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On the eosinophilic bone granuloma with regard to localization in jaws and relation to general histiocytosis.

By

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As far as we were able to ascertain, the disease to be described in detail in this paper has not been previously discussed in the Scandinavian dental literature. The further reason for this article is that the conception of the eosinophilic bone granuloma has decisively changed, since the first cases were published. Nowadays it is believed that the question is not of an independent, localized disease, but of a disease being part of a more general affection of the reticulo-endothelial system (a *histiocytosis*). Therefore, we think it of interest to discuss three cases showing the different phases of this disease in the jaws and examine whether the pathogenesis set up on basis of processes in other organs and tissues does also apply to the manifestations of the disease in the jaws.

I. History and terminology.

This disease called "eosinophilic granuloma of bone" (LICHTENSTEIN and JAFFE, 1940) and later on dealt with in a considerable number of publications was first mentioned by TARATYNOW in 1914. Cases of this bone disease were published under different terms during the intermediary period. FINZI, 1929, mentions "an eosinophilic myeloma"; MIGNON, 1930, "a tumor of granulation tissue"; BENEKE and STIEDA, 1930, "a giant-cell myeloid sarcoma"; SCHAIRER, 1938, 1944, "an osteomyelitis with eosino-

philic reaction"; and OTANI and EHRLICH, 1940, "a solitary bone granuloma". After 1940 several authors have not been satisfied with the designation proposed by LICHTENSTEIN and JAFFE and have for that reason made other propositions: BECK, 1943, prefers the expression of "a benign, giant-cell containing reticuloma of bone marrow with eosinophilia"; ŠKORPIL, 1946, "a histiocytic-eosinophilic bone granuloma"; and HELD and RUTISHAUSER, 1948, the designation of "benign histiocytic-eosinophilic granulomatosis". Most interesting is FRISCHKNECHT's conception (1949) of the disease as being an isolated tumor of bone marrow ("eosinophilic reticuloma of bone marrow") like *e. g.* the chlorome. In the second edition of his book of "Lipidoses" THANNHAUSER designates eosinophilic granuloma, Schüller-Christian's syndrome, and essential xanthomatosis of the normo-cholesterinemic type as being "eosinophilic xanthomatous granuloma".

II. Occurrence and clinic.

Although the eosinophilic bone granuloma may occur in multiple forms it is generally seen as a solitary lesion. The bones most frequently attacked are the flat bones of the skull (at least half of all the cases according to CAMPBELL and ALEXANDER, 1944), ribs and pelvis. However, other bones of the skeleton may also be attacked by the disease. In the long bones as in tumors and osteomyelitis it usually effects the metaphysis. Although cases have been found in people up to 78 years, the eosinophilic bone granuloma appears mainly in individuals during the first two decades of life. There seems to be no doubt that males are attacked more frequently than females, although among others, HAMILTON et al., 1946, have collected their material among soldiers and in this way made an evaluation of the proportion according to sex difficult.

The eosinophilic bone granuloma may occur without symptoms, but usually the affected bone shows swelling and tenderness to pressure. At localization in the skull, pressure from the eosinophilic bone granuloma may cause pronounced neurologic symptoms (CABOT case 28481, 1942, and OSBORNE et al., 1944). As far as ordinary symptoms are concerned a slight fever, anorexia, and migraine may be noticed, and sometimes the patients are fatigued. Macroscopically the contents from the bone defects are like gran-

ulation tissue; and according to the amount of blood and fat present may have a reddish, yellowish, reddish-brown, or greyish color. Apart from an occasionally slight leucocytosis and eosinophilia the laboratory findings show no deviations from the normal, especially, no increase of the serum-cholesterol values is noticeable. In several cases bacteriologic culture from eosinophilic bone granulomas has been undertaken, but with no positive result.

III. Roentgenologic findings.

On the roentgenograms the eosinophilic bone granulomas appear as round, oval, or irregular areas of radiolucency resembling those seen in cysts. On rare occasions sclerosis of the periphery of the lesions may be seen; more often on account of the extended growth periosteal regeneration of bone may be noticed. If the periosteal apposition is too slight or absent, spontaneous fractures may occur. The lesions, ordinarily with a diameter of 1—4 cm, are of varying sizes.

The eosinophilic bone granuloma may progress very rapidly. SALOMON and ENGELSHER (1946) reported a case in which there was a 50 per cent increase in the size of the granuloma within 10 days, and in CABOT case 28481, 1942, a defect of 2 × 3 cm in the frontal bone developed in 9 weeks (see also BAKER et al., 1948).

