the food had a stronger effect: In the 2nd generation the mortality was high, and there was no 3rd generation at all. In experiments with cattle, in which either sodium fluoride (800) or rock phosphate (387) was given, the calf died at birth or immediately after. Reed and Huffman (670), on the other hand, saw good reproduction in their experiments extending over five years, in which the dose was more moderate, about 3 mg. fluorine daily per kg. body weight (in the form of rock phosphate). Phillips et al. (647) have subjected the question to a critical study. On the basis of experiments with rats they consider that sodium fluoride has no direct and specific-ally unfavourable effect on the mechanism of reproduction. The effect is secondary and is due to inanition. For sodium fluoride, 25 mg. fluorine per kg. daily stands as a threshold value; where it was exceeded there was almost complete cessation of oestrus. With lower concentrations in experiments extending over five generations there was no evidence of a cumulative effect on reproduction. Experiments by Smith and Leverton (756) point in the same direction: Reproduction was good at a dose of 24 mg. fluorine per kg. body weight, but the offspring were somewhat affected; where the rats received 36 mg. per kg. all reproduction ceased. In rats a reduction of milk secretion seems to occur at similar values and must be taken to be a secondary phenomenon, caused by anorexia and consequent inanition (647). In cattle, an unfavourable effect on milk secretion was characteristic, even with a fluorine intake that did not compromise reproduction (670). Egg production declines when poultry are given a fluoric mineral supplement (117, 393, 378).

The cachectic condition which develops when intoxication proceeds has been emphasized by Goldemberg (342) and later Cristiani and co-workers as being especially characteristic of fluorine poisoning (*la cachexie fluorique*). It is a question of dosage, of course, whether real cachexia develops. In the case of rats, growth and general condition begin to suffer at a daily intake of about 20 mg. fluorine per kg. body weight. For cattle the threshold is much lower, about 2—3 mg. fluorine per kg. daily (644); pigs seem to be less sensitive to fluorine than cattle and more sensitive than rats.

2. Gastro-Intestinal Tract

Apart from the lack of appetite that accompanies loss of weight, symptoms are sometimes seen which indicate direct action on the gastro-intestinal tract and its glandular organs. When the fluorine compounds are carefully mixed with the food, such phenomena are rarely observed. Where relatively large doses are given at one time to cattle or sheep, for instance in solution or suspended in water, acute symptoms may appear in the form of vomiting and especially diarrhoea (114, 408, 687). Poultry which had unlimited access to rock phosphate had diarrhoea, in contrast to the controls which received supplements of other mineral mixtures (117).

As a rule when necropsy results are described, no mention is made of gastric and intestinal changes. This does not apply, however, when the fluorine intake is relatively high. Marconi (557) described hyperæmia of the gastric and intestinal mucous membranes of guinea pigs, which for about one month received orally up to 159 mg. sodium fluoride per kg. body weight in dissolved form. Hauck and co-workers observed minor hæmorrhages in the pyloric mucous membrane of rats that had received 0.15 per cent. sodium fluoride in their diet (393), and in the duodenum of chickens receiving a supplement of up to 1.2 per cent. sodium fluoride (392). Lambs fed on hay containing fluorine had thickening and hyperæmia of the mucous membrane of the abomasum and the first part of the large intestine (742).

There are no records on the pancreas, whereas it seems that the *liver* may suffer injury. In an early experiment Carlau (126) injected sodium fluosilicate into guinea pigs and rabbits in daily doses ranging from about 120 to 430 mg. per day. After 10 to 25 days the liver was macroscopically normal, but microscopy revealed scattered islands with degeneration of the protoplasm of the cells, and accumulation of amorphous or crystalline bodies which were presumed to be calcium fluosilicate. Velu and Zottner (835) describe distinct changes in the liver of sheep which in protracted experiments were intoxicated with calcium fluoride, phosphorite, or water which had been subjected to a lengthy treatment with phosphorite in a tank. The size of the liver was normal or slightly enlarged, the surface smooth, and the colour greyish-yellow. The consistency was soft and friable. Microscopic examination showed fatty cell degeneration, localized especially to the area round the hepatic vein. Inflammatory phenomena were not observable. The changes were compared with those observed after intoxication with arsenic, phosphorus and mercury. Smyth and Smyth (758) state briefly that the livers of rats intoxicated with barium fluosilicate and cryolite showed microscopic signs of degeneration of

ordinary type. In their protracted intoxication experiments with cattle Phillips and co-workers (644) found degeneration of the liver parenchyma, of various types.

Constantini (182) has shown that the functions of the gastro-intestinal tract can be inhibited during fluorine intoxication. Guinea pigs were killed after intoxication carried to emaciation with 40 mg. sodium fluoride per kg. body weight daily, administered perorally or injected intraperitoneally. The extracts made from the stomach, intestines and pancreas were less effective in splitting protein than extracts from normal animals.

3. Urinary System

The marked thirst and simultaneous polyuria seen in experiments with pigs (536, 454) may be taken as a sign of a renal irritation. In earlier literature there are only few records. Hewelke (412) showed albumin and blood in the urine of dogs which received orally about 12—18 mg. sodium fluoride daily per kg. for 47 and 100 days; on necropsy the kidneys were found to be hyperæmic. Goldemberg (338), Smyth and Smyth (758) and Hauck, Steenbock and Parsons (393) have summary records of chronic inflammatory changes in the kidneys of rats. In guinea pigs Marconi (557) described a severe, acute, parenchymatous nephritis; the animals died after sub-chronic intoxication with considerable quantities of sodium fluoride. Slagsvold (742) mentions signs of chronic nephritis in sheep.

Very considerable changes were seen by Kick, Bethke and Edgington (454) in recent years in experiments on young pigs, which were given 0.032—0.070 per cent. fluorine as rock phosphate in their food for 144—160 days. The kidneys were pale and diminished, the surface uneven with small nodules and shrunken areas. The capsule was slightly thickened, partly adherent. On section, the cortex was found to be narrower, and the medulla often with fat infiltration. Microscopy showed nephritis with varying degrees of degeneration of the tubular epithelium, and partial replacement of tubuli and glomeruli with fibrous tissue. The kidneys were normal in pigs which during the same period were given 0.016 per cent. fluorine as rock phosphate, as also in all animals which received sodium fluoride (up to 0.097 per cent. fluorine) in their food.

4. Blood and Bone Marrow. Spleen

In 1903 and 1914 Schwyzer (724, 725) published experimental works devoted especially to changes in the blood and bone-marrow after ingestion of fluorine compounds. The blood of rabbits which had received 30 mg. sodium fluoride

perorally for up to 20 days contained 90 per cent. uninuclear cells, exclusively myelocytes, and the time of coagulation was considerably reduced. The marrow in the long bones resembled raspberry jelly and contained, though not in every case, crystalline bodies which were taken to be calcium fluoride. In pigeons which received up to 2 mg. sodium fluoride perorally for 30 to 60 days, increased coagulability of the blood as well as myelocytosis were also observed. Under the microscope the marrow of femur and tibia revealed a total absence of fat and pronounced hyperæmia; it consisted mostly of round cells, which were identified as myelocytes or lymphocytes. The conclusion was that there was a state of acute irritation in the bone marrow. Schwyzer's works call for criticism. Technical details are lacking; the descriptions are not so comprehensive that one can form an opinion of the patho-anatomical findings; the interpretation of the cell forms of the blood seems to be incorrect. When dealing with chronic fluorine intoxication (1922, 1927) Cristiani and Gautier (205), and Cristiani (190) indicate as a characteristic phenomenon an atrophy, sometimes gelatinous, of the bone marrow of animals intoxicated both with fluorine compounds and with fodder exposed to fluoric emanations. The microscopic finding was characterized by reduction of both fat tissue and marrow tissue proper, and the development of a hyperæmic tissue with a copious fluid content.

The works of Schwyzer and Cristiani indicate considerable changes of bone marrow, blood picture and coagulability. The results of subsequent investigations, however, have not cleared these points up. Valjavec (813) gave 9 rabbits 10—30 mg. sodium fluoride per kg. intravenously throughout a period varying between 105 and 159 days. In some animals, but not all, she observed a moderate reduction in the hæmoglobin percentage and the number of erythrocytes. There was nothing characteristic about the white blood corpuscles. In dogs, which were given 125 mg. sodium fluoride through a stomach tube once or twice weekly for ten weeks, Leake and Ritchie (496) observed a fall of the erythrocytes and a reduction of 5 volume per cent. in the blood's oxygen-binding efficiency. In the blood picture they demonstrated the presence of anisocytosis and normoblasts, in the moderately increased red bone marrow and in the spleen an abnormal deposit of ferrous pigment. Slagsvold (742) saw considerable anæmia develop in sheep during protracted intoxication with sodium fluoride and cryolite.

The influence of fluorine on the coagulability induced Stuber and Lang (778) to present the hypothesis that hæmophilia is due to an abnormally high fluorine content in the blood. As stated on page 59, that theory has met with criticism in several places. Later investigators have been unable to prove any

increased fluorine concentration in the blood of hæmophiles (266, 419, 276). Greenwood, Hewitt and Nelson (365) found no change in the blood-coagulation rate in pups which for 18 weeks had been given sodium fluoride perorally in doses varying between 0.45 and 5.52 mg. fluorine per kg. daily. An observation by Kick, Bethke and Record (455) stands alone: An increased supplement of sodium fluoride or rock phosphate to the food shortened the blood-coagulation rate in chickens almost proportionately. In a batch put on practically non-fluoric food the average coagulation rate was 159—196 seconds, but it fell to 17 seconds where the fluorine content in the food was 0.108 per cent. Thus the published observations are extremely contradictory.

Only few observations are recorded on marrow changes. Kick, Bethke and Edgington (454) saw no change in the bone marrow of pigs and rats on a diet with a varying, often high content of fluorine. In sheep Slagsvold (742) found an atrophy of the marrow of the long bones, of the same kind as that met with in other states of inanition.

5. Nervous System and Musculature

As a rule, nothing is said of symptoms from the central nervous system. In a few experiments with dogs and cattle mention is made of a certain irritability (496, 789). It is also the rule that no mention is made of any particular nervous symptoms connected with the transition from the cachectic state to death. In experiments with guinea pigs Cristiani and Gautier (209) observed that death occurred regularly under bulbo-medullary symptoms (dyspnoea, muscular rigidity, convulsions) when the intoxication lasted some weeks. Marconi (557) describes a similar experience, also with guinea pigs. Roholm (687) saw death occur in sheep after 51—71 days, under dyspnoea and muscular twitching. Cristiani (190), experimenting on guinea pigs, describes an exaggerated curving of columna as typical of chronic fluorine intoxication. This opinion is also advanced by several French authors (821, 307).

Impairment of gait does not seem to be prominent in small experimental animals, though Bergara (57) states that the gait of rats was rather stiff and dragging. Larger animals sometimes present a much more distinct impairment. In Brandl and Tappeiner's (108) experiments with a dog the gait was rather difficult in the last months, there being stiffness, especially in the hindquarters. McClure and Mitchell (536) state that their pigs had difficulty in standing, Kick, Bethke and Edgington (454) that the gait was stiff and toilsome. Painful and laborious gait, and even paralysis, in heifers are described by Du Toit and co-workers (800).

6. Endocrine Glands

a. Thyroid Gland

In 1854 Maumené (567) announced that by giving a dog in all about 10 g. sodium fluoride in the course of over four months, he produced a persistent struma-like swelling of the throat. The animal was not examined post mortem. Maumené propounded the idea that a high percentage of fluorine in drinking water might be the cause of endemic struma (568). In ignorance of that work the theory was again advanced in 1919—1921 by Goldemberg (337, 338) and in 1923 by Pighini (654). In white rats, which for 6—8 months received 2—3 mg. sodium fluoride daily in their food, Goldemberg observed an increase in the size of the thyroid gland up to five or six-fold. The histological examination revealed a parenchymatous struma. At the same time he pointed out that in several animals fluorine compounds caused an inhibition of their development, both physical and psychical (*crétinisme fluorique*). Pighini could produce volume increase and structural changes of the thyroid gland by giving rats, chickens and dogs fluoric water from a struma region. In the same kinds of animals the ingestion of sodium fluoride caused changes in the thyroid which histologically resembled the endemic struma*).

In guinea pigs which died of fluorine poisoning after an average of 55 days, Cristiani (193) saw microscopic changes in the thyroid gland, especially a proliferation of the parenchymatous tissue. Tolle and Maynard (802) found the weight of this gland to be the same in fluorine-intoxicated rats and in the controls. Chaneles (155) was unable to find either macroscopic or microscopic changes. In a recent work Phillips and Lamb (646) state, on the basis of a large number of microscopic investigations on the organs of rats, which had been given 15—30 mg. fluorine per kg. daily for a long period, that the thyroid gland showed microscopic changes in about half of the animals, but also in 10—11 per cent. of the controls. They found slight parenchymatous proliferation, and occasionally some fibrosis. As a rule part of the gland was normal.

Recent investigations suggest an interesting relation between fluorine and the thyroid gland. In organs of cows, which for a long time had been subjected to fluorine intoxication, Chang et al. (159) found the normal low fluorine content doubled. The thyroid alone increased its fluorine content notably: up to 24-fold. In experiments with rats and chickens, Phillips and co-workers (640, 641) showed that non-toxic levels of desiccated thyroid were made distinctly toxic by simultaneous administration of sodium fluoride in doses which alone did not give pronounced toxic effects.

*) According to McKay (542), Grevers has shown that in rats the drinking water at Utrecht (Holland) can cause struma, and also dental changes resembling *mottled enamel*. This dental disease is said to occur endemically round Utrecht.

b. Parathyroid Glands

In addition to the already mentioned acute changes in the parathyroids, Pavlovic and Tihomirov (633) saw chronic changes in the form of fatty degeneration and hæmorrhage in rabbits which had received 10—30 mg. sodium fluoride per kg. intravenously for 105 to 122 days. Hauck and co-workers examined the parathyroids of rats (393) and chickens (392) which had been given 0.15 and up to 1.2 per cent. sodium fluoride respectively in their food. No changes were seen, macroscopically or microscopically. In the chickens the weight of the glands was normal, in the rats it was reduced, but no more than corresponded to the general loss of weight caused by the intoxication.

c. Other Glands

Hypophysis. In 1930 Cristiani (194, 195) stated that the weight of the hypophysis was diminished in adult guinea pigs which died of chronic fluorine intoxication. Only two animals served as controls, however. Microscopic investigation disclosed atrophy of the specific cells and relative increase of the connective tissue. In investigations with rats, Phillips, Lamb and co-workers (487, 647, 646) found the weight of the hypophysis, the microscopic picture and the gonad-stimulating function normal.

Suprarenal Glands. In the same rats Phillips and co-workers (647) found the weight of the suprarenal glands increased and, by microscopic examination, a tendency towards passive hyperæmia, especially of zona reticularis of the medulla. In some cases there was also fatty degeneration (646).

Testes, Ovaries. A certain tendency towards atrophy of testes and perhaps of ovaries was seen by Phillips and Lamb (646) in rats when the fluorine ingestion rose to 20—30 mg. per kg. daily. Hauck, Steenbock and Parsons (393) state that a supplement of 0.15 per cent. sodium fluoride to the food of rats produced considerable atrophy of the specific tissue in testes and a complete absence of sperma. It has been mentioned in the foregoing that a reduction of fertility or cessation of reproduction is observed when the intoxication seriously interferes with nutrition.

7. Various Functions

a. Inorganic Components of the Blood

Whereas an even considerable reduction of the blood calcium has been found in acute intoxication, it is a phenomenon less frequently observed, and less pronounced, in chronic intoxication. In a series of investigations on rats, in which the sodium fluoride content of the food varied between 0.001 and 0.15 per cent., it was not possible to establish any deviation from the normal

values (26, 394). Even a daily dose as considerable as 0.05 g. sodium fluoride per kg. gave no definite changes in the serum-Ca of the rat (155). Phillips (637) saw a tendency towards a fall of serum-Ca in heifers which were given up to 0.087 per cent. fluorine as rock phosphate, and Hauck et al. (393) saw the same in young chickens whose food contained 0.6—1.2 per cent. sodium fluoride. A distinct, if moderate fall was observed by Jodlbauer (443) in rabbits which, on a calcium-poor diet, received 15 mg. sodium fluoride per kg. body weight subcutaneously on 22 consecutive days. A determination made 24 hours after the last injection gave a fall of serum-Ca amounting to 12.8 per cent.; in acute intoxication the maximum fall was 50 per cent. Pavlovic and Bogdanovic (632) also found a moderate decrease of blood-Ca (on an average from 16.6 to 14.5 mg. per 100 c. c.) in rabbits which up to 122 days received 10—30 mg. sodium fluoride per kg. intravenously. On using smaller quantities a tendency towards higher values was observed in serum-Ca and inorganic phosphorus (89). According to investigations by Price (662), rats whose food contained the high concentration of 1 per cent. sodium fluoride, showed signs of general disturbance in the mineral metabolism, almost solely in the form of a fall of the inorganic components of the blood. Available determinations of the blood phosphorus do not give uniform results; observations have been made both of a tendency to rise (637) and a tendency to fall (632), and also of unchanged values (394, 532).

b. Calcium and Phosphorus Metabolism

In 1921 Forbes et al. (277) observed that a supplement of rock phosphate to young pigs gave a lower calcium and phosphorus retention than other calcium sources used in practice (calcium carbonate, bone-meal, lime-stone). It is reasonable to presume that the bad effect was due to the fluorine in rock phosphate. McClure and Mitchell (537, 536) in 1931 performed metabolism experiments on rats and pigs. A diet supplement of 0.0106 and 0.0313 per cent. fluorine in the form of sodium fluoride had no effect on the Ca-retention of albino rats. On the other hand, it was more than probable that 0.0623 per cent. fluorine, in the form of both sodium and calcium fluoride, caused a reduction of the Ca-retention in two balance periods of 10 days. In the experiment on pigs the individual variations were so great that the authors dared not make any definite pronouncement, but there, too, it was probable that the Ca-retention was reduced when the supplement was 0.017 and 0.026 per cent. fluorine, given as calcium fluoride and rock phosphate.

Lantz and Smith (491) made important observations in 1934 by experiments on young rats on a diet with 0.1 per cent. sodium fluoride. In the period of

rapid growth (28th to 52nd day) the Ca-retention, expressed in proportion to body weight, was lower than half of that of the controls. The phosphorus retention was also reduced, but less so. The ratio between retained Ca and P fell from just over 1 normally to a value as low as 0.54. The normal steep fall in the retention at the end of the period of rapid growth (about the 60th day) failed to materialize in the fluorine rats; on the contrary, the Ca-retention after that time was just as high as, or even higher than, that of the controls (expressed per weight unit). On the fluoric diet the rats excreted much more calcium and more phosphorus in fæces than the controls, and more Ca in proportion to P. At the same time there was a marked retardation of growth, and the rats presented the short, stunted build that is typical of calcium deficiency. Gradually as the animals grew heavier their legs became considerably curved. A concentration of 0.05 per cent. sodium fluoride in the diet had the same effects, but to nothing like the same degree. In a more recent work Rek (673) observed no uniform effect from different fluorine compounds in small doses on the phosphorus metabolism of the rabbit.

c. Other Functions

Sugar Metabolism. All we have is the record that in a lamb which for months received 0.3 g. sodium fluoride daily Goldemberg (343) saw a glycosuria, which lasted for some months and then spontaneously disappeared, without the dosage having been altered. Luy and Thormählen (532) found no change in the blood sugar of a cow given fluoric factory dust in its food.

Phosphatase. On the basis of experiments with heifers Phillips (637) states that the plasma phosphatase rose in proportion to the fluorine intake. The average for control animals was 0.1763 units per c. c. Animals receiving 0.02, 0.04 and 0.087 per cent. fluorine in the grain ration as rock phosphate had on an average 0.2366, 0.2751 and 0.3366 units per c. c. respectively. Hauck et al. (392) found that the kidney phosphatase did not alter in chickens whose diet contained up to 1.2 per cent. of sodium fluoride.

8. Dental Tissue

Changes in the teeth are among the most easily reproducible and most easily recognizable of all the symptoms of chronic fluorine poisoning. Consequently they have been well studied, and there is far-reaching agreement among the results arrived at by the various investigators.

Disregarding the brief statement by v. Stubenrauch (776a) and Rost (692), the first description was given in 1925 by McCollum, Simmonds, Becker and

Bunting (538). Working on the observation that the state of the teeth of rats varies on different forms of diet, they considered it probable that a slight addition of fluorine to the food would have a favourable effect on the development of the teeth. To an adequate basal diet, which gave good teeth, they added 0.0226 per cent. of fluorine as sodium fluoride. On this diet the young rats grew and reproduced, though weight and lifetime were somewhat inferior to those of the controls. Very marked changes were observed in the incisors. In the upper jaw the incisors were apparently overgrown, with a rearward curvature and faulty occlusion. Instead of the normal orange tinge, all the incisors had a dull, white colour with darker transversal bands. The quality of the teeth was poor, the lower incisors especially being very brittle. Changes of a similar kind were described in 1927 by Bergara (57) and in 1929 by Chaneles (150). The details of the macroscopic changes were particularly described in works by Margaret C. Smith and co-workers (753, 751, 756).

Fluorine has a detrimental effect on the growth of the teeth, whereby the part of a tooth calcifying during the period of fluorine intake will acquire permanent defects. Apparently, teeth or parts of teeth that already are calcified before the administration of fluorine begins, do not change. Therefore the changes are particularly easy to study in rodents, especially rats, whose incisors grow continuously from a persistent pulp.

a. Gross Changes

The macroscopic picture depends upon the nature of the ingested fluorine compound, its quantity, and the manner of administration. With the lowest degree of influence the pigment which normally causes the dark orange colour of the rat incisor disappears. The enamel becomes lighter, loses its lustre, and finally assumes a chalky-white colour. Stronger effect results in localized hypoplasia of the enamel, which becomes less resistent and chips off. There is a marked reduction of the strength of the teeth. The sharp, chisel-like cutting edge of the incisors wears off and becomes more or less flat. Sometimes the teeth are worn down to the gums. Occasionally one or more incisors break off, and the consequent absence of occlusion is followed by overgrowth of the opposite tooth. Elongation may be observed in all incisors, but is conspicuous in the upper jaw, where they curve back and may penetrate the roof of the mouth. Position anomalies are secondary and not pathognomonic of fluorine poisoning; they are seen now and then when occlusion ceases on account of the fracture of a tooth or asymmetry of the skull (380, 802).

The lowest degrees of fluorine effect produce alternate rings or bands of pale pathological enamel and dark, normal enamel. Often the rings are arched,

with the concavity towards the point of the tooth. The same phenomenon is observable when sodium fluoride is added to the drinking water (226). Intermittent injections of sodium fluoride cause the development of alternating bands of pathological and normal enamel; there is a light and a dark layer for every injection (715).

b. Threshold Values for Rats

The quantity of fluorine required to bring about the characteristic changes in rats is extremely small. With a concentration of 0.0007 per cent. fluorine (as sodium fluoride) in the food, Smith and Leverton (756) with a hand-lens were able to see distinct effects on some rats, with 0.0014 per cent. on all. With twice the fluorine concentration the alternately colourless and orange lines or bands became visible to the naked eye; or the layering of rings became irregular and the whole surface of the tooth gradually turned dull, white and chalky. The most marked changes, with chipping of the enamel, set in when the fluorine concentration was 0.014 per cent. These dental changes appear on a dose that is considerably smaller than that necessary to influence the general condition unfavourably. A concentration of 0.0014 per cent. in the food means that a rat ingests about 0.2 mg. fluorine per day, or about 1 mg. per kg. body weight. Cryolite and calcium fluoride were just as effective in producing the slightest changes as fluorides and silicofluorides; the quantities are so small that the question of the solubility apparently is of no significance. Still, the severe dental lesions only occurred when the quantity of these two compounds was increased several fold compared with sodium fluoride. By determining the minimum toxic quantity for rats DeEds and Thomas (229) found the same value: 0.5—1 mg. fluorine per kg. daily. By adding sodium fluoride to rats' drinking water Dean et al. (226) found that 0.0025 per cent. sodium fluoride (0.00113 per cent. fluorine) was the lowest concentration producing typical changes, which appeared on the lower incisors at the gingival margin 23 days after the beginning of the experiment, and gradually spread with the growth of the tooth. The same quantity of sodium fluoride given in the food was less toxic. It is typical that the changes are first recognizable on the lower incisors, which grow quickest, after a period depending upon the fluorine concentration. As a rule this period is from two to three weeks; after a few weeks more the upper incisors show signs of being affected.

c. Other Animals

In animals whose teeth grow from a non-persistent pulp, the changes are limited to those teeth or parts of tooth which calcify contemporaneously with

the ingestion of the fluorine. The fully grown teeth do not seem to alter in appearance or strength. Bethke, Kick, Hill and Chase (71) gave both young and adult pigs from 0.01 to 0.07 per cent. fluorine in their food as sodium fluoride or rock phosphate, over periods varying from 23 weeks to 26 months. The teeth which had calcified during the experiment displayed severe enamel hypoplasia and increased brittleness. The amount of wear was not exceptionally great. In young sheep, which for about two years received either 3 per cent. phosphorite in their food, or drinking water treated with phosphorite, Velu (824) saw changes in the permanent teeth quite identical with the picture of the spontaneous dental disease *darmous*. Dentition was retarded, the enamel proved to be yellowish and more or less corroded. The teeth wore down quickly, and the dental arch was very irregular. The molars of two young sheep (5 and 10 months old) which Slagsvold (742) fed for 14—16 months on hay containing fluorine, were irregularly worn with inclined surfaces and large points of enamel which wedged themselves down into corresponding hollows in the opposite teeth. Two 2-year old sheep, which were given 1 g. sodium fluoride and 1 g. cryolite daily for almost the same period, had normal teeth. Reed and Huffman (670) in 1930 reported on the results of an experiment with cattle which had had a rock-phosphate supplement from birth till the age of about 5 years. The grain ration (from the 6th month) contained about 0.0525 per cent. fluorine. After $2^1/_2$ years the animals would not drink cold water. Inspection showed that the teeth were badly worn, so that in some cases the pulp was exposed; the dental arch was very irregular. In dairy cattle which had been subject to fluorine toxicosis for years, Phillips et al. (644) saw molar abrasion and gingival inflammation.

d. Histopathology

Histological examination of teeth from fluorine-intoxicated animals were made in 1929 by Chaneles (155) and Bergara (58), later especially by Pachaly (626), Bethke et al. (71) and by Schour and Smith (715). Broadly speaking, the descriptions agree. The characteristic features are certain morphological changes in the enamel organ and a hypoplastic, deficiently calcified enamel and dentine.

The inner limits of the ameloblast layer are irregular, the individual cells are flatter. According to Pachaly (626), stronger influence causes atrophy of the entire enamel organ, which may result in aseptic necrosis. The least perspicuous changes in the enamel are (in rats) lack of pigment. The enamel is often hypoplastic in limited areas, corresponding to the characteristic localized pits in the surface of the tooth. Sometimes the enamel is entirely missing in patches. Enamel calcification is poor and circumstances attending the colouring indicate an abnormal composition.

The enamel prisms are irregular in shape and position and may be the seat of various morphological peculiarities (transversal bands, emphasizing of the Retzius' striæ etc.). Parallel with the enamel changes it is the rule to see hypoplasia and deficient calcification of the dentine, increased width of the predentine, and irregular limitation between the two layers. Schour and Smith (715) in an excellent work (1934) have shown that both enamel and dentine have an abnormal striping parallel with the surface, caused by alternating calcium-poor and calcium-rich layers. This stratification, which seems to be a characteristic fluorine effect, is especially marked under subcutaneous injection of sodium fluoride (page 75), but is also observable when fluorine is added to the diet. Öhnell, Westin and Hjärre (615) recently studied the dental changes in guinea pigs after intoxication by sodium fluosilicate. They observed calcification anomalies rachitic in type. The predentine was abnormally wide, and, as a sign of defective calcification, the dentine had large interglobular spaces and few and small globules. In guinea pigs fed on C-vitamin-free basal diet, with varying supplements of sodium fluosilicate and orange juice (up to 7 g. daily) they found a deposition of irregular, dark-staining granules. These were observed mainly between the odontoblasts and the predentine and in the dentine, but also in the enamel. The animals displayed signs of scurvy.

e. Chemical Composition

The chemical composition of teeth from fluorine-intoxicated animals has been the subject of several investigations. There is general agreement that the fluorine content is increased; the results of these analyses are treated in Chapter IX. On the other hand, it has not been determined whether the ash content and the composition of the ash undergo demonstrable changes through chronic fluorine intoxication. Kick, Bethke and Edgington (454) found no change in the ash content or in the Ca, P, Mg and CO_2 content of the ash in teeth of pigs which had received up to 0.097 per cent. fluorine in their food. Analyses by Smith and Lantz (752) and Hauck, Steenbock and Parsons (394) seem to indicate that incisors of rats given 0.1 to 0.15 per cent. sodium fluoride in the diet have a low ash content and perhaps an increase of the ratio Ca:P. By studying Röntgen spectra, Phillips et al. (644) have found that the crystalline character of tooth ash is similar to fluorapatite. In principle, enamel and dentine gave the same spectrum, both from normal cows and from cows intoxicated by fluorine.

9. Bone Tissue

The changes in the osseous system are among the most interesting of the symptoms of chronic fluorine intoxication. In a long series of investigations on animals of various kinds, no mention is made of clinical symptoms likely to draw attention to the skeleton. In other experiments, the patho-anatomical investigations have revealed normal conditions. Although a few early experimental results indicate that fluorine compounds have a marked effect

upon the osseous tissue, it is only with the investigations of the past few years that research has begun to turn towards it. It makes it more complicated that the various kinds of animals used for experimenting (rats, guinea pigs, cattle, sheep, dogs, pigs) seem not to react in quite the same manner. It will be practical to deal successively with (a) the gross changes found by clinical and macroscopical examination of the various animal species, and the results of (b) X-ray examination, (c) histopathological studies, and (d) analysis of strength and ash content of the bones. A discussion of the rather conflicting results will be found in Chapter XXVII.

a. Gross Changes

Two earlier European investigations with *dogs* called attention to the bone system. Brandl and Tappeiner (108) gave a dog about 22 mg. fluorine daily per kg. body weight for 648 days. The bones were distinctly white and ground surfaces presented a lively, glittering reflection. More force than usual was required to divide the bones, with the result that the lamina vitria frequently flaked off cranial bones and vertebral bodies in numerous pieces, like broken glass. The cartilages and intervertebral disks were a dazzling white and the fracture surface had a velvety sheen, as if the tissue were the seat of a salt deposition. The intervertebral disks were harder and less elastic than normally. All we know of some experiments by Rost (692) is a summary dating from 1907. By feeding growing dogs for 8 to 12 weeks with 0.2—0.5 g. sodium fluoride daily, he succeeded, despite a calcium-rich diet, in producing severe changes of osteoplastic and osteoporotic nature in the bones. The exostoses were localized at the carpal joints and the skull, at the attachments of the muscles that normally are much used. Clinically there was a certain stiffness of the joints and pains when jumping.

When McCollum et al. (538) for the first time (1925) described the characteristic dental changes in *rats,* they observed certain abnormities in the cranial bones. The colour seemed to be whiter than normally and the quality poorer. The surface was porous and lacked the normal lustre. The rami mandibulæ were thinner and less prominent than usual, and the interval between the dental arches of the maxillary was reduced by 1 mm. There was also an osteoporotic process round an alveolus. The white, dull surface of rat bones is noted by later investigators. Bethke et al. (71) were unable to show measurable deviations in the dimensions of the cranial bones, though the mandibles seemed to be shorter than normally. In contrast, Tolle and Maynard (802) found the skulls of rats that had dental changes were abnormally short and deep. In young rats on a diet with 0.1 per cent. sodium fluoride Lantz

and Smith (491) described a short, stunted build and curved legs as typical signs of calcium deficiency.

In works published in 1932 Cristiani (200, 201) described the bone changes which developed late in the course of the intoxication in *guinea pigs*, after ingestion of both sodium fluoride and sodium fluosilicate. The details of dosage and the duration of the experiments are insufficient. Changes were seen in the size, shape and structure of the bones attacked, but only in especially pronounced cases were the changes visible on the animal while alive. Tibia seemed to be the principal seat of attack and the description comprises that bone alone. Under fluorine intoxication the fat in the marrow disappears, for which reason the bone seems to be whiter than normally, where the fatty marrow imparts a dark tone to the rather translucent bone. The diaphysis thickens, especially the distal part, sometimes to twice the normal breadth. The surface changes character and becomes irregular.

In lengthy experiments on *cattle*, published in 1930 by Reed and Huffman (670) and Du Toit et al. (800) in 1932, limited thickenings resembling exostoses were observed, particularly of the diaphysis of metacarpals and metatarsals. Reed and Huffman also state that the mandibles were thickened and that the surface was rougher than normally. There seemed to be a layer of osteoid tissue over the mandibles. Contrary to this, Du Toit et al. say that the surface of the thickened extremity bones was smooth and gave the impression that the abnormal, new growth of bone had originated from compacta, and that periosteum was not involved. Bröss (114) and Hennemann (408) tried in vain to produce palpable bone changes in cows by means of oral administration of various fluorine compounds. In their experiment on heifers Phillips et al. (644) saw considerable bone changes. The long bones and the mandibles had exostoses; the bone was softer and thicker than normally. In all small joints there was calcification of the cartilage, resulting in ankylosis.

Bone changes in *sheep*, comprising white, porous exostoses on mandible, skull and long bones, were observed by Slagsvold (742), Roholm (687) and, to a certain degree, by Velu (824). Slagsvold fed lambs for 14—16 months on hay from a district close to a Norwegian aluminium factory, where spontaneous bone diseases occur among ruminants. The air-dried hay contained 20—25 mg. fluorine per 100 g. and relatively little calcium. In a kid, which received a food supplement of sodium silicofluoride ($^1/_{20}$th of dosis minima letalis) daily for 20 months Cristiani (197) found palpable, more or less irregular thickenings of the extremity bones, especially carpus and tarsus.

Bethke et al. (71) in their experiments on *pigs* (1933) observed an increase

of the corpus of the mandible, the more pronounced the greater the fluorine quantity in the food. In the molar region the bucco-lingual diameter was increased by up to 60 per cent., the vertical by up to 29 per cent. of that of the controls. The breadth of the dental arch was increased. The surface of the bone was rough, uneven, beset with exostoses and less translucent than normally. In cross-section the compacta was greatly thickened and the medullary cavity correspondingly increased.

b. X-Ray Picture

In 1927 Bergara (57) X-rayed fluorine-intoxicated rats and found that the skeleton gave weaker shadows than those of the controls. The width of the epiphysial lines in the lower extremities was pathologically increased. Chaneles (155), who gave his rats smaller doses than Bergara, found no osseous changes on the Röntgen picture. Marconi (557) arrived at a similar result when examining guinea pigs intoxicated with rather high doses of fluorine.

Gaud, Charnot and Langlais (307) X-rayed two guinea pigs which had received 10 mg. fluorine per kg. daily for $3^1/_2$ months, one as sodium fluoride, the other as calcium fluoride. In the former animal the skeleton showed increased transparency and there was a hypertrophy reminiscent of rachitic changes in certain skeletal parts (processus spinosi of the dorsal vertebræ, proximal epiphyses of humerus, ribs and sternum). In the animal that had received calcium fluoride, however, a general increase of the density of the bones was observed on the Röntgen picture.

On young rats Loewe (520) produced changes which on the Röntgen plate resembled rickets, by giving the animals calcium fluoride in colloid form: 80—160 mg. daily per kg. body weight. Besides the characteristic calcium deficiency in the ossification zone he observed constant densification, that is to say calcium deposition, in the neighbouring zones. The rachitic phenomena disappeared entirely with the increasing age of the animal, despite the unchanged fluorine intake. Sutro (783) X-rayed rats which for months had received 25—50 mg. sodium fluoride daily per kg. body weight. The diet was adequate as regards calcium. The shadows on the radiograph were normal in appearance or slightly denser than normally. Brašovan and Serdarušić (109) studied the healing of the radius in rabbits after resection. The daily intravenous administration of 30 mg. sodium fluoride per kg. resulted in an abnormally early and dense callus; the bone showed blurred outlines on account of periosteal deposits. A dose of 5 mg. sodium fluoride per kg. gave a normal callus but periosteal deposits.

c. Histopathology

By microscopic examination of their dog, Brandl and Tappeiner (108) saw no structural changes of the bone tissue, but all cavities in both compact and spongious bone were crowded with small crystals, mostly octahedral. A crystallographic examination made it probable that they were fluorspar crystals (CaF_2). This find was confirmed by Jodlbauer and Stubenrauch (442) in 1902, but not by later investigators. On examining bone slides from the experiments of Rost (692) nothing remarkable was found*). Observations by Schwyzer (724), Lewy (506) and Strong and Smyth (776) do not contribute much to the elucidation of the question.

Marconi (557) in 1930 experimented with guinea pigs, 20 days old, which for 29 to 53 days received up to 159 mg. sodium fluoride per kg. body weight daily, or every second day. In the proximal epiphyses of tibia and humerus signs were found of bone atrophy, especially of the spongiosa, but the compacta and the epiphysial cartilage were also affected. On the whole the osseous tissue was poorly coloured. The structure of the lamellary systems was not changed and the periosteum was quite normal. No osteoclasts or signs of lacunary absorption were observed anywhere. In 1932 Dittrich (233) published histological studies on the long bones and vertebral column of guinea pigs, rabbits and young rats which had received 120—250 mg. sodium fluoride pr. kg. for 66 to 140 days. Some of the rats were given a calcium supplement after the fluorine ingestion had ceased. Abundant quantities of red marrow were observed macroscopically in all bones. In the young rats there was disturbance in the ossification of the femur in the epiphysial line, with inhibition of longitudinal growth. The palisade zone lost its columnar arrangement and the cancellous bone tissue atrophied under the formation of cavities. In the diaphyses of the long bones the number and size of the Volkmann canals increased, as also the extent of the Haversian canals. Blurred and irregular absorption lines were observed around the canals; here the lamellary structure of the bone was indistinct. In the medullary half of the compacta there was vascularization, increasing centrally, and large, irregular, partly confluent cavities filled with reddish masses. Increasing dissolution and irregularity of the bone substance towards the medullary cavity was observed. In columna's spongiosa the peripheral parts of the trabeculæ disappeared under similar decay phenomena. The colouring observed in young rats on a moderate fluorine intake indicated reduced or retarded calcium apposition. In animals killed after ingesting calcium reparative changes were observed. Bethke et al. (71) in 1933 found normal histological conditions in bones of fluorine-intoxicated rats. In the thickened mandibles of pigs, compacta proved to be hyperplastic and only incompletely transformed from the cancellous, precursory stage. The concentric lamellæ systems were irregular, the Haversian canals often of more than normal size. Compacta gave the impression of having been formed at high speed. The medullary cavities everywhere were full of normal, yellow marrow.

In 1934 Lilleengen (510) made a microscopic examination of bones from the sheep in Slagsvold's experiments (742). In sections of jaw, frontal and

*) Personal communication.

long bones of two lambs fed up to 16 months on hay containing fluorine, he found changes which he compared with the phenomena observed in human osteomalacia. There was considerable diffuse atrophy of the bones, particularly prominent in the medullary parts of compacta and in the spongiosa trabeculæ. Around the extended marrow cavities and Haversian canals were well-developed (up to 133 μ wide) osteoid borders. In some places compacta was almost cancellous in appearance. To a greater or smaller degree the marrow revealed serous atrophy. On the periosteum of jaw and long bones there were exostoses with lively cell and vascular proliferation. Everywhere osteoclasts were absent or extremely sparse; there was no sign of rebuilding of the bone structure. Only in the jaw were there scattered areas of hyperæmic fibrous marrow and new, more or less compact, poorly calcified osseous tissue; some osteoclasts were observed in these areas.

Sutro (783) examined bones of growing rats which for up to one year or more through their drinking water had daily received 25, 50 or 75 mg. sodium fluoride per kg. body weight. At the 50 mg. level no unusual changes were found in the bones after three to five months. After one year or more the fibrils of the matrix showed irregularity, and among the fibrils numerous coarse and fine dark-staining granules were noted. Granules were also observed in the atypically staining matrix about pyknotic bone cells and in the borders of the Haversian canals. Some of the cortices showed a stratified arrangement with alternating dark-staining and light-staining bone areas. In one animal large irregular granules were found in the interpubic ligament. Rats, which for 75 days received 75 mg. sodium fluoride per kg. daily, showed an abnormal amount of osteoid tissue round the Haversian canals. Numerous dark granules were present at the osteoid borders as well as in the matrix. No osteoclastic activity was noted. Rats on a diet low in calcium died after one to two months' administration of fluoride and displayed a marked generalized osteoporosis.

In a recent work Öhnell, Westin and Hjärre (615) describe calcification anomalies of rachitic type in guinea pigs, which received rather large quantities of sodium silicofluoride. In the mandible and at the costo-chondral junction abnormal amounts of osteoid tissue were found. In bones of guinea pigs on C-vitamin-free diet with varying supplements of sodium silicofluoride and orange juice they also observed gross dark-staining granules, which were presumed to consist of calcium fluoride. The granules occurred most frequently in the calcification zone, but also sporadically in the bone and along the border of the Haversian canals. At the same time the animals showed more or less pronounced signs of scurvy.

d. Strength and Chemical Composition

In chronic intoxication the fluorine content of the bones increases considerably. This phenomenon, demonstrated by several investigators, will be dealt with in Chapter IX. Below is a reference to observations on the quantity and composition of the bone ash and the strength of the bone.

Forbes et al. (277, 278, 279) showed in 1921 that a mineral supplement given to growing pigs in the form of rock phosphate resulted in poor bone development. Compared with other mineral mixtures, rock phosphate gave lower ash per volume unit and greater fragility. Analysis revealed a relative increase of magnesium and phosphorus and a relative reduction of calcium and carbon dioxyde; the ratio P:Ca was increased. In 1922 Cristiani and Gautier (205) stated that the bones of fluorine-poisoned guinea pigs were more brittle than normally. Tibia's resistance to flexion on an average was lower by 20 per cent. Chaneles (155) would not draw any definite conclusions from his analyses of rat bones; compared with the controls the deviations were too small. Smith and Lantz (752) found normal values for ash and content of calcium and phosphorus by analysing tibia of rats which for 60—120 days had been given 0.05 per cent. sodium fluoride in their food. A content of 0.1 per cent. in the food reduced the ash by 2 per cent. and increased the calcium by 3 per cent., so that the ratio Ca:P was increased. Contrary to these results, McClure and Mitchell (537), also experimenting on rats, found that a content of 0.0313 and 0.0623 per cent. fluorine in the food as sodium fluoride produced an increase in the ash content of 1.3 per cent. The phosphorus content was unchanged, the calcium quantity reduced by 1.05 per cent., so that the ratio Ca:P was lowered. In experiments at the Iowa Agricultural Experimental Station (27) no change could be seen in the calcium and phosphorus content, though the bones of rats on diets of varying fluorine content became soft. On the other hand, Hauck, Steenbock and Parsons (394), in rats that received 0.15 per cent. sodium fluoride in their food, found a lowering of the ash quantity, absolute and relative, both when the calcium content of the diet was moderately high and when it was low.

In experiments on young pigs Bethke et al. (69, 71) were able to show that the brittleness of the bones increased proportionately as the fluorine content of the diet increased. The ash content was reduced at the higher fluorine concentrations, but only when expressed in weight per volume unit of bone. The calcium and phosphorus content was not changed, but with increasing fluorine in the food the magnesium content increased and the carbon dioxyde content decreased. McClure and Mitchell (536) state that the bones of young pigs which received calcium fluoride and rock phosphate were unusually soft. Slagsvold (742) says the same about the bones of the skull and trunk of sheep fed with hay containing fluorine. In a series of experiments on chickens, some of which received rock phosphate *ad libitum* (117), some up to 1.2 per cent. sodium fluoride in their food (455, 392), no perceptible effect on the ash content of the bones was observed. In their lengthy intoxication experiments on cattle, which for 4½ years received a rock phosphate supplement, Phillips et al. (644) observed an increase of the breaking strength of metacarpals from an average of 1772 in the controls to up to 3076 in the fluorine cows.

CHAPTER IX

ABSORPTION, STORAGE AND EXCRETION

1. Absorption

Under this heading there are certain observations but only few systematic investigations. It is not known definitely where and in what form fluorine is absorbed when a fluorine compound is intaken orally. Wieland and Kurtzahn (855) have set up the likely theory that, with the hydrochloric acid of the stomach, fluorides and fluosilicates form hydrogen fluoride which, in undissociated form, permeates the gastric mucous membrane, accompanied by corrosion phenomena. It is also probable that the undissociated HF-molecule is able to permeate intact epidermis (357). Simply composed fluorine compounds such as the alkali fluorides can probably be absorbed from the intestine. By means of chemical analysis fluorine has been found in most organs in acute spontaneous poisoning, but most frequently and readily in the tissues of the stomach and intestine. In the frog, sodium fluoride in solution is absorbed through the skin (214, 435). Insects, too, seem to be able to absorb fluorine compounds through the integuments (417). With subcutaneous and intramuscular injection the soluble fluorine compounds are easily absorbable and highly toxic. It is not known in what form fluorine is transported in the organism.

2. Storage

After absorption, fluorine is stored especially in bones and teeth, following the deposition of calcium and phosphorus. This fact was first established by Brandl and Tappeiner (108) in their still outstanding experiment on a dog. The animal was placed in a metabolism cage, and urine and fæces were collected in periods of three weeks. In the course of about three months the dosage rose from 0.1 to 1 g. sodium fluoride daily; later the daily dose for about 12 months was 0.5 g., and finally it rose to 0.9 g. at the discontinuation of the experiment after 22 months. In the first three weeks fluorine could not be found in urine or fæces. Thereafter commenced an excretion which gradu-

TABLE 13.

Deposition of Fluorine in a Dog which received 402.9 g. Sodium Fluoride perorally in the Course of 648 Days (Brandl and Tappeiner 1891).

Tissue	Weight in fresh condition	Absolute quantity NaF	NaF in dry substance	Fluorine per 100 g. dry substance
	g.	g.	%	mg.
Blood...................	750	0.14	0.12	54
Muscle.................	5710	1.84	0.13	59
Liver...................	360	0.51	0.59	267
Skin....................	1430	1.98	0.33	149
Bones and cartilage	2039	59.94	5.19	2348
Teeth..................	25	0.23	1.00	452

ally rose and, for short periods, even exceeded the intake. As a rule the excreted quantity was about half of the intake. In all, the dog received 402.9 g. sodium fluoride and excreted 330.5 g. Of the 72.6 g. deposited, 64.64 g. was found in the tissues shown in Table 13. Deposition took place mainly in the osseous system. In addition, the investigators found a relatively high fluorine content in teeth and in various organs, especially liver and skin.

TABBI

Storage of Ingested Po

Investigator	Year	Animal	Duration of experiment	Fluorine compound used	Fluorine in diet	Flu ing mg. di (ap ave
					%	
Brandl and Tappeiner (108)	1881	Dog	648 days	NaF		
Sonntag (761)	1917	Dogs	?	NaF		I
Kick, Bethke and Edgington (454)	1933	Pigs	144 days	NaF	0.029 0.058 0.097	I 2 3
			160 days	NaF	0.010 0.029 0.058	I

That ingested fluorine is deposited in bones and teeth was afterwards affirmed by Sonntag (761), Bethke et al. (69), Kick, Bethke and Edgington (454) and later by several investigators. The results of some of these analyses are shown in Table 14. The increase of the fluorine content of the bones is very considerable (up to 10—30 times the normal small quantity) and seems to be directly dependent partly on the daily intake of fluorine per kg. body weight, and partly on the duration of the experiment. Deposition in the teeth seems more moderate; the increase as a rule does not exceed about 10 times the normal content. A relatively high content of fluorine in bones and teeth must therefore be looked upon as an important sign that the organism has absorbed fluorine over a long period. The highest observed fluorine content was recorded for Brandl and Tappeiner's dog: $36.9\,^0/_{00}$ in the bone ash. This corresponds practically to a pure fluorapatite of the formula $3\,Ca_3(PO_4)_2 . CaF_2$ with a theoretic fluorine content of 3.77 per cent.

Judging from Brandl and Tappeiner's analyses, it seems that fluorine is also deposited to a considerable degree in the organs (Table 13). This does not agree with the results of modern investigators. Gaud, Charnot and Langlais (307) analysed the organs of an ass four years old, attacked by *darmous*, and found up to 2 mg. fluorine per 100 g. dry substance, or a content not in excess of the figures given by Gautier and Clausmann (316, 318) as normal.

TABLE 14.

ested Fluorines and Teeth.

Fluorine ingested mg. per daily (approx average)	Fluorine in dry substance (non-fatty)				Analytical method
	Bones	Bones of controls	Teeth	Teeth of controls	
22	$^0/_{00}$ 23.5	$^0/_{00}$ 0	$^0/_{00}$ 4.5	$^0/_{00}$	Wöhler (modification)
?	17.3 (max.)	ca. 0.6—1.9	12.9		Glass etching
10.6 21.1 36.9	5.34 7.75 11.08	0.36—0.39	1.81 2.81 3.61	0.83—0.92	Reynolds, Ross and Jacob
3.5 9.8 19.7	3.16 6.71 10.77	0.57	1.27 2.62 3.73	0.43	

In bone ash from the same ass they found 8.65 $^o/_{oo}$ fluorine. It must also be mentioned here that Boissevain and Drea (90) were unable to demonstrate the presence of fluorine by spectrographic examination of organs of individuals whose bones contained up to 8 $^o/_{oo}$ fluorine in the ash. In organs of cows, which for a long time had been subjected to fluorine intoxication, Chang et al. (159) found the normal, low fluorine content doubled. The thyroid alone increased its fluorine content notably: up to 24-fold. These findings do not indicate that fluorine is deposited in the organs to a degree that is comparable with deposition in the bones.

3. Excretion

Fluorine seems mostly to be excreted in the urine, in what form is not known. After a single subcutaneous injection of sodium fluoride in a dog Brandl and Tappeiner (108) found that about one-fifth of the intaken quantity was excreted in the urine during the next two days. In their aforesaid experiment with a dog the fluorine quantity excreted in the urine was usually about half of the ingested quantity. As fæces contained only one-tenth to one-fifth of the excreted quantity, Brandl and Tappeiner interpreted this phenomenon as an actual excretion through the gastro-intestinal tract and not merely as defective absorption; they supported this assumption on the fact that fæces contained no fluorine at all in the first three weeks of the experiment, when the total excretion was nil. We must take it that fluorine is excreted rather slowly. This is also indicated by the considerable storage in intoxication experiments and also the fact that the fluorine content of organs and bones seems to increase with age (317, 318, 736). The daily physiological excretion in man was determined by Gautier and Clausmann (318) at about 1 mg. fluorine.

It is rather uncertain to what degree fluorine may be excreted through other channels than the kidneys. Gautier and Clausmann (316) found a relatively high fluorine content in epidermis, hair and nails, but this observation still remains unsupported; they also demonstrated the presence of fluorine in gall and in milk (318). Janaud (435) was able to show fluorine in saliva from a dog killed by intravenous injection of sodium fluoride. Contrary to this, Boissevain and Drea (90) were indeed able by spectographic examination to show the presence of fluorine in urine, but not in saliva or cow's milk.

4. Maternal Transference

The question of the *excretion of fluorine with the milk* is one of great importance having regard to the pathogenesis of *mottled enamel*. Gautier and Clausmann

(318) give rather high values for the content of fluorine in milk of normal individuals, on an average 0.48 mg. in 1 kg. woman's milk and 1.80 mg. in cow's milk. Phillips, Hart and Bohstedt (645) found that normal cow's milk contained 0.05—0.25 mg. fluorine per litre, averaging 0.138 mg. The fluorine content in milk of cows which for a long time had been given about 1—3 g. fluorine daily by means of a rock phosphate supplement was not distinctly increased. Rats given a supplement of this milk did not differ from the controls, which received milk from normal cows. Gaud, Charnot and Langlais (307) found no definite difference between the fluorine content in milk from a normal sheep and that from a sheep suffering from darmous. However, two observations prove that fluorine can be excreted in milk in noteworthy quantities. Brinch and Roholm (112) observed mottled teeth in children who had been nursed for long periods by fluorine-intoxicated mothers, and Murray (600a) analysed the bones of young rats suckled by mothers receiving 0.05 per cent. fluorine in the diet and found a fluorine content of 0.021 per cent. as compared with 0.0007 per cent. in the controls.

The *placenta* seems to be impermeable to fluorine, at any rate where the quantity in the mother's blood is only small. This is indicated by the fact that temporary teeth are hardly ever attacked by mottled enamel. Possibly, however, there are differences according to species, as Velu (828) has observed the specific changes in the deciduous teeth of the horse. Recently Smith and Smith (757) found mottling of the temporary teeth of breast-fed children in a locality where the fluorine content of the drinking water is excessively high. The only explanation of this is that fluorine passes the placenta or is excreted with the milk, the first possibility perhaps being the most probable. Murray (600a), in experiments with rats, was able to show that the new-born young received significant amounts of fluorine when the maternal rats received 0.05 per cent. sodium fluoride in the diet. It is uncertain whether or not the small quantities of fluorine in an average diet passes the placenta; the investigations on the fluorine content in the bones of the foetus and new-born young are contradictory.

Middleton (583) found fluorine in the femur of a 6 months' human foetus but not in the arm of a 3$\frac{1}{2}$ months' foetus. In bone ash· of new-born rabbits and guinea pigs Jodlbauer (441) found 1.5—1.8 $^0/_{00}$ fluorine, or almost the same quantity as in adult animals. Gautier and Clausmann (317, 318) constantly found a rather considerable quantity of fluorine in organs and bones of new born children. Sharpless and McCollum (736) state that it was doubtful whether rats 16—18 days old contained any fluorine at all; the bones of stock animals on the whole displayed a fluorine content increasing with age. In bone ash from children 4—5 years old and from young lambs Salinas y Ferrer (699) found from 0 to 0.1 $^0/_{00}$ fluorine, in the ash from adult individuals as a rule much more. Gaud, Charnot and Langlais (307)

in the foetus of a sheep attacked by *darmous* found 0.892 mg. fluorine per 100 g. or in all 2.7 mg. They conclude that fluorine no doubt passes the placenta, but with difficulty, and that accordingly the foetus is protected from the injurious effects of fluorine on the teeth.

Tamman (785) and later Gautier (311) report rather considerable quantities of fluorine in the various constituents of the hen's egg, most in the yolk. Purjesz et al. (664) could not find fluorine in eggs of normal hens, but in those of fluorine-intoxicated fowls. In a recent work Phillips, Halpin and Hart (642) show that the fluorine content of the egg increases perceptibly, if laying hens are given 3 per cent. rock phosphate in their food. Fluorine is deposited almost exclusively in the lipoid-fraction of the yolk. In 100 g. yolk there was 0.32 mg. fluorine, as against 0.09 mg. in control material.

PART II

TECHNIQUE EMPLOYED IN OWN
INVESTIGATIONS

CHAPTER X

TECHNIQUE

1. Determining the Dust Quantity

Based upon a principle described by Næslund (601), an apparatus was constructed for the gravimetrical determination of dust (Fig. 10). The dust is caught on passing through a container with glass balls treated with oil. The container consists of a U-shaped glass tube with a flat bottom (a). Small pieces of glass tubing have been substituted for glass balls as they are lighter and have a larger surface. The viscous oil employed for Pfeiffer's air-pump proved to be suitable for the purpose, as its weight does not alter when the air passes through. The dust-receiver, which weighs about 45 g., is placed in an air-tight glass bell. The air passes through the apparatus from b to d. The connection at c has been ground so that the receiver is easy to connect and disconnect. The volume of air passing through is measured by a gasometer. A small rotary pump provides the suction. On passing through the receiver the air leaves its entire dust content, and this is checked by weighing the receiver before and after.
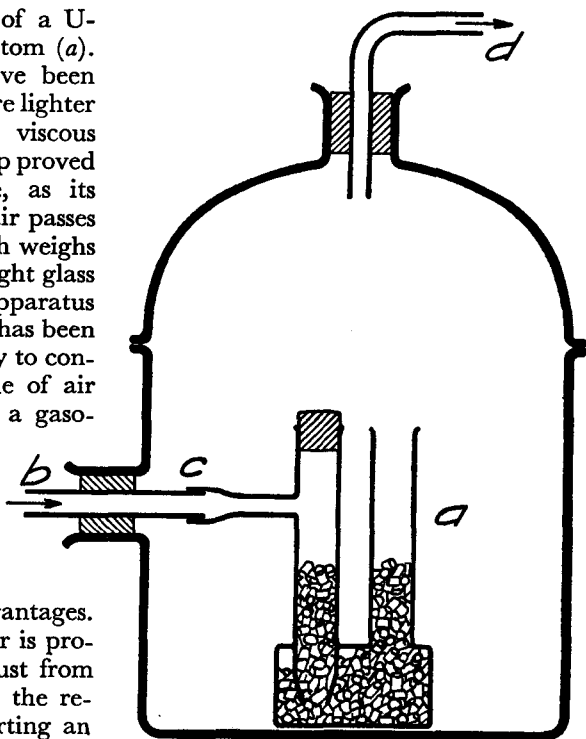
This apparatus has several advantages. The design is simple. The receiver is protected from contamination by dust from the outside. That no dust passes the receiver can be controlled by inserting an extra receiver on the same principle at d. Where very dusty atmosphere is concerned, as in the present case, it is sufficient to pass 1 to 3 cbm. of air through. If the dust content is low, the quantity of air may be increased and the weight of the receiver reduced if necessary. On testing with laboratory air which first had been passed through a cotton filter the weight of the receiver was found to vary less than 1 mg. This accuracy is sufficient for the purpose if 10 mg. or more dust is deposited in one test.

FIG. 10. Apparatus for gravimetric dust measurement. The dust is caught on the oiled pieces of glass tubing in the container a, which is placed in an air-tight glass bell.

2. Analytical Technique

a. Preparation of Organic Material

Organs were cut into small pieces and placed at once into absolute alcohol in clean vessels with cork stoppers. Prior to incineration the material was dried for 24 hours at 105° C., powdered by means of a mill or an iron mortar and dried again at 105° to constant weight. About 2 per cent. calcium oxyde was then added, mixing thoroughly all the time. To blood the same volume of absolute alcohol was added; evaporation proceeded after the addition of 2 per cent. calcium oxyde. The materials were incinerated in porcelain or nickel crucibles over Argand burners. The lowest possible temperature was employed for both carbonization and incineration; 24 to 48 hours was the time mostly used for complete incineration. The temperature did not exceed red-heat (about 500° C.). *Bones* were skeletonized very carefully, and periosteum and marrow removed as far as possible. Soxhlet's apparatus, or a rotating benzine drum, was used for defatting. The material abstracted for analysis was carbonized at low temperature and pulverized in an iron mortar. Incineration proceeded as with the organs, as a rule taking 3—5 hours. No calcium oxyde was added to bones and teeth. *Teeth* were treated with alcohol and ether after mechanical cleansing, and incinerated like the bones. It proved difficult to separate enamel from dentine. The enamel flies off at a blow on a heated tooth, but rarely in pure form. The following two procedures*) were employed: (1) The tooth was sawn longitudinally with an emery-wheel and the dentine cut off with steel drills under a hand-lens. The method is laborious, but it was possible to get fairly pure enamel in that way. (2) After heating, the tooth was coarsely broken up and the enamel fragments with more or less dentine on them were sorted out under a hand-lens. After further pulverization in an agate mortar the material was centrifuged in a mixture of methylene iodide and ether with a specific gravity of about 3. In this the enamel sank to the bottom, and the lighter dentine, and dentine with enamel fragments, were decanted off. The enamel was thoroughly washed in ether. Purity was checked under the polarization microscope by means of the refractive difference between enamel and dentine. Enamel isolated in this manner was practically pure. The dentine employed was partly dental roots cut away below the enamel boundary after the cement had been removed by grinding, and partly residue from the method described under (1). The isolated enamel was not incinerated; the dentine was incinerated in the usual manner.

b. Qualitative Test for Fluorine

The tests used were the silicomolybdene acid test described by Feigl and Krumholz (264) and the ordinary silicic acid test. In both tests fluorine is demonstrated indirectly by means of the silicic acid liberated when silicon tetrafluoride reacts with water. In the former test the silicic acid together with ammonia molybdate forms the yellow silicomolybdene acid which, in weak acid solution, is reduced by benzidine to molybdene blue, whilst benzidine is converted to benzidine blue. The blue colour is a sign of the presence of fluorine. By means of Feigl and Krumholz's technique there was no difficulty in demonstrating 0.005 mg. fluorine in the form of sodium fluoride.

For the second of the tests named a small distillation apparatus of Pyrex glass was used, modified according to Mayrhofer et al. (573), originally constructed for

*) For kind assistance in this work I thank Professor J. J. Holst, the Copenhagen School of Dentistry, and R. Bøgvad, M. Sc.

liberating fluorine in the form of silicon tetrafluoride and determination of the quantity of silicic acid equivalent to fluorine. This method proved to be inapplicable, but the apparatus was suitable for qualitative determinations of up to 0.075 mg. fluorine. The material was placed in the flask mixed with about 1 g. finely powdered non-fluoric window-glass. After adding 3 c.c. sulphuric acid (98.5 per cent.) through the separating funnel it was heated to 150° for about one hour (glycerine bath), dry air being sucked through continuously. The receiver contained 0.1 N sodium hydroxyde. When fluorine is present a white ring of silicic acid is deposited in the inlet-tube some distance above the surface of the liquid. The apparatus must previously have been washed in alcohol and ether and dried in an incubator; the material must not contain water. The ring of silicic acid is best observed after the tube has become dry.

c. Quantitative Determination of Fluorine

After several abortive attempts to perfect a method capable of determining about 0.1—1 mg. fluorine, attention was directed to the method published in 1933 by Willard and Winter (861), which was thereafter employed, with a few unimportant alterations. In this method fluorine is liberated in the form of hydrofluosilicic acid by means of perchloric acid. The hydrofluosilicic acid is distilled and the fluorine is determined titrimetrically in alcoholic solution by means of thorium nitrate with zirconium alizarine as indicator. The method has several advantages. The ability of perchloric acid to split fluorine compounds seems to be considerable; most perchlorates are readily soluble. A new and simple principle is introduced in the distillation, permitting the presence of silica in the initial material and not requiring a dry apparatus. Titration is based on the fact that thorium fluoride (ThF_4) is not easily soluble and that most other thorium compounds are much more soluble in alcoholic media. When titration proceeds in weakly acid fluids the indicator is colourless; the addition of an excess of thorium causes the formation of a lake of red colour. Armstrong (32) has modified the indicator by employing sodium alizarine sulphonate; this facilitates titration.

Reagents. 1. A solution of thorium nitrate, standardized on a solution of sodium fluoride of known content. A preparation from Merck (*Thorium nitricum siccum*, $Th(NO_3)_4 +$ ca. $4 H_2O$) was used. The fluorine preparation used was *Natrium fluoratum pur.* (Merck), which on analysis (according to Hawley) proved to contain 45.46 per cent. fluorine. In practice three solutions of thorium nitrate were used, which per c.c. were equivalent to 0.30, 1.52 and 1.48 mg. fluorine respectively. 2. A 0.05 per cent. aqueous solution of sodium alizarine sulphonate. 3. Hydrochloric acid, ca. 1:50. 4. Perchloric acid 70 per cent. (Merck).

Apparatus. Consists of an ordinary distillation set with flask, water cooler and receiver. The flask is of Pyrex glass and holds 125 c.c.; Claisen's model is recommended, as the liquid is apt to be restive when boiling. The distillation flask has a thermometer (200° C.) and a separating funnel holding about 70 c.c., the point of which is drawn out to a capillary. The receiver consists of an Erlenmeyer flask with a capacity of 300 c.c. Rubber stoppers are employed everywhere. The distillation flask is placed on an asbestos plate with a hole so large that one-third of the flask is exposed to the flame. This arrangement ensures the most undisturbed distillation.

Analytical Technique. The material is placed in the distillation flask together with five or six small pieces of glass tubing. After rinsing with a little water, 5 c.c. perchloric acid is added and the stopper put in. The thermometer but not the point of the separating funnel must dip down into the liquid. A large Bunsen flame is required for heating. The addition of water must be so adjusted that the boiling point for

8

TABLE 15.

Determination of Error of Willard and Winter's Method of Fluorine Analysis.

F used (as NaF)	Direct titration			Titration after distillation			Notes
	Th(NO₃)₄	F found	Deviation	Th(NO₃)₄	F found	Deviation	
mg.	c.c.	mg.	%	c.c.	mg.	%	
0.095	0.31	0.093	− 2.11	0.29	0.087	− 8.42	Unless otherwise indicated 1 c.c. Th(NO₃)₄ is equivalent to 0.3 mg. fluorine
0.19	0.69	0.21	+10.53	0.67	0.20	+ 5.26	
0.38	1.31	0.39	+ 2.63	1.38	0.41	+ 7.90	
0.94	3.20	0.96	+ 2.13	3.11	0.93	− 1.06	
1.89	6.17	1.88	− 0.53	6.11	1.83	− 3.18	
3.78	2.56	3.89	+ 2.91	2.49	3.79	+ 0.26	1 c.c. Th(NO₃)₄ ∽ 1.52 mg. F
0.38	..	..	..	1.30	0.39	+ 2.63	
0.38	..	..	..	1.38	0.41	+ 7.90	
0.38	..	..	..	1.29	0.39	+ 2.63	
0.38	..	..	..	1.27	0.38	0	
0.38	..	..	..	1.33	0.40	+ 5.26	Added: 1.03 g. Ca₃(PO₄)₄; 0.32 g. NaCl; 0.40 g. CaCO₃; 0.10 g. MgSO₄
0.94	..	..	..	3.09	0.93	− 1.06	Added: 0.51 g. Ca₃(PO₄)₄; 0.33 g. NaCl; 0.40 g. CaCo₃; 0.10 g. MgSO₄

the mixture of water and perchloric acid lies at about 110°. When the temperature has reached 135°, water is added continuously from the separating funnel at such a rate that the temperature remains between 130° and 145°. When the separating funnel is empty, distillation is discontinued, after having usually taken slightly more than half an hour. The same volume of alcohol of about 90 per cent. is added to the distillate and 5 drops of the alazarine solution. N-sodium hydroxyde is then added drop by drop until the colour is red, and thereafter hydrochloric acid (1 : 50) drop by drop till the solution is just bleached. Then titrating proceeds with thorium nitrate until a faint but distinct pink colour appears. It is necessary to titrate in good daylight and over a white plate.

Discussion. Experiments showed that the total quantity of fluorine is transferred when about 70 c.c. water are distilled at a temperature of 130° to 145°. At the same time a certain quantity of acid is transferred, perchloric acid and, if the original material contains any organic substance at all, chlorine and hydrogen chloride. If the temperature does not exceed 140° the quantities will be small and cause no inconvenience. As a rule about 1 c.c. N NaOH was used for neutralization. The salt concentration does not seem to be of any great significance. Addition of 1 g. sodium chloride to a solution of sodium fluoride did not affect the accuracy of the titration. Large

TABLE 16.

Double Analyses of Fluorine Content in Bone Ash, Willard and Winter's Method.

Materials	Bone Ash used	Th(NO₃)₄	1 c.c. Th(NO₃)₄ ∽ mg. F	Fluorine per g. bone ash	Deviation from average value
	g.	c.c.		mg.	%
Sternum, former cryolite worker No. 200	0.2299 0.1712	1.50 1.11	1.52 1.52	9.92 9.86	± 0.30
Corpus femoris, Same	0.1899 0.2114	0.99 1.01	1.52 1.52	7.93 7.26	± 4.41
Corpus femoris, Dog 3	1.1150 2.0010	2.90 1.09	0.30 1.52	0.78 0.83	± 3.11
Costa, Dog 2	0.1458 0.1214	2.92 2.50	1.52 1.52	30.44 31.22	± 1.27
Mandible, Calf 1	0.2568 0.2193	2.31 1.93	1.52 1.52	13.67 13.38	± 1.07

quantities of acid may destroy the indicator, but this can be prevented by a preliminary neutralization (lithmus paper) before adding the indicator. If the material contains sulphide, amorphous colloidal sulphur will be precipitated in the distillate; in small quantities this makes no difference, whereas in larger quantities it disturbs the titration. Phosphoric acid does not distil at the temperature employed. The following ions do not interfere with the titration: Cl^-, SO_3^{--}, SO_4^{--}, ClO_4^-. Willard and Winter state that complete distillation is disturbed by boracic acid, gelatinous silica and large quantities of aluminium salts. The fluorine content in cryolite passes over quantitatively. The titration itself is not perfect, as the end point is not quite clear. When the change of colour has set in, the colour intensity increases only slowly with the further addition of thorium nitrate. Titration requires some practice. By means of blanks it should be made sure that the apparatus does not give off fluorine. Standardization of the thorium solution employed must be carried out under the same conditions as the final titration. Diminishing the volume of the distillate by means of evaporation makes it possible to use smaller quantities of the indicator and thereby to increase the sensitivity.

The technique described above proved useful as a routine method for the analysis of material with a fluorine content of between about 0.1 and 4 mg. Table 15 contains a number of experiments made in order to test its accuracy. The material consisted of various quantities of NaF-solutions (N 0.02, N 0.01 and N 0.005), measured with controlled pipettes. When using fluorine in quantities between 0.095 and 3.78 mg. the error does not exceed 10 per cent. The quantity of fluorine is determined with the same accuracy when the material contains a synthetic mixture of the most important compounds in bone ash (Table 15). Double analyses of bone ash (Table 16)

show that the deviation from the mean is less than 5 per cent. Thus in practice one may take it that the error does not exceed 10 per cent., which must be said to be satisfactory for this reason alone, that there is scarcely any better method in existence at present. If no greater accuracy is required it is superfluous to make corrections for the slight excess of thorium nitrate that must be added in order to produce the pink colour. When titrating a distillate that did not contain fluorine 0.09 c.c. of thorium nitrate solution was used, corresponding to 0.03 mg. fluorine.

3. Histological Technique

The routine method chosen for histological examination of *organs* was fixation in 10 per cent. formalin (24 hours), dehydration in alcohol of increasing concentrations, clearing in xylol and embedding in paraffin. Staining was carried out partly by means of hæmalum-eosin, partly according to Hansen with iron trioxy-hæmatin and acid fuchsin-picric acid.

Two different procedures were employed for examining the bones: (1) Fixation in Orth's fluid for 8—10 days; decalcification in 5 per cent. nitric acid; treating with 5 per cent. potassium alum for 24 hours; washing in running water for 24 hours; dehydrating in alcohol of increasing concentrations up to absolute alcohol 3 × 4 hours; treating with toluol up to 2 hours; embedding in paraffin; staining as under organs. (2) The technique described by Bock (85): Hardening up to one month in Müller-formalin, which was frequently renewed; decalcification in 5 per cent. nitric acid; deacidifying in 5 per cent. potassium alum; washing 24 hours; thorough dehydration in increasing concentrations of alcohol, finally ether-alcohol; embedding in colloidin; staining with hæmatoxylin and counter-staining with eosin.

R. Bøgvad has kindly prepared and examined ground sections of various bones. The method was as follows: Sawn plates of bone were boiled in a mixture of balsam and xylol, whereby the cavities are filled and the balsam attains a suitable degree of hardness. The plates were ground on rotating steel and glass disks on one side, which then were fixed to a slide by means of balsam of suitable consistency. The preparation was then ground on the other side until transparent and examined through a polarization microscope.

4. Hæmatological Technique

The methods employed have not deviated from clinically approved systems*). Blood from man was taken by venal puncture after the least possible stasis, with a syringe containing so much 3 per cent. Na-citrate solution that the ratio of blood-citrate was 9:1. From animals the blood was taken after severing the throat vessels into a tube with Na-citrate in the same proportions. As a rule the blood examinations were made within 12 hours after collecting. The hæmoglobin percentage was determined with a Sahli-Leitz hæmometer corrected to Haldane's standard (100 per cent. = 18.5 vol. per cent. oxygen). The same apparatus was used for all hæmoglobin determinations. Erythrocytes were counted in Bürker-Türk's counting chamber after diluting 1:200 with Hayem-Jørgensen's fluid according to Ellerman's principle. At each count ten "large squares" were counted. Leucocytes were counted in the same manner after diluting 1:20; five large fields were counted. The smears were made immediately after taking the blood; the

*) See Meulengracht and Gram: Hæmatologisk Teknik. Copenhagen 1930.

methods of staining were partly Leishman's, partly a combination of May-Grün-wald-Giemsa's. In differential counts 200 cells as a rule were counted. Platelets were counted in undiluted citrate-plasma according to Windfeld (872). The osmotic resistance of the erythrocytes was determined by Hamburger's dilution method. The blood-coagulation time was determined by Howell-Gram's method (recalcin-ated citrate-plasma), bleeding time after pricking both ear lobes with Franck's needle and drawing the blood up on filter-paper every half minute till bleeding ceased. For practical reasons the sedimentation rate of the blood corpuscles was determined in citrate-blood (1:9) by means of Westergren's apparatus. The figures have been corrected to the hæmoglobin percentage by means of Gram's table. Bile pigment in the blood (plasma-colour) was determined according to Meulen-gracht's method.

5. Fluorine Compounds Used

Various fluorine compounds were used for the experimental investigations. The preparations are described below; the analyses were kindly made by H. Buchwald.

Sodium Fluoride. Natrium fluoratum pur. Merck was used, a very pure preparation with a weak basic reaction to phenolphthalein. Fluorine was determined by Hawley's method (396), sodium as Na_2SO_4 after treatment with sulphuric acid.

	Found	Theoretic
Sodium	54.38 per cent.	54.74 per cent.
Fluorine	45.46 ,,	45.24 ,,

Sodium Silicofluoride. Natrium siliciofluoratum Schering-Kahlbaum was used. The degree of purity was determined according to Treadwell at 99.87 per cent. The analysis showed:

	Found	Theoretic
Sodium	24.40 per cent.	24.46 per cent.
Silicium	14.87 ,,	14.92 ,,
Fluorine	60.57 ,,	60.62 ,,

Mineral Cryolite. For most of the experimental examinations the material was a product obtained from the factory (No. 1), which was ground still more so that it passed screen cloth mesh No. 200. The composition of this product was:

Cryolite	99.85 per cent.
Quartz	0.09 ,,
Sulphides	traces

For a small part of the experiments a product was used with a particularly small grain size (No. 2), produced by elutriating the product No. 1. The grain size of the two cryolite products was determined by Andreasen's (17) sedimentation method.

Grain size	Cryolite No. 1	Cryolite No. 2
40—68 μ	32.8 per cent.	. .
20—40 μ	22.1 ,,	. .
10—20 μ	13.0 ,,	. .
5—10 μ	14.4 ,,	15 per cent.
< 5 μ	17.7 ,,	85 ,,

Synthetic Cryolite. A commercial product was used, a fine white powder, odourless and tasteless. The solution had a weak acid reaction. The analysis showed the following composition:

$$Al^{+++} \dotfill 13.9 \text{ per cent.}$$
$$Na^{+} \dotfill 28.2 \quad \text{,,}$$
$$F^{-} \dotfill 52.5 \quad \text{,,}$$
$$H_2O \ (110^{\circ}) \dotfill 0.7 \quad \text{,,}$$
$$F_2O_3 \dotfill 0.4 \quad \text{,,}$$
$$Ca^{+} \dotfill 0.6 \quad \text{,,}$$
$$Si^{++++} \dotfill 0.2 \quad \text{,,}$$
$$SO_4^{--} \dotfill 0.1 \quad \text{,,}$$
$$SiO_2 \ (amorph.) \dotfill 1.6 \quad \text{,,}$$
$$Fixed \ H_2O \ ca. \dotfill 2.0 \quad \text{,,}$$

Consequently the total quantity of Al, Na and F cannot be present as Na_3AlF_6; the quantity of Na and F corresponding to Si^{++++} is present as Na_2SiF_6.

PART III

INVESTIGATIONS INTO SPONTANEOUS
CRYOLITE POISONING

CRYOLITE AND ITS MANUFACTURE

1. Occurrence and Mining

Cryolite is a rare mineral of the composition Na_3AlF_6, found in workable quantities only at Ivigtut, in Southwest Greenland. There are smaller occurrences in the Urals and in Pikes Peak in Colorado, but they are commercially insignificant. The mineral was first mentioned in 1795 by Schumacher (718), but the Greenlanders knew of it before then: they are said to have used it for mixing with snuff. The first — but incomplete — analysis was published in 1799 by Abildgaard (1), the first correct one by Berzelius (67).

Cryolite means ice-stone ($\varkappa\varrho\acute{v}o\varsigma$, ice, frost, and $\lambda\acute{\iota}\theta o\varsigma$, stone). This name was given to the mineral by d'Andrada e Silva (16) on account of its appearance and fusibility. Giesecke (331) examined the deposit in 1806 and brought some tons of it home. However, it was only when Julius Thomsen was given a ten years' concession to use the method he invented for manufacturing the cryolite, that the mineral began to acquire the great practical importance which has since been maintained and expanded by men like Howitz, Weber, Hagemann, Vilh. Jørgensen and C. F. Jarl.

The cryolite occurrence at Ivigtut consists of a large collective deposit of great purity. The irregular mass, the principal component of which is white cryolite, contains varying quantities of quartz (SiO_2), siderite ($FeCO_3$), zincblende (ZnS), galena (PbS), chalcopyrite ($CuFeS_2$) and pyrite (FeS_2). Besides other minerals*) there are sporadic occurrences in the main deposit of a number of related fluorine compounds such as thomsenolite ($AlF_3 \cdot CaF_2 \cdot NaF \cdot H_2O$), pachnolite ($AlF_3 \cdot CaF_2 \cdot NaF \cdot H_2O$), hagemannite (blends of thomsenolite, iron compounds, etc.), cryolithionite ($2\ AlF_3 \cdot 3\ NaF \cdot 3\ LiF$), chiolite ($3\ AlF_3 \cdot 5\ NaF$) and fluorspar ($CaF_2$). One area, mostly consisting of quartz and microcline ($KAlSi_3O_8$) with small quantities of cryolite, ivigtite ($Al_3NaH_2\ (SiO_4)_3$) and other minerals is found outside the main occurrence, sometimes alternating with fluorspar areas; there is also a limited

*) Bøggild (88) mentions several other minerals found in the deposit, such as arsenopyrite, molybdenite, tinstone and columbite. The quantity of these minerals is extremely small in the raw cryolite and for that reason alone they are of no toxicological interest. The mineral *sericite*, which according to Jones' (447) theory plays a rôle in the pathogenesis of silicosis, has not been found with the cryolite at Ivigtut nor during the regular mineralogical examination of raw cryolite in Copenhagen.

occurrence of topaz $(Al_2(OH·F)_2SiO_4)$. The whole formation is separated from the surrounding gneiss by a cover of granite and granitic porphyry. Opinions have differed as to its origin, but there is no doubt that it is an eruptive mass, the result of the volcanic activity of former times (795).

The cryolite occurrence lies on the south side of Arsuk Fjord, directly out to the coast; it once extended up to the surface and is worked in an open quarry. At the deepest spot the quarry is about 60 metres below sea level; the greatest dimensions are given as 56×160 metres. The mass seems to increase in dimensions downwards. Quarrying proceeds for the most part by blasting, i.e. the workers suspended down the face of the quarry bore holes for the explosive with pneumatic drills (Fig. 11). When the charges are detonated the material falls to the bottom of the quarry, where it is loaded into tip-waggons by steam excavators and taken by elevators to the quay, where it is loaded loose into the ship. One method little used is the blasting of galleries and extracting the cryolite, making large holes (caves) in the mass itself. There is no actual sorting of the raw cryolite at Ivigtut, but as the cryolite content varies rather considerably in different parts of the quarry, in both a horizontal and a vertical direction, it is possible to ship whole cargoes separated in different qualities, for instance with cryolite contents of 80 and 95 per cent. Navigation to Ivigtut is only possible from April to November, and therefore quarrying is mainly carried on in summer; then every autumn most of the fifty to a hundred workers return home. Some frequently go back again.

The cryolite quarry belongs to the Danish State. *Kryolith Mine og Handels Selskabet A/S* (The Cryolite Mining and Trading Company Ltd.) was formed in 1865 and ever since has had a concession for quarrying and shipping cryolite from Ivigtut. The raw cryolite has only two buyers: *Øresund's chemiske Fabriker* (The Øresund Chemical Works), Copenhagen, and the *Pennsylvania Salt Manufacturing Company*, Philadelphia. The latter company has by contract the sole selling rights in U. S. A. and Canada, whereas the first-named company holds them for the remainder of the world. In the course of time the quantities of cryolite have been distributed in the proportions of about two-thirds to the Danish company and one-third to the American company. The Danish State receives a royalty per ton raw cryolite shipped from Greenland.