As far as the roentgenologic differential diagnosis is concerned, conditions as myeloma, meningeoma, cysts, osteomyelitis, osteitis, osteogenic sarcoma, Ewing's tumor, giant-cell tumor, tumor metastasis, and certain of the lipoidoses have been mentioned. Several of these diseases cannot be separated from the eosinophilic bone granuloma roentgenologically; a histologic examination is necessary for a correct diagnosis.

IV. Histologic findings.

The eosinophilic bone granuloma is characterized histologically by a highly vascular tissue containing a reticulum of large pale-stained cells, 10—20 μ long (histiocytes). The nucleus contains a slight amount of chromatin and may be either oval, kidney-shaped, lobed and sometimes vacuolized. In some cases it may be noticed that the cells have absorbed lipoid material (foam cells) and fragments of eosinophilic cells together with pigment

from degenerated erythrocytes. In sections impregnated with silver a rather dense net of reticular fibers can be seen, in the meshes of which there are partly single, partly groups of histiocytes (BECK, 1943, and ŠKORPIL, 1946). Scattered around in the tissue numerous eosinophilic leucocytes are noticeable often in such dense infiltrations that the picture looks like an abscess. OSBORNE et al., 1940, and DUNDON et al., 1946, have pointed out that eosinophilic myelocytes may also be present. The presence of neutrophil leucocytes, lymphocytes, and plasma-cells is more scarce. Generally, in the eosinophilic bone granuloma giant-cells may be noticed, the genesis of which has caused rather diverging points of view. LICHTENSTEIN and JAFFE, 1940 BECK, 1943, and KERNWEIN and QUEEN, 1943, are of the opinion that the giant-cells have been produced by fusion of the proliferating histiocytes, and that they phagocytose the eosinophilic leucocytes. In contradiction OTANI and EHRLICH, 1940; GREENBERG and SCHEIN, 1945; and SALOMON and ENGELSHER, 1946, think that the giant-cells are of the osteoclastic type. SCHAIRER, 1944, distinguishes two forms of giant-cells: one is like osteoclasts, and the other is characterized by the fact that the histiocytes have phagocytosed so many eosinophilic leucocytes that they look like giant-cells. Occasional necrosis and fibrosis may be mentioned as another histologic feature of the eosinophilic bone granuloma.

FRISCHKNECHT, 1949, has shown transitions between the reticulum cells (histiocytes) and phagocyting macrophages and lipophages. He has also shown — like ŠKORPIL, 1946, — that Charcot-Leyden crystals, probably originating from decomposed eosinophilic leucocytes, are phagocytosed; a condition that best can be seen in a phase contrast microscope.

The varying findings of histiocytes, foam cells, eosinophilic leucocytes, giant-cells, necrosis and fibrosis "represent different stages of the granulomatous process". This conception has been elaborated by DUNDON et al., 1946, who distinguishes three stages in the eosinophilic bone granuloma. In *the first stage* necrotic foci and bleeding, histiocytes, eosinophilic leucocytes, lymphocytes, plasma cells, neutrophilic leucocytes, and phagocytic multinucleated giant-cells, can be seen. In *the intermediary stage* mononuclear cells (the histiocytes) become vacuolized (foam cells) and the eosinophilic cells become more scarce. In *the final stage* proliferation of connective tissue and bone regeneration, if any, are to be observed.

As far as the histologic differential diagnosis is concerned tuberculosis, lipogranulomatosis, Ewing's tumor, and eosinophilic leukemia have been mentioned.

V. Cutaneous and visceral complications.

In 1923 MARTINOTTI described some cases of eosinophilic granulomas in the skin. Later on this disease was discussed in American dermatologic literature in detail. In his paper on histiocytic-eosinophilic bone granulomas ŠKORPIL, 1946, mentions two cases of eosinophilic skin granulomas without simultaneous bone lesions. Cases where both the skeleton and the skin were affected, have been mentioned by CURTIS and CAWLEY, 1947; LAYMON and SEVENANTS, 1948; MCCREARY, 1948; WENTHOLT and HADDERS, 1949; PINKUS et al., 1949; and LEVER and LEEPER, 1950. The characteristic of these cases is occurrence in small children and improvement or healing after radio treatment. There seems to be a qualitative difference between eosinophilic skin granulomas with osseous manifestation and those without bone lesions. In the former the disease is localized in the face and there is a marked resistance to X-ray treatment. The eosinophilic skin granulomas associated with bone defects in their histologic picture are similar to the eosinophilic bone granuloma, but differ from it clinically. The simultaneous appearance of skin affections in certain cases of eosinophilic bone granuloma does also prove the close connection of this disease with Letterer-Siwe's and Schüller-Christian's diseases. At the two last-mentioned conditions skin affections are often noticed, and BJERRE HANSEN, 1949, has described identical histological conditions in skin and bone lesions of a case that represents third phase according to ENGELBRETH-HOLM, TEILUM and CHRISTENSEN, 1944.