The annual quantity shipped varies a good deal, but on the whole it has been increasing. For the ten years ending with 1934 the annual average was 22,542 tons, with a minimum of 10,351 tons in 1933 and a maximum of 35,762 tons in 1930. Since extraction began in 1853 (regularly after 1859)

and up to 1934 inclusive the total quantity shipped has been about 750,000 tons, or on an average 10,000 tons a year. In the period 1900—1934 there were shipped 145,764 tons of cryolite to North America and 319,946 tons to Copenhagen*).

2. The Properties of Cryolite

Cryolite is an anhydrous double fluoride of sodium and aluminium with the formula Na_3AlF_6. The corresponding hypothetical acid is H_3AlF_6. Absolutely pure cryolite has the following composition corresponding to the formula:

Sodium..............	32.86 per cent.
Aluminium...........	12.84 per cent.
Fluorine............	54.30 per cent.

Thus more than half of cryolite is fluorine; the content is higher than in sodium fluoride and calcium fluoride, which contain about 45 and 49 per cent. fluorine respectively (see Table 1, page 2).

Cryolite is a colourless, white, semi-transparent mineral, though sometimes the colour may be reddish or black. The fragments produced by quarrying may be fairly pure, in which case they cleave readily on being struck, with planes of cleavage in three directions almost at right-angles to each other. Smaller pieces, that are mixed with other minerals, are irregular in appearance (Fig. 12). The mineral crystallizes monoclinically into cube-like crystals. With its slight hardness (2.5) its cleavability makes it very liable to form dust. The specific gravity is about 3. The average refractive index is 1.339, or only little higher than that of water, for which reason cryolite becomes as clear as ice and almost invisible when immersed in water. Cryolite fuses at about 1000°. When heated under the influence of steam it decomposes into hydrogen fluoride and sodium aluminate.

Cryolite is not very soluble; at 25° C. one litre of water dissolves 0.39 g. cryolite. The aqueous solution has a neutral reaction, so that there is no hydrolysis. When boiled with a solution of certain aluminium salts cryolite dissolves readily, forming aluminium double salts. Under the influence of a base, for

*) These figures and most of those in the following referring to the commercial and technical side of the cryolite industry, have been provided by *The Øresund Chemical Works*. A description of the cryolite occurrence at Ivigtut was given by Johnstrup (446), Ussing (812) and Baldauf (45). The method of extracting was described by Ball (47), Gordon (354) and Corp (176). The history of the cryolite industry itself has been treated in works by Julius Thomsen (795), S. M. Jørgensen (448), Halland (377) and Grünwald (369). The principal work is Jarl's (438), written on the occasion of *The Øresund Chemical Works'* 50th anniversary (1909).

instance sodium hydroxyde, cryolite decomposes forming sodium fluoride and sodium aluminates; on being treated with lime it forms sodium hydroxyde, calcium fluoride and calcium aluminates.

Cryolite is decomposed rather readily by a number of acids, including the strong mineral acids. Unpublished investigations by Buchwald seem to indicate that in the slightly hydrochloric, saturated cryolite solution a dissociation takes place according to the following system:

$$Na_3AlF_6 \rightleftarrows 3Na^+ + AlF_4^- + 2F^-$$
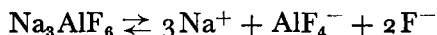
Accordingly, cryolite yields only one-third of its fluorine content, appearing in the solution partly in ionogenous form, partly as undissociated hydrogen fluorine, depending on the hydrogen-ion concentration which regulates the degree of dissociation of the fluoric acid. Cryolite's solubility increases with increasing hydrogen-ion concentration. At my request Buchwald has determined the solubility of the principal fluorine compounds in a solution of 0.5 per cent. hydrochloric acid at 25°. Compared with their solubility in water of the same temperature (Table 1) the result was as follows, expressed in g. per 100 c.c.

	0.5 per cent. Hydrochloric acid	Water
NaF	4.190	4.210
CaF_2, fluorspar	0.032	0.0017
Na_2SiF_6	0.942	0.759
Na_3AlF_6, cryolite......	0.270	0.039

Whereas the solubility of sodium fluoride and sodium fluosilicate is not altered much, that of cryolite and fluorspar in 0.5 per cent. hydrochloric acid is increased about 7 and 13 times respectively, compared with water; 100 c c. of 0.5 per cent. hydrochloric acid dissolves no less than 0.27 g. cryolite. It is to be assumed that this circumstance plays a great rôle in the absorption from the gastro-intestinal tract.

The *practical application of cryolite* is a result of various properties in the mineral. In the years 1859—1870 the cryolite treated in Copenhagen was used for producing crystal soda according to Julius Thomsen's method; the sodium content was freed by treating with lime under great heat. Useful by-products were obtained in the form of calcium fluoride and aluminium hydroxyde. Between 1870 and 1894 the soda factory was gradually beaten by competitors with new and cheaper methods. Round about 1870 cryolite began to be used for the manufacturing of opal glass, and a little later in the enamel industry. To a high degree cryolite possesses the ability of the fluorine compounds to act as a flux, i. e. facilitate the smelting of other minerals, at the same time acting as an opacifier. The latter property is a result of the
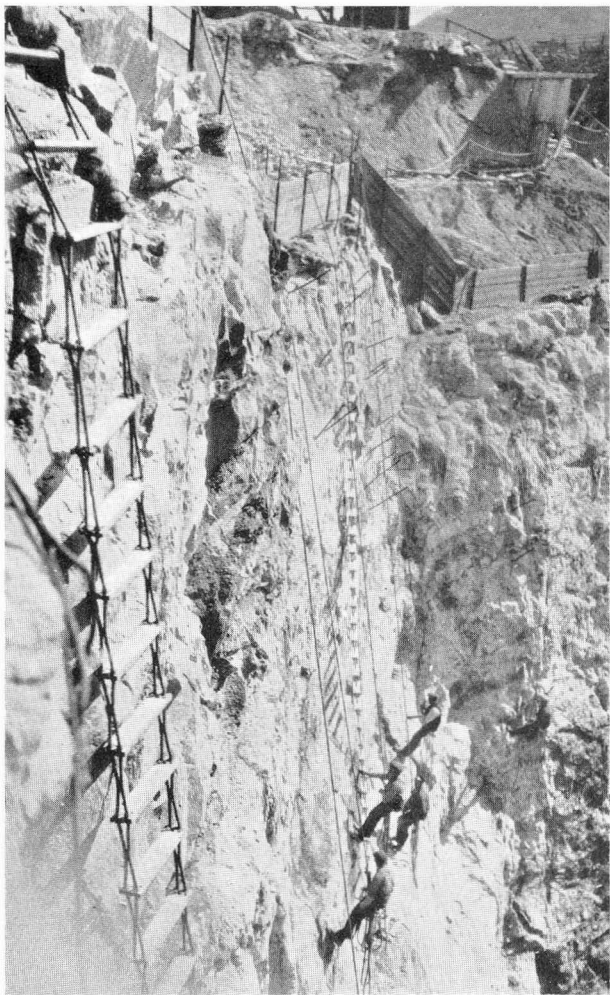
FIG. II. Mining for cryolite at Ivigtut, Greenland. Blasting in the open; drilling holes for explosive with pneumatic drills.
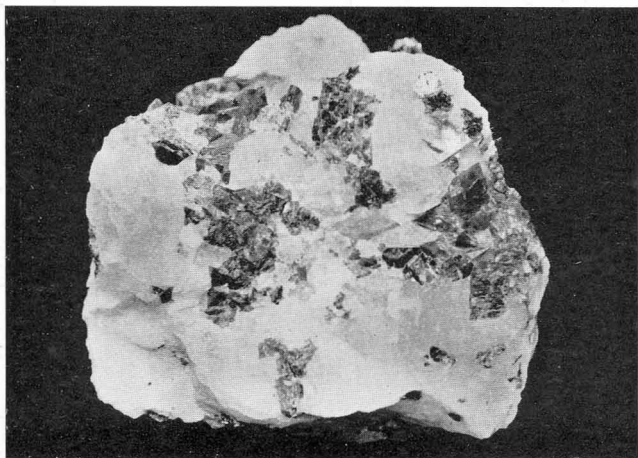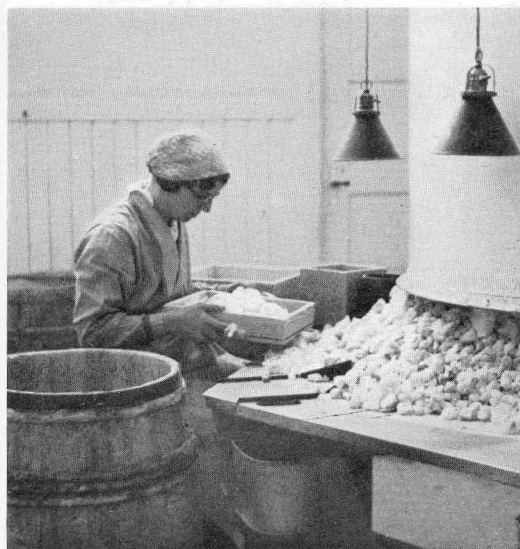
FIG. 12. Cryolite with impurities (siderite, quartz and galena).

FIG. 13. Raw cryolite store. Transporting material by wheelbarrow.

FIG. 14. Female workers hand-sorting small pieces of cryolite at the "picking machine" (table with conveyor belt).

(a) (b)

FIG. 15. (a) Hand-sorting larger pieces of cryolite. (b) Packing the finished product in sacks with a shovel.

fact that when cooling, fluorine separates out in the form of small crystals of sodium fluoride, causing a frequent reflection of the light in the otherwise clear glass body. As from about 1890 began the real industrial use of cryolite in the aluminium industry by means of the Hall-Héroult process, electrolysis of aluminium oxyde (Al_2O_3) in a bath of melted cryolite. The raw material proper is aluminium oxyde; cryolite plays the rôle as flux and electrolyte. During the past few years cryolite has come into favour as a dusting and spraying insecticide.

The percentual distribution of *The Øresund Chemical Works'* sales of purified cryolite varies a good deal from year to year. The following average figures are given for a long period of years (the last 25 years):

> To the aluminium industry .... 60 per cent.
> To the enamel industry .... 27 per cent.
> To the glass industry .... 10 per cent.
> For other purposes .... 3 per cent.

Spread over the same period the percentual distribution of sales to the different markets has been as follows: to Germany 22 per cent., to France 19 per cent., to England 14 per cent., to Norway 12 per cent., to Switzerland 9 per cent., and to the remainder of the 25 countries 24 per cent. Denmark herself uses 0.33 per cent. Thus the cryolite business is decidedly an export one. The price of cryolite varies round about £ 38 to £ 40 per ton f.o.b. Copenhagen.

3. Processes in Cryolite Manufacturing

The following contains an account of the manufacturing methods at *The Øresund Chemical Works*, with particular reference to circumstances that may be of interest hygienically.

When discharging in Copenhagen the cryolite is shovelled into tubs, lifted out of the holds by the ship's winches and emptied down chutes into large boxes on lorries. After arriving at the factory the boxes are lifted off the lorries by travelling cranes and emptied through hatchways in the roof down into the raw cryolite store (Fig. 13). The cryolite content of the raw material varies from 75 to 95 per cent. in each ship-load. The size varies from large pieces of 50—100 cm. right down to the finest particles of the size-order of 5 μ and less. Of siderite, the principal impurity, there may be as much as 15 to 20 per cent.; quartz occurs in quantities of from 1 to 5 per cent. Galena, zincblende, pyrite and chalcopyrite occur in only small quantities; the same applies to the fluorine minerals related to cryolite.

The manufacture of cryolite aims at removing the various accompanying minerals and grinding the purified cryolite down to a suitable fineness. It is placed on the market as aluminium quality with a cryolite content of about 99.7 per cent., 0.3 per cent. quartz and about 0.04 per cent. iron, and also as enamel quality with 99 per cent. cryolite, 1 per cent. quartz, about 0.04 per cent. iron, and a trace of other substances scarcely demonstrable by analysis. Both quali-

ties are ground to pass screen cloth mesh No. 100 (i. e. the maximum particle size is about 150 μ). In addition, various products are sold as insecticides with a smaller cryolite content (80—90 per cent.) but of a much finer grinding (grain size less than 20 μ). The manufacturing processes of cryolite are based upon the various physical properties of the cryolite itself and the accompanying minerals:—

(1) *Colour difference*, which as regards the large pieces permits of very thorough hand-sorting. Coarse hand-sorting proceeds in the raw cryolite store (Fig. 13), coarser and finer sorting in separate rooms on sorting belts, tables (Fig. 15) and by means of "picking machines" (Fig. 14). Female labour is mostly employed on this work.

(2) *Difference in magnetizability*, whereby the minerals are separated according to degree of magnetizability in magnetic machines of various designs (band-magnets, drum magnets, "Aushebe" magnets, lamellar-roller magnets). By this means the ferric minerals (siderite, hagemannite, zincblende, pyrite and chalcopyrite) are separated from the others.

(3) *Difference in specific gravity*, whereby the minerals in wet condition are separated according to specific gravity by means of jigs and sorting tables. The ores have a higher specific gravity than cryolite.

(4) *Difference in buoyancy*, i. e. the property of binding larger or smaller quantities of an added oil to the surface, whereafter this oil, under certain chemical and physical conditions, binds a certain quantity of air and can thereby form a layer of froth on the fluid suspension in which the process takes place (flotation).

(5) *Difference in hardness and cleavage*; separation takes place by selective grinding in edge-running mills and ball mills. The accompanying minerals present in this process usually are of greater hardness than cryolite.

For the purpose of bringing the cryolite into such a form that it is suitable for the different manufacturing requirements, or for the final treatment of the finished product, a number of special processes are put into the various phases of manufacturing:—

(1) *Crushing and grading*. Rough crushing is done by means of hand hammers and jaw-crushers, finer crushing under rollers. For the fine grades sieves alone are used, for the very finest sieves in conjunction with wind-separation.

(2) *Drying* on stoves after wet processes.

(3) *Conveyance* between departments, partly by falling through closed pipes or chutes, partly by mechanical transporting devices such as worm conveyors, bucket-elevators, Redler-chain transporters or conveyor belts, and partly by manual labour with shovel and wheel-barrow.

(4) *Dust removal*. By means of suction with exhausters an underpressure is created in rooms where various machines are installed. The dust is removed from the dusty air by being forced or sucked through dust collectors or dust filters. The dust collected is used in manufacturing.

(5) *Packing* the finished product mostly proceeds on automatic, dust-free packing machines, and otherwise into bags by means of shovels (Fig. 15).

It will appear from this summary that the manufacturing process is very complicated and comprises a technically highly developed mineral separation.

In most of the manufacturing processes the material is handled dry and thus favours the development of *dust*. Cryolite is a relatively soft material with a pronounced cleavage, and therefore every mechanical influence causes the formation of dust. The main dust-developing processes are crushing and grinding with grading, drying, and magnetic processes and all handling of fine-grained material (i. e. capable of passing screen cloth mesh No. 100). And finally, all conveyance of dry material, whether by means of wheel-barrow or by special conveyors, as both loading and unloading the conveyors cause dust to rise. It is especially the conveying conditions that result in *the dust-hazard being communicated more or less to all working rooms and thereby to all workers in the factory.*

When Flemming Møller and Gudjonsson's discovery made it plain that cryolite has toxic properties, the Inspectorate of Factories and Workshops demanded in 1932 that measures should be taken to prevent the mixing of dust with the atmosphere. At that time various measures had already been taken. In the period from 1923 to 1926 the grinding process and the magnetic process were partially made dustless, mills and magnetic machines being built into enclosed spaces where a certain underpressure was maintained. At the same time drying stoves and grading plants were fitted with dust-filters or suction-ventilators; masks were supplied to the workers and regular shifts were introduced in the particularly dusty processes. During the time it has taken to complete the present investigation (1932—1935) these endeavours have constantly been continued and conditions are perceptibly better.

The factory is an old one (erected 1859) and is relatively extensive in plan. The premises put up in more recent years are spacious as a whole, but several older rooms are small and their ceilings low. There has been a good deal of adding-on in the course of time, and to a great extent there is direct communication, without doors, between the various parts of the factory. As owing to the dust it is necessary to allow free access to the open air, it is liable to be cold and draughty. Having regard to the generally coarse character of the work the lighting conditions are fairly good. For transporting material the male workers use wheel-barrows, which formerly were loaded with 400 kilos, but now only 250 kilos. Older workers tend machines, etc., which does not make great demands on their physique. The women's work is mainly done in a sitting posture but requires considerable dexterity. The large number of machines cause a good deal of noise. Apart from the dust the state of cleanliness everywhere is good, great importance being attached to the product's having a clean white colour. The workers, especially the males, have spacious rooms in which to change their clothes, but have no bathing facilities. The male workers have a dining-room in the office building, far away from any dusty process. The women's dining-room, which also serves as a dressing-room, is next to the working rooms and therefore is not dust-free.*)

*) In 1936 a separate dust-free dressing-room was built for the women.

As a toxic substance is concerned, it is important to know the absolute quantity of dust in the air, and therefore in August-September 1932 a number of *gravimetric dust tests* were made with the apparatus described on page 111. The formation of dust varies a good deal in intensity in the factory premises, according to the nature of the process. Furthermore, the quantity of dust in the same room varies somewhat according to the working tempo, the nature of the material, atmospheric movement, etc. For these reasons the dust tests were made in two working rooms where, on account of the nature of the work and their situation, the quantity of dust was likely to be of average value and fairly constant, viz. the mill-house and the room where hand-sorting takes place (the so-called "picking room"). In the latter room all the female workers at the factory are employed. The dust-testing apparatus was placed at breast-height close by the work benches, etc. Finally, one or two tests were made in the enclosed room where a magnetic separator is installed. The machine is tended from the outside, and the machine-minder comes inside only occasionally in order to make adjustments; he is then wearing a mask.

The results of these tests are given in Table 17, which shows that the *dust content lies at about 30—40 mg. per cubic metre of air.* According to a rough estimate the dust content in the other working places in the factory fluctuates round about that figure. At some places it may be higher, for instance where fine-grained cryolite is handled and in the enclosed spaces around machinery (measured up to 994 mg. per cbm.). Working periods under such conditions

TABLE 17.

Gravimetric Determination of Dust Content in the Air at Various Working Places.

Premises	Date of test	Air passed through apparatus	Dust content per cbm. air
		cbm.	mg.
Grinding room ("mill-house")	$^9/_8$ 32	7.46	32
	$^{22}/_8$ 32	2.16	36
	$^{24}/_8$ 32	2.48	48
	$^{26}/_8$ 32	4.72	35
Hand-sorting room ("picking room")	$^{30}/_8$ 32	2.20	22
	$^{31}/_8$ 32	1.56	24
	$^1/_9$ 32	1.04	45
	$^2/_9$ 32	1.70	33
Space around enclosed machine-separator ("magnet house")	$^{26}/_8$ 32	0.79	994
	$^{30}/_8$ 32	0.61	815

will usually be of short duration and the worker will be masked. At other work there is much less dust, for instance in the raw cryolite store, when transporting in the open, in connection with the wet processes, etc. In former times the dust-content has been higher, especially prior to 1923—24 when the proprietors began to enclose the machinery.

For the purpose of examining the *composition of the dust*, samples of dust from horizontal surfaces at different heights were taken in 12 different working rooms. An analysis made by the factory laboratory showed that the average quartz content was 1.42 per cent., varying between 0.36 and 2.36 per cent. The remainder was practically all cryolite, as other components (sulphides, siderite, topaz, fluorspar etc.) were present in only very small quantities (on

TABLE 18.

Grain Size in Dust Samples from Factory.

Particle diameter	Dust from *Mill House* (97.9 % cryolite, 1 % quartz)	Dust from *Hand-sorting room* (96.2 % cryolite, 1.8 % quartz)	Finished cryolite product, aluminium quality (99.7 % cryolite, 0.3 % quartz)
μ	%	%	%
> 60	0.1	0.1	32.5
40—60	0.3	0.4	15.0
20—40	2.3	3.2	22.2
10—20	12.9	13.7	13.3
5—10	31.0	32.6	6.8
< 5	53.4	50.0	10.2

an average 1.99 per cent.). The cryolite content of the dust was 97.0 per cent. on an average, varying from 94.17 to 99.04 per cent. In dust from the two rooms where the dust-content of the air was determined, the grain size was examined according to Andreasen's (17) sedimentation method. The result is shown in Table 18, which for comparison includes the grain size in a sample of the factory's finished cryolite product (aluminium quality). It proved that the grain size in the dust was very small, half or more than half being lower than 5 μ in diameter. Of the finished product only about 10 per cent. was of similar size. The small size of the particles is of great importance in relation to the toxic effect of the dust. Its ability to make its way well down into the air-passage must also be regarded as considerable. Furthermore, it is assumable that the dust floating in the air has a smaller average particle size than dust collected from horizontal surfaces.

CHAPTER XII

NUMBER AND EMPLOYMENT-PERIOD OF WORKERS

1. Length of Employment-Period

In the course of the years the factory has employed a varying number of workers. In former times (1900—1916), when the manufacturing processes comprised more hand-sorting, up to 400 women were employed. In the last 10—15 years the average of workers employed has been 100—150, with about equal numbers of men and women. The number of workers seems to be declining, in spite of unchanged or increased output, due to the constantly decreasing use of hand-sorting.

For the purpose of gaining an idea of the subjective disadvantage, or perhaps disease risk, connected with the work, an enquiry has been made*) as to how long the workers discharged (or died) in a certain period had worked in the factory (Table 19). The results may only be applied with caution, as the period of employment is also dependent on other factors than the character of the work and the working conditions on the whole, viz. mainly the factory's possibilities of employment at the given moment and the prevailing unemployment. As a working place the factory has both advantages and drawbacks. It stands on the outskirts of a densely built-up working-class quarter. The pay is relatively good, partly based on piece-work. The working week consists of 48 hours. For a number of years the workers have had a week's summer holiday with pay, and with every form of illness about one-fourth of the wage in sick benefit for a maximum of 13 weeks. On discharge, older, deserving workers receive a small pension. The drawbacks are, apart from the toxic effect of the cryolite, the generally laborious character of the work and the almost omnipresent dust. Though the factory has considerable stocks of finished products, the state of the markets causes fluctuation in production and consequently in the degree of employment. The prevailing unemployment, especially during

*) The particulars in this and the following section regarding number, period of employment and morbidity of workers are based upon the factory's books, which have been placed at my disposal.

TABLE 19.

Employment Period of Discharged Male and Female Cryolite Workers.

Period of employment	No. discharged male workers in 13 years (1921—1933)			No. discharged female workers in 9 years (1925—1933)		
	Total	Unbroken employment	Broken periods	Total	Unbroken employment	Broken periods
1 day......................	1	1	..	6	6	..
2—7 days	7	7	..	8	8	..
8 days —under 1 month	15	15	..	25	25	..
1 month — „ 3 months....	19	17	2	38	37	1
3 months— „ 6 „	25	24	1	30	25	5
6 „ — „ 1 year	29	24	5	19	9	10
1 year — „ 2 years......	19	10	9	29	15	14
2 years — „ 5 „	13	8	5	25	9	16
5 „ — „ 10 „	4	3	1	12	6	6
10 „ — „ 20 „	4	3	1	4	3	1
20 „ or more.............	6	6	..	2	2	..
Total...	142	118	24	198	145	53

the past few years, may, however, on the other hand have the effect that the workers are reluctant to leave a job, even if it is an unsatisfactory one.

During the past ten years for which it has been possible to obtain information, a certain number of the workers have only been employed a short time; it is possible that to a certain degree this is due to the character of the work. In the period comprised by Table 19, 23 men (16.2 per cent.) and 39 women (19.6 per cent.) worked for less than a month. In both groups are persons who were only one or few days at work and have not since been taken on again. It seems probable that for these workers it may just as well have been discomfort at the work as unfitness for it. No doubt the work makes considerable demands on the physique, but otherwise it is not especially exacting for the great majority of the workers. The relatively large number of re-engagements in both the male and the female group (16.9 and 26.8 per cent.) on the other hand indicates that the drawbacks of the work are not deterringly great. Similar importance may be attached to the circumstance that many of the former and present workers are related to one another. Though most of the workers in the period have worked for less than two years, a number have been employed for much longer: sixteen, of both sexes (4.7 per cent.) for ten years or more, generally uninterruptedly. As will be seen later, the average period

of employment for the persons working at the time of this investigation was much longer (10 years). Although suitable comparative material is lacking, it would seem to appear from the statistics, however, that the work is connected with certain drawbacks, the effect of which is that the average period of employment is rather short, but that the injurious effect is not so considerable that it prevents employment over a long stretch of years.

2. Extent of Investigation

The present investigation concerning the workers at the factory was made mostly in the latter half of 1933. In that period the factory had 69 hands in employment; none were discharged or taken on. The investigation was voluntary, but it comprised all the workers except one, who declined to take any part in it. Of the 68 workers examined, 47 were males and 21 females; on July 1st, 1933 their age distribution and length of employment were as shown in Tables 20 and 21. No worker was under 20 years of age. Most of

TABLE 20.

Age Distribution of Examined Cryolite Workers.

Age	No. of males	No. of females	No. in all
20—29 years	5	6	11
30—39 „	23	7	30
40—49 „	10	1	11
50—59 „	5	6	11
60—69 „	4	1	5
Total...	47	21	68

the men were between 30 and 50; almost two-thirds of the women were between 20 and 40 and one-third between 50 and 60. In many cases the length of employment was considerable, on an average 10 years; 21 workers (30.9 per cent.) had worked there for ten years or more, 5 workers (7.4 per cent.) for 25 years or more. This picture of the length of employment is much more favourable than that of conditions considered over a longer period of years (Table 19). Probably the cause of this is that the number of hands at the factory has gone down in the course of the last few years and that on principle the hands discharged were those who had been employed the shortest time. Still, there is no doubt that some selection is made, whereby workers who tolerate the work best remain longest at the factory.

TABLE 21.

Period of Employment of Examined Cryolite Workers.

Period of employment	Males			Females			Both sexes		
	Un-broken em-ploy-ment	Broken em-ploy-ment	Total	Un-broken em-ploy-ment	Broken em-ploy-ment	Total	Un-broken em-ploy-ment	Broken em-ploy-ment	Total
3—under 5 years ...	10	1	11	2	2	4	12	3	15
5— „ 10 „ ...	11	11	22	8	2	10	19	13	32
10— „ 15 „ ...	6	1	7	0	0	0	6	1	7
15— „ 20 „ ...	1	2	3	1	1	2	2	3	5
20— „ 25 „ ...	1	0	1	1	2	3	2	2	4
25— „ 30 „ ...	2	0	2	1	0	1	3	0	3
30— „ 40 „ ...	0	1	1	1	0	1	1	1	2
Total...	31	16	47	14	7	21	45	23	68

The clinical examination was made at the factory during working hours in a room placed at my disposal for the purpose. The Röntgen examination was made at the Rigshospital's Röntgen Dep't. The material from the earlier investigation, made by Flemming Møller and Gudjonsson (591), has been at my disposal. For practical reasons it was possible only to make examinations not requiring much time or complicated apparatus. As a rule two or three workers were examined every day in the hours from 9 to 12 a. m.; the blood examinations were made on the afternoon of the same day. Taking them all round the workers were very willing to be examined. There is no reason for assuming that they suppressed anything, for they were expressly informed at a mass meeting before the investigation was commenced and afterwards individually, that the information secured about each person would be with-held from the knowledge of the management.

The investigation comprised the compiling of the medical history and an objective examination. The following system was followed.

Medical History.

(1) *Occupations.* The subject was asked as to former employment with a view to ascertaining whether the physical findings could have any relation to former unhealthy work. Regarding present occupation particulars were taken of the period of employment, nature of the work, and quantity of dust at the working place. The latter particulars were checked by means of the company's books and own observations.
(2) *Morbidity prior to employment* at the factory, particular weight being attached to conditions that might help in appraising the morbidity after entering the factory.

(3) *Morbidity after employment.* Here the aim was to obtain a picture of the condition of the subject throughout the whole period of employment at the factory, not merely status præsens. After the worker had made a voluntary statement he was asked systematically as to certain symptoms which with more or less probability might be connected with the work. Particulars were also taken of the cases of sickness that had involved absence from work, and these particulars were supplemented and checked through enquiries at the sick-clubs.

Physical Examination.

(1) Judgment of the *general condition*; height and weight noted.
(2) *General medical examination*, with particular reference to teeth, bones and lungs.
(3) Examination of *blood*: hæmoglobin percentage; number of erythrocytes and leucocytes; differential count; bleeding time and coagulation time; sedimentation rate of erythrocytes and their resistance to hypotonic solutions.
(4) Examination of *urine* for albumin and sugar; microscopy of discharged urine.
(5) *Röntgen* examination of lungs, pelvis and columna lumbalis; other bones and the teeth were also X-rayed on some workers.
(6) Certain supplementary examinations on some workers: Serum calcium, fluorine content of teeth and urine, etc.

On account of the relatively large number of workers it was not possible to make the complete examination on them all. They were all questioned and subjected to a general medical examination. Blood examinations were made to an extent that will appear from the discussion of the results. When it was found that the röntgenological bone and lung changes had not altered since Flemming Møller and Gudjonsson's examination (November 1931), it was considered sufficient to re-photograph only some of the workers previously X-rayed. All those who had not been examined before were X-rayed, so that I had pictures of thorax, pelvis and vertebral column of all workers. In addition to the factory hands Röntgen pictures were made of twelve of the *male office and other staff*, who are only exposed to dust now and then.

With the assistance of the factory's books a search was also made for *former workers*, and it was possible to get in touch with 131 people, 69 men and 62 women, who had worked at the factory for at least six months. Of these, 95 sent in answers to a question-form containing the following questions; the remainder were questioned by means of personal calls. They were informed that the particulars would be considered as confidential and would only be communicated to the doctor.

(1) How long were you employed at *The Øresund Chemical Works?*
(2) Did the dust trouble you?
(3) Did you have nausea, vomiting, lack of appetite, irregular motions, tiredness, headache or cough?
(4) Did you feel other discomforts while working at the factory?
(5) State the name of your sick-club and your number.

A small number of these former workers were X-rayed, those who had been at the factory at least four years, 32 in all, 15 men and 17 women. Enquiries were made through the sick-clubs as to the morbidity of present and past workers. Particulars were received of 141 persons, 83 men and 58 women. Finally, there was an opportunity of questioning and X-raying 9 male workers from the cryolite mine at Ivigtut, Greenland.

For the sake of simplicity all those examined were given a serial number which is used in this work as a discretionary measure when referring to matters relating to the various individuals. A detailed report on the examination of the present workers will be handed to the Inspectorate of Factories and Workshops.

Nos.   1— 68: Present workers at *The Øresund Chemical Works.*

Nos. 69—199: Former workers at same factory.

Nos. 200—215: Former workers, now dead.

Nos. 216—277: Present office and other staff.

Nos. 228—236: Workers at the cryolite mine at Ivigtut, Greenland.

COMPLAINTS OF WORKERS

The *occupational history* showed that 9 male and 2 female workers had previously been employed on work of a kind that is generally regarded as unhealthy. In only three of these cases, however, was it considered necessary to bear this in mind when estimating the injurious effects of working with cryolite. A man had for fourteen or fifteen successive seasons worked in the cryolite mine at Ivigtut; two men had previously worked at a porcelain factory for 12 and 3 years respectively; according to Gudjonsson's (372) investigations the risk of silicosis there is considerable. The other cases had reference to occupations that can have had no significance for the present investigation (working with lead, file-making, rag-sorting, cigar-sorting, foundry-work, carpet beating).

All the workers complained of *dust*, but in varying quantities. On the basis of the workers' statements, own observations, and information from the factory management, endeavours were made to divide the workers into three groups according to their exposure to dust: slight, moderate and great. In this grouping consideration was given to the entire period of employment at the factory. The group with slight exposure comprised 8 male workers, whose work took them a good deal into the open air. The group "moderately exposed" comprised all the female workers (21) and 28 males, i. e. much the greater part of the workers. Those under "great exposure" numbered 11 males, most of them men who worked constantly at one place.

When compiling the histories a record was made of a large number of *complaints* of both transitory and more chronic character. As already stated, importance was attached to getting a picture of the condition during the whole period of employment and not of status præsens alone, which is liable to be affected by casual fluctuations in the state of health, adaptation to changed conditions, etc. Symptoms to be recorded had to be of a certain intensity or duration, so that accidental feelings and the like were disregarded. Naturally a certain amount of error is inherent in personal decisions of this kind. In such a method the numerical statement of symptom frequency leaves a summary,

TABLE 22.

Frequency of Various Complaints by Cryolite Workers.

	No. males	No. females	Both sexes	Per cent. of all workers examined (68)
Lack of appetite	31	7	38	55.9
Nausea	27	9	36	52.9
Shortness of breath	20	9	29	42.7
Constipation	12	7	19	27.9
Localized rheumatic pains	14	5	19	27.9
Susceptibility to colds	9	4	13	19.1
Vomiting	7	4	11	16.2
Cough	8	2	10	14.7
Tiredness	7	2	9	13.2
Feeling of stiffness in body	6	2	8	11.8
Rash on skin	8	0	8	11.8
Indisposition	6	1	7	10.3
Palpitation	4	3	7	10.3
Tendency to diarrhoea	5	1	6	8.8
Indefinite or alternating rheumatic pains	4	1	5	7.4
Drowsiness	3	0	3	4.4
Expectoration	2	1	3	4.4
Clogging of the nose	2	1	3	4.4
Dry throat	2	1	3	4.4
Headache	1	1	2	2.9
Salivation	1	0	1	1.5
Thirst*)	0	1	1	1.5
Giddiness	0	1	1	1.5

*) One female worker suffering from diabetes is not included in this column.

massive impression that does not correspond to the discomforts present at the daily work. Only two of the workers, one male and one female, denied ever having felt discomfort from the work or having noticed morbid symptoms at all. The others indicated a whole conglomeration of symptoms which are recorded in Table 22 according to frequency. The commonest complaints were of various dyspeptic phenomena, shortness of breath and rheumatic attacks. In Table 23 the symptoms as far as possible are grouped according to systems of organs, and simultaneously it is shown how many workers had or previously had had one or more symptoms belonging to the same group. On the whole, men and women complained of the same symptoms.

Acute or Subacute Gastric Symptoms. Arranged according to frequency this group comprises the symptoms: loss of appetite, nausea, cardialgia and vomiting.

TABLE 23.

Frequency of Complaints Arranged in Groups.

	No. men	No. women	Total	Per cent. of all workers examined (68)
Gastric symptoms, mainly acute (lack of appetite, cardialgia, nausea, vomiting)	42	13	55	80.9
Intestinal symptoms, mainly chronic (disposition to diarrhoea, constipation)	15	8	23	33.8
Symptoms from circulation or respiration (shortness of breath, palpitation, cough, expectoration)	23	12	35	51.5
Symptoms from bones, joints, and muscles (feeling of stiffness, indefinite or localized rheumatic pains)	18	6	24	35.3
Symptoms of nervous character (tiredness, sleepiness, indisposition, headache, giddiness)......................	12	3	15	22.1
Skin symptoms (rash)	8	0	8	11.8

No fewer than 80.9 per cent. of all workers, 42 men and 13 women, complained of symptoms of this nature. As far as three of the symptoms are concerned (loss of appetite, nausea, vomiting) the connection with the work was distinct. The symptoms are transitory, develop after working for some time in dusty atmosphere and disappear again after a short period in the open air, the poor appetite being the last to go. It was often stated that the appetite for the first two meals of the day (before commencing work and after $2^1/_2$ hours' work) was decidedly better than that for the later meals. It is of great significance, however, that the workers do not experience much discomfort from these symptoms; they distinctly become inured. The rule is that for a period of some few days to some few weeks after starting at the factory the worker suffers from these acute gastric attacks, whereafter they disappear, especially the nausea and vomiting. Thereafter some of the workers tolerate the dust without observing the symptoms; others will still have transitory symptoms after holidays, or if the dust quantity temporarily becomes especially high. Cardialgia is less distinctly connected with working in the dust. Sometimes the aforesaid gastric symptoms are accompanied by a slight, passing pressure or pain in cardia, at other times it is a more chronic symptom of irregular occurrence, perhaps aggravated when working in dust.

Intestinal Symptoms. Of these 23 workers complained, representing 33.8 per cent. Six individuals complained of a certain, not very pronounced propensity for diarrhoea which more or less definitely was connected with working in dust. A total of 7 workers complained of constipation, either continuous constipation or constipation and diarrhoea alternately; in most cases the symptoms had arisen after starting at the factory and the dust was regarded as the cause. Continuous chronic symptoms from the gastro-intestinal tract were complained of by 22 workers (12 men and 10 women). They were mostly constipation with or without symptoms from the stomach, more rarely chronic banal gastric dyspepsia. Judging from the clinical picture there was no reason to suspect the presence of an ulcer in any of the cases. Of the 22 persons with chronic trouble 9 had had symptoms from the gastro-intestinal tract prior to coming to the factory.

Symptoms from Circulation and Respiration. The symptoms in this group, arranged in order of frequency, comprise dyspnoea on action, cough, palpitation and expectoration. They were complained of by 23 men and 12 women, or in all 51.5 per cent. of all workers. The dyspnoea, the most frequent symptom by far (29 workers), was of a varying, mostly moderate degree. It was common to hear that respiration difficulty increased when working in thick dust, but there were no asthmatic attacks. There were no cases of dyspnoea while resting. Coughing was complained of by 10 persons, either as a tendency to cough, especially in winter, or as a cough brought on by dust. During work 7 workers had palpitation occasionally; only 3 complained of expectoration.

Symptoms from Bones, Joints, and Muscles. Rather more than one-third (35.3 per cent.) of all workers complained of phenomena which with more or less justification may be placed in connection with affections in bones, joints or muscles, viz. localized or indefinite pains of a rheumatic character and a feeling of stiffness in the body. The localized rheumatic pains (19 workers in all) were of banal kind. In 9 workers it was the back or loins, principally in the form of lumbago; three times it was symptoms resembling sciatica. Pains in divers extremities were complained of by 5 workers; two localized the pains to the anterior surface of tibia. Rheumatic-like pains of indefinite or varying localization were complained of by 5 workers, and 8, especially elderly, men had a feeling of bodily stiffness.

Symptoms of Nervous Character. These were symptoms of rather indeterminable origin, viz. headache, tiredness, giddiness, sleepiness and indisposition.

Twelve male and only three female workers were liable to these attacks; tiredness and indisposition were far the most frequent symptoms in this group.

Skin Symptoms. Referred to by 8 men, who complained that at intervals they had rash on breast and back when working in dust, especially in summer.

Other Symptoms. This group comprises the rest of the complaints, which are very varying in character. Thirteen workers stated they were liable to complaints arising from colds and attributed this to cold, draughts and heavy work. In three individuals working in dust caused dryness in the throat, in other three clogging of the nose. Only one woman complained of extraordinary thirst. Whereas it was generally stated that working in dust gave rise to spitting, only one man described phenomena that were characterizable as salivation proper. None of the workers had a disposition for bleeding from the skin or mucous membranes or difficulty in stopping accidental bleedings. Among the women there was no case of any serious menstruation anomaly. The men were asked about libido but there was nothing abnormal. To supplement the information regarding the functioning of sexual organs the married workers were asked about the number of their children. For 55 married persons the average number of children was 1.84, of which 0.78 born in the period after starting at the factory. Among the 25 workers who had had one or more children while working at the factory the average number of children was 1.60. Straitened circumstances were usually put down as the cause of childlessness. Morbidity among workmen, judged according to the information from the sick-clubs, will be dealt with in Chapter XVII.

EXAMINATION OF OSSEOUS SYSTEM

In the course of the physical examination various pathological changes were observed, especially in the osseous system. It will therefore be practical to deal with these bone changes first and leave the other results of the physical examination till the next chapter. The bone changes are very characteristic and form the basis for a division of the disease into phases. The examination of bones and joints was partly clinical, partly röntgenological. As the bone changes can be recognized almost solely on the Röntgen film, that part of the examination will be dealt with first.

1. Röntgen Examination

A radiograph was taken of each worker's thorax, pelvis and columna lumbalis from the front and from the side. Other pictures were taken of a considerable number of workers (cranium, upper part of columna, extremities). Some of the radiographs are from the first examination in the winter of 1931. The re-photographing of several workers revealed no definite changes from the first examination. The period between the two was about two years. In this manner columna-pelvis of 12 workers were X-rayed twice and thorax of 45 workers twice.

From the X-ray picture it is possible to differentiate between three phases of the same osteosclerotic process, each overlapping the next without any sharp boundary. In all essentials the following description agrees with that given by Flemming Møller and Gudjonsson (591).

1st Phase.

The changes are observed in pelvis and columna, but are doubtful or absent elsewhere. The density of the bone is very little increased. The trabeculæ are rough, blurred and give deep shadows; this is often distinct in corpora of the lower lumbar vertebræ. The bone has both a more prominent and a more blurred structure at the same time, which is very characteristic when the operator is familiar with the phenomenon, but otherwise is easily

overlooked (Fig. 17). The bone contour is sharp. In some few cases there is incipient osteophyte formation on the edge of corpora of the lumbar vertebræ. The boundary against the normal bone structure is not sharp, and in an isolated case it will be difficult to decide whether the change is a normal variation or a pathological finding. In serial examinations, however, the difference is distinct.

2nd Phase.

The bone structure is blurred, the trabeculæ merging together. Over often rather large areas the bone gives a diffuse, structureless shadow. At first glance the negative seems to have been underexposed, but it is difficult or impossible to distinguish details even when the time of exposure or the tension is increased. The bone contours are uneven and somewhat blurred. The changes are most distinct in pelvis (Fig. 18) and columna (Fig. 20), but also in the ribs (Fig. 27) and in the bones of the extremities, even if there they are less pronounced and often resemble the changes described as 1st phase. In the extremity bones the medullary cavity is usually moderately narrowed. In columna there are incipient or moderate ligament calcifications, especially caudally; they appear in the form of pointed, beaked osteophytes with an inclination to form bridges between the vertebral bodies or as a diffuse blur lying posteriorly to corpora. In some cases (particularly among the younger individuals) the ligament calcifications are absent, though the bone structure is so changed that the case must be placed to the 2nd phase.

3rd Phase.

On the negative the bone presents itself as a more or less diffuse marble-white shadow, in which the details cannot be distinguished. Changes are observable in all bones but are still greatest centrally, being most conspicuous in bones with cancellous structure, pelvis (Fig. 19), columna (Fig. 21—24), ribs and sternum (Fig. 28). In the bones of the extremities there are changes in the structure that recall the 2nd phase, or fairly often only the 1st phase. Among the worst affected individuals changes are to be seen in the cranium, usually rather moderate in intensity (Fig. 26). Theca is denser and gives a deeper shadow than normally, sutures and vessel grooves are indistinct, and the same applies to impressiones digitatæ. The air-sinuses in the cranial bones are not diminished in size. The region around sella turcica gives a deep shadow but is normal as to contour. No distinct thickening of processus clinoidei was observed.

The bone contours almost everywhere are woolly and blurred. Very often the bones or certain parts of them have a rough and slightly enlarged ap-

pearance, but otherwise the shape is not altered. On the extremity bones are irregular periostal thicknesses, some flat, others more rough (Fig. 29). The interosseous membrane in antibrachium and crus are calcified to a greater or smaller extent. The normal cristæ corresponding to the muscle attachments are increased in size and resemble exostoses. On costæ, especially vertebrally, there is calcification of the insertions of the intercostal muscles, which appear like "rime frost needles" or irregular shadows to both sides (Fig. 24). There are considerable ligament calcifications, varying up to very severe, in columna, particularly in pars lumbalis and thoracalis. In columna cervicalis these changes are less pronounced, but distinct (Fig. 25). The ligament calcifications appear partly in the form of bridge-like connections with fairly sharp borders between corpora, partly as a diffuse opacity and density round about the intervertebral and costovertebral articulations. Processus transversi and spinosi are rough and thickened; between the latter are considerable ligament calcifications with irregular borders. In the pelvis, ligamentum sacrotuberosum in sometimes calcified (Fig. 19). The intensity of the calcification and the diffuse density of the bone usually are in conformity with each other; in some elderly workers, however, there is a density of the osseous tissue which does not attain to the extreme degree, side by side with very pronounced ligament calcification.

In the extremity bones, both short and long, the medullary cavity is diminished in width and the boundary against compacta is less sharp than normally. The width of compacta is correspondingly increased. In tibia and femur the width of the medullary cavity sometimes decreases to half the normal, in metacarpals and phalanges there is sometimes a partial occlusion of the cavity (Fig. 30).

The interarticular spaces are of normal width everywhere and the contours sharp. Limited calcifications of the capsule in hip and knee joints are seen. The intervertebral disks are not visibly changed and the calcification of the costal cartilage does not exceed the normal.

If the result of the Röntgen examination is to be summarized, the first thing to emphasize is the fact that the affection is a system-disease, for it attacks all bones, though it has a predilection for certain places. The pathological process may be characterized as a diffuse osteosclerosis, in which the pathological formation of bone starts both in periosteum and in endosteum. Compacta densifies and thickens; the spongiosa trabeculæ thicken and fuse together. The medullary cavity decreases in diameter. There is a considerable new-formation of bone from periosteum, and ligaments that normally do not calcify or only in advanced age undergo a considerable degree of calcification. All signs of bone destruction are absent from the picture.

The characteristic changes of the osseous system were frequently found. *Of the 68 workers 57, or 83,8 per cent., had bone changes* which were assignable to one of the aforesaid three phases*). Their actual distribution appears from Table 24. Taking them all round, men and women were attacked equally severely. In 11 workers (16.2 per cent.), 9 men and 2 women, conditions were normal. About the same number of cases could be placed to 1st and 2nd phases, 38.2 and 35.3 per cent. respectively. Only 7 workers had changes of the 3rd phase, and six of them were men.

The degree of the osteosclerosis was on the whole connected with the period of employment; but there were quite a number of exceptions (Fig. 32). The average period of occupation for the group without bone changes was 8 years, for the 1st phase 9.3 years and for the 2nd phase 9.7 years; in other words, it was fairly uniform. On the other hand, workers with bone changes of the 3rd phase had been employed on an average 21.1 years. It is in conformity with this fact that the average age at the time of the investigation was much the highest for workers in the 3rd phase (58.2 years), but varied only little within the other groups (36—40.5 years). One point of practical importance is the shortest period of employment within each group. Cases of the 1st phase were observed after $2^5/_{12}$ years work, of the 2nd phase after $4^{10}/_{12}$ years, of the 3rd phase after $11^2/_{12}$ years. On the other hand the changes were slight in a certain small number of the workers, even after long employment; changes of the 1st phase were observed in persons who had been employed 18, 24 and

TABLE 24.

Frequency of Osteosclerosis and its Relation to Period of Employment, Exposure to Dust, etc.

Osteosclerosis	No. of Workers		Total	Per cent. of total workers	Average age at examination	Employment period in years			Exposure to dust		
	Male	Female				Average	Shortest	Longest	Slight	Moderate	Great
None............	9	2	11	16.2	36	8.0	2.8	24	2	9	0
1st phase	17	9	26	38.2	36.8	9.3	2.4	33.8	5	19	2
2nd phase	15	9	24	35.3	40.5	9.7	4.8	28.9	1	18	5
3rd phase........	6	1	7	10.3	58.2	21.1	11.2	31.2	0	3	4

*) At the first examination Flemming Møller and Gudjonsson found 30 cases of osteosclerosis among 78 workers. The increased frequency found now is due to the fact that some workers were not completely examined on the first occasion, and also that the demarcation between the normal state and the incipient osteosclerosis on the plate is approximate only.

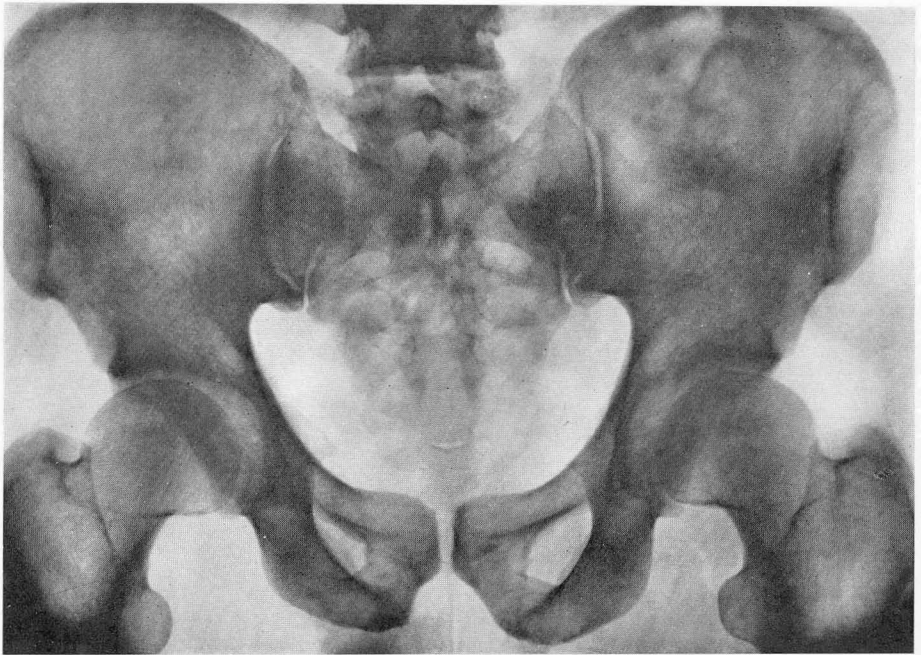FIG. 16. Röntgen picture of normal pelvis.

FIG. 17. Röntgen picture of pelvis, showing 1st phase of osteosclerosis: coarse and blurred trabeculæ, slight diffuse increase of density. Male cryolite worker (No. 1), 38 years old, employed 7 years.
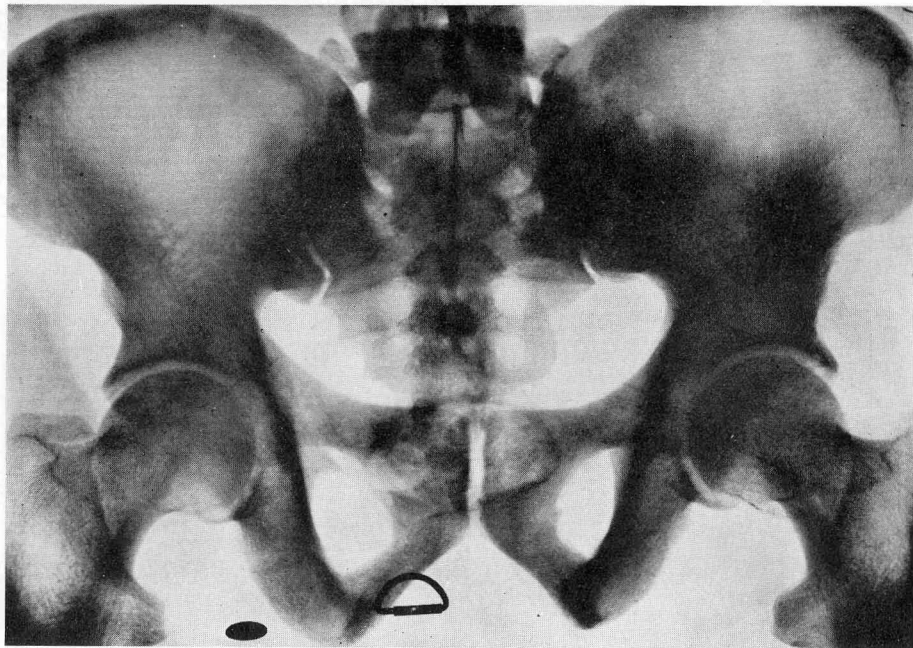
FIG. 18. Röntgen picture of pelvis, taken about 1 year after leaving factory. Osteosclerosis of slight 2nd phase: increased density, blurred contours. Male cryolite worker (No. 200), 51 years old, employed 9 years.

FIG. 19. Röntgen picture of pelvis. Osteosclerosis of 3rd phase: greatly increased density, irregular and blurred contours, ligament calcifications. Male cryolite worker (No. 60), 55 years old, employed 25 years.
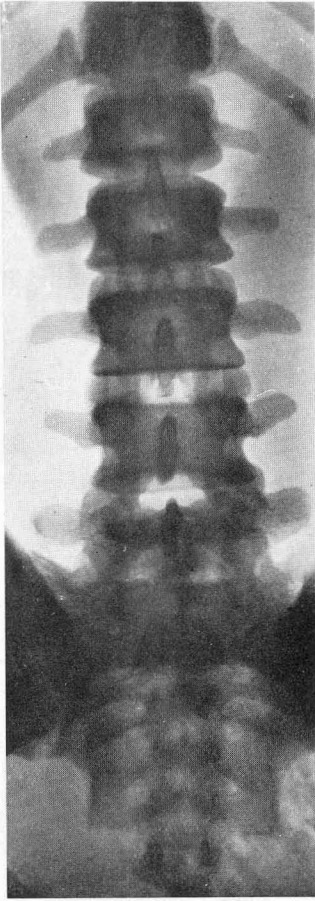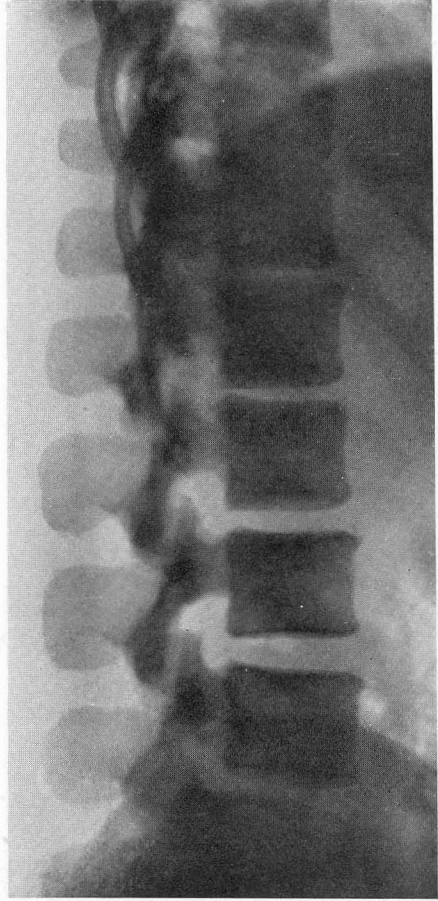
(a)   (b)

FIG. 20. Röntgen picture of columna lumbalis, (a) anterior view, (b) lateral view. Osteosclerosis of 2nd phase, no great ligament calcifications. Female cryolite worker (No. 58), 30 years old, employed 7 years.
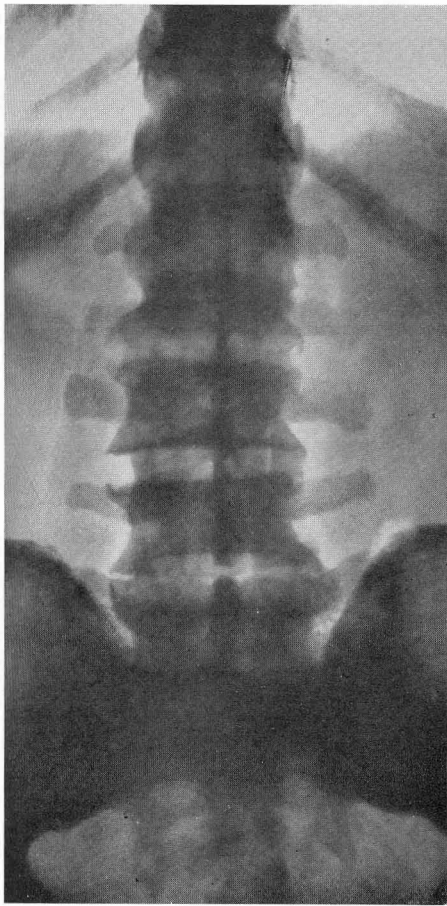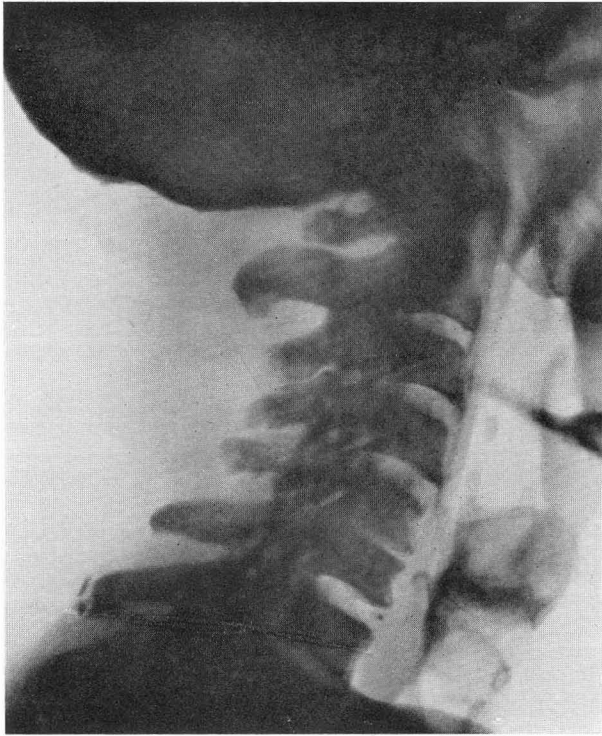
FIG. 21. Röntgen picture of columna lumbalis. Osteosclerosis of 3rd phase, considerable ligament calcifications. Male cryolite worker (No. 55), 63 years old, employed 20 years.
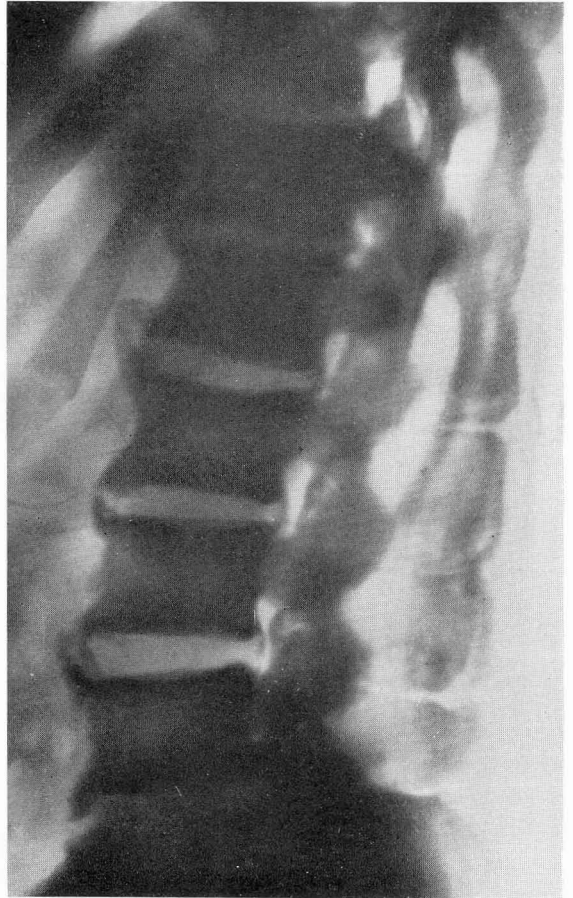

FIG. 22. Röntgen picture of columna lumbalis. Osteosclerosis of 3rd phase, severe ligament calcifications. Male cryolite worker (No. 25), 56 years old, employed 11 years.
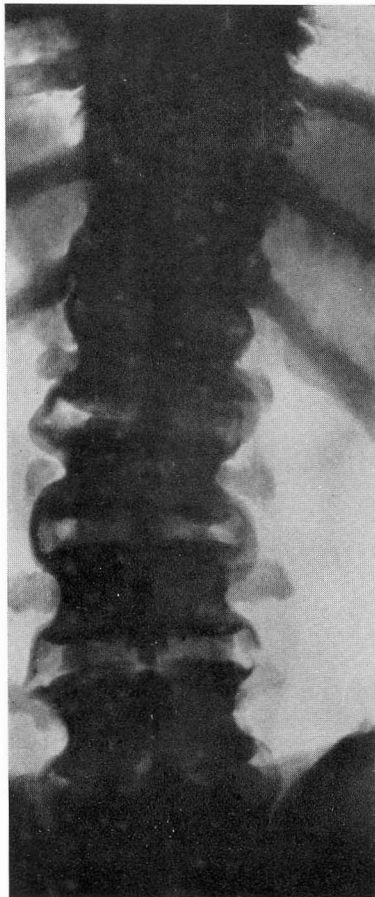
Fig. 23. Röntgen picture of columna lumbalis. Osteosclerosis of 3rd phase, severe ligament calcifications. Male cryolite worker (No. 60), 55 years old, employed 25 years.

Fig. 24. Same. Röntgen picture of costæ X—XII on left side, close to columna. Calcification of muscle insertions.

FIG. 25. Röntgen picture of columna cervicalis. Osteosclerosis of 3rd phase, moderate ligament calcifications. Male cryolite worker (No. 55), 63 years old, employed 20 years.
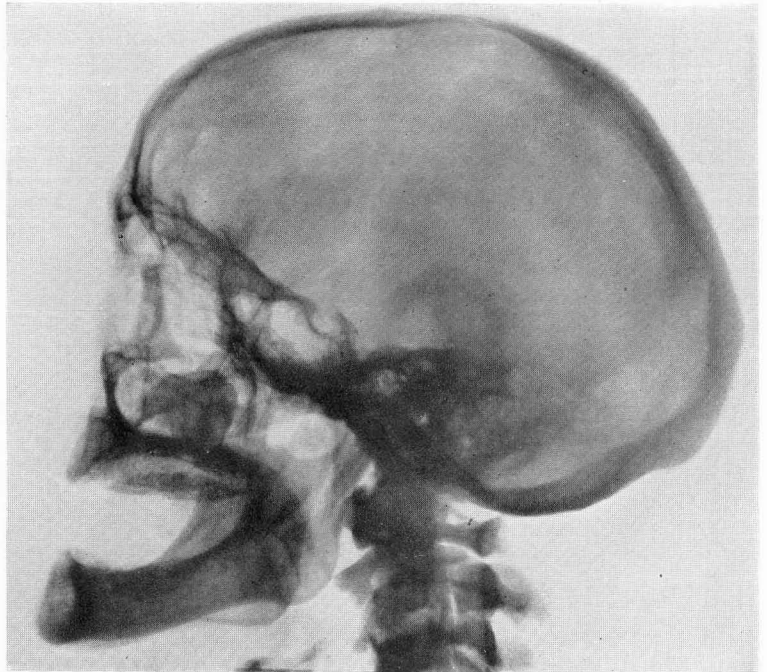
FIG. 26. Röntgen picture of skull. Diffuse but fairly moderate osteosclerosis. No changes in processus clinoidei. Male cryolite worker (No. 60), 55 years old, employed 25 years.
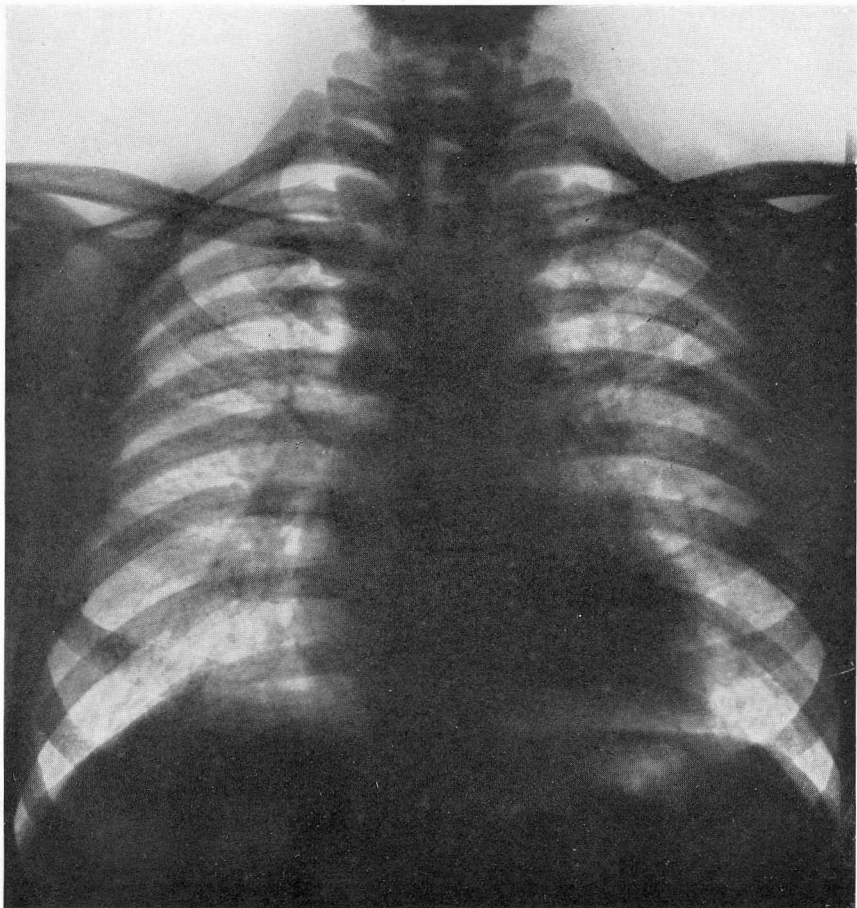
FIG. 27. Röntgen picture of thorax. Osteosclerosis of 2nd phase. Diffuse pulmonary fibrosis, disseminated form (2nd grade). Male cryolite worker (No. 6), 33 years old, employed 8 years.
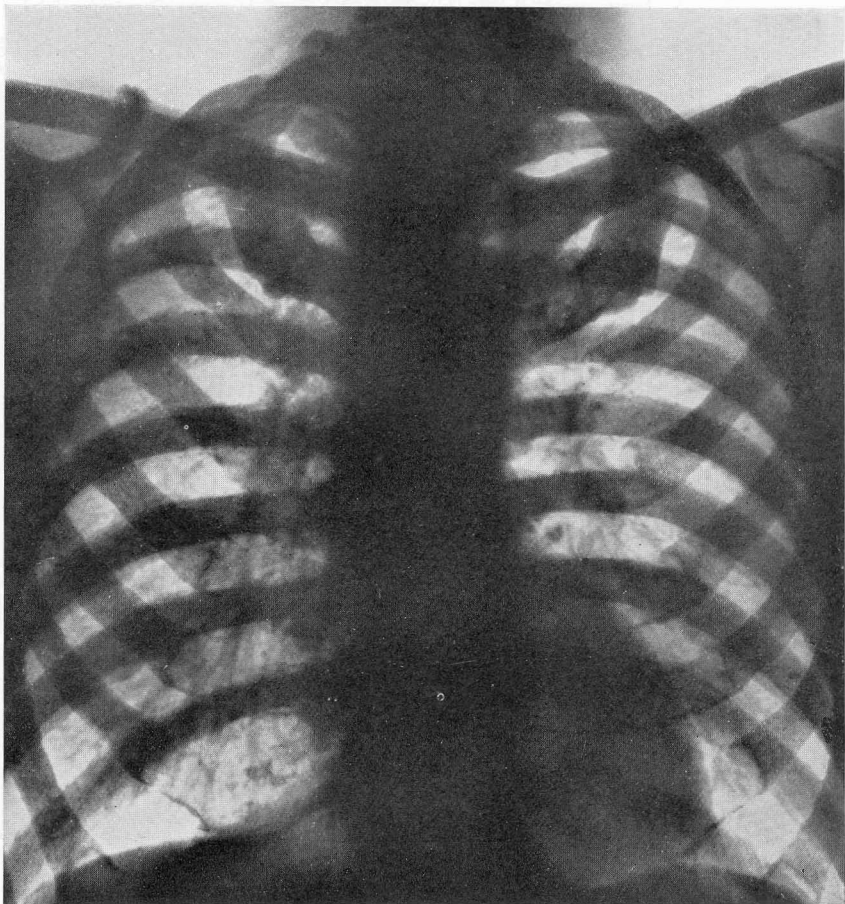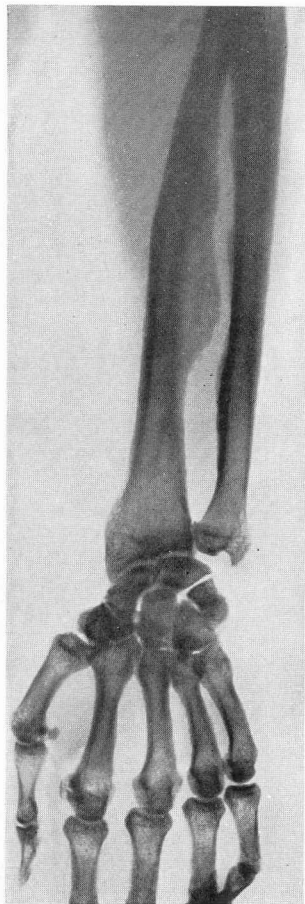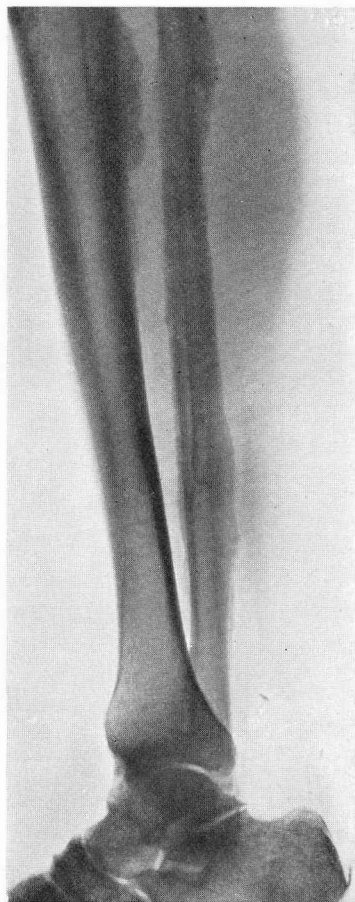
FIG. 28. Röntgen picture of thorax. Osteosclerosis of 3rd phase. Pulmonary fibrosis (slight 2nd grade). Male cryolite worker (No. 60), 55 years old, employed 25 years.
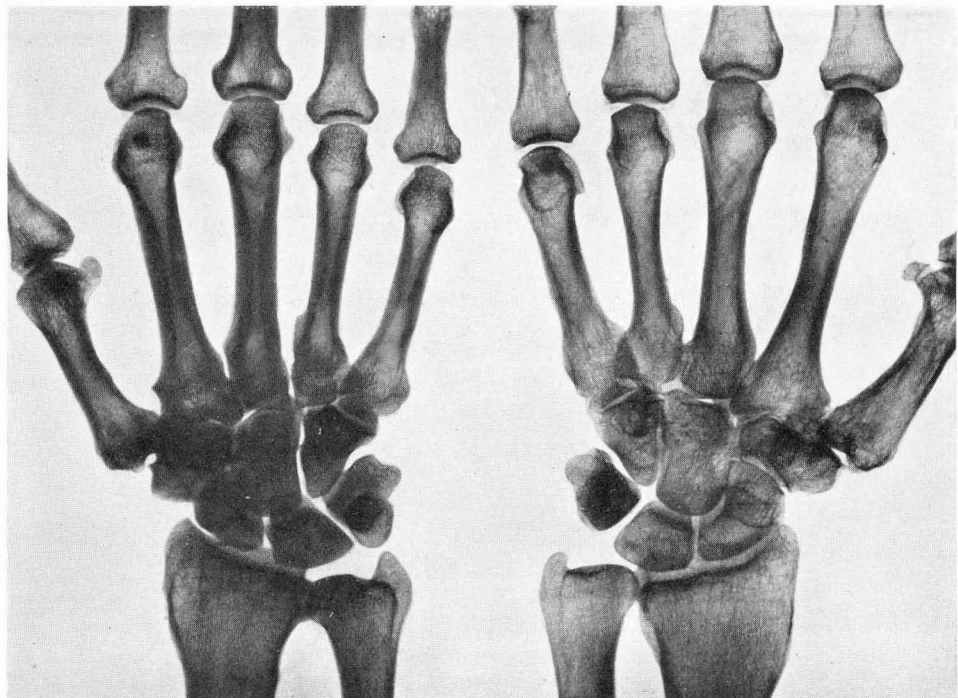
FIG. 29. Röntgen picture of (a) forearm and hand, (b) leg. Osteosclerosis of 3rd phase. Thickening of compacta, irregular periosteal new-formations. Male cryolite worker (No. 60), 55 years old, employed 25 years.

(a)   (b)

FIG. 30. Röntgen picture of hand (a) compared with normal hand (b). Osteosclerosis of 3rd phase. Thickening of compacta, marked narrowing of marrow cavities in metacarpals and phalanges. Female cryolite worker (No. 90) 46 years old, employed 13 years. The picture taken 9 years after leaving factory.
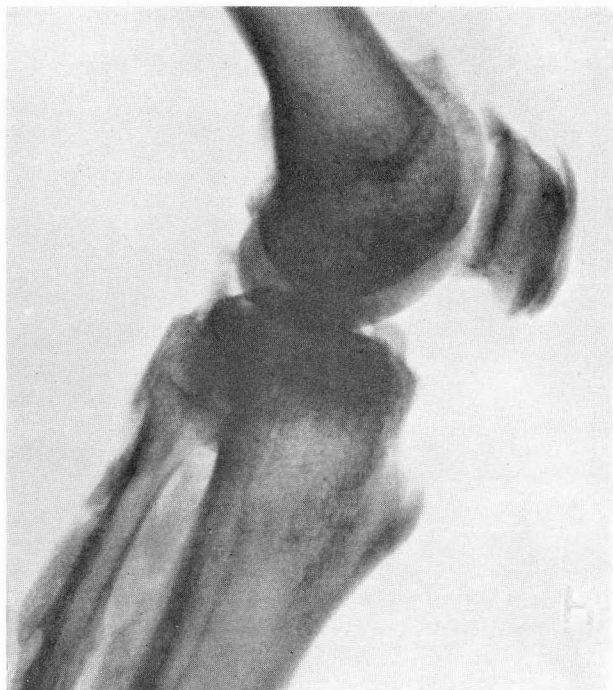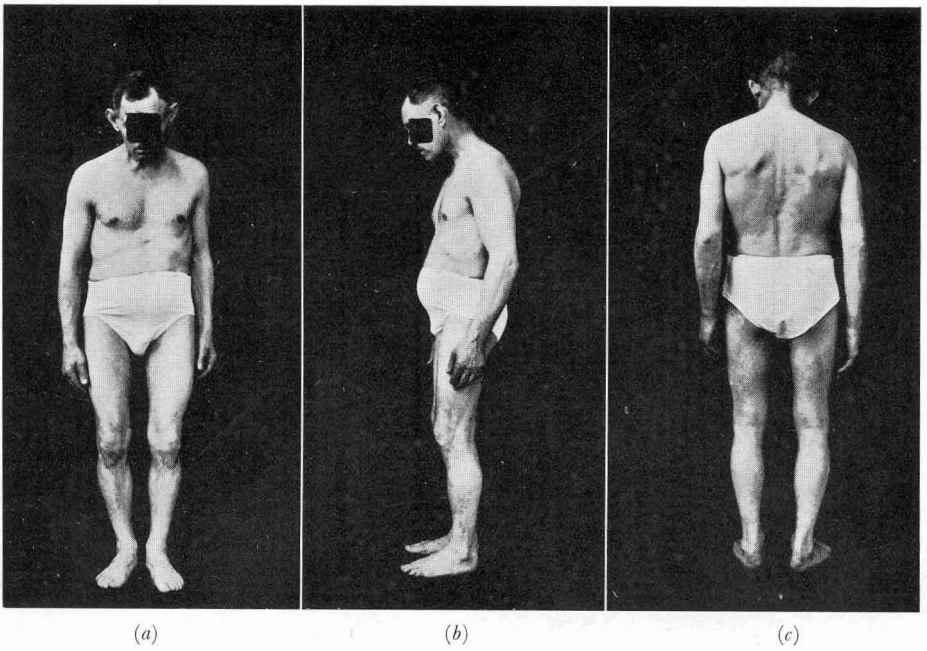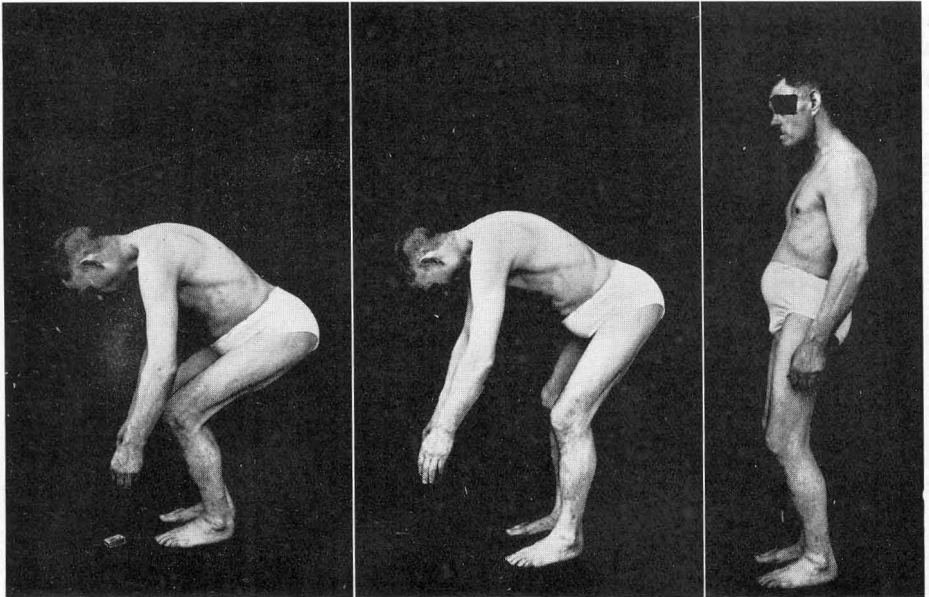

FIG. 31. Röntgen picture of knee. Osteosclerosis of 3rd phase. Diffuse calcification of ligaments and muscle attachments. Male cryolite worker (No. 60), 55 years old, employed 25 years.

FIG. 33. Male cryolite worker (No. 25), 57 years old, employed 12 years. Motility of columna completely lost. Head almost fixed in drooping position, slightly turned. Asymmetry of shoulders, slightly barrel-shaped thorax, moderate atrophy of long extensor muscles of the back. (a) Front view, (b) side view, (c) back view, (d) and (e) abortive attempt to pick an object up from the floor, (f) abortive attempt to bend columna backwards.

33 years respectively. One female worker had no bone changes, though she had been employed for 24 years with one interruption.

The relation between exposure to dust and the degree of osteosclerosis is shown in Table 24. Of the 39 workers exposed to moderate dust 9 had no bone changes; among the remainder all phases were represented, but mostly phases 1 and 2. In the group with slight exposure to dust there was only one case of 2nd phase and none of 3rd. On the other hand there were bone changes,
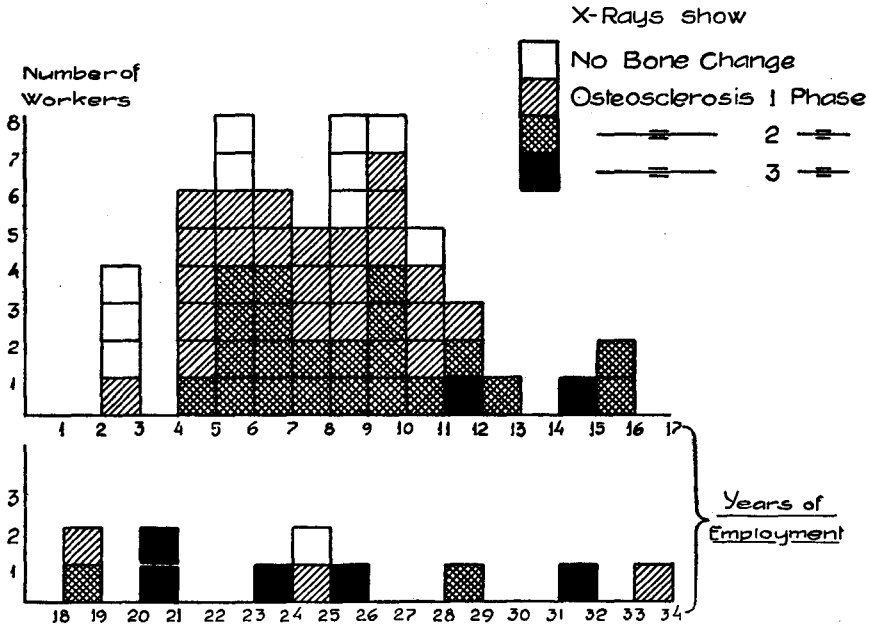

FIG. 32. Diagram illustrating the proportion between cryolite workers' length of employment and occurrence of osteosclerosis.

severe as a whole, in all workers who had been exposed to much dust. Broadly speaking it is thus possible to demonstrate an actual relationship between the exposure to dust and the degree of bone changes.