Besides cutaneous complications certain viscera may also be affected (HENSCHEN, 1943; ŠKORPIL, 1946; ACKERMAN, 1947; GILBERT and VOLUTER, 1947; WEINSTEIN et al., 1947; and KRUGER et al., 1949).

VI. Etiology and treatment.

The etiology of the eosinophilic bone granuloma is not known. Trauma has been mentioned as being the cause of many cases, but this assertion has not yet been proved. Nevertheless, it is the

opinion that in certain cases trauma has been the contributory factor. Some have mentioned an infection as being the cause and several bacteriologic cultivations from eosinophilic bone granuloma have been undertaken, but in all cases the results have been negative. A virus could be a possible cause. If a connection between eosinophilic bone granuloma and certain general histiocytes is taken for granted, the question of the etiology of the eosinophilic bone granuloma must be considered from quite another point of view.

As mentioned before, several authors (FINZI, 1929; BENEKE and STIEDA, 1930; BECK, 1943; and FRISCHKNECHT, 1949) consider the eosinophilic bone granuloma as being a tumor.

The prognosis of the eosinophilic bone granuloma — especially as far as the solitary form is concerned — is good. Healing without treatment has been reported. Generally curettage or radiologic treatment or both are undertaken. In case of pains, the treatment (irradiation) will give immediate relief. Complete healing of bone defects after radiologic treatment has been observed after 5—9 months.

VII. The occurrence of the eosinophilic bone granuloma in the jaws.

A. Previous cases.

Since there are intermediary forms between the eosinophilic bone granuloma and Schüller-Christian's disease, only clear cut cases of eosinophilic bone granuloma are included in table 1.

As shown in table 1 24 cases of eosinophilic bone granuloma in the jaws have been published. The eosinophilic bone granuloma occurs most frequently in the mandible (17 cases) and in the maxilla only in connection with attacks in the mandible (7 cases). Multiple attacks have occurred in 12 cases. Males are most often affected and average age in 24 reported cases was 26 years.

In several cases it has been the localization in the jaws that has lead to the diagnosis of eosinophilic bone granuloma. Unlike most skull defects the eosinophilic jaw bone granuloma shows symptoms at an early stage. There are the loosening of teeth, swelling or recession of gingiva together with poor healing of alveolus after extraction. On basis of these symptoms a paradentosis or periodontitis is as a rule the diagnosis, but a radiologic examination will

Table 1.

Tabulation of previously published cases of eosinophilic bone granuloma localized to the jaws.

Author	Year	Sex	Age in year	Eosinophilic bone granuloma in mandible	Eosinophilic bone granuloma in maxilla	Other bones attacked	Comments
Wassmund and Anders...	1932	♂	31	+			
			32	+	+		Eosinophilic granuloma in both auditory channels
			78	+			
Henschen	1943	♂	24	+			
Bailey and Freis	1944	♂	21	+	+	+	Some cases as Osborne et al. 1944
Hamilton et alii	1946	♂	21	+		+	
Cox	1946	♂	28	+		+	
		♂	20	+		+	
Škorpil	1946	♂	3 3/12	+			Foci in pulpa
		♂	36	+		+	
Goldin	1947	♂	25	+			
Mezl and Škorpil	1947	♂	19	+			Foci in pulpa
Gilbert and Voluter	1947	♂	20	+		+	
Weinstein et alii	1947	♂	31	+		+	
Kauffman	1948	♂	3 3/12	+		+	
Conran	1948	♂	17	+			
Held and Rutishauser...	1948	♂	26	+	+	+	
		♂	30	+	+	+	
Schroff	1948	♂	31	+	+		Anal fistel with eosinophilic granulomatous reaction
Kruger et alii	1949	♂	25	+	+	+	
Grupe and Orban	1950	♀	26	+	+		Ear complication
Brody and Gillespie	1951	♂	24	+		+	
Nanta and Charoubeau ..	1951	♂	28			+	
Holst, Husted and Pindborg	1951	♂	14	+			

reveal that the destructive process is more extensive than in the periodontal disease. The disease commences at first in the bone marrow of the jaws, and thereupon it attacks the osseous part of the paradentium, which soon is completely destroyed. The sizes of the granulomas may vary; sometimes most of the mandible is affected. According to the literature the eosinophilic bone granuloma in the jaws may appear differently in the roentgenograms; some assert that it may be mistaken for dental cysts,

while others (SONESSON, 1950), state that there is no difficulty in distinguishing one condition from the other; the question may however be of mistaking eosinophilic bone granuloma for osteitis or malignant tumors.

The histologic structure of the eosinophilic bone granulomas in the jaws does not deviate from the histopathology of the other bone lesions. As mentioned above the pathologic process commences in the bone marrow and thereafter it attacks — secondarily — the paradental tissue. WASSMUND and ANDERS, 1932, gave the most detailed description of the dissemination of the eosinophilic granulation tissue in the paradental tissue; gradually the periodontium is replaced completely by the granulation tissue and on the roots more or less clear resorptions are noticeable. WASSMUND and ANDERS think that when speaking about the pathology of the eosinophilic bone granuloma, the question is of unspecific inflamed resorption tumors being close to the brown tumors of fibrous dystrophia considered from a biologic point of view. Moreover, they consider it possible that the pulp can be attacked by contiguity. However, it was ŠKORPIL, 1946, and MEŽL and ŠKORPIL, 1947, who first proved the occurrence of the eosinophilic bone granuloma in the pulp in the form of small foci. Moreover, a description of the histopathology of the paradental tissue at the eosinophilic bone granuloma has been given by HELD and RUTISHAUSER, 1948.

B. Personal observations.

1. First case.

A 14-year-old boy who previously had no diseases of any significance. The present disease started three weeks before the hospitalization, when the patient felt shooting pains localized to the left side of the ramus. Consulted a dentist who ascertained in the X-ray picture a radiolucency in the jaw.

At hospitalization the pains were decreasing, but after three days they recommenced, and simultaneously a pronounced swelling in connection with the lower border of the mandible was noticeable. The swelling was painful to palpation; intra-orally no swelling or pain could be seen. Below the lower border of the mandible a painful lymph node could be palpated.

a. *Radiographic Examination* showed a well defined radiolucent area in the region of the mandibular angle on the left side (Fig. 1). It extended upwards into the ramus and downward to the lower border

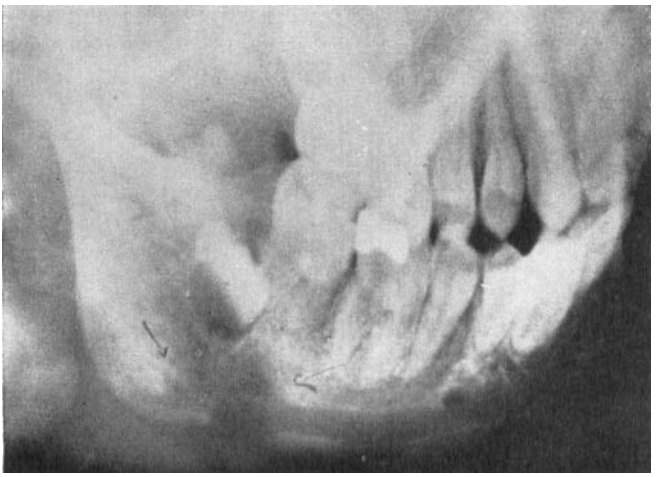

Fig. 1. Case 1. Roentgenogram of the left side of the mandible. Note radiolucent area.

of the mandible. This area of radiolucency was not related to the teeth.

b. *Laboratory Examinations.* Hemoglobin 111 per cent, leucocytes 10,100; differential counting: lymphocytes 24 per cent, monocytes 1 per cent, neutrophilic leucocytes 67 per cent, eosinophilic 7 per cent. Sedimentation rate: 8 mm; serum calcium: 10.3 mg per cent; serum cholesterol: 153 mg per cent.