2. Clinical Examination

In addition to inspection, the clinical examination comprised a palpation of the subcutaneous areas of the bones (cranium, maxillary, clavicula, costæ, ulna, tibia) and an estimate of the function in columna, shoulder, elbow, wrist, hip and knee joints.

Inspection revealed no bone deformities or posture anomalies that could be taken to be typical. During palpation of the subcutaneous bones the surface was sometimes felt to be irregularly rugged. This was the case with all workers

with röntgenological bone changes of the 3rd phase and a few of the 2nd phase, but not in the others. Corresponding to the subcutaneous edges of ulna and tibia one could feel irregular, bone-hard, indolent nodules up to just under pea size, sometimes many in number, sometimes only few, recalling periosteal changes of a syphilitic nature. Less pronounced changes of the same kind were perceptible on clavicula and round the knee joints of thin workers. Digital exploration revealed nothing abnormal in cranium and maxillary. In some persons the surface of the ribs was possibly more irregular than normal. Bone tenderness was never found during palpation and percussion.

When examining the motility very considerable changes of columna were observed. In 35, or rather more than half of all workers (23 men and 12 women), motility in columna was restricted, both flexion-extension and rotation. The workers were divided into three groups according to the degree of restriction (Table 25). In the slightest cases there was merely a little stiffness of pars lumbalis and thoracalis with slight restriction especially of extension and rotation. Much the greater number, 21 persons, belonged to this group. The moderate cases presented a rather marked rigidity of the lumbar and dorsal region, but not of the cervical region. It was possible for them, as a rule with some difficulty, to pick up an object from the floor by bending the knees; this group contained 10 workers. Among the most severe cases, four elderly men (Nos. 25, 55, 59 and 60), there was practically complete rigidity of the entire spine and a more or less pronounced restriction of the head movements. This was particularly marked in a 57-year old male worker (No. 25), who had been employed at the factory for 12 years (Fig. 33). The head was fixed in a bent-over position and turned as in torticollis; movement was possible only to an extent of 5—10°, in both saggital and frontal planes. In order to look sideways he had to turn the whole body. Simultaneously there was an increase of the normal dorsal kyphosis and asymmetry of the shoulder region. This man was unable to picking anything up from the floor by bending the knees and could not put on his socks without aid. In the four workers of this group there was a moderate but distinct atrophy of the long extensor muscles of the back.

The relationship between the restriction of motility in columna and the osteosclerosis is shown in Table 25. On the whole the restriction increases parallel with the osseous changes. Of the 57 workers with osteosclerosis, motility of columna was reduced in 33. All persons with bone changes of the 3rd phase had severe or moderate fixation of columna. Of the workers with osteosclerosis of 1st and 2nd phase, motility was affected in about half of them, but to a small or moderate degree. In two persons who had no osteosclerosis

TABLE 25.

Relationship between Osteosclerosis and Restriction of Motility in Columna.

Osteosclerosis	No. of workers	Restriction of motility in columna			No. of workers who complained of	
		Slight	Mod-erate	Great	Rheuma-tic pains	Stiffness in body
None............	11	2	..	..	1	..
1st phase	26	12	2	..	10	2
2nd phase	24	7	5	..	7	2
3rd phase........	7	..	3	4	4	4
Total...	68	21	10	4	22	8

there was a motility restriction of the slightest degree. It was noteworthy that only some of the workers whose motility in columna was moderately restricted complained of stiffness (Table 25). Even those most severely affected complained of surprisingly little inconvenience from it.

Examination of the other joints revealed more or less normal conditions. In the case of some of the elderly workers there was crepitation when moving knee or shoulder, but not to any outstanding degree. In 4 workers only, all elderly men with bone changes of 3rd phase, there was a distinct but moderate restriction of motility in the hips, especially on attempting abduction and rotation.

CHAPTER XV

OTHER RESULTS OF PHYSICAL EXAMINATION

The other results of the physical examination have been collected according to systems of organs and are dealt with in the following order: General condition, teeth, respiratory organs, cardio-vascular system, blood, nervous system, endocrine glands, skin, urine and sundry examinations.

1. General Condition

To all outward appearances the general condition did not seem to differ from that of the Copenhagen factory hand as a whole. There was no particular paleness, thinness or tiredness. The ratio of height to body weight has been employed in arriving at the true general condition. When weighed the men wore trousers, the women underclothing. Sample weighings showed that this clothing had an average weight of 0.5 kg., which was thereafter deducted from the gross weight. Compared with the normal weight according to Brugsch*), 49 workers were too heavy (from 1 to 42 per cent.) and 18 too light (from 1 to 14 per cent.). The average deviation from normal weight was + 9 per cent. The calculation of Kaup's index: $\dfrac{\text{body weight}}{\text{body height}^2}$ gave figures varying between 2.0 and 3.6, with an average of 2.7. According to Kaup this index is a constant, normally 2.3. A value of less than 2 will indicate a state of insufficient nutrition. Thus from the foregoing there is no indication that the state of nutrition suffers among cryolite workers.

2. Teeth

The state of the teeth was examined by inspection and, in a few cases, by X-ray. For 66 workers the total number of teeth was counted and the number of carious and filled teeth; the result is shown in Table 26. On the whole the

*) With body height of 155—164 cm.: the body height — 100 kg.
     ,,   ,,   ,,   ,, 165—174 ,, : ,, ,, ,, — 105 ,,
     ,,   ,,   ,,   ,, 175—185 ,, : ,, ,, ,, — 110 ,,

The indices applied are given in Secher: Medicinske Tal, Copenhagen 1934, page 68.

TABLE 26.

Condition of Teeth in 66 Cryolite Workers.

Age	No. of workers	Average number of teeth		
		Total	Carious	Filled
20—29 years........	11	21.4	6.8	2.4
30—39 „	30	19.3	5.9	1.6
40—49 „	10	14.6	4.1	0.6
50—59 „	10	7.8	5.5	0
60—69 „	5	8.7	4.0	0

state of the teeth was bad, with a high caries frequency and unsatisfactory care. Decay increased with rising age. In a young male worker there was a case of *mottled enamel*, which will be dealt with later (page 198), as this affection has no relation to his work at the factory. Otherwise only banal changes in the enamel were observed (rachitic hypoplasia, tartar accretions, tobacco discoloration etc.). In some elderly workers there was more or less widespread inflammatory paradentosis, but otherwise gingiva were normal; in particular no bleeding was observed. The wear of the teeth was not pronouncedly great. Though there is a lack of suitable comparative material, the impression gained was that the state of the teeth outwardly was no different from the average among Copenhagen workers of the same age.

Radiographs of the teeth in the left maxillary of two male workers (Nos. 25 and 68) with bone changes of 3rd phase showed various deviations from the normal. The structure in the jaw had the characteristic appearance of the bones: coarse and blurred trabeculæ, almost corresponding to changes of the 1st phase in pelvis or columna. The periodontal spaces were irregular in contour and sometimes blurred. In the teeth the pulp cavity and especially the root canal were markedly narrow.

3. Respiratory System

Inspection of the *nasal cavity* and *pharynx* revealed no changes that could indicate that cryolite dust has a local irritative effect on the mucous membranes. On examination of the *lungs* three different pathological changes were observed: An emphysematous condition, pulmonary fibrosis, and tuberculosis.

In 11 workers, 8 men and 3 women, there was a condition that must be described as a kind of *emphysema*, motility of thorax being greatly reduced or totally impaired. Respiration was of the abdominal type. On measuring thorax at the level of papillæ with maximum inspiration and expiration I

found reduced or even total absence of excursion. For this group of workers the average excursion was 0.7 cm., with variations from 0 to 2 cm. For the other workers the excursion varied from 2.5 to 7 cm. and on an average was 4.5 cm. Other signs of emphysema were more or less pronounced. They all presented a moderate degree of barrel-shaped thorax, distended lung area and reduced expansion on inspiration. In some the percussion note was tympanitic, in others it was not. On auscultation a certain prolongation of expiration was the rule, but otherwise conditions were normal; in particular, no case of bronchitis was observed. All these people complained of dyspnoea

TABLE 27.

Frequency of Pulmonary Fibrosis Found by X-ray Examination.

	Men	Women	Total	
No fibrosis.................................	19	15	34	..
Perhaps incipient fibrosis.....................	4	2	6	} 10
Incipient or slight fibrosis	3	1	4	
Apparently incipient 2nd grade...............	3	0	3	} 24
Slight 2nd grade	11	3	14	
2nd grade	7	0	7	
Total...	47	21	68	

on action, but only two of an inclination to cough. They were all elderly workers, with an average age of 57.6 years and an average period of employment at the factory of 21.7 years.

X-ray examination of thorax showed signs of *pulmonary fibrosis* in 34 workers, or half of all those examined, 28 men and 6 women. According to the degree of the changes a grouping in grades*) was made as with the grouping for silicosis. If the groups "perhaps incipient fibrosis" and "probably incipient 2nd grade" are regarded as belonging to 1st and 2nd grades respectively, 10 of the affected workers had fibrosis of 1st grade, 24 of 2nd grade. The frequency of the various grades is given in Table 27. The relation between grade of fibrosis and period of employment is shown in Table 28. Of persons who had worked 9 years or more the majority (13 of 18) had fibrosis. The greatest changes (slight 2nd grade and 2nd grade) were not observed until after five or six years' employment, the lighter grades already after less than three years.

*) The X-ray photographs have been judged by Professor P. Flemming Møller, chief of the Rigshospital Röntgen Department.

TABLE 28.

Relation between Period of Employment and Occurrence of Pulmonary Fibrosis.

Employed, years	No fibrosis	Perhaps incipient fibrosis	Incipient or slight fibrosis	Apparently incipient 2nd grade	Slight 2nd grade	2nd grade	No. of workers
2 but less than 3	8	1	..	1	..	..	10
3— 4	5	..	1	..	..	..	6
4— 5	1	..	..	..	..	..	1
5— 6	3	..	..	..	1	1	5
6— 7	5	1	1	1	2	..	10
7— 8	3	1	..	..	4	1	9
8— 9	4	2	1	..	1	1	9
9—10	..	..	..	..	1	1	2
10—12	..	..	..	..	1	..	1
12—14	..	..	..	1	..	..	1
14—16	..	..	1	..	1	1	3
16—18	1	..	..	..	..	..	1
18—20	1	..	..	..	..	..	1
20—25	2	..	..	..	2	1	5
25—30	..	1	..	..	1	1	3
30—35	1	..	..	..	..	..	1
	34	6	4	3	14	7	68

But even long employment does not always cause fibrosis; the lungs were normal in five workers after 16—33 years work. Gudjonsson (374) has published an account of this form of fibrosis.

The röntgenological picture of the fibrosis shall be described merely in broad terms. It being possible that these changes have been caused by cryolite and not by the few per cent. of quartz in the cryolite, the term fibrosis is preferred instead of silicosis. According to the division made by Pancoast and Pendergrass (627) it is a fibrosis of the peribronchial-perivascular type, with a tendency to rather early interstitial changes; this picture is uncharacteristic, in so far as it may be produced by the action of dust of different kinds. For instance, the silicosis among porcelain workers described by Flemming Møller (590) is very similar to cryolite fibrosis. The first change is a diffuse, reduced transparency of the lung. The lung picture is denser than normally and its individual lines vague and blurred. The division into grades is based upon the varying intensity of these processes. No severe changes were observed, no great degree of density, neither patchy nor confluent. Hilus shadows were not strikingly enlarged. There were no pleural changes nor local emphysematous areas. On the whole the fibrosis observed must from its röntgenological picture be described as fairly benign. Fig. 27 is of one of the most pronounced cases, 2nd grade of rather disseminated form, in a male worker after $8^{1}/_{2}$ years' employment; Fig. 28 reproduces a form in which fibrous streaks are more marked.

It must be emphasized that the stethoscopic examination did not reveal changes which could be placed in relation to the existing fibrosis. In the great majority of these workers the stethoscopy divulged nothing abnormal.

Four cases of *tuberculosis* were found by the clinical and röntgenological examination. In three of them it was a matter of older, localized tuberculous processes; two had no fibrosis, the third had incipient fibrosis. In addition, there was a case of more recent tuberculous processes in apex, combined with incipient fibrosis. Thus the tuberculosis frequency was not remarkably high, and it is not possible to demonstrate any relation between tuberculosis and fibrosis.

The proportions of fibrosis to emphysema, and of pulmonary to bone changes are shown by means of Table 29. It is a question whether the emphysematic changes (rigidity of thorax, dilated and more or less unchangeable lung boundaries) are caused by the lung fibrosis or by the osteosclerosis. In the clinical picture of silicosis, emphysema appears in the more severe grades. In the present material only a fraction of the fibrosis cases, even the most severe, were accompanied by emphysema. Among the workers who had no lung fibrosis there were four cases of emphysema. This distribution does not indicate any close relationship. All workers with osteosclerosis of 3rd phase had emphysema, but with one exception these elderly workers also had fibrosis. There is also a case of emphysema in the group without osteosclerosis, and two in the

TABLE 29.

Relation between Changes in Lungs and Bones in Cryolite Workers.

		No. in all	No. cases of emphysema	Excursion of thorax			No. of workers complaining of			
				Av. cm.	Max. cm.	Min. cm.	Short breath	Cough	Expectoration	Palpitations
Emphysema	Present ..	11	11	0.7	2	0	11	2	1	3
	None	57	0	4.5	7	2.5	18	8	2	4
Pulmonary fibrosis	None	34	4	4.4	7	0.5	12	5	1	3
	1st grade	10	2	3.4	6	0.5	2	2	0	2
	2nd grade	24	8	2.2	7	0	15	3	2	2
Osteosclerosis	None	11	1	4.2	7	0.5	6	2	1	0
	1st phase	26	2	4.5	7	1	8	4	0	2
	2nd phase	24	4	3.5	6	0.5	8	3	2	4
	3rd phase	7	7	0.5	2	0	7	1	0	1

group with bone changes of 1st phase, where it is doubtful whether or not there is reason for assuming influence on the elasticity of thorax*). The average excursion of thorax decreased with increasing fibrosis and increasing osteosclerosis, but mostly in the latter. In the individual case of emphysema it may be difficult to discover the pathogenesis, but presumably three factors are of significance: (1) The bone sclerosis and ligament calcification caused by cryolite, which by reducing or inhibiting the movement of thorax may be capable of producing secondary pulmonary emphysema; (2) the pulmonary fibrosis and the consequent reduction of the elasticity of the lung and reduction of functionable tissue; (3) the character of the work, as prolonged hard physical effort favours the development of emphysema.

4. Circulatory System

In the course of the stethoscopic or X-ray examination of thorax it was found in five cases that there were changes of the heart or the large vessels that were describable as pathological or probably pathological. Nothing abnormal was found among the others examined. The changes found were: (1) two cases of slight cardiac hypertrophy with systolic murmurs over præcordia in male workers; (2) a moderately pronounced and well compensated mb. cordis mitralis in a young female worker; (3) two cases of arteriosclerotic changes in aorta in elderly female workers.

Blood pressure was tested for 66 workers. The age of the individual in years + 100 is reckoned as the upper normal limit for systolic blood pressure expressed in mm. On this basis the systolic blood pressure was normal for 39 and raised for 27 workers. As a rule the increase was small, 16.7 on an average, with variations from 1 to 56 mm. In only four workers was the systolic blood pressure $\geqq$ 180 mm., viz. three women aged 54—57 years, who had 200, 180 and 210 respectively, and a man, 57 years, who had 180 mm. Remarkably low systolic blood pressure was not observed; no values under 105 mm. were recorded. Bearing in mind that the blood pressure was taken only once, there are no grounds on the whole for assuming any deviation from what is usual in a similar material.

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*) The average excursion of thorax was 4.5 cm. in the group without clinical signs of emphysema. According to the table of the *Hafnia* Insurance Company the average excursion according to age and height should be 5.8 cm. for these workers. The method of measurement is somewhat liable to error, but, as the material is of some compass, it is exceedingly probable that the reduction is a real one. This indicates that the elasticity of thorax is affected by the osteosclerotic changes, even if they are only moderate in degree.

5. The Blood

The examination of the blood comprised the following factors; in parentheses is the number of workers on whom the particular determination was made. Where the number examined was only small, an endeavour was made to take workers with different periods of employment and different phases of osteosclerosis. The technique is referred to on page 116.

Hæmoglobin percentage................ (66)
Erythrocytes, number .... (51)
Leucocytes, number................... (48)
Composition of the white blood picture .. (58)
Bleeding time .... (33)
Coagulation time..................... (15)
Blood platelets, number .... (15)
Erythrocytes, resistance to hæmolysis.... (15)
Plasma colour........................ (15)
Sedimentation rate of erythrocytes...... (57)

On the whole the deviations from the normal were few and not very marked. The deviations became distinct especially on considering the average figures (Table 30).

The *hæmoglobin percentage* for male workers varied between 87 and 128, for female workers between 75 and 102. The figures show that only a very slight anæmia occurred. The average percentage for men was 105 and for women 98. According to Gram and Norgaard*) the normal average hæmoglobin percentage is 109 for men and 94 for women, determined by a hæmometer corrected to Haldane's standard (oxygen capacity 18.5 per cent. = 100 per cent. hæmoglobin). With this as the norm, the average hæmoglobin content in cryolite workers must be regarded as normal.

The *number of erythrocytes* in the male workers varied between 3.89 and 5.81 millions, with the average at 4.92 millions; in the women the outer values were 3.90 and 5.94 millions and the average 4.29 millions. Compared with Gram and Norgaard's normal averages (men 5.454, women 4.654 millions) there was a slight reduction, amounting to 9.8 per cent. for the male workers and 7.8 per cent. for the females. Only in 5 of the 51 cases in which both hæmoglobin percentage and erythrocyte number were determined, the *colour index* was below 1 (minimum 0.73). In 21 cases the index was 1.00—1.09, in 22

*) In Meulengracht and Gram: Hæmatologisk Teknik. Copenhagen 1930.

TABLE 30.

Average of Blood Composition in Cryolite Workers.

(Figures in parentheses indicate the number of workers examined).

		Men	Women
Hæmoglobin	%	105 (45)	98 (21)
Erythrocytes, number........	mill.	4.92 (34)	4.29 (17)
Leucocytes, number.........		7291 (30)	6613 (18)
Polymorphonuclears	%	46.2 (39)	49.3 (19)
Staff-nuclears..............	%	11.8	9.6
Metamyelocytes.............	%	0.6	0.3
Eosinophil L................	%	2.0	1.3
Basophil L.................	%	0.4	0.8
Lymphocytes	%	34.6	32.2
Monocytes	%	5.2	5.6

cases 1.10—1.19 and in three cases between 1.20 and 1.27. Simultaneously with the reduction of the number of erythrocytes there is an increase of the average hæmoglobin content of the corpuscles.

The *number of leucocytes* varied between 4,020 and 12,680; average for men 7,291, for women 6,613, for both sexes 7,037. In consideration of the fact that the blood was taken during working hours, in some cases after a meal, there is nothing to show that the leucocyte number differs from the normal.

Film-preparations on the whole gave normal conditions. The shape and size of the red corpuscles varied within normal limits. No immature forms of these cells were observed, especially no basophilic stippling of erythrocytes. The morphology of the white corpuscles was normal; a few metamyelocytes were observed, but no myelocytes or myeloblasts.

The result of the *differential count* appears from Table 30, which contains the average figures. The most striking finding was an increase in the number of the juvenile stab- or staff-nuclear leucocytes from the normal of 4—5 to 11.1 per cent. Of 58 workers, 55 had more than 5 per cent. of staff-nuclears (maximum 27 per cent.). In 27 workers I observed metamyelocytes, which normally do not occur in the blood, in numbers from 0.5 to 4 per cent.; the average for all those examined was 0.5 per cent. The total of polymorphonuclear and staff-nuclear leucocytes, which normally form about 65 to 70 per cent. of the white corpuscles, was 58.3 per cent., or somewhat reduced. The lymphocytes, whose normal percentage is 20—25, were relatively increased, though moderately (33.8 per cent.). The number of eosinophil leucocytes (1.8 per cent.) was just below the normal (2—4 per cent.). The basophil leucocytes and monocytes scarcely deviated from the normal (0.6 and 5.4 per cent. respectively).

In the white blood picture there was no marked difference between men and women.

Coagulation was tested by determining the bleeding time after cutting the ear, the coagulation time of recalcinated citrate plasma, and the number of blood platelets. Bleeding time varied between 1 and 7 seconds; for the male workers the average was 3.37 seconds, for the females 3.61. The average coagulation time was 3.23 seconds, with variations from 2.5 to 4.25 seconds. The number of blood platelets varied between 343,000 and 561,000, and on an average was 461,000. All these values may be regarded as being within the normal boundaries.

The *resistance of erythrocytes* to hæmolysis was determined for 8 men and 7 women. The results were practically all within Meulengracht's normal limits. In the men there was observed incipient hæmolysis at 0.46—0.42 per cent. NaCl and total hæmolysis at 0.36—0.32 per cent. For the women the corresponding outer values were 0.44—0.42 and 0.36—0.28 per cent. NaCl. On examining the *plasma colour* by Meulengracht's method, values were found of from 2 to 8; the average was 5.1, which must be considered as normal. When determining the *sedimentation rate*, citrate blood in the dilution of 1:9 was employed for practical reasons. The readings were corrected to a hæmoglobin percentage of 100 by means of Gram's curve, which, as shown by Windfeld*), is also

TABLE 31.

Relation between Osteosclerosis and Blood Picture.

(Figures in parentheses indicate number of workers examined).

	Workers without bone changes	Workers with osteosclerosis			All workers
		1st phase	2nd phase	3rd phase	
Hæmoglobin ..... %	105 (11)	99 (26)	99 (23)	105 (6)	101 (66)
Erythrocytes, numb. mill.	4.94 (9)	4.61 (21)	4.68 (15)	4.78 (6)	4.71 (51)
Leucocytes, number	6843 (6)	6451 (20)	7919 (18)	6287 (4)	7037 (48)
Polymorphonuclears %	47.4 (10)	47.6 (23)	48 (20)	41.6 (5)	47.2 (58)
Staff-nuclears .... %	8.8 -	9.9 -	12 -	17.7 -	11.1 -
Metamyelocytes... %	0.7 -	0.5 -	0.4 -	0.3 -	0.5 -
Eosinophil L. ..... %	2.1 -	2.2 -	1.4 -	0.8 -	1.8 -
Basophil L. ...... %	0.5 -	0.8 -	0.3 -	0.7 -	0.6 -
Lymphocytes..... %	34.9 -	34 -	32.4 -	36.6 -	33.8 -
Monocytes .... %	5.6 -	5.8 -	4.9 -	5.1 -	5.4 -

*) P. Windfeld: Beiträge zur Kenntnis der postoperativen Blutveränderungen. Kopenhagen 1933.

applicable to this dilution. For 39 male workers the average sedimentation rate was 4 mm., with variations from 0.5 to 28 mm.; for 18 female workers the average was 3.3 mm., the outer limits being 1 and 9 mm. Values $\leqq 8$ mm. were found in 35 men and 17 women in all. There is scarcely any reason for assuming that the sedimentation rate in cryolite workers differs from the average in a similar material.

The blood changes might be thought to have some connection with the reduction of the medullary cavity brought about by the osteosclerosis. In that case the degree of the blood changes and of the sclerosis would be parallel. This is not the case, however (Table 31).

Summarizing, it may be said of *the blood changes* that the following deviations from the normal average were found:

(1) Slight reduction of the number of erythrocytes, simultaneously with an increase of the average hæmoglobin content of the corpuscles.
(2) Moderate relative reduction of the number of leucocytes.
(3) Moderate relative increase of the number of lymphocytes.
(4) Considerable increase of the number of staff-nuclear leucocytes.
(5) Occurrence of a small number of metamyelocytes.

6. Nervous System

Having regard to the pronounced changes in the vertebral column, attention was particularly directed towards the possible occurrence of radicular symptoms. Sensibility to touch and pain was therefore tested on truncus and the lower extremities, the power in the extremities, and various reflexes (abdominal, patellar and plantar). Among the workers with bone changes of 3rd phase the examination was extended to a general, thorough neurological examination. However, nothing abnormal was found in the examination of the nervous system. A number of workers complained of pains of a rheumatic character, and as a rule it was possible to find myalgia as the cause. There were no pains of a radicular type.

7. Endocrine Glands

The size of the thyroid gland was determined on all workers by inspection and palpation. In a number of the male workers, including all the older ones, testes were palpated. A woman, 28 years old, had a diffuse struma with doubtful signs of thyreotoxicosis. Among the other workers the thyroid gland was not changed in size. Examination of testes showed nothing abnormal, especially no case of atrophy.

8. The Skin

On eight male workers I observed a rather uniform affection of the skin round about the shirt-neck and on the upper part of chest and back. It consisted of a chronic folliculitis with varying degree of suppuration, scars and pigmentation. They all stated that the affection came especially in summer when the dust clung to the skin and made it itch. Otherwise no change of the skin was observed, particularly not on the hands and forearms which come in direct contact with the cryolite.

9. Urine

The urine of 65 workers was examined for albumin (Heller's test) and sugar (Almén's and Fehling's test). In all cases a microscopic examination was made as well. The male workers evacuated the bladder during the examination, the female workers just before or just after. In the great majority of cases normal conditions were found. In the case of a man 33 years old there were signs of chronic nephritis (albumin, erythrocytes and casts); the history could give no definite information as to the ætiology. A 37-year old female worker, who stated that she suffered from diabetes, had glycosuria. For three female workers the microscope revealed hæmaturia to an insignificant degree as the examination was made on urine passed in the ordinary manner. Urine-microscopy for 11 male workers revealed from a single to a few erythrocytes in the field (magnification about × 200).

10. Sundry Examinations

(1) For *sero-reaction for syphilis*, blood was taken from 16 male and 12 female workers, all arbitrarily chosen. In one case only was the reaction positive, a 33-year old male worker without clinical signs of syphilis.

(2) *Serum calcium* was determined on 18 workers (9 men and 9 women) by means of Tisdall's (798) modification of Kramer and Tisdall's method (474). The results are given in Table 32; undoubtedly they may be regarded as normal. Though some values are round about 12 mg. per 100 c. c., they can scarcely be regarded as pathologically increased, as the blood was taken 1—2 hours after a meal. Apparently there is no regular relation between the phase of the osteosclerosis and the calcium content of serum.

(3) *Fluorine content in the teeth.* In conjunction with the examination five workers supplied teeth or tooth remains from accidental extraction. Beyond the frequent occurrence of hypercementosis these teeth presented nothing abnormal macroscopically. The fluorine content in the total ash was deter-

TABLE 32.

Serum Calcium of Cryolite Workers.

No.	Sex, age	Employed, years	Osteo-sclerosis, phase	Serum Ca mg. per 100 c.c.
1........................	♂ 40	9	1	11.2; 11.4
6........................	♂ 34	10	2	10.8
7........................	♀ 37	8	2	10.8
10........................	♀ 59	21	3	10.6
11........................	♀ 32	9	1	10.5
15........................	♂ 58	16	2	12.1; 12.0
23........................	♀ 27	4	2	10.6
25........................	♂ 57	12	3	11.9; 11.7
29........................	♀ 39	8	1	11.2
31........................	♂ 43	7	0	10.9
34........................	♂ 44	16	3	11.6
50........................	♂ 55	10	2	11.1
52........................	♀ 58	22	1	10.0
57........................	♀ 34	8	2	11.2
58........................	♀ 32	8	2	10.6
60........................	♂ 57	27	3	10.8
62........................	♀ 57	17	1	11.2
68........................	♂ 49	18	2	12.3
Normal	♂ 21	—	—	10.5; 10.5
Normal	♀ 22	—	—	11.4; 11.2

mined by the usual technique. For purposes of comparison the fluorine content was determined in the total ash of normal, permanent teeth of individuals whose age was not known. In addition, in some cases the enamel and dentine were analysed after isolation by the method described on page 112 (1). The results of these investigations are given in Table 33. The fluorine content in the total ash of normal teeth varied from 0.19 to 0.30 $^0/_{00}$; incisors had the highest fluorine content, molars the lowest. In isolated enamel of incisors only 0.044 $^0/_{00}$ was found, in enamel of molars 0.057 $^0/_{00}$. Ash of dentine contained 0.31 and 0.30 $^0/_{00}$. Thus normally there are five to seven times as much fluorine in dentine as in enamel.

A constant and considerable *increase of the fluorine content was found in the teeth of cryolite workers.* In the total ash the content varied from 1.1 to 5.3 $^0/_{00}$. The most carious teeth contained the greatest quantity of fluorine. In the only case where several teeth from one person were analysed (Worker No. 36), the fluorine content was more than twice as high in the molars (5.3 $^0/_{00}$) as in the incisors, canines and premolars (2.2—2.5 $^0/_{00}$). All the workers

TABLE 33.

Fluorine Content in Teeth of Cryolite Workers Compared with Normal Teeth.

No.	Sex, age	Em-ployed, years	Material	Ash used*)	Th(NO₃)₄ used	Fluor-ine per g. ash*)	Remarks
				g.	c. c.	mg.	
36	♂ 32	10	Incisors	0.1833	0.30	2.5	Advanced
			Canines	0.1848	0.30	2.5	caries,
			Premolars	0.2428	0.35	2.2	some only
			Molars	0.8165	2.85	5.3	stumps
22	♀ 30	8	Molar	0.8935	0.82	1.4	Slight caries
19	♂ 32	9	Premolar	0.5292	0.51	1.4	Moderate caries
33	♂ 35	10	Molar	0.3150	0.42	2.0	Severe caries
3	♂ 38	9	Incisors, premolars and molars	enamel 0.3351	0.32	0.29	Slight caries
				dentine 0.4172	1.16	0.83	
Normal permanent teeth of individuals of unknown age			Incisors	1.1792	1.19	0.30	
			Canines	1.3230	1.20	0.27	
			Premolars	1.1197	1.06	0.28	
			Molars	1.1419	0.73	0.19	
			Incisors	enamel 2.0470	0.30	0.044	5 teeth in each portion
				dentine 2.2252	2.32	0.31	
			Molars	enamel 2.1068	0.40	0.057	
				dentine 2.7914	2.80	0.30	

had been employed about ten years at the factory; three had osteosclerosis, two had no bone changes. Compared with the normal figures the fluorine content had increased from about 4 to 18 times. It was possible to separate enamel and dentine in teeth of cryolite worker No. 3. The enamel contained 0.29 °/₀₀ fluorine, the dentine 0.83 °/₀₀. Compared with the normal figures the fluorine content was about 6 times higher in the enamel and about 3 times in the dentine.

*) The enamel was not incinerated, therefore the result is expressed in °/₀₀ of non-incinerated enamel.

(4) *24-hour excretion of fluorine in urine.* On account of the dust everywhere it was difficult to avoid the inclusion of small quantities of dust when the urine was being voided. For the same reason collection of fæces was abandoned. Systematic investigation in that domain was therefore relinquished, and I made do with a random sample. Two elderly, reliable workmen, both with osteosclerosis and much exposed to dust, voided urine at the factory in a dust-free room after washing their hands, and at home in a flask supplied to them. It having proved difficult to obtain complete incineration of the 24-hour urine the following procedure was adopted. 50 c.c. saturated solution of barium chloride was added to the urine; the sediment was collected by filtering. The filtrate could not be entirely incinerated, but a qualitative test (precipitation of silicic acid) was negative, which means that the filtrate contained less than 0.075 mg. fluorine. Sediment + filter were carefully incinerated after adding 2 c.c. N NaOH. The 24-hour urine from two adult men not connected with the factory and living on an average diet was treated in a similar manner. The analysis turned out as follows:

Worker No. 25, 57 years ...... 2.54 mg. fluorine
    „   „ 15, 58 „ ...... 2.09 „   „
Normal man, 32   „ ...... 0.22 „   „
    „   „   26   „ ...... 0.12 „   „

The normal excretion of fluorine in the urine is very small, only fractions of a milligramme in the course of the 24 hours. As might have been expected, the fluorine excretion of the cryolite workers was much greater, up to 2.5 mg., or about 10—20 times the normal.

EXAMINATION OF FORMER CRYOLITE WORKERS

With the object of finding out the state of health of former cryolite workers, a search was made for all discharged workers whose personalia were obtainable. It was also the intention to enquire about the discomforts connected with their former work, for the purpose of obtaining a possible correction to the picture arrived at by examining the present workers. The search was made mostly on the basis of the factory's books, and also on information given by the present workers and their trade union. As the regular recording of workers' personalia was only commenced a few years ago, it was quite accidental who was actually traced, but no selection was made.

1. Questionnaire on Discomforts of Work

The addresses of 170 former workers were traced. To 134 of these, all who had worked at least six months at the factory, were sent the question-form mentioned on page 134, and it was replied to by 95. Of these, four had to be left out, the reply being that the person was unable to remember anything. The same questions were put verbally to 36 previous workers with whom personal contact was made. In all, then, there were useful answers from 127 people, 66 men and 61 women. For practical reasons I elected to enquire about the following symptoms only: loss of appetite, nausea, vomiting, irregular movement of bowels, cough, headache and tiredness. In all, 23 persons (13 men and 10 women) answered that they had not had troubles of these kinds, and 104 (53 men and 51 women) complained of one or more symptoms. The result of the enquiry is summarized in Table 34, where the frequency of the same complaints among the present workers is added for comparison.

It appears from Table 34 that these symptoms as a whole were complained of more frequently by the former than by the present workers, but that otherwise there is great conformity between them. The acute gastric symptoms were more frequent; vomiting, which must be taken as reflecting the severest effect, was as much as twice as frequent among the former workers. Irregular defæcation is the only symptom with the highest frequency among the present

TABLE 34.

Frequency of Various Complaints of Former and Present Cryolite Workers.

Complaints	Former workers			Per cent.	Frequency of same complaints of present workers, per cent.
	Men	Women	Both sexes		
Loss of appetite	41	40	81	63.8	55.9
Nausea	34	37	71	55.9	52.9
Vomiting	19	22	41	32.3	16.2
Irregular motions	15	22	37	29.1	36.8
Cough.................	15	11	26	20.5	14.7
Headache..............	22	30	52	40.9	2.9
Tiredness	31	37	68	53.5	13.2

workers. Tiredness and headache were much the more frequent among the discharged workers, viz. 53.5 and 40.9 per cent. as against 13.2 and 2.9 per cent. With the reservation one must take when comparing particulars collected in different ways, the result seems to permit of two conclusions: (1) The statements of the present workers regarding the discomforts of their work are correct; (2) in the course of time a selection takes place, whereby the individuals suffering least discomfort from the work, either primarily or by habituation, remain at the factory. That this latter conclusion is correct is supported when we consider the relation between the length of the period of employment and the frequency of the complaints (Table 35). Of the workers who had been employed between six months and three years, 89.9 per cent. made complaints; in the group with a period of employment of five years or more, only 76.9 per cent. of the workers complained of having or of having had the discomforts concerned.

TABLE 35.

Relation between Length of Employment and Frequency of Certain Complaints among Cryolite Workers.

Employed years	No. of present workers	Of which complained	No. of former workers	Of which complained	Total workers	Of which complained	Frequency of complainers in per cent.
1/2—less than 3 ...	0	0	69	62	69	62	89.9
3—less than 5	15	13	20	16	35	29	82.9
5 or more	53	43	38	27	91	70	76.9

2. Result of Röntgen Examination

It was not possible to make an objective examination of all the former workers. Thirty-three persons who had previously worked at the factory for

TABLE 36.

Frequency of Osteosclerosis and Pulmonary Fibrosis among Former Cryolite Workers.

No.	Sex, age at examination	Employed years	Acute gastric symptoms	No. of years between discharge and examination	Osteosclerosis	Röntgenological signs of pulm. fibrosis	Spondylitis deformans
72	♂ 61	26	+	1½	—	—	+
87	♀ 48	16	+	1½	1st phase	Light 2nd phase	—
82	♀ 56	14	+	2	1st phase	Light 2nd phase	+
80	♂ 30	7	+	2	—	Light 2nd phase	—
94	♀ 27	6	—	2	1st phase	—	—
98	♀ 27	6	+	2	2nd phase	—	(+)
100	♀ 38	12	+	2	2nd phase	—	(+)
91	♂ 72	30	+	2½	—	{ Light or inc. fibrosis }	+
88	♀ 67	31	—	2½	—	{ Light or inc. fibrosis }	—
71	♂ 41	6	+	2½	1st phase	Light 2nd phase	—
79	♂ 73	38	—	3	—	—	+
83	♀ 70	17	+	3½	—	—	—
76	♀ 63	19	—	4	—	—	+
70	♂ 60	11	+	5	1st phase	—	+
99	♀ 70	25	+	5½	—	—	+
93	♀ 65	15	+	6	—	—	+
89	♂ 39	5	+	6½	—	{ Light or inc. fibrosis }	—
77	♂ 49	4	—	7	—	—	—
73	♀ 68	16	+	11	—	—	+
78	♀ 44	12	—	12	—	—	—
81	♂ 71	10	+	13	—	—	+
90	♀ 49	13	+	13	3rd phase	—	(+)
97	♂ 66	11	+	14	2nd phase	—	(+)
84	♂ 50	10	+	14	—	—	+
75	♂ 51	10	+	15	—	—	+
85	♂ 49	7	+	16	—	—	+
86	♀ 70	9	+	16	—	—	—
96	♂ 66	8	—	16	—	—	+
69	♂ 54	7	—	20	—	—	+
74	♂ 68	7	—	23	—	—	+
92	♂ 49	4	+	25	—	—	—
95	♀ 95	10	?	30	—	—	—

at least four years were requested to submit to an X-ray examination; 31 complied. The usual radiographs were made of pelvis and columna lumbalis, and of 29 the lungs as well. Application to the Almindelig Hospital, Copenhagen, also resulted in the securing of Röntgen films of a former female worker, now an inmate in the hospital. Thus the total of those X-rayed was 32, 17 men and 15 women. Their data and the result of the examination are shown in Table 36.

They were mostly elderly people. The period of employment at the factory was from 4 to 38 years, averaging 13.5 years. The average period of employment for the present workers was 10 years. For 9 people (28.1 per cent.) the radiograph revealed the typical bone changes, viz. 5 cases of 1st phase, 3 of 2nd and 1 of 3rd. This is a surprisingly low frequency compared with the present workers, of whom 86.2 per cent. had signs of osteosclerosis. Still more striking is the difference when we consider the group of former workers who had been away from the factory at least three years. Of 22 persons only 3 had osteosclerosis (13.6 per cent.); there was one case in each phase. This finding makes it *exceedingly probable that the specific bone changes caused by cryolite are capable of diminishing and disappearing entirely after cessation of work, and that this is the rule.* A priori it would be reasonable to suppose that osteosclerosis would occur with the same or even higher frequency among earlier workers than among present ones. The average period of employment is longest among the former workers, and if anything exposure to dust has been worse than it is now. There is hardly any reason to presume that mortality has increased among individuals with osteosclerosis (at any rate not of 1st and 2nd phase), and there was no selection when looking up the former workers. The material is not large, it is true, but presumably large enough to exclude chance results.

Any definitive settlement of the question of whether or not the bone changes are reparable can only be arrived at by repeated X-ray examinations over a sufficiently long period. This has been impossible, as the affection was first recognized towards the close of 1931. The only possibility of recognizing changes in the intensity of the osteosclerosis was provided by the cases of four female workers who were radiographed in 1931, discharged in 1932 and again radiographed in 1934. On comparing the films from the two examinations no definite change could be seen, but in these cases no more than two years had elapsed between their discharge and the last Röntgen examination. The female worker (No. 90) who 13 years after ceasing work still had changes of 3rd phase (considerable changes, too; see Fig. 30), was radiographed at the Kommunehospital Röntgen Department in 1930, or 3 years before the present investigation. As might have been expected, no recognizable change had occurred in that

period. Thus, even if it is the rule that osteosclerosis diminishes in time, there are exceptions.

In the X-ray examination of the columna of the former cryolite workers a surprisingly large number of cases of *spondylitis deformans* of ordinary type was observed, but often of a pronounced character. Of the 23 people whose bones did not show the characteristic sclerosis, 14 had spondylitis deformans. It is possible that this must be taken to be a remnant of the ligament calcification accompanying bone changes of the 2nd and 3rd phase, on the radiograph more or less resembling spondylitis deformans. In that case, ligament calcification would be less amenable to repair than bone changes. The question cannot be decided with the present material. The spondylitis deformans observed may be a banal phenomenon. All those affected were elderly individuals of the working class; the age varied from 49 to 73 years.

For the purpose of throwing some light on the post-discharge course of the *pulmonary fibrosis* which occurs so frequently among cryolite workers, the lungs of 30 of the former workers were X-rayed. The films have been judged in the same manner as in the examination of the present workers. The result is given in Table 36. Signs of fibrosis were observed in 7 people, or 23.3 per cent.; of these, three cases were slight or incipient fibrosis, four slight 2nd grade. Among the present workers, half had pulmonary fibrosis. Accordingly, here again it seems that the lung changes observed on the radiographs are capable of recovering. Conditions become still more marked if we consider the 20 people who, at the time of the examination, had been away from the factory at least three years. In that group there was only 1 case of fibrosis (1st grade), and that in a man who, before being taken on at the factory, had worked for $2^1/_2$ years at a porcelain works, where the silicosis frequency among the workers is considerable, even after a few years' work. Though the material is small, it seems justifiable to conclude that the pulmonary fibrosis caused by cryolite dust does not progress after cessation of the work, but perhaps even has a tendency to diminish. As this does not apply to the genuine silicosis caused by quartz, the indication is that cryolite is the active agent in the present case, and not the quartz in the cryolite.

3. Workers from the Cryolite Mine at Ivigtut

With the assistance of *The Cryolite Mine and Trading Co. Ltd.* an opportunity was given of X-raying 9 male workers from the cryolite mine at Ivigtut immediately after their return home from Greenland (October 1933). According to information by Dr. P. Fischer, who has been physician at the mine for many years, the state of health among the workers at Ivigtut must be described as

good. No symptoms of lung or bone affections have ever been observed that have led to the diagnosis of silicosis or fluorosis. A Röntgen apparatus was installed at Ivigtut in 1929. Among the workers acute gastric symptoms such as loss of appetite, nausea and vomiting are familiar when working in dust, but they do not consult the doctor on that account. Otherwise gastro-intestinal affections are not very frequent.

The results of the examination of the nine workers appear from Table 37. The effective period of employment at the mine has varied from $1^1/_3$ years to nearly 8 years, spread over a period of up to twice as long with repeated sojourns in Denmark. All had been employed on blasting, i. e. the work which develops most dust. Seven of the workers said they had had transitory gastric symptoms, as a rule every year when the work began. The X-ray examination revealed the characteristic bone changes (of 1st phase) in only one worker, whereas the osseous system of the others was normal. In this one worker (No. 228), who in the course of 13 years had worked $7^1/_4$ years at the mine, there was also pulmonary fibrosis, apparently the beginning of the 2nd grade. Among the other workers other two cases of fibrosis of 1st grade were observed, both after about 5 years of effective work.

This examination indicates that the osteosclerosis caused by cryolite occurs only rarely among the workers at Ivigtut, but that pulmonary fibrosis is a

TABLE 37.

Results of Röntgen Examination of 9 Male Workers from the Cryolite Mine at Ivigtut, Greenland.

No.	Age	Effective period of employment in mine, years	Employment spread over years	Acute gastric attacks	Osteosclerosis	Röntgenological signs of pulm. fibrosis
228	43	$7^3/_{12}$	$13^5/_{12}$	+	1. phase	Apparently incipient 2. grade
229	45	$4^6/_{12}$	$4^6/_{12}$	+	—	1. grade
230	37	$1^4/_{12}$	$1^4/_{12}$	—	—	—
231	33	$7^{11}/_{12}$	$10^7/_{12}$	+	—	—
232	38	$5^5/_{12}$	$9^7/_{12}$	+	—	Perhaps incipient fibrosis
233	49	$4^6/_{12}$	$5^6/_{12}$	+	—	—
234	29	4	$4^6/_{12}$	+	—	—
235	36	$2^4/_{12}$	5	+	—	—
236	31	$7^2/_{12}$	$12^7/_{12}$	—	—	—

rather more frequent phenomenon. Judging from the experience gained during the examination of the cryolite workers in Copenhagen, it is also presumable that bone changes have little chance of developing among the mine workers. The work is seasonal, mostly goes on in the open air, and the workers are rarely employed for a long period of years, even if it is the rule that they return to the mine regularly for some years*).

*) The officials, machine-workers etc. in the cryolite factory in Copenhagen who are only exposed to dust now and then have no bone or lung changes. Röntgen examination of columna, pelvis and lungs of twelve males (Nos. 216—227) of the ages between 23 and 66 years, with an average period of employment of 17.2 years, displayed no definite signs of osteosclerosis or pulmonary fibrosis. Some had or previously had had acute gastric symptoms through being in dusty atmosphere.

MORBIDITY AND MORTALITY

Cryolite being a toxic substance, it is necessary to see whether morbidity and mortality are higher among cryolite workers than others. Information bearing on these matters has been secured from various sources.

1. Morbidity

As is usual in such cases, it has been possible only to record that part of the morbidity that is expressed in days on sick benefit, absence from work. The factory pays benefit for every absence on account of sickness, both with and without relation to accidents. The amount is about one-fourth of the wages and is continued up to 13 weeks. As a rule a medical certificate is only required for absence extending over more than a few days. Benefit is paid even for single day absences on account of sickness. It may therefore be assumed that the factory's morbidity statistics are very comprehensive.

On the basis of the factory's wages books I have made up the morbidity for the period from January 1st, 1923 to January 4th, 1933. The material is collected into Table 38. The average employment time in the period has been 3.3 years for men and 2.0 years for women, a working year being put at

TABLE 38.

Morbidity of Cryolite Workers in the Period January 1st, 1923 to January 4th, 1933, recorded by the Factory.

	No. of workers	No. of working days	No. of sick-days	Average No. of working days per worker	No. of sick-days per working year (300 working days)	No. of sick-days per calendar year
Men	118	153206	3415	1298	6.69	8.14
Women	214	129674	3078	606	7.11	8.65

TABLE 39.

Morbidity before, during and after Empthe Cryolite

Age	Before employment						employment		
	Men			Women			Men		
	No. of insurance years	No. of sick-days	No. of sick-days per year	No. of insurance years	No. of sick-days	No. of sick-days per year	No. of insurance years	No. of sick-days	No. of insurance years
21—30 years.....	57	231	4.1	134	92	0.7	128	719	172
31—40 „	41	63	1.5	36	102	2.8	221	1367	76
41—60 „	45	101	2.2	18	194	10.7	252	2319	173
Over 60 years....	—	—	—	—	—	—	55	664	12
Total.....	143	395	2.8	188	388	2.1	656	5069	383

300 working days. As we must take it that sickness on non-working days is just as high as on working days, we arrive at the number of sick-days per calendar year by multiplying the number of sick-days per working year by the quotient 365/300. This gives *the male workers* an average in the period of *8.1 sick-days, the female workers 8.7 sick-days a year.*

The *sick-clubs* were requested to supply information as to the sickness among all workers comprised by the investigation, both present and past.

For each person the sick-club was sent a form to be filled in as to the number of sick-days and the nature of the sickness from the date of admission to the club up to and including the year 1934. The replies were afterwards checked and, if required, corrected by personal visits to the clubs. By this means information was collected for 141 persons, 83 men and 58 women; 58 of them were still at the factory, the remainder were previous workers. The total number of sickness-insurance years was 1876, or on an average 13.3 years per individual. The average period of employment at the factory was 8.8 years. The material covers the period 1900—1934, but mostly its latter half. The sickness in the period before, during and after employment at the factory was compiled for every person. All the particulars received were used, even if for the individual they merely covered one of the said periods or a part of one. When determining the sickness during employment I included the total sickness in the calendar year in which the worker was taken on or discharged from the factory. Where a worker was taken on several times, the period of employment was reckoned from the first engagement to the last discharge. The material is set up according to age groups in Table 39.

The material seems to be too slender to judge of the morbidity before, and perhaps after, employment. For the period of work at the factory the distribution into age groups is fairly regular and the morbidity rising from one age group to the next. For all age groups *the average number of sick-days a year during*

TABLE 39.

...after Employ... Cryolite Factory, Recorded by Sick-Clubs.

During employment					After employment					
Men			Women		Men			Women		
No. of sick-days	No. of sick-days per year	No. of insurance years	No. of sick-days	No. of sick-days per year	No. of insurance years	No. of sick-days	No. of sick-days per year	No. of insurance years	No. of sick-days	No. of sick-days per year
719	5	172	685	4.0	31	89	2.9	41	558	13.6
1367	6	76	662	8.7	88	845	9.6	33	381	11.6
2319	9	173	1777	10.3	167	1962	11.8	61	889	14.6
664	12	12	202	17.7	44	117	2.7	34	285	8.4
5069	7	83	3326	8.7	330	3013	9.0	176	2113	12.0

employment at the factory was 7.7 for men and 8.7 for women. These figures conform well with the morbidity arrived at from the factory's own records (men 8.1, women 8.7 sick-days per annum). Morbidity after discharge from the factory is somewhat higher, the men averaging 9 days a year and the women 12.

In order to judge of the morbidity among cryolite workers there must be a comparative material. Their morbidity is dependent on a number of factors, one of them being the toxic effect of the cryolite, especially interesting in this connection, whereas the other factors are more or less common to all factory workers: age, state of health on starting work, the demands of the work on physique and nervous system, wages, sickness benefit, housing conditions, food, etc. The ideal comparative material would be the simultaneous morbidity among factory workers whose age distribution, working conditions and life in every respect were identical, with the one exception that the material handled had no bearing on health. There are no such statistics, however, and one is therefore compelled to illustrate the problem by comparing with the morbidity of the whole population and that in other industries. Below are certain Danish statistics which, where nothing else is indicated, are based upon information received from the sick-clubs.

(1) *The Statistical Department*'s statistics*) of sickness in the *population of Denmark* in the year 1908, arranged i. a. into occupational groups. The material comprises 98,655 members of sick-clubs. Whereas the average morbidity for the population of the whole country was 7.6 sick-days per annum for men and 5.9 for women, it was higher for the population of Copenhagen (men 9.4, women 6.4 sick-days),

*) Sygelighedsstatistik. Statistiske Meddelelser. 4. række, 34. bind, 4. hæfte, Copenhagen 1910.

and still higher for factory workers in Copenhagen (men 10 and women 8.9 sick-days).

(2) Gudjonsson's (372) statistics on the morbidity among *porcelain workers in Copenhagen* in the years 1910—32, which on an annual average comprise 211 male and 161 female workers. The average number of sick-days a year was 4.7 for men (varying from 1.8 to 6.7) and for women 6.5 (varying from 4 to 8 days). The work in the porcelain factories is dangerous to health, in so far as Flemming Møller (590) found silicosis in 361 out of 798 workers examined in 1932.

(3) Garde's (300) investigation into the morbidity of *workers in Danish paper mills* in the years 1914—15. The material comprised 1083 men and 587 women. The male workers on an average had 8.3 sick-days per year, the female 12.5. This is an industry that does not handle toxic material but where the form of work (continuous running) and the working conditions (warm and damp air, draught) contain certain injurious elements.

(4) Gudjonsson and Harrsen's (373) statistics on the morbidity among 193 male and 200 female *brewery workers in Copenhagen* (1930—32) as communicated by the brewery. The average number of sick-days per annum in this period for men was 10, for women 29.1. In this establishment no toxic substances are handled and the hygienic conditions are good. The economic and cultural status is high and employment very regular. The brewery pays full wages in case of sickness lasting less than three days. After six weeks' work the male workers have a right to half wages in sickness benefit up to 26 weeks. The female workers have the right to the same sick pay for up to 30 days after three months' seniority.

(5) Morbidity among *workers* in more permanent employment and a right to sick pay *under the Corporation of Copenhagen**) in the period from April 1st, 1931 to March 3rd, 1934. The material comprises an average of 2161 men and 971 women per annum. The average number of sick-days per annum was for men 19.4 and for women 21.7. Set up in age groups the sick-days are distributed as follows:

Age	Men	Women
Under 35 years	11.9	11.9
35—44 years	14.8	17.2
45—54 „	18.6	24.1
55 years or over	31.0	26.4
All...	19.4	21.7

(6) Reports of the *Directorate of Sick-Clubs* on morbidity among *club members in Copenhagen* in the period 1920—31. The average number of sick-club members per annum was 112,344 men and 155,906 women. On an average the male members had 7.2 sick-days a year, with variations from 5.7 to 7.8 days. For females the figures were 8 sick-days, varying between 6.3 and 8.6.

(7) On approaching *The Danish Fertilizer Company*, Copenhagen, I was given the opportunity of examining the sickness statistics for the company's five superphosphate and sulphuric acid factories in large Danish provincial towns for the years 1927—34. The statistics are kept by the company on the basis of specified sick reports from the workers' own physicians. The factories employ men only, many of them being casual workers employed only part of the year; no sick pay is given. The period comprised 2974 worker-years, or an average of 649 per calendar year. The

*) Staden Københavns Regnskab og Beretning om Kommunens Anliggender for 1931—32, 1932—33, 1933—34.

average number of sick-days per calendar year for the whole period was 7.3, with variations from 5 to 9 days. The number of sick-days per calendar year is arrived at by multiplying the number of sick-days per working year by 365/300. The factories handle fluoric material (phosphorite), but as far as is known the toxic possibilities are insignificant in practice.

Certain conclusions may be drawn from these statistics. There is no ideal comparative material; one is compelled to compare figures which, strictly speaking, are not comparable. Morbidity varies greatly within the various industries. It is beyond doubt that the direct danger to health through the work is only one of the many factors that determine the morbidity. The regularity of the work and the access to sick benefit plays a considerable part. For instance, workers in a Copenhagen brewery (4) had a very high sickness absence in 1930—32 (men 10 sick-days a year, women 29.1). Their work is very regular, the sick pay is high and is issued over long periods, but the workers are not exposed to known noxious influences. Male workers in more regular employment under the Corporation of Copenhagen (5) have a still higher number of sick-days in the year, though their working conditions must be said to be particularly good. Porcelain workers, who are much exposed to silicosis, had a much lower morbidity in 1930—32, viz. 6.7 sick-days a year for men and 8 for women (2).

If the recorded morbidity is to prove that a class of work is harmful to health, it is necessary to have either an ideal comparative material or a marked deviation from the average morbidity in industry. As to the latter we know only little. The average number of sick-days in 1908 was higher among factory hands in Copenhagen than among male and female sick-club members in the same town (1). No later material is available concerning this, so we must take it that it still exists unchanged. In the period 1920—31, from which much the greater part of the material for judging the morbidity among cryolite workers dates, the average number of sick-days a year for male and female sick-club members in Copenhagen (6) was 7.2 and 8 respectively. The morbidity among the cryolite workers (men 7.7—8.1 sick-days per annum, women 8.7) is somewhat higher, but not more than was relatively the case for all factory workers in Copenhagen in 1908. *The morbidity of cryolite workers, measured by the number of sick-days in the year, scarcely exceeds the average in industry as a whole.* The injurious effects of working in the factory are of such a nature that they are reflected in complaints from the workers, but not in a strikingly large number of absences. This may seem surprising, having regard to the considerable pathological changes in those attacked, but no doubt the cause is that these changes develop at an extremely slow rate and make habituation

possible. On the other hand, it is conceivable that the increase in the number of sick-days observable in most age groups after discharge from the factory (Table 39) expresses an injurious influence brought to bear in the course of the work and only manifested later.

2. The Various Affections

A priori it is presumable (in a material of a certain compass) that the distribution of the sick-days over the various affections is influenced by fewer factors than is the actual number of sick-days, though uncertainty in diagnosis and grouping must not be underrated. In a small material the picture may be disproportionately disturbed by incidentals, such as a single case of illness of long duration.

Making use of the particulars from the sick-clubs the affections were divided into 13 groups and set up with the absolute and the relative number of sick-days within each group (Table 40). A comparison was also made with

TABLE 40.

Distribution of Sick-D idual Disea

Disease	Cryolite workers during employment (1900—1934)				Cryolite workers after employ ment (1900—1934)				erphosphate Danish pro towns (1927-
	Men		Women		Men		Wom		Men
	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	
		%		%		%			
In nervous system and sensory organs	426	8.4	127	3.8	546	18.1	365	812	
Throat	125	2.5	43	1.3	4	0.1	28	162	
In respiratory organs	245	4.8	141	4.2	100	3.3	91	1436	
Heart	91	1.8	178	5.4	17	0.6	167	637	
Gastric & intestinal	312	6.2	132	4.0	172	5.7	265	1522	
In urinary system; venereal	0	0	109	3.3	0	0	261	503	
Skin	29	0.6	313	9.4	46	1.5	126	223	
Tuberculosis	0	0	448	13.5	9	0.3	97	36	
Influenza	384	7.6	221	6.7	247	8.2	63	1315	
Rheumatism and rheumatic affections	1145	22.6	550	16.5	618	20.5	103	1390	
Bone fractures	82	1.6	353	10.6	206	6.8	0	1108	
Other diseases caused by accidents	808	15.9	79	2.4	538	17.9	114	7553	
Other and unindicated diseases	1422	28.1	632	19.0	510	16.9	433	1287	
Total	5069	100	3326	100	3013	100	2113	7978	

the distribution of the sick-days over the same disease-groups in three of the statistics already mentioned: the population of Denmark 1908 (1), workers in paper mills 1914—15 (3), and workers in superphosphate factories 1927 —34 (7). The latter were drawn up simultaneously with and in the same manner as the statistics on the morbidity of cryolite workers.

The material concerning the cryolite workers is so slender that it is possible only to pay attention to marked deviations from the average. As men and women are equally exposed and react in the same way, the probability of a deviation being due to cryolite effect is the greater the more uniformly it is recorded for both sexes. A consideration of conditions during employment will show that *affections of the nervous system and sensory organs*, and *throat diseases*, are not outstandingly frequent. *Disease in the respiratory organs* comprises fewer sick-days than in all comparative materials. *Cardiac affections* are not particularly frequent among the male workers, but frequent among the females. The frequency of *gastro-intestinal affections* is below the average. In the group *diseases in the urinary system* as well as *venereal diseases* there are no sick-days for the men, but a relatively high total for the women. *Skin diseases* are strikingly scarce in their occurrence among the male workers, pronouncedly

TABLE 40.

Sick-Days on Individual Diseases or Disease-Groups.

...after employ... —1934)	...phosphate workers Danish provincial ...wns (1927—34)		Factory workers in Denmark in all industries (1908)		Workers at paper mills in Denmark (1914—15)		Sick-club members in Denmark, all occupations (1908)	
Women		Men	Men	Women	Men	Women	Men	Women
Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days	Sick-days
%	%	%	%	%	%	%	%	%
365 / 28	17. / 1.	012 / 162	4.5 / 0.9	} 6.4	7.0	5.3	11.1	8.0	10.2
91	4.	436	8.0	8.9	6.1	12.9	7.2	10.1	9.0
167	7.	937	3.5	2.1	2.0	0	0.8	1.8	2.1
265	12.	522	8.5	9.2	14.9	6.3	11.9	8.0	12.4
261	12.	503	2.8	2.2	2.8	3.5	5.1	2.3	2.9
126	6.	223	1.2	2.8	3.1	3.2	2.5	3.5	4.7
97	4.	36	0.2	10.0	8.7	6.9	4.5	11.0	12.1
63	3.	15	7.3	6.7	5.3	3.9	4.6	7.0	6.2
103	4.	190	7.7	11.7	5.1	14.2	10.6	10.3	4.7
0	0	108	6.2	} 20.3	6.9	21.7	2.8	18.1	4.1
114	5.	553	42.0						
433	20.	87	7.1	19.7	38.1	22.1	38.9	19.8	31.6
113	100	78	100	100	100	100	100	100	100

TABLE 41.

Cause of Death and Post-examination of

No.	Sex	Age at death	Employed at factory, years	Period between discharge and death, years	Place of death	Case No. or date of death	Diagnosis	
200*)	♂	51	8	1	The Rigshospital, Dpt. B.	259/1933	Mb. cordis aortæ lues cerebrospinalis	rtitis syphili itis mucopu
201	♂	46	5	21	Home	4/7 1930	Tuberculosis pulm.	ne.
202	♂	80	24	5	Aged People's Home	12/5 1927	Pneumonia duplex	postases pu
203	♂	58	21	0	The Rigshospital, Dpt. D.	630/1928	Peritonitis	pendicitis;
204	♂	53	27	0	The Øresund Hospital, Med. Dpt.	770/1910	Cancer oesophagi; sclerosis; exostoses	ncer oesoph physema pu
205	♂	37	12	7	The Kommunehospital, I. Dpt.	444/26	Ulcus ventriculi p... tum	cera ventr. on. fibrosa
206	♂	67	38	1	Aged People's Home	7/3 31	Cancer intestini	ne.
207	♂	69	15	8	The Bispebjerg Hospital, Dpt. A.	63/3/ 1929	Diabetes mellitus; gangræna cruris	eumonia fib tæ et a. cord ris.
208	♂	47	14	0	The Øresund Hospital, Med. Dpt.	1946/ 1921	Tuberculosis pulm. kyphoscoliosis	bercul. fibro osa totalis ertrophia c um; abscess
209	♀	24	2	0	The Kommunehospital, II. Dpt.	191/1929	Asthma bronchiale; chitis; emphysema	nchitis puru
210	♂	51	7	1	Home	27/7 1918	Cancer oesophagi; coxæ	ne.
211	♂	62	10	4	The Øresund Hospital, Med. Dpt.	100/ 1927	Tuberculosis pulm.; ritis exsudat. sin.; a... nuria	berculosis pu ulcerosa in carditis adl
212	♂	55	2	4	The Bispebjerg Hospital, Dpt. A.	4/3 1932	Cancer coli; metas...	cer coli; m
213	♂	47	7	0	The Øresund Hospital	573/ 1926	Tuberculosis pulm. intestini; amyloido...	berculosis pu stini tenuis;
214	♂	54	5	0	The Øresund Hospital	285/ 1921	Tuberculosis pulm. ryngis et urogenit... intestini	ne.

*) The necropsy is treated in Chapter XVIII.

TABLE 41.

Post-mortem examination of Former Cryolite Workers.

	Necropsy
osis	
aortæ luid inalis	tis syphilitica; ectasia aortæ; mb. cordis aortæ; hypertrophia cordis m.g.; stasis organorum; bronchis mucopurulenta; infarctus pulm. sin.; anthracosis pulm.; leptomeningitis chron. fibrosa l. g.
pulm. dupl	
uplex	postases pulm.
	endicitis; ulcus penetrans recti; embolia a. pulm.
agi; arter toses	cer oesophagi; metastases; absces. perisplenica; arteriosclerosis; atrophia granul. renum; hysema pulm.; pleuritis fibrinosa; hypertrophia ventric. sin. cordis; exostoses multiplic.
culi perfor	ra ventr. et duodeni perforantia; peritonitis fibrinosa diffusa; aortitis syphilitica; pleuritis n. fibrosa bilateralis.
ini	
tus; anæml ris	monia fibrinosa; pleuritis fibrin. sin.; emphysema pulm.; myofibrosis cordis; arteriosclerosis et a. coronar.; atrophia pancreatis; cystis renis dxt.; vesica trabecularis; status post amputat.
pulm.;	ercul. fibrosa pulm. duplex; peribronchitides, retractio et bronchiectasiæ l. g.; pleuritis adhæs. sa totalis dupl.; focus calculosus gland. bronchial.; hyperplasia et anthracosis gl. bronch.; trophia cordis; dislocatio cordis ad dext.; degeneratio amyloidea lienis; tubercul. caseosus m; abscessus perirenalis sin.; enteritis follicularis chron.
chiale; br sema pul	chitis purulenta; emphysema pulm.; oedema pulm.; hypertrophia cordis.
hagi; mal	
pulm.; pl sin.; albu	rculosis pulm. utriusq. m. g. (cavernosa etc.); pleuritis adhæs. duplex; tub. caseos. gl. bronch.; ulcerosa intest. ten.; endocarditis verrucosa chron. aortæ; steatosis hepatis; hyperplasia lienis; carditis adhæsiva.
metastases	er coli; metastases.
pulm.; t yloidosis	rculosis pulm. utriusq. m. g. (cavernosa etc.); pleuritis adhæsiva fibrosa duplex; tub. ulcerosa ini tenuis; degeneratio amyloidea lienis et renum.
pulm. et rogenitalis	

frequent among the females. *Tuberculosis* has no sick-days among the men but a total above the average among the women. This, however, is due to one female worker suffering from chronic pulmonary tuberculosis with relapsing hæmoptysis. The frequency of *influenza* lies about the normal. *Arthritic and rheumatic affections* have a marked frequency among cryolite workers, 22.6 per cent. of the men's and 16.5 per cent. of the women's sick-days falling within this group. In appraising the frequency of *bone fractures* it is only possible to compare with superphosphate workers, among whom accidents are of high frequency. According to this comparison bone fractures are not especially frequent among the male cryolite workers, but more so among the females. This again is affected by the case of a single person: a complicated fracture with repeated absences over several years. On the whole, *diseases caused by accidents* are not especially frequent among cryolite workers.

With regard to post-employment affections only one or two points need be discussed. *Affections of the nervous system* and *sensory organs* have a very high frequency among both men and women (17—18 per cent. of all sick-days). These include especially such sickness reports as neurasthenia, neuralgia, nervous rheumatism, etc. *Tuberculosis* is still a disease of rather infrequent occurrence. *Arthritic and rheumatic affections* again are very frequent among the men, but no longer among the women.

On comparing the kinds of diseases with the workers' complaints and the physical findings, it is apparent that the acute and chronic symptoms from the gastro-intestinal canal are not signs of grave affections involving absence. The same applies to pulmonary fibrosis and the emphysematous condition. The extraordinarily frequent rheumatoid affections may be due to the nature of the work (cold, draughts, hard manual labour), but they may also be taken to be symptoms of the bone disease. The marked frequency of nervous disorders after employment has ceased might indicate that cryolite has a particularly harmful effect on the central nervous system. Or it is probable that even after the termination of employment at the factory the bone changes may give symptoms for which there is no organic substratum observable during an ordinary examination. There is nothing to show that the bone changes involve a fracture frequency deviating from the average, nor that the excretion of fluorine causes renal lesions.

3. Mortality and Causes of Death

In the course of the search for former cryolite workers a total of 24 (21 men and 3 women) were stated to have died after leaving the factory. It was possible to procure ample details concerning 15 of these persons, 14 men and one woman, as to place and cause of death and any results of post-mortem examination. These details were unobtainable for the others, but as a whole their period of employment at the factory was short; seven of these former employées had worked there only three years or less.

The material does not permit of an appraisal of the mortality, not even

approximately. It must suffice to consider the data of the various individuals as given in Table 41. They were mostly people who had worked long at the factory, the average period being 13 years. Most of them died while working there or in the course of a few years after leaving. For the 14 men the average age at death was 55.6 years, i. e. not particularly low. The causes of death were as follows:

Pulmonary tuberculosis	5	cases
Cancer in alimentary canal	4	,,
Appendicitis (operation)	1	case
Perforating gastric ulcer (operation)	1	,,
Syphilitic heart disease	1	,,
Pneumonia in senility	1	,,
Diabetes	1	,,
Bronchial asthma	1	,,

The results of the post-mortems in 11 cases are shown in Table 41. In one case (No. 204) there were changes (multiple exostoses) making it extremely probable that the worker had had a pronounced osteosclerosis. That the other necropsy reports*) mention nothing of bone changes need not mean that there were none; diagnosis on the post-mortem table is too difficult for that. The examination of the organs otherwise showed no pathological changes that cannot reasonably be explained by the diseases actually present. Thus no mention is made of any certain signs of pulmonary fibrosis of non-tubercular origin, and no changes in gastro-intestinal tract and kidneys that may be considered as having been caused by cryolite.

The examination of the deceased cryolite workers shows that a considerable number of them died of pulmonary tuberculosis and cancer in the gastro-intestinal tract. Like the others, these diseases are among the generally occurring causes of death, and the small material provides no basis for a discussion of the possible connection between working with cryolite and the cause of death. *There is nothing to show that working with cryolite reduces the period of life or that cryolite workers acquire macroscopically recognizable organic lesions apart from the bone changes.*

*) Further reference is made in Chapter XVIII to the necropsy on worker No. 200.

POST-MORTEM EXAMINATION OF TWO CRYOLITE WORKERS

In the period occupied by the present investigation two cryolite workers died of intercurrent diseases. Both of these workers, one of whom was a present worker, the other a former worker, had been long employed at the factory, about 24 and 9 years respectively; they had previously been examined clinically. Below are the histories, the results of the physical examination and of the necropsy. Finally, the results are given of various fluorine analyses of organs and bones.

1. Cryolite Worker No. 55

Male cryolite worker No. 55, born 1867. Formerly worked on the land. Taken on at the factory 1910 and worked there without a break until some weeks before his death in January 1935, in all $24^2/_{12}$ years. X-rayed in November 1931 together with the other workers (Flemming Møller and Gudjonsson). Examined clinically June 21st, 1933. Reported sick January 4th, 1935, admitted January 24th to the Kommunehospital's 1st Dept. for incarcerated crural hernia (Case No. 145/1935). Radical herniotomy was performed at once. Death occurred on January 29th under signs of pneumonia and intestinal obstruction.

Medical History.

States that he has always had good health, has never had any serious illness. While at the factory he has only lost 9 days in 1919 (sprained foot) and 18 days in 1925 (influenza). As a rule he has worked in thick dust. When again exposed to dust after holidays or temporary work in dustless rooms he has loss of appetite and diarrhoea or constipation; these complaints disappear entirely after one or two days. Otherwise suffers no inconvenience from the dust. During past two years some dyspnoea when walking quickly or going upstairs; he has no cough or expectoration. Complains of increasing stiffness of limbs and back, has difficulty in moving after rest. Does his work (not particularly heavy) at the factory without much trouble. About a year ago he had a short period with

indefinite rheumatoid pains in body and extremities. Has never suffered from salivation, thirst, polyuria or bleeding tendency.

Clinical Examination.

General Condition. Healthy appearance corresponding to age and employment. Rather thin. Height 168.8 cm., weight 62.5 kg.

Nasal cavity, pharynx. Doubtful hyperæmia of mucous membrane. Complete denture. *Thorax* emaciated, slightly barrel-shaped. Respiratory movements almost nil. Circumference of thorax (measured over angulus scapulæ and papilla) 87.5 and 87 cm. for maximum inspiration and expiration respectively. Respiration of abdominal type.

Heart covered by lung. Heart sounds distant, no murmurs. Action regular, not hurried. Blood pressure 150/80. Slight peripheral sclerosis of arteries.

Lungs. Anterior boundary 7. costa, posterior 11. intercostal space, almost immobile. Percussion note not greatly changed. Slight dulness round right clavicula; respiration here over a limited area feeble-bronchial with occasional dry râles. Otherwise auscultation reveals normal conditions apart from a somewhat prolonged expiration.

Abdomen. Nothing abnormal.

Testes, gl. thyreoidea. Normal size and consistency.

Nervous System. Cranial nerves present nothing in particular. Power good and equal in all extremities. No sensory disturbances on truncus or lower extremities. Abdominal, Achilles and plantar reflexes normal, patellar reflexes unobtainable.

Bones and Joints. The subcutaneous surfaces of clavicula, tibia and ulna irregularly rugged. No bone tenderness on percussion. Thoracic kyphosis of spine increased. Complete rigidity in lumbar and thoracic regions. Movement in the cervical region limited, flexion and rotation being confined to 10—15°, extension about 5°. There is moderate but distinct atrophy of the long extensor muscles of the back. Examination of the other joints reveals normal motility except in both hips, where flexion is good, but abduction and rotation restricted to about 15°.

Blood. Hæmoglobin 102, erythrocytes 4.86 mill., index 1.05. Leucocytes 6040; polymorphonuclears 31 per cent., staff-nuclears 27 per cent., metamyelocytes 1 per cent., eosinophil 1 per cent., basophil 0, lymphocytes 37 per cent., monocytes 2 per cent. Blood platelets 554,000, bleeding time $2^1/_4$ seconds, coagulation time $3^1/_4$ seconds, sedimentation rate 1 mm. (1 hour), plasma colour 5.

Urine contains no albumin or sugar. Nothing abnormal by microscopy.

X-Ray Examination.

Columna. Both in pars lumbalis (Fig. 21) and in pars thoracalis the vertebral corpora give a dense shadow without distinct structure. On the whole the shape of the vertebræ is retained. The inter-vertebral spaces are rather sharply outlined and of normal width. Processus transversi are gross and blurred in outlines. There is considerable calcification of ligaments. Beak-shaped osteophytes extend from the edge of the lower lumbar vertebral corpora. Between the bodies of the upper lumbar and all dorsal vertebræ the ligaments form regular dense bridges. From the side it is possible to see a dense, diffuse and irregularly bounded shadow corresponding to processus articulares. Processus spinosi are very wide, give a dense shadow and have blurred contours. There are widespread calcifications of ligamenta spinalia posteriora and ligamenta interspinalia. In the cervical region (Fig. 25) the osseous structure is not so

dense but greatly changed. The ligament calcification is less pronounced than it is caudally. Ligamenta longitudinalia anteriora appear in the form of a band of rather dense shadow from basis cranii down along the anterior surface of the vertebræ with more or less complete bridges between corpora of cervical 3—5. The calcium content of larynx seems to be increased.

Pelvis has the characteristic, very diffuse density, and it is only possible here and there to distinguish any structure. All contours are blurred, especially of crista ilei, the edges of which are very irregular, more shaggy than anything. There is considerable calcification of ligamentum sacrotuberosum. In the capsule of the hip joint is a small marginal calcification. There is moderate sclerosis of the pelvic arteries.

Thorax. Costæ are broad, give dense shadows with coarse, irregular structure and blurred, raggy outlines. The lungs are intensified and present a diffuse, uniform, rather coarse-meshed density with no marked spots. Sporadic fibrous streaks extend from hilus to apices. There seem to be fibrous changes in right apex, but apices are difficult to judge on account of clavicula and the dense, broad costa 1. Hilus is not pronouncedly enlarged. Position of diaphragm low.

Summary. X-ray examination reveals a universal diffuse osteosclerosis of 3rd phase with marked ligament calcification. The lung changes may be characterized as diffuse fibrosis, presumably of 2nd grade.

Necropsy.

Necropsy (No. 71/1935) took place 27 hours after death (cold chamber). The body was of medium build, thin and pale. The exterior examination otherwise revealed nothing abnormal than irregular, rough, subcutaneous edges of ulna and tibia.

Mouth cavity. Nothing abnormal beyond complete upper and lower denture.

Gl. thyreoidea. Size, consistency and cut surface normal. *Microscopy :* Nothing abnormal except some hyperæmia.

Lungs. Complete symphysis of pleuræ on right side, hæmorrhages and fresh fibrin coatings on left. The entire upper lobe of the right lung is fibrous, with prominent fibrous streaks surrounding a cavity the size of an apple, coated with granular, yellowish-green masses. No fresh tuberculous processes anywhere. No definite signs of silicosis in lower lobe nor in left lung, no marked change of consistency on palpation and cutting, no nodules. In both lungs the lower lobes closely interspersed with bronchopneumonias, some fibrinous, some hæmorrhagic. In the bronchiæ the mucous membrane is reddish and covered with much mucopus. Hilus and bronchial glands only slightly enlarged, black, almost soft, without calcification or caseation.

Microscopy of lower and upper lobes of right lung: Spread catarrhal, fibrinous and purulent pneumonias. In several places there are necrotic areas surrounded by typical tubercles (Langhans' giant cells, epitheloid cells and lymphocytes). There is moderate hyperæmia. No sign of silicosis in the sections. In the bronchial gland is a slight proliferation of connective tissue and some anthracosis, but otherwise nothing abnormal.

Thymus : Nothing abnormal.

Heart. Pericardium normal. Heart not enlarged (measures $9^1/_2 \times 11$ cm., weighs 300 g.). Endocardium normal. Myocardium is brownish but without fibrosis. Very slight arteriosclerosis in the coronary arteries, aorta and the large arteries. *Microscopy* of myocardium: Some fragmentation and sporadic small bleedings.

Abdominal organs. Intestines moderately dilated and infiltrated, with scattered fibrino-purulent coatings. About $^1/_2$ m. from the ileo-coecal junction a limited area of the ileum has a thick coating of fibrin and is blue in colour; there are traces of a stricture.

The stomach is somewhat distended. In pars pylorica are faint signs of mamillation of the mucous membrane, which otherwise is normal. Duodenum, small and large intestines are normal apart from the changes already described. *Microscopy* of stomach, duodenum, small and large intestines: There is considerable cadaverositas and a varying, mostly slight round-cell infiltration in tunica propria in all sections. In the small intestine some hyperæmia and on the serosa surface fibrin coatings with a varying number of white blood corpuscles.

The liver is slightly diminished, the surface a little wrinkled and here and there thickened. No change in consistency. The colour is rather more brownish than normally, on both surface and cut surfaces. The gall-bladder system presents nothing abnormal. *Microscopy:* Nothing abnormal beyond some hyperæmia.

Pancreas perhaps slightly atrophic, consistency unchanged.

Spleen slightly diminished, a little wrinkled on the surface. In the cut section the trabeculæ are clearly marked. Consistency somewhat firmer than normal. *Microscopy:* Follicles few and small, some hyperplasia of pulpa visible. The quantity of iron pigment relatively abundant. Connective tissue not pronouncedly proliferated.

Suprarenals macroscopically normal. *Microscopy:* Nothing abnormal except some hyperæmia.

Kidneys are of normal size, the capsule slightly adherent but the surface almost smooth. Cut section shows moderately pronounced stasis, but otherwise normal. *Microscopy:* Glomeruli well preserved on the whole. A number of tubuli are dilated, cystic in places and containing serous fluid in which is a moderate quantity of small amorphous granules staining deeply with hæmatoxylin (presumably calcium deposits). The interstitial connective tissue everywhere is slightly proliferous with inflammatory infiltration, especially with lymphocytes. The vessels are amply supplied with blood. The changes must be regarded as a slight grade of chronic nephritis, preponderantly of interstitial type.

Ureteres and vesica. Nothing abnormal.

Genitalia are normal. *Microscopy* of testis: Nothing abnormal beyond some hyperæmia. The *brain* presents nothing abnormal macroscopically. Hypophysis of normal size. Dura difficult to remove everywhere. *Microscopy:* Except for slight hydrocephalus in the form of dilated perivascular spaces the cerebrum displays nothing abnormal; hypophysis normal.

Macroscopic Examination of Bones.

Sternum, clavicula, several costæ, lumbar and thoracic parts of columna removed in toto as well as parts of os frontale and sections of the diaphyses of femur and tibia. The bones are heavy and markedly hard to the saw. The cancellous bones are distinctly more brittle than normally; corpus of lumbar 5 was split off with a moderate blow, and a piece of the pelvis was easily broken off by means of a chisel. Marrow in femur and tibia diaphysis is bright red and fairly firm. On cutting through lumbar vertebra 4 and costæ bright red marrow is seen in the greatly reduced cavity.

Radiographs of the bones display as a common feature a very dense shadow

and a coarse-meshed, partly blurred structure. *Sternum* is short and gross, with very coarse spongiosa trabeculæ which fuse together here and there, especially opposite the insertions of costæ 1 and 2. Lobate calcifications extend from sternum out on to costæ and costal cartilages; the latter are not calcified. The costosternal joints present nothing abnormal. *Costæ*, in addition to the dense, coarse-meshed structure, have a blurred and fleecy outline. In claviculæ compacta is very wide and the medullary cavity correspondingly narrow. *Columna* (Fig. 38 *c*) gives the same picture as that taken in vivo, but the details are clearer. The spongiosa structure is recognizable only in the middle of corpora. The inter-vertebral spaces are sharply delimited, as also the joint spaces between processus articulares. Foramina intervertebralia are narrowed and very irregularly bounded, but total occlusion does not occur anywhere. The pronounced ligament calcifications between and along processus spinosi are very distinct.

After *skeletonizing* the bones present marked changes. All are of a chalky-white colour, the surface is irregular and the weight considerably increased. *Columna* (Fig. 34) has an increase of the normal dorsal kyphosis. The weight of the air-dried preparation (cervical 7 to lumbar 3) is 1031 g.; it displaces 623.5 c.c. water, i. e. the weight of 100 c.c. is 165 g. The various parts of the bones are gross and thickened. All surfaces are uneven, nodose or porous, and there is more or less widespread calcification of all ligaments. Ligamentum longitudinale anterius stretches like an osseous band all along columna; corresponding to the intervertebral spaces it is very prominent and the surface relatively smooth. Only between the lower vertebræ are parts of the intervertebral disks visible; otherwise calcification is complete along the entire periphery of corpora (Fig. 34 *b*). The ligaments between capitulum costæ and the various parts of columna are calcified, as are ligamentum intertransversarium and the capsule round the intervertebral joints. Foramina inververtebralia are irregularly diminished, but relatively little. Ligamentum interspinale and supraspinale are extensively calcified and, together with processus spinosi, form an irregular osseous plate. Often the calcifications radiate out into the ligaments, which gives them a fantastic, stalactitic appearance (Fig. 34 *c*). These calcifications are brittle like chalk. The ligaments lining the inside of the spinal canal are also calcified, but only to a moderate extent and with no prominences, so that the lumen of the canal is unchanged. The intervertebral disks at lumbar vertebra 4 seem normal to macroscopic examination and of normal elasticity. On the cut surface the normal architecture is entirely effaced; the various spongiosa trabeculæ are thickened, of irregular course and partly fused (Fig. 35). On loosening a costa the articulat-
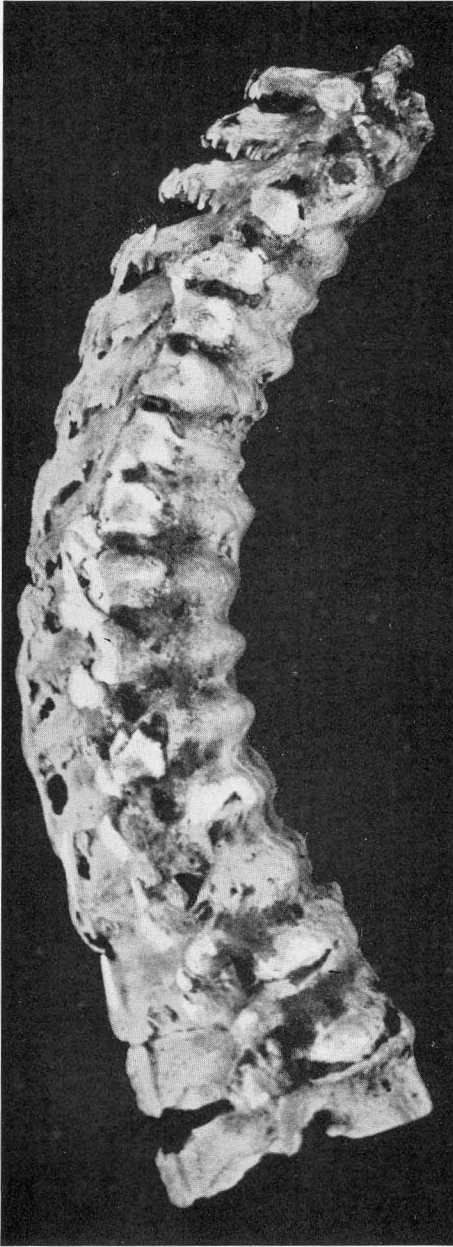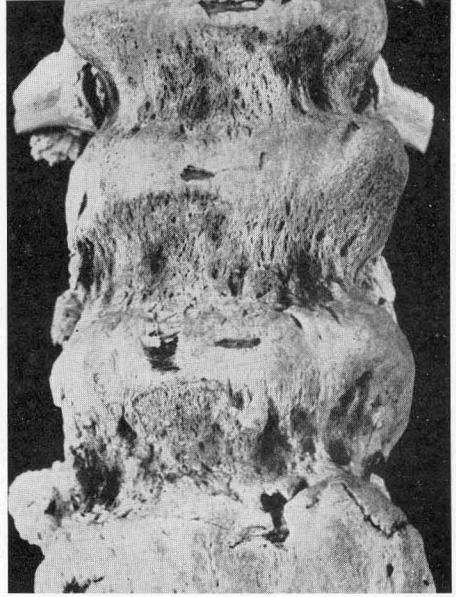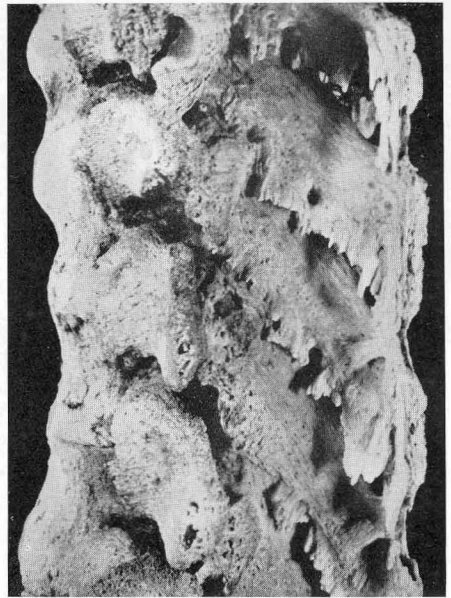
FIG. 34. Columna of male cryolite worker No. 55, employed 24 years. (*a*) 7. cervical—3. lumbar vertebræ, side view. Chalky white bone, uneven surface, severe ligament calcifications. (*b*) Transition from pars thoracalis to pars lumbalis. Complete osseous connection between corpora. (*c*) Pars thoracalis, seen laterally and posteriorily. Irregular stalactiform ligament calcifications.
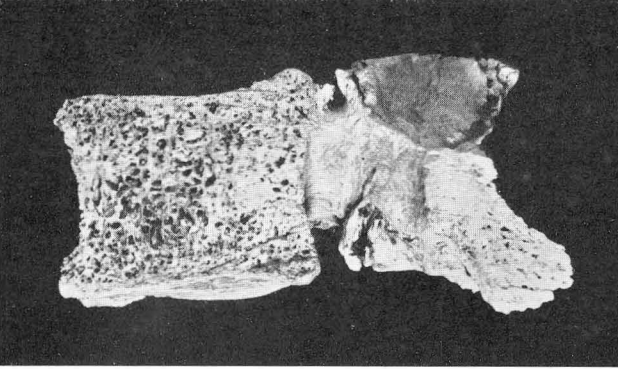
Fig. 35. Saggital section of lumbar vertebræ. (a) Normal, 50-year old male. (b) Cryolite worker No. 55. Irregularly thickened, partly fused spongiosa.

(a)

(b)
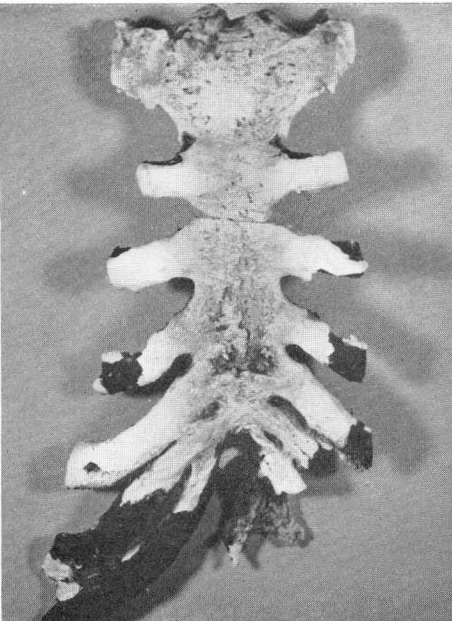
Fig. 36. Sternum of cryolite worker No. 55. Diffuse ligament calcifications, no calcification of costal cartilages.
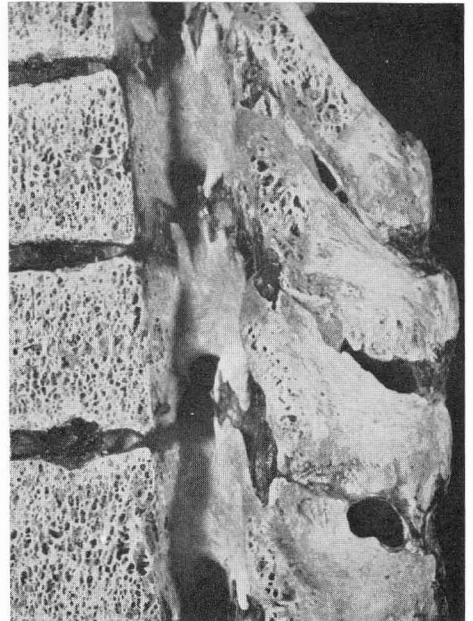
Fig. 32. Saggital section of columna thoracalis, cryolite worker No. 200. Irregular partial calcification of ligamenta flava et interspinalia.
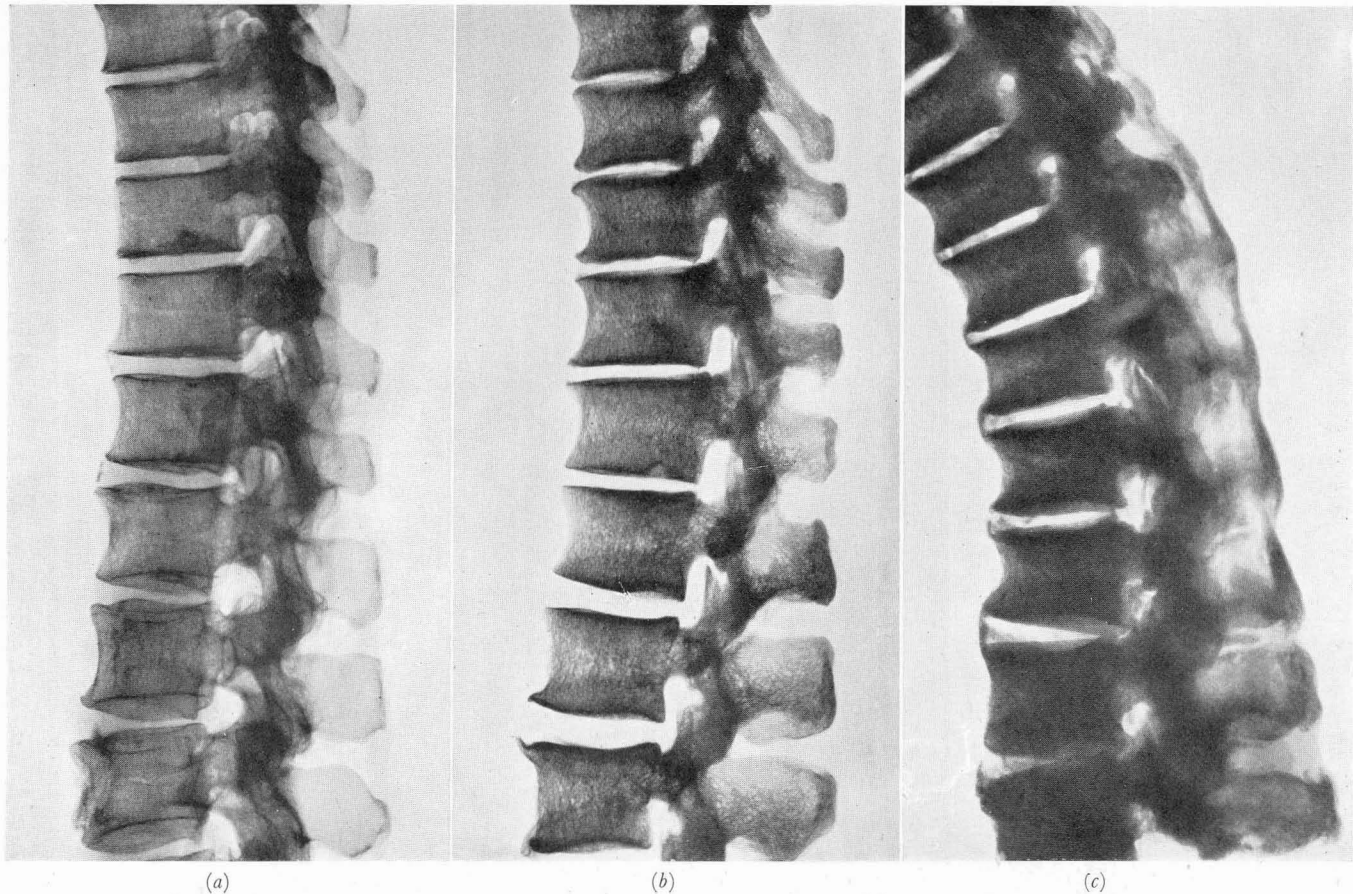
Fig. 38. Röntgen picture of skeletonized columna. (a) Normal, 50-year old male. (b) Cryolite worker No. 200. Osteosclerosis of 2nd phase, coarse, irregular, dense spongiosa, incipient ligament calcifications (columna sawn through). (c) Cryolite worker No. 55. Osteosclerosis of 3rd phase, partial obliteration of osseous structure, severe ligament calcifications, moderate narrowing of foramina intervertebralia.
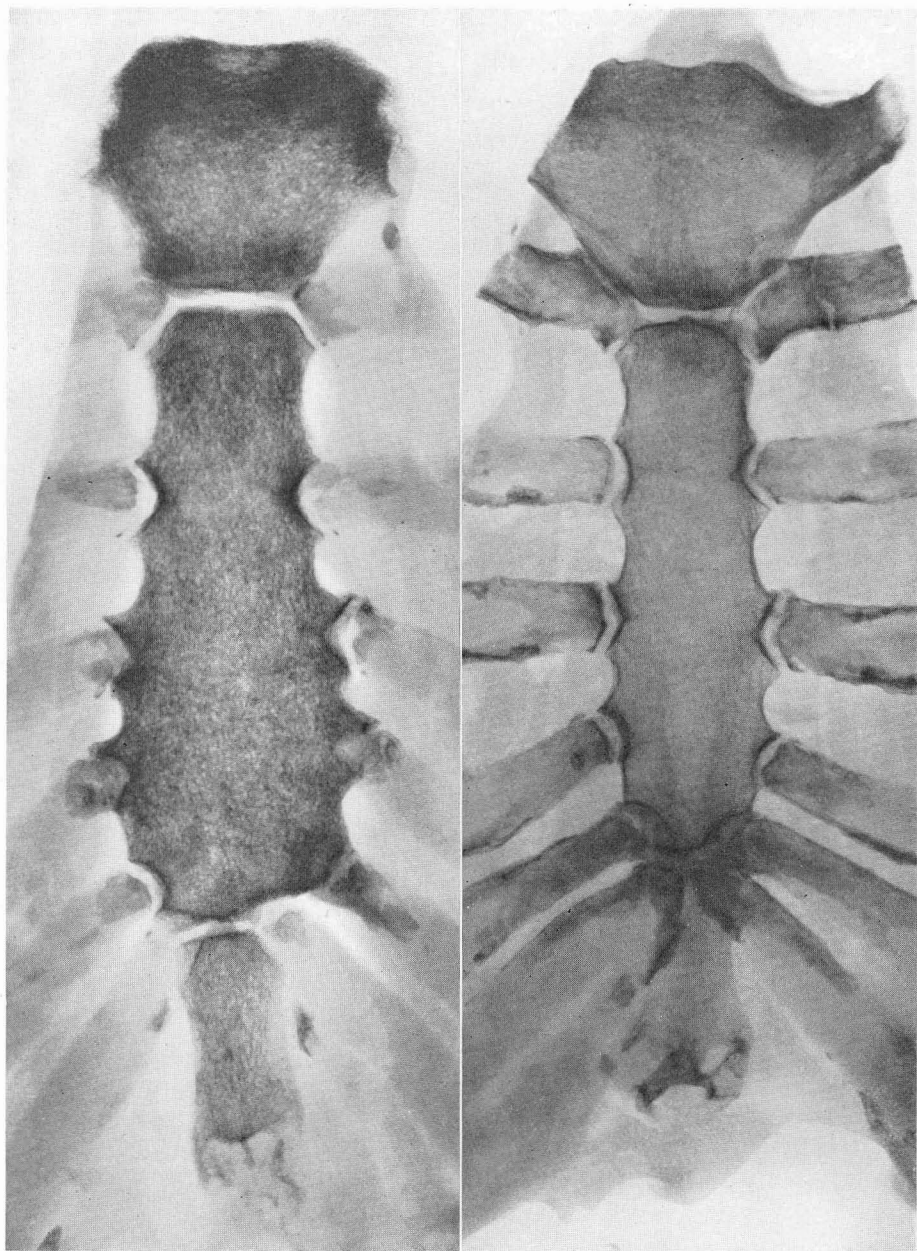
FIG. 39. Röntgen picture of dissected sternum with costal cartilage. (a) Cryolite worker No. 200, 51 years old. Diffuse sclerosis of the bone, no great calcification of costal cartilages. (b) Normal, 50-year old male. Considerable calcification of costal cartilages.
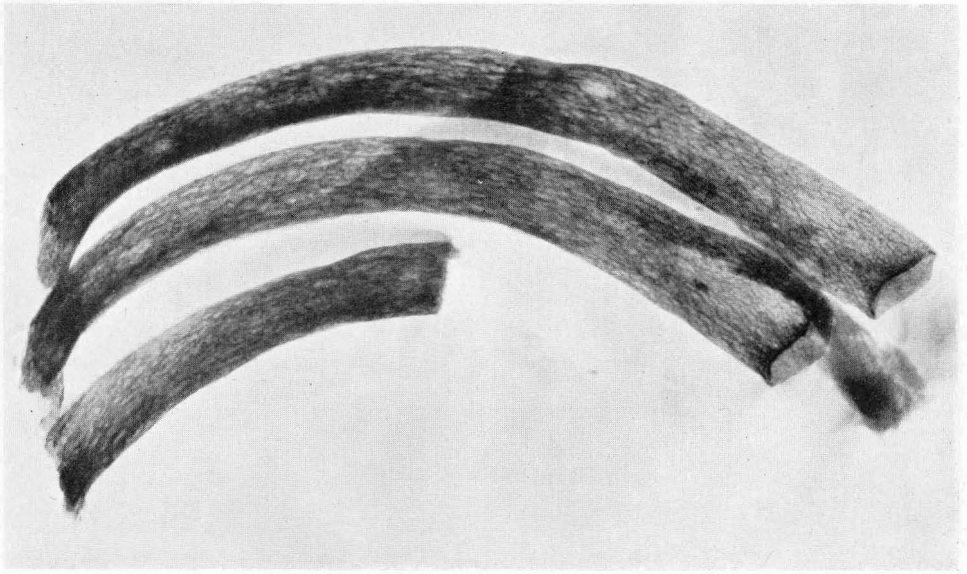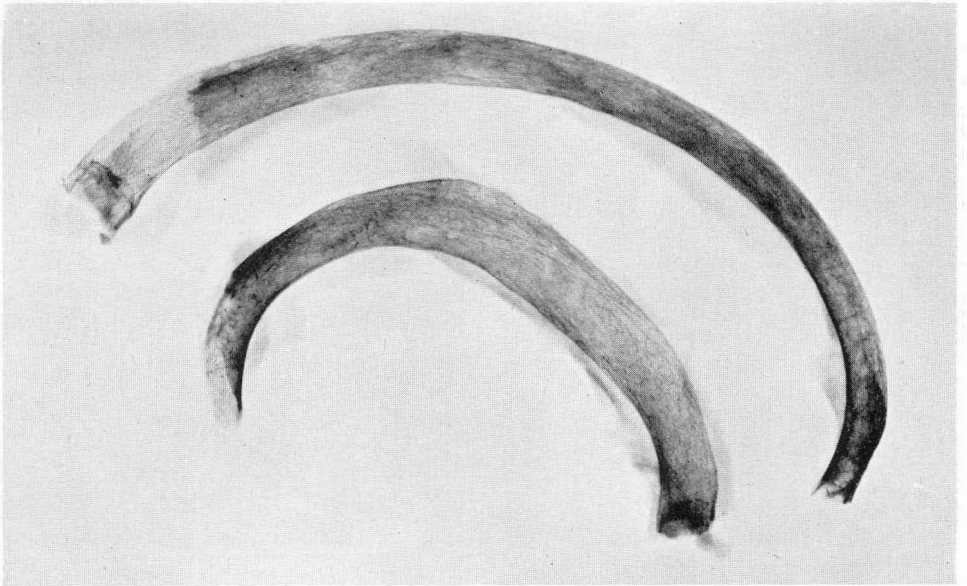
FIG. 40. Röntgen pictures of dissected ribs. (a) Cryolite worker No. 200. Diffuse sclerosis of the bone, spongiosa coarse, very dense. No great changes in contour. (b) Normal, 50-year old male.
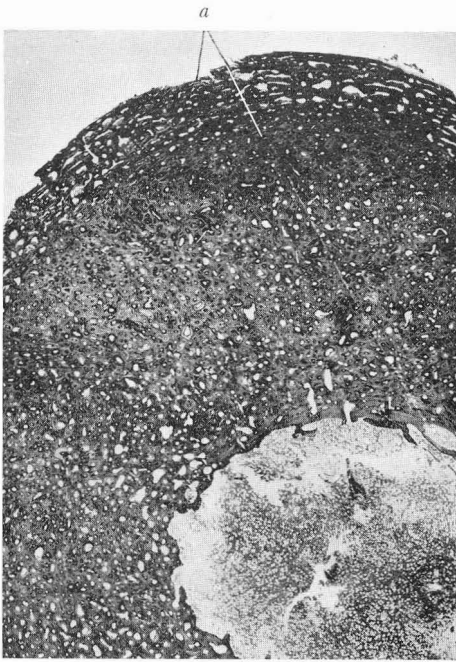
FIG. 41. Cross section of femoral diaphysis, cryolite worker No. 55, employed 24 years. Compacta thickened, marrow cavity narrowed. *a* Subperiosteal layer of irregular osseous tissue $(4^1/_2 \times)$. Staining by Bock's method.
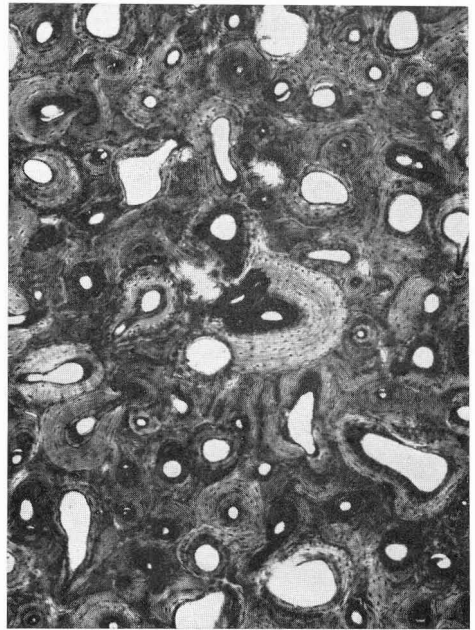
FIG. 42. Same preparation as Fig. 41, compacta. Tissue deeply staining in ring-shaped zones round the vascular canals $(40 \times)$.
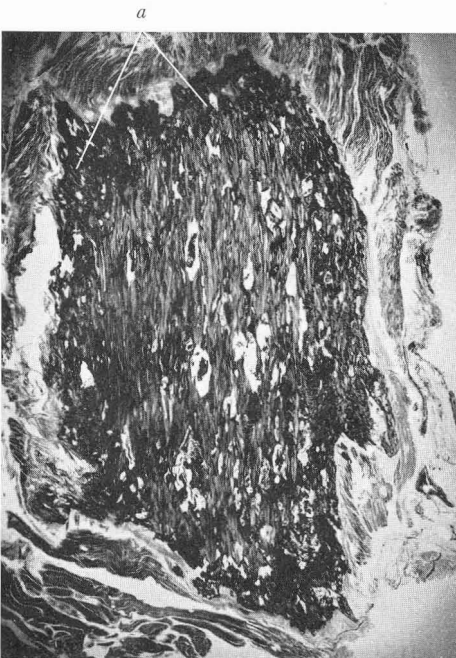
FIG. 43. Cross section of costa, cryolite worker No. 55. Complete obliteration of the normal structure, marrow cavity reduced to fissures. *a* Peripheral, very calcareous layer with irregular boundaries $(3^1/_2 \times)$. Staining by Bock's method.
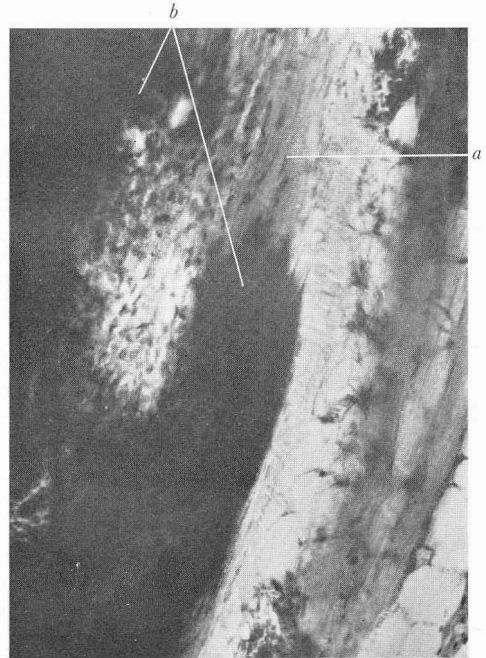
FIG. 44. Same preparation as Fig. 43. Calcification of the peri-osseous fibrous tissue. *a* Tendon tissue. *b* Calcified tendon tissue; the calcium salts are precipitated as coarse granules $(180 \times)$.
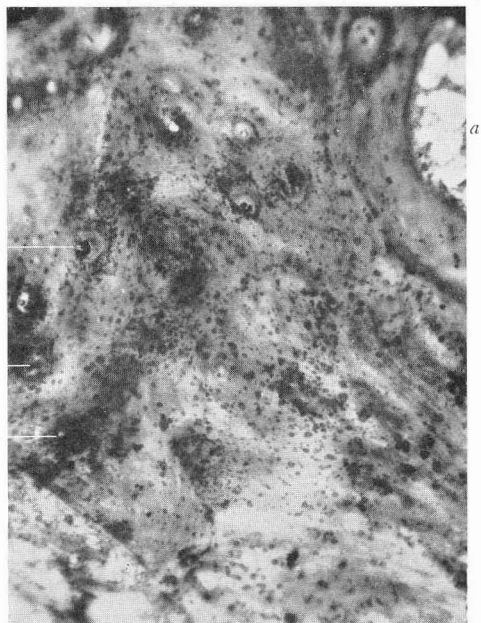
FIG. 45. Cross-section of corpus of 4. lumbar vertebra, spongiosa. Cryolite worker No. 55. In the matrix irregular coarse and fine deeply staining granules and lumps. *a* Marrow cavity. *b* Vascular canals, filled with granules (90 ×). Staining by Bocks' method.

FIG. 46. Cross-section of costa of cryolite worker No. 200, died from intercurrent disease 17 months after discharge from factory. *a* Periosteal surface with irregular lacunary border. *b* Marrow cavity. *c* New-formed osseous tissue, which stains lighter and more homogeneously than the older osseous tissue (90 ×). Hæmatoxylin-eosin.
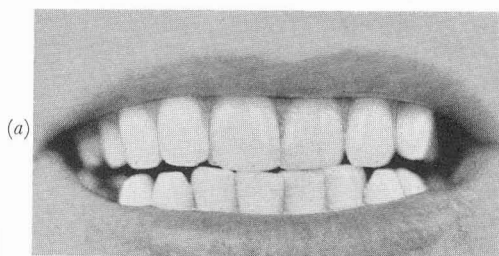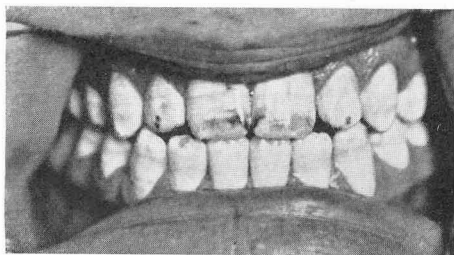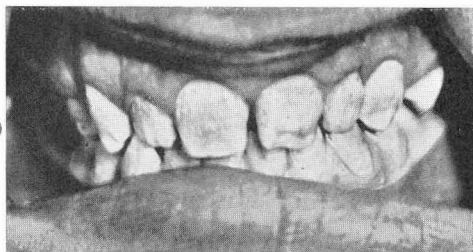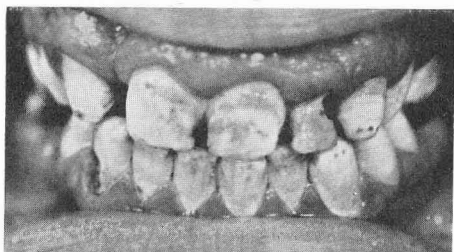
FIG. 47. *Mottled teeth* of children of female cryolite workers. The children were all suckled for long periods (1—2 years). The teeth show more or less diffuse, chalky-white enamel and brownish or black pigmentation. (*a*) Normal dentition. (*b*) Case *1 a*, 15 year-old girl. (*c*) Case *1 b*, 12 year-old boy. (*d*) Case *3 c*, 24 year-old male.

ing surfaces in articulatio capituli are seen to be normally smooth. *Sternum* is covered with calcified ligaments extending tongue-wise or sheath-like out over the costæ and the costal cartilages (Fig. 36). There is no noteworthy calcification of the latter. Sternum weighs 176 g. In the transverse section the same dense spongiosa structure as in the vertebræ. The surface of *costæ* is very irregular, with sharp or more rounded periosteal new-formations. The normal, smooth, more yellowish surface is visible in limited areas. Costæ are very hard to cut, compacta is enormously thickened and the medullary cavity reduced to a few fissures. The surface of *clavicula* has a similar appearance. Compacta and medullary cavity are of about the same breadth. The weight is 42 g.

Microscopic Examination of Bones.

Sections of femur, tibia, costæ, lumbar vertebra and pelvis revealed changes of quite the same nature. The method described by Bock (85) was employed in making the slides (page 116).

Femur, section of diaphysis (Figg. 41—42).

The width of compacta is considerably increased (7—11 mm). Compacta is built up of osteones, though their form and arrangement are rather more irregular than normally. The outer lamellæ are lacking or merely indicated. Peripherally compacta passes without any delimitation into a layer, 1—2 mm. wide, of irregular, almost spongy bone tissue which is coated with a periosteum rich in cells. Compacta's limits against the marrow cavity are mostly irregular, with fair-sized spaces which sometimes communicate with the cavity.

The calcium content of the osseous tissue is high but irregular in its distribution. Around the lumen of the Haversian canals, and often that of the Volkmann canals too, there is a ring-shaped, deeply staining zone the outer boundary of which is scarcely definable. Most frequently the breadth of this zone is about $10\,\mu$. Often two or more zones lie concentrically like the annular rings of a tree. The area around the lacunæ and their off-shoots also stains deeply with hæmatoxylin. In the bone tissue near periosteum and marrow cavity the staining is also pronounced, partly around the irregularly arranged osteocytes, partly along more or less parallel lines of apposition. At these places are seen deeply staining granules which in most cases are just visible, but sometimes, especially around the Haversian canals, are fairly large ($1—2\,\mu$) and irregular in shape. In the other part of the matrix the calcification is homogeneous as in normal bone. The calcium content of adjacent osteones is sometimes very different. The lacunæ to a great extent are empty or contain the remains of cells which stain deeply with hæmatoxylin. It seems as if the osteocytes mostly are lacking in the intervals between the Haversian systems and peripherally in those osteones which stain excessively around the central canal; but there are many exceptions to this rule.

The Haversian canals are coated with osteoid borders of varying, often slight width ($1—2\,\mu$) covered with flat or fusiform cells. The boundary between the osteoid tissue and the highly calcified zone is vague everywhere and the granules are very

distinct. Many Haversian canals have a very narrow lumen, some are entirely closed and are marked solely by a circular area of increased staining. The tissue in the canals is rich in blood vessels but otherwise has a low cell content. In the peripheral, spongeous layer all spaces are almost everywhere coated with rather wide osteoid borders $(4—8 \mu)$; rows of osteoblast-like cells occur here and there, but generally the osteoid tissue is covered with fusiform cells. The irregular periosteal surface also has a narrow osteoid border covered with fusiform cells. Everywhere on the border zone between osteoid tissue and bone the deposition of calcium salts proceeds in the same irregular manner. Towards the marrow cavity osteoid borders $(4—8 \mu)$ are coated with fusiform or flat endosteal cells; here and there, however, they are absent. A few isolated osteoclasts are visible here in Howship lacunæ, whereas in the other parts of the slide the presence of osteoclasts cannot be definitely verified. The *marrow* is extraordinarily rich in blood; it consists of the normal cell elements in apparently normal quantitative distribution. The fat-cell content is low.

Costa, transverse section (Figg. 43—44).

   The shape is greatly altered. The bone is gross, with an irregular, shaggy outline. The normal structure with compacta and spongiosa is obliterated. Low magnification reveals two zones: (1) a peripheral zone, deeply staining, quite irregular in structure and peripheral boundary, and (2) a central zone, consisting of a fairly regular, dense interlacing of lamellated trabeculæ mostly vertical, with fissure-shaped lumina. Between the two zones is a blurred but recognizable boundary.

   The peripheral zone consists mostly of calcified, fibrous connective tissue. The process is observable over a wide expanse along the entire surface. The cells in the vascularized, peri-osseous fibrous tissue increase in size, the nucleus becomes round or oval, whereafter fine or coarse deeply staining granules are deposited round the cells. The degree of calcification varies, but on the whole is high. The cells themselves seem to absorb calcium; gradually as calcification advances the cell nuclei decrease in size and are deeply stained by hæmatoxylin. The tissue formed is of quite irregular structure with large spaces filled with a loosely built and particularly vascular connective tissue. Osseous tissue is formed along the walls of the spaces, where there are fairly wide osteoid borders $(4—10 \mu)$ coated with high, osteoblastic cells or with fusiform cells. The calcification of the osteoid tissue proceeds in exactly the same irregular manner as described under femur. Only very few osteoclasts are observable, but a rather active breaking down of the calcified tissue seems to take place by direct capillary action.

   The central part is much more regular in its structure. The fibrillary bundles are mostly parallel and the bone cells arranged in fairly regular rows. The tissue contains an extraordinarily large number of vascular canals of the character of perforating canals. They are rather uniform in size and mostly run parallel to the trabeculæ. The fissure-shaped cavities are of moderate extent and are occupied by an extremely vascular tissue containing a small number of normal marrow cells and a few fat cells. To a great extent the walls of the cavities are covered with fairly well-developed osteoid borders coated with mostly voluminous cells. Osteoclasts are observable here and there in Howship lacunæ. The staining is deepest around lumina, where ossification is taking place, around the lacunæ and along the vascular canals. Deeply staining granules are visible here and this also occurs sporadically in the otherwise homogeneously staining matrix.

Lumbar vertebra, section of corpus (Fig. 45).

The tissue consists of a spongiosa of very irregular appearance, varying greatly from the normal. The trabeculæ are thickened, often fused into large bone areas. The marrow cavities are considerably narrowed. The bone is of lamellar structure, but the course of the fibrillary bundles is often irregular. Calcification of the tissue is high and most peculiar. Almost everywhere deeply staining, round or more irregular granules, of very varying size are seen, most irregularly distributed in the matrix. Side by side are just recognizable, dust-like granules and irregularly outlined lumps and balls of up to 23 μ in diameter. Most frequently the grain size lies between 2 and 12 μ. The staining is deepest along the periphery of the spongiosa trabeculæ and around vascular canals in the bone tissue, i. e. where the new bone formation proceeds. In the matrix the granules lie along irregular lines of apposition, but also occur in irregular accumulations and streaks which contain granules of all sizes.

The *marrow* consists of apparently normal marrow parenchyma with a low content of fat cells and an abundant supply of vessels. The spongiosa trabeculæ almost everywhere are covered with an osteoid border, 2—8 μ wide, which is coated with fusiform cells, and only rarely with rows of cells like osteoblasts. The deposition of the calcium salts takes place in the form of discrete fine or coarse granules extending in cloudy formations out into the osteoid tissue. Often the calcification is excessive, and at such places there are accumulations of deeply staining granules in the surrounding part of the marrow cavity, between (and apparently also *in*) the marrow cells. Small lumina are sometimes entirely blocked by granules. The osteoblasts seem capable of absorbing calcium during their transformation to osteocytes; as a rule the latter are present in the lacunæ and stain deeply with hæmatoxylin.

Peripherally (corresponding to the anterior surface of corpus) the bone is bounded by a most irregular, closely meshed tissue resembling the peripheral layer on the diaphysis of femur. At the transition from the anterior to the superior surface of corpus are widespread ligament calcifications of the same kind as those described under costa. Discus intervertebralis on the whole is normal. Towards the osseous border there is a moderate, deeply staining granular deposit in the elastic tissue; at the same time the cells become large, round and look like cartilage cells. In a section which cuts through a processus articularis the cartilage is of normal thickness, with well-coloured cells and without pathological calcification.

Examination of *ground slides* of os frontale, costa, lumbar vertebra and diaphysis of tibia in the polarization microscope (R. Bøgvad): Apart from the grinding débris no foreign bodies observed in the osseous tissue or in canals or lacunæ, especially no deposits of calcium fluoride. Nor was this found by examining the bone powder treated with diluted hydrochloric acid.

2. Cryolite Worker No. 200

Male, former cryolite worker (No. 200), born 1881. Previously employed as messenger, forest worker and at a dye works. Worked continuously in the cryolite factory from 1922 till 1931, in all $8^{10}/_{12}$ years. Employed on various processes such as grinding, packing, transport; has been exposed to dust of moderate degree. Became ill suddenly in October 1931, with acute pulmonary oedema.

Admitted to the Rigshospital Dept. B. on October 12th and treated there for syphilitic heart disease in three periods, with steadily increasing insufficiency until death occurred on March 29th, 1933 (Case No. 259/33). The patient died about 17 months after leaving the factory. Between the last two hospital periods I had an opportunity of examining this patient.

Medical History.

Except for scarlatina when a child he had previously been well. Knows nothing of syphilis; unmarried. About a year before his first admittance shortness of breath, palpitations, cough and expectoration. Disposed to crural oedema. Did his work at the factory until the affection began; does not seem to have been troubled much by the dust.

Clinical Examination.

On the basis of the case record from the hospital period, supplemented with own observations, a brief summary will be given of the physical findings:

General condition. Varying, good in periods.

Nasal cavity and pharynx. No hyperæmia of mucous membranes.

Teeth. Most missing, remainder very carious.

Thorax. Nothing abnormal on inspection, movements judged to be normal; size not measured.

Heart. Covered by lung; absolute boundaries: right sternal margin, 2nd intercostal space and anterior axillary line. At apex a soft systolic murmur and over aorta a loud systolic and diastolic murmur. Corrigans' pulse.

Electro-cardiogram: R_{III} divided, S-T interval negative, T_I, T_{II} and T_{III} negative.

Lungs. Mostly extended. Subcrepitant râles spread over both posterior surfaces. Expectorate: no T. B.

Abdomen. Nothing abnormal.

Testes and *gl. thyreoidea.* Normal size and consistency.

Nervous system. Pupils angular, unresponsive to light. Mental state euphoric.

Bones and joints. No definite changes on palpation of the bones, no bone tenderness. Moderate but distinct restriction of movement in columna lumbalis and thoracalis: rotation practically inhibited, extension and flexion somewhat reduced. Movement in pars cervicalis free. Nothing abnormal on examination of other joints.

Blood. The following results were obtained:

	$^{14}/_{10}$ 31	$^9/_3$ 33	$^8/_4$ 33	
Hæmoglobin	69	63	62	%
Erythrocytes	3.50	3.78	4.37	mill.
Colour index	0.9	0.85	0.75	
Leucocytes	23,000	9160	8440	
Neutrophil polymorphonuclears	66	69	54	%
Neutrophil staff-nuclears		5	8	-
Eosinophil L.	—	1	1	-
Basophil L.	—	—	1	-
Lymphocytes	33	22	30	-
Lymphoblasts	—	2	5	-
Monocytes	1	1	—	-

Sero-reaction for syphilis (Wassermann, Kahn) +.

Urine. Contained no albumin or sugar.

Röntgen examination (January 1st, 1932). *Columna* has sclerotic changes typical of 2nd phase. The trabeculæ are coarse, partly fused. There are moderate ligament calcifications, partly in the form of beak-shaped or more coarse osteophytes from the edge of vertebral corpora, partly as a diffuse intensification around processes articulares. *Pelvis* also shows typical sclerosis, of not very pronounced 2nd phase (Fig. 18). *Thorax :* Structure in costæ coarse and blurred, the contour vague. The heart is diffusely enlarged without typical changes; the breadth is 18.5 cm., of thorax 30 cm. Vessels display nothing abnormal. Lung picture is dense, possibly due to stasis. No definite signs of silicosis.

<center>*Necropsy.*</center>

Immediately post mortem 1500 c.c. 10 per cent. formalin were injected in abdomen and thorax. Necropsy was made 14 hours later (No. 75/1933). — The body was of powerful build and in a moderate state of nutrition; length 169 cm., weight 67 kg. Superficial examination revealed nothing abnormal except a doubtful nodulous thickening of the anterior edge of tibia.

Gl. thyreoidea. Size, consistency and cut surface normal. *Microscopy :* No definite proliferation of the interstitial tissue. Lumina somewhat varying in size, contain some colloid.

Lungs. Moderate anthracosis, no recognizable sign of silicosis. In the lower part of the left lung a fairly fresh infarct of walnut-size. There is some stasis, but otherwise nothing abnormal. The bronchial mucous membrane is red and covered with mucopurulent secretion. Hilus and bronchial glands very anthracotic, but not enlarged. *Microscopy* of right lung, middle and lower lobe: Signs of emphysema, chronic stasis and oedema. Many epithelial cells containing blood pigment. No definite inflammatory changes. The connective tissue somewhat proliferated (as in chronic stasis), but there are no definite silicotic changes. Moderate anthracosis of both lung and bronchial gland.

Heart. Pericardium normal. The heart is of normal shape but very large (weight 780 g.). The aortic valves are somewhat thickened, perhaps shrunk a little; the other valves and orifices are normal. Endocardium normal. There is no myofibrosis. The wall of the left ventricle measures 25 mm. Aorta ascendens and arcus are markedly ectatic, and measure 11 cm. in width when cut open; they are the seat of typical and pronounced syphilitic changes. There is no distinct arteriosclerosis. *Microscopy* of myocardium: The amount of connective tissue perhaps pathologically increased.

Oesophagus, stomach and intestine present nothing abnormal. *Microscopy* of stomach: Nothing definitely abnormal. Mucous membrane not atrophic. In the deepest layer of mucosa there are fairly abundant accumulations of lymphocytes, not especially perivascular. No hyperæmia. Large and small intestines: nothing abnormal, macroscopically or microscopically.

The liver. Shape and size normal, surface a little irregular. The organ is full of blood with pronounced stasis. *Microscopy :* Considerable stasis; some of the liver cells are greatly vacuolised (fatty degeneration?).

Gall-bladder system and pancreas. Nothing abnormal.

Spleen. Slightly enlarged, with a rather fibrous, thickened capsule, but otherwise normal. *Microscopy :* Rather considerable hyperæmia (stasis) and some sclerosis. The follicles are rather small and scattered.

Kidneys. Size normal, surface smooth, capsule easily separable. On the cut surface some stasis, but otherwise nothing abnormal. *Microscopy :* Some stasis, otherwise nothing abnormal.

Ureteres, vesica and suprarenals. Nothing abnormal.

Genitalia. Nothing abnormal.

Nervous system. Dura is normal, difficult to separate. There is some thickening of the fine membranes, especially along the vessels. Cerebrum, cerebellum and hypophysis: No macroscopic or microscopic changes.

Bones.

Sternum, several costæ, part of columna, pieces of femur, radius, pelvis and os frontale removed. The bones have distinctly increased in weight, and they are decidedly hard to the saw, but not brittle. The marrow in femur's diaphysis is yellow, fat marrow, in costæ and lumbar vertebra red, of normal appearance.

Röntgen examination of these bones reveals changes of the same kind as in cryolite worker No. 55, but less pronounced. In *columna* the coarse, very dense spongiosa structure is prominent, as also the gross form of processus spinosi (Fig. 38 *b*). Here and there are ligament calcifications in the form of beak-shaped osteophytes on the lumbar vertebræ. *Sternum* gives almost the same picture as in the former case, though there is no particular calcification of the ligaments. The costal cartilages are only slightly calcified (Fig. 39). *Costæ* give a dense shadow, with coarse spongiosa trabeculæ; the outline is fairly sharp and even (Fig. 40). *Os frontale* and *ala ossis sacri* have the same coarse structure and deep contrast.

After *skeletonizing* the bones reveal the same changes as in worker No. 55, but to a much lower degree. The colour is white, chalky, the surface irregular, and the weight increased. There is uncertain narrowing of the marrow cavity in the diaphysis of femur and of radius. *Columna* presents no positional anomalies. The weight of the air-dried preparation (5. lumbar to 8. thoracal vertebra) is 624 g. On corpora the ligament calcifications are confined to very hard osteophytes from the upper edge of one body to the lower edge of the one above. There is moderate calcification of the ligaments between costæ and columna and between processus spinosi. In section the spongiosa trabeculæ in corpus are much thickened and the normal architecture obliterated. On the inside of the spinal canal the ligaments are calcified to a considerable extent, especially ligamenta flava (Fig. 37). Processus spinosi consist almost entirely of compact osseous tissue. The intervertebral disks are macroscopically unchanged. There is no marked narrowing of foramina intervertebralia.

Microscopic examination of sections of sternum, costa, lumbar vertebra, pelvis and femur gave a picture differing in some way from that of worker No. 55. Besides a diffuse bone sclerosis of identical character but of much lower degree, there were signs of *active breakdown of the sclerotic osseous tissue and the*

formation of a mainly normal osseous tissue. As the changes were more or less identical in all bones, conditions in costa may be described as a typical example.

Costa, transverse section (Fig. 46).

In the main the normal structure is preserved, though compacta is wider than normally and the spongiosa trabeculæ coarse. The surface of costa is irregular. The marrow cavities only moderately narrowed. Staining of the tissue is very uneven, as two different kinds of osseous tissue can be discerned everywhere, (1) an older one, irregular in structure and dark-staining, and (2) a younger tissue, of regular, almost normal structure, with a homogeneous and distinctly lighter staining. The younger tissue partly forms a number of the osteons in compacta, and partly lies as a peripheral layer on the spongiosa trabeculæ, which centrally consist of the older tissue. The limits of the older tissue are most frequently irregularly winding, lacunary.

There are signs of both active breakdown and formation of osseous tissue. Lacunary absorption is taking place to a considerable extent where the older tissue has free edges to the marrow cavity. The osteoclasts are often mononuclear. Only very rarely is there any breakdown of the younger tissue. Very frequently there are osteoid borders of considerable width (most often 10—12 μ) covering both new and old bone tissue. The cells coating the osteoid borders are of varying and often considerable size. The boundary between osteoid tissue and bone is marked by a zone which, as regards staining, width and boundaries, varies considerably. Mostly, however, the staining is moderate, the width small and the boundary against the osteoid tissue fairly sharp, especially as compared with the corresponding condition in the bones of worker No. 55. In the calcification zone discrete granules are visible, but always of such small size that they are just recognizable. Whereas in the older bone tissue one can frequently observe fine deeply staining granules, this is not the case as a rule in the newly-formed bone tissue outside the calcification zone.

Periosteum is rich in cells. Lively lacunary absorption of the older osseous tissue is observable, resulting in a very irregular contour. Side by side with this breaking-down process is a new-forming of bone from periosteum, the cells in the cambium layer becoming enlarged, arranging themselves in rows which form osteoid tissue, which later calcifies. No sign of calcification of fibrous tissue is to be seen (but this is seen on the surface of sternum and pelvis). The *marrow* is rich in blood vessels but otherwise consists of a normal marrow parenchyma with a small quantity of fat cells.

Examination of *ground slides* of femur, costa and lumbar vertebra in polarization microscope (R. Bøgvad): Apart from the grinding débris no foreign bodies are found in the osseous tissue or in canals or lacunæ, and particularly no deposit of calcium fluoride. The picture of the grinding débris (corundum) in the canals of femur is very like the corresponding figure in Brandl and Tappeiner's work (108).

3. Analyses

Samples of various organs were taken from both individuals for determining the fluorine content. The following organs were used: Stomach, liver, spleen,

TABLE 42.

Fluorine Content in Organs of Cryolite Workers.

	Normal man			Cryolite worker No. 200			Cryolite worker No. 55		
	Dry sub-stance used	Th(NO₃)₄ used	Fluorine content in 100 g.	Dry sub-stance used	Th(NO₃)₄ used	Fluorine content in 100 g.	Dry sub-stance used	Th(NO₃)₄ used	Fluorine content in 100 g.
	g.	c. c.	mg.	g.	c. c.	mg.	g.	c. c.	mg.
Stomach	10.78	0.50	1.4	5.73	0.30	1.6	17.01	0.66	1.2
Liver ..	27.70	0.46	0.50	40.28	0.43	0.32	26.81	0.40	0.44
Spleen..	16.89	1.02	1.8	14.14	0.31	0.66	12.04	0.27	0.67
Kidney .	20.83	0.78	1.1	20.54	1.57	2.3	16.90	1.37	2.4
Lung...	16.51	0.40	0.73	16.43	5.92	10.8	16.95	9.07	79.2
Heart ..	32.08	0.86	0.81	23.90	0.42	0.53	20.21	0.47	0.70

kidney, lung and heart. The results are given in Table 42. The source of the bone samples and their fluorine content will be seen from Table 43. For comparison, analyses were made of the organs of a normal man*), 50 years old, who died after an accident, and costæ from 11 individuals**) who died of various affections (Table 44).

The results show that it is open to doubt whether there is a deposition of fluorine in the *organs* of cryolite workers. In the normal man I found from 0.50 to 1.8 mg. fluorine per 100 g. dry substance; in the cryolite workers from 0.32 to 2.4 mg. In the kidney, however, the fluorine content seemed high, (from 1.1 to 2.4 mg.). As a matter of fact, however, the normal comparative material is so small in compass that no other conclusions can be drawn. In lung tissue from both cryolite workers there was a high fluorine content, 79.2 and 10.8 mg. for workers No. 55 and 200 respectively. Compared with the normal value (0.73 mg.) this is a very considerable increase.

The fluorine content of the *bones* was very high. Expressed per thousand of the bone ash the fluorine content of worker No. 55 varied from 7.6 (femur) to 13.1 (lumbar vertebra), of worker No. 200 from 3.1 (os frontale) to 9.9 (sternum, costa). Thus the fluorine content was highest in the worker with the longest period of employment. There is no constant relation between the fluorine content in the same bones from the two individuals. Deposition apparently proceeds diffusely in the osseous system, though mostly in the

*) The Copenhagen University's Institute of Forensic Medicine.
**) The University's Institute of Pathological Anatomy.

TABLE 43.

Fluorine Content of Bones in Cryolite Workers.

	Material	Ash used	Th(NO₃)₄ used	Fluorine content per g. ash
		g.	c.c.	mg.
Cryolite worker No. 200	Sternum	0.2299	1.50	9.9
	Costa..................	0.1990	1.30	9.9
	Lumbar vertebra, corpus ..	0.1792	1.10	9.3
	do., calcified ligament....	0.5270	3.23	9.1
	Os frontale..............	0.3291	0.67	3.1
	Pelvis..................	0.2158	1.30	9.2
	Femur, corpus...........	0.1899	0.99	7.9
	Radius, capitulum	0.1712	1.11	9.9
Cryolite worker No. 55	Sternum	0.2182	1.61	10.9
	Costa..................	0.2108	1.60	11.2
	Clavicula	0.3116	1.72	8.2
	Lumbar vertebra, corpus..	0.2446	2.16	13.1
	Os frontale..............	0.2208	1.74	11.7
	Femur, corpus...........	0.1645	0.84	7.6
	Tibia, corpus...........	0.1752	0.96	8.1

TABLE 44.

Fluorine Content in Costæ of Normal Individuals.

Sex	Age	Necropsy No.	Ash used	Th(NO₃)₄ used	Fluorine content per g. ash
			g.	c. c.	mg.
♀	33	10-1935	1.0110	2.00	0.59
♀	41	9-1935	1.2880	2.08	0.48
♀	41	21-1935	1.1146	2.73	0.73
♂	50	337-1934	1.0804	4.74	1.3
♂	51	15-1935	1.2673	2.28	0.54
♂	51	17-1935	1.0942	3.09	0.85
♂	53	12-1935	1.1570	3.73	0.97
♀	61	32-1935	1.8195	4.82	0.79
♂	62	26-1935	1.0995	7.64	2.1
♀	67	19-1935	1.0743	2.86	0.80
♀	80	11-1935	1.2716	4.48	1.1

cancellous bones. A calcified ligament in columna contained the same quantity of fluorine as the adjacent bone. In costæ of individuals not known to have been exposed to fluorine ingestion beyond the average I found 0.48—2.1 $^0/_{00}$ fluorine, in most cases less than 1 $^0/_{00}$.

In making an approximate calculation of the absolute quantity of fluorine in the osseous system it is necessary to take the weight of the bones into consideration. The total air-dried skeleton of three adult male individuals*) weighed 4270, 4805 and 4780 g. respectively, or an average of about 4600 g. If we take it that 65 per cent. of the skeleton consist of ash and that the distribution of fluorine is uniform in the bones, it means that the osseous system of an adult individual normally contains between 1.5 and 6 g. of fluorine. As has been stated, the weight of the bones of the cryolite workers was considerably increased. For each of the skeletonized and air-dried bones or bone preparations the weight was determined of the corresponding bones of three normal men. The weight of the cryolite workers' bones was as follows compared with the normal averages (shown in brackets):

Cryolite worker No. 55,   columna (3. lumbar—7. cervical vert.) 1031 (320) g.
      „   „   „ 55,   sternum   176 (32) g.
      „   „   „ 55,   clavicula   42 (24) g.
      „   „   „ 200, columna (5. lumbar—8. thoracal vert.) 624 (296) g.

The weight of the bones examined was roughly three times the normal in the first case, and twice in the second case. If we reckon the ash content as normal and the average fluorine content 10 and 8 $^0/_{00}$ respectively, it means that the *osseous system of the two cryolite workers contained* about 90 and about 50 g. fluorine. This corresponds to a content of *up to 60 times the normal fluorine content.*

*) The University's Institute of Normal Anatomy.

CHAPTER XIX

EXAMINATION OF CHILDREN OF FEMALE CRYOLITE WORKERS

When examining former cryolite workers I had opportunities of observing and to some extent examining some children of women who formerly had worked a number of years at the factory. Conditions prevented any systematic examination. There were three women with in all eight children, of very different ages. My attention was particularly focussed on the possibility of congenital or acquired tooth or bone affections among the children*).

1.

The mother is former worker No. 100, born 1895. She had worked at the factory about 12 years, 1916—18 and 1922—32, at ordinary women's work, i. e. sorting cryolite. Had inflammation of the lungs three times as a child; influenza in 1918 with pneumonia; in 1925 inflammation of a tendon sheath in right forearm. Otherwise well.

Examined on November 10th, 1931 (Flemming Møller and Gudjonsson): Stated that she suffered from nausea and lack of appetite when the dust was thick; during past year or so some shortness of breath and palpitations. Thought she was pregnant in 2nd month. Röntgen examination of pelvis and columna lumbalis revealed diffuse osteosclerosis of 2nd phase; no definite fibrosis of lungs. Repeated Röntgen examination (April 28th, 1934) of pelvis, columna and lungs showed no change from the first examination. Teeth inspected on same occasion: Partial denture in upper jaw, teeth defective, very carious, but otherwise normal.

Has 3 children (*a*), (*b*) and (*c*).

(*a*) 15-year old girl, born on December 11th, 1918. Mother began work at the factory in 1916 and ceased in the summer of 1918 when she had been pregnant some months. She was confined at the normal time. *The child was fed on the breast as its sole nutriment for 18 months;* it began to walk at $10^1/_2$ months. Eruption of both deciduous and permanent teeth at the normal time. The shape and colour of the former said to have been normal. The permanent teeth on eruption were of normal white, but

*) The state of the teeth of 2 of the children referred to here has previously been dealt with in a paper by Brinch and Roholm (112).

13*

gradually brown spots began to appear on them. She has had the usual infantile maladies but otherwise has never been ill; in particular never had rickets.

Examination of teeth (Sept. 33). Shape very regular, occlusion and articulation quite normal. The surface of the teeth is quite smooth, except that on the labial surface of both upper medial incisors there is a narrow, very slightly pronounced transversal groove between the gingival and middle third of the crown. Gingiva is normal. In the entire dentition there are a few small (filled) carious processes in the molar region. The abnormal colour of the teeth is very conspicuous (Fig. 47 *b*). It is possible to distinguish three colour zones, which are most distinct on the upper medial incisors. The incisal edge has quite a normal, whitish-grey, translucent colour. Towards gingiva follows a transversal, irregularly bordered zone, 1—2 mm. wide, where the colour is yellowish-brown, brown to dark brown. Between this brown zone and the gingival margin the enamel is chalky-white and non-translucent. This colour is not regular, as there are scattered, more or less irregular patches that are whiter than their surroundings. The upper lateral incisors have the same colour distribution, except that an almost black spot about 1 mm. wide appears just above the incisal edge. Upper canines and premolars are chalky-white; on them the brown is limited to almost black spots on cusps. The incisal edge of the inferior incisors has a zone, barely 2 mm. wide, in which the brown colour occurs in two to three patches on each tooth. For the rest the labial surface is of whitish-brown, non-translucent colour with scattered chalky-white patches. The other teeth are all more or less chalky-white with rather darker transversal zones. The cusps of the molars are perhaps somewhat hypoplastic. The wisdom teeth have not yet erupted. The oral surface of the front teeth displays colour anomalies which on the whole correspond to those described, but they are much less pronounced.

(*b*) 12-year old boy, born on March 14th, 1921. His mother had, after two years at the factory, left it in the summer of 1918 and not resumed work there until 1922, more than a year after the birth of the child. *The boy received the breast as his sole nutrition for about 12 months.* He began to walk when a year old, has not had much sickness, especially not rickets. Both deciduous and permanent teeth erupted at the normal time. A dark tint observed appearing on the front teeth during growth.

Examination of teeth (Sept. 33). On the whole conditions are the same as those observed on his sister, but less pronounced (Fig. 47 *c*). Here and there the enamel is hypoplastic, especially of the superior medial incisors, but everywhere of the same chalky-white colour, non-translucent. The yellowish-brown discoloration, which has the form of irregular patches and bands, is especially pronounced on the labial surface of + 1; it is traceable, however, on the visible parts of the teeth everywhere. The dark spots seen on the sister's teeth are absent.

(*c*) 1-month old boy, born on June 7th, 1932. The mother was again at the factory from 1922 till April 1st, 1932, i. e. until about two months before confinement, which took place at the proper time and naturally. Weight at birth 3500 g.

Examined on July 5th, 1932: Healthy, normal-looking, suckled child, thriving well. Weight 4600 g. Nothing abnormal under ordinary medical examination. Extremities normal, no palpable bone changes. Röntgen examination of osseous system: Nothing abnormal.

2.

The mother is a former worker at the factory (No. 98), born 1907. Worked at the factory 1926—1932. Previously well except for influenza and periodic

dysmenorrhoea. *Examined* on November 9th, 1931 (Flemming Møller and Gud-jonsson). Stated that she suffered from loss of appetite and shortness of breath when the dust was thick. Pregnant, 3rd month. Röntgen examination of pelvis and columna lumbalis showed diffuse osteosclerosis of 2nd phase; of lungs: no certain sign of fibrosis. Repeated Röntgen examination (April 24th, 1934) of pelvis, columna and lungs: No change from first examination. The teeth then displayed nothing abnormal beyond widespread caries.

Has two children (*a*) and (*b*).

(*a*) 8-year old boy, born on July 17th, 1927. The mother worked without discomfort throughout pregnancy until the day before confinement. The child has received only artificial nutriment. No sickness while growing beyond the usual infantile affections. *Examination of teeth* (August 10th, 1935). Has changed all incisors, the enamel of which is slightly hypoplastic. Otherwise the enamel of both deciduous and permanent teeth normal. Slight caries of deciduous teeth, not of incisors.

(*b*) 2-months old girl, born on May 5th, 1932. The mother worked at the factory till March 31th, 1932 and on the whole was well. Birth took place at the normal time (placenta prævia); the child was full-grown, weight 3400 g.
Examined on July 5th, 1932: Healthy, normal appearance, suckled, thriving well, weight 4730 g. Nothing abnormal under the physical examination. Röntgen examination of skeleton: Nothing abnormal.
Again examined on August 10th, 1935: Is now over three years old. The mother had to cease suckling the child at three months owing to lack of milk. The child has not had serious illnesses. *Teeth*: All deciduous teeth present, well developed, with quite normal enamel; no caries.

3.

The mother a former worker at the factory, born 1870. Refuses to be examined; states that she cannot remember any discomfort at work. Employed continuously at the factory from 1909 to 1919.

Has three children (*a*), (*b*) and (*c*).

(*a*) 33-year old man, born on July 23th, 1899, now a worker at the factory (No. 20). Born before the mother began at the factory. Suckled about 8 months. Began as a cryolite worker when 20 years old.
Examined on June 26th, 1933. *Teeth*: Partial denture in upper and lower jaw; remaining teeth (11 in all) very carious but otherwise with normal enamel. *Röntgen examination of pelvis and columna lumbalis* November 18th, 1931: Diffuse osteosclerosis of 2nd phase.

(*b*) 30-year old woman, born on December 7th, 1903, now a worker at the factory (No. 22). Born before the mother began at the factory. Suckled about 12 months. Started at the factory when 21 years old.
Examined on November 21th, 1933. *Teeth*: Total number 25, well preserved, only little caries. Enamel normal. *Röntgen examination of pelvis and columna lumbalis*: Diffuse osteosclerosis of 1st phase.

(*c*) 24-year old man, born on August 21th, 1909. Now a cryolite worker (No. 21). The mother began to work at the factory six weeks after his birth; *suckled 2 years, the first year as sole nutriment.* Has not had rickets; began to walk at about 12 months. Beyond inflammation of the lungs no particular illness in infancy. Started at the factory 19 years old, and has since worked there continuously.

Examined on November 16th, 1933. *Teeth:* Total number 27. Some caries, especially of + 2 and 3 —. Round the latter tooth gingiva inflamed, but otherwise normal. The enamel is the seat of considerable changes (Fig. 47 *d*). On the superior medial incisors the enamel is hypoplastic but otherwise fairly normal in development. The enamel on all teeth diffusely chalky-white. Surface smooth. There are irregular, partly confluent patches and bands of brownish colour, especially on the surfaces exposed to the light. On the oral surface of incisors and canines is a similar but much fainter discoloration. On cusps of canines and premolars there are a few, almost black spots. The changes on the whole are of the same nature as those described under I (*a*) and (*b*). *Röntgen examination of pelvis and columna:* Diffuse osteosclerosis of 1st phase.

Summary: An account is given of the teeth of five children born of women who either worked at the cryolite factory before or during pregnancy or started to work there soon after the birth. In three of these children, all of whom received the breast for a relatively long period (1—2 years) an identical anomaly of the permanent teeth was observed. It is characterized by two changes in the enamel: a more or less diffuse, chalky-white colour, and a patchy, paler or darker, brown discoloration which cannot be removed by mechanical treatment. Otherwise the quality of the enamel was not conspicuously changed.

Furthermore, two infants were examined of female cryolite workers with manifest symptoms of chronic cryolite intoxication. The children displayed nothing abnormal, especially under Röntgen examination of the skeleton.

As regards the *diagnosis* of the disease observed in the teeth it is beyond question that the anomaly is that described under the name of *mottled teeth*. All three cases present the two changes in the enamel that are described as characteristic: diffuse, chalky-white colour, and the brownish pigmentation, mostly on the surfaces exposed to the light, in patches and bands which cannot be removed.

From a differential-diagnostic point of view one possibility that must be considered is that of a rachitic tooth anomaly, which the white colour of the enamel would seem to indicate. The individuals presented no objective sign of earlier rickets; the shape of the teeth was on the whole normal, as also the thickness and smooth surface of the enamel. The histories contain nothing to indicate rickets. The long suckling and the normal eruption and shedding periods permit of the preclusion of this disease with fairly great certainty.

The brown colour of the teeth resembles the discoloration frequently caused by tobacco, but the latter is easy to remove. The brother and sister (Cases 1 *a* and *b*) in fact had never smoked. Cases 3 *a* and *b* show that no familiar affection is involved.

According to Dean's (223) *classification* of the various degrees of mottled teeth these cases may be characterized as *moderate*, according to Smith et al. (754) as *moderately severe*. Changes of this grade are caused by drinking water containing *1—2 mg. fluorine per litre*. The strength of the enamel is not affected, or only very slightly, at these grades.

Ætiologically this tooth disease is thus caused by the intake of a relatively large quantity of fluorine during the period of the calcification of the permanent teeth. There can be no doubt as to the *pathogenesis*: The fluorine intoxication has occurred through the mother's milk. This is established in various ways. In all three cases the children were suckled, and for an unusually long period. On the other hand the teeth were normal in Case 2 *a*, which child had not received the breast. The brown pigmentation, which must be assumed to correspond to the most pronounced calcification anomalies in the tooth, is mostly localized to those parts of the teeth that calcify in the 1st and 2nd years of life. The degree of the changes is roughly dependent upon the length of the nursing period, which was longest in Case 3 *c* (up to 2 years) and shortest in Case 1 *b* (about 1 year). Accordingly, Case 3 *c* displayed the greatest changes, Case 1 *b* the least. Case 1 *a* occupied a mid-way position (about $1^1/_2$ years' breast-feeding).

These cases show that *fluorine is excreted in the milk of the female* after both short and long exposure to cryolite dust. In Case 3 *c* the mother only began to work at the factory about 6 weeks after the child was born. Furthermore, Case 1 *b* shows that in the course of the chronic intoxication a *deposition of fluorine proceeds in the organism*, whence there is a constant mobilisation, even years after the fluorine ingestion has ceased. The normal enamel of the deciduous teeth is a sign that *fluorine does not pass the placenta*, in any case not in the (small) quantities involved here. The circumstance that the examination of the infants (Cases 1 *c* and 2 *b*) showed no röntgenologically recognizable bone changes points in the same direction.

SURVEY OF SPONTANEOUS CRYOLITE INTOXICATION

1. Agent and Dose

It is an established fact that cryolite dust contains the toxic substance, and a priori it is probable that this toxic substance is the fluorine contained in the cryolite. Sodium is not toxic in this particular connection. According to experience so far, there is good reason for the assumption that aluminium compounds are not toxic when ingested perorally, presumably because they are not absorbed at all from the alimentary canal. As to the toxicity of aluminium I would refer to critical works, including Smith (744), Lehmann (501) and Roholm (688). In a weak hydrochloric solution cryolite splits, forming hydrogen fluoride, and we must take it that this process goes on in the stomach. In subsequent chapters it will be shown that sodium fluoride and cryolite qualitatively have the same toxic effects in animal experiments.

It has not been possible to make an exact determination of how much fluorine the cryolite workers ingest; nevertheless, an approximate determination may be made in two different ways.

(1) The air in the factory's work premises contained an average of about 35 mg. cryolite per cbm. (Table 17). If we take it that a worker inspires 500 c.c. of air 16 times a minute, in the course of a working day of 8 hours he will inspire about 4 cbm. of air. This means $4 \times 35 = 140$ mg. cryolite, or about 70 mg. fluorine. Of course, it is a most difficult matter to decide how large a part of this is absorbed. Lehmann et al. (502) found that half of the inhaled dust (white lead) is filtered off on the mucous membranes of the nose and throat. Up to 40 per cent. is taken into the bronchi and lungs, and of this portion a considerable part will no doubt be carried back to the upper air-passages or the mouth. What is not removed by sneezing, nose-blowing or spitting is swallowed together with nasal mucus and saliva. A certain fraction of the inhaled quantity of dust gets down into the stomach, with a possibility of absorption. Saito (698) in animal experiments showed that this fraction varied from $1/10$th to one-half.

(2) When dealing with cryolite worker No. 55, who was examined post mortem, it was calculated approximately that his bones contained about 90 g. of fluorine. That man had been employed about 25 years at the factory, or roughly 7500 working days. This corresponds to a daily absorption of 12 mg. fluorine. If to this we add the daily excretion in the urine, which according to the sample test is small (2—3 mg.), we arrive at values of 14 to 15 mg. of fluorine.

These calculations can only be used as a guide. It sounds quite plausible that with the inhalation of 70 mg. fluorine, about 15 mg., or one-fourth to one-fifth, is absorbed. On a weight basis it may be said that the quantity of *fluorine daily absorbed* under cryolite intoxication is probably *between 0.2 and 1 mg. per kg. body weight,* and nearest the first-mentioned value.

2. Subjective Symptoms

The nature and frequency of the complaints of the 68 workers appear from Tables 22 and 23. When appraising the frequency it must be remembered that the statement comprises the entire period of employment at the factory, and not merely status præsens. The various complaints may be placed in relation to the intoxication with a higher or lower degree of certainty. The acute gastric symptoms: *loss of appetite, nausea* and *vomiting* were among the most frequent, as 80.9 per cent. of the workers had, or had had symptoms of that group. The dependence of these complaints on work in dusty atmosphere was very evident. In the great majority of cases they were transitory, disappearing after a few days of habituation, loss of appetite being the most persistent. One-third of the workers complained of chronic symptoms from the gastro-intestinal tract, most frequently *constipation* with or without gastric dyspepsia. Though in their clinical picture these affections did not differ from the banal, in themselves frequent gastro-intestinal affections, it is exceedingly probable that they are a manifestation of the intoxication, as only the fewest of these people had had symptoms prior to starting at the factory.

Shortness of breath in the form of *dyspnoea on motion* was complained of by 42.7 per cent. of the workers. Working in a dusty atmosphere did not cause any marked aggravation of the dyspnoea, and in particular there were no asthmatic attacks. Among a relatively small number of workers there were palpitations, cough and expectoration. The relation of the dyspnoea to cryolite work is obvious.

Something more than one-third of the workers (35.3 per cent.) complained of *rheumatic attacks, pains* or a *feeling of stiffness.* Though the work in itself means a certain exposure to rheumatic affections, it is possible that these symptoms are a sign of the intoxication; the feeling of stiffness may definitely be regarded as such. A number of nervous symptoms of a rather indeterminable nature: *tiredness, sleepiness, headache, giddiness* were complained of by relatively few workers; 22.1 per cent. complained of one or more symptoms in the group. Among the discharged workers these symptoms seem to have been more prevalent (Table 34). Questions as to the following symptoms gave a negative result: Salivation, thirst, polyuria, bleeding tendency.

3. Physical Findings

The symptoms have relation to bones, teeth, lungs, blood and skin. Clinically the *bone symptoms* in pronounced cases appeared as an irregularly nodose, indolent *thickening of subcutaneous bone surfaces* (especially tibia and ulna) and a *reduction of motility in columna and thorax*. In 20.6 per cent. of the workers there was a considerable reduction of columna's motility; in some there was almost complete fixation of the entire columna. Motility of thorax was reduced in 16.2 per cent. of the workers, who had an average excursion of thorax of 0.7 cm. Movement in the other joints of the body was normal on the whole. Röntgen examination revealed signs of *diffuse osteosclerosis* in 83.8 per cent. of the workers. The sclerosis, which is characterized by bone formation from both periosteum and endosteum, principally affects the central, cancellous bones. The individual bone trabeculæ are thickened, give a denser shadow and sometimes fuse. Compacta becomes wider, marrow cavities decrease in size. The bone contours become irregular on account of periosteal deposits; there is an extensive *calcification of ligaments*, especially in columna. Röntgenologically the sclerosis is divided into three phases; 10.3 per cent. of the workers had changes of the most severe grade (3rd phase). On the whole there was conformity between the phase of the osteosclerosis and the reduction of motility.

At the clinical examination the *teeth* showed no changes that could be put in relation to the intoxication. By means of Röntgen examination of the teeth of two workers with severe bone changes an irregular blurring of the periodontal spaces and a narrowing of the pulp cavity were observed.

Examination of the *lungs* revealed a *condition resembling emphysema* in 16.2 per cent. of the workers, characterized by rigidity of thorax and extended lung boundaries. On the Röntgen plate there were faint or moderate signs of pulmonary fibrosis of the peribronchial-perivascular type among half of the workers. The fibrosis was not recognizable by the stethoscopic examination.

The moderate changes in the *blood* appeared most distinctly in the average values. The hæmoglobin content was not changed. The number of erythrocytes was reduced by 9.8 and 7.8 per cent. for men and women respectively; the index as a rule lay between 1.00 and 1.20. The number of white corpuscles was not changed. The differential count showed a moderate, relative reduction of the number of neutrophil leucocytes (58.3 per cent.) and a corresponding, relative increase of the number of lymphocytes (33.8 per cent.). The most pronounced change was a considerable increase in the number of juvenile, staff-nuclear leucocytes (average 11.1 per cent., maximum 27 per cent.).

In 11.8 per cent. of the workers (males only) there was a *chronic furunculosis*, localized to the areas of chest and back most exposed to dust. The remainder of the examination revealed no deviations from the normal that could be related to the intoxication. The general condition was good. There was no irritation of the mucous membranes of nose and throat. Heart affections, lung affections other than those referred to, and pulmonary tuberculosis especially, were not strikingly frequent. In practically all the blood pressure was within normal limits. The coagulation time and sedimentation rate of the blood were normal, as also the plasma colour and the resistance of the erythrocytes. The nervous system presented nothing abnormal, and in particular there were no radicular symptoms. The thyroid gland was not changed as to size. Urine contained no albumin or sugar; microscopy showed no pathological components beyond occasional erythrocytes.

The *morbidity* of the workers, as expressed by the registered number of sick-days per year, did not exceed the average in industry as a whole. A consideration of the various diseases gave results which on the whole did not deviate from comparative materials. Bone fracture was not particularly frequent. Rheumatic affections had a conspicuously high frequency (22.6 per cent. of the sick-days for males, 16.5 per cent. for females).

4. Pathological Anatomy

On the basis of the post-mortem examination of 10 former cryolite workers (Table 41) and the two necropsies described in detail in Chapter XVIII, it must be stated as a fact that poisoning with cryolite produces *considerable changes of bones and ligaments, but no changes — or at the most doubtful changes — of the organs.*

As regards the *organs*, mention must be made of the difficulty of drawing conclusions when the number of necropsies is small and the changes slight and of banal character. A priori one will be very attentive to the alimentary canal, the liver and the kidney. On the whole, no changes were found in these or other organs that either could not reasonably be explained by the diseases actually present or could be regarded as frequent and banal post-mortem findings. The moderate chronic interstitial nephritis in cryolite worker No. 55 (employed about 24 years) alone gives rise to some uncertainty, especially on the background of the experimental results. On the other hand, the kidney of worker No. 200 (employed about 9 years) was normal. In the lungs no changes were revealed that could be characterized as silicosis or resembling silicosis. This also applies to worker No. 55, for whom the Röntgen picture indicated fibrosis. No abnormal calcium deposits were observed in the organs.

The *osseous system* presented marked changes in the two cases that were examined with this particularly in view. All the bones examined were attacked, the pelvis, columna and thorax especially. The bones were normal in shape, if a little gross. The colour was chalky-white, the surfaces irregular, with widespread periosteal deposits and ligament calcifications. The weight of the bones was increased up to three times the normal. The hardness was judged to be increased and the elasticity reduced. Compacta was thickened more or less, spongiosa fused and the normal structure obliterated. The medullary cavities were narrowed. Joint cartilages and intervertebral disks were unchanged macroscopically. Foramina intervertebralia were irregularly narrowed, but there was no question of total or even threatening occlusion. The distribution of the bone marrow was normal in worker No. 200; there was abnormal extension of red marrow to the diaphyses of tibia and femur in worker No. 55, who had the most pronounced bone changes.

Histologically the sclerosis is characterized by an increased formation of osseous tissue, both from periosteum and from endosteum. The new-formed osseous tissue is irregular in structure. Calcification is irregular, on the whole abnormally high. The calcium salts are deposited in granules and lumps, often considerable in size and often in marrow cavity and canals. The calcification zone between osteoid and bone tissue is abnormally wide and irregularly limited. The bone cells occasionally give the impression of being calcified; not infrequently they are absent. However, it is difficult to preclude the possibility that these are artificial products. Besides the formation of osseous tissue proper, a direct calcification of the peri-osseous fibrous connective tissue occurs to a large extent. Bone formation seems to proceed with varying, usually moderate rapidity. Only very rare signs are observable of lacunary absòrption. No deposits of calcium fluoride were found anywhere, neither in crystalline nor in amorphous form. The marrow was hyperæmic, but contained the normal cell-forms in normal distribution. In this connection it may be noted that the spleen presented nothing abnormal.

5. Biochemistry

The investigation has resulted in only few observations regarding *absorption* and *excretion*. The seat of the absorption is not known. In two workers an excretion of 2.09 and 2.54 mg. fluorine was found in the urine in the course of 24 hours; in the same period two normal men on an average diet excreted 0.12 and 0.22 mg. fluorine. Analysis of diverse parenchymatous organs of cryolite workers Nos. 55 and 200 gave no indication that fluorine after

absorption is deposited in the *organs*. The kidney, however, was outstanding, the fluorine content being twofold. In normal organs from 0.50 to 1.8 mg. fluorine per 100 g. dry substance was found. In both cryolite workers the lung gave a high fluorine content, up to 79.2 mg. This proves that cryolite is accumulated in the lung, but nothing as to an absorption. Having regard to the low solubility of cryolite, it is presumable that there is very little absorption through that organ.

Fluorine is deposited in large quantities in the osseous tissue. In several bones the fluorine content varied from 3.1 to 13.1 $^o/_{oo}$, measured on the ash. The fluorine content was highest in the cancellous bones and greatest in the worker who had been exposed longest. In the ash of costæ of 11 adult individuals not known to have been exposed to fluorine the fluorine content varied from 0.48 to 2.1 $^o/_{oo}$. Based on the weight of the skeleton the total fluorine content in the osseous system of the two cryolite workers was calculated at approximately 50 and 90 g. A corresponding calculation for normal individuals gave 1.5—6 g. fluorine.

Fluorine is also deposited in the teeth. The ash of various teeth of four cryolite workers who had worked at the factory about 10 years contained an average of 2.5 $^o/_{oo}$ fluorine (varying from 1.4 to 5.4 $^o/_{oo}$). Normal teeth of unknown persons contained an average of 0.26 $^o/_{oo}$ fluorine (0.19—0.30 $^o/_{oo}$). In Chapter XIX clinical evidence is given that in the female workers *fluorine is excreted in the milk*. It is also established that fluorine is mobilized from the depots in the organism and excreted when exposure to cryolite ceases. In 18 workers the calcium content of serum varied from 10 to 12.3 mg. per 100 c.c., which is considered to be normal having regard to the circumstances under which the blood was taken.

6. Pathogenesis

Cryolite qua cryolite has no local effect. This is proved by the absence of irritation symptoms from skin and mucous membranes. The furunculosis found on the chest and back of a few workers was due to a purely mechanical effect of the sharp cryolite particles in conjunction with neglect of skin hygiene. Judging from the Röntgen picture, cryolite dust in the lungs causes a fibrosis. It is an open question which is the active agent, the cryolite or the quartz contained in the cryolite (1—5 per cent.). The very slightly marked changes and the prognosis would seem to be more an indication of the first possibility.

The acute gastric symptoms are presumably the result of a local-irritating effect on the gastric mucous membrane by hydrogen fluoride, which is formed by

cryolite under the action of the gastric acid. The chronic symptoms from the alimentary canal would also seem to be produced by a local effect from an active fluorine compound. There is nothing to indicate that these locally irritating fluorine compounds produce pathologico-anatomical changes in the gastro-intestinal tract. The indefinite nervous symptoms (headache, tiredness, giddiness, sleepiness, indisposition) may be gastrogenous. For some of the male workers the microscopic examination of the urine revealed a single or some few erythrocytes in the field (magnification × 200). It is difficult to decide whether this phenomenon expresses a renal irritation caused by the excretion of fluorine, or it may be placed in connection with the heavy manual work. The former possibility seems to be the more probable.

The most important effect of fluorine is on the osseous and dental systems. Fluorine disturbs the normal balance between apposition and absorption in the bone, so that the result is a *relative preponderance of the bone-forming processes.* According to the histological picture there is apparently an absolute reduction of the normal lacunary absorption, whilst the bone formation does not give the impression of being especially active (rather narrow osteoid borders coated with mostly flat cells). The *qualitative changes in the genesis of the osseous tissue* are very conspicuous. The osseous tissue presents irregularities in the position of lamellæ and the arrangement of osteocytes. The calcification anomaly is manifested by the following:

(1) The calcium content varies within adjacent bone areas, but as a whole it must be regarded as pathologically increased.

(2) The zone in which the calcium salts normally are deposited as discrete grains is wider and more irregular than normally, but also in the bone there are calcium globules and lumps of varying size. The globules fuse more slowly and less completely than normally into a homogeneous mass.

(3) The calcium salts are deposited in the osseous system where normally there is no deposition (marrow cavity, canals).