c. *Operation.* As the diagnosis was uncertain, the mass was removed. In accordance with the roentgenogram, a lesion the size of a hazel-nut was found a few cm in front of the mandibular angle. The compacta on the outer surface and lower border of the mandible had been destroyed. The cavity was well defined, round, with smooth walls, and was filled with a solid tissue which was more firm than ordinary granulation tissue; it was greyish with scattered reddish parts. Pus could not be seen. The cavity was well scraped. The socket healed without complications.

d. *Histologic Examination* (Fig. 2). "The tissue is of a somewhat varying compactness; especially at the very edge it is fibrous in a rather compact way. At other areas it is loose and relatively scarce. The cells have round or oval, rather homogeneous nuclei with one or two medium size nucleoli. Especially in the more open parts a heavy infiltration of eosinophilic leucocytes with polymorphic nuclei are seen. Scattered around in the tissue also big cells with up to a dozen nuclei are noticed varying only a little in size and content of chromatine. At several spots bleedings can be observed, and sometimes an accumulation of blood pigment in the cells is noticeable. No necrotic processes or significance of malignancy are observable. Histologic diagnosis: *eosinophilic*

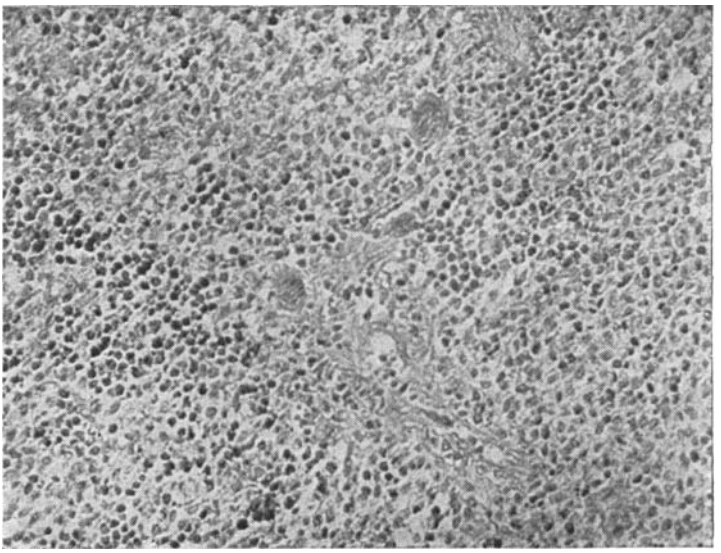

Fig. 2. Case 2. Photomicrograph of tissue from the cavity shown in Fig. 1. Note the predominance of eosinophilic leucocytes among the bright histiocytes. Original magnification: 10 × 12.

granuloma" (signed Dr. V. ESKELUND). By a clinical and roentgenographic control examination 4 years later completely normal conditions were recorded. Discussion of this case is postponed till later when the two other cases will be discussed in detail.

VIII. The connection between the eosinophilic bone granuloma and the diseases of Schüller-Christian and Letterer-Siwe.

Already in 1941 — only a year after LICHTENSTEIN and JAFFE used the term "eosinophilic granuloma of bone" — FARBER asserted that the eosinophilic bone granuloma, and the diseases of Letterer-Siwe and Schüller-Christian "represent variations in degree, stage of involvement and localization of the same basic disease process" (more detailed by GREEN and FARBER, 1942). GROSS and JACOX, 1942, expressed more definitely that an eosinophilic bone granuloma "is probably identical with what has been recognized as instances of Hand-Schüller-Christian's disease in which the bone lesions are solitary". MALLORY, 1942, and AHLSTRÖM and WELIN, 1943, likewise pointed out that there

must be a connection between the three diseases, but, however, it was ENGELBRETH-HOLM, TEILUM, and CHRISTENSEN 1944, who proved that the question is of one basic disease. Before a detailed statement of this argument the diseases of Schüller-Christian and Letterer-Siwe will be mentioned briefly.

a. *Schüller-Christian's disease* (sometimes also called Hand-Schüller-Christian or lipoid granulomatosis) occurs most often in children and is characterized by the triad: exophthalmus, diabetes insipidus, and multiple bone lesions, especially in the skull, where the well defined defects like cysts have caused the expression of "map-skull". The triad need not occur in all cases of the disease, and as other typical symptoms anemia, skin lesions, splenomegaly, infiltrations in the lungs, and flood of pus from the ears may be mentioned. The mortality is about 60 per cent. The bone defects are filled up with yellowish granulation tissue in which numerous xanthom cells containing cholesterol, histiocytes, and collagenous connective tissue are noticeable. More seldom eosinophilic leucocytes with polymorphic nuclei can be seen.

b. *Letterer-Siwe's disease* (also called reticulo-endotheliosis or non-lipoid histiocytosis) attacks children under two years and is often acute with a fatal issue. The symptoms are: fever, anemia, cutaneous eruptions, hemorrhagic diathesis, destructive bone lesions (especially in the skull), enlargement of spleen, liver, and lymph nodes. Histologically a marked proliferation of histiocytic elements in the organs attacked can be seen, and silver impregnation shows increase of the reticulum.