Conditions as to the bone cells would seem to indicate that certain parts of the osseous tissue, more especially peripherally in osteones with excessive calcification around the central canal, are exposed to nutrition difficulties with subsequently reduced vitality. On this point, however, the histological picture permits of no definite conclusions. Besides the direct effect on the osseous tissue, fluorine causes a *calcification,* of the same irregular and excessive character, of the *peri-osseous fibrous tissue,* which normally does not calcify, or only in old age. Later on this calcified connective tissue may be absorbed and replaced by osseous tissue.

The disturbance in the calcium metabolism is limited to the osseous tissue

and the peri-osseous tissue. The calcium content of the blood is not increased, and there is no abnormal calcium deposition in other tissues — cartilaginous tissue or in fibrous tissue outside of the osseous system. By what processes the effect of fluorine is established is not known. Various possibilities are discussed in Chapter XXVII, 5. For the rest the investigation has shown that considerable quantities of fluorine are deposited in the osseous tissue formed under the influence of fluorine, and that the granules observed in the bone matrix do not consist of calcium fluoride.

The changes in bones and ligaments explain the reduced motility observed in columna and thorax. As already stated (page 153), in some cases it may be impossible to ascertain the pathogenesis of the emphysematic condition. The specific bone and ligament changes, pulmonary fibrosis and banal age changes may all be capable of affecting the action of the lungs; the first-named are probably the most important. It is an open question whether or not the bone processes are accompanied by pain. This last possibility is indicated by the frequent rheumatoid affections and perhaps the frequent nervous symptoms of former cryolite workers (page 178). On the other hand, about two-thirds of the workers had never felt pains that could be referred to the osseous system, and diffuse osteosclerosis is not usually accompanied by bone pains.

The *bone marrow* showed no change (beyond hyperæmia) in cryolite worker No. 200, whose sclerosis was moderate; in worker No. 55, who had severe sclerosis, there was red marrow in the diaphysis of tibia and femur. This probably means that the hypertrophy is compensatory on account of the general reduction of the size of the marrow cavity. The changes observed in the blood picture may be taken as an expression of a direct toxic effect of fluorine either on the blood cells or on the marrow; they are not secondary to the bone changes, as there was no definite parallelism between the degree of the blood changes and the osteosclerosis.

The changes in the *teeth* indicated an increased growth of both cement (hypercementosis) and dentine (narrowed pulp cavity). A priori it is presumable that processes are occurring in the dental tissues similar to those in the bones. There is also a deposition of fluorine in the teeth.

7. Diagnosis

Diagnosis may cause difficulty in cases where there is no occupational intoxication with obvious exposure to fluorine. The clinical symptoms are not characteristic. Cases with rigid vertebral column may clinically resemble chronic ankylosing spondyloarthritis (Bechterew), though this principally is a joint

disease. Röntgen examination is of vital importance to the practical question of diagnosis; the changes are first recognizable in pelvis and columna lumbalis. The Röntgen picture of the osteosclerosis caused by fluorine differs from the picture of other diffuse osteoscleroses.

Osteosclerotic anæmia is characterized by a sclerosis of spongiosa, whereas corticalis is not thickened. The sclerosis does not attain to such severity that the structure of the bone cannot be seen. At the same time there are in most cases a severe anæmia and pathological cell forms in the blood. In *marble disease* (Albers-Schönberg) the bone shadow is dense, without structure, but there are no periosteal deposits and ligament calcifications. The long bones of the extremities are observed to be clavated, with transverse bands of higher calcification. Here again the clinical picture deviates (opticus-atrophy, increased brittleness of the bones, anæmia). *Osteitis deformans* (Paget) differs by its irregular bone outline and deformations. *Osteoblastic carcinosis* may present a similar picture, but the process is rarely completely generalized, and it will often be possible to find limited areas of bone destruction.

In pronounced cases the röntgenological picture of fluorsclerosis is pathognomonic; incipient changes (1st phase) may be difficult to distinguish from physiological variations. In such cases the finding of an increased fluorine content in the urine or if possible the teeth will be of value. Where post-mortem examination is possible, microscopic examination of the osseous tissue may reveal the characteristic changes, and a chemical analysis the abnormally high fluorine content in the bones.

8. Prognosis

The workers have certain momentary discomforts when working in a dusty atmosphere; for the great majority, however, the discomforts are only moderate, as an habituation takes place. Among the elderly workers the stiffness of columna and thorax involves a certain invalidity, but no greater than that all the workers examined could do their work. This is owing to the fact that elderly employees are put on work that makes relatively little demands on their physique.

In the doses coming into question in this connection, cryolite has no definitely recognizable injurious effect on the general condition, or on certain organs or systems of organs, except bones, blood and lungs. The lifetime does not seem to be reduced, even after protracted occupation at the factory, but the material does not permit of any reliable conclusions on this point. The local effect on the gastro-intestinal tract does not result in anatomical changes in

the mucous membrane. The excretion of fluorine in the urine does not cause nephritis to a degree ascertainable by ordinary clinical examination.

In themselves, changes in the bone tissue seem to be of limited significance to the organism; they do not involve a markedly increased fracture frequency, but in severe cases the elasticity of the bone tissue is reduced. *Calcification of the ligaments and the consequent restriction of motility in columna and thorax are the principal phenomena in a prognostic sense.* The development of these changes requires a regular, perhaps daily ingestion of fluorine over a long period. Officials etc. at the factory and workers at the cryolite mine at Ivigtut, who are subject only to intermittent exposure to dust, either do not acquire osteosclerosis or only to a very slight degree. The average period of employment for workers with incipient or moderate ligament calcification (2nd phase) was 9.7 years; the severe calcifications were found in workers who on an average had worked at the factory for 21.1 years. It is of practical importance that *sclerosis of the 2nd phase was already observed after $4^{10}/_{12}$ years' work, of the 3rd phase after $11^{2}/_{12}$ years.* Incipient sclerosis (1st phase) may or may not affect motility.

There are grounds, both röntgenological and histological, for the assumption that *after cessation of work with cryolite there are reparatory changes in the bones.* The sclerotic bone tissue is absorbed and replaced by an essentially normal bone tissue. At the same time there is a mobilisation of fluorine from the bones, and this circumstance is probably the reason why the new-formed bone tissue may display faint degrees of the same calcification anomaly that characterizes the sclerotic bone tissue. The complete rebuilding of the bone tissue takes several years at any rate and does not seem to occur in all cases (Table 36). Spondylitis deformans being remarkably frequent among former cryolite workers, the possibility may be suggested that the ligament calcifications disappear still more slowly than the bone changes.

It cannot be assumed that the *blood changes* observed play any part of importance. No true anæmia develops, and the oligocytæmia observed is very moderate, even among old workers. The *pulmonary fibrosis* caused by the cryolite dust seems to be benign in nature. The tuberculosis frequency was not markedly high among the present cryolite workers, but the cause of death of earlier workers would seem to indicate that the work has an unfavourable effect on pre-existing pulmonary tuberculosis. The lung fibrosis has been ascertained only by Röntgen examination; post-mortem examination gave no grounds for assuming the presence of silicotic changes either in the ten former workers (Table 41) or in workers No. 55 and 200. Röntgen examination of a number of previous workers (Table 36) provided a basis for the view that the fibrosis

14

does not grow worse after exposure to the dust ceases, and that perhaps it may even recede.

One matter of some bearing on the prognosis may be referred to. In female workers *fluorine is excreted in the milk* in such quantities, even after leaving the factory, that children suckled for a long period may acquire specific, degenerative changes of the permanent teeth (Chapter XIX).

PART IV

OWN EXPERIMENTAL INVESTIGATIONS

CHAPTER XXI

EXPERIMENTS ON RATS

1. Technique

The rats used were 30-day old offspring of the institute's breeding stock. Each rat had its own wire cage and was weighed every week. The basic diet was Gudjonsson's (371) breeding diet 4, which has the following ingredients: Powdered skim milk 30 per cent., rice flour 40 per cent., autolyzed yeast 15 per cent., solidified cocoa butter and shark oil 15 per cent. A supplement was added to the food every day or every second day; the drinking water was renewed twice a week. The 42 animals were put into 8 groups, six of which were given a supplement of various fluorine compounds in their diet. Of the fluoric food 1 kg. was prepared at a time by carefully mixing on a tray. The quantity of food consumed was weighed in groups 1 to 5.

Group No.	No. of Rats	Rat Nos.	Fluorine Compound in Diet, per cent.	Fluorine in Diet, per cent.
1	2	1— 2	None	—
2	6	3— 8	0.05 mineral cryolite No. 1	0.0271
3	6	9—14	0.10 ,, ,,	0.0543
4	6	15—20	0.15 ,, ,,	0.0814
5	5	31—25	0.05 sodium fluoride	0.0226
6	5	26—30	None	—
7	6	31—36	0.15 mineral cryolite No. 2	0.0814
8	6	37—42	0.18 sodium fluoride	0.0814

The detailed data regarding Rats 1—25 appear from Table 45. Weight curves for all rats are reproduced in Figg. 48—52. The animals in groups 1—5 were examined post mortem, the others were not. No systematic microscopical examination was made, but organs for microscopy were taken from some of the rats when pathological changes were found or anticipated. A few animals of groups 1—2 and 3—4 were skeletonized and X-rayed. The experiment began on August 24th, 1932.

TABLE 45.

Data concerning Rats 1—25.

No. and sex.	Group No.	Fluorine compound in diet	Average daily food intake	Approx. daily dose of fluorine	Original weight	Weight at death	No. of days in experiment	Spontaneously died
			g.	mg./kg.	g.	g.		
1 ♀	1	None	12.34	—	50	260	585	
2 ♂			12.32	—	62	250	458	
3 ♂	2	0.05 % cryolite No. 1 (0.0271 % F)	12.73	14	52	330	585	
4 ♂			11.74	19	67	192	585	
5 ♀			11.71	18	65	216	458	
6 ♂			12.41	14	100	282	458	
7 ♂			12.62	14	82	247	572	+
8 ♂			12.37	15	76	258	585	
9 ♂	3	0.10 % cryolite No. 1 (0.0543 % F)	12.10	31	85	283	585	
10 ♂			11.49	40	75	179	458	
11 ♀			11.63	39	51	208	585	
12 ♀			10.68	41	77	102	232	+
13 ♀			8.24	50	58	76	107	+
14 ♂			11.44	36	61	165	560	+
15 ♂	4	0.15 % cryolite No. 1 (0.0814 % F)	9.63	61	69	115	140	+
16 ♂			11.30	56	58	168	283	+
17 ♀			8.16	86	60	76	62	+
18 ♂			7.33	82	64	70	49	+
19 ♀			8.81	76	65	78	67	+
20 ♂			11.12	53	60	153	340	+
21 ♀	5	0.05 % sodium fluoride (0.0226 % F)	10.57	16	54	172	518	+
22 ♂			11.06	16	53	165	432	+
23 ♂			10.50	19	49	130	294	+
24 ♀			10.52	20	47	108	231	+
25 ♂			10.79	17	54	172	422	+

2. Subchronic Intoxication

Symptoms of subchronic intoxication were observed among the animals in groups 7 and 8, which had received 0.15 per cent. mineral cryolite No. 2 and 0.18 per cent. sodium fluoride respectively in their diet. The symptoms were identical in both groups, but more pronounced in group 8. The weight of these animals remained constant or decreased, differing greatly from that

of group 6, which served as controls (Fig. 52). After one or two days the animals were less lively than normally and adopted an attitude with exaggerated curving of columna. This attitude became more pronounced as the intoxication advanced. No real gait anomalies were observed. The coat became untidy and bristling. A bloody secretion appeared from the conjunctival margins, and palpebræ were kept more or less closed (Fig. 53). Traces of blood were observed sub finem around nares. Food consumption was perceptibly reduced, but the animals drank considerably more than the controls. All the fluorine animals had diarrhoea more or less. No spasms or pareses were observed prior to death, but most of the animals were found dead in the cages in the mornings. Death occurred after 8—10 days in group 8 and after 20—52 days in group 7. All the animals were then greatly emaciated. No changes were observed in the incisors of these animals.

3. Chronic Intoxication

Symptoms of chronic intoxication developed among the animals of groups 2—5, though in different degrees. During the course of the experiment all rats in group 4 died spontaneously, and some of those in groups 3 and 5. On the 458th day of the experiment one control (Rat 2), and Rats 5, 6 and 10, were killed. The other control (Rat 1) was killed after 585 days experiment, together with the surviving animals.

Growth and Mortality. Influence on growth was manifested in various ways, as will be seen from Figg. 48—51. Within the same group the individual reaction varied considerably. In group 2 (0.05 per cent. cryolite No. 1) growth was if anything slightly better than that of the controls, and no animal died within 458 days of the commencement of the experiment. In group 3 (0.10 per cent. cryolite No. 1) growth on the whole was slightly inferior to that of the controls, and two animals died spontaneously within the same period after previous loss of weight. All animals in group 4 (0.15 per cent. cryolite No. 1) at first had a weight-increase more or less parallel to that of the controls; afterwards loss of weight and death occurred at very different times. For all animals in group 5 (0.05 per cent. sodium fluoride) growth was clearly below that of the controls, and four out of five animals died before the 458th day, most of them in the latter half of the period.

Attitude and Gait. The fluorine rats took up a crouching position with columna more curved than normally. The phenomenon was the more pronounced the
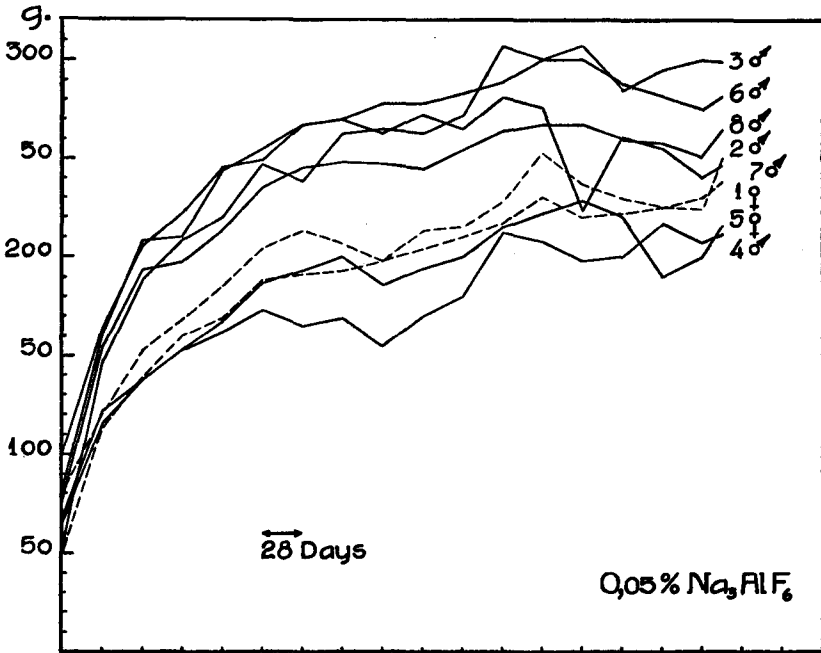
FIG. 48. Weight curves for Rats 3—8 (0.05 per cent. mineral cryolite No. 1 in diet) and Rats 1—2 (controls) for 458 days.
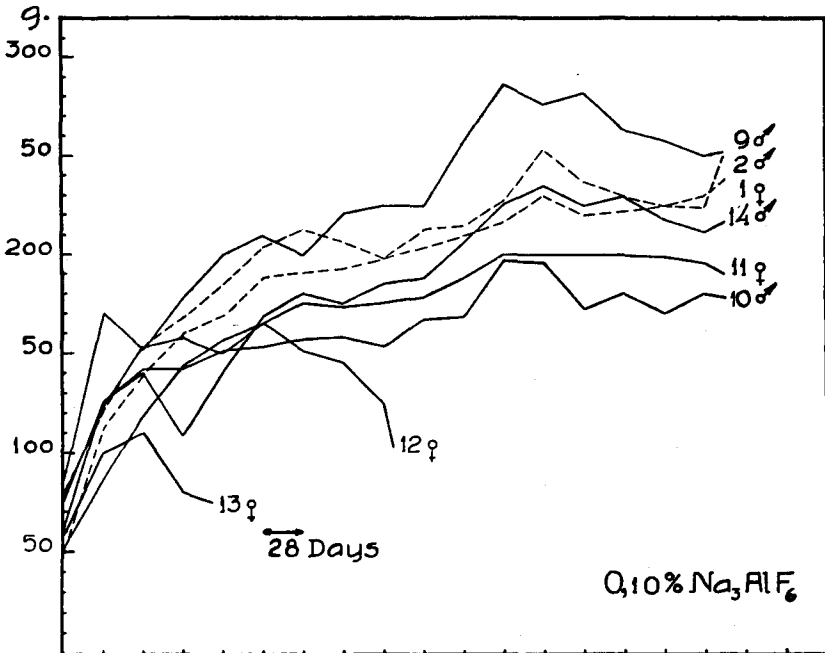
FIG. 49. Weight curves for Rats 9—14 (0.10 per cent. mineral cryolite No. 1 in diet) and Rats 1—2 (controls) up to 458 days.
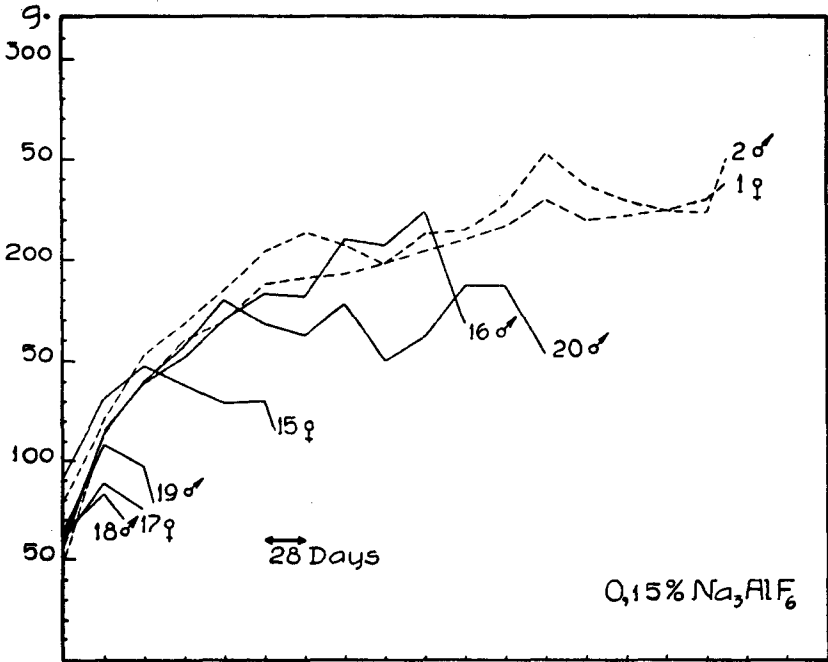
FIG. 50. Weight curves for Rats 15—20 (0.15 per cent. mineral cryolite No. 1 in diet) and Rats 1—2 (controls) up to 458 days.
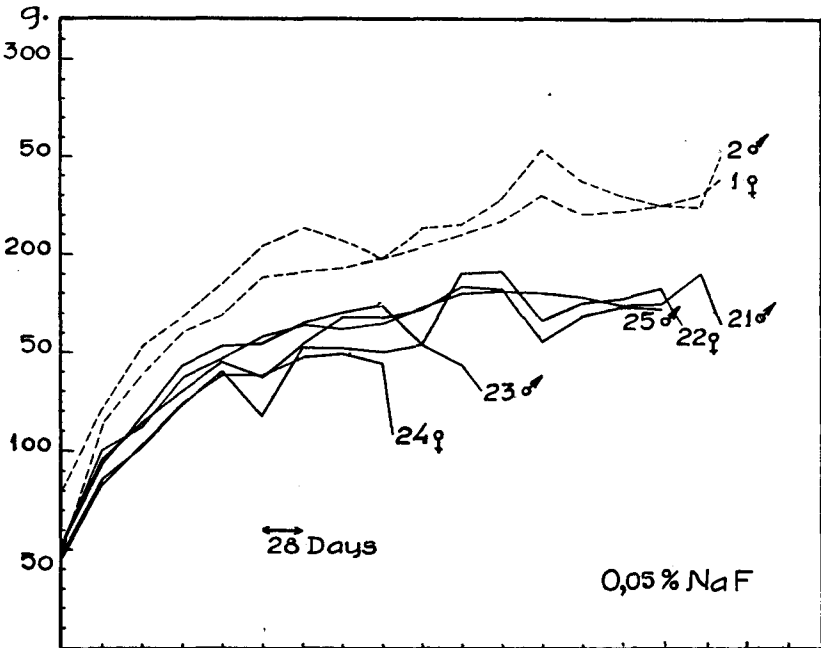
FIG. 51. Weight curves for Rats 21—25 (0.05 per cent. sodium fluoride in diet) and Rats 1—2 (controls) up to 458 days.

more the general condition was affected; it was most in evidence in group 4, and doubtful in group 2. No characteristic anomalies of gait were observed, but the animals moved about less than normally. No thickening or curving of extremities was observed, nor spasms or pareses.

Symptoms from Alimentary Canal. The average daily intake of food (Table 45) was unaffected in group 2 and reduced in groups 3—5, most in group 4. In the latter group, but not in the others, the animals had diarrhoea at times. All the fluorine rats drank a great deal; their drinking water had to be renewed more often than that of the controls.

Skin and Eye Symptoms. On all animals receiving a fluorine supplement the fur gradually became untidy, bristling, the colour more yellowish, and the hairs coarser than normally. During the experiment transitory symptoms appeared in the eyes of 4 rats, a bloody-serous secretion being observed round the conjunctival margin of one or both eyes. There was no change in cornea. This phenomenon, which was accompanied by loss of weight, disappeared spontaneously after from one to five weeks. The following rats were attacked:

Rat No.	Group	Eye	Began after weeks of experiment	Lasted approximately, weeks
5	2	left	47	5
9	3	right + left	7	1
14	3	right	17	1
21	5	right	48	3

Teeth. In the albino rat the dentition is monophyodont with the following formula: $I\frac{1}{1} C\frac{0}{0} PM\frac{0}{0} M\frac{3}{3}$. Eruption takes place in the course of about 35 days after birth. The incisors grow continuously from a persistent pulp (2). Necropsy of the first rats to die revealed various changes in the incisors: Irregular colour of the enamel, abnormal length of the teeth and abnormal wear. As the experiment proceeded, similar changes were noticed in the incisors of all the animals. The molars presented nothing abnormal beyond increased wear in those animals with defective incisor occlusion. The teeth of the control rats were normal. The pathological phenomena were least pronounced in group 2, and more pronounced and fairly identical in groups 3—5; they comprised the following (Fig. 54):

(1) *Enamel.* The normal orange-brown, translucent enamel was replaced in spots or diffusely by a chalky-white enamel with an irregular, seemingly corroded surface. Sometimes the enamel was lacking over certain areas.

(2) *Form and position anomalies*. The normal cutting edge had more or less the character of a flat surface. The superior incisors in most cases were longer than normally, the inferior abnormally short, resulting in defective occlusion. In a few rats one incisor in the upper jaw had curved backwards where the opposite tooth was defective. Considerable lateral deviations of incisors were observed in other animals.

Organs. The only organ found to be changed macroscopically was the kidney. It should be stated that no definite changes were observed of the mucous membrane in stomach and duodenum, and that the thyroid gland apparently was not changed as to size. The *kidneys* all had the same appearance, being contracted and paler in colour than normally; the surface was irregular, in most cases granulated. Only some of the rats displayed macroscopic kidney changes of this kind. In group 2 there was only one case (Rat 4), in group 3 there were four (9, 10, 11 and 14), in group 4 three (15, 16 and 20). All animals in group 5 had pronounced kidney changes. The affected animals in groups 3 and 4 were the survivors. Under the *microscope* the kidneys of Rats 4, 5, 6, 10, 11, 21, 22, 25 all showed signs of a chronic, mostly interstitial nephritis of uniform character; the changes were slight in Rats 5 and 6, which had not shown macroscopic changes, pronounced in the others. The kidney of Rat 2 was normal. The changes in the kidney of Rat 21 (Fig. 58) are described below as being typical:

The kidney is contracted, the surface very uneven. The changes are diffusely spread. Many glomeruli show serous or hyaline degeneration. The lumina of tubuli in most cases are irregularly dilated; this often forms cystic areas with an abundant serous content. Epithelium in the tubuli is low but well preserved. Universally there is proliferous development of connective tissue; the tissue is hyperæmic and contains scattered round-cell infiltration. A slight calcification in the tissue is observed in one place. Vessels normal.

Bones. Rats 1, 3, 9 and 21 were completely *skeletonized*, and of Rats 2, 4, 5, 10 and 22 the head only. All these animals had received the fluorine supplement for 432 to 585 days. The bones of the fluorine rats were brittle and chalky-white, and formed a marked contrast to the normal greyish-yellow colour (Fig. 55). Under low magnification the surface appeared uneven. On the whole the shape of the bones was normal, though more gross as a rule, with thickening of processes and cristæ. Flat bones (pelvis, scapula) were not transparent as they are normally. Thickening was observed on the skull, e. g. of the mandible corpus and the zygomatic arch. The skull was often asym-

metrical in cases where there were marked positional anomalies of incisors. There was no observation of any ligament calcification. The length of the claws had increased up to twice the normal. These bone changes were most pronounced in Rat 3 (0.05 per cent. cryolite No. 1). Rat 9 (0.10 per cent. cryolite No. 1) and Rat 21 (0.05 per cent. sodium fluoride) had almost identical changes in skull, columna and thorax, but the white colour of the bones of the extremities was less marked.

By means of *Röntgen examination* of the skeletonized animals (Figg. 56 and 57) certain common features and various deviations were found. The common features were the slightly gross bones, especially the processes. There was no change in the width or form of the epiphysial lines.

Rat 3 showed signs of *diffuse sclerosis* of the bones of the body and skull, but not of the extremities. The sclerosis was characterized by thickened compacta, coarse spongiosa and greater density. The degree of the sclerosis varied a little in the different bones, but as a whole it was considerable. The bones of the extremities bore no signs of definite deviation from those of the control. Though Rat 3 weighed about 27 per cent. more than Rat 1 (control), the changes were much in excess of what could be explained by the weight difference.

Rat 9. The skeleton showed *moderate and limited signs of sclerosis* in skull, sternum and perhaps in costæ, but not in columna, pelvis or extremities, where structure and density were what might be called normal.

Rat 21. There were signs *both* of *sclerosis* and of *atrophy* in various parts of the skeleton. The skull had fairly considerable diffuse sclerosis; there was also some sclerosis of sternum. In costæ and columna the condition was not describable as sclerosis; in several costæ compacta was of irregular breadth and the margin against the marrow cavity blurred. Pelvis must be described as atrophic, compacta being narrower than normal and the density less. In the long bones compacta was rather narrower than normally, here and there with blurred and irregular margins against the marrow cavity.

Microscopic examination was made of tibia or femur of Rats 2, 5, 6, 8, 10, 11, 22, 23 and 25. On the whole the histological picture was the same for groups 2 and 3, only few deviations from the normal being observed, mostly signs of increased and irregular periosteal bone formation. The rats of group 5 had very marked changes, viz. (1) an abnormal but varying degree of calcification of the osseous tissue, which showed calcium salts in the form of discrete granules; (2) partial fibrous transformation of the marrow; (3) lively formation and absorption of osseous tissue from both endosteum and periosteum. I would underline the fact that no crystalline deposits were observed in the osseous system. Tibia of Rat 5 (group 2) and femur of Rat 23 (group 5) are described below as characteristic specimens:

Rat 5, tibia, longitudinal section of proximal half.

Compared with tibia of Rat 2 (control) there are only slight deviations from the normal. The shape of the bone is unchanged, the *cartilage towards the knee joint* is normal. The *epiphysial line* is not changed either in width or in shape. The cartilage cells both in the proliferation zone and in the zone of temporary calcification are normal in appearance and position. Trabeculæ in epiphysis and *metaphysis* are normal in number and form; often they are surrounded by a fairly broad osteoid border, whereas osteoid tissue is observed only as a very narrow margin in Rat 2. In both animals the osteoid tissue is coated with fusiform or quite flat cells, and the marrow cavities are occupied by a uniform tissue, rich in cells. Only very occasionally is there an osteoclast in a Howship lacuna. The calcification of the bone presents nothing definitely abnormal in Rat 5. *Compacta* is normal as a whole with regard to thickness, distribution of Haversian canals and arrangement of osteocytes. *Periosteum* is rather more cellular than normally, and on the whole the cells are larger. Whereas the subperiosteal part of the diaphysis of Rat 2 has five or six close, linear and parallel lines of apposition, the interval between these lines is greater in Rat 5, the lines themselves are wider, more calcareous and their course is irregular, winding. As a consequence the surface of diaphysis is more irregular than normally. In compacta, too, the calcification of the bone is normal and homogeneous. *Endosteum* consists of flat or fusiform cells. In limited areas endosteum is thickened and consists of several layers of fusiform cells. At these places there are isolated osteoclasts in Howship lacunæ, but otherwise the signs of building up and breaking down of osseous tissue are sparse in compacta, as in tibia of Rat 2. The marrow parenchyma contains scattered fat cells and otherwise consists qualitatively and quantitatively of normal marrow cells.

Rat 23, femur, longitudinal section of diaphysis and distal epiphysis (Figg. 59 and 60).

Joint cartilage normal; but the basal, calcified part of the cartilage varies in width and often is quite narrow. The width and form of the *epiphysial line* are not markedly changed, the cartilage cells are on the whole normal in appearance and arrangement. In the zone of temporary calcification the calcium salts are just recognizable in the form of fine, closely packed granules. The trabecular structure in both epiphysis and *metaphysis* is completely obliterated. The space is occupied by an irregular interlacing of osteoid trabeculæ, parts of which are slightly calcified. Here and there are irregular remains of a more normally calcified osseous tissue. Between the osteoid trabeculæ there is a tissue consisting of a matrix rich in collagenous fibrils, numerous large cells like fibroblasts, many giant cells, and scattered accumulations of marrow cells. The osteoid trabeculæ contain an abundance of collagen; they are coated with rows of mostly high osteoblast-like cells. The calcification of the osteoid tissue is sparse, in the form of fine granules, and the boundary between calcified and non-calcified tissue is irregular. The osteocytes are well preserved, their shape and position very irregular. There is lively lacunary absorption, both of the poorly calcified and of the scattered remains of more normally calcified osseous tissue. The calcified part of the joint cartilage is also irregularly absorbed by osteoclast activity.

The width of *compacta* varies, being mostly normal, but its boundaries are irregular, especially towards the marrow cavity. The subperiosteal part of compacta displays several wide, very calcareous lines of apposition, relatively wide apart. On the whole the structure of compacta is normal, though the arrangement of Haversian canals and bone cells is rather more irregular. Calcification deviates considerably from the normal. The calcium content of the bone is high, in excess of the normal if anything. Everywhere in the matrix are fine or coarse, deeply staining granules, accumulated

especially around the lumen of the Haversian canals and around the bone cells. Sometimes the granules occur in irregular, concentric zones around the Haversian canals.

To a limited extent only, particularly centrally, the *marrow* consists of marrow parenchyma. This is the seat of some hyperplasia, especially of the leucocytary system, whereas the precursors of the erythrocytes are relatively sparsely represented. Towards the bone the marrow cavity over a wide belt is full of fibrous marrow of exactly the same character as in metaphysis and epiphysis. The number of giant cells is large. Lively bone formation and breaking-down is proceeding in this tissue. The building-up processes result in the formation of numerous osteoid trabeculæ, which calcify sparsely and irregularly. Side by side with the bone formation there is a breaking-down process by osteoclast activity, partly of the poorly calcified bone tissue, partly of compacta. Under lively osteoclast activity the fibrous marrow extends into compacta, with the formation of irregular cavities. *Periosteum* is rich in cells and in certain places thickened enormously. Here the tissue is very similar to the fibrous marrow. Giant cells occur, and compacta is broken down by lacunary absorption. At the same time islands of osteoid tissue are formed in periosteum.

4. Summary

The *subchronic intoxication* was manifested by the development of a cachectic condition accompanied by reduced food consumption and signs of irritation of the gastro-intestinal tract (diarrhoea). Prior to death there were spontaneous hæmorrhages from the mucous membranes. The appearance and posture of the intoxicated rat otherwise presented nothing definitely characteristic compared with a rapidly developed cachectic condition from other causes. The increased water drinking may be taken as a sign that during excretion fluorine acts as a diuretic. It is not possible to indicate the effective dose of fluorine, as the food consumption was not determined.

Chronic intoxication was seen in rats which had received a supplement of fluorine in their diet for a period of up to 585 days. At a certain concentration of fluorine, food consumption and growth were reduced and mortality increased, and these phenomena became the more pronounced the greater was the content of fluorine in the diet. Other symptoms of the intoxication were: (1) impaired vitality and crouching attitude; (2) untidy, bristling, coarse fur; (3) prolific growth of claws; (4) transitory eye symptoms which in most cases were unilateral, but clinically resembled the initial stages of xerophthalmia. It was remarkable that the skin and eye symptoms also occurred where food consumption, growth and mortality were not affected (group 2). On the basis of the macroscopic examination the systemic effect of fluorine was localized to three organs or organ-systems: The kidneys, the teeth and the bones.

In the longest-surviving animals in all groups there were macroscopical or microscopical signs of a chronic, diffuse, mostly interstitial nephritis with a

tendency towards contraction. The effect on the *kidney* may explain the water drinking among the fluorine rats. The effects on the *teeth* were localized to the incisors, which in some cases presented lateral deviations, while the enamel and dentine were constantly of poor quality and of low resistance. Secondary phenomena observed were defective occlusion, prolongation of individual incisors, and increased wear of molars.

Changes in the *osseous system* presented a very variegated picture. In all groups the bones, especially those of the trunk and the skull, were chalky-white and brittle, the surface irregular, processes and cristæ thickened. Among those rats which had received cryolite (groups 2 and 3) the bones of the skull and trunk showed a more or less diffuse sclerosis on the radiograph; histological examination (tibia) revealed signs of prolific and irregular periosteal bone formation. In group 5 (sodium fluoride) the sclerosis observed by X-ray was localized to skull and sternum, and the

FIG. 52. Weight curves for rats whose diet contained 0.0814 per cent. fluorine in various forms; up to 56 days. Group 4: 0.15 per cent. mineral cryolite No. 1 (17.7 per cent. has grain size $< 5\,\mu$). Group 7: 0.15 per cent. mineral cryolite No. 2 (85 per cent. has grain size $< 5\,\mu$). Group 8: 0.18 per cent. sodium fluoride. Group 6: controls.

greater part of the remaining bones (costæ, pelvis, extremities) had diffuse or more localized signs of atrophy. The histological picture (tibia, femur) could not be identified with known pathological conditions. The marrow showed fibrous changes, and there was a lively formation and absorption

of osseous tissue both from endosteum and from periosteum. Calcification everywhere was peculiar; the calcium salts were seen as discrete granules in the matrix, but in some places the calcium content was higher, in others lower, than normally. The form of calcium deposition recalled conditions in human cryolite intoxication; other details in the histology of the bones were rather like osteitis fibrosa and osteomalacia. Neither röntgenologically nor histologically were there any massive changes in the enchondral ossification of the fluorine rats.

The approximate *dose* of fluorine ingested in the experiment is determinable on the basis of the food consumption:

Group No.	Daily fluorine ingestion mg./kg.	Average daily fluorine ingestion mg./kg.
2	14—19	15.7
3	31—50	39.5
4	53—86	69
5	16—20	17.6

From the clinical and pathologico-anatomical picture one may draw the conclusion that mineral cryolite has the same qualitative effect as sodium fluoride. A priori it is probable that cryolite is less toxic than sodium fluoride, considering the fluorine content, primarily because of the difference in grain size and the consequent difference in absorption. That this is correct is shown by a comparison of the growth curves for groups 4 and 7 (Fig. 52). With the same concentration in the food the relatively fine-grained mineral cryolite No. 2 was much more toxic than the coarse-grained mineral cryolite No. 1, but the same fluorine concentration in the form of sodium fluoride was still more toxic (group 8). Only part of the fluorine content of the cryolite was active, but the material does not permit of an exact determination of that quantity. If we consider growth and food consumption especially, it is evident that 0.05 per cent. sodium fluoride was more toxic in effect than 0.10, and less toxic than 0.15 per cent. mineral cryolite No. 1. This indicates that only about one-third of the fluorine content of cryolite was active. Therefore it is extremely likely that protracted daily ingestion of about 5 to 20 mg. fluorine per kg. in the rat produces a generalized bone disease which, at the lowest doses within these limits, takes the form of sclerosis, and at the highest doses a combination of sclerotic and atrophic processes. The deleterious effect on teeth formation and on the kidney was also observed with the lowest doses, where growth, food consumption and lethality were not affected.
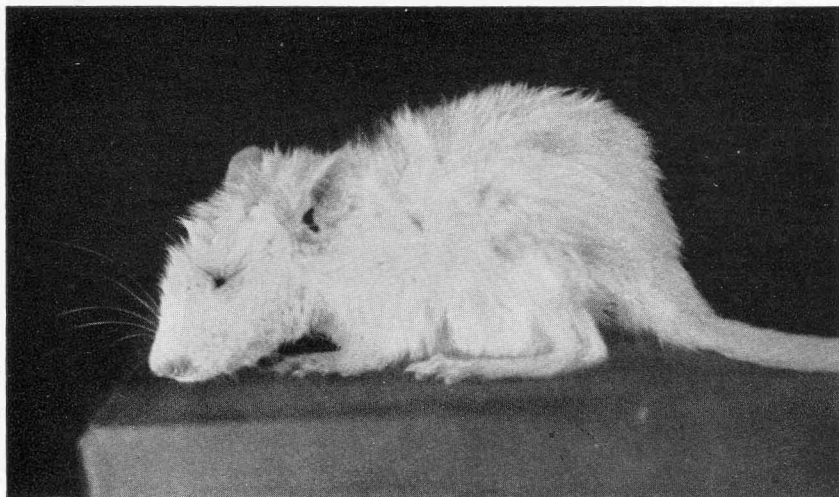
(a)
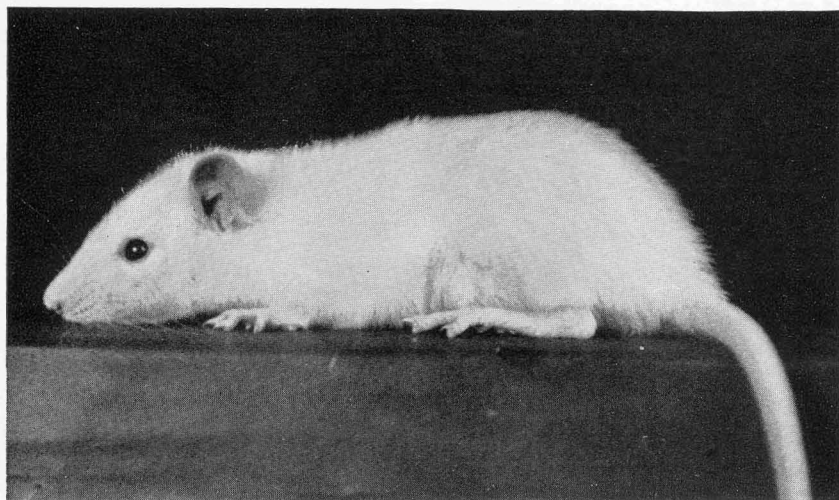
(b)

FIG. 53. Rats, 8 weeks old. (a) Rat 33, for four weeks fed on diet containing 0.15 per cent. mineral cryolite No. 2. Subchronic fluorine intoxication: emaciation, crouching posture, untidy coat, eye changes. (b) Rat 29, control.
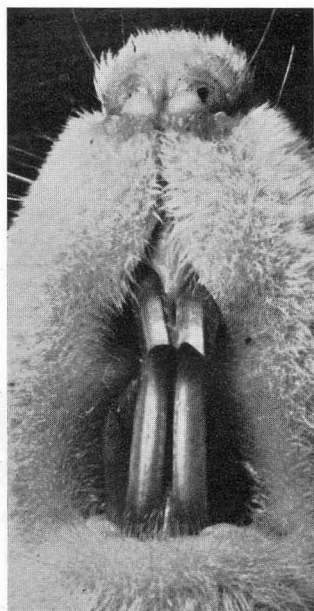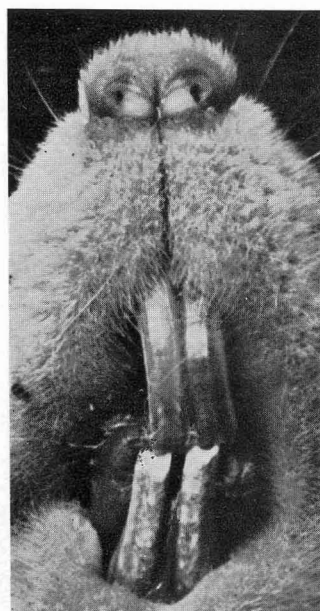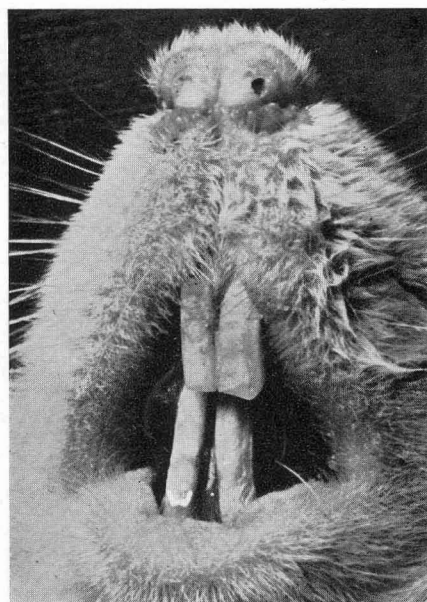
FIG. 54. Incisors of rats on fluoric diet for 432—458 days. Increased length of superior incisors, diminished length of inferior incisors; lateral deviations; cutting edge transformed into a flat surface; enamel more or less diffusely chalky-white, with irregular surface, sometimes lacking. (a) Rat 2, control. (b) Rat 5, 0.05 per cent. mineral cryolite. (c) Rat 10, 0.10 per cent. mineral cryolite. (d) Rat 22, 0.05 per cent. NaF.
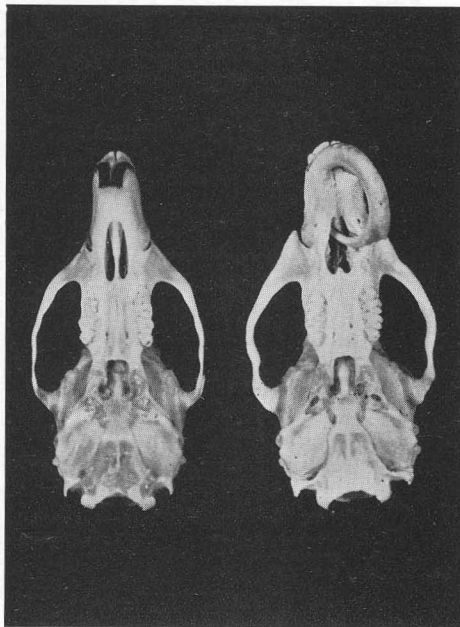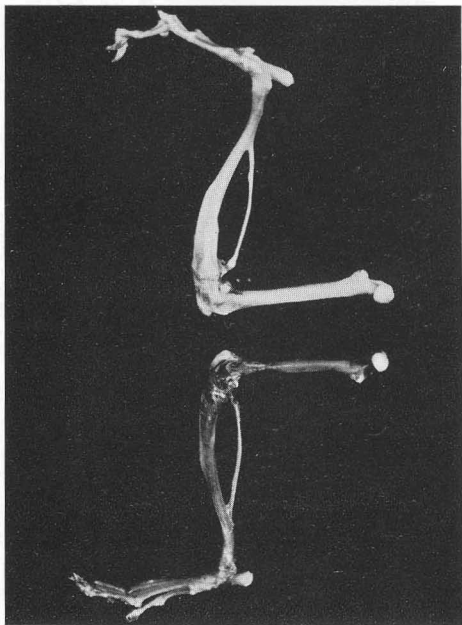
FIG. 55. Changes in bones and teeth of Rat 3, which for 585 days received 0.05 per cent. mineral cryolite in diet. (a) Skull from below, left Rat 1 (control), right Rat 3. (b) Lower extremity, above Rat 3, below Rat 1 (control).
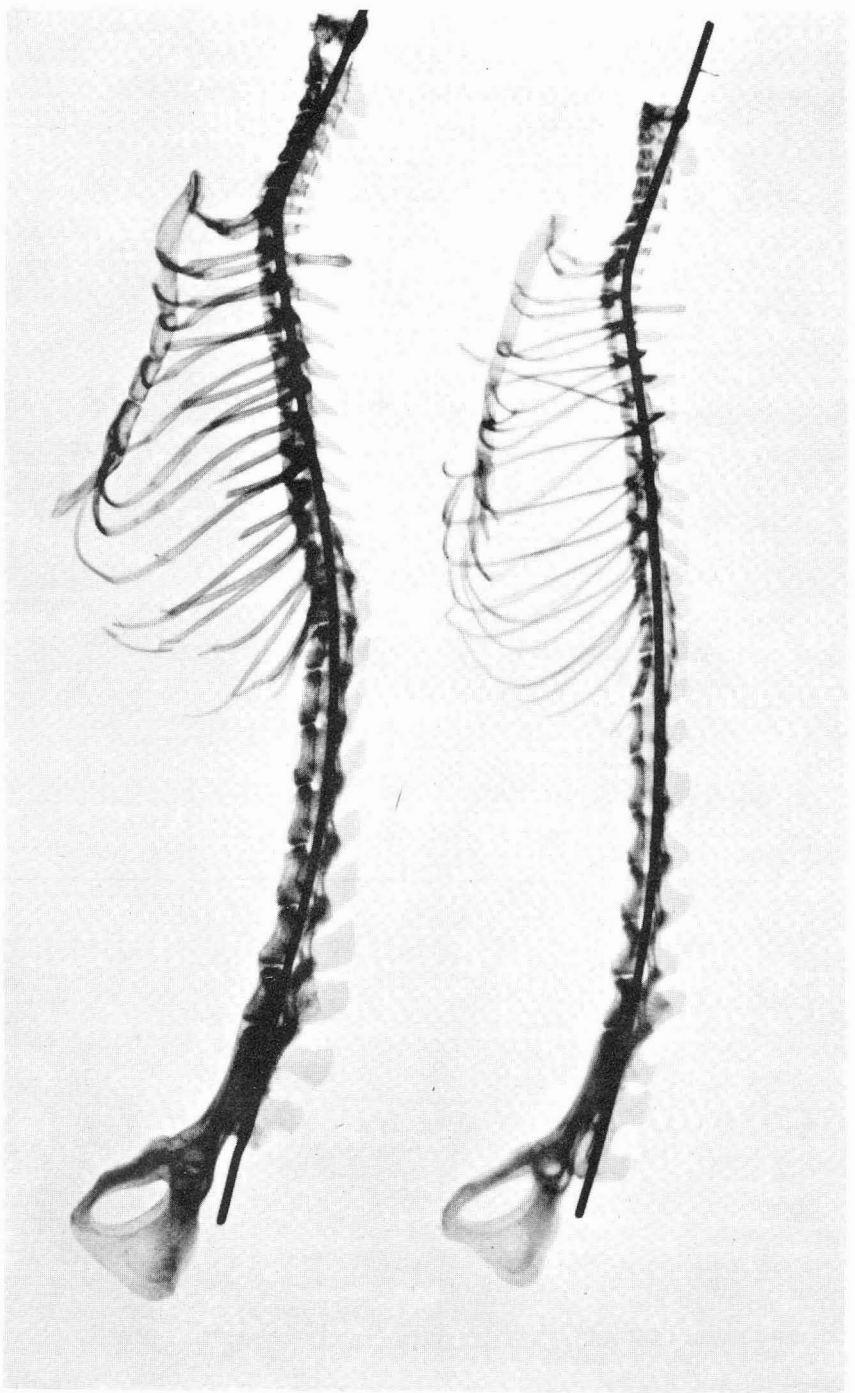
FIG. 56. Röntgen picture of trunk skeleton of rats which had been 585 days in experiment. (a) Rat 3, 0.05 per cent. mineral cryolite in diet. Diffuse osteosclerosis. (b) Rat 1, control.
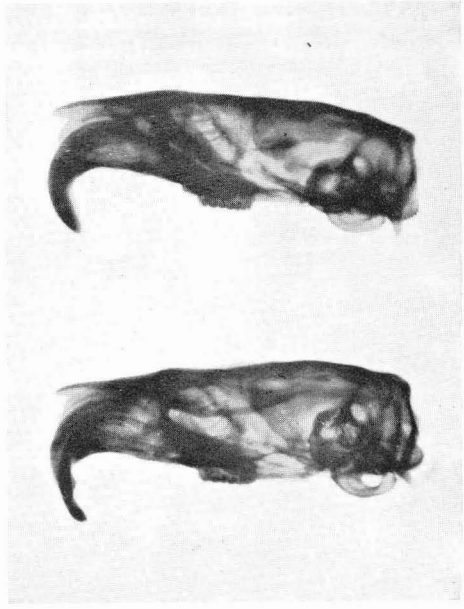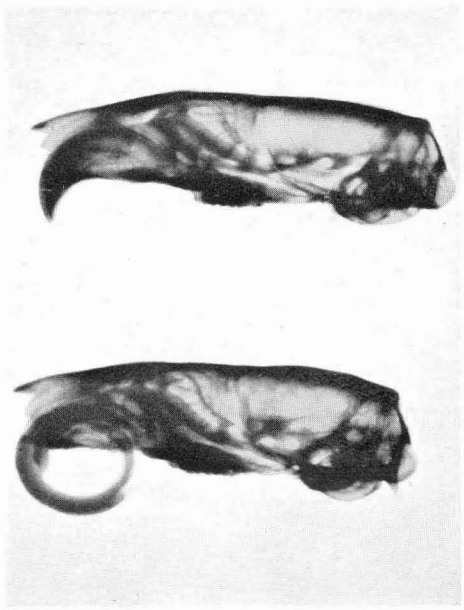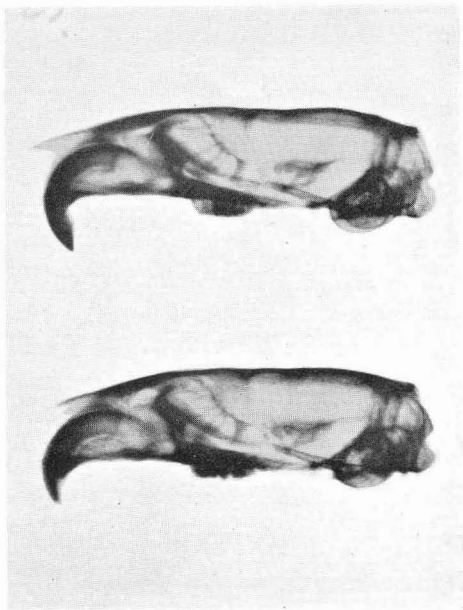
Fɪɢ. 57. Röntgen pictures of skulls of rats on fluoric diet for 432—585 days. The number of the rat is given. Rats 1 and 2: controls. Rats 3 and 4: 0.05 per cent. mineral cryolite. Rats 9 and 10: 0.10 per cent. mineral cryolite. Rats 21 and 22: 0.05 per cent. NaF. Diffuse sclerosis of cranial bones; varying prolongation of superior incisors.
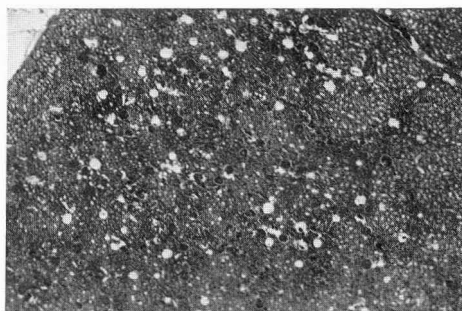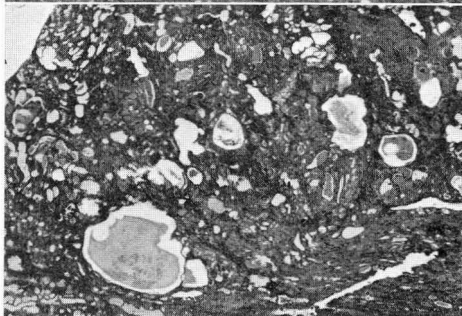
FIG. 58. Section of kidneys. (a) Rat 2, control. (b) Rat 21, 0.05 per cent. sodium fluoride in diet for 158 days. Chronic interstitial nephritis (12 ×). Hæmatoxylin-eosin.
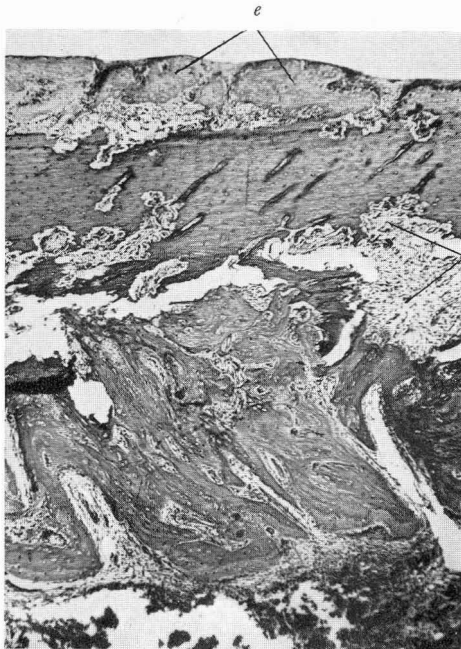
FIG. 59. Longitudinal section of femoral diaphysis, Rat 23 (0.05 per cent. sodium fluoride in diet for 294 days). a Periosteum. b Compacta. c Fibrous marrow with irregular, badly calcified osseous tissue. d Marrow parenchyma. e Osteoid tissue in periosteum. f Fibrous marrow absorbing compacta by osteoclast activity (42 ×). Staining according to Hansen.
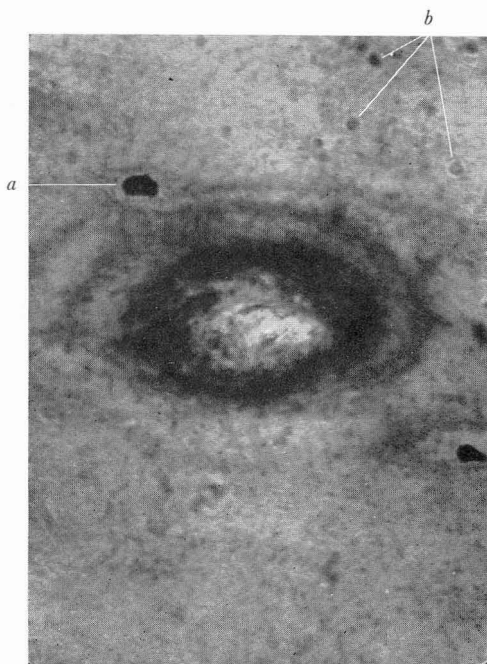
FIG. 60. Compacta of femoral diaphysis, Rat 23. Haversian canal, surrounded by irregular, very calcareous zones. a Osteocyte. b Discrete deeply staining globules in matrix (700 ×, immersion). Hæmatoxylin-eosin.

EXPERIMENTS ON PIGS

1. Technique

Ten pigs of the Danish "land breed" were used, all of the same litter and about eight weeks old. They were placed in couples in 5 stalls in a light and roomy stable. The following mixture was given as food: Barley 82.5 per cent., maize 12.5 per cent., supplement 5 per cent., until the animals weighed 40 kg., and thereafter barley 52.5 per cent., maize 43.5 per cent., supplement 4 per cent. The supplement had the following composition: Herring meal 15 per cent., blood meal 28 per cent., meat and bone meal 37 per cent., dry yeast 15 per cent., iodide of potassium, iodine and iron 5 per cent. During the whole experiment every pig was given daily about 5 g. cod liver oil containing per g. 0.2 mg. phosphorus, 500 curative rat doses of Vitamin A and 250 international vitamin D units. Experience shows that pigs thrive well on this diet, and the bone formation is good.

The animals were fed three times a day. In the midday feed various fluorine compounds were mixed in such quantities that the *daily dose for all animals was 15 mg. fluorine per kg. body weight.* The evening feed was not given till the midday feed had been consumed. Weighing and adjustment of doses took place every fourteenth day. *The fluorine compounds employed were sodium fluoride, sodium fluosilicate, mineral cryolite No. 1 and synthetic cryolite.* Table 46 shows how the animals were stabled. Pigs in the same stall were given the same fluorine compound. The experiment began on February 16th, 1933.

2. Course of Experiment. Symptoms

In the course of some weeks Pig 10 (control) acquired diarrhoea and growth stopped, for which reason this animal was excluded. At first the other animals thrived well; the weight curve is given on Fig. 61. After about one month it was obvious that Pigs 1—4 excreted a large quantity of urine and drank greedily when water was given them. After about four months Pigs 1 and 3 began to display definitely morbid symptoms; they ate poorly, lay about a good

TABLE 46.

Data from Experiment on Pigs, Concerning Stabling of Animals, Fluorine Compounds Used,
Weight.

No., sex	Fluorine compound	Weight at beginning of experiment	Weight at end of experiment	Average daily weight increase
		kg.	kg.	kg.
1 ♂	NaF..............	14	54.5	0.24
2 ♀		13.1	58.4	0.27
3 ♂	Na_2SiF_6	13.3	42.4	0.17
4 ♀		13.6	77.2	0.38
5 ♂	Na_3AlF_6 (mineral) ...	15.7	133.7	0.70
6 ♀		12.8	59.1	0.28
7 ♂	Na_3AlF_6 (synthetic) ..	16	131.6	0.69
8 ♀		15.7	74.5	0.35
9 ♂	None..............	16.6	109.4	0.55
10 ♂		14.6	excluded	..
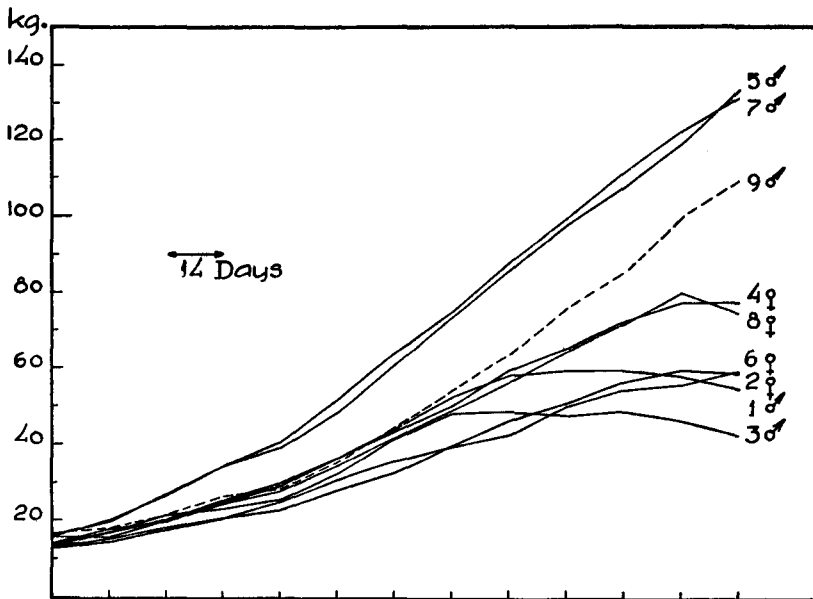
FIG. 61. Weight curves for Pigs 1—9 (168 days). Pigs 1—8 received daily 15 mg. fluorine per kg. in their food in the form of various fluorine compounds. Pig 9 served as a control.

deal and had an uncertain, stiff and unsteady gait. Identical symptoms developed in Pigs 2 and 4 and later, but not so pronounced, in Pigs 7 and 8. Pigs 5 and 6 displayed nothing remarkable beyond abundant diuresis and, for Pig 6, little appetite.

The intoxicated pigs lay down a good deal, had difficulty in getting up, and were disinclined to use their hind legs; often they moved about by dragging themselves along with the hind-quarters on the floor. In the standing position there was a peculiar stiff tripping, accompanied by quivering or spasm of the extremity muscles. This muscular unrest also occurred in the lying position; the pigs had difficulty in finding rest and frequently changed their position. As a rule the animals ate only little, always drank greedily and had heavy diuresis. As time went on the general condition suffered somewhat, and the animals acquired a gaunt appearance; Pig 5 and 7, however, were still thriving well. Towards the close of the experiment the hair was coarse and rather shaggy on all the pigs intoxicated with fluorine. The control animal, Pig 9, presented nothing abnormal. The pigs were regularly examined for thickening of the bones, but nothing definitely abnormal was observed.

Pig 3, which suffered most, died on the 171st day after a fit of general convulsions, whereafter the other animals were killed. Pieces of organs and bones (femur or humerus, costa) of all pigs were taken for microscopy, except from Pig 3. Various organs for analysis were taken from Pigs 2 and 9. After removing the bones, Röntgen pictures were made of half the skull, the pelvis and columna lumbalis, and a fore and hind leg of each animal. Thereafter the bones of Pig 2, 3, 6, 8 and 9 were skeletonized or macerated.

3. Organs

During necropsy no signs were observed of anæmia or outstanding changes in the coagulation time of the blood. The only macroscopically changed organs were the kidneys. The following organs presented nothing definitely abnormal on microscopic examination: Cerebrum, thyroid gland, thymus, heart, lungs, liver, spleen, stomach, duodenum, small intestine, suprarenals.

The *kidneys* of all fluorine animals displayed very considerable changes, but were normal in Pig 9. In Pigs 1—4 the kidney was contracted, especially that of Pig 1 (Fig. 63). The colour was paler than normal, the surface uneven, sometimes very finely granulated, sometimes irregularly lumpy (Fig. 64). In cross-section cortex was narrower than normal, with lighter and darker radial stripes (Fig. 67). In consistence it was much more resistant. In Pigs 5—8 the changes were perceptibly smaller, but very uniform. The size of the kidney

was unchanged except in Pig 6, where there was some reduction. The brownish-grey surface was studded everywhere with close, round, partly confluent spots, from lentil to pea size, pale yellow in colour. Corresponding to these spots the surface was slightly depressed (Fig. 65). In transverse section the radial striping of cortex was distinct; the consistence was also more resistant. Under the *microscope* the kidney of Pig 9 (control) was normal; in the other pigs there were signs of *chronic nephritis*, mostly of interstitial type. The changes, which were identical in all fluorine animals, were very considerable in Pigs 1, 2 and 4, less so in Pigs 5—8. The kidney of Pig 1 will be described as the typical example (Fig. 73).

The surface is uneven, the renal parenchyma has disappeared in patches and is replaced by large quantities of connective tissue, in which are remains of tubuli and glomeruli; the latter are more or less transformed into connective tissue. Also in areas where the renal parenchyma is fairly well preserved there is an increase of connective tissue. In these areas glomeruli are large, rich in cells and with a high content of erythrocytes. The endothelium of the capsular space is well preserved, adherences being observable only in one place. The lumina of the tubuli are extremely irregular, often dilated; the cells are remarkably flat, but on the whole well preserved. Lumina contain scarcely anything. In some places in the connective tissue there is infiltration of round cells and leucocytes. The vessels are unchanged. No calcium deposits observed anywhere.

4. Bones

When skeletonizing the fluorine animals nodose thickenings of the mandibles were observed and to a lesser extent of the diaphyses of the long bones; otherwise the shape of the bones was normal. Periosteum was everywhere hyperæmic. Macroscopically nothing abnormal was observed in the joints. When sawing through the bones it was found that their strength was very considerably reduced. The epiphysial region and the marrow in the long bones revealed nothing different from those of Pig 9.

As the most conspicious phenomenon the *Röntgen examination* of the bone samples showed a general, rather considerable halisteresis of the whole osseous system, most pronounced in the central bones. Spongiosa everywhere gave an indistinct, blurred picture. Compacta on the whole was of normal width, but blurred in its peripheral limits. Compacta of the diaphyses of the long bones and of corpus mandibulæ was somewhat wider than normally, but the density of the peripheral part was less than that of the central part. Sometimes the thickening of the compacta of these bones had the character of small delimited exostoses. The epiphysial regions presented nothing definitely abnormal; the epiphysial lines were of normal width. The diffuse halisteresis was most pronounced in Pigs 1—4.

TABLE 47.

Change of Form of Corpus Mandibulæ in Pigs.

Pig. No.	Fluorine compound	Height at 1st molar	Maximum thickness of corpus	Maximum thickness of compacta
		mm.	mm.	mm.
2	NaF...............	42.4	26	6.8
3	Na_2SiF_6	44	23.5	11.5
6	Na_3AlF_6 (mineral) ...	43.1	25.4	9.3
8	Na_3AlF_6 (synthetic) ..	43.7	27	7.2
9	None...............	37.2	19.6	5.8

After *maceration*, all periosteum-covered surfaces were found to be coated with a layer of up to 2 mm. of soft white osseous tissue. The mandible corpus of all the fluorine animals was shorter, thicker and higher than that of Pig 9 and studded with irregular, nodose exostoses (Figg. 68 and 69). The change of shape was especially the result of an increase of the marrow cavity, but compacta was also thickened (Fig. 70). These changes were fairly uniform in all groups (Table 47), whereas the other macroscopic bone changes were most pronounced in Pigs 1—4.

Microscopic examination of the bones on the whole revealed the following changes: (1) Moderate atrophy of the osseous tissue, especially of spongiosa and the central part of compacta; (2) formation of irregular, loosely built osseous tissue, especially from periosteum; (3) irregular and defective calcification of newly-formed osseous tissue. No crystalline deposits were observed anywhere. Transverse section of costa of Pig 1 and humerus of Pig 4 are described below as typical examples. The phenomena were distinct and qualitatively identical in all fluorine animals, but rather more pronounced in Pigs 1—4 than in the others. The bones of Pig 9 appeared normal under the microscope.

Pig 1, costa, transverse section (Figg. 74 and 75).
    Compacta has retained its normal width and in fact is thickened over limited areas. The structure differs greatly from the normal, the greater part of compacta consisting of an interlacing of trabeculæ without distinct lamellary structure, which towards the marrow cavity mostly lies concentrically, but towards periosteum is more radial. In the centre, compacta passes from large irregular cavities into a rather slender spongiosa. All lumina are coated with broad osteoid borders (up to $39\,\mu$, most frequently 15—$20\,\mu$); the same applies to the spongiosa trabeculæ and the irregular periosteal surface. Sometimes the osteoid tissue is covered with rows of high, osteoblast-like cells, sometimes with fusiform or quite flat cells. The boundary between osteoid and calcified bone is everywhere vague and irregular; the calcium salts are

deposited in the form of fine and coarse granules. The staining of the bone is relatively bad; as a rule a granular structure is recognizable. The position of the Haversian canals is quite irregular. The osteocytes are well preserved. Where the bone is not covered with osteoid tissue, which is rare, single osteoclasts are seen in Howship lacunæ.

Periosteum is particularly rich in cells. The large cells resembling fibroblasts lie in a matrix rich in collagenous fibrils. Towards the bone the cells are enlarged, arranged in irregular rows and assuming the character of osteoblasts, which cover osteoid trabeculæ. These contain abundant collagen, whose connection with collagenous fibrils in the surrounding tissue can often be followed. The osteoid trabeculæ gradually calcify in their axial part. The *marrow* consists of a normal medullary parenchyma with a rather large number of fat cells.

Pig 4, humerus, transverse section of diaphysis (Fig. 76).

Compacta is loosely built, consisting mainly of a finely meshed interlacing lying concentrically and consisting of trabeculæ of lamellary structure. Towards the marrow cavity there are large, irregular spaces. Peripherally, separated by a rather distinct border line, compacta continues in a layer of mostly radial, irregular bone trabeculæ without distinct lamellary structure and with rather numerous cavities. The width of this peripheral layer, which is covered by a periosteum, rich in cells, varies from about 1—4 mm. The bone trabeculæ in the peripheral layer are covered with osteoid borders 15—20 μ wide and coated with rows of high cells resembling osteoblasts. In compacta's inner layer there are either quite narrow osteoid borders covered with flat cells, or none at all. In the irregular spaces towards the marrow cavity there are again osteoid borders, 8—10 μ wide. In this part of the bone osteoclasts are often seen in Howship lacunæ, whereas these are absent in the other part of the bone.

In *periosteum* the formation of osteoid trabeculæ takes place in the same manner as that described under costa. The many cavities in the peripheral layer are full of tissue of the same character as periosteum. Calcification proceeds in the same irregular manner. In the inner layer the calcification is more homogenous, but here again the granular character of the bone substance is recognizable. On the whole the bone stains badly. The bone cells are well preserved, but irregularly distributed. The *marrow* is fat marrow with scattered accumulations of normal marrow cells and a rich content of erythrocytes. In some places there are small homogenous gelatinous areas between the fat cells.

5. Teeth

The dentition of the pig is diphyodont, with the formula $i\frac{3}{3}$, $c\frac{1}{1}$, $m\frac{4}{4}$ for 1st dentition, and $i\frac{3}{3}$, $c\frac{1}{1}$, $pm\frac{4}{4}$, $m\frac{3}{3}$ for 2nd dentition. Details of the calcification periods are not known. The eruption of the deciduous teeth takes place within two months after birth (with the exception of m_1, which is permanent). The eruption of the first permanent molar (M_1) occurs after 4—6 months; M_2 and the permanent incisors, canines and premolars erupt 7—14 months after birth. As these pigs were 2 months old when taken for experiment, it means that their deciduous teeth were already formed at the commencement of the experiment

and that it is presumable that the permanent teeth calcified to a greater or smaller extent during the almost six months' period of intoxication.

In all the fluorine pigs M_1 was worn down to an abnormal degree, and in places the enamel was lacking. The deciduous teeth were normal, except that the wear of the two rearmost molars (m_3, m_4) was somewhat increased where the corresponding M_1 was worn down (Fig. 68). Röntgen photographs of the jaws (Figg. 71 and 72) revealed no definite changes in the deciduous teeth. M_1 had a much lower mineral content than normally over its whole extent; the crown was low, with an irregular upper limit. The unerupted M_2 was very backward in development. In Pig 9 the width of the crown of this tooth was 4—5 mm. maximum, in the fluorine animals not over 1 mm. At the same time calcification of the permanent incisors, canines and premolars was extremely poor compared with those of Pig 9. The periodontal space was, corresponding to all erupted teeth of both 1st and 2nd dentition, blurred or entirely lost in the Röntgen picture. The alveolar septa, especially the intra-alveolar septa, were narrow and the spongious tissue indistinct and blurred in structure in all fluorine animals. The changes in the teeth observed were rather more pronounced in Pigs 1—4 than in Pigs 5—8, but the difference was only small.

6. Analyses

The fluorine content was determined in the following organs of Pig 2 (NaF) and Pig 9 (control): Stomach, small intestine, liver, spleen, kidney, lung, heart.

TABLE 48.
Fluorine Content of Organs in Pigs.

Organ	Pig 2 (NaF)			Pig 9 (Control)		
	Dry substance used	Th(NO₃)₄ used	Fluorine in 100 g. dry substance	Dry substance used	Th(NO₃)₄ used	Fluorine in 100 g. dry substance
	g.	c. c.	mg.	g.	c. c.	mg.
Stomach..........	21.70	1.14	1.6	24.31	0.88	1.1
Small intestine	14.93	0.54	1.1	14.08	0.47	1.0
Liver.............	27.65	0.49	0.53	21.18	0.43	0.61
Spleen............	17.15	0.64	1.1	17.88	0.28	0.47
Kidney	7.76	1.28	4.9	20.27	0.80	1.2
Lung.............	15.75	0.63	1.2	9.12	0.39	1.3
Heart	23.10	0.86	1.1	30.63	0.87	0.85
Musculature	25.64	0.58	0.68	33.45	0.91	0.82
Blood.............	(200 c.c.)	1.98	0.30*)	(200 c.c.)	1.84	0.28*)

*) Expressed per 100 c.c. blood.

TABLE 49.

Fluorine Content of Bones and Teeth in Pigs.

Material	Pig 2 (NaF)			Pig 3 (Na_2SiF_6)		
	Ash used	$Th(NO_3)_4$ used	Fluorine per g. ash	Ash used	$Th(NO_3)_4$ used	Fluorine per g. ash
	g.	c. c.	mg.	g.	c. c.	mg.
Femur, corpus.....	0.3742	3.77	14.9	0.2920	3.41	17.3
Tibia, corpus......	0.3443	2.90	12.5	0.2731	3.38	18.3
Mandible	0.6440	6.59	15.2	0.2436	2.87	17.4
Teeth ($m_4 + M_1$) ..	0.9310	3.86	6.1	0.7548	3.78	7.4

Material	Pig 8 (Na_3AlF_6, synth.)			Pig 9 (Control)		
	Ash used	$Th(NO_3)_4$ used	Fluorine per g. ash	Ash used	$Th(NO_3)_4$ used	Fluorine per g. ash
	g.	c. c.	mg.	g.	c. c.	mg.
Femur, corpus.....	0.1990	1.40	10.4	1.1780	0.46	0.12
Tibia, corpus......	0.2356	1.43	9.0	1.1950	1.29	0.32
Mandible	0.2120	1.96	13.7	1.1693	1.40	0.36
Teeth ($m_4 + M_1$) ..	0.4031	1.12	4.1	1.2720	0.70	0.17

Analyses were also made of the blood and a sample of the gluteal musculature. The results are given in Table 48. In the organs of Pig 9 the fluorine content varied between 0.47 and 1.3 mg. per 100 g. dry substance; in 100 c.c. blood there was 0.28 mg. fluorine. The kidney of Pig 2 contained 4.9 mg. fluorine; in the other organs the fluorine content was almost normal (0.53—1.6 mg.). The blood contained 0.30 mg. fluorine per 100 c.c.

Of Pigs 2, 3, 8 and 9 analyses were made of pieces of the diaphyses of femur and tibia and of corpus mandibulæ; of the teeth, m_4 and M_1 were analysed together. The results are shown in Table 49. Whereas in Pig 9 the fluorine content in the bone ash was low (0.12—0.36 $^0/_{00}$), it was greatly increased in the fluorine animals, most in Pig 3 (17.3—18.3 $^0/_{00}$), least in Pig 8 (9—13.7 $^0/_{00}$). The increase was observed in all bones examined, though it varied slightly; the fluorine content varied between about 30 and 55 times the normal. In the tooth ash the fluorine content was likewise increased considerably in all pigs that had received fluorine, from the normal 0.17 to maximum 7.4 $^0/_{00}$.

7. Summary

Qualitatively the fluorine compounds employed had identical effects. Judged according to the degree of the clinical symptoms and the pathologico-anatomical

FIG. 62. Kidney of Pig 9 (control).
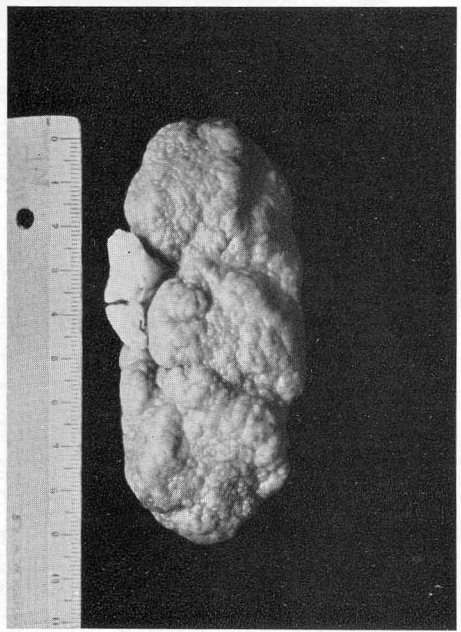
FIG. 63. Kidney of Pig 1 (NaF); greatly diminished, surface irregularly granulated, colour pale.
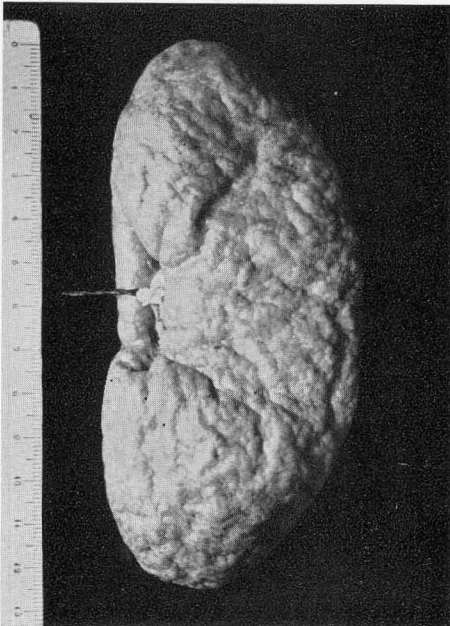

FIG. 64. Kidney of Pig 4 (Na_2SiF_6); slightly diminished, surface irregularly granulated, colour pale.
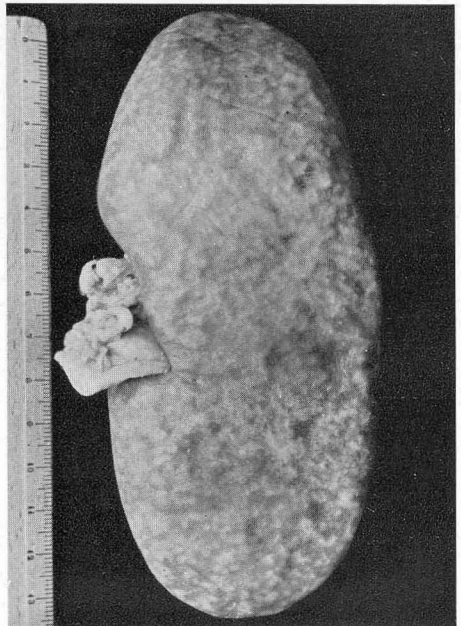

FIG. 65. Kidney of Pig 8 (mineral cryolite). Surface interspersed with numerous pale-yellow, slightly depressed spots.
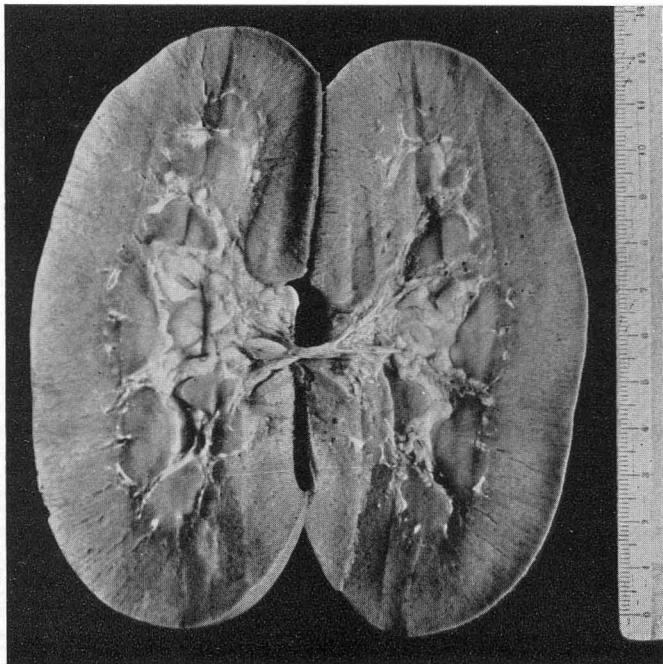
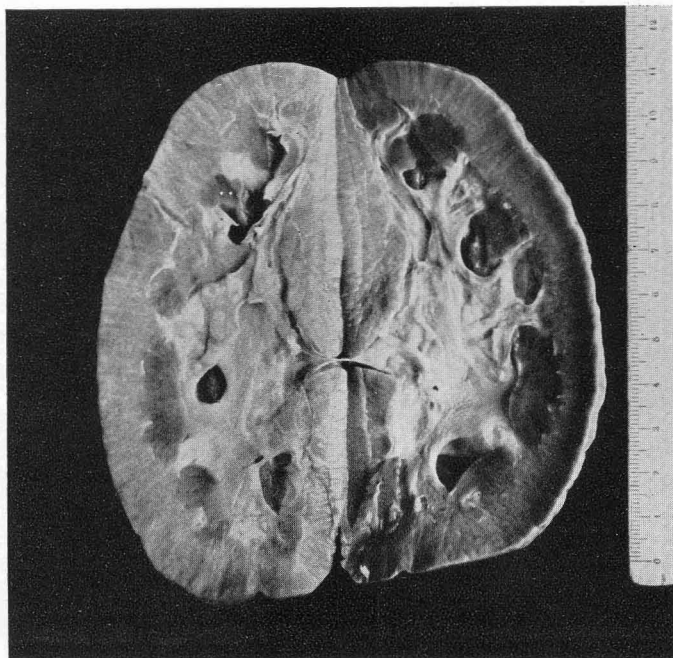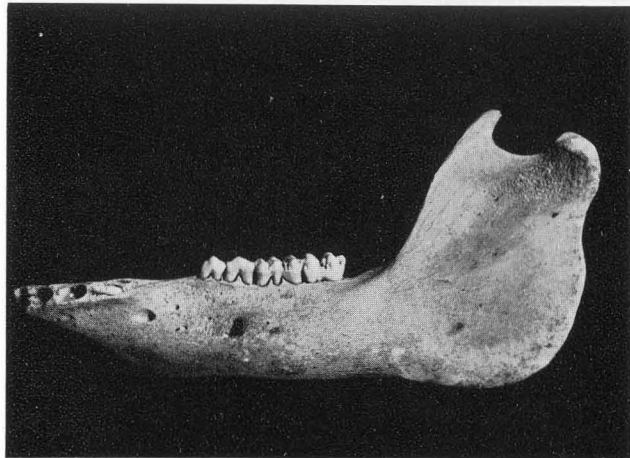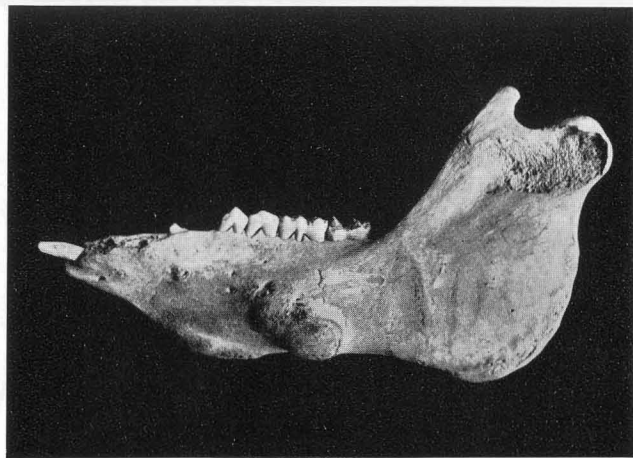FIG. 66. Kidney of Pig 9 (control).
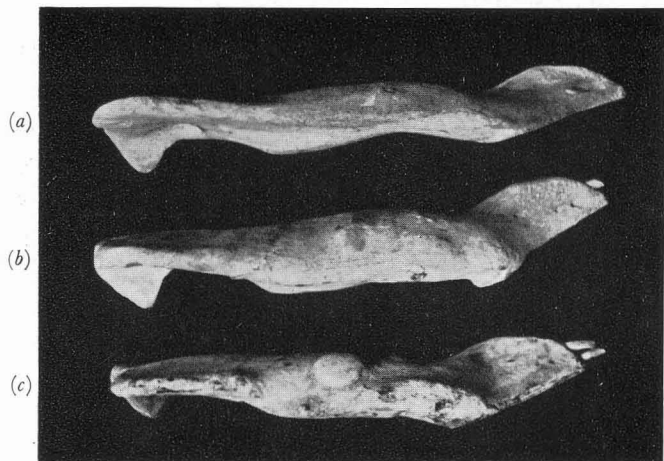

FIG. 67. Kidney of Pig 4 (Na$_2$SiF$_4$). Cortex narrow, striped.

FIG. 68. Mandibles of pigs, lateral view. (a) Pig 9, control. (b) Pig 3, (Na_2SiF_6). Corpus shorter and higher, with exostose; surface irregular. Teeth of 1st dentition not altered, 1st permanent molar worn down irregularly.

FIG. 69. Mandibles of pigs, seen from below. Irregular thickening of corpus. (a) Pig 9, control. (b) Pig 8, mineral cryolite. (c) Pig 3, Na_2SiF_6.

FIG. 70. Frontal section of mandible at 1. molar. (a) Pig 9, control. (b) Pig 8, mineral cryolite. Height and width increased; marrow cavity enlarged; compacta thickened, the peripheral part loose in structure.

m_2 m_3 m_4 M_1 M_2
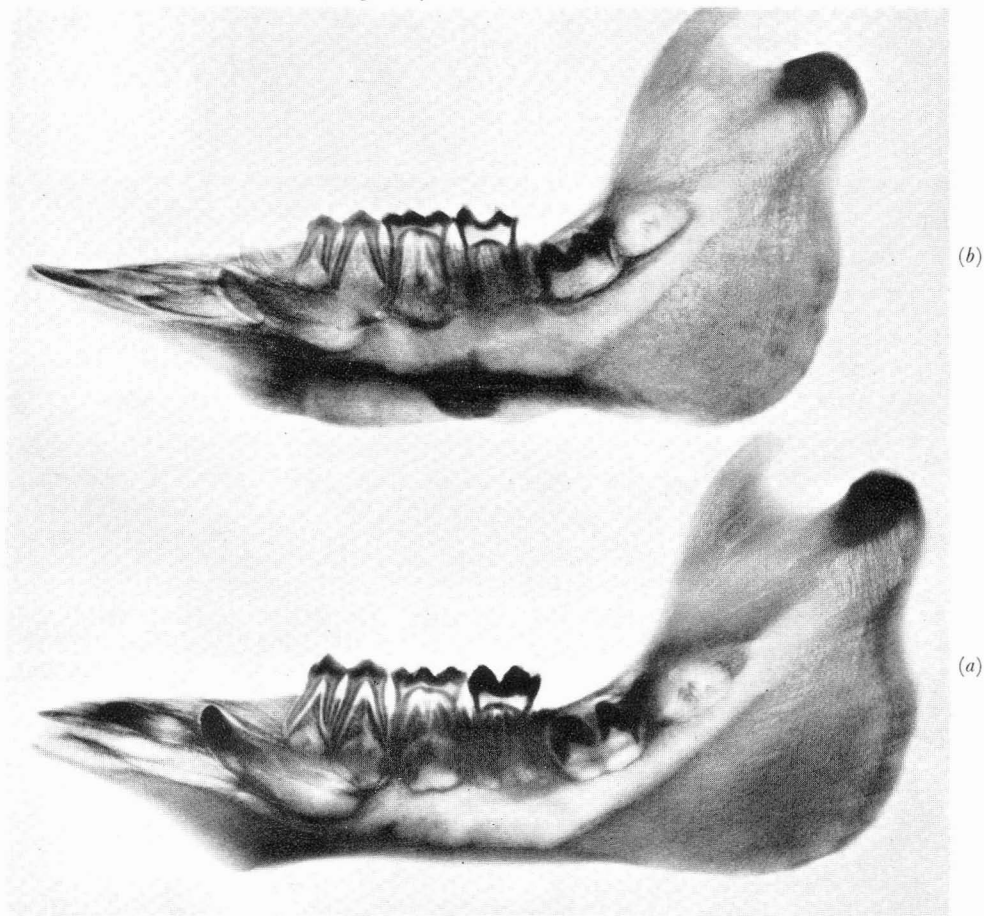
FIG. 71. Röntgen picture of pig mandibles. (a) Pig 9, control. (b) Pig 3, Na_2SiF_6. Diffuse halisteresis of the bone, spongiosa structure indistinct and blurred. Abnormal wear of 1. permanent molar, reduced mineral content in the unerupted permanent teeth.
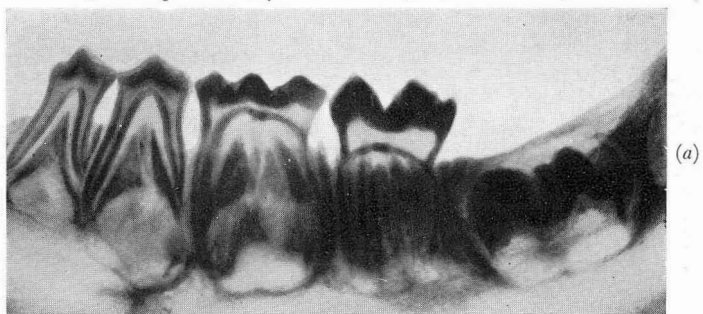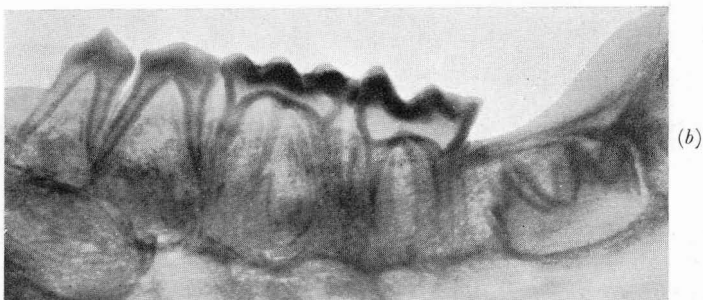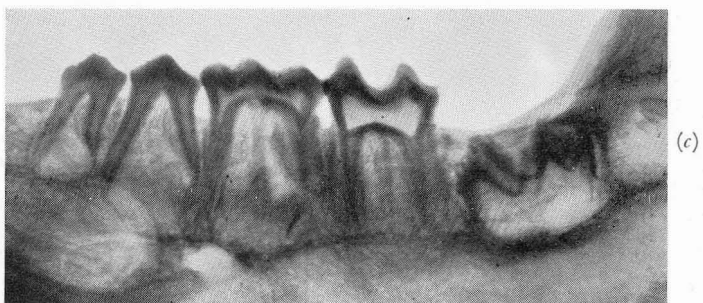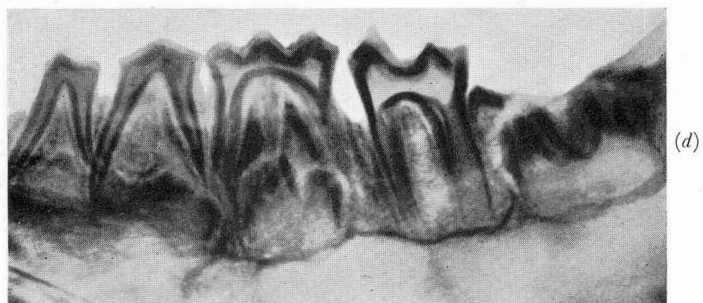
FIG. 72. Röntgen picture of pig mandibles, comprising m_2, m_3, m_4 and M_I and M_2. (a) Pig 9, control. (b) Pig 1, NaF. (c) Pig 3, Na_2SiF_6. (d) Pig 5, synthetic cryolite. (b)—(d) No definite changes of m_2—m_4. M_I shows abnormal wear; severe hypoplasia of M_2. Osseous structure indistinct; periodontal spaces narrow, blurred in places.
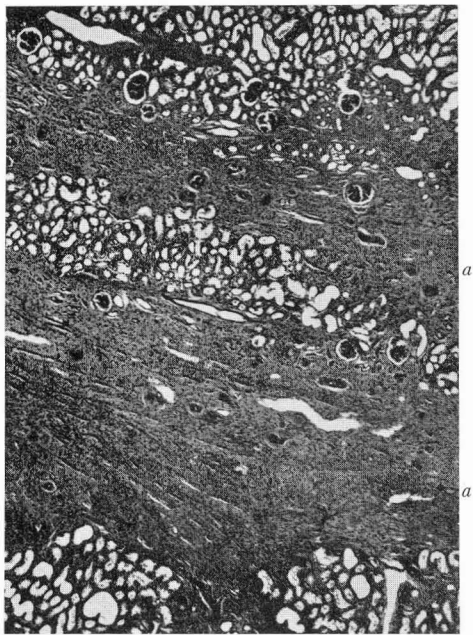
FIG. 73. Section of kidney, Pig 1 (NaF). Chronic interstitial, contracting nephritis. *aa* Connective tissue with remains of glomeruli. Urinary canals irregularly dilated (25 ×). Hæmatoxylin-eosin.
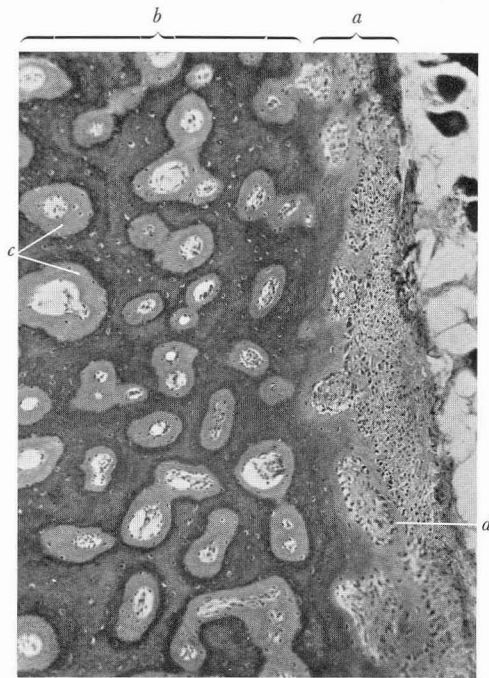

FIG. 74. Cross-section of costa, Pig 1 (NaF). *a* Periosteum rich in cells, with osteoid trabeculæ (*d*). *b* Bone, irregular in structure and with low calcium content. Lumen of all canals lined with wide osteoid borders (*c*). (90 ×). Hæmatoxylin-eosin.
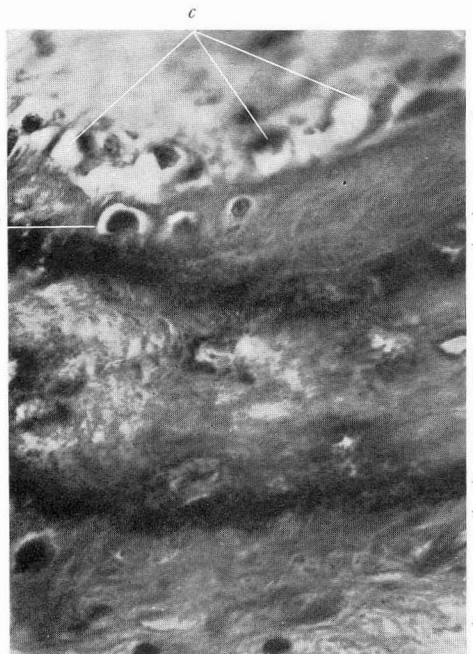

FIG. 75. Cross-section of costa, Pig 1 (NaF). Bone-trabecula (*a*) in periosteum. The calcium salts precipitated in the form of granules. The boundary between osteoid tissue (*b*) and bone is irregular. *c* Osteoblasts. *d* Irregularly situated osteocytes (700 ×, immersion). Staining according to Hansen.
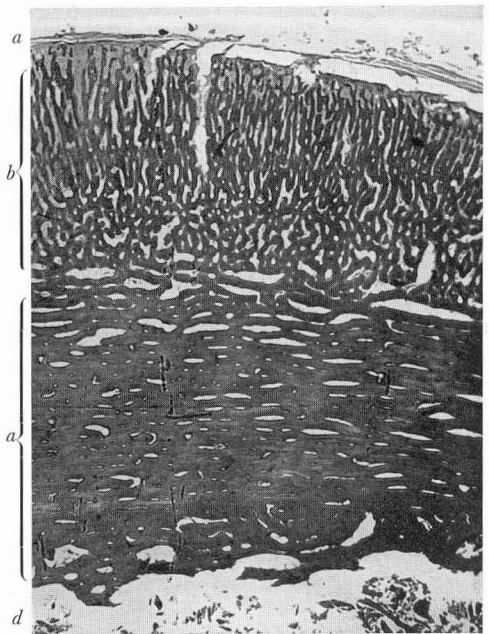

FIG. 76. Cross-section of humerus diaphysis, Pig 4 (Na$_2$SiF$_6$). *a* Periosteum. *b* Outer layer of mostly radial, badly calcified trabeculæ. *c* Inner layer of concentrically arranged trabeculæ relatively well calcified. *d* Marrow cavity (12 ×). Hæmatoxylin-eosin.

and analytical findings, fluorine had practically the same toxicity in the form of sodium fluoride and sodium fluosilicate. The two cryolites were distinctly less toxic, the mineral cryolite especially, as was reasonable to expect from the grain size. That the fine-grained synthetic cryolite was also less toxic indicates that only a part of the fluorine in cryolite is active.

Retardation of growth was varied in degree and was not observed at all in Pigs 5 and 7, where the average daily increase of weight was actually greater than in the control pig (Table 46). Among the pigs whose weight was deleteriously affected, a poor general condition was observed towards the close of the experiment, but no real cachexia developed.

It was not possible to prove any local effect on the mucous membrane of the gastro-intestinal tract. The severe *nephritis* is a sign that fluorine in the pig is excreted in a locally-irritating compound. The effect on the renal parenchyma seems to be diffuse. The clinical symptoms, abundant diuresis and excessive liquid intake, are explainable by the renal effect.

There was no observable deposition of fluorine in the organs during intoxication except for the kidney, where the increase of the fluorine content was only small. There was, however, a very considerable deposition of fluorine in *bones* and teeth, and the pathologico-anatomical changes (apart from the kidney) were limited to these organ-systems. The general bone affection may be described as a condition resembling osteomalacia, mainly characterized by a moderate bone atrophy and defective calcification of the irregularly structured osseous tissue. On the whole the periosteal bone formation was particularly active, whereas the endosteal bone production was relatively small. In the long bones the marrow displayed signs of incipient gelatinous atrophy. The Röntgen picture did not indicate any great disturbance of the enchondral ossification. It is probable that the deficient calcium deposition in the bones is the result of reduced calcium retention, as the symptoms from the musculature, which formed an essential feature in the clinical picture of the intoxication, resembled spasms caused by hypocalcæmia.

The effect of the fluorine on the *dental system* was the development of a hypoplastic, defectively calcified enamel and dentine in the teeth or parts of those teeth which calcified during the ingestion of the fluorine. The teeth formed prior to the experiment were unchanged, both macroscopically and under the X-ray.

EXPERIMENTS ON CALVES

1. Technique

Two new-born cow-calves of the "Red Danish" dairy breed were used, Calves 1 and 2. They were isolated in a roomy stall in a light byre. Both were tuberculin tested, with a negative result. The daily feed is shown in the table below:

Age, in days	Whole milk kg.	Skim milk kg.	
3— 6	3	. .	
7— 9	4	. .	Green fodder
10— 12	5	. .	
13— 21	6	. .	
22— 24	5	1	Rolled oats, turnips, hay
25— 27	4	2	
28— 39	3	3	
40— 60	. .	6	
61—120	. .	5	
over 120	. .	. .	

There were periods when it was difficult to get the animals to take the full quantity owing to lack of appetite. They were weighed every month; the weight curves are given on Fig. 77. Feeding with fluorine compounds commenced eight days after birth. *Calf 1 received sodium fluoride, Calf 2 mineral cryolite No. 1.* The weighed dose, dissolved and suspended in about 100 c.c. water, was given daily by means of a bottle. The dose, which is given on Fig. 77 and Table 50, varied somewhat, the intention being to produce both a severe and a protracted intoxication. During the intoxication the ingestion had to be stopped for a period of 3 days in order not to lose the animals. The dose of sodium fluoride varied from 0.5 to 4 g.; *in the course of 195 days Calf 1 was given a total of 481.5 g. sodium fluoride, or 2.47 g. daily average, or, taking the average weight, 20.4 mg. fluorine per kg. per day. Calf 2 received 1439 g. cryolite in the course of 195 days*

in doses varying between 2 to 10 g. This corresponds to 7.38 g. cryolite daily, *or 60 mg. fluorine per kg. per day.*

Fluorine ingestion was started on March 10th, 1933. The comparative material employed was a cow-calf of the same age and race (Calf 3), which had been given similar food but which had been out on grass for some time; its weight on killing was 201 kg.

2. Course of Experiment. Symptoms

The details are given in Table 50. The symptoms developed uniformly in both animals, though Calf 1 (sodium fluoride) was most affected in the end.

TABLE 50.

Intoxication Symptoms in Calves.

Calf 1 (NaF)			Calf 2 (mineral cryolite)		
Daily intake NaF	Duration of period	Symptoms	Daily intake cryolite	Duration of period	Symptoms
g.	days		g.	days	
0.5	28	Appetite reduced the first days, afterwards good. Fæces normal.	2	28	Good appetite; fæces normal.
1.5	15		5	15	
3	27	Poor appetite immediately; diarrhoea. At close of period exostoses on hind leg and poor general condition.	10	27	Poor appetite immediately; diarrhoea. At close of period exostoses on fore and hind legs. Bad general condition.
0	3	Recovers quickly; eats better, fæces normal. Exostoses decrease in size though without disappearing.	0	3	Recovers quickly, eats better; fæces normal. Exostoses decrease in size.
1.5	30		5	30	
3	33	Bad appetite; diarrhoea. Exostoses increase in size and also appear on foreleg. General condition extremely bad; eyes dull; gait stiff and laborious.	10	76	Eats badly; periodical diarrhoea. Exostoses increase in size. General condition becoming bad; eyes dull; gait stiff and laborious.
4	43				
3	16		8	16	
481.5	195	...Total	1439	195	...Total

During the first 43 days of the experiment the condition seemed to be normal, the weight increasing rapidly and the appetite being good. When the dose was increased to 3 g. sodium fluoride and 10 g. cryolite daily there was an immediate reaction: The animals took their milk reluctantly, had continuous diarrhoea, and, in the course of the 27 days during which the dose was maintained unchanged, turned thin and drowsy. Towards the close of that period exostoses were observed developing on the diaphysis of metatarsals and meta-
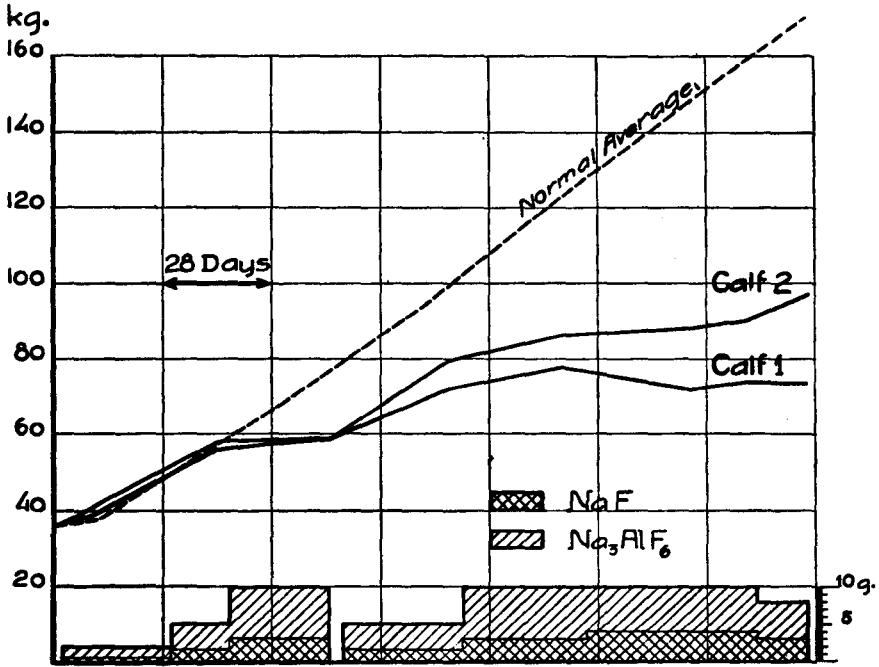

FIG. 77. Weight curves for Calf 1 (NaF) and Calf 2 (mineral cryolite), 195 days. Average weight curve for normal calves on similar diet (see text).

carpals; they were circular, 4—5 cm. wide, about 2 cm. thick, bone-hard and indolent. When the fluorine dosing was suspended for three days and thereafter continued in a smaller quantity, the exostoses became distinctly reduced in size in the course of 5—6 days, and the general condition improved. After renewed increase of the dose the exostoses grew to their previous extent and the general condition again became poor. At the close of the experiment the calves were very emaciated, the hair coarse and untidy. The eyes were dull; there was some photophobia, and sero-purulent secretion collected in the inner corner of the eye. Corneæ were clear. The animals were less lively than normally, but did not lie down to any marked extent. The normal concavity of the hinder end of the back line disappeared, the animals "hunched their

backs" (Fig. 78). Their gait was peculiarly stiff and laborious; this was especially pronounced in the hind legs. No spasms, pareses or joint swelling were observed.

Retardation of growth was considerable in both calves. At the beginning of the experiment Calf 1 weighed 36.4 kg., at its conclusion 73.4 kg.; the daily weight increase was 0.19 kg. For Calf 2 the figures were 36.1, 97.2 and 0.31. For comparison we have the average weight curve for 150 cow-calves on a similar basic diet during an experiment at the State Experimental Laboratory (Fig. 77). There the average daily weight increase in the same period was about 0.71 kg.*).

The animals were killed by gunshot in the brain, cutting of neck arteries and bleeding. Samples of blood were taken for ordinary blood test; the coagulation time was not changed to any marked degree. Sections of the parenchymatous organs and of metatarsals and costæ were taken for microscopy**). For each animal Röntgen pictures were made of the divided skull, columna lumbalis and pelvis, and one fore and hind leg. Thereafter the bones were skeletonized or macerated.

3. Blood and Organs

The result of the blood examination is shown in Table 51. In Calves 1 and 2 were found moderate anæmia, the hæmoglobin percentage was 68 and 81 respectively, as against 99 for Calf 3. The erythrocytes were reduced in number to a corresponding degree. There was not much change in the number of white blood corpuscles, though in Calf 1 the figure was relatively low (5240). Differential counts revealed a relative diminution of the number of granulocytes and a corresponding increase of lymphocytes, again most pronounced in Calf 1, which on the whole was the more intoxicated. The erythrocytes exhibited a slight anisocytosis, but no immature cell forms were observed, neither of the red nor of the white corpuscles.

No macroscopic changes of the organs were found during necropsy. The following organs were examined microscopically: Oesophagus, stomach, small and large intestines, salivary glands, pancreas, liver, spleen, lung, heart, kidney, vesica, cerebrum, medulla, parathyroid glands, thyroid gland, thymus, suprarenals and ovarium.

No great structural changes were observed in the organs. In liver, kidney, heart muscle and central nervous system the cell protoplasm exhibited certain

*) 142de Beretning fra Forsøgslaboratoriet, Copenhagen 1931, page 3.
**) Fragments of jaws with teeth were examined microscopically by Dr. Ove Brinch, who will publish the result later (111 a).

TABLE 51.

Blood Picture in Calves.

	Calf 1 (NaF)	Calf 2 (mineral cryolite)	Calf 3 (normal)
Hæmoglobin .... %	68	81	99
Erythrocytes, number ...... mill.	8.01	7.91	9.86
Leucocytes, number........	5,240	10,310	9,070
Polymorphonuclears........ %	7	23	32
Staff-nuclears.............. -	$4^2/_3$	$9^1/_3$	$4^2/_3$
Eosinophil L. .... -	$^2/_3$	$1^1/_3$	$3^1/_3$
Basophil L. .... -	0	$^1/_3$	0
Lymphocytes.............. -	86	60	$52^2/_3$
Monocytes .... -	$1^2/_3$	6	$7^1/_3$

degenerative changes. Whereas the cell nuclei as a rule were well preserved and stained, the structure of the protoplasm was less compact, granular or vesicular, and stained badly. Similar changes, which in the said organs were widespread but varying in intensity in the same organ, were observable with more or less certainty in other parenchymatous organs. There was no marked increase in the hæmosiderin content of liver and spleen with the staining method employed. It is particularly pointed out that the kidney did not reveal any definite inflammatory changes, and that the actual diminution of the parathyroids was not considered to be in excess of the relative diminution corresponding to the retarded growth. On the whole the changes described were identical in both calves, both qualitatively and quantitatively.

4. Bones

The form of some bones was changed. The long bones of the extremities were gross, with irregularly thickened diaphyses (Figs. 80 and 81). Periosteum everywhere was hyperæmic and markedly adherent. Joint cartilage and capsules presented nothing abnormal. On cutting through the bones they were found to be very much reduced in strength in comparison with the bones of Calf 3. The marrow in the long bones was diffusely red, shiny, gelatinous. The epiphysial regions presented nothing definitely abnormal to macroscopic examination.

After *maceration* all bones were chalky-white, the normal, firm, smooth surface being replaced by a brittle, porous, osseous tissue. Compacta of costæ, pelvis and cranium had diminished considerably in thickness. The osteoporotic

process was particularly pronounced in costæ, which could be broken by finger pressure (Fig. 83). On the long bones the exostoses represented a considerable thickening, especially of metacarpals and metatarsals (Figg. 81, 84, 85), but thickenings were also observed on the other extremity bones (Fig. 80) and on the corpus of the mandible (Fig. 82). In section the compacta and marrow cavity of these bones consisted of a firmer and darker osseous layer several mm. thick, and peripherally of deposits of loose, lamellary structure with irregular, longitudinal spaces filled with hyperæmic tissue. Seen from the surface the exostoses had the appearance of pumice stone (Figg. 84, 85).

The *Röntgen examination* revealed a severe, diffuse halisteresis in all the bones. Compacta was narrow, the medullary cavity enlarged and the structure of spongiosa indistinct and blurred. Simultaneously there was a varying periosteal formation of osseous tissue low in mineral content, but little or no endosteal bone formation. On the radiographs of several bones (long bones, mandible, pelvis) there were more or less regular longitudinal spaces between the inner, homogeneous, relatively dense compacta areas and the irregular periosteal deposits (Fig. 86). The epiphysial lines as a whole were of normal width and shape. In the metaphysis of the bones were transversal, more dense lines or bands lying parallel to the epiphysial line. The number and width of these lines, like their mutual distance apart, were rather variable; in costæ close to the costochondral junction and in the metaphyses of the long bones (Fig. 86) it was possible to count up to 10 or 12, corresponding to the epiphyses in columna and pelvis, 2 to 3 such lines. All these changes in the bones were identical in both calves, but more advanced in Calf 1.

The *microscopic examination* of the bones revealed qualitatively and quantitatively fairly uniform changes in both calves, consisting of (1) considerable atrophy of the osseous tissue, especially of spongiosa and the central part of compacta; (2) the formation of irregular, loosely built osseous tissue, especially from periosteum, where the bone formation was often excessive; (3) irregular and deficient calcification of newly-formed osseous tissue; (4) gelatinous atrophy of the marrow of the long bones. No deposits were observed anywhere, particularly of calcium fluoride. Sections of costa of Calf 1 and metatarsus of Calf 2 are described below as typical examples.

Calf 1, costa, transverse section (Fig. 88).
  Compacta is of varying, almost normal breadth, but transformed into a spongy interlace of irregular trabeculæ without distinct lamellary structure. Only towards the marrow cavity is here and there a narrow layer of osseous tissue resembling normal compacta. The spongiosa trabeculæ in the marrow cavity are sparse and slender. Nearly all cavities are coated with broad osteoid borders measuring up to 66 μ, most frequently 20—25 μ. The osteoid tissue is covered with cells, some packed

together, high, like osteoblasts, others fusiform or flat, like endothelial cells. The boundary between osteoid tissue and bone is irregular; the calcium salts are deposited in the form of coarse or fine granules, often extending in cloudy formations into the osteoid tissue. The calcium content of the bone is low, and a heterogeneous, more or less granular structure of the bone substance is observed everywhere. The osteocytes are well preserved, but their mutual position is quite irregular. Only scattered osteoclasts are visible in Howship lacunæ, especially in the central part of compacta; but cells resembling osteoclasts are often observed in lumina, outside of the osteoid tissue. The *marrow* consists of a normal medullary parenchyma with a moderate content of fat cells and fairly numerous giant cells. *Periosteum* is very wide and extremely rich in cells. The matrix contains numerous collagenous fibrils. Numerous irregular osteoid trabeculæ are observable, rich in collagen, of which the fibrillary structure and connection with the collagenous fibrils of the matrix is evident. The osteoid trabeculæ are coated with large cells resembling osteoblasts, often arranged in irregular rows. The axial part of the osteoid trabeculæ is calcified in the same irregular and sparse manner as in the bone itself.

Calf 2, metatarsus with exostosis, transverse section (Figg. 89 and 90).
     The bone consists of several, more or less separate layers, the structure of which is mostly spongy. Nearest the marrow cavity compacta consists of a rather narrow zone, with Haversian canal systems, though their lamellary structure is only vague. Through a layer with large, irregular spaces one comes into the outer part of compacta, which consists of a rather broad, spongy interlacing, with mostly radial trabeculæ. The boundary between the exostosis and compacta is very distinctly marked by a few circumferential trabeculæ. The width of the exostosis is considerable, but varying; it is built of the same loose osseous tissue as compacta's outer part and consists of two parts, an inner one adhering to compacta, and an outer one lying like an isolated bone island in the very broad periosteum, which is rich in cells and vessels.
     In the central layers of compacta and in the zone with the large cavities there is an almost total lack of osteoid tissue. In the peripheral compacta layer and in the exostosis almost all trabeculæ are covered with broad osteoid borders measuring up to 55 μ, but in most cases 15—20 μ. The osteoid tissue is frequently coated with flat endothelial cells; in the exostosis, however, the coating often consists of rows of osteoblast-like cells, especially in the peripheral parts. The boundary between the osteoid tissue and bone almost everywhere presents the same irregular picture as that described under costa. The bone substance on the whole has a heterogeneous structure, often actually granular. The calcium content of the bone is low except in the innermost part of compacta, which is distinctly more homogeneous and stains better than it does peripherally. The osteocytes are well preserved; their position is irregular.
   *Periosteum* consists of a reticulum of large cells like fibroblasts in a matrix rich in collagenous fibrils. Bone formation proceeds by the cells' collecting in rows and enlarging, the collagen becoming homogenized and forming osteoid tissue; one can follow the course of the collagen fibrils into the osteoid tissue. In time a sparse axial calcification of the osteoid trabeculæ occurs. Side by side with the bone formation there is a lively lacunary absorption by numerous osteoclasts. In the remainder of the bone only very few osteoclasts are seen in Howship lacunæ. The *marrow* is very atrophic. The ground substance is structureless, gelatinous, with scattered fat cells. Only occasional marrow cells are seen here and there, whereas there are many erythrocytes and leucocytes as well as scattered connective tissue and reticulum cells. The large cavities in compacta contain a similar tissue, appearing as a net-formed stroma with very sparse cells.

FIG. 78. Calf 1 after 195 days peroral ingestion of an average of about 20 mg. fluorine per kg. daily (as NaF). Retarded growth and cachexia; coat coarse; extremities thickened; photophobia and purulent secretion from conjunctiva.

FIG. 79. Normal calf of same age (Calf 3).
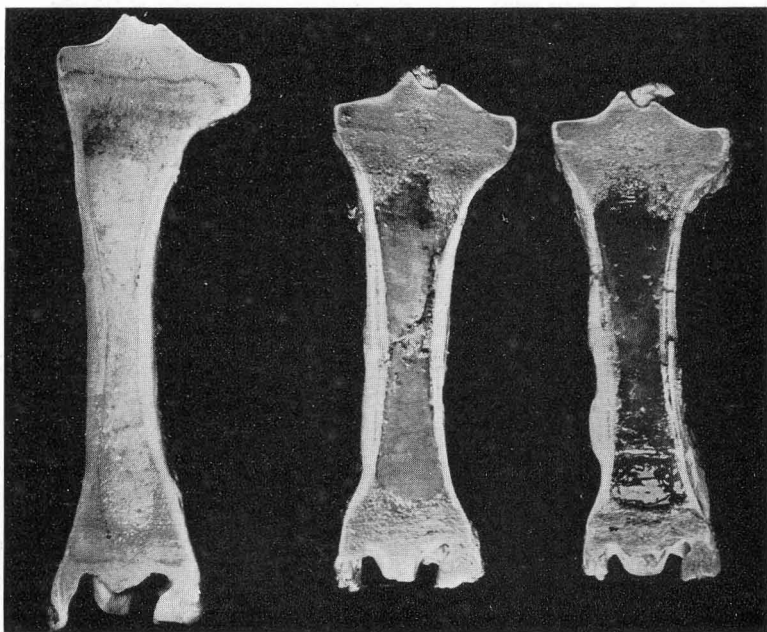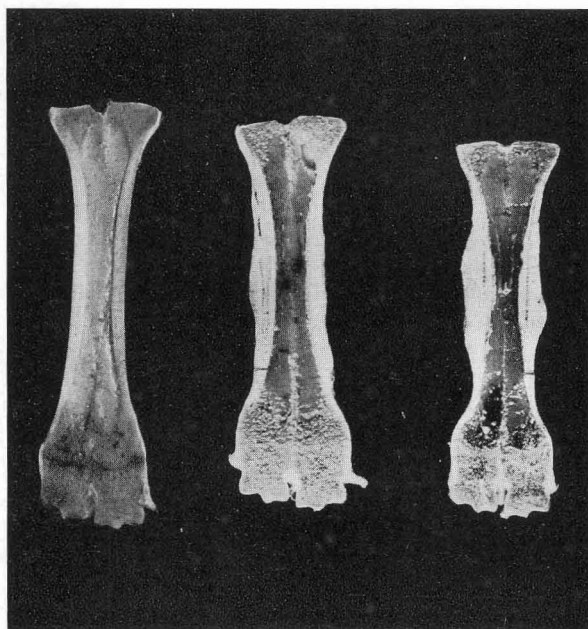
FIG. 80. Tibia of calves, divided. (a) Calf 3, normal. (b) Calf 2, mineral cryolite. (c) Calf 1, NaF. Bone thickened, with considerable periosteal deposits. Medullary cavity wide, marrow gelatinously degenerated.

FIG. 81. Metatarsus of calves, divided. (a) Calf 3, normal. (b) Calf 2, mineral cryolite. (c) Calf 1, NaF. Changes similar in kind to those in tibia (Fig. 80).
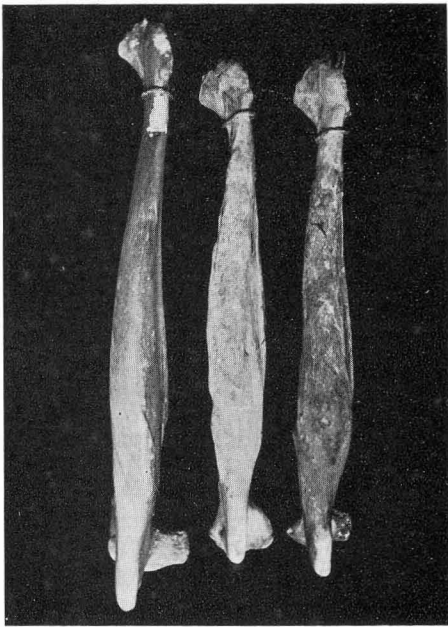
(a)   (b)   (c)

FIG. 82. Mandibles of calves, from below. (a) Calf 3, normal. (b) Calf 1, NaF. (c) Calf 2, mineral cryolite. Corpus slightly thickened, surface irregular.
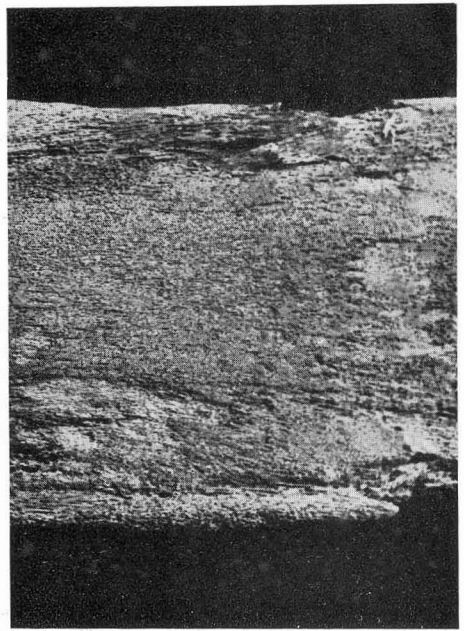
FIG. 83. Costa of Calf 1 (NaF). Pronouncedly porous on surface.
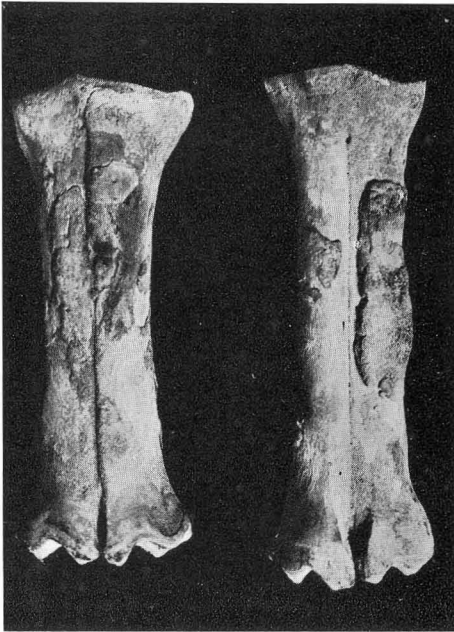
(a)   (b)

FIG. 84. Metacarpus (a) and metatarsus (b) of Calf 2 (mineral cryolite). Diffuse periosteal deposits resembling pumice stone.
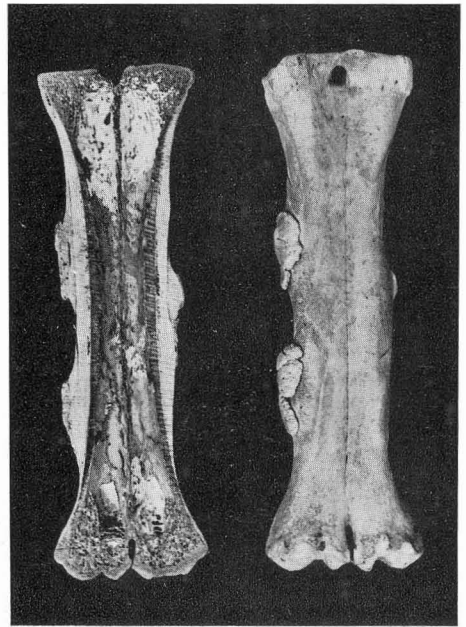
FIG. 85. Metatarsus of Calf 1 (NaF). Note the central, dark coloured and relatively firm part of compacta, and the white, stratified periosteal deposits.
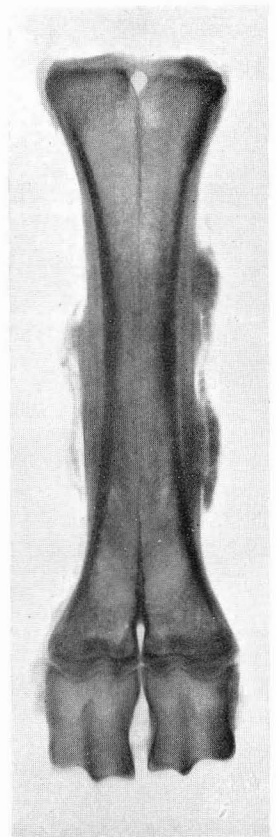
FIG. 86. Röntgen pictures. (a) Ulna of Calf 3, normal. (b) Ulna and (c) metatarsus of Calf 1, NaF. Diffuse halisteresis; compacta narrow, medullary cavity wide; irregular periosteal deposits, low in mineral content. In ulna's distal metaphyses numerous "lines of arrested growth".
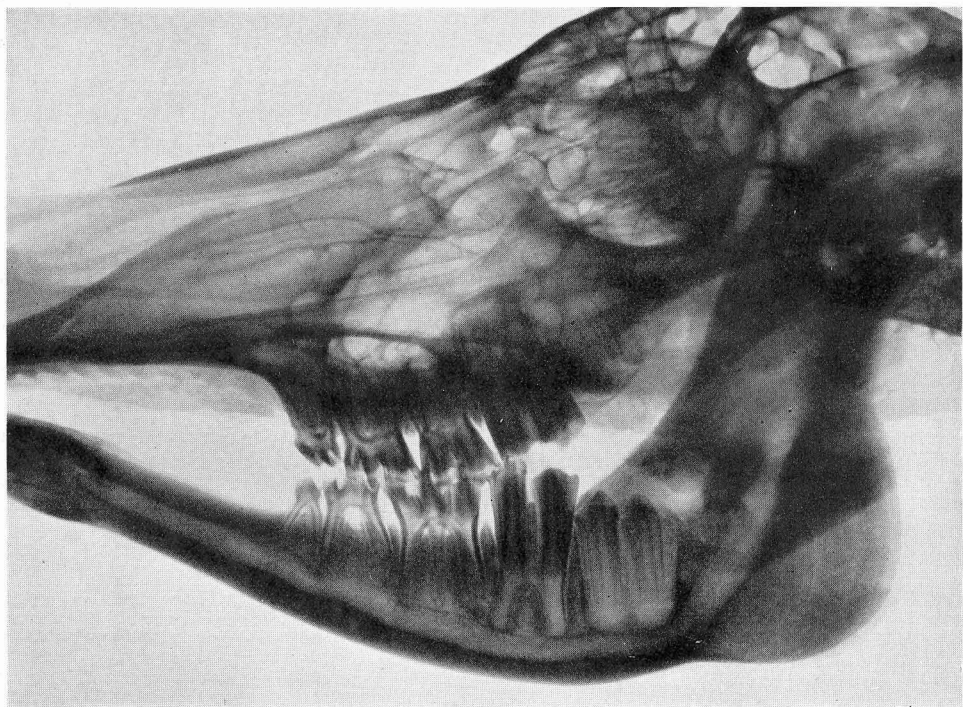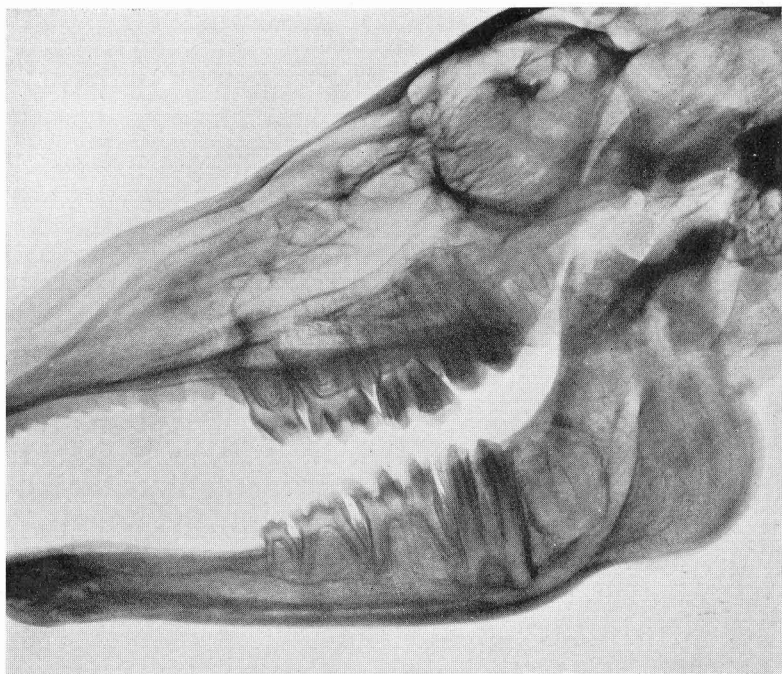
$$m_1 \quad m_2 \quad m_3 \quad M_1 \quad M_2$$

FIG. 87. Röntgen pictures of divided calf skulls. (a) Calf 3, normal. (b) Calf 1, NaF. Diffuse hali-steresis; spongiosa indistinct and blurred, compacta narrow with periosteal deposits. M_1 has reduced mineral content in apical half, M_2 gives hardly any shadow.
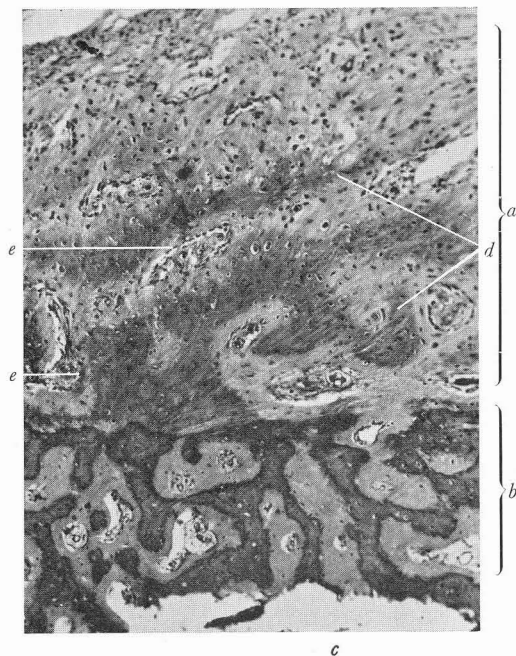
FIG. 88. Cross-section of costa, Calf 1 (NaF). *a* The enormously wide periosteum with sparsely calcified osteoid trabeculæ (*d*) coated with rows of osteoblast-like cells (*e*). *b* Compacta, deficiently calcified, with considerable quantities of osteoid tissue. *c* Marrow cavity (90×). Hæmatoxylin-eosin.

FIG. 89. Cross-section of metatarsal diaphysis, Calf 2 (mineral cryolite). *a* Periosteum with isolated osseous tissue. *b* Exostosis on compacta (*c*) which is divided by a zone of irregular cavities into an outer and an inner part. *d* Marrow cavity. × Area of Fig. 90. (9×). Hæmatoxylin-eosin.
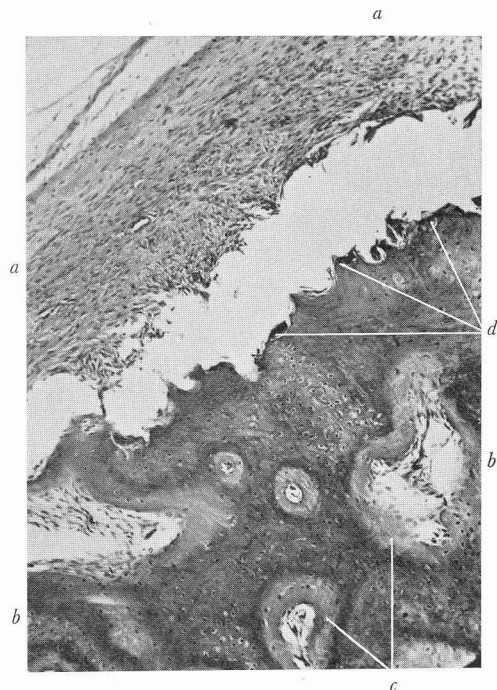
FIG. 90. Detail of Fig. 89. *aa* Periosteum. *bb* Bone, with irregular and deficient calcification. *c* Osteoid tissue. Along the border of the bone against periosteum are numerous osteoclasts in Howship lacunæ (*d*). (90×). Hæmatoxylin-eosin.

5. Teeth

The dentition of the ox is diphyodont, with the formula $i\frac{0}{4}$, $m\frac{3}{3}$ for 1st dentition, and $I\frac{0}{4}$, $PM\frac{3}{3}$, $M\frac{3}{3}$ for 2nd dentition. The eruption of the deciduous teeth takes place prior to birth or in the course of the first two weeks of life. The first permanent molar (M_1) erupts at the age of 4—6 months, M_2 after 5—18 months. The eruption of the other permanent teeth is late (20—48th month). In the present case the deciduous teeth were fully formed at the beginning of the experiment, and it is presumable that M_1 and M_2 became more or less calcified during the $6^1/_2$ months of the intoxication.

Macroscopically the teeth presented nothing abnormal in the two calves. The *radiographs* of the skull (Fig. 87) revealed nothing abnormal in the molars of the 1st dentition (m_1, m_2, m_3). The first permanent molar had a much reduced mineral content in the apical half. The unerupted M_2 was practically not calcified and the contour just observable in Calves 1 and 2. In Calf 3 the whole of M_1 and the coronal two-thirds of M_2 were well developed and gave a very dense shadow. The periodontal space was irregularly blurred round all erupted teeth in the fluorine calves, the alveolar septa and the spongy tissue round the teeth indistinct in outline. The halisteresis was very considerable in the bones of the jaws.

6. Analyses

Samples were taken for analysis from all three calves, of mandible, costa, lumbar vertebra and metatarsus. The incisors (i_1—i_4) were analysed collectively and the molars (m_3—M_4) separately (Table 52). The fluorine content in the bone ash, which in Calf 3 varied from 0.15—0.43 $^0/_{00}$, was much increased in Calves 1 and 2, especially the former (10—19.6 $^0/_{00}$). The increase was most considerable in pelvis, lumbar vertebra and costa, where the fluorine content amounted to about 48 times the normal.

In the ash of incisors and molars of Calves 1 and 2 there was from 4.1 to 5.5 $^0/_{00}$ fluorine, most in incisors and least in m_3, but the difference was not great. The ash of the same teeth of Calf 3 contained very little fluorine (0.078—0.34 $^0/_{00}$). For the purpose of examining how the fluorine is deposited in the teeth, enamel and dentine of m_2 and m_3 were separated by means of a steel drill (Calves 1 and 3). In the dentine there is a very considerable deposition of fluorine; dentine ash of Calf 1 contained 7.8 $^0/_{00}$ fluorine, of Calf 3 only 0.22 $^0/_{00}$. Whereas the enamel of Calf 3 contained 0.057 $^0/_{00}$ fluorine, the content in the corresponding material of Calf 1 was about 8 times as large, viz. 0.51 $^0/_{00}$. The figures indicate that fluorine is depos-

TABLE 52.

Fluorine Content of Bones and Teeth in Calves.

Material	Calf 1 (NaF)			Calf 2 (mineral cryolite)			Calf 3 (normal)		
	Ash used	$Th(NO_3)_4$ used	Fluorine content per g. ash	Ash used	$Th(NO_3)_4$ used	Fluorine content per g. ash	Ash used	$Th(NO_3)_4$ used	Fluorine content per g. ash
	g.	c. c.	mg.	g.	c. c.	mg.	g.	c. c.	mg.
Incisors	0.4729	1.70	5.5	0.4384	1.43	5.0	0.4390	0.50	0.34
Molar (m_3)	0.2171	0.62	4.3	0.1991	0.54	4.1	2.4679	0.81	0.098
Molar (m_1)	0.2613	0.91	5.3	0.1973	0.58	4.5	2.1462	0.56	0.078
m_2⌠ Enamel...	1.1220	1.92	0.51	—	—	—	1.4811	0.28	0.057
+m_3⌡ Dentine ..	0.6609	3.48	7.8	—	—	—	1.2041	0.88	0.22
Mandible	0.2568	2.31	13.7	0.2000	1.38	10.5	0.7190	0.66	0.28
Costa	0.1357	1.50	16.8	0.2038	1.64	12.5	1.9541	2.50	0.38
Pelvis	0.1628	2.10	19.6	0.1848	1.78	14.6	1.1283	1.62	0.43
Lumbar vertebra	0.2775	3.49	19.3	0.2550	2.56	15.3	0.9801	1.21	0.37
Metatarsus	0.2253	1.52	10.0	0.2066	1.47	10.8	2.0127	1.02	0.15
do., central comp.	0.2274	0.48	3.2	—	—	—	—	—	—
do.,periosteal dep.	0.1610	1.96	18.5	—	—	—	—	—	—

ited in preformed enamel, but the question is a difficult one to decide with certainty, because the presence of small quantities of the relatively fluorine-rich dentine in the isolated enamel may cause a large error.

In order to examine whether the fluorine is deposited generally in the bone, the fluorine content of the relatively firm inner, compacta layer of metatarsus of Calf 1 was determined (3.2 $^0/_{00}$), and also of the periosteal deposits (18.5 $^0/_{00}$). A cross section of the entire diaphysis contained 10 $^0/_{00}$ fluorine. Accordingly, the deposition of fluorine seems to take place mostly in the new-formed osseous tissue.

7. Summary

In the experiment, sodium fluoride and cryolite had qualitatively identical effects; as Calf 1 was most intoxicated, this means that sodium fluoride was more than three times as toxic as the mineral cryolite employed, having regard to the fluorine content.

The growth of both calves was considerably retarded, and finally a *cachectic condition* developed. Symptoms of irritation of the gastro-intestinal tract were manifested by lack of appetite and a tendency towards diarrhoea; on the other hand no definite pathologico-anatomical changes were found in the mucous membrane of the gastro-intestinal tract.

The systemic effect was principally the development of a universal *bone disease* which, from the X-ray and pathologico-anatomical pictures, must be regarded as a kind of osteomalacia. The condition is characterized by (1) bone atrophy, (2) irregular and inadequate calcification of the new-formed, abnormally structured osseous tissue, (3) considerable universal periosteal bone formation. The enchondral ossification showed (on the radiograph) signs of intermittent inhibition, but otherwise nothing abnormal. The metaphysial lines or bands must be identified with the "lines of arrested growth" described particularly by Harris (383), observable in a number of pathological states which affect the general condition. Consequently, it is uncertain whether the effect on the enchondral ossification is a primary fluorine effect or a secondary consequence of the poor general condition. The disturbance in the calcium metabolism did not cause tetany spasms, but it is reasonable to regard the peculiar stiff, laborious gait as a sign of existing hypocalcæmia.

Fluorine caused a defective development of those *teeth,* or parts of them, which calcified during the experiment (M_1 and M_2). There was a considerable storing of fluorine in bones (especially new-formed osseous tissue) and teeth. In the teeth fluorine is deposited mostly in the dentine, but probably to a small extent in preformed enamel as well.

The result of the microscopic examination of the *parenchymatous organs* indicates that fluorine has a general degenerative effect on protoplasm, of a character similar to that known from toxic influences of other kinds. Microscopically the kidney exhibited a picture recalling nephrosis, but as there were no definite inflammatory changes, the necessary conclusion is that, in the calf, fluorine is excreted in another and less locally-irritating compound than in the pig. The partial bone-marrow atrophy may be an unspecific cachectic phenomenon or the manifestation of a direct fluorine effect. The same view must be accepted as regards the blood changes, the moderate, simple anæmia and the diminution of the number of granulocytes.

EXPERIMENTS ON DOGS

1. Technique

The dogs employed were two healthy, lively animals about 2 years old, No. 1 (fox terrier) weighing 9.100 kg., No. 2 (rough-haired terrier, mongrel) weighing 11.470 kg. Dog 1 was in a good state of nutrition, Dog 2 was thin. Each animal was placed in a bright and roomy kennel, with a fenced-in run in the open air. The food given was coarse rye-bread, liver paste, raw minced beef, plenty of bones, and water ad libitum. Both dogs were given a daily supplement of fluorine compounds mixed in their food; Dog 1 received mineral cryolite No. 1, Dog. 2 sodium fluoride. There was some difficulty about exact dosage, as at intervals the animals had no appetite and very reluctantly took the food with the fluorine. They were weighed every month. The dogs were X-rayed at the beginning of the experiment and after 140, 240, 407 and 494 days. Each time the skull, columna, pelvis and a fore and hind leg were photographed after injection of 0.05 g. chloretum morphicum. The experiment was started on August 24th, 1932.

The dosage of the fluorine compounds varied, small doses being given at first in order to find the tolerance. The dosage is shown in Table 53. Dog 1 began with 0.5 g. cryolite daily, and it was increased steadily in the course of 222 days to 2.4 g. daily. After the animal had been taking this latter dose for 47 days it developed severe symptoms of intoxication; administration was therefore suspended for 17 days, whereafter cryolite was again given in smaller doses (0.75—1.5 g.), interrupted by several periods with poisoning symptoms which necessitated a temporary cessation of the ingestion. *Dog 1 was killed after 587 days*; it had then *received 859.25 g. cryolite* spread over the 533 days, *or*, expressed in terms of average weight and the entire experimental period, *79.8 mg. fluorine per kg. per day*. Dog 2 began with a daily dose of 0.1 g. sodium fluoride, rising steadily in the course of 78 days to 0.7 g. per day. After receiving this latter dose for 27 days the dog exhibited severe general symptoms, for which reason the ingestion was stopped for 5 days. Later, smaller doses were given (0.3—0.6 g. daily), with intermittent aggravation of the condition. *Dog 2 was*

killed after 626 days, when it had received 195.8 g. sodium fluoride over 531 days, or *13.8 mg. fluorine per kg. per day.* At the close of the experiment a 3-year old fox terrier (bitch), weighing 11.600 kg., was used as comparative material (Dog 3).

2. Course of Experiment. Symptoms

Both dogs developed identical symptoms of intoxication, which appeared in periods and disappeared in the course of a short time when the fluorine ingestion was suspended. In the latter part of the experiment there were symptoms of a more chronic character. The periodic, more acute intoxication symptoms began invariably with lack of appetite and loss of weight. After some days the dogs were drowsy, with uncertain and staggering gait, photophobia, and purulent secretion from conjunctivæ. No changes of corneæ were observed. After the fluorine had been discontinued for a few days the dogs began to brighten up again, they ate well and put on weight, until the same symptoms appeared again after a period varying according to the size of the dose and the point of time in the experiment (See Table 53). The eye symptoms always disappeared in the course of few days after the dog had begun to improve.

In the latter half of the experiment there were various gait anomalies of chronic character. In the standing position the dogs seemed reluctant to put any weight on the hind legs and sat down a good deal, even when their liveliness did not seem impaired and running seemed to cause no difficulty. For long periods Dog 2 did not stand on the right hind leg at all, though it was impossible to find local changes by physical examination. No definite bone tenderness was observed on palpation. Ultimately, both dogs carried their hindquarters rather stiffly and awkwardly; no abnormal curvature of the vertebral column was observed.

Towards the close of the experiment a severe cachectic condition developed in both dogs, with little appetite and emaciation, reduced liveliness, dyspnoea during muscular work, anæmia of mucous membranes, photophobia, purulent secretion from conjunctivæ, as well as scaly and itchy dermatitis of the facial skin, especially around the mouth. In the end the condition was practically the same in both dogs, whereas in the course of the experiment Dog 2 had on the whole been more affected. In the last two weeks there were diffuse ulcerations (decubitus) on the hind legs of Dog 1. On the last day Dogs 1 and 2 weighed 6.500 and 10.070 kg. respectively.

Throughout the experiment both dogs drank unusually much and passed large quantities of urine. There was never any vomiting or diarrhoea in conjunction with the acute exacerbations of the intoxication; sub finem Dog 1

TABLE 53.

Summary of Doses of Fluorine Compounds used in Experiments with Dogs.

Dog 1			Dog 2		
Change of dose, day of experiment	Daily intake of cryolite	Intoxication symptoms	Change of dose, day of experiment	Daily intake of NaF	Intoxication symptoms
	g.			g.	
1	0.5	..	1	0.1	..
6	0.6	..	7	0.2	..
8	0.7	..	14	0.3	..
11	0.8	..	19	0.4	..
14	0.9	..	37	0.5	..
16	1.0	..	51	0.6	..
18	1.1	..	78	0.7	..
20	1.2	..	105	0	+
29	1.3	..	110	0.4	..
44	1.4	..	155	0	+
51	1.5	..	161	0.2	..
61	1.6	..	222	0.3	..
72	1.7	..	269	0	+
85	1.8	..	287	0.2	..
97	1.9	..	326	0.3	..
110	2.0	..	387	0	+
131	2.1	..	413	0.3	..
160	2.2	..	469	0.4	..
222	2.4	..	496	0.5	..
269	0	+	510	0.6	..
287	1.5	..	518	0	+
407	0	+	527	0.5	..
413	1.5	..	566	0.6	..
442	0	+	582	0	+
444	1	..	594	0.5	+
469	1.5	..	601	0.3	+
533	0.75	+	616	0	+
576	0	+	626	0	(mors)
587	..	(mors)	..	..	..
Total 859.25 g.	..		195.8 g.	..	

vomited twice. No abnormal salivation was observed, no spasms or pareses (beyond the gait anomalies referred to). Neither of the dogs exhibited distinct periods of sexual excitement during the experiment.

After 140 days, the Röntgen pictures revealed a doubtful — after 240 days a definite but rather moderate, diffuse halisteresis of the bone system in both dogs. Under the subsequent Röntgen examinations the halisteresis was prac-

tically unchanged, but it was now observed that in both animals there was a general diminution of the compacta breadth (particularly distinct in the extremity bones) and a loose, rather blurred spongiosa structure. On the whole the changes were of the same intensity in both animals.

The animals were killed by cutting a. carotis under ether narcosis. The blood coagulated slowly, and samples of the blood of both animals were taken for examination. Microscopic examination was made of the parenchymatous organs and of sundry bones (costa, pelvis, femur). Skull, columna lumbalis and pelvis and various extremity bones were examined by X-ray. Finally, the fluorine content of various bone samples and of the molars was determined.

3. Blood and Organs

Both dogs had very severe anæmia (Table 54). The *blood* of Dog 1 contained 16 per cent. hæmoglobin and 2.60 million erythrocytes, of Dog 2 14 per cent. hæmoglobin and 0.93 million erythrocytes. The film preparations showed some anisocytosis and pronounced macrocytosis, but no nucleated red blood corpuscles were observed. In Dog 2 the white blood picture presented only few deviations from the normal, mostly a relative lymphocytosis. Dog 1 had a pronounced neutrophile leucocytosis, 97 per cent. of the 117,000 leucocytes being neutrophile polymorphonuclears, staff-nuclears or metamyelocytes. There were no myelocytes or myeloblasts. Remarkably few blood platelets were observed in both animals.

The *organs* of both dogs were very pale and flabby, but otherwise only the

TABLE 54.

Blood Picture in Dogs after Fluorine Ingestion.

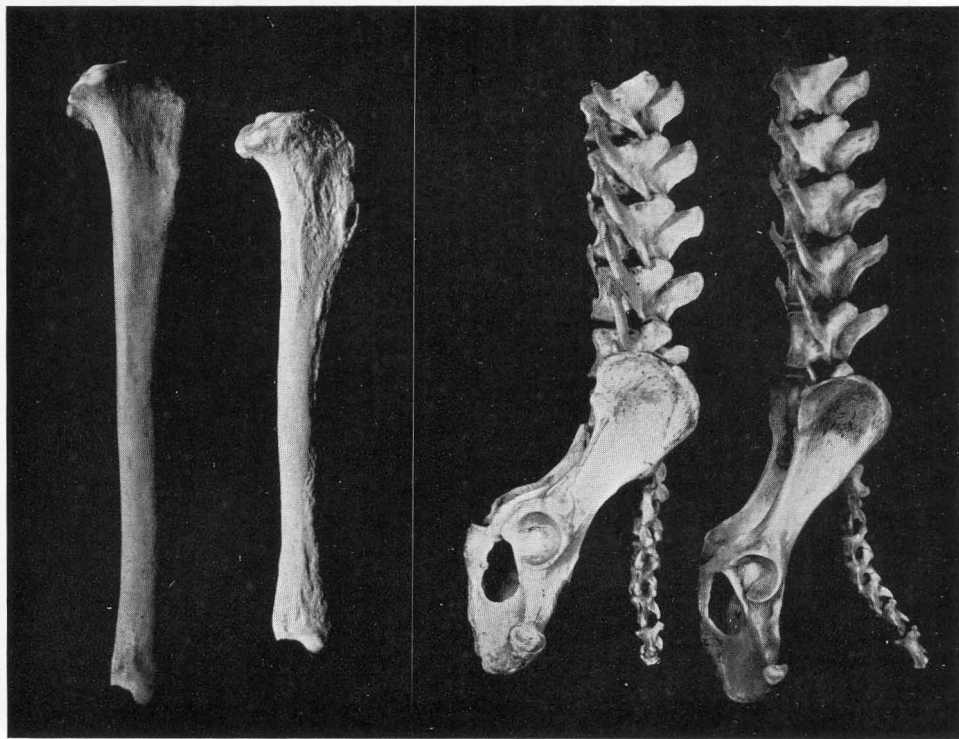|		Dog 1 (mineral cryolite)	Dog 2 (NaF)	Dog 3 (normal)
Hæmoglobin	%	16	14	103
Erythrocytes, number	mill.	2.60	0.93	6.16
Colour index		0.31	0.75	0.84
Leucocytes, number		117,000	14,960	9,630
Neutrophil segment-nuclears	%	$78^1/_3$	$36^1/_3$	$69^1/_3$
Neutrophil staff-nuclears	%	$12^1/_3$	$2^1/_3$	4
Metamyelocytes	%	$6^1/_3$	—	—
Eosinophil L.	%	$^2/_3$	$3^1/_3$	$2^2/_3$
Monocytes	%	1	$8^1/_3$	$5^1/_3$
Lymphocytes	%	$1^1/_3$	$49^2/_3$	$18^2/_3$

kidney presented macroscopic changes. In both dogs it was somewhat diminished and the surface was uneven, finely or coarsely granulated. The colour as a whole was paler than normally, but darker and lighter in patches. The capsule was very adherent and the consistence greatly increased. Cross-section showed that the cortex was narrower than normally, and irregularly striped. Microscopy revealed signs of a chronic, mostly interstitial nephritis and also diffuse degeneration of the epithelium of the tubules. A section of the *kidney of Dog 1* will be described as an example (Fig. 94).

The surface is uneven. The renal substance is replaced by connective tissue in streaky areas. Glomeruli are relatively well preserved, large and rich in cells. Often, however, there are coagulated masses in the capsular cavity, and here and there the capillary tuft is seen to be shrunken and badly stained. The tubules are irregular in their course and very often dilated. The epithelial coat is the site of considerable changes, the intensity of which varies somewhat in different parts of the kidney. The nuclei are fairly well preserved and well coloured, but the protoplasm is swollen, of granular, cloudy structure, and the boundaries between the cells and against the lumen is blurred. The protoplasm stains badly. In lumina there are often structureless or finely-grained masses. No calcification of the tissue is seen anywhere. The connective tissue is pathologically increased everywhere, including those parts of the organ where the parenchyma is relatively well preserved; round-cell infiltration is observed in the connective tissue. The vessels are normal.

The following organs were examined microscopically: Oesophagus, stomach, small intestine, salivary glands, liver, spleen, lymph gland, lung, heart, vesica, thyroid gland, thymus, suprarenals and ovarium. The one definite deviation from the normal found was a diffuse change in the cell protoplasm, of degenerative nature. Whereas the nuclei on the whole were well preserved and well stained, protoplasm was of an indistinct, granular structure and badly stained. These changes were most pronounced in liver and heart muscle, but were observable more or less in all parenchymatous organs. The hæmosiderin content of spleen and liver was not markedly increased with the staining method employed. The changes in the organs, both macroscopic and microscopic, were identical in character in Dogs 1 and 2, but generally slightly more pronounced in the latter.

4. Bones

After skeletonizing, the bones were not abnormal as to shape. Periosteum stripped easily and was not markedly hyperæmic. On being cut the bones were distinctly less resistant than normally and at the same time more brittle, though not to any high degree. The marrow in the long bones everywhere

FIG. 91. Bones of Dog 1 (mineral cryolite), compared with bones of Dog 3 (normal). (a) Tibia; left, Dog 3, right, Dog 1. (b) Pelvis and columna lumbalis, right, Dog 3, left, Dog 1. Bones of Dog 1 chalky-white, with irregular surface and thickened processes.

FIG. 92. Röntgen picture of tibiæ of dogs. (a) Dog 3, normal, (b) Dog 2, NaF. (c) Dog 1, mineral cryolite. Tibia of Dogs 1 and 2 show diffuse halisteresis, narrow compacta, broad marrow cavity and blurred, irregular spongiosa.
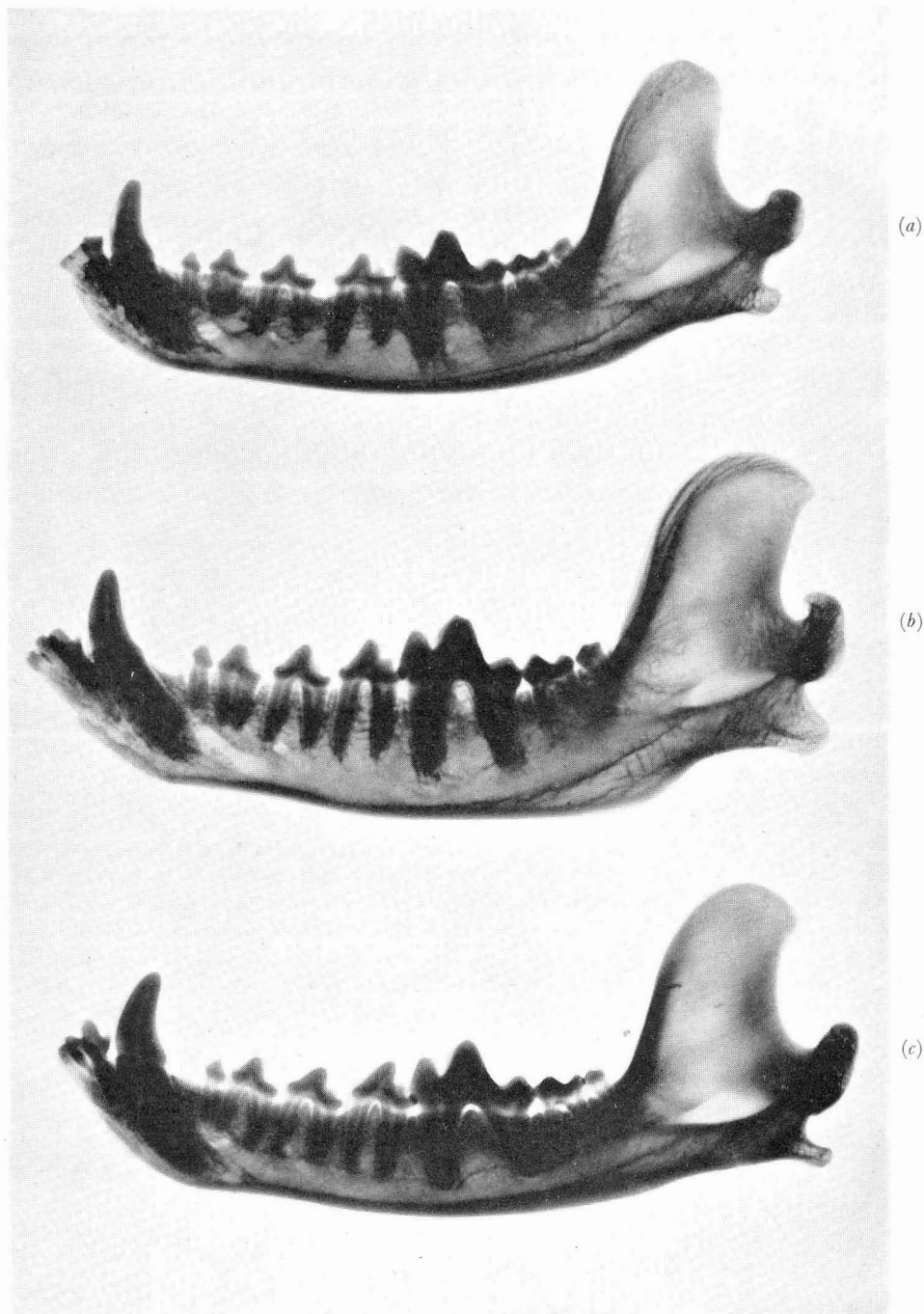
FIG. 93. Röntgen picture of dog mandibles. (a) Dog 1, mineral cryolite. (b) Dog 2, NaF. (c) Dog 3, normal. The mandibles of Dogs 1 and 2 show changes of the bone similar to those described under Fig. 92. The teeth present no definite pathological changes. The periodontal space is more or less blurred around all teeth.
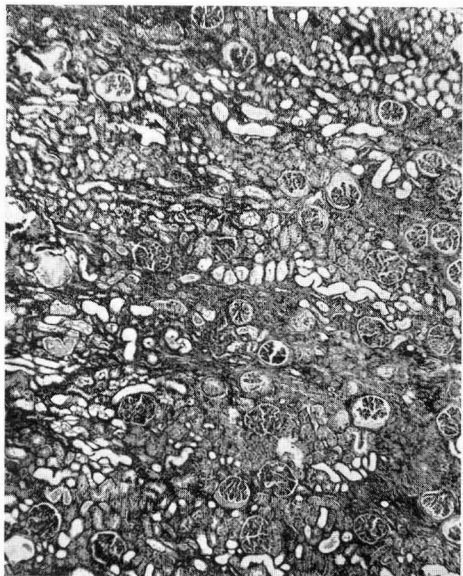
FIG. 94. Section of kidney of Dog 1 (mineral cryolite). Chronic interstitial nephritis. Diffuse proliferation of connective tissue. Urinary canals irregularly dilated, the epithelium stains badly. (28 ×). Staining according to Hansen.

FIG. 95. Cross-section of costa, Dog 1 (mineral cryolite). *aa* Irregular boundary against periosteum. *b* Marrow cavity, with limited degeneration of the marrow (*d*). *c* Osteoid tissue. The bone is irregular in structure and calcification deficient. (180 ×). Hæmatoxylin-eosin.
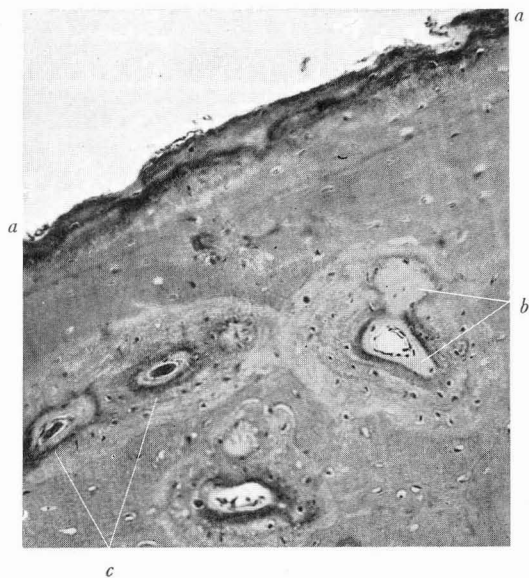
FIG. 96. Cross-section of femur, Dog 2 (NaF). *aa* Irregular boundary against periosteum (lacking). *b* Osteoid tissue. *c* Irregular, granular deposition of calcium salts around Haversian canals. Calcium content of the bone varying, on the whole low. (180 ×). Hæmatoxylin-eosin.

was reddish-brown and of fairly firm consistence. Joint cartilage and capsules presented nothing abnormal.

After *maceration* all the bone surfaces were chalky-white and less smooth than normally, with thickening of the normal cristæ and muscle attachments. On the extremity bones these phenomena were so pronounced that they might be called limited, flat periosteal deposits, but massive exostoses in the proper sense of the word were not present. The shape of some processes was often conspicuously gross, for instance in columna (Fig. 91).

The *radiographs* betrayed a considerable degree of diffuse halisteresis of all bones examined. Corticalis was narrow everywhere, with blurred central and peripheral outlines. The marrow cavities were abnormally wide and the structure of spongiosa indistinct, blurred and irregular (Figg. 92 and 93). Like the other macroscopic changes described, these phenomena were fairly uniformly distributed over all the bones, and there was no great difference in their intensity in the two dogs.

The *microscopical examination* of the bones revealed qualitively and quantitatively uniform changes in both dogs, comprising (1) atrophy of the bone, especially of spongiosa and the central part of compacta, (2) irregular and deficient calcification of the new-formed, irregularly structured, osseous tissue, (3) lively periosteal bone formation, (4) hyperplasia of the bone marrow, with incipient gelatinous degeneration. As examples, sections of costa of Dog 1 and femur of Dog 2 will be described.

Dog 1, costa, transverse section (Fig. 95).
Compacta is narrow, the breadth often not exceeding that of the spongiosa trabeculæ; these form an interlace with large marrow cavities. Compacta peripherally, and over large areas exclusively, consists of an osseous tissue without lamellar structure and with very irregular peripheral boundaries. Separated from this layer by broad, irregular lines of apposition are narrower or broader areas of bone where an indistinct lamellar structure is observable, either in the form of irregular Haversian systems or as longitudinal bone trabeculæ. The osteocytes are well preserved, but everywhere quite irregular in position. The marrow cavities and vascular canals to a great extent are coated with well developed osteoid borders, the breadth of which reaches 20 μ, but in most cases 8—12 μ. As a rule the osteoid tissue is covered with flat, endothelial cells; only rarely are the cells of such a character that they can be called osteoblasts. The boundary between osteoid tissue and calcified bone is irregular everywhere and indistinct, and in a relatively broad zone the calcium salts are seen in the form of fine granules. The calcium content of the bone is small, judging from its staining with hæmatoxylin, and the granular structure of the bone substance is often to be seen. Osteoclast activity from the marrow cavities is frequently observed.

Periosteum is broad and very rich in cells; the matrix is rich in collagenous fibrils. Towards the bone the cells increase in size, become round or oval and arranged in irregular rows, coating a well developed border of osteoid tissue. One can trace

how the collagenous fibrils come together in bundles, become homogenized and form the osteoid tissue. Here the calcification is very irregular, granular, and the border zone between osteoid tissue and bone has a fleecy appearance. There is no breaking down of bone from periosteum. The *marrow* is very hyperplastic; it contains many vessels, but hardly any fat cells. In a reticulated stroma are closely packed quantities of leucocytes and their precursors, but only very few immature red blood corpuscles. There are numerous megacaryocytes. In irregular patches and streaks there are homogenous, gelatinous areas between the cells.

Dog 2, femur, transverse section (Fig. 96).