On basis of five cases showing a gradual transition from solitary eosinophilic bone granuloma to fully developed Schüller-Christian's syndroma, ENGELBRETH-HOLM, TEILUM and CHRISTENSEN, 1944, state that "the concept of 'eosinophilic granuloma' may hardly be maintained as a nosological entity but has to be taken as a not altogether infrequent, clinically monosymptomatic form of Schüller's disease, which most often heals without becoming generalized, while in rare cases it is generalized and then often accompanied by other classical symptoms from the triad characteristic of Schüller-Christian's disease". With the histopathologic changes as a basis four histogenetic phases are stated: 1: a hyperplastic proliferative phase with more or less diffuse reticulohistiocytic proliferation (corresponds to Letterer-Siwe's disease); 2: a granulomatous phase where, besides newly formed capillaries and collagen fibrils as basic element, also histiocytes can be ob-

served among which numerous eosinophilic leucocytes with polymorph nuclei; also giant-cells can be seen, both Touton cells and osteoclastic cells, together with a commencing phagocytosis of lipoid and hemosiderin (this phase corresponding to the eosinophilic bone granuloma and certain cases of Schüller-Christian's disease); 3: a xanthomatous phase (corresponding to most instances of Schüller-Christian), and 4: a fibrous, reparative phase. Of course the transitions between the different phases are vague.

Until 1935 Schüller-Christian's disease was taken as a primary lipoidosis, but actually the opinion is that the primary feature is a proliferation of the reticulo-endothelial cells, in which secondarily a deposit of cholesterol occurs. This opinion is supported, among others, in the cases of Schüller-Christian, where the tissue does not contain lipoid (GROSS and JACOX, 1942; ENGELBRETH-HOLM et al., 1944; and BJERRE HANSEN 1949). The connection between Letterer-Siwe and the eosinophilic bone granuloma appears also from the circumstance that in the case of Letterer-Siwe accumulations of eosinophilic leucocytes can be seen, and that transition from the acute form to the chronic Schüller-Christian is sometimes noticeable.

IX. Cases of Schüller-Christian's disease localized in the jaws.

A. Previous cases.

Table 2 shows some of the previously described cases of Schüller-Christian's disease with localization in jaws. Moreover, cases have been included that ought to be designated as cases of transition, *i. e.* cases with *e. g.* only one bone defect, but showing pronounced xanthomatosis, or patients having the triad, but no foam cells. As it appears from the table, in the 37 cases the average age is $6^1/_2$ years and the proportion of male : female attacked is 24 : 13. Schüller-Christian's disease is localized in the mandible rather than in the maxilla.

Many of the previous investigators have pointed out that the first symptoms are often seen in the oral cavity, where pronounced inflammation and loose teeth can be seen. In his thesis KOCH, 1933, has gathered all cases published until that year of Schüller-Christian's disease with oral manifestations and has stated the different types of changes in the teeth and the cavity of the

Table 2.

Tabulation of previously published cases of Schüller-Christian's disease localized in the jaws.

Author	Year	Sex	Age in year	Attack in maxilla	Attack in mandible	Other bones attacked	Visceral and cutaneous complications	Diabetes insipidus	Exophthalmus	Histology				Serum cholesterol
										Histiocytes	Foam cells	Eosinophilic leucocytes	Giant cells	
Grosh and Stifel	1923	♀	7		+	+	(+)	+	+					
Thompson et alii	1925	♂	9	+	+	+		+	+	+	+	+	+	
Rowland	1928	♂	5 1/6	+	+	+	+		+		+		+	
		♂	3 11/12	+		+		+	+					256
Pickhan and Joel	1929	♂	5		+	+			(+)		+		+	
Sosman	1930	♂	2 1/2	+	+	+	+	+	+					
Henschen	1931	♂	3 1/6	+		+		+	+					185
Schaefer and Williams	1932	♀	30	+	+	+	+	+	+					
Rietschel	1933	♂	3 1/12		+	+		+	+					150—190
Fraser	1935	♂	3		+		+	+	+	+	+		+	267
		♂	4		+	+		+	+					236
		♀	2/3		+	+					+			
Natali	1935	♂	4		+	+	+	+	+		+			
Radding	1935	♂	3 1/4		+	+		+	+					219—300
Schroff	1936	♂	23		+									238—110
Wätjen	1936	♂	5/6	+	+	+	+			+	+	+		
Hankey	1938	♂	36		+			+		+	+	+	+	
Zitka	1942	♀			+	+	+							
Thoma	1943	♂	6		+	+		+		+		+		236
Engelbreth-Holm et al.	1944	♂	5		+	+				+	+	+	+	164—165
		♂	5		+	+	+	+		+		+		160—179
Salman and Darlington	1945	♂	28		+	+		+			+			
Cox (case 2)	1946	♂	28	+	+	+				+	+	+		
Austin	1946	♂	3		+	+		+	+					
Blanchard and Boone	1948	♂	2 1/2		+	+	+		+	+	+	+		230
Love and Fashena	1948	♂	6		+	+		+	+	+	+	+	+	
Ponsetti	1948	♀	3 1/2		+	+	+		+					205
Talley	1948	♀	26	+	+	+		+		+		+	+	
		♂	3 1/2		+	+	+	+	+	+	+	+		
		♀	53	+	+	+	+							
Bjerre Hansen	1949	♂	3 1/2		+	+	+	+	+	+	+	+		131
Wallace	1949	♂	12		+	+								222—267
		♂	4		+	+	+	+	+					
		♀	29		+	+								278—480
		♀	37		+	+	+	+	+	+				182
Holst, Husted and Pindborg	1951	♂	1 1/2		+	+	+				+	+	+	177—275
		♂	3 1/2	+	+	+	+				(+)	+	+	172

mouth that are noticeable in case of this disease. In roentgenograms the process may be mistaken for a cyst, but owing to the multiple occurrence and the histologic findings the correct diagnosis can most often be obtained.

ENGELBRETH-HOLM et al., 1944; LOVE and FASHENA, 1948; and BJERRE HANSEN, 1949, have described interesting cases, where biopsies from defects in the mandible have given valuable information as to the histogenesis of the process. LOVE and FASHENA, 1948, have had the chance to inspect a patient for more than 4 years, and they have seen how during this time a deposit of lipoid took place in the tissue that was previously characterized as eosinophilic bone granuloma.

B. Personal observations.

1. Second case.[1]

Boy, 18 months old (born 10/28 1944); hospitalized on 3/20 1946. No previous illness. The disease commenced July 1945 with little red blemishes on his back; later they expanded to the scalp and the gluteal region. Two weeks before the hospitalization the boy became irritable and simultaneously an inflammation of the mouth set in.

a. *Clinical Examination.* The back, chest, anal region, external auditory canal and the scalp showed numerous lesions which were about 5 mm in diameter and were either dried pustules or were covered with a thick, easily loosened crust. The mucous membrane of the hard palate was red and showed vesicles, and a couple of ulcerations with pus which was localized in the gingival parts pertaining to the molars. In the neck and the submandibular region some lymph nodes could be palpated. During hospitalization both ears showed a discharge.

b. *Laboratory Examinations.* Sedimentation rate: 35 mm; hemoglobin: 82 per cent (3/23) and 68 per cent (5/3) despite iron treatment, white blood corpuscles: 11,200; lymphocytes: 25 per cent; monocytes: 3 per cent; neutrophilic: 71 per cent; and eosinophilic: 1 per cent; serum cholesterol: 177.5—275—217.5 mg per cent. During hospitalization the patient lost weight.

c. *Dental Examination.* On April 11, it was discovered that 05—[2] was loose. Radiograph showed a radiolucent area in the region of the first molar. 05— and 04— were extracted and the radiolucent area in the

[1] Demonstrated by professor H. HAXTHAUSEN, M. D., in Danish dermatologic society May 8, 1946, as "Case of Hand-Schüller-Christian (lipoid granulomatosis) with changes in skin". Professor Haxthausen is thanked for kind permission to publishing.

[2] According to the Haderup system of dental designation, + signifies the upper jaw, — the lower jaw. If the symbol is placed to the right of the figure the right side is indicated, and