Compacta is narrow. The bone is built up of osteons, though their structure is more irregular than normally. Lumina in the Haversian canals and the perforating canals are relatively large. In the central half of compacta are numerous irregular spaces, sometimes enormous in size, some of them communicating with the marrow cavity. Centrally compacta is bounded by a narrow and irregular layer of inner lamellæ. Peripherally it is coated with a well-developed layer containing concentrically-arranged lamellæ, which again by a line of apposition is divided from a subperiosteal layer of very irregular structure. The width of this outer layer is variable, sometimes being considerable, corresponding to the muscle insertions. The boundary against periosteum is very irregular. There is no lamellar structure, or at the most it is just indicated, and here the bone exhibits several coarse, close, irregular and relatively deeply staining lines of apposition.

The vascular canals, the irregular spaces in compacta and the marrow cavity are almost everywhere coated with osteoid borders, the breadth of which in most cases is 4—8 μ, but the maximum reaches 18 μ. The coating cells are flat, fusiform, or resembling endothelial cells; in only very few places are there high, osteoblastlike cells. As described under costa of Dog 1, the boundary between osteoid tissue and bone is everywhere blurred and irregular, and the calcium salts are seen in the form of discrete granules, which often are very coarse. As usual, the calcium content of the bone is relatively high, corresponding to the calcification zone. Around the lumen of the Haversian canals there is frequently one, sometimes several concentric, deeply staining, ring-shaped zones. The calcium content of the osseous tissue is otherwise moderate or low, and the bone substance often has an irregular, finely granulated structure. In younger areas of the osseous tissue the calcium content is often lower than in older areas. The osteocytes everywhere in the bone are quite irregularly distributed; as a rule they are well preserved.

The periosteal bone formation proceeds in exactly the same way as described under costa; the granular structure of the osseous tissue is very distinct in the subperiosteal layer. In the large spaces filled with marrow tissue in compacta, and along the boundary of the bone against the marrow cavity, there often are osteoclasts in Howship lacunæ. The *marrow* is of a character similar to the marrow in costa, but contains a moderate number of fat cells.

The microscopic examination revealed no abnormal deposits in the sections examined. Examinations of ground sections of costa and femur from both dogs in the polarization microscope (R. Bøgvad) showed no abnormal deposits in the osseous tissue, neither crystalline nor amorphous. Attention was particularly directed to the possible presence of calcium fluoride. The examination of pulverized samples of the same bones gave the same negative result, even after treating with diluted hydrochloric acid.

5. Teeth

In the dog the formula of the permanent teeth is $I\frac{3}{3}$, $C\frac{1}{1}$, $PM\frac{4}{4}$, $M\frac{2}{3}$; eruption takes place in the course of some months after birth. Thus in the dogs employed the permanent teeth had long been formed before the experiment began.

The teeth of Dogs 1 and 2 presented nothing abnormal *macroscopically*. Compared with Dog 3, the incisors and 1st molar in both fluorine dogs were rather more worn, and this may or may not be connected with the fluorine ingestion. The *Röntgen examination* showed normal condition of all the teeth, but various pathological changes in the mandible of Dogs 1 and 2; the periodontal spaces corresponding to all teeth were irregularly outlined and more or less indistinct. The alveolar septa were narrow, and the spongiosa structure indistinct and blurred. The spongiosa trabecula which normally extends from apex to apex, was just indicated or entirely absent.

6. Analyses

The fluorine content of a number of the bones of Dogs 1 and 2 is shown in Table 55. In Dog 1 the fluorine quantity in the bone ash varied between 19.1 $^0/_{00}$ (tibia) and 30.2 $^0/_{00}$ (pelvis), and in Dog 2 between 19.7 $^0/_{00}$ (meta-

TABLE 55.

Fluorine Content in Bones and Teeth of Dogs.

Material	Dog 1 (mineral cryolite)			Dog 2 (sodium fluoride)		
	Ash used	Th(NO₃)₄ used	Fluorine per g. ash	Ash used	Th(NO₃)₄ used	Fluorine per g. ash
	g.	c. c.	mg.	g.	c. c.	mg.
Costa...................	0.1021	2.00	29.8	0.1214	2.50	31.2
Pelvis..................	0.0801	1.59	30.2	0.1390	2.41	26.4
Cerv. vertebra.........	0.1028	1.82	27.0	0.1492	2.19	22.4
Os frontale............	0.2543	3.95	23.0	0.2466	4.20	25.2
Scapula................	0.1411	2.47	26.6	0.1697	3.43	30.8
Ulna, corpus	0.1085	1.35	18.9	0.1316	2.00	23.1
Femur, corpus.........	0.1216	1.54	19.3	0.2229	3.91	26.7
Tibia, corpus..........	0.1234	1.55	19.1	0.1711	2.47	21.4
Fibula, corpus.........	0.1851	2.97	23.7	0.1359	2.12	23.7
Metatarses	0.1521	1.92	19.2	0.1414	1.83	19.7
Phalanges.............	0.1500	2.14	21.7	0.1278	1.76	20.9
Mandible	0.2457	3.42	20.6	0.2544	3.84	22.3
Molars.................	0.3908	1.33	5.0	0.4418	1.79	6.0

tarsus) and 31.2 $^{0}/_{00}$ (costa); in other words, it was rather uniform in the two animals. On the whole, the fluorine content was highest in the bones of the trunk and lowest in those of the extremities, but there are several exceptions to that rule. Corpus femoris of Dog 3 was analysed (Table 16) and two analyses showed that the fluorine content was 0.78 and 0.83 $^{0}/_{00}$. Thus the increase of the fluorine content of the bone system was very considerable during the intoxication. The fluorine content in dental ash was 5 $^{0}/_{00}$ for Dog 1 and 6 $^{0}/_{00}$ for Dog 2.

7. Summary

In all essentials mineral cryolite and sodium fluoride in the doses employed had the same effect, qualitatively and quantitatively. This means that sodium fluoride, having regard to the fluorine content and the average dose, was between 5 and 6 times as toxic as mineral cryolite.

In both dogs there was a severe effect on the general condition, intermittent at first, of permanent character at the end. Only few characteristic features were presented by the *cachexia*, particularly eye changes (photophobia, secretion from conjunctiva) and localised dermatitis. At times the appetite was poor, but there were no distinct signs of local effect on the gastro-intestinal tract, either clinical or pathologico-anatomical. In the dog, fluorine is excreted in a locally irritating form, judging from the *renal changes*, which were a mixture of an interstitial, contracting nephritis and a degeneration of the epithelium of the urinary tubules resembling nephrosis.

During the intoxication the *fluorine content of bones and teeth* was increased, especially in the cancellous bones. The maximum fluorine content observed in the bone ash was 31.2 $^{0}/_{00}$ (costa). The quantity of fluorine deposited in these tissues, however, formed only a small part of the quantity ingested.

The systematic effect of fluorine was, partly, a universal effect of degenerative nature on the organs, and partly, a special effect on osseous tissue as well as blood and bone marrow. The microscopic examination revealed a diffuse degeneration of the cell protoplasm in the *parenchymatous organs*, similar in kind to that observed in other intoxications. Having regard to the severe anæmia, the cell changes in the present case must undoubtedly be regarded as the result of both degenerative and atrophic processes.

Röntgenologically and pathologico-anatomically the *bone changes* proved to be a kind of osteomalacia, which attacked all the bones examined. Histologically the condition was characterized by (1) atrophy of the bones, especially of spongiosa and the central part of compacta; (2) irregular and very inade-

quate calcification of the new-formed, irregularly structured osseous tissue; (3) universal, but moderate increase of the periosteal bone formation, especially corresponding to the muscle insertions. Abnormal deposits, especially deposits of calcium fluoride, were not observed anywhere in the bone system. The disturbance in the calcium metabolism, of which the bone affection is a sign, was not accompanied by manifest symptoms of hypocalcæmia, especially spasms. The stiff and awkward gait observed towards the close of the experiment may possibly be regarded as a pre-tetany phenomenon.

The effect on *blood and bone marrow* was very considerable, above all an injury to the erythropoetic system. The severe anæmia was hypochromous, with pronounced macrocytosis, but otherwise without signs of forced or atypical regeneration. The erythropoetic marrow exhibited atrophy. Fluorine must be assumed to have a direct effect on the marrow, as no definite signs were observed of increased destruction of the erythrocytes (hæmosiderosis). The leucocytary system seemed to be subjected to an irritation characterized by marrow hyperplasia and (in Dog 2) neutrophile leucocytosis. Nothing definite could be found as to the cause of the different reactions in the two dogs. The lymphocytary system exhibited no great changes.

The *permanent teeth*, which were all formed before the fluorine ingestion began, showed no definite changes under macroscopic and X-ray examination.

PART V

DISCUSSION AND GENERAL CONCLUSIONS

CHAPTER XXV

THE NORMAL FLUORINE CONTENT OF ORGANIC MATERIAL

Normally, organic tissue contains small amounts of fluorine. This is the consequence of (1) the widespread occurrence of the element in inanimate nature, and (2) the fact that fluorine, ingested through water or food, is excreted slowly and incompletely. For several reasons it is of practical importance to know this normal or "natural" content of fluorine in organic material. As fluorine has a toxic effect in relatively small quantities, it is necessary to examine whether the normal fluorine content in vegetable and animal tissue may cause any risk of poisoning through ordinary food. The natural fluorine content must be considered when judging the quantity of fluorine that may be deposited on plants sprayed with fluorine compounds, or that may be absorbed by the plants, for example when dressing the soil with fluoric superphosphate. Finally, an increased fluorine content of certain tissues is a constant phenomenon in chronic fluorine intoxication and of significance to diagnosis.

1. The Analytical Problem

The qualitative demonstration of fluorine is fairly simple, even if the quantity is as small as 0.005 mg. The quantitative determination of the amounts of fluorine contained in organic tissue is a matter of considerable difficulty. Any one who has worked on the subject will endorse this statement. The difficulties lie both in the isolation and in the final determination of the element. A good many of the analytical methods employed in earlier works may be regarded as unreliable. It does not lie within the author's scope, or in fact his ability, to give a critical study of this aspect of the fluorine literature. It will be sufficient to point out the circumstance, one that applies to much analytical work in this field, that the method has been employed only by the author who launched it, that determinations of the error have only been very few in number, or have not been made at all, and that it is difficult to reproduce these methods. This for instance applies to the very complicated method of

Gautier and Clausmann (314, 315), with which a large number of analyses were made. The glass-etching method employed, for instance by Mayrhofer et al. (573) for quantitative determinations, suffers from conspicuous defects. It is well to regard the majority of the earlier analyses with scepticism.

It is only within recent years that sensitive methods have been published combining simplicity with relative reliability. In the main they are founded upon a reaction described by de Boer and Basart (87), which permits of both a colorimetric and a titrimetric determination of small quantities of fluorine. Willard and Winter (861) have introduced a new and simple principle for the isolation of fluorine, which is distilled as hydrofluosilicic acid (H_2SiF_6). The employment of these modern methods is only limited, however, and the problem of a simple, specific and accurate method for the determination of the fluorine quantities normally occuring in organic tissue (about 0.005—0.1 mg. fluorine), can scarcely be regarded as solved at the present moment.

2. Vegetable Tissue

The presence of fluorine has been proved in most plants, which was only what might be expected considering the occurrence of fluorine in the soil. The published analyses have been dealt with in Chapter IV, 1. Gaud et al. (307) have shown that the fluorine concentration in the soil is of decisive importance to the content of the element in plants. According to Gautier and Clausmann (322), the fluorine content of a number of plants and parts of plants varies between 0.01 and 5.9 mg. per 100 g. fresh tissue. Mayrhofer et al. (573) in a number of cultivated plants found between 0.006 and 0.048 mg. fluorine, expressed in the same manner. As the results of the analyses are few and rather diverging, *it is impossible at present to form a definite opinion of the normal content of fluorine in vegetable tissue.*

3. Bones

The question of the normal fluorine content of bone is dealt with in Chapter IV, 2. The available analyses have been collected in Table 9. The results vary a good deal, especially those of earlier investigators, but also to some extent the more recent ones. The great majority of the analyses show that bone ash contains between 0.1 and 1.5 $^0/_{00}$ fluorine.

A number of the author's analyses of older, skeletonized and air-dried bones of various animals are contained in Table 56. In connection with the animal and human bones analysed as control material (Tables 16, 44, 49 and 52), the

TABLE 56.

Fluorine Content of Bones and Teeth of Normal Animals.

Animal	Material	Ash used	Th(NO₃)₄ used	Fluorine content per g. ash
		g.	c.c.	mg.
Cow	Lumbar vertebra	1.0089	1.84	0.55
Cow	Radius, diaphysis	1.1128	2.04	0.55
Sheep	Humerus, diaphysis	1.0910	0.64	0.18
Sheep	Scapula	1.1420	0.74	0.19
Horse	Thoracic vertebra	1.4775	4.00	0.81
Horse	Metatarsus	1.1302	0.81	0.22
Dog	Humerus, diaphysis	1.0762	1.60	0.45
Dog	Humerus, diaphysis	0.9352	2.21	0.71
Walrus, young . . .	Vertebra	1.2844	1.44	0.34
Spotted seal, young	Vertebra	0.7028	0.75	0.32
White-beaked dolphin	Rib	0.7520	2.22	4.4
Greenland whale . .	Cranial bone	0.7197	3.00	6.2
Porpoise	Vertebra	0.7113	3.11	6.5
White whale	Hæmapophysis	1.2028	6.62	8.2
Saw-fish	Vertebral column	0.7397	1.20	2.0
Cod	Vertebral column	1.0996	1.47	2.4
Shark	Teeth	1.308	6.83	8.9

following figures may be given as the extreme values of the fluorine content of bone ash:

Man, adult. . . . .   0.48—2.1 $^0/_{00}$

Pig, young. . . . .   0.12—0.36 -

Ox, young. . . . .   0.15—0.38 -

„ mature . . . .   0.55 -

Sheep . . . .   0.18—0.19 -

Horse . . . .   0.28—0.81 -

Dog. . . . .   0.45—0.78 -

Marine mammals, young . . . .   0.32—0.34 -

„   „   mature. . . . .   4.4 —6.5 -

Fish. . . . .   2.0 —8.2 -

The bone ash of terrestrial mammals normally contains about 0.1—$1\,^0/_{00}$ fluorine. As a whole, the bones of older animals contain more fluorine than those of younger animals; the content of human bones may be relatively great. Fluorine is deposited generally in the bone system, but in all probability in cancellated bones most of all. The bones of animals

living in the sea contain up to about 10 times the quantity of fluorine found in the bones of non-marine mammals.

The figures relating to marine animals are evidence that the fluorine content of the medium, *the local factor, decides the quantity of fluorine absorbed and stored* in the bones. Sea water contains about 1 mg. fluorine per litre. Investigations by Boissevain and Drea (90) point in the same direction, for they found 7 $^0/_{00}$ fluorine in the ash of bones of individuals in Colorado, U.S.A.; according to present investigations, the soil in that region is relatively rich in fluorine (water analyses, occurrence of mottled teeth). When judging analytical results that are apparently contradictory, attention must be given not only to the technique employed, but also to the significance of the local factor.

4. Teeth

The factors determining the fluorine content of bone are of equal importance to the teeth. The large number of analyses published are extremely varying (Table 9). In the author's control material (Tables 33, 49 and 52), supplemented with tooth analyses in Table 56, the fluorine content of tooth ash varied as follows:

Man .... 0.19 —0.30 $^0/_{00}$
Pig (young)..................... 0.17 -
Calf............................ 0.078—0.34 -
Shark .... 8.9 -

Tooth ash usually contains less than 1 $^0/_{00}$ fluorine, more often 0.1—0.4 $^0/_{00}$. Teeth of animals living in the sea contain much greater quantities.

The question of the distribution of fluorine in enamel and dentine has been answered in earlier investigations by the assertion that enamel contains just as much, or even more, fluorine than dentine does. It is still the popular view that fluorine is preferably deposited in the dental enamel, but undoubtedly it is wrong. The author's investigations, Tables 33 and 52, have shown that *fluorine is deposited principally in dentine, and to a smaller extent in enamel:*

Man { enamel.................. 0.044—0.057 $^0/_{00}$
      { dentine (ash) .... 0.30 —0.31 -
Calf { enamel.................. 0.057 -
      { dentine (ash) .... 0.22 -

It is uncertain whether or not fluorine may be deposited in enamel that has finished calcifying. Investigations on this problem might throw light on the question of whether metabolism takes place in the mature enamel or not.

5. Other Animal Tissues

It is most likely that other animal tissues than bone and teeth contain small quantities of fluorine, as the animal organism constantly absorbs this element. The question has been dealt with in Chapter IV, 3. The analyses available are few (Table 10), and the results quite diverging. At present it is only possible to say that *animal tissue seems to contain from a few tenths of mg. to a few mg. fluorine per 100 g. dry substance*, or probably less than vegetable tissue.

The author's investigations (Tables 44, 50), showed the following fluorine content in parenchymatous organs, expressed per 100 g. dry substance:

Man (50 years old) .... 0.40—1.02 mg.
Pig (young) .... 0.28—0.91 mg.

As to the fluorine content of the blood, matters are still more divergent. The values given in Table 10 vary about 0.5 mg. per 100 c.c. In a recent work Goldemberg and Schraiber (352) put down 0.05—0.08 mg. fluorine per 100 c.c. human serum; red blood corpuscles did not contain fluorine, or at any rate only insignificant quantities.

CHAPTER XXVI

ACUTE FLUORINE INTOXICATION

The symptoms of acute intoxication are familiar, especially from the often fatal intoxications of man (Chapter I, 2) and animals (Chapter II, 2), which occur most frequently through taking fluorine compounds by mouth. In addition, we have the experience gained from experimental investigations on acute and sub-acute intoxication (Chapter VII).

1. Clinical Symptoms

Very soon after the ingestion of the toxic compound symptoms are observed of acute irritation of the gastro-intestinal tract: *Vomiting*, often with blood, *diffuse abdominal pains* and *diarrhoea*. Symptoms due to absorption occur after a varying, usually short, period as *alternating convulsions or spasms and pareses*, which may be localized or universal. The spasms are very painful and occur simultaneously with *pains and paræsthesiæ in the extremities*. Between the convulsions there is a universal *weakness or sluggishness*. Various inconstant symptoms are: Rise in temperature, difficulties of speech and swallowing, and uncoordinate movements of the eyeballs. *Thirst, salivation* and *perspiration* are fairly frequent symptoms. In most cases death occurs after a few hours under prostration, *dyspnoea* and *failing pulse*. Consciousness is unaffected. Several of these symptoms may be absent. When the intoxication is not fatal there are signs of *toxic nephritis* (albumin, blood and casts in the urine).

The experimental investigations have confirmed and supplemented this picture. In man, ingestion of toxic but not lethal doses of an active fluorine compound gives less severe symptoms from the gastro-intestinal tract (nausea, eructation, possibly vomiting, cardialgia, salivation); following intravenous injection there are abdominal pains, vomiting, thirst and tremor. In all essentials the animal experiments agree with spontaneous intoxication. Following parenteral administration there are also symptoms from the gastro-intestinal tract, but they are less pronounced. After intravenous and sub-

cutaneous injection of sodium fluoride a transitory *fall in the calcium content of the blood* has been observed. The effect on the blood picture is not synonymous in the published investigations; there seems to be a tendency towards a reduction of the hæmoglobin content and number of erythrocytes. Lethal doses seem to cause a *retardation of the blood coagulation*. An *increase in diuresis* has repeatedly been observed in the case of toxic doses. Isolated investigations indicate that acute fluorine intoxication in various ways affects metabolism (hyperglycæmia, increased nitrogen excretion, reduced total metabolism). In the rat a single subcutaneous injection of sodium fluoride produces *disturbance in the formation of the teeth,* which appears macroscopically on the incisors after about 4 weeks as a circular, distinctly delimited band of white, unpigmented enamel. Subacute intoxication manifests itself in the rat by the development of a cachectic condition with spontaneous hæmorrhage from the mucous membranes.

The effect of *gaseous fluorine compounds* is known only from rather limited material (Chapter VI, 2). The local irritating effect on the mucous membranes is predominant: Sneezing, cough, epiphora, dyspnoea, sometimes vomiting. Universal spasms are observed in some animals, not in others. In the little known human intoxication pronounced dyspnoea seems to be the principal symptom.

2. Morbid Anatomy

In general there is conformity in the observations of spontaneous and experimental intoxication. Often, however, the investigations are fragmentary. In peroral intoxication a practically constant observation is an *acute hæmorrhagic gastro-enteritis* with more or less pronounced *necroses*. The mucous membranes in stomach and duodenum are most severely attacked; the inflammatory phenomena decrease anally. Changes of a similar kind are observed following parenteral administration of active fluorine compounds. A relatively frequent observation is signs of *acute toxic nephritis* (hyperæmia, epithelial degeneration). Changes in the other organs are reported by some observers, not by others. *Hæmorrhages,* with or without cell *degeneration,* are found *in various organs*, especially in the liver, in the thymus, and in the parathyroid glands. Gellerstedt's (327) observations suggest that a systematic investigation will disclose a widespread cell degeneration in the organs.

The histological changes observed by Schour and Smith (715) in the *incisors of the rat* after a single subcutaneous injection of sodium fluoride were as follows: After twelve to twenty-four hours they observed in the posterior part of the incisor an abnormal character and distribution of the calcium globules

in the ameloblast layer, as well as an irregular limitation of the enamel layer. After twenty-four to forty-eight hours both enamel and dentine displayed two layers, the one light, consisting of hypoplastic and inadequately calcified tissue, the other dark, normal in structure and normally or excessively calcified. A similar pair of light and dark layers was observed for every injection made.

When acid solutions of active fluorine compounds are ingested, corroding phenomena are observed in the mucous membranes of mouth, throat and oesophagus, with more or less distinct formation of superficial necroses. Gaseous fluorine compounds produce inflammatory phenomena in the corneæ, conjunctivæ and the mucous membranes of the air-passages. In the lungs there are severe changes (hyperæmia, emphysema, oedema and signs of broncho-pneumonia). In the other organs the changes are more uncertain, but there seem to be indications of hæmorrhage in the gastro-intestinal tract as well as hyperæmia, and perhaps parenchymatous degeneration of several organs.

3. The Dose

From a practical toxicological point of view the fluorine compounds may be divided into four groups:

(1) *Gaseous fluorine compounds,* partly the very toxic hydrogen fluoride (HF) and silicon tetrafluoride (SiF_4), partly a number of less toxic organic compounds (CCl_2F_2, $C_2Cl_2F_4$, and others).

(2) *Solutions of hydrofluoric acid* (HF) and *hydrofluosilicic acid* (H_2SiF_6), which are extremely toxic. This group includes acid solutions of fluorides and silicofluorides and bifluorides in substance.

(3) *Relatively easily-soluble fluorides and fluosilicates,* which have a high degree of toxicity: NaF, KF, NH_4F, etc., Na_2SiF_6, K_2SiF_6, $(NH_4)_2SiF_6$, etc.

(4) *Almost insoluble fluorine compounds,* whose toxicity is moderate or low: Cryolite (Na_3AlF_6), calcium fluoride (CaF_2).

Only small material is available for estimating the toxic and lethal dose. Among the compounds in group 1, hydrogen fluoride has especially been examined. The following concentrations for this compound are given below after Ronzani (689) and Machle et al. (541):

Death after 5 minutes' respiration of	1.5 mg.	HF per litre	}	Rabbit and
„ „ $\frac{1}{2}$—$1\frac{1}{2}$ hours „	0.6	„ „	}	guinea pig
„ „ 1 day „	0.03	„ „		Guinea pig
Tolerable for several minutes, but un-pleasant....................	0.026	„ „		Man

The compounds of group 3 are best known, as there has been considerable experience with sodium fluoride and sodium fluosilicate, from both spontaneous intoxications and experiments. These compounds are equally toxic in proportion to their fluorine content. As mentioned on page 70, there are difficulties in determining the exact *dosis minima letalis*. For rats, dogs and rabbits it varies between 23 and 90 mg. fluorine per kg. body weight taken perorally, and between 13 and 46 mg. per kg. with parenteral administration (Table 11). In human intoxication death has been seen from a dose as low as about 6—8.6 mg. fluorine per kg. body weight, corresponding to 0.7—1 g. sodium fluosilicate (327). The lethal dose has probably been smaller still, but the records are not precise (237). Most lethal doses are much higher; as much as 10 g. sodium fluoride have been survived, corresponding to about 65 mg. fluorine per kg. (Table 6). *Man seems to be more sensitive to fluorine compounds than the experimental animals generally employed. The risk of a fatal ending in acute peroral intoxication is considerably reduced by vomiting, which occurs almost constantly.*

The fluorine compounds mentioned in group 2 must be regarded as particularly toxic, but it is impossible to state the dosis minima letalis. Beyond the cases of acute gastric symptoms among the cryolite workers, no spontaneous intoxications are known from cryolite and calcium fluoride (group 4) and there have been no attempts to determine d. m. l. Smith and Leverton (756) have shown that rats die in the course of 9—11 days, when given 40 mg. fluorine daily per kg. through the diet as sodium fluoride. Using mineral cryolite and calcium fluoride, 1900 and 3400 mg. fluorine per kg. per day was required to obtain the same effect. The author's experiments with rats have shown that *the toxicity of cryolite is greatly dependent on the grain size.* When a particularly fine-grained cryolite was used (85 per cent. had a grain size of $< 5 \mu$), the toxicity increased considerably, though it did not reach that of sodium fluoride. Various circumstances indicate that cryolite in a weak acid solution splits off only one third of its fluorine content, but the question has not been definitively settled. *Cryolite and calcium fluoride have a much lower toxicity than sodium fluoride, and the possibility of acute intoxication is without practical interest.*

4. Pathogenesis

The fluorides belong to the group of calcium-precipitating substances that contain oxalic acid, citric acid and oleic acid, and their salts. This was first demonstrated about the year 1900 by Loeb (514, 515), who found that fibrillary twitches appear at once in a frog muscle when dipped in a solution of sodium fluoride. Friedenthal (291) showed experimentally that, on intravenous injection, the sodium salts of these acids produce an intoxication in which fibrillary twitchings in the skeleton

musculature form a characteristic symptom of the entire group. The rate of injection plays a very important part, for the toxic ion is bound by the calcium mobilized from the tissues, and the tolerance is increased enormously when the injection proceeds slowly. There can thus be no question of a fixed lethal dose. Schlick (712) has given direct evidence that the toxic effect of sodium fluoride depends upon a binding of calcium. The toxic effect on frogs and rabbits was neutralized when an equivalent quantity of calcium chloride was injected together with the fluoride.

A comparison between the clinically and experimentally well-known acute oxalic acid intoxication and acute fluorine intoxication is very useful. There are far-reaching conformities and various deviations. Both intoxications are characterized by local as well as systemic symptoms. As Wieland and Kurtzahn (855) have pointed out, the often pronounced corroding phenomena, seen especially in the stomach after ingestion of soluble fluorine compounds, are not due to a simple acid effect. Hydrogen fluoride, which is liberated by the gastric acid, is a weak acid with a far lower dissociation than that of hydrochloric acid of the same concentration. On the other hand it is probable that the non-dissociated molecule of hydrogen fluoride can permeate the mucous membrane and exercise a deleterious effect in the tissue, the exact nature of which is not known. This view is supported by the fact that the HF-molecule may penetrate the skin and cause inflammation under the undamaged epidermis.

In both acute oxalate and acute fluoride intoxications Jodlbauer (443) was able demonstrate a fall in the calcium content of the blood. The symptoms of irritation and paralyzation of the nervous-muscular system, often violent in character, are common to the two intoxications. The clinical picture and experimental experience (437) both seem to indicate that the effect of oxalic acid as a heart poison exceeds that of fluorine. However, recent investigations (359, 360) show that fluorine has a deleterious effect on the heart. In both intoxications there is a renal effect, but nothing is known of an excretion (and deposition in the kidney) of fluorine corresponding to oxaluria. Fluorine is presumably excreted as alkali fluoride, judging from the considerable local irritating effect, but we know of no investigations on this question. As acute inflammatory phenomena are observed in the mucous membranes of the gastro-intestinal tract after parenteral administration of a fluorine compound, it is presumable that fluorine in toxic form is also excreted through that channel.

The lethal doses of the calcium-precipitating substances are inversely proportional to the solubility of their calcium salts (682). According to Wieland and Kurtzahn's investigations, sodium oxalate is more toxic by parenteral administration than sodium fluoride, corresponding to the fact that the solubility of $\dfrac{CaF_2}{Ca\text{-oxalate}}$ in one litre water is $\dfrac{1.6 \times 10^{-2}}{0.8 \times 10^{-2}}$. On the other hand, sodium fluoride is much more toxic perorally, which presumably is due to the fact that the oxalate ion as a diatomic ion is absorbed much more slowly than the fluorine ion. Correspondingly, the dose in the fatal oxalic acid intoxications is considerably higher than in the fluorine poisoning (as a rule 15—30 g. oxalate). The relative sensibility of man to fluorine may be due to a greater sensitiveness to calcium deficiency than that of animals.

Thus it seems probable that fluorine mostly exercises its acute effect by arresting the calcium in the organism. The question is whether every effect of fluorine in the organism may be explained in this manner, or whether fluorine has effects on any special tissue elements or functions. Loew (517, 519) showed that low plants and animals (certain algæ, bacteria and flagellates), whose calcium requirement is low

or nil, can grow and reproduce themselves in weak oxalate solutions. In fluoride solutions of the same strength a certain toxic effect was constantly observed, even though it was much lower than for the higher species within the same groups. On the basis of these experiments Loew considered that, in addition to its calcium precipitating effect, fluorine has an alkaloid effect, due to the fact that the fluorides, owing to their marked ability to form complexes, can unite with the albuminoid substances of the active protoplasm and thereby inhibit its function. Later experiments by Loucks and De Graff (523) may also indicate that fluorine has a special effect on protoplasm.

The acute effects of fluorine compounds cannot be explained as the result of a purely calcioprive mechanism, or at any rate only with difficulty. For example this is true of the blocking of the cell membrane of the erythrocytes, with the subsequent inhibition of the coagulation of the blood, the formation of fluorhæmoglobin (513), and the destructive effect on the development of the teeth. One must here refer to the very considerable effect which fluorine has on both protoplasm and enzymatic activity *in vitro* (Chapter V), and which opens up wide possibilities regarding our understanding of the actual effect of fluorine in the organism. Some of these problems will be discussed at greater length when treating the genesis of chronic intoxication.

In what form fluorine exists in the organism is not known. Presumably it circulates in some compounds with calcium, which, however, considering the great tendency of fluorine to form complexes, need not be calcium fluoride. Schulz (719) assumed that sodium fluoride is split by the carbonic acid in the tissues, whereby the fluorine becomes free and exercises its effect in elementary form. Frese (287) found it more probable that hydrogen fluoride arises from the splitting process. Nothing is known of these matters, but the element fluorine and hydrogen fluoride must both be assumed to be too chemically active to exist as such in the organism.

5. Diagnosis

Neither in the clinical nor in the anatomical picture does acute fluorine poisoning present any special peculiarity, let alone pathognomonically. Acute gastro-intestinal symptoms followed by spasms and pareses may be produced by a number of substances (As-compounds, mercury salts, barium salts, oxalic acid, etc.), just as acute gastro-enteritis and nephritis may be. Consequently, it is also a fact that the ætiology of the intoxication usually has become known in other ways than by clinical and post-mortem observations.

Various authors, including Raestrup (666), have endeavoured to characterize the changes in the mucous membrane of the stomach as being so peculiar that they make diagnosis possible. The decisive feature was supposed to be the bright red, inflammated mucous membrane without much corrosive crust, combined with a hæmorrhagic, acid-reacting stomach content. As previously stated, this picture no doubt is relatively frequent, but by no means pathognomonic. The changes are much more diversified.

The clinical symptoms as well as the patho-anatomical changes *may*

be very faint, indefinite, or even be absent. McNally (549) describes a case in which both gastro-intestinal symptoms and spasms were absent. All that was noticed was indisposition and weakness in the $3^1/_2$ hours which elapsed between the ingestion of an unknown quantity of sodium fluoride and death. In one of Lührig's cases (528) no changes were found by post-mortem examination.

As a general rule the analysis of the ingested preparation has been a guide in cases of poisoning. A definite diagnosis can be made when fluorine is discovered in the gastro-intestinal contents and in the organs. The normal fluorine content of the organs being so small, it will be no great source of error in practice. Lührig (530) has shown that fluorine can be found in the urine two or three days after ingestion of relatively small quantities. *A search for fluorine ought to form part of the routine of forensic-chemical investigation.* In a few cases its presence in exhumed bodies has been demonstrated without difficulty.

6. Prognosis and Therapy

On the whole, the prognosis must be characterized as bad; the mortality is high. Of the 112 cases of human poisoning published in the period 1873—1935, sixty, or 53.6 per cent., were fatal. The intoxication has a rapid course. All cases of suicide were fatal. In the non-fatal cases the symptoms quickly subsided and the patient recovered in the course of days or weeks; nothing has been published as to subsequent ill-effects. Whether or not there is vomiting is a matter of vital importance to the prognosis. It is presumable that the quantity and nature of the stomach contents also have some bearing. It is possible that an existing anacidity reduces the possibility of absorption and thereby improves the prognosis.

On the whole, no definitely effective treatment has been used. The rational therapy is intravenous injection of a soluble calcium salt, to which must be added gastric lavage and peroral administration of a solution of calcium chloride, perhaps milk. Treatment must be commenced quickly to have any chance of being effective.

CHAPTER XXVII

CHRONIC FLUORINE INTOXICATION

In this chapter an attempt will be made to give a survey over chronic fluorine intoxication, on the basis of present knowledge. The material is voluminous, and the outline must necessarily be brief, for which reason principal weight will be laid upon the phenomena that may be regarded as certain or probable. A detailed discussion of all works is out of the question, and reference is made to the systematic review in Chapters I, 3, II, 3 and VIII. Consideration is given to peroral intoxication only. Judging from the few experimental investigations (Chapter VI, 2), protracted respiration of gaseous fluorine compounds results in both changes of the respiratory passages and phenomena due to absorption.

The following factors may be pointed out by way of introduction. The effect of fluorine depends upon the dose, the duration of ingestion, the age of the individual, the species, the composition of the diet and probably upon other circumstances as yet unknown. Only some of the various forms of the intoxication are known. Fluorine has a specific effect on osseous and dental tissue. The effect on the teeth results in the forming of hypoplastic, badly calcified enamel and dentine. The reaction of the osseous tissue varies, for we know of both a diffuse osteosclerosis, and a generalized bone disease resembling to a certain extent the classical osteomalacia, and for practical reasons called by that name. It is curious that the dental changes and the osteosclerosis may be produced by doses which have no other deleterious effect on the organism (or at any rate only slightly), whereas the osteomalacia is accompanied by more or less marked general symptoms.

The known spontaneous chronic fluorine intoxications comprise the following diseases:

(1) *Mottled teeth*, an affection of the teeth, which is endemic in man in certain parts of Europe, America, Africa and Asia.

(2) *Osteosclerosis*, an occupational disease among cryolite workers in Copenhagen*).

(3) A disease like *osteomalacia*, endemic among herbivora in the environs of certain factories in Europe.

(4) *Darmous*, a dental and mandible disease among herbivora in certain parts of North Africa.

(5) *Gaddur*, a dental and bone disease among herbivora in Iceland after volcanic eruptions.

1. Clinical Symptoms

Growth. General Condition. Reproduction. Fluorine resembles other toxic substances in that a certain degree of influence on the organism causes a loss of weight, absolute or relative. Vitality is lowered, the animal becomes quiet and moves about less. The poor general condition is accompanied by an untidy appearance, the coat turning coarse, ragged and dry. The skin may become scaly. Abnormal growth of claws (rats) and of hooves (sheep) has been observed. Certain eye symptoms like photophobia, and seropurulent or hæmorrhagic secretion from the conjunctivæ, have been seen so frequently that they must be described as characteristic. Changes of the cornea are not the rule. The rat may present the aforesaid skin and eye symptoms without a distinctly affected general condition. Other symptoms accompanying the poor general condition are reduced or inhibited reproduction, reduced milk-secretion and egg production. In the end a cachectic condition develops which is not especially characteristic, and cannot be identified with cretinism as Goldemberg does (339).

Gastro-Intestinal Tract. Side by side with the loss of weight there is anorexia and poor utilization of food. When the fluorine compound is intimately mixed with the food, the irritation symptoms from the alimentary canal are not very marked, or they may be lacking. Direct ingestion of fluorine compounds or

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*) Bone sclerosis as a sign of chronic fluorine intoxication was recently observed by two authors. (1) By X-ray examination Spéder (763a) found generalized osteosclerosis in natives attacked by *darmous* (Morocco). On the radiographs the changes show great conformity with the osteosclerosis caused by cryolite. All the persons examined had bone changes. Attention was drawn to the condition on examining a case of spontaneous fracture. (2) Bishop (78a) accidentally found osteosclerosis in a coloured man, 48 years of age, who had been employed for 18 years in a fertilizer factory (Philadelphia, U.S.A.), where he had handled finely ground rock phosphate (3.43 per cent. fluorine). There was no history of gastric disturbances. The bone changes on the radiographs were identical with those of a pronounced case of cryolite poisoning. Necropsy showed increased density of bones. No evidence of abnormality of bone structure was found on microscopical examination. The fluorine content of the bones varied from 2.9 $^o/_{oo}$ (femur) to 7.0 $^o/_{oo}$ (lumbar vertebra).

high fluorine concentration in the food often causes diarrhoea, more rarely vomiting. Inspiration of cryolite in dust form may be accompanied by various acute and chronic gastro-intestinal symptoms (nausea, vomiting, constipation, diarrhoea).

Urinary System. Abundant liquid intake and polyuria is a common symptom in several species of animals in experimental intoxication. In only a few cases have there been urine investigations; albuminuria and hæmaturia have been observed in dogs (412), transitory glycosuria in lambs (343).

The Blood. The conditions are not very clear. A pronounced intoxication is accompanied by hypochromous anæmia, often considerable. As a rule there are no signs of forced regeneration. The number of white blood corpuscles presents nothing characteristic. Signs of both increased and reduced activity of the myeloid marrow have been seen (leucocytosis, displacement to the left; relative lymphocytosis). In human cryolite intoxication the hæmoglobin percentage is unaffected, the number of erythrocytes slightly reduced and the colour index increased (1—1.20). Clinical observations have not proved that the blood coagulation is affected in spontaneous intoxication; Stuber and Lang's hypothesis (778) can therefore scarcely be maintained. The experimental results are very contradictory.

Nervous System. Musculature. A crouching position, with increased curvature of columna, is observed, especially among small animals (rats, guinea-pigs), but is also seen at times in cattle. This posture anomaly cannot be regarded as being pathognomonic of fluorine intoxication, as a similar posture is observed in other morbid conditions where the general condition is affected. A stiff, laborious and probably painful gait is a frequent phenomenon. Larger animals lie about a good deal and have difficulty in rising. The musculature may be the site of a certain state of irritation, manifesting itself in the form of restlessness, shivering or actually fibrillations, especially of the extremity musculature. Universal spasms are observed only when the intoxication has a rapid course. Pareses are normally absent; where isolated extremity pareses have been observed, e. g. among cattle, they were presumably phenomena governed by the bone disease, and not pareses in the proper sense of the word.

Endocrine Glands. In human cryolite intoxication no change was observed in the size of the thyroid gland. With the exception of Maumené's (567) insufficiently described case, no clinical observations are known from spontaneous or experimental intoxication to indicate any effect on this or any other endocrine gland. The hypothesis of the struma-producing effect of the fluorine (337, 338, 654) cannot be generally applicable.

The Teeth. Judging from the result of clinical and röntgenological examination, mature dental tissue does not seem to be changed during fluorine ingestion. An exception from this rule was found in human cryolite intoxication, where the X-ray examination revealed signs of increased dentine formation (restricted pulpa cavity).

Teeth, or parts of teeth, calcifying in the period of intoxication, display degenerative changes in the form of hypoplastic and insufficiently calcified enamel and dentine. These conditions have been studied in detail in experiments on the rat. Under the weakest influence of fluorine the pigment giving the incisors their normal orange-brown colour disappears. Transversal, banded stripes of opaque white enamel alternate with bands of normal enamel. Under stronger influence the enamel becomes diffusely white and displays more or less pronounced hypoplasia. The pathological enamel is brittle and readily chips off. The incisors wear down abnormally, which sometimes leads to defective occlusion and, as a secondary phenomenon, abnormal growth of opposing teeth. The incisors often exhibit lateral deviations; growth is retarded.

In experimental intoxication of animals whose teeth are formed from non-persistent pulp, there are changes of a similar kind: abnormal and often irregular wear, especially of the molars. X-ray examination reveals defective calcification of the affected teeth. In sheep, where the dental changes have been well studied, there has been observed a brownish-black pigmenting of the opaque enamel, which has an uneven, almost corroded appearance.

There is far-reaching agreement between the experimental results and the clinical observations of the teeth in spontaneous intoxication. Besides a defective, pigmented and not very resistant enamel, abnormities in size (nanism, gigantism), shape and position of the teeth have been observed in the animal diseases *darmous* and *gaddur*. *Mottled teeth*, which in man attacks the permanent teeth, rarely the milk-teeth, is characterized by the fact that the enamel has an opaque, chalky-white colour in spots or diffusely, and an irregular brownish-black pigmenting. The latter anomaly occurs particularly on those parts of the teeth that are exposed to the light. In more severe degrees the enamel is more or less hypoplastic, often in restricted areas (pits), abnormally brittle and very little resistant. The form of darmous occurring in man, which must be regarded as the most severe degree of mottled teeth, is accompanied by pronounced development anomalies. The teeth may be delayed in eruption and have abnormities in size, shape and position, and the resistance of such teeth is low. In both man and animal the severe degrees of this disease are accompanied by difficulties in mastication and increased sensitivity to cold. Secondary inflammation of the gingiva often develops.

The Bones. The effects of fluorine on the osseous system are complicated, which may explain some of the apparently contradictory experimental observations. Both diffuse sclerosing processes, and a generalized condition resembling osteomalacia are observed. Transitional forms, or combinations between the two conditions, have been observed in the rat and, perhaps, in cattle.

Osteosclerosis as a spontaneous disease is known in human cryolite intoxication. The clinical examination reveals an irregular, nodose surface of certain subcutaneous bone surfaces and a restriction of the motility of the vertebral column and thorax. There is no bone tenderness, and it is doubtful if the sclerosing processes are accompanied by bone pains. The fracture frequency is not markedly increased. On the radiograph the osteosclerosis is characterized by an increased endosteal and periosteal bone formation, with thickening of the cristæ and processes, narrowing of the medullary cavity and more or less obliteration of the structure of the spongiosa. The disease, which has been observed only in adult individuals, principally attacks the cancellated bones. Side by side with the osteosclerosis there is widespread calcification of the osseous ligaments. In the rat, experimental osteosclerosis displays great similarity to the spontaneous variety in the X-ray picture. The conformity is not complete, however, as no definite observation of, for instance, ligament calcification has been made.

The condition resembling *osteomalacia* has been produced experimentally and studied more or less thoroughly in several animals, both immature and adult (rats, guinea-pigs, pigs, oxen, sheep, dogs). Clinically it is characterized by a more or less widespread tendency to form exostoses, especially on the mandible and on the long bones. The exostoses are hard and indolent, but the animals give the impression of suffering, as limping or pseudopareses are sometimes observed. The epiphysial regions present nothing abnormal to clinical examination. The fracture frequency is not distinctly affected in the experiment. Curving of the extremities has been seen in the rat. Röntgenologically the condition is principally characterized by a diffuse, more or less pronounced halisteresis, atrophy of the compacta and spongiosa and enlargement of the medullary cavities. In addition, there is a widespread periosteal deposition of deficiently calcified osseous tissue. The epiphysial regions may exhibit signs of inhibition of enchondral ossification (atrophy, lines of arrested growth), but more marked changes of the configuration of the epiphysial lines do not seem to be the rule.

The spontaneous disease, which may be identified with the experimentally produced osteomalacic condition, is known only among herbivora, and has

18

not been thoroughly examined. The tendency to form exostoses varies, but often exceeds what is observed under experimental conditions. The exostoses are localized to the same bones (mandible, long bones, ribs, cranial bones). Spontaneous fractures are fairly frequent. The bones do not seem to be tender. The only X-ray examinations we know are of bones of sheep attacked by *gaddur*; the striking feature here was the pronounced exostoses and a doubtful halisteresis.

Although certain observations may differ, it seems to be the rule that the joints are intact in both the clinical and the X-ray examination.

2. Morbid Anatomy

Gastro-Intestinal Tract. The experimental results vary somewhat, but, taking them all round, they intimate that fluorine compounds in moderate quantities, and intimately mixed with food, do not cause distinct changes in the gastro-intestinal tract. Where the fluorine concentration in the food is high, or where the compound is administered in dissolved form, inflammatory changes with hæmorrhages and necroses are observed in the mucous membranes of the stomach and the duodenum. In human cryolite intoxication no definite changes were observed in the mucous membranes of the gastro-intestinal tract; there are no observations concerning other spontaneous fluorine intoxications.

The Kidney. Signs are very often found of chronic contracting nephritis in experimental intoxication of a certain duration. The early stages of this process are little known. Macroscopically the late changes appear as a diminution of the kidney and fine or coarse granulation of the surface; the colour is paler than normally. The consistency is firmer; in section the cortex is narrow, with a streaky surface. Microscopically the process is characterized by a diffuse development of connective tissue, which is intensified in disseminated foci. The glomeruli are relatively well preserved, the tubules are irregularly dilated, often with low epithelium. The process is mostly interstitial in character. In more severe degrees of intoxication this picture is supplemented by a degeneration of the epithelium of the tubules resembling the changes in nephrosis. Calcium precipitation in the tissue does not form part of the picture. The different animals react variously, the interstitial contracting process having been observed in rats, pigs and dogs, but not in calves. In spontaneous intoxication nothing is mentioned of renal changes, which indicates that at any rate the more severe degrees of nephritis do not develop in herbivora. In human cryolite intoxication renal lesion was doubtful, probably absent.

The Teeth. The effect of protracted ingestion of fluorine on the development of the teeth has especially been studied by microscopical examination of rat incisors. Very considerable and very characteristic changes are observed. The enamel epithelium exhibits signs of atrophic or degenerative processes: irregularities in the position and appearance of the ameloblasts, increasing to localized necroses. The enamel shows localized hypoplasia or defects occupying more or less of the thickness of the enamel, or an abnormal striping parallel with the surface, produced by alternating calcium-poor and calcium-rich layers. The pathological enamel is both hypoplastic and deficiently calcified, and the changes affect both the enamel prisms and the interprismatic substance. A corresponding striping occurs in the dentine; interglobular dentine is often prominent. The predentine is wide. The odontoblasts do not seem to suffer marked changes, nor does the pulp. The microscopical and macroscopical changes agree. The alternating bands of light and dark enamel observed with the naked eye on the incisors of the rat correspond to the alternating layers of poorly and well-calcified enamel seen in very oblique sections as the tooth grows. The varying pigment content contributes essentially to making the contrast between the two kinds of enamel macroscopically distinct. The pitted appearance of the enamel is the macroscopical expression of the localized enamel hypoplasia.

The dental changes in spontaneous fluorine intoxication have scarcely been studied microscopically at all. The results of the few examinations of sections of mottled teeth from man are not directly identifiable with the experimental results. They agree in so far as anomalies in structure and calcification of the enamel and the dentine are observed in mottled teeth. It is most probable that future investigations will reveal further conformities.

The Bones. In spontaneous human *osteosclerosis* the bones are gross but otherwise unchanged as to shape. The surface is chalky-white, uneven, with widespread ligament calcifications. The weight and hardness of the bones are increased. Histological examination reveals an increased periosteal and endosteal apposition of an irregularly structured osseous tissue, with secondary narrowing of the medullary cavities. Calcification of the osteoid tissue seems to be increased and the calcium salts are deposited in an irregular manner as granules and lumps of considerable size. The granules are also observed in the Haversian canals and the medullary spaces. In addition, there is a calcification of the peri-osseous ligaments. Bone absorption by osteoclasts is sparse. Experimental osteosclerosis is known only in the rat, where the macroscopical (and röntgenological) picture reveals marked points of resemblance to spontaneous osteosclerosis. Microscopically there is an increased and

irregular periosteal apposition, and a more or less pronounced granular deposition of the calcium salts.

The *osteomalacic condition* to some extent varies with the species and age of the animal. Certain features are common, however. The osseous system is attacked diffusely and the changes consist of a combination of atrophic (osteoporotic) and hyperplastic processes. The bones are often coarser than normally; the weight is reduced and also the resistance. Compacta and spongiosa are atrophic and the marrow cavities are enlarged. The hyperplastic processes are particularly marked in growing animals and mostly localized to periosteum. The periosteal deposits are loose in structure and poorly calcified; often they have the form of exostoses, especially localized to the long bones and the mandible. The combination of atrophic and hyperplastic processes may involve considerable form changes (for example of the mandible of the pig). Macroscopic examination usually reveals a lack of endosteal bone formation, and the epiphysial lines do not seem to exhibit marked changes. Histologically, the condition may broadly be characterized by the following: (1) Atrophy of spongiosa and the central part of compacta; (2) lively periosteal, more rarely endosteal, apposition of an osseous tissue of irregular structure; (3) retarded calcification of a rachitic type of the osteoid tissue, as well as qualitatively abnormal calcification, the calcium salts being deposited in the form of discrete, often coarse granules which only incompletely fuse together; (4) varying, usually considerable, bone absorption by osteoclasts, sometimes (rats, sheep) from a fibrously transformed marrow.

Up to the present the rat occupies a special position, as simultaneously it is possible to observe processes resembling osteosclerosis (excessive calcium precipitation in the form of coarse granules), and osteomalacia (breaking down of the calcareous bone and formation of poorly calcified osseous tissue).

The deposition of crystalline calcium fluoride in the Haversian canals observed by earlier investigators (108, 442) is most certainly a misinterpretation; this phenomenon has not been observed in later investigations. A distinct change in the joints does not form part of the picture; the cartilage (joint cartilage, costal cartilage) in most cases displays no pathological calcification.

Bone Marrow. Spleen. In human osteosclerosis the bone marrow exhibits no certain changes. In a cryolite worker in whom the osteosclerotic processes had produced a considerable reduction of the medullary cavities in the cancellated bones, there was a diffusion of red marrow to the diaphysis of the long bones, presumably compensatory. Where the osteomalacic condition is accompanied by general toxic symptoms, gelatinous degeneration of the

marrow has been observed in the long bones, especially of herbivora. Protracted intoxication of dogs and rats was accompanied by hyperplasia of the myeloid and atrophy of the erythropoetic marrow, combined with limited gelatinous degenerations and fibrous transformation respectively. Thus the bone marrow reacts differently, though degenerative changes, especially of the erythropoetic tissue, are predominant in severe intoxication. The spleen has no marked changes; there are no gross signs of hæmosiderosis in spleen or in liver.

Other Organs. The severe intoxications in which the general condition is affected are accompanied by more or less pronounced degeneration of the parenchymatous organs. The changes are especially localized to the cell protoplasm, and morphologically resemble the non-inflammatory degenerations that are caused by other toxic substances (granular or vesicular structure, reduced staining property, fatty degeneration etc.). Liver and kidneys are affected most. It is difficult to decide how great a rôle atrophic processes play in the occurrence of the cell changes observed. There are no abnormal calcium deposits.

Changes have been observed, especially in the size, of a number of endocrine glands (Chapter VIII, 6). Having regard to the difficulties combined with investigations of this kind, it is at present impossible to form any opinion as to these few and often contradictory observations. This refers particularly to the thyroid gland (strumous changes), the parathyroids and suprarenals (hyperplastic processes). The result of the author's experiments does not indicate that the thyroid changes under the intoxication.

3. Biochemistry

Absorption and Excretion. As was mentioned when discussing the acute intoxication, fluorine is absorbed from the gastro-intestinal tract and excreted through the kidneys. These processes have not been investigated in detail; for example we do not know in what form fluorine is absorbed, or in what form it is circulated and excreted. That fluorine can be excreted in the *milk* of women is proved by the occurrence of mottled teeth in the children of female cryolite workers. The excretion of fluorine in the milk is observed in rats, but is dubious in cattle and sheep. As the deciduous teeth only seldom display the changes characteristic of mottled teeth, this must mean that fluorine as a rule does not permeate the *placenta*. The correctness of this view is indicated by the absence on the radiograph of bone changes in children of female cryolite workers. Earlier investigators have demonstrated

the presence of a not inconsiderable fluorine content in the bones and teeth of new-born individuals; later investigations, however, often reveal a low or doubtful fluorine content in these tissues in very young individuals; yet, recent work indicates that maternal transference of fluorine through the placenta may play a rôle in woman and the rat. Placenta in the horse is permeable, as typical changes of the teeth of the first dentition are described.

Composition of the Blood. The fluorine content of the blood in chronic intoxication is as insufficiently elucidated as under normal conditions. The few analyses available scarcely permit of conclusions. The fall in the calcium content of the blood, which is evident in acute intoxication, is not so prominent in chronic intoxication. Still, a moderate fall in the serum Ca has been observed repeatedly, especially in young animals. In human cryolite intoxication, serum Ca is not changed. The phosphorus content of the blood does not exhibit constant changes. Phillips (637) found that plasma phosphatasis is increased in cows during fluorine ingestion.

The Organs. Conflicting with earlier analyses fluorine does not seem to be deposited in the organs to any great extent. Nevertheless, a remarkable accumulation of fluorine seems to take place in the thyroid gland and a moderate one in the kidney. Through inspiration of dust cryolite workers have an accumulation of fluorine in the lungs.

The Bones. The considerable deposition of fluorine in the bones is a fact that has been confirmed by numerous investigators. The quantity deposited depends, for instance, on dose and duration of the ingestion. Deposition is diffuse in the osseous system, but the cancellated bones as a rule seem to contain more fluorine than the long bones. In exostoses the fluorine content may be essentially higher than in compact bone. Brandl and Tappeiner (108) found up to $36.9\,^0/_{00}$ fluorine in the bone ash of their dog, the largest quantity ever found. In the author's experiments on dogs the maximum fluorine content was $31.2\,^0/_{00}$. Values round about $10\,^0/_{00}$ are common. In human cryolite intoxication the fluorine content of the bone ash varied round about $10\,^0/_{00}$ (from 3.1 to $13.1\,^0/_{00}$); here, however, it must be remembered that the weight of the bones was greatly increased. In the spontaneous intoxication of herbivora the following fluorine contents have been found in bone ash:

Cattle disease at aluminium factory	Switzerland 3.1— $3.4\,^0/_{00}$
	Norway $4.5\,^0/_{00}$
	Italy 2.1— $8.0\,^0/_{00}$
Darmous, North Africa.................................	4.6— $7.0\,^0/_{00}$
Gaddur, Iceland..	5.6—$16.7\,^0/_{00}$

In the osteomalacic affection the mineral content of the bones is more or less reduced. This is indicated by their lowered resistance and by the result of the X-ray and histological examination. The phenomenon has also been demonstrated by analysis, but in such cases the diminution of the ash content has usually been moderate. Studies on the composition of bone ash have not given synonymous results. The form in which fluorine is deposited in the bone is not known, but presumably it is as CaF_2 or fluorapatite $3 Ca_3(PO_4)_2 \cdot CaF_2$, which contains 3.8 per cent. fluorine.

The Teeth. Fluorine is deposited in the teeth, though not so much as in the bones. Values round about 3—10 mg. fluorine per g. tooth ash are common in experimental investigations. In spontaneous cryolite intoxication an average of 2.5 $^o/_{oo}$ fluorine was found in the tooth ash. Teeth of sheep attacked by darmous contained 6 $^o/_{oo}$, by gaddur 2.8 $^o/_{oo}$ fluorine; in sheep from the neighbourhood of a Norwegian aluminium factory the tooth ash contained 4.5—4.9 $^o/_{oo}$. Fluorine is deposited both in enamel and dentine, probably mostly in the latter. The author's analyses indicate that fluorine is deposited in the enamel in only small quantities. The question is difficult to decide with certainty, but here there is a possibility of determining whether the mature enamel has a metabolism or not.

Metabolism. In young growing animals fluorine in toxic doses seems to produce a reduction in the calcium and phosphorus retention. This fact is shown clearly by Lantz and Smith (491) in young rats receiving 0.1 per cent. sodium fluoride in the diet. Balance experiments on young rats and pigs, where the fluorine ingestion was lower, indicated the same thing (277, 536, 537). Examination of children whose drinking water contained 4 mg. fluorine per litre showed no deviation from the normal calcium and phosphorus retention. Probably the effect of fluorine on the Ca-metabolism varies according to the age of the animal or the rate of growth of the skeleton.

4. The Question of the Dose

The effect of chronic ingestion of fluorine depends on the dose. Previous chapters will already have made this clear, and it is obvious when considering Table 12, which gathers together the experimental fluorine intoxications so far published. It must be admitted with respect to the important question of dose, that the observations available are sporadic and to some extent contradictory; in most of the spontaneous intoxications the intaken quantity of fluorine is not known at all. Furthermore, it may be stated that a number of circumstances affect the sensitivity of the organism to fluorine; a uniform

condition can be produced with varying doses. Apart from the quantity of fluorine in proportion to the body weight, there are such important aspects as the fluorine compound employed and the time factor, the nature and age of the individual, and the diet.

Reaction of the Rat. Among the animals used for research work on fluorine, the rat is the one preferred. It is possible to set up the following schema, based partly on Table 12, partly on the author's experiments, showing the relation between the symptoms of chronic intoxication and the dose for the rat. It should be pointed out that the doses in this summary can be considered only as *approximate*, as an attempt at orientation. In the first place, the figures of the various investigators differ, and in the second place, the determination of the dose in the author's experiments with rats is uncertain. Future investigations must undertake the definitive laying down of the limits.

	mg. fluorine per kg. body weight per day
Incipient tooth changes	1
Incipient bone changes, nephritis......................	5
First effects on general condition......................	10— 15
Severe influence on general condition, organ degenerations	20— 25
Death in one or few weeks...........................	50—100

According to this summary, fluorine has a deleterious effect on tooth development even with a dose which has no other injurious effect on the organism of the rat. A somewhat higher dose affects the osseous system and causes renal lesion. By steadily increasing the dose we pass through a condition with initial general symptoms to severe cachexia, which is accompanied by universal organ degeneration, pronounced dental and osseous symptoms and, finally, death.

The details of the reaction of the osseous tissue cannot be laid clear on the basis of our present knowledge. The animal's rate of growth seems to be of significance. In the growing rat nothing has been observed but the osteomalacia, which possibly means that rapid growth conduces to this condition. In the mature rat we know of both the osteomalacic and the osteosclerotic condition; the former seems to develop under relatively large doses, which affect the general condition, whereas the latter has been observed under relatively small doses and without the accompaniment of general symptoms. That the calcium retention depends on the rate of growth is evidenced by Lantz and Smith's experiments (491), in which rats fed with 0.1 per cent. sodium fluoride in their diet had a negative Ca-balance during the period

of rapid growth, but afterwards an abnormally high Ca-retention, despite an unchanged fluorine intake.

Other Species. The various kinds of animals differ in their quantitative, and perhaps qualitative, reaction to fluorine ingestion. *Cattle*, for example, vary considerably in their resistance to the fluorine effect. In the author's experiments with calves, 20 mg. fluorine per kg. body weight per day caused an effect on the general condition, dental changes and osteomalacia. Du Toit et al. (800) saw general symptoms and bone disease in cows with a dose of 6—7 mg. fluorine per kg. Effects on teeth, bones and general condition in calves have been described after a protracted daily intake of about 3 mg. fluorine per kg. body weight (789, 670, 644). A similar dose was the cause of intoxications with fluoric lees (page 45). In all the cases mentioned the bone disease observed seems to have been osteomalacia or perhaps transitional forms between the osteomalacic and the osteosclerotic condition.

In the author's experiments, dental changes and osteomalacia were observed in *pigs* with a dose of 15 mg. fluorine per kg. daily; Kick et al. (454) saw similar phenomena with 10—37 mg. per kg. The *dog*, which in own experiments received about 14 mg. fluorine per kg. per day, developed severe general symptoms and bone atrophy to a considerable degree. *Chickens* seem especially insensitive to the noxious effects of fluorine. To produce growth inhibition it was necessary to employ a daily supply of 70 mg. fluorine per kg. (641).

It is possible to compute the approximate dose in the known forms of chronic fluorine intoxication in *man*. According to the latest investigations, 1 mg. per litre is the lowest concentration of fluorine in drinking water causing mottled teeth. The average weight of a child in the period during which the permanent teeth calcify (from the first to about the tenth year of life) is about 15 kg. If the daily intake of drinking water is put at 1 litre, this means that about 0.07 mg. fluorine per kg. per day is capable of producing mottled teeth. In spontaneous osteosclerosis caused by cryolite, the fluorine intake could be approximated at 0.2—1 mg. per kg. per day. As the experimental investigations have shown that only a fraction (one third or less) of the fluorine content of cryolite is toxic, it is extremely probable that the effective daily fluorine intake lies between 0.20 and 0.35 mg. per kg. Accordingly, the relation between the smallest dose of fluorine that affects the development of teeth, and the dose which causes osteosclerosis, is almost the same as in the case of the rat; but *man is much more sensitive to fluorine than the rat*.

The Time Factor. The period in which fluorine must work on the organism before the symptoms of intoxication develop is extremely variable and

chiefly dependent on the dose. Some intoxication symptoms appear early, others late. The clinical manifestation of the dental changes, which have their commencement immediately after the absorption of fluorine, depends upon the rate at which the development and eruption of the tooth proceed. In a rat that is put on food containing fluorine, a bleaching of the incisors is observed after two weeks, alternating bands of normal and pathological enamel after four weeks. Where tooth development proceeds from non-persistent pulp, it takes from months to years (as in man) for the changed tooth to erupt. Human osteosclerosis develops only after several year's ingestion of fluorine. The average period of employment of the cryolite workers who had just-recognizable sclerosis, was 9.3 years, for those affected most it was 21.1 years. Experimental osteosclerosis in the rat is observed about a year after the commencement of the fluorine ingestion; this corresponds to about a third of the normal lifetime of the rat. It must be borne in mind, however, that no attempt is made to fix the time of the commencement of the sclerosis. Clinical experience indicates that the osteomalacic condition may be relatively quick in appearing, after the course of months or even weeks. In the experiment the fatal cachexia may develop within the same time limits.

Various Fluorine Compounds. As far as experience shows, the qualitative effect of the various fluorine compounds is the same in chronic as in acute intoxication. Having regard to the fluorine content, the quantitative effect of certain low-soluble fluorine compounds is less; this applies particularly to cryolite and calcium fluoride (756). In own experiments, mineral cryolite had only a fraction (about one third to one sixth) of the toxicity of sodium fluoride, calculated according to the fluorine content. Calcium fluoride also is less toxic than the easily soluble fluorides, though in some experiments it has a remarkably high toxicity. Velu (821) caused fatal cachexia in the course of 96—298 days in rats which had been given 33 mg. fluorine per kg. per day in the form of calcium fluoride. Rock phosphate, the fluorine content of which presumably occurs as calcium fluoride, had considerable toxicity in experiments with cattle and pigs (670, 644, 454). The material available for judging the comparative toxicity is limited, however, (Table 12). To no small extent the toxicity of the low-soluble compounds depends on the grain size of the preparation employed.

Composition of the Diet. Sensitivity to fluorine is influenced by the content of calcium, phosphorus and vitamin D in the diet. The growth of rats was poorer on a food containing 0.15 per cent. sodium fluoride when the calcium content was low than when it was the average quantity. A supplement

of vitamin D reduced the toxicity of the calcium-poor food, but not of the calcium-rich (394). The dental changes developed more quickly in the rat when the food was calcium-poor than when it was rich in Ca, P, and vitamin D (753).

5. Pathogenesis

As on essential points our knowledge is very limited, this question can only be handled in broad outlines. In acute intoxication the effects of fluorine in the main might be explained by a monopolizing of the calcium in the organism. A variety of circumstances indicates, however, that a direct effect on protoplasm and enzymatic activity might play some part. In chronic intoxication, too, the effects of fluorine on *the calcium metabolism* may explain some phenomena, but not all. Apart from the intoxication symptoms themselves, a number of observations connected with both experimental and spontaneous intoxication direct attention to the calcium metabolism. Chaneles (156) showed that radiating fluorine-intoxicated rats with ultra violet rays counteracts the intoxication. As mentioned above, the content of Ca, P, and vitamin D in the diet has an influence on the sensitivity of the organism to fluorine*). It is probable that a food poor in minerals plays a part in the occurrence of spontaneous intoxication among herbivora, possibly in conjunction with poor stabling and lack of sunlight. This is indicated by observations by Slagsvold (742) and Askanazy (40). A large calcium requirement in the organism increases the sensitivity to fluorine. Bone symptoms are produced most readily in young, growing individuals. The toxic effect on cattle becomes visible especially in conjunction with pregnancy and lactation. Habituation, which seems to have some influence in various forms of the intoxication, may be the result of increased ability to mobilize Ca from the depôts. It may be that differences in this ability may explain the individual reactions observed in experimental intoxications.

Under circumstances where fluorine causes a pronounced effect on the general condition, a negative calcium balance seems to be the rule. This appears from the intoxication symptoms: Tendency towards reduction of blood calcium, more or less manifest tetany (muscle fibrillation, stiff gait), halisteresis of the bones. The reduced calcium retention has also been shown in balance experiments. Smith (747) draws attention to the fact that the reduced Ca-

*) In growth experiments with plants Loew (519) and Price (662) have shown that the toxicity of sodium fluoride in solution is considerably reduced when the soil is rich in Ca, or when Ca and P are added to the solution.

retention possibly plays a great part in the pathogenesis, as in the rat its course is parallel both with the general growth inhibition and with the reduction of the rate of growth of the incisors.

The question of whether the whole fluorine effect may have its explanation in a negative Ca-balance must be answered in the negative. The osteosclerosis and the dental changes cannot be explained in that manner. Apparently, osteosclerosis is accompanied by a considerable Ca deposition, even if it may proceed so slowly that it may be difficult to prove it. The dental changes occur with doses so small that a direct deficiency in calcium cannot be the cause. In addition, there is the fact that the intoxication on certain points may resemble, but cannot be identified with, known pathological conditions, in which the Ca-deposition for some reason or other is reduced. A diet rich in Ca, P, and vitamin D has an influence on the course of the intoxication, but does not prevent its occurrence (715, 754). Fluorine being active in small quantities and having the same effect with parenteral administration as after absorption from the gastro-intestinal tract, it is obvious that the fluorine effect is a primary, systemic effect and not a secondary consequence of altered conditions of absorption in the intestine.

It must be assumed that *fluorine has a special tissue effect apart from the calcioprive mechanism*. The influence on tooth formation results in the growth of an abnormally structured dental tissue, a reduced and retarded calcification and an irregular deposition of the calcium. Schour and Smith (715) describe as the first change in acute fluorine intoxication an abnormal character and distribution of the calcium globules in the ameloblast layer. The osteosclerosis is characterized by the formation of an osseous tissue of irregular structure and an increased calcification, in which the calcium salts are deposited in the form of irregular granules and lumps, both in and outside of the osteoid tissue. The calcification zone is broad and irregular. In the osteomalacic bone affection the calcification anomaly is manifested by an abnormal width of the osteoid tissue, a broad and irregular calcification zone and a defective calcification of the bone. Here again the calcium salts have a varying tendency to precipitate in the form of irregular grains, and the osseous tissue has quite an abnormal structure.

It will be seen that *osseous and dental tissue formed under the influence of fluorine display certain common features in the different forms of the intoxication, viz. a calcification anomaly, characterized by an abnormal, irregular precipitation of the mineral salts as coarse granules, and an abnormal, irregular structure of the organic matrix. The genetic dental tissue* (ameloblasts, odontoblasts) *must be characterized as electively sensible to fluorine*, since similar disorders only occur in the osseous tissue at much

higher doses. *The osseous tissue displays a curious double reaction:* sometimes an increased precipitation of mineral salts accompanied by stimulated growth, sometimes a reduced mineralization with mostly atrophying processes. In the adult the osteosclerotic process seems to be produced by comparatively small quantities of fluorine, the osteoporotic process by comparatively large quantities.

The cause of this peculiar reaction is not known. In connection with the effect of fluorine on tooth formation, Schour and Smith (715) mention that the insoluble calcium fluoride may have the effect of a foreign body when it is taken up by the cells which form enamel and dentine, and thereby disturb their function. Öhnell et al. (615), who observed the granules very distinctly in teeth and bones of fluorine-poisoned, scorbutic guinea pigs, considered the grains to be of calcium fluoride. Judging from the author's experiments this is not likely. In the first place one never succeeded in proving the presence of calcium fluoride by the use of the polarization microscope, and secondly, in chronic intoxication the fluorine content of the bones is so low that only a small part of the Ca content of the bone can occur as calcium fluoride. Having regard to the considerable enzymatic effect of fluorine, it is more probable that fluorine affects the enzymatic processes, whereby the mineral salts of the tissue fluid are precipitated during the calcification of osseous and dental tissue. As the enzymatic effect of fluorine may be stimulating or inhibiting, all according to the concentration, it will be possible in this way to explain the quantitatively different effect on the osseous tissue. The difference in dose necessary for producing osseous and dental changes in the various animals is probably connected with a difference in the rate of growth. Thus the rat, whose bones and teeth grow much more quickly than those of man, requires much higher doses. In experiments with growing rats DeEds (228 a) recently showed a decrease in bone phosphatase activity, the extent of which agreed roughly with the deviation of the growth curve from the normal.

The irregular, often loose structure of the osseous tissue is perhaps a special effect of the fluorine, perhaps not. Bone tissue formed under pathological conditions often has an irregular structure. The lively periosteal apposition which is characteristic in fluorine intoxication, is also observable in other bone diseases where calcification is reduced (rickets, classical osteomalacia). As a general rule the periosteal bone formation is said to be connected with mechanical conditions (muscular action, load) and is regarded as a compensatory attempt to strengthen a weak bone. The former view seems probable, the latter doubtful. In Icelandic sheep attacked by *gaddur*, the periosteal bone production was more prolific than in experimental fluorine intoxication (687). Presumably it is of importance whether the animals move about briskly when

grazing in the mountains (as the Icelandic sheep do), or they are kept indoors. Diffused periosteal deposits need not be accompanied by recognizable halisteresis of the bone on the radiograph (Figg. 4—6).

In relatively large doses fluorine has a deleterious *effect on protoplasm,* which effect cannot be described as specific according to the morphological picture; it is impossible to say whether this effect is due to a monopolization of the calcium of the cell or to a special toxic effect. The kidney occupies a position of its own among the parenchymatous organs, as fluorine is excreted as a compound which produces local irritation and inflammation. The various animals do not react in the same way, which perhaps is owing to differences in the degree of acidity of the urine. Hydrogen fluoride can be formed in acid urine. We must assume that the effect of fluorine on protoplasm and on enzymatic processes is capable of causing *profound changes in the metabolism* of the organism; this is indicated by several features in the phenomena observed in chronic intoxication. The whole of this sphere, however, is only little explored. Besides the mineral metabolism, attention is being directed especially to the carbohydrate metabolism (643) and to the relation between fluorine and the thyroid gland (641) and the vitamins, particularly vitamin C. At the present moment it is impossible to explain the toxic effect of fluorine as an action on a limited number of processes in the organism. It is extremely probable that fluorine acts on the metabolism in various ways and that the symptoms of chronic intoxication have a complicated genesis.

Phillips and co-workers have pointed out a relation between vitamin C and chronic fluorine intoxication. Guinea pigs on food poor in vitamin C, intoxicated with 25—30 mg. fluorine (as NaF) per kg. daily, developed symptoms of scurvy, although they were given several times the normal anti-scorbutic dose of orange juice (638). In cattle, which for years had been intoxicated with fluoric phosphate, profound changes were ascertained in the cellular respiration (reduced total respiration, increase of the anaerobic phase). At the same time the vitamin C content of the tissues was increased (648). The content of vitamin C in the suprarenal glands and the anterior lobe of the hypophysis increased in fluorine-intoxicated rats (639). The results of experiments on guinea pigs indicate that fluorine either inactivates the ascorbin acid or inhibits the effects of an enzyme system in which the ascorbin acid forms a part (649). It would seem that these investigations indicate that fluorine causes scurvy, and that the symptoms (at any rate some of them) in chronic fluorine intoxication may be due to a deficiency in vitamin C. However, neither the clinical symptoms nor the bone changes are directly identifiable as scorbutic. Deficiency in vitamin C causes a disappearance of the collagen tissue in the osteoid tissue and an increased degenerative amorphous calcification (420). In the osteomalacic condition caused by fluorine the collagen content of the osteoid tissue is not perceptibly reduced, and the calcification, though in a way degenerative, is reduced and not increased. Öhnell et al. (615) have shown that calcification disturbances in scurvy and fluorine intoxication are directly opposed and may nullify each other to a

certain extent. The granular precipitation of the calcium salts, however, was very pronounced in fluorine-intoxicated guinea pigs which simultaneously showed signs of scurvy, but was absent in fluorine-intoxicated guinea pigs on ordinary diet. This would indicate that a relative deficiency in vitamin C plays some part in the peculiar precipitation of the mineral salts and may explain the varying degree of this phenomenon in the author's experiments. The clinical symptoms in both the experimental and the spontaneous intoxications, however, also draw attention to other avitaminoses, though it is not possible to make any identification. The eye changes (in any case those in the rat) might indicate A deficiency, the skin changes B_2 deficiency.

Chaneles (155) in 1929 gave expression to the thought that fluorine exercises its effect on the calcium metabolism through an influence on the parathyroid glands. He supported this hypothesis on the fact that the incisors of parathyroidectomized rats go through changes resembling those produced by fluorine ingestion (256, 257, 258, 803, 379). These dental changes, however, seem unspecific, in so far as similar changes are observable when the organism is unable to deposit calcium (Ca-deficiency, rickets, osteogenesis imperfecta, etc.). Microscopically the dental changes caused by fluorine occupy a position of their own (715). The bone changes resulting from hypo- and hyperfunction of the parathyroids are not identifiable with those of fluorine intoxication. As has been stated, an examination of these glands in chronic fluorine intoxication has not given synonymous results.

Hupka and Luy (426) considered that fluorine worked essentially as an acid (HF), and that calcium was mobilized from the bone system in order to neutralize the acid. This view is undoubtedly incorrect, for in that case several of the effects of fluorine would be incomprehensible (for example the effect on tooth development under small doses). The bone affection observed under acid feeding of herbivora (406, 771, 613) differs from that of fluorine intoxication. On the other hand, a simultaneous ingestion of acid will presumably accelerate the fluorine intoxication, especially among herbivora.

6. Diagnosis

Considered from a diagnostic angle, chronic fluorine intoxication presents itself in the form of three clinical units: The tooth anomaly, the osteosclerosis, and the ostemalacic condition accompanied by general symptoms. The dental anomaly may occur alone or may accompany the others, but not necessarily. All three forms are known as spontaneous intoxications.

The Dental Anomaly. In man the tooth disease is known as *mottled teeth, mottled enamel, darmous, dientes veteados* and *denti scritti*; in herbivora the terms *darmous* and *gaddur* are used. As the names cover only some of the peculiarities

characterizing the affection, it is reasonable to call it neutrally the dental disease caused by fluorine. It is diagnostically an advantage that the spread of the disease in the dentition indicates how long the injurious effects have been at work; only those teeth, or parts of teeth, calcifying during the fluorine ingestion display the characteristic changes*). From this same point of view it is certainly a drawback that much time may elapse before the changes are observable clinically, and that they do not occur in individuals whose teeth are completely formed. Judging from the available odontological literature, the clinical picture of the dental disease is very characteristic, probably pathognomonic of fluorine intoxication. Here we must pay particular attention to the chalky, opaque, pigmented enamel, and, in more severe degrees, the low resistance of enamel and dentine combined with abnormities in the shape, size and position of the teeth. The colour of the pigment may be yellow, red-brown, brown or black. According to Schour and Smith (715) the changes characterizing fluorine intoxication are not the same as those observed in other pathological conditions like deficiency in vitamin A, rickets, parathyroidectomy, hyperparathyroidism and hypophysectomy. Among the herbivora, where the increase and irregular wear of the molars in particular is conspicuous, age changes may present a similar picture. In certain cases exogenous factors (for example sand in the food) may increase the wear of the teeth among younger animals too. In these cases the diagnosis will depend on the characteristic enamel changes which are most easily observed on the incisors.

Osteosclerosis. The best known form, the human form, representing a hitherto unknown pathological condition, has been dealt with from a diagnostic point of view in Chapter XX, 7. Röntgen examination of pelvis and columna lumbalis gives a pathognomonic picture. In this connection weight must be attached to the uniform density of bone tissue, which may proceed to the obliteration of the spongiosa structure; furthermore, the calcification of the ligaments, the absence of destructive processes, and the absence of effect on the general condition. Pronounced cases manifest themselves clinically by a reduction of motility in the vertebral column and the thorax. The other symptoms are not very characteristic as a whole.

The Osteomalacic Condition. For practical reasons the bone affection resulting from the severe fluorine intoxication, accompanied by general symptoms, has been called osteomalacia. This is justifiable, as clinically the condition

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*) On the basis of the dental changes in the children of two of the female cryolite workers, Brinch and Roholm (112) have advanced the theory that fluorine not only affects the ameloblasts which are active during the fluorine ingestion, but also produces a permanent injury to the ameloblasts, whose enamel-forming activity set in after the cessation of the fluorine effect. I am unable to say whether this is generally applicable to man or not.

resembles that form of osteomalacia which, with more or less vague ætiology, is described among herbivora. Common features are the reduced strength of the bones, the tendency to form exostoses, bone atrophy, and a deficient calcification. On one important point there is a difference, as the bone affection caused by fluorine is accompanied by a more or less pronounced cachexia, though its form does not seem to be strikingly characteristic. Rickets, too, lacks cachexia, and in this disease the reaction of the epiphysial lines differs both clinically and anatomically. No doubt the deficient calcification is of the same type, but in fluorine intoxication the hyperproduction of osteoid tissue in the enchondral ossification is nothing like so pronounced as in rickets. Both ordinary osteomalacia and rickets (as far as is known) lack the characteristic granular precipitation of the calcium salts. It must be admitted, however, that the degree of this phenomenon varies among the fluorine animals and that possibly it may occur in other pathological conditions. The details of the histological picture of the bones under fluorine intoxication may be observed in other bone diseases (for example, increased periosteal apposition, fibrous transformation of the marrow, bone absorption by giant cells). Here, however, it must be borne in mind that the number of ways in which the osseous tissue can react morphologically is limited. There may be a certain practical difficulty in the circumstance that fluorine-intoxicated animals may simultaneously, and perhaps often, be exposed to dietary deficiencies (Ca, P, vitamins). The increase of plasma phosphatase shown by Phillips (637) in chronic fluorine intoxication cannot be regarded as pathognomonic, as it is also observed in rickets and ordinary osteomalacia.

One common feature of the three manifestations of chronic fluorine intoxication is that *isolated cases may be difficult to diagnose.* When occurrence is endemic, which up to now has been the rule, one vital factor for the diagnosis may be whether fluorine is present in drinking water, dust, plants, etc. in quantities corresponding to the degree of the disease and its topographical distribution, and whether the disease ceases when the fluorine ingestion is stopped. Another feature of diagnostical importance (apart from an abnormally high fluorine excretion in the urine) is an increased fluorine content in bones and teeth. This, however, is not of decisive importance to the diagnosis. In a region where there is a possibility of ingesting fluorine in toxic quantities, there will be individuals who ingest it without giving clinical symptoms of intoxication. Cristiani (192) has applied the term *latent fluorine intoxication* to this condition. The manifest intoxication symptoms then develop if the fluorine intake is raised or the sensibility to fluorine increases for some reason (Ca or vitamin deficiency, etc.). This explains why bones and teeth sometimes contain the

same quantity of fluorine in apparently healthy individuals as in individuals with definite symptoms of intoxication. Comparative material must comprise individuals from regions where the fluorine intake does not exceed the average. It is difficult to indicate limits, for one reason because the available material is limited (Chapter XXV). A fluorine content of more than $2\,^0/_{00}$ in bone ash and more than $1\,^0/_{00}$ in tooth ash would, however, cause one to suspect an abnormally high fluorine intake.

7. Prognosis and Therapy

Dental Anomaly. The enamel changes must be regarded as irreparable; they are very disfiguring, especially when accompanied by pigmentation. In the mild degrees the strength of the tooth does not seem to be reduced and the caries frequency is not remarkably high. In the severe degrees the enamel is brittle and the tooth as a whole little resistant. The consequence is an abnormal, often irregular wear, with mastication difficulties as a result. This is particularly pronounced among the ruminants, whose nutrition may therefore be affected. The sharp, prominent parts of the molars may injure the opposing gingiva and alveolar margin. Secondary dyspepsia is mentioned as a consequence of severe tooth changes in man. Deposition of fluorine in a mature tooth does not seem to affect its strength, though this question is not definitely settled. **Osteosclerosis.** In man the bone sclerosis is not accompanied by effects on the general condition and there is nothing to show that other organs than bones and ligaments are injuriously affected. In a prognostic sense the ligament calcifications and the consequent limitation of the motility of the vertebral column and thorax are of greatest importance. Severe changes, however, do not develop until after years of exposure to fluorine. The subjective discomforts of the cryolite workers were strikingly few, and their morbidity (measured by the number of sick-days) did not exceed the average in industry as a whole. Though the sclerosis involves reduced elasticity of the osseous tissue, the fracture frequency was not remarkably high; it is probable that a larger material would give more positive figures. The bone changes must be regarded as reparable, for in time the sclerotic osseous tissue is replaced by normal tissue when the fluorine ingestion ceases. The ligament calcifications seem to disappear slowly and incompletely. Experimental osteosclerosis in the rat is accompanied by certain less pronounced general symptoms and a chronic interstitial nephritis.
Osteomalacia. The prognosis of the osteomalacia depends very greatly on the dose, the time factor and different conditions which affect the sensitivity of

the organism to fluorine. In the spontaneous animal diseases where the dose is unknown the animals sometimes succumb in cachexia after the course of weeks or months, or the condition may be stationary and be accompanied by only slightly pronounced symptoms. The available observations indicate that the animals recover rather quickly when further fluorine ingestion is prevented. The general condition improves and the exostoses disappear. The few experimental observations point in the same direction. Sollman et al. (759) in experiments with rats found that recovery after cessation of fluorine ingestion was not complete if the general condition had become distinctly affected. Prognostically it is fortunate that the osseous tissue is relatively sensitive and that degeneration of the parenchymatous organs seems to require higher doses. The kidney, however, must be considered separately, though in herbivora the renal effect is relatively small. Presumably the most frequent cause of death is cachexia, sometimes perhaps secondary consequences of spontaneous fracture. In certain circumstances an effect on the renal function may also play some part.

It is probable that fluorine as a rule does not permeate the placenta and thus has no direct effect on the foetus. Where the general condition is bad, the foetus may be poorly developed, but this must be regarded as a secondary phenomenon. Reduced milk secretion may also have an unfavourable effect on the offspring. There is not much information on the subject of fluorine's excretion in the milk; in woman there is so much excretion that the specific tooth changes may develop in the child.

As to the *treatment* of chronic fluorine intoxication, very little may be said. Continued fluorine ingestion must be prevented, if possible. The tooth changes are unaffected by therapy; the pigment can be bleached by oxygenous means, but the effect is not permanent. On the basis of what has been explained under the pathogenesis it will be logical to put the intoxicated individual on a food rich in Ca, P, and vitamins, especially C and D. This is directly obvious in pronounced intoxication, where the Ca-retention is affected, and marked changes in the metabolism have probably occurred. In osteosclerosis and the dental disease the theoretic basis for this therapy is more problematical, but on the other hand it will presumably do no harm.

CHAPTER XXVIII

POSSIBILITIES OF INTOXICATION

The following is a consideration of the chances of intoxication connected with the occurrence of fluorine in nature, with the extraction of fluorine compounds and their multilateral uses. From a practical-toxicological point of view, fluorine intoxications may be placed in three groups:

(1) *Local corrosions* of skin or mucous membranes, which may be caused by hydrofluoric acid, hydrofluosilicic acid, acid solutions of their salts, and certain gaseous fluorine compounds (HF, SiF_4).

(2) *Acute intoxication* through ingestion of dissolved or relatively easily soluble fluorine compounds or by respiration of gaseous forms.

(3) *Chronic intoxication*, which may be divided into three clinical units combinable in various ways: (a) degenerative changes in the teeth, (b) osteosclerosis, and (c) osteomalacia. The quantity of fluorine necessary to produce the various forms depends on different factors, but on the whole seems to increase from (a) to (c). The dental disease is the most frequent, the osteosclerosis the most infrequent form.

From a hygienic point of view the chronic intoxication is of greatest interest. In the known spontaneous intoxications, fluorine is ingested in dissolved or solid form (drinking water, dust, plants) and is absorbed from the gastro-intestinal tract. A chronic intoxication can be developed by absorption of gaseous fluorine compounds from the mucous membranes of the respiratory tract (539, 540). Provided that the total quantity of fluorine permeates the mucous membranes, a man in order to absorb 15 mg. fluorine in the course of 8 hours must breathe air containing about 0.004 mg. hydrogen fluoride per litre (about 0.00045 per cent.). A concentration of this magnitude is probably respirable for long periods. It is presumable that easily soluble fluorine compounds (NaF, Na_2SiF_6) can be absorbed from the lungs, whereas the non-solubles (Na_3AlF_6, CaF_2) cannot.

1. Occurrence of Fluorine

Drinking water. Where the soil contains fluoric minerals the fluorine content of the ground-water may be relatively high. The occurrence of fluorine does not seem to be associated with certain types of water or to be in relation to the depth from which the water is drawn. Mineral springs, especially hot springs, often carry fluorine; they may be alkaline, sulphurous and presumably, of other types*). In regions where the fluorine content of drinking water is 1 mg. per litre or more, the specific changes in the teeth, *mottled teeth*, may be expected in individuals drinking this water during the period when the permanent teeth calcify. In recent investigations by Dean and Elvove (225a, 225b) both the incidence and the percentage distribution of severity of the condition has been found to vary in relation to the fluorine concentration of the water. The threshold concentration will probably prove to be variable, for example depending on the other mineral constituents of the water. According to the analyses, which are not recent in character (Table 7), it is to be presumed that this tooth anomaly has a wider distribution than that known at the present time. As the fluorine content in drinking water rarely exceeds some few mg. per litre, other symptoms of the intoxication, especially from the bone system, can hardly be caused through the water. However, where the fluorine content is unusually high we cannot primarily exclude the possibility. Smith and Smith (757) have reported up to 18 mg. fluorine per litre in Arizona, Elvove 20 mg. per litre in tap-water in Marion, Kentucky (250). Investigations into the condition of the osseous tissue, in both adults and children, will be of interest in such places.

Food. In regions where soil and water are relatively rich in fluorine, the plants may be expected to contain fluorine in quantities exceeding the average. Possibly this may play a part in the genesis of the dental changes, but the analytical material at present available does not suffice for an estimate of that risk. It is possible, but not probable, that fluorine in the plants occurs in a non-toxic form. Gaud et al. (307) have shown that in the areas of the large phosphorite deposits in North Africa the high fluorine content of the plants plays a part in the pathogenesis of the dental disease, though in combination with simple contamination of plants and drinking water with dust rich in fluorine. As the musculature and the parenchymatous organs store only

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*) During a journey in Iceland in the autumn of 1935 the author analysed the fluorine content in 20 hot springs, both alkaline and sulphurous, and found variations from 1.4 to 13.3 mg. per litre. Water from these springs is used only exceptionally for drinking or cooking purposes.

small quantities of fluorine, the eating of meat from fluorine-intoxicated animals probably means little danger of poisoning. The possibility of the excretion of fluorine through the milk must be considered in the spontaneous intoxication of cattle.

Volcanoes. During volcanic eruptions fluoric products may be emitted in gaseous form; this holds good of a number of volcanoes in various parts of the world (Table 8). In conjunction with eruptions of Icelandic volcanoes there have often been mass intoxications of herbivora, both acute and chronic (dental changes, osteomalacia). The mechanism is presumably that gaseous fluorine compounds (HF, SiF_4) corrode the plants which serve the animals for food. There is little information*) on the subject of human intoxication by volcanic activity. Judging from conditions in Iceland, serious cases of acute intoxication are rare, and the chronic diseases which in former times accompanied volcanic eruptions may be explained in another manner (starvation, scurvy). The fluorine compounds originating from volcanic activity are oftenest easily soluble, and therefore as a rule will be washed out by the rain water, so that there is no danger of intoxication between the eruptions. However, mottled teeth seems to be a frequent affection in regions of former volcanic activity**).

2. Extraction of Fluoric Minerals

Of the fluoric minerals and rocks occurring in nature the varieties extracted are fluorspar, cryolite and phosphorite (Chapter III, 1).

Fluorspar (CaF_2) is a vein mineral of widespread occurrence. Extraction as a rule is from subterranean dikes. The product often contains quartz; it is sometimes crushed at the place of extraction, sometimes at a later stage. The world's production is 200,000 to 300,000 tons per annum. On the basis of the average figures for the period 1913—1922 the output is stated to be distributed as follows: U.S.A. 56.3 per cent., England 17.9, Germany 16.4,

*) In a very interesting work Johnston-Lavis (445) concluded that there is no *direct* connection between volcanic eruption and disease in man or animal. The knowledge of fluorine intoxication alters that view. The possibility cannot be precluded that some of the examples quoted by Johnston-Lavis of acute disease in man are the result of fluorine intoxication (Vivinzio's cases of pulmonary disease, da Corogna's cases of disease in the respiratory tract and alimentary canal). The marked effect on plants and lower animals, often observed after volcanic eruption, are likewise of interest in this connection. It may be mentioned that Gautier (310) found 0.11 mg. fluorine per litre air during the Vesuvius eruption in 1913 (see Chapter III).

**) On a journey in the autumn of 1935 in Rangárvallasýsla and Vesturskaptafellssýsla in South Iceland, the region of the great volcanic eruptions, the author observed no case of mottled teeth in man or animal. The fluorine content of 35 samples of drinking water (well, spring, stream) varied from 0 to 0.6 mg. per litre.

other countries 4.6 per cent. (577). Fluorspar is mainly employed in the countries where it is extracted. Most of it (82 per cent.) is used as a flux in the metal industry, smaller quantities in the glass industry (12 per cent.) and the chemical industry (5 per cent.). *Cryolite* (Na_3AlF_6) is extracted solely at Ivigtut, Greenland. The quantity amounts to only 4—5 per cent. of the total fluorine production. The conditions attending the extraction and manufacturing of cryolite are dealt with in Chapter XI. *Phosphorite*, or crude phosphate, occurs in the form of deposits in a number of countries. The annual world output is stated to be eight or nine million tons. The main producing countries are North Africa, U.S.A. and a number of islands in the South Seas and West Indies (577). Extraction usually proceeds from open shafts. Manufacturing comprises a number of processes, some of which produce dust. Much the greater quantity of the mineral is used in the production of superphosphate. Smaller quantities go to the chemical industry for making phosphoric acid and for use in metallurgy. The fluorine content varies round about some few per cent.; very probably the fluorine occurs in the form of a complex calcium-fluorphosphate of the same empirical formula as apatite.

Manifest fluorine intoxication is known only among cryolite workers who constantly are employed in dusty atmosphere. According to Nicol's investigations (612), fluorspar workers are subject to silicosis, of considerable severity, because the fluorspar contains quartz. Nothing is stated as to acute dyspeptic symptoms or osteosclerosis. It is not probable that fluorspar workers are exposed to fluorine influence to such a degree that osteosclerosis can develop, but the possibility cannot a priori be dismissed. It is true that fluorspar has only about one-eighth of the solubility of cryolite in weak hydrochloric acid solution (page 124), but experimentally calcium fluoride shows a not inconsiderable degree of toxicity. Working on the extraction of phosphorite presents no risk of intoxication, apparently, probably on account of the low fluorine content of the mineral and the low solubility of the fluorine compounds involved*).

*) Recent observations show that the slightly soluble complex compounds between fluorine and calcium phosphate in apatite and phosphorite may produce fluorine intoxication. Bishop (78a) describes a case of osteosclerosis in a man employed for 18 years in a fertilizer factory, where he had handled finely ground rock phosphate (3.13 per cent. fluorine). Spéder (763a) found osteosclerosis in natives attacked by *darmous* (Morocco). The intoxication is caused by dust rich in fluorine from the great deposits of phosphorite in North Africa. Wolter, Ablina and Kremnewa (883a) have shown experimentally that the fluorine compounds in apatite, phosphorite and superphosphate are toxic. Signs of chronic fluorine intoxication (bone changes on X-ray examination, anomalies in tooth development, increased fluorine content of bones) were seen in dogs which for up to 14 months received 1—9 mg. fluorine daily per kg. body weight in the form of dust of the products mentioned above. Gastric acid plays an important rôle in the transition of fluorine to soluble form.

3. Industrial Use of Fluorine Materials

In certain industries which handle fluoric raw materials or employ fluorides in conjunction with their raw materials, gaseous fluorine compounds are developed as by-products; these are of interest in toxicology.

In the *manufacture of superphosphate* the raw material, phosphorite, is treated in enclosed systems with sulphuric acid, whereby the phosphoric acid is converted into a water-soluble form that is absorbable by plants. Treating with acid results in the development of hydrogen fluoride (HF) and hydrofluosilicic acid (H_2SiF_6), which, by absorption in water and with the addition of sodium chloride, can be converted to the by-product sodium silicofluoride (Na_2SiF_6). In former times it seems to have been the normal method to eject the volatile fluorine compounds into the atmosphere through the factory chimney, or to lead the liquid from the absorption chamber to the waste water after neutralization with lime (249). Nowadays the fluorine compounds are collected and extracted to a certain extent, but the problem is still discussed in various industrial countries. For example, DeEds (228) calculated recently that in the manufacturing of superphosphate in U.S.A. there is an annual loss of 25,000 tons of fluorine, ejected in gaseous form.

The *manufacturing of aluminium* by the Hall-Héroult process takes place by the electrolysis of aluminium oxide in a bath of molten cryolite at a temperature of about 925°. During electrolysis the cryolite is decomposed, especially when there is insufficient Al_2O_3 in the bath and the pressure rises as a consequence. The manufacturing of a certain quantity of aluminium requires the consumption of 5—10 per cent. cryolite. Some of the cryolite can be substituted by other fluorides. The decomposition processes are not known with certainty; fluorine compounds have been sought for over the open melting baths but without success. Nevertheless it is beyond all doubt that active fluorine compounds are given off, for the windows in the factories become etched (118, 742); even at some distance from the factory there is sometimes an effect on windows, whereby they lose their gloss (196). In all probability silicon tetrafluoride (SiF_4) is formed, and this, with the humidity of the atmosphere, is converted into H_2SiF_6 and HF. This is the explanation advanced for the damage actually observed on the vegetation round about these factories. Presumably the reaction of the melting bath has something to do with the composition of the decomposition products; there is a possibility of the formation of other volatile fluorine compounds (NaF, AlF_3).

In *steel and metal works* fluorspar (CaF_2) is extensively employed as a flux in the melting process (576a). This applies both to iron refining (Thomas,

Bessemer and Siemens-Martin processes) and iron founding (cupola furnace), as well as in the manufacturing of other metals (e.g. lead, copper and nickel). Eighty per cent. of the world's production of fluorspar is used in the metal industry. It is calculated that 3 to 5 kg. fluorspar are employed to the average ton of steel (577). During the melting process SiF_4 escapes, being freed according to the following reaction:

$$3\,SiO_2 + 2\,CaF_2 \rightarrow SiF_4 + 2\,CaSiO_3$$
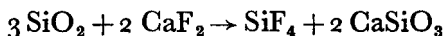
Certain ores like zinc ore may contain fluorspar (267, 576a). In *glass and enamel manufacturing* fluorine compounds are often added to the raw material to facilitate melting and to give the finished product certain properties. As the raw materials contain silica or silicates, volatile fluorine compounds may be produced (4). The emanation of gaseous fluorine compounds has also been observed from *chemical works* (manufacturing of hydrofluoric acid) and from *brick-works* (fluorine-rich clay).

The *risk of intoxication* in these industries varies. Where the volatile fluorine compounds are given off direct into the air of the factory premises (especially aluminium-factories) *the workers* may be exposed to acute, perhaps chronic intoxication*). As a general rule, however, it may be assumed that dilution takes place to such an extent that the risk of intoxication is limited. In superphosphate works with modern equipment all manufacturing proceeds in enclosed systems, and the possibility of intoxication occurs only when cleaning certain types of plant.

In the *environs of the factories* referred to in this chapter the danger is principally to the vegetation and the consequent chronic intoxication of herbivora so often observed (Chapter II, 3). Besides the damage to the plants, it may be that contamination by dust containing fluorine from the factory must be taken into consideration. Chronic intoxication of the population in the vicinity of such a factory will scarcely occur in the same manner, as vegetables form only a part of human food, and they are usually cleansed. It is not impossible that there may be acute intoxications among the people living round the factory; but no doubt it is a rare phenomenon which, before it can occur, requires a certain constellation of circumstances to constitute a danger, viz.

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*) On pages 10 and 11 reference is made to acute fluorine intoxication among workers employed on the manufacturing of aluminium, superphosphate and beryllium. A fatal case of poisoning by the flue gas from a cupola, reported by Herzog (411 a) probably was a fluorine intoxication. Frostad (293) describes bone changes, suspected as being incipient osteosclerosis, in elderly workers in an aluminium factory.

considerable fluorine emanation in conjunction with fog, calm, and topo-graphical conditions which prevent the renewal of the air*).

4. Various Uses of Fluorine Compounds in Technical Processes

Hydrofluoric acid, hydrofluosilicic acid and their salts are employed for many purposes in industry and handicrafts (451 a), especially in the production of other chemical substances (hydrogen peroxyde, alkali hydroxides and carbonates, silicium, various metals, etc.). The uses of fluorine compounds in some other technical processes are given in Table 57, mostly according to Ull-mann (811). In many cases they are extremely toxic compounds. Probably the risks of intoxication vary a great deal; in some cases there is only a limited

*) The mysterious *fog disaster* which occurred *in the Meuse Valley near Liége* (*Belgium*) in the beginning of *December 1930*, most probably was an acute fluorine intoxication. That idea has been advanced before, by Storm van Leeuwen (498), Gram (362a) and Fenner (267, 267a), but without sufficient grounds to make it acceptable or even generally known. A critical analysis of the catastrophe in the light of present knowledge (688d) gives circumstantial evidence that the theory of fluorine intoxication is right.

In the days of the catastrophe a thick mist lay over large parts of Belgium. It was cold, and there was practically no wind. Several thousand cases of acute pulmonary attacks, with 60 deaths, occurred in the densely populated Meuse Valley on the 20 kilometre stretch from Seraing west of Liége to Huy. This region contains numerous factories; the valley is narrow and surrounded by rather high hills. The smoke from the factories was beaten down and mingled with the fog. The symptoms of the affection were dyspnoea (asthmatic attacks or polypnoea) cough, expectoration, more or less pronounced hoarseness and lachrymation, nausea and occasional vomiting. In the fatal cases an acute circulatory insufficiency set in with rapid and poor pulse, pale — more rarely cyanotic — face, and extension of the heart dullness. Those affected were elderly people mostly, or people whose lungs and heart were already weak. In most cases death occurred within 24 hours. On necropsy diffuse hyperæmia of the mucous membranes was observed in the trachea and in the larger bronchi. Microscopical examination revealed epithelial desquamation and cell degeneration of the mucous membranes; in the lungs were found limited areas with moderate oedema, hæmorrhage and desquamation of the alveolar epithelium.

The symptoms developed indicate the presence of a very toxic poison, with a moderate local effect and a pronounced general effect due to absorption. The symptoms subsided quickly when people ascended the hills and thus got beyond the fog. No further deaths occurred as soon as the fog lifted, and the survivors recovered in a few days. Of the 27 factories in the region, 15 were of industrial branches which either manufacture from raw materials containing fluorine (superphosphate works, zink works) or add fluorine compounds to the raw materials (steel works, iron foundries, glass works) involving the possibility of passing gaseous fluorine compounds (SiF_4, HF) into the chimney smoke. In a part of the region concerned window panes and electric bulbs lost their gloss more quickly than normally, and the cattle, after grazing a short time, contracted serious bone diseases. A rough calculation showed that the fluorine concentration in the Meuse Valley may have exceeded the lethal dose for man in the days of the catastrophe. There was a similar but less disastrous episode in 1911.

TABLE 57.

Various Uses of Fluorine Compounds in Technical Processes.

Use	Fluorine compound employed
Binder for emery wheels (216)	CaF_2(fluorspar)
Removing sand from castings (811)...............	HF
Glass etching (811)	HF; NH_4F
Silicate analysis in laboratory	HF
Rust removing from steel and iron (232).........	HF
Disinfection of hose and tanks in breweries (811)..	H_2SiF_6; $NH_4F \cdot HF$
Disinfection of hides and skins (811).............	H_2SiF_6; silicofluorides
Window-cleaner (722)	H_2SiF_6; silicofluorides
Bleacher in laundries (811)	Na_2SiF_6
Bleaching of cane for chair seats (700)...........	HF
Making synthetic stones (811)..................	Sundry compounds
Coagulating rubber (811).......................	Na_2SiF_6, $MgSiF_6$
Wood-staining (811)...........................	CrF_3
Making glue, paste and adhesives (811)..........	HBF_4
Preserving wood (building timber, telegraph poles) (811)	NaF, ZnF_2, $MgSiF_6$
Hardening (fluating) cement (811)...............	$MgSiF_6$, $ZnSiF_6$
Fixing of tannin on cotton in dye-works and printing works (811)	SbF_3
Silk dyeing (232)	HF
Refrigerating industry (585).....................	CCl_2F_2; $C_2Cl_2F_4$
Cleansing graphite (811)........................	HF
Treating anthracite for making gas coal (811)	HF
Optical industry (216)..........................	CaF_2 (fluorspar)
Electrolytic manufacturing of beryllium (848).....	Na_2SiF_6

use of the substance, but perhaps just for that reason it may be under primitive forms without sufficient prophylactic precautions. The most frequent form of intoxication is local corrosions. Very important is glass etching, a much used process and carried out in several ways. An object dipped in diluted hydrofluoric acid acquires a clear and transparent etched surface. If the glass is exposed to hydrofluoric acid vapour it becomes opaque in the course of a few minutes. The latter process is often carried out over a leaden vessel in which pulverized fluorspar is treated with concentrated sulphuric acid under heat. In industry, matt etching (for example the matting of incandescent bulbs) is performed by dipping the object into a solution of acid ammonia fluoride. Local corrosions through these processes often appear in the official reports on occupational diseases (111). There will scarcely be any risk of

poisoning due to absorption from a local corrosion. Chronic intoxication may possibly occur in workers constantly employed on glass etching with hydrofluoric acid vapour*).

5. Use of Superphosphate

In superphosphate there is almost always fluorine, for the raw material, phosphorite, as a rule contains about 3.5 per cent. fluorine. In consequence of the manufacturing method the fluorine content of superphosphate varies round about 1.2 per cent. The world's annual production of superphosphate is about 11 million tons (216). This means that large quantities of fluorine are constantly being added to the arable land. In Denmark, where agriculture is pursued intensively, about 300,000 tons of superphosphate are used every year, or about 4,000 tons of fluorine.

Having regard to the fact that fluorine has a toxic effect in very small doses, this circumstance provides food for thought. We know practically nothing of what happens to the fluorine in the superphosphate. The greater part of the phosphoric acid is absorbed by the plants and a small quantity no doubt accumulates in the top soil. There is no leaching, for ground water and draining water contain hardly any phosphoric acid. It is possible that fluorine follows the circulation of the phosphates. This need not be the case, however; other possibilities are leaching or accumulation in the soil in the form of non-soluble compounds (calcium fluoride, fluor-apatite, complex compounds with Fe and Al).

Only few investigations dealing with these matters are available. Gaud et al. (307) have shown that a considerable storage of fluorine takes place in plants (fig-tree, wheat, barley) growing in the regions in North Africa where *darmous* is endemic. Grains of wheat from such a region contained 22.6 mg. fluorine per 100 g. dry substance, and the same material from a darmous-free region 0.2 mg. fluorine. This proves that the plants are able to absorb fluorine under the circumstances where the element occurs in the phosphorite. Hart et al. (385) studied the fluorine content of plants cultivated on areas which for many years had been fertilized with rock phosphate or superphosphate. Comparison with material from areas dressed with bone meal showed no definite increase of the fluorine content, which in both cases was 0.026—0.2 mg. fluorine per 100 g. air-dried substance. Draining water from areas dressed with fluorine-rich phosphate revealed a moderately increased

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*) Flemming Møller and Gudjonsson (591) examined 20 workers who had been exposed to gaseous fluorine compounds for a varying, often large, number of years, without finding osteosclerosis.

content of fluorine, viz. 0.118—1.71 mg. per litre after the use of rock phosphate, and 0.084—0.106 mg. where superphosphate had been employed. Water from control areas had 0.044—0.050 mg. fluorine per litre. Conditions in North Africa are scarcely directly comparable with the ordinary use of super-phosphate, in which the quantity of fluorine is smaller. Nevertheless, the problem is interesting and further investigations are desirable.

6. Fluorine Compounds as a Poison for Noxious Animals and Plants

The high toxicity of the fluorine compounds has led to their application as a *rat and mouse poison*. In most cases they are used in the form of sodium fluoride or sodium fluosilicate, which are effective, relatively cheap, and have no pronounced taste. They are sold on the market under proprietary names and seem to have been used for this purpose for the first time in Germany after the war. Their use against *noxious insects* dates from last century. The first case of poisoning with one of these preparations was in 1899. Judging from the many patent-preparations and the number of poisoning accidents, their use is wide-spread. Sodium fluoride and sodium silicofluoride are used especially as powders for cockroaches etc. Sodium fluoride has also been employed with good effect against animal parasites like vermin on poultry, in solution or as dusting-powder (78). In particular, these preparations occasion acute intoxications of man and animals through their being confused with some-thing else.

A modern use, one that is constantly growing, is as an *insecticide for plants*. The fluorine compounds were introduced 1924 into this sphere by Ripley (679) in South Africa and Marcovitch (558) in U.S.A. A comprehensive literature has since appeared on the subject (376). The interest taken in it is considerable, partly because it is hoped the fluorine compounds will be a remedy just as effective as the arsenic compounds and less dangerous to man, partly because the industry requires an outlet for the fluorine compounds gained as by-products of superphosphate manufacturing. At first the compounds used were the relatively easily soluble kinds (NaF, Na_2SiF_6), but the draw-back of these is that they "burn" the plants. During the last few years the manufacturers have mostly used non-soluble compounds whose toxicity vis-à-vis the insects corresponds to their fluorine content (737), but which do not harm the plants and are not so easily washed away by the rain. The substance is either sprayed on in solution (sometimes mixed with an emulsion-izer) or in powder form. For special purposes a sugary "bait" may be added.

The fluoride is consumed by the insects when they cleanse extremities and antennæ of adhering dust; there also seems to be a percutaneous absorption, especially at the junctures (417). Many different insects have been dealt with effectively*).

This application of the fluorine compounds has raised the important question of whether there is any risk of poisoning through eating the small quantities of fluorine that may remain on parts of plants (for instance fruit) after spraying. Carter (145) found this residue on fruit after repeated sprayings with barium fluosilicate to be 0.02—0.04 grains of fluorine per pound (i.e. 2.9—5.8 mg. per kg.). The greater part could be removed by washing the fruit with acid or alkali. Having regard to the fact that a daily intake of about 1 mg. fluorine in a child may produce specific changes in the teeth, the *risk of poisoning when eating sprayed but unwashed fruit must be considered as a possibility*. It is difficult to judge the practical risk, as the analytical material is so small. Factors which reduce the risk of poisoning are: that only a certain part of human food consists of vegetable matter, and that more or less of the fluorine can be removed by ordinary washing, peeling the fruit, etc.

The danger of poisoning to persons carrying out the spraying with insoluble fluorine compounds may be regarded as minimal, as this work proceeds in the open air and presumably only intermittently. There is probably a very small chance that plants or ground-water under these circumstances can absorb fluorine from the soil in quantities sufficient to form any real source of intoxication.

7. Employment of Fluorine Compounds in the Food Industry

According to communications here and there in the literature, fluorine compounds have been used or are being used in the food industry in various ways, whereby fluorine, directly or indirectly, is added to the food. In some industries (breweries, slaughteries) fluoric solutions are employed for the disinfection of tanks, hose and bottles. In the manufacturing of spirits the Effront method with the addition of hydrofluoric acid or fluorides to the mash once was of importance (page 44). In the sugar industry, too, the suggestion has been made of suppressing undesirable fermentation in the diffusion juice by adding fluoride (840), a process which scarcely is of much practical importance.

On the other hand, a direct addition of fluorine compounds to food for

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*) Fluorine compounds have also been used with effect against various plant diseases not due to insects, for example mildew and bunt fungus. The widespread use of soluble fluorides as a means of preserving wood is due to their toxic effect on mould and dry-rot (849).

preserving purposes is of some practical interest. This use began in the nineties of last century, after the disinfecting properties of the fluorides had become known (606). Alkali fluorides are suitable for the purpose, in so far as they have a strong antiseptic effect, do not change the product and have no taste. Up to quite recently the general opinion has been that fluorides are relatively non-poisonous. Judging from the literature, the employment of fluorine compounds has been limited compared with preservatives such as boracic acid, sulphurous acid, etc. To some extent this may be due to the fact that test for fluorine only rarely forms part of the routine analysis of food-stuffs. A systematic investigation might perhaps reveal more widespread use.

Wine. Fluorine is added partly to the must, partly to the grapes themselves in order to prevent injurious fermentations. The addition may be made by disinfecting casks and bottles with the fluoric solution. The presence of fluorine is reported in wine from Hungary (13), Italy (710, 624, 891), France (815), Switzerland (422), Spain (873, 456, 657), Portugal (456), and Argentina (375). The latest reports date from about the year 1920. The question has caused some controversy, for sometimes small quantities of fluorine were found in the pure grape, sometimes the presence of the element in unadulterated wines was denied. Most probably the explanation is that the normal quantity of fluorine in grapes as in other plants depends upon the fluorine content of the soil. Nevertheless it is generally agreed that a macroscopically distinct qualitative reaction (glass etching) from 100 c.c. of wine is always due to the addition of fluorine to the product. It is difficult to state the quantity added in practice, as there are no quantitative analyses. According to Meisner (578) an addition of 8—10 g. fluoride per hl. is employed against after-fermentation (1901). Certain reports (400, 723) indicate that about the beginning of the present century fluorides were also used as a preservative for *beer*.

Fruit Juice. The addition of fluorine compounds to the raw juice prevents after-fermentation. Cohn (172) recommended the addition of up to 200 g. hydrofluoric acid to 100 kg. of juice, with subsequent precipitation of fluorine as calcium fluoride. The method was opposed in various quarters on the grounds that it is not possible to remove fluorine quantitatively by means of precipitation.

Other Food. A comparatively high content of fluorine (presumably added) has been reported in butter (401), milk (625), eggs (659, 530), minced meat and sausage (563), and canned tomatoes (135). Lehmann (500) wrote in 1901 that milk can be kept fresh by adding 3—4 g. sodium fluoride per litre. For butter the addition of 1—3 $^o/_{oo}$ sodium fluoride is recommended, if necessary with

later removal by washing (636). Hehner and Hehner (401) in French butter found 1—4 grains of this compound per pound (1902).

Besides the direct use of fluorine compound as a preservative, experiments have been made on other uses which may be of interest hygienically. Soluble fluorides have been suggested for softening water on account of the low solubility of calcium fluoride (82). The easily-soluble silver fluoride has been recommended for the disinfection of drinking water (631) and vegetables (125). According to Sollmann et al. (759) there is a limited use of rock phosphate in the manufacture of phosphate employed in making baking powder. In practice this substance may contain from 0.04 to 0.5 per cent. fluorine. Schwartze calculates the daily intake of fluorine through the use of such baking powders as being between 0.35 and 35 mg. (759).

The risk of intoxication through the use of fluorine in food manufacturing comprises first of all the development of the specific degenerative dental changes. Other forms of chronic intoxications will scarcely arise by these means, or at any rate rarely. Acute intoxication (symptoms from the gastrointestinal tract) may occur when the fluorine content is high; Schaffer (710) refers to cases of sickness in several persons after drinking a sweet Italian wine with sodium fluoride added.

8. Use of Fluorine in Therapy

Compared with the other halogens, fluorine has been little used in therapy. Most of the uses rest on a slender foundation, often indeed erroneous, and in many cases apply to diseases in which the effect of the treatment is difficult to judge.

Pulmonary Tuberculosis. According to Chevy (164), the origin of the use of hydrofluoric acid against pulmonary tuberculosis was the discovery that in French glass-works the workers who contracted pulmonary diseases endeavoured to get work on glass etching with hydrofluoric acid. In the 1880's this led to treating pulmonary tuberculosis with inhalations of air containing about 0.004 per cent. hydrogen fluoride (689). A variety of devices made their appearance, including a chamber to which the air was conveyed through a solution of hydrofluoric acid (490). The excellent results recorded at first were evidently due to too optimistic conclusions; very soon we hear no more about the method. Attempts to consolidate the therapy experimentally gave negative or uncertain results. Since then Casares (146) and Goldemberg (346) have attempted — not very convincingly — to treat pulmonary tuberculosis with intravenous injections of sodium fluoride; the toxic effects have been referred to on page 68.

Bones. Teeth. On a purely speculative basis Chrichton-Browne (185) in 1892 recommended fluoric food for pregnant women and for children for the purpose of counteracting caries: there being fluorine in the teeth, the element must be of importance to their strength. Brissemoret (113) had similar ideas as regards the osseous system, and advocated a strengthening therapy with administration of calcium fluoride. In homoeopathy this treatment is still persisted in to some extent (720). Calcium fluoride in small quantities is used against both otospongiosis (260) and otosclerosis (506). On the basis of the productive bone changes in human cryolite poisoning Flemming Møller and Gudjonsson (591) suggested the possibility of treating rarefying bone diseases by fluorine compounds. The use of phosphorite as a mineral supplement in animal husbandry may be regarded as abandoned, now that the toxic effect of fluorine has become known. Fluorine poisoning through the use of adulterated bone-meal has been observed (290).

Hyperthyroidism. In 1881 Woakes (878) tried treating struma with small doses of hydrofluoric acid administered perorally. Goldemberg (345) reintroduced the treatment in 1930; he employed intravenous injections of sodium fluoride (0.04—0.06 g. at a time, a total of 1 g. being given over a period of several days), or peroral administration. Curative effect has been observed even in severe cases where other therapy proved ineffective. The treatment has been tried elsewhere, apparently with good results (350, 569, 570). Gorlitzer (357) employs baths with hydrofluoric acid and considers that the undissociated HF-molecule can permeate the intact skin. Phillips and co-workers (640, 641) recently showed in experiments with rats and chickens, that non-toxic levels of desiccated thyroid were made distinctly toxic by simultaneous administration of sodium fluoride in doses which alone did not give pronounced toxic effects. This experience calls for caution in therapy.

Disinfection. Fluorine compounds for this purpose were first used in 1887 by Thomson (796). For surgical use he recommended a saturated solution of sodium fluosilicate (0.61 per cent.) as being more effective than 2 $^o/_{oo}$ sublimate, non-poisonous, inodorous, and with no local irritative effect. Mayo Robson (684) employed the same compound for rinsing cavities. A "halogen solution" employed in Germany in recent years and recommended for wounds (6) and urological practice (294), contains an unstated quantity of fluorine. Head (397) has introduced ammonium bifluoride solution for local treatment of alveolar pyorrhoea, and many of the preparations sold as remedies for this disease are said to contain the same fluorine compound (155).

Other Uses. Inhalation of air containing hydrogen fluoride has been tried for diptheria and malaria. A number of organic fluorine compounds have been

employed, for example fluoroform (CHF$_3$) for surgical tuberculosis and lupus (770), difluordiphenyl (C$_6$H$_4$F·C$_6$H$_4$F) for slowly-healing wounds (793) and various skin diseases (478). In various forms fluorine has been used for whooping cough; Krause (480) when using difluordiphenyl in ointment saw no effect on whooping cough, but the development of slowly-healing ulcerations of the skin.

The particular danger in the therapeutic use of fluorine compounds is the development of a chronic intoxication, though the possibility of an acute intoxication may be present too. One unfortunate application, apparently by no means rare, is the use of fluorine in preparations containing mineral salts given prophylactically against caries to pregnant women and young children. The possibility of the excretion of fluorine in the milk of women must be borne in mind.

PROPHYLACTIC PROBLEMS

Fluorine intoxication brings hygiene face to face with many problems, some of them already tackled, others new. For the purpose of finding out what had been done by legislation, a questionnaire was sent to various states in 1934, with the kind assistance of the Danish National Health Service and the Ministry for Foreign Affairs. The inquiry comprised the following questions:

(1) Are there any regulations restricting *trade* in fluorine compounds (hydrofluoric acid (HF), hydrofluosilicic acid (H_2SiF_6), salts of these acids, or other fluorine compounds)?

(2) Are there any regulations for preventing the use of fluorine compounds as *preservatives* for food?

(3) Are there any regulations concerning *other uses* of fluorine compounds, for example as insecticides, ingredients of rat poisons, etc.?

(4) Are there any regulations concerning *work on fluorine compounds*, for example prohibition against employing women or young people?

(5) Are there any regulations making it obligatory for physicians to *notify* diseases contracted while working with fluorine compounds?

(6) Are there any regulations recognizing such diseases as *compensatory occupational diseases*?

More or less exhaustive replies were received from the following states: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czechoslovakia, England, Estonia, Finland, France, Germany, Holland, Italy, Japan, Latvia, Lithuania, New Zealand, Norway, Poland, Russia (U.S.S.R.), Sweden, Switzerland, U.S.A. A summary of the prophylactic problems connected with fluorine is given in the following. An attempt is made to draw up the main outlines of the measures which it is necessary or desirable that the public should take, illustrated by the prevailing regulations revealed by the aforesaid inquiry. It would be impossible to comprise within the scope of this work a detailed examination of the regulations in each of the states, and therefore they will be given in summarized form.

1. Trade in Fluorine Compounds

The high degree of acute toxicity of fluorine compounds makes it necessary to regulate the trade in some of them. Generally speaking, this has been done

by including these compounds in the schedule of the Poisons Act, with its rules as to storage, sale and marking. The compounds that ought to be placed on the list are (1) hydrofluoric acid, its neutral and acid water-soluble salts; and (2) hydrofluosilicic acid and its water-soluble salts. Where the poisons list is divided into several sections according to toxicity, it would be best to place hydrofluoric acid and hydrofluosilicic acid among the more poisonous, the salts among the less poisonous substances. It would be desirable to extend the regulations regarding the pure substances to include preparations containing these compounds, and to require declaration, danger marking, and instructions for use.

Most countries have regulations which more or less restrict the free trade in fluorine compounds, but often only hydrofluoric acid is mentioned, sometimes together with its salts. The form recommended above for inclusion in the poisons list conforms to the rules in force in Germany. The following states have no restrictions on the trade in fluorine compounds: England, Finland, France, Holland and Switzerland.

2. Use as Preservative in Food

The addition of fluorine compounds to food of every kind should be forbidden. This is best achieved by a general prohibition against the use of non-permitted substances and by not including fluorine among those permitted. A control of the fluorine content in food may then be necessary, and this again involves that the so-called "natural" quantity of fluorine, due to its widespread occurrence in nature, must be established. The employment of fluorine compounds for disinfection or other treatment of tanks, hose, implements, etc. used in the manufacturing of food, should be restricted or perhaps forbidden.

Attention has previously been turned to fluorine compounds in this connection. In their conclusions read before the 14th International Congress of Hygiene in Berlin 1907 Gruber, Lehmann and Paul included the fluorine compounds among the non-permittable preservatives (692a). Almost all states have regulations for the prevention of the addition of fluorine compounds to food, though some Australian states (Western Australia, Tasmania), Holland and Lithuania have none. There is no reply from Italy, Latvia and U.S.S.R. as to Question 2. Argentina permits 5 mg. fluorine per litre in Spanish wine, but no adulteration of any kind to Argentine wines.

3. Use as Insecticide

This modern and steadily increasing use of fluorine compounds is of considerable hygienic interest, as it is mostly applied to food plants. The tendency

is to employ relatively slowly soluble compounds (Na_3AlF_6, $BaSiF_6$), the acute toxicity of which may be said to be moderate, so that they need not come in under regulations restricting their free sale. The spray residue problem is one that has attracted great interest in U.S.A. From this angle fluorine is regarded as the same as arsenic and lead, for which elements the U.S. of America have established maximum permissible limits for their content in fruit*). In an Announcement of 20th June 1933 the United States Department of Agriculture laid down the permissible maximum for fluorine content in fruit at 0.01 grain per pound (i. e. 1.43 mg. fluorine per kilo). As fluorine-sprayed fruit may contain several times that quantity of fluorine, it will be reasonable, having regard to our present knowledge of the toxicity of fluorine, to introduce a maximum limit and to fix it at the value current in U.S.A. Nevertheless, the problem cannot be regarded as settled finally. More analytical work is required, especially on the subject of the "natural" content of fluorine in fruit and other edible parts of plants. The toxicity of cryolite must be established, as experience seems to indicate that only part of the fluorine content of cryolite is toxic to mammals in contrast to insects; here the significance of the grain size of the preparation must be taken into consideration. Then the maximum limit may possibly be alterable in the future. A further development in the technique of washing fluorine-sprayed fruit may probably be obtainable.

It must be considered inadvisable to employ fluorine compounds for treating plants whose edible parts are above ground and cannot be washed or treated in some other way in order that the fluorine may be effectively removed. On the other hand there are scarcely sufficient grounds for a complete prohibition against the use of fluorine compounds for spraying. In the first place fluorine seems to be very effective against certain parasites, and secondly, it is difficult to find less toxic substitutes. It must be remembered that fluorine in the small quantities here concerned may affect tooth development, but has no other deleterious effect on the organism as far as is known. The risk of poisoning may be put down as non-existent in practice if the aforesaid maximum limit is adhered to.

4. Industrial Problems

The prophylactic problems associated with the extraction, manufacturing and employment of fluorine compounds in industry have reference to both the worker and the surroundings of the factory.

*) In 1927—32 the maximum limit for arsentrioxyde was gradually reduced to 0.01 grain per pound; in 1933 0.02 grain was laid down for lead.

It would be desirable to forbid the employment of males under 18 years, and females as a whole, on work with fluorine compounds which give off dust or vapour. Brazil, Japan and U.S.S.R. have a direct prohibition against the employment of females and young people on such work. Belgium, Finland, France, Germany, Holland and Poland have more or less far-reaching prohibitions in the same direction (mostly concerning the manufacturing and use of hydrogen fluoride). In other states prohibitions of a general character open up the possibility of securing similar protection (Czechoslovakia, Norway, Switzerland). Glass etching in solutions of hydrofluoric acid or ammonium fluoride, which is often performed by women, can scarcely present any danger of intoxication due to absorption through the skin. Local effects on the hands may be prevented by the use of rubber gloves. Where fluoric vapour or dust develop in working places there should be regulations as to ventilation and the usual measures for coping with the dust. As toxic substances are concerned, attention must be given to the workers' personal hygiene; in certain circumstances the use of masks may be necessary.

Physicians should be obliged to notify all diseases acquired while working with fluorine compounds. This is only practised in U.S.S.R. and Sweden, where all occupation diseases are notifiable. The acute lesions, for example corrosion by hydrofluoric acid, in many states will come in under the prevailing accident insurance laws, in which cases compensation will be payable and, under certain circumstances, the physicians will be under obligation to notify them. Chronic fluorine intoxication should be recognized as an occupation disease calling for compensation. Workers exposed to a constant intake of fluorine compounds in one form or another should be examined at intervals and temporarily taken away from the work at the first sign of intoxication. In the labour legislation of U.S.S.R. great consideration is given to persons working with fluorine compounds (shorter day, extra holidays, lower pension age, increased pension in the event of invalidity).

Industrial establishments whose waste products contain fluorine must give attention to the subject. Where the factory smoke contains fluorine compounds it should be conducted through effective condensation plant before being sent out into the atmosphere*). Open processes giving off volatile fluorine compounds must be covered over and furnished with suction plant. Waste water containing fluorine must be led to receivers with sufficient renewal of the water, or dispersed at proper distances from areas from which drinking water is obtained.

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*) No observations have been published which permit of fixing the upper limit for the permissable content of fluorine in waste gas. Attention must here be called to an observation by Wislicenus (877), who describes damage to a wood around a brickworks. The waste gas contained 0.6 g. fluorine per cbm.

5. Other Prophylactic Problems

The working out of a reliable and rapid *method* for the quantitative determination of small amounts of fluorine will be of great importance to future work on fluorine intoxication, also with regard to diagnosis and prophylaxis. Examination for fluorine ought to form a part of the medico-forensic investigation of acute intoxications of vague ætiology, in the routine analysis of drinking water*), and in the chemical analysis of food.

The therapeutic employment of fluorine compounds must be limited. Every form of fluorine ingestion is counter-indicated in children in the period when the permanent teeth are calcifying. When treating adults the considerable toxicity of fluorine must be borne in mind; all protracted administration of fluorine involves a risk of bone changes. In the female there is also the possibility of excreting fluorine in the milk, even after fluorine ingestion ceases. A prohibition against the presence of fluorine in patent medicine may be necessary. It is possible that the stimulating effect of fluorine on the osseous tissue may be utilized when treating rarefying bone diseases in adults. It may be necessary to prohibit the presence of fluorine in feeding stuffs in quantities that are deleterious to domestic animals. As regards cattle the possibility of its excretion in the milk must be taken into consideration. The necessity of manufacturing a non-fluoric superphosphate must be ventilated.

The prophylactic measures to be introduced where drinking water contains toxic amounts of fluorine may give rise to certain difficulties. The rational solution of the problem is the changing of the water supply to a source that is free of fluorine in toxic amounts. In areas where an acceptable water cannot be procured, attempts must be made to remove or reduce the quantity of fluorine contained in the available water. Boruff (100) has shown that the fluorine quantity in water can be reduced to 0.5 mg. per litre by precipitating with aluminium sulphate, but in all probability this method will be too expensive in practice. Smith (745) has indicated other possibilities, though they are scarcely practicable. As far as is known, the possibility of intoxication through drinking water is confined to children in the first 10 to 12 years of life, when the permanent teeth calcify.

*) Sanchi's method (703) is satisfactory for the rapid analysis of drinking water.

THE PHYSIOLOGICAL RÔLE OF FLUORINE

The constant presence of small quantities of fluorine in organic material might indicate that the element plays some rôle in the physiology of the organism. The mere presence of the element is no confirmation that it does so, but a necessary consequence of the widespread occurrence of fluorine in inanimate nature. Three questions arise in this connection: (1) Is fluorine necessary to the normal growth and function of the organism? (2) Has fluorine a recognizable effect on the organism when present in quantities between the hypothetical necessary minimum and the lowest toxic dose? (3) How does fluorine in these small quantities act in the organism?

1. The Necessity of Fluorine

In 1861 Salm-Horstmar (702) demonstrated in growth experiments with rye in synthetic medium that a small quantity of fluorine is necessary in order to obtain normal fruit formation. In a similar manner Mazé (574, 575) has since shown it to be probable that the normal development of the maize plant requires the presence of fluorine. Daniels and Hutton (217) observed in 1925 that mice reproduce poorly on a uniform milk diet. Prompted by an observation by Ruhrah they added to the diet ash of soya beans, which are credited with containing relatively large quantities of fluorine, manganese, aluminium and silicium, and obtained good reproduction in four generations. Mitchell and Smith (586) arrived at similar results. Rats which had become anæmic on a uniform milk diet reproduced better, though without improving the anæmia, when traces of fluorine, manganese, silicium, aluminium and iodine were added to the milk. Osborne and Mendel (618) discovered in 1913 that the addition of the same elements promoted the growth of the rats fed on a synthetic product resembling milk. In a standard diet published later small quantities of sodium fluoride were included (619).

Sharpless and McCollum (736) gave young rats a diet which as far as possible contained no fluorine. Growth and reproduction down to the third

generation were not inferior compared with rats whose diet contained 0.001 per cent. fluorine. The bones of the rats on the fluorine-free diet contained extremely small quantities of fluorine; in the teeth it was impossible to find the element. Otherwise there was no definite reason for assuming that these particular tissues were deleteriously affected by the absence of fluorine. Observations which might indicate that fluorine is necessary to normal growth include the demonstration of the presence of the element in the egg, especially in the yolk, in milk and in the newly born individual. According to earlier analyses (317, 318, 441) there are rather considerable quantities of fluorine in organs, bones and teeth of newly born children and animals. Sharpless and McCollum (736) on the contrary were unable to establish definitely the presence of fluorine in rats 16—18 days old (1933).

The question of the necessity of fluorine to the organism cannot be regarded as settled finally. Several investigations, particularly of older date, indicate that fluorine is necessary to reproduction, and perhaps to normal growth as well. The results of the earlier analyses should be regarded with some scepticism. When judging Sharpless and McCollum's experiments it must be remembered that it is difficult to compose a diet that is completely free of fluorine; the bones of the rats contained small quantities of fluorine even on the fluorine-free diet. Fluorine may be compared with other elements which normally occur in the organism in small quantities (Mn, Zn, Cu, Ni, B, As, etc.). Earlier investigators, Bertrand (62, 63) especially, considered these to be of importance, whereas most frequently their presence was regarded as accidental, as a kind of impurity. The investigations of recent years have shown that several of these elements (Cu, B, Mn) have an important biological function. We cannot reject the possibility that future research may demonstrate something of the same kind as regards fluorine.

2. Stimulating Effect of Small Quantities of Fluorine

In growth experiments the addition of about 0.001 per cent. fluorine in the form of sodium fluoride or hydrofluoric acid has a favourable effect both on low plants like algæ and fungi (616) and on cereals and garden plants (41, 42, 43, 44, 95, 662). Plants vary in their behaviour; some are sensitive, others not (810, 313, 323). In field experiments the supplement of 0.1—1 kg. sodium fluoride per hectare usually has a favourable effect; rye seems particularly sensitive, the yield being perceptibly above that of the control areas when 5 kg. sodium fluoride per hectare were added (810). Stimulating effect of fluorspar in field experiments were also observed (12).

There is only little experience from investigations on animals. Schulz and Lamb (721) state that rats on a diet containing 0.05 per cent. sodium fluoride had better growth in an experiment lasting nine months than the controls, though their reproduction was affected. Krasnow and Serle (476) observed that female rats grew better on a diet containing 0.0025 per cent. sodium fluoride than the control rats whose diet contained only traces of fluorine.

The apparently real stimulating effect of small quantities of fluorine, at any rate on the growth and fruit formation of some plants, is scarcely to be regarded as a specific fluorine effect, as similar effects have been observed with other elements.

3. The Action of Fluorine in Physiological Doses

In 1888 Tamman (785) found that the fluorine content was perceptibly greater in the yolk of the hen's egg than in the white and shell. On the basis of this observation he advanced the thought that fluorine especially is contained in the organs which are rich in phosphorus, and that an important physiological rôle may probably be ascribed to fluorine. Gautier (311) has determined the content of fluorine and phosphorus in a number of organs and divides the tissues of the organism into three groups, based upon the phosphorus/fluorine ratio.

(1) *Organs and tissues with particularly lively metabolism.* The quantity of fluorine is low, from 0.5 mg. (musculature) to 8 mg. (medulla) per 100 g. dry substance. The P/F ratio varies between 321 and 776.

(2) *Supporting and connective tissues* have a moderate content of fluorine, from 4.5 mg. (cartilage) to 88 mg. (bone). The P/F ratio is 52—189, average 125.

(3) *Low-metabolizing and non-metabolizing tissues*, skin, hair, nails, etc. are rich in fluorine and contain up to 180 mg. (enamel). The P/F ratio is 3.48—7.5, average 5.7.

In the latter group the P/F ratio approaches that in apatite (4.89), for which reason Gautier considers that fluorine possibly occurs in the organism in this compound, in more or less complete form. He furthermore presents the hypothesis that fluorine has some bearing on the binding of phosphorus in the cell, and that fluorine contributes to the hardness and resistance of certain tissues against chemical influence. As previously mentioned it is possible that fluorine is present in bone in the form of fluorapatite, which in that case must have the form of mixed crystals between hydroxyl- and fluorapatite. There is a similar possibility as regards other tissues. As a matter of fact the foundation

of Gautier's hypothesis is very slender and mainly speculative; there is no confirmation of the analyses he gives. *At present we know of no observation which enables us to form any well-based theory on the action of fluorine under physiological conditions. The once general assumption that fluorine is necessary to the quality of the enamel rests upon an insufficient foundation. Our present knowledge most decidedly indicates that fluorine is not necessary to the quality of that tissue, but that on the contrary the enamel organ is electively sensitive to the deleterious effects of fluorine.*

SUMMARY

The starting-point of the author's investigations lies in Flemming Møller and Gudjonsson's description of the previously unknown fluorine intoxication among workers at a Copenhagen factory, where cryolite is purified and ground, giving off quantities of dust. As fluorine intoxication has not hitherto been thoroughly enquired into, a systematic, critical-synthetic examination is made in Part I of the numerous and little known works concerning *the rôle played by fluorine in biology*. Most importance is attached to the genesis of the various forms of intoxication, as well as to their clinical and patho-anatomical picture. The occurrence of fluorine in inanimate and animate nature is discussed in detail. After explaining *the technique employed in the author's investigations* (Part II), a full account is given in Part III of the results of the author's *studies on human cryolite intoxication* from the point of view of the clinical picture, morbid anatomy and industrial hygiene. A synoptic digest concludes this part. Part IV contains a description of *the author's intoxication experiments* on rats, pigs, calves and dogs, with a concluding summary of the results obtained for each species of animal. In Part V, *Discussion and Conclusions*, the results of the literature studies and the author's investigations are summarized by means of a brief, systematic examination of acute and chronic fluorine intoxication, the possibilities of intoxication, and the prophylactic problems. A final chapter discusses the physiological rôle possibly played by fluorine. The principal conclusions of the work are outlined below.

Occurrence of Fluorine in Nature

As a constant ingredient of eruptive rocks, fluorine is a widely diffused element in inanimate nature. Fluorine in soil, fresh water and sea water comes from that source. Volcanic products may contain fluorine. Deposits of fluorine minerals and rocks occur in the form of fluorspar, cryolite, apatite, phosphorite. Normally, plants and animals absorb small quantities of fluorine according to local factors. It is probable that there are traces of fluorine in all organic tissue. As there is an affinity between fluorine and calcium phosphate, fluorine

is stored particularly in bones and teeth. As a rule bone ash of terrestrial mammals contains $0.1—1\ ^0/_{00}$, tooth ash $0.1—0.4\ ^0/_{00}$ fluorine. Bones and teeth of animals living in the sea contain about ten times as much fluorine. In the teeth fluorine is principally deposited in the dentine, to a lower degree in the enamel.

Effect on Enzymatic Processes and Protoplasm

Fluorine compounds affect a large number of enzymatic processes (e. g. tissue respiration, blood coagulation, lactic acid formation in muscle, the splitting of starch by yeast). Generally the effect is inhibitory, but often a weak concentration of fluorine is stimulating, a stronger one inhibitory. Active fluorine compounds destroy protoplasm and arrest bacterial growth. Yeast cells can become habituated to fluorine compounds. It is doubtful whether the quantity of fluorine absorbed under normal conditions is of any physiological significance. Experimentally, fluorine in quantities below the toxic limit has a stimulating effect on growth processes. It has never been demonstrated, nor is it probable, that fluorine in physiological doses is necessary to or has a beneficial effect on the development of the teeth.

Fluorine Compounds

From a toxicological point of view the fluorine compounds may be divided into four groups: (1) *Gaseous*, hydrogen fluoride (HF), silicon tetrafluoride (SiF_4) and certain organic compounds; (2) *solutions of hydrofluoric acid* (HF) and hydrofluosilicic acid (H_2SiF_6); (3) *relatively easily soluble fluorides* and silico-fluorides; (4) *slowly soluble* compounds, especially cryolite (Na_3AlF_6) and calcium fluoride (CaF_2). The first three groups play a part in acute intoxications, all of them in chronic intoxications.

Acute Intoxication

Acute intoxication manifests itself by a mixture of local irritation or corroding phenomena and symptoms due to absorption. Ingested perorally, fluorine compounds in man produce vomiting, often hæmorrhagic, diffuse abdominal pains, diarrhoea, alternation between painful spasms and pareses, both localized and universal, weakness, thirst, salivation, perspiration, dyspnoea, weak pulse, possibly death. One or more of the symptoms may be absent. Mammals present a similar picture, also under parenteral administration of fluorine. The calcium content of the blood is lowered. On respiration of gaseous fluorine compounds there are irritation symptoms from the mucous membranes of

the eye and air-passage, and more or less pronounced symptoms due to absorption.

In acute intoxication the post-mortem findings are hæmorrhagic gastroenteritis with a tendency to necrosis, acute toxic nephritis, and varying parenchymatous degeneration of the organs. Gaseous compounds cause inflammatory changes in the lungs. *Dosis minima letalis* depends upon the rate of absorption. For the mammals generally used in the laboratory, d.m.l. is 23—90 mg. fluorine per kg. body weight with peroral administration. Man is much more sensitive, 6—9 mg. fluorine per kg. having caused death. As a rule the lethal dose is much higher, about 5—15 g. sodium fluoride. The lethal intoxications mostly have a course of hours only.

Chronic Intoxication

The symptoms depend upon the dose, the time factor, the animal species, the age of the individual, the composition of the diet, and other factors, some of them unknown. The injurious effect of fluorine is especially localized to bones and teeth. The intoxication has three different forms which are capable of various combinations: (1) Degenerative tooth changes; (2) diffuse osteosclerosis; (3) a generalized bone disease accompanied by general symptoms and resembling the classical osteomalacia. The smallest dose that can produce the various forms is uncertain as yet, but seems to rise from (1) to (3).

Dental changes have been observed in man and in many animals. Teeth already calcified are not affected, or only slightly so, by fluorine ingestion. Teeth or parts of teeth calcifying during the period of ingestion display degenerative changes which seem to be pathognomonic. In the lightest degrees the enamel is dull, chalky-white, with yellow, brown or black pigmentation of the areas of the teeth that are exposed to the light. The more severe degrees are characterized by a hypoplastic, low-resistant enamel and dentine. The abnormally heavy wear may cause considerable functional disturbances. The teeth may present abnormities as to size, shape and position. Histologically degenerative changes are observed of the enamel epithelium and formation of a hypoplastic, defectively calcified enamel and dentine. The smallest dose capable of producing just recognizable changes in the rat (under the hand glass) is about 1 mg. fluorine per kg. body weight per day. Man is much more sensitive, as about 0.07 mg. fluorine per kg. daily will cause macroscopic changes. These doses are not accompanied by other known injurious effects on the organism.

Osteosclerosis in man is known as a systemic disease attacking all bones, and

especially the cancellous bones. The X-ray examination reveals increased bone formation from both periosteum and endosteum (narrowed medullary cavity, periosteal deposits). Cancellous bones densify and may give a diffuse, structureless shadow. The osseous ligaments calcify, especially those of the vertebral column. Clinical observations include irregular thickenings of the subcutaneous bone surfaces and reduction of motility in the vertebral column and the thorax. Post-mortem examination shows the bones to be massive, up to three times as heavy as normal bone, and relatively brittle. The surface is uneven, ligaments and joint capsules calcified, but not the cartilage. Microscopical examination reveals abnormally structured osseous tissue and excessive calcium deposition; the calcium salts are partly precipitated in the form of irregular granules. The general condition is not affected, and no definite changes in other organs are observed; the teeth, however, show signs of increased formation of cement and dentine. In man the disease is probably caused by 0.20—0.35 mg. fluorine daily per kg. body weight. The changes appear, however, only after several years of regular fluorine ingestion. In the rat a similar, if not identical, condition can be produced experimentally by administration of fluorine over a period of months.

The *osteomalacic condition* is known to occur in a number of mammals, but not in man. It is a link in a more or less pronounced cachexia, manifested in the form of anorexia, emaciation, anæmia, coarse and untidy coat, and sundry eye changes. Simultaneously there usually are signs of manifest or latent tetany, especially a stiff and laborious gait, a tendency to a reduction of blood calcium and tremor. The osseous system displays varying formation of exostoses, especially on mandible and extremity bones. On necropsy the bones are found to be light and soft, spongiosa and compacta atrophic, but their thickness owing to periosteal deposits is sometimes surprising. Microscopically the disease is characterized by the formation of an abnormally structured osseous tissue and a reduced and irregular calcification of the osteoid tissue, with a tendency towards a granular precipitation of the calcium salts. The pathoanatomical changes are similar to rickets and classical osteomalacia, but cannot be identified with them. The parenchymatous organs, including the bone marrow, display varying degrees of degeneration phenomena, and the kidney also a mostly interstitial, contracting nephritis. The renal effect is not equally great in the various animals. The dose varies, but most frequently is about 15—20 mg. fluorine daily per kg. body weight (growing rats, pigs, dogs). Herbivora seem to be more sensitive. The condition develops and death may occur in the course of weeks or months. An increased calcium requirement (growth, pregnancy, lactation) expedites the development of the intoxication.

Mode of Action of Fluorine

Fluorine is absorbed from the gastro-intestinal tract; gaseous fluorine compounds may be absorbed through the lung. In what form fluorine is absorbed, circulated, stored or excreted is not known. The heaviest storage takes place in the bones and teeth, probably as a mixture of hydroxyl- and fluorapatite. There is no deposition as crystalline calcium fluoride. Fluorine is deposited diffusely in the osseous system, but especially in the cancellous bones. Most probably fluorine can be deposited in preformed enamel. All forms of chronic intoxication have an increased fluorine content in bone and tooth ash (from about 2 to about $30\,^0/_{00}$). As a rule, fluorine in small quantities does not permeate placenta; yet the various species react differently. In woman and the rat fluorine is excreted in the milk.

In relatively large doses fluorine causes a negative calcium balance, presumably by monopolizing the calcium of the organism; calcium fluoride is very slowly soluble. The calcioprive effect of fluorine cannot explain all the symptoms of the intoxication. The osteosclerosis is accompanied by increased mineral deposition, the tooth changes occur at such small doses that direct calcium deficiency is out of the question. Fluorine must be assumed to have a special effect on tissue. The effect on osseous and dental tissue appears universally by (1) the formation of an abnormally structured organic matrix, and (2) a calcification anomaly, whereby the mineral salts of the bone are precipitated irregularly and in discrete granules. Comparatively small doses seem to produce increased growth and increased calcification, comparatively large doses produce mostly atrophic processes and reduced calcification. The osseous effect of fluorine probably is the result of an influence on enzymatic processes connected with the precipitation of the mineral salts, stimulative or inhibitive according to circumstances. It is possible, but not probable, that the effect on the calcium metabolism is exerted *via* the parathyroid glands. Fluorine affects several metabolic processes, and presumably the symptoms of intoxication have a complicated pathogenesis. There is a special relation between vitamin C and fluorine.

Possibilities of Intoxication

Local corrosion phenomena are common in industry. Acute intoxication is particularly often the result of an accident (mistaken identity); suicide and murder are not unknown. In the period from 1873 to 1935 a total of 112 cases of human poisoning were published, 60 of them fatal. Many cases of animal poisoning have been described.

The cases of spontaneous, chronic intoxication all arise from the ingestion of fluorine through the gastro-intestinal tract. Gaseous fluorine compounds may bring about chronic intoxication by absorption through the lung. The known chronic intoxications comprise (1) *mottled teeth*, a dental disease that is endemic in man in certain parts of Europe, America, Africa and Asia; (2) *osteosclerosis**), an occupation disease among cryolite workers in Copenhagen; (3) *osteomalacia*, endemic among herbivora in the vicinity of certain manufacturing plants in Europe; (4) *darmous*, a dental and mandible disease in herbivora in certain parts of North Africa; (5) *gaddur*, a dental and osseous disease among herbivora in Iceland after volcanic eruption.

Greater or smaller possibilities of intoxication are offered by: Drinking water containing more than 1 mg. fluorine per litre; plants cultivated in regions where the soil is especially rich in fluorine; extraction and use of fluoric products in industry; fluoric waste products of factories; fluoric volcanic products. A number of the uses of fluorine compounds are of interest, though they have not caused intoxication so far as is known, i. e. spraying of edible plants with fluorine compounds as insecticides, manuring with fluoric superphosphate, the addition of fluorine compounds to food for preserving purposes, and the therapeutic employment of fluorine compounds.

Prophylaxis

Restriction of the trade in fluorine compounds with the highest acute toxicity. Prohibition against the addition of fluorine compounds to food as preservatives. Maximum limits for the fluorine content in edible plants sprayed with insecticides containing fluorine. Prohibition against the employment of females and young people on work with fluorine compounds developing dust or vapour. Protection and control of workers exposed to the effects of fluorine. Recognition of chronic fluorine intoxication as an occupation disease rating for compensation. Demand that industrial establishments should neutralize waste products containing fluorine. Cessation of the therapeutic use of fluorine compounds for children. Test for fluorine in the routine analysis of drinking water, food, and cases of poisoning with vague ætiology.

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*) Recently, the osteosclerosis has been observed in persons attacked by darmous (763d) and in a man employed in a fertilizer factory, where he had handled rock phosphate containing fluorine (78a).

SAMMENFATNING

Udgangspunktet for forf.s undersøgelser er den af Flemming Møller og Gudjonsson beskrevne, hidtil ukendte, fluorforgiftning hos arbejdere i en københavnsk fabrik, hvor man under støvdannelse renser og formaler kryolit. Da fluorforgiftningen ikke tidligere har været genstand for en omfattende undersøgelse foretages i Afsnit I en systematisk, kritisk-syntetisk gennemgang af de i literaturen foreliggende talrige og lidet kendte arbejder vedrørende *fluors rolle i biologien.* Hovedvægten lægges paa en undersøgelse af de forskellige forgiftningsformers genese og deres kliniske og patologisk-anatomiske billede. Fluors forekomst i den livløse og levende natur behandles indgaaende. Efter omtale af *teknikken ved egne undersøgelser* (Afsnit II) gives i Afsnit III en detaljeret redegørelse for resultaterne af forf.s kliniske, patologisk-anatomiske og erhvervshygiejniske *studier over den humane kryolitforgiftning.* En sammenfattende oversigt afslutter dette afsnit. I Afsnit IV beskrives *forf.s intoksikationsforsøg* med rotter, svin, kalve og hunde, idet der for hver dyreart gives en afsluttende oversigt over de opnaaede resultater. I Afsnit V *Diskussion og konklusioner* sammenfattes resultaterne af literaturstudierne og forf.s undersøgelser ved en kortfattet systematisk gennemgang af den akute og kroniske fluorforgiftning, forgiftningsmulighederne og de profylaktiske problemer. Fluors mulige fysiologiske rolle behandles i et afsluttende kapitel. Nedenfor gøres rede for de vigtigste konklusioner, der fremgaar af arbejdet.

Fluors forekomst i naturen

Som en konstant bestanddel af eruptive bjærgarter er fluor et udbredt element i den livløse natur. Fra denne kilde stammer fluor i jordbund, ferskvand og havvand. Vulkanske produkter kan indeholde fluor. Aflejringer af fluorholdige mineraler og bjærgarter forekommer som flusspat, kryolit, apatit og fosforit. Planter og dyr optager normalt smaa mængder fluor, afhængig af lokale faktorer. Spor af fluor findes sandsynligvis i alt organisk væv. Da der bestaar en affinitet mellem fluor og calciumfosfat, aflejres fluor navnlig i knogler og tænder. Som regel indeholder knogleaske af landpattedyr $0,1—1\ ^0/_{00},$

tandaske 0,1—0,4 °/$_{00}$ fluor. Knogler og tænder af dyr, der lever i havet, indeholder omkring 10 gange saa meget fluor. I tænderne aflejres fluor fortrinsvis i dentin, i ringere grad i emalje.

Virkning paa enzymatiske processer og protoplasma

Fluorforbindelser paavirker en mængde enzymatiske processer (bl. a. vævsrespirationen, blodets koagulation, mælkesyredannelsen i musklen, gærens spaltning af stivelse). Virkningen er som regel hæmmende, men ofte har en svag koncentration af fluor stimulerende, en stærkere hæmmende effekt. Aktive fluorforbindelser destruerer protoplasma og hæmmer bakterievækst. Gærceller har tilvænningsevne overfor fluorforbindelser. Det er tvivlsomt, om den under normale forhold optagne fluormængde har fysiologisk betydning. Eksperimentelt har fluor stimulerende virkning paa vækstprocesser i mængder, der ligger under den toksiske grænse. Det er aldrig paavist og ikke sandsynligt, at fluor i fysiologiske doser skulde være nødvendig for eller have gavnlig virkning paa tanddannelsen.

Fluorforbindelser

Fra et toksikologisk synspunkt kan fluorforbindelserne deles i fire grupper: (1) *Luftformige*, fluorbrinte (HF), siliciumtetrafluorid (SiF_4) og visse organiske forbindelser; (2) *opløsninger af flussyre* (HF) og kieselflussyre (H_2SiF_6); (3) *relativt letopløselige fluorider* og silikofluorider; (4) *tungtopløselige forbindelser*, navnlig kryolit (Na_3AlF_6) og calciumfluorid (CaF_2). De tre førstnævnte grupper spiller en rolle ved akute forgiftninger, alle ved kroniske.

Akut forgiftning

Den akute forgiftning viser sig ved en blanding af lokale irritations- eller ætsfænomener og resorptive symptomer. Indtaget per os fremkalder fluorforbindelser hos mennesket opkastninger, ofte blodige, diffuse abdominalsmærter, diarré, vekslen mellem smærtefulde kramper og lammelser, baade lokaliserede og universelle, svaghed, tørst, spytflod, sved, dyspnoe, pulssvækkelse, evt. mors. Flere eller færre symptomer kan mangle. Pattedyr viser et lignende billede, ogsaa ved parenteral indgift af fluor. Blodets calciumindhold nedsættes. Ved respiration af luftformige fluorforbindelser iagttages irritationssymptomer fra øjets og luftvejenes slimhinder og mere eller mindre udtalte resorptive symptomer.

Post mortem findes ved akut forgiftning hæmorrhagisk gastroenteritis med tendens til nekrosedannelse, akut toksisk nefritis og varierende parenkymatøs

degeneration af organerne. Luftformige forbindelser fremkalder betændelses-
forandringer i lungerne. Dosis minima letalis afhænger af den hastighed, hvor-
med fluor resorberes. For de almindeligt i laboratoriet anvendte pattedyr er
d. m. l. 23—90 mg fluor per kg legemsvægt ved peroral indgift. Mennesket er
langt mere følsomt, idet 6—9 mg fluor per kg har fremkaldt mors. Som regel
ligger dødelig dosis væsentligt højere (omkring 5—15 g natriumfluorid). De
dødelige forgiftninger forløber oftest i løbet af timer.

Kronisk forgiftning

Symptomerne afhænger af dosis, indgiftens varighed, dyrearten, individets
alder, fødens sammensætning og andre, tildels ukendte, forhold. Fluors skade-
lige virkning er navnlig lokaliseret til knogler og tænder. Forgiftningen viser
tre forskellige former, der kan kombineres paa forskellig maade: (1) Degene-
rative tandforandringer; (2) diffus osteosklerose; (3) en af almensymptomer
ledsaget diffus knoglelidelse, der ligner den klassiske osteomalaci. Den mindste
dosis, der kan fremkalde de forskellige former, er endnu ret usikker, men synes
at være stigende fra (1) til (3).

Tandforandringerne er iagttaget hos mennesket og mange dyrearter. Færdig-
forkalkede tænder paavirkes ikke eller kun i ringe grad af fluorindgift. Tænder
eller tandafsnit, der forkalker under fluorindgiften, viser degenerative for-
andringer, der synes at være patognomoniske. Ved de letteste grader er emaljen
uklar, kridtagtig hvid med gul, brun eller sort pigmentering af de for lyset
udsatte partier af tænderne. De sværere grader karakteriseres ved hypoplastisk,
lidet resistent emalje og dentin. Det abnormt stærke slid kan foraarsage be-
tydelige funktionsforstyrrelser. Tænderne kan vise abnormiteter i størrelse,
form og stilling. Histologisk iagttages degenerative forandringer af emalje-
epithelet og lagformet aflejring af hypoplastisk, mangelfuldt forkalket emalje
og dentin. Den mindste daglige dosis fluor, der hos rotten kan fremkalde netop
erkendelige forandringer (lup), er ca. 1 mg fluor per kg legemsvægt. Mennesket
er langt følsommere, idet ca. 0,07 mg fluor per kg daglig kan give makrosko-
piske forandringer. Disse doser ledsages ikke af anden kendt skadelig paavirk-
ning af organismen.

Osteosklerosen kendes hos mennesket som en systemsygdom, der angriber alle
knogler, men navnlig de spongiøse. Paa røntgenpladen iagttages forøget knogle-
produktion, saavel fra periost som endost (forsnævrede marvrum, periostale
aflejringer). Spongiøse knogler fortættes og kan give en diffus, strukturløs skygge.
De ossøse ligamenter forkalker, navnlig i columna. Klinisk iagttages uregelmæs-
sig fortykkelse af subkutane knogleflader og indskrænkning af bevægeligheden

i columna og thorax. Knoglerne viser sig ved post-mortem undersøgelse plumpe, indtil tre gange saa tunge som normalt og relativt skøre. Overfladen er ujævn, ligamenter og ledkapsler forkalkede, men ikke brusken. Mikroskopisk undersøgelse viser et abnormt struktureret knoglevæv og en excessiv kalkaflejring; kalken udfældes tildels som uregelmæssige klumper og korn. Almentilstanden er ikke paavirket, og der iagttages ingen sikre forandringer af andre organer; tænderne viser dog tegn paa forøget dannelse af cement og dentin. Lidelsen fremkaldes hos mennesket sandsynligvis ved en daglig optagelse af 0,20—0,35 mg fluor per kg legemsvægt. Forandringerne udvikles dog først efter flere aars regelmæssig fluoroptagelse. Hos rotten kan eksperimentelt fremkaldes en lignende, om ikke identisk, tilstand ved maaneders indgift af fluor.

Den *osteomalaciske tilstand* kendes hos en række pattedyr, men ikke hos mennesket. Den er led i en mere eller mindre udtalt kakeksi, der viser sig ved anorexi, afmagring, anæmi, groft og sjusket haarlag samt diverse øjenforandringer. Samtidig iagttages som regel tegn paa latent eller manifest tetani, nemlig stiv og besværet gang, tendens til nedsættelse af blodcalcium og tremor. Knoglesystemet viser varierende exostosedannelse, navnlig paa mandibel og ekstremitetsknogler. Ved sektionen er knoglerne lette og bløde, spongiosa og compacta atrofisk, men knoglerne kan imponere som fortykkede paa grund af periostale aflejringer. Mikroskopisk er knoglelidelsen karakteriseret ved dannelsen af et abnormt struktureret knoglevæv og en nedsat og uregelmæssig forkalkning af det osteoide væv, med tilbøjelighed til kornet udfældning af kalken. Patologisk-anatomisk minder forandringerne om rakitis og klassisk osteomalaci, men kan dog ikke identificeres med disse. De parenkymatøse organer, inklusive knoglemarven, viser varierende grad af degenerationsfænomener, nyren tillige en overvejende interstitiel, skrumpende nefritis. Nyrevirkningen er ulige stærk hos de forskellige dyrearter. Dosis varierer, men er oftest omkring 15—20 mg fluor per kg daglig (voksende rotter, svin, hunde). Planteædere synes særlig følsomme. Tilstanden udvikles, og mors kan indtræde i løbet af uger eller maaneder. Et forøget kalkbehov (vækst, graviditet, laktation) fremskynder forgiftningens udvikling.

Fluors virkemaade

Fluor resorberes fra mave-tarmkanalen; luftformige fluorforbindelser kan resorberes gennem lungen. Det vides ikke, i hvilken form fluor resorberes, circulerer, aflejres eller udskilles. Den største aflejring sker i knogler og tænder, sandsynligvis som en blanding af hydroksyl- og fluorapatit. Aflejring som krystallinsk calciumfluorid finder ikke sted. Fluor aflejres diffust i knoglesystemet,

men navnlig i de spongiøse knogler. Fluor kan sandsynligvis aflejres i færdig-
dannet emalje. Alle former af kronisk forgiftning viser forhøjet indhold af
fluor i knogle- og tandaske (fra ca. 2 til ca. 30 $^0/_{00}$). Fluor passerer som regel
ikke placenta i smaa mængder; de forskellige dyrearter forholder sig dog for-
skelligt. Hos kvinden og rotten udskilles fluor i mælken.

I relativt store doser fremkalder fluor en negativ calciumbalance, formentlig
ved at beslaglægge organismens calcium; calciumfluorid er meget tungtopløse-
ligt. Fluors calcioprive virkning kan ikke forklare alle forgiftningens symptomer.
Osteosklerosen ledsages af forøget mineralaflejring, tandforandringerne frem-
kommer ved saa smaa doser, at en direkte kalkmangel er udelukket. Fluor maa
antages at have en særlig vævseffekt. Virkningen paa knogle- og tandvæv viser
sig generelt ved (1) dannelsen af en abnormt struktureret organisk matrix og
(2) en forkalkningsanomali, hvorved knoglens mineralsalte udfældes uregel-
mæssigt og i diskrete korn og klumper. Relativt smaa doser synes at fremkalde
forøget vækst og forøget forkalkning, relativt store doser overvejende atrofiske
processer og nedsat forkalkning. Fluors knoglevirkning beror rimeligvis paa
en paavirkning af de enzymatiske processer knyttet til mineralsaltenes ud-
fældning, efter omstændighederne stimulerende eller hæmmende. Det er mu-
ligt, men ikke sandsynligt, at virkningen paa kalkstofskiftet udøves via glan-
dulae parathyreoideae. Fluor paavirker adskillige stofskifteprocesser, og for-
giftningssymptomerne har formentlig en kompliceret patogenese. Mellem vita-
min C og fluor bestaar en særlig relation.

Forgiftningsmuligheder

Lokale ætsfænomener er hyppige i industrien. Den akute forgiftning opstaar
navnlig ved ulykkestilfælde (forveksling); ogsaa selvmord og mord kendes.
I tidsrummet 1873—1935 offentliggjordes 112 humane forgiftningstilfælde,
heraf 60 dødelige. Adskillige forgiftninger af dyr er beskrevet.

De spontane, kroniske forgiftninger opstaar alle ved optagelse af fluor gennem
mave-tarmkanalen. Luftformige fluorforbindelser kan fremkalde kronisk for-
giftning ved resorption gennem lungen. De kendte spontane kroniske forgift-
ninger omfatter (1) *mottled teeth*, en tandsygdom, der er endemisk hos menne-
sket visse steder i Europa, Amerika, Afrika og Asien; (2) *osteosklerose**), erhvervs-
sygdom hos kryolitarbejdere i København; (3) *osteomalaci*, endemisk hos plante-
ædere i omegnen af diverse fabriker i Europa; (4) *darmous*, en tand- og kæbe-
sygdom hos planteædere i visse egne i Nordafrika; (5) *gaddur*, en tand- og
knoglelidelse hos planteædere i Island efter vulkanudbrud.

*) Fornylig er osteosklerosen iagttaget hos personer lidende af darmous (763 d) og hos en
mand, beskæftiget med fremstilling af gødning af fluorholdig fosforit (78 a).

Større eller mindre mulighed for forgiftning yder: Drikkevand, der inde-
holder mere end 1 mg fluor per liter; planter, dyrket i egne, hvor jorden er
særlig rig paa fluor; udvinding og anvendelse af fluorholdige produkter i
industrien; fluorholdige affaldsprodukter fra fabriker; fluorholdige vulkanske
produkter. En række anvendelser af fluorforbindelser er af interesse, uden at
de dog, saavidt vides, har foraarsaget forgiftning, nemlig sprøjtebehandling af
spiselige planter med fluorforbindelser mod parasiter, gødning med fluor-
holdig superfosfat, tilsætning af fluorforbindelser til levnedsmidler i konser-
verende øjemed og terapeutisk anvendelse af fluorforbindelser.

Profylakse

Indskrænkning af den frie handel med de fluorforbindelser, der har størst
akut toksicitet. Forbud mod tilsætning af fluorforbindelser til levnedsmidler
i konserverende øjemed. Maksimalgrænse for indhold af fluor i spiselige plante-
dele, behandlet med fluorholdige sprøjtemidler. Forbud mod anvendelse af
kvinder og mindreaarige ved arbejde med fluorforbindelser, der udvikler støv
eller dampe. Beskyttelse af og kontrol med arbejdere, der udsættes for fluor-
paavirkning. Anerkendelse af den kroniske fluorforgiftning som erstatnings-
pligtig erhvervssygdom. Krav til industrielle virksomheder om at uskadelig-
gøre fluorholdige affaldsprodukter. Ophør med terapeutisk anvendelse af
fluorforbindelser til børn. Undersøgelse for fluor ved den rutinemæssige ana-
lyse af drikkevand, levnedsmidler og forgiftningstilfælde med uklar ætiologi.

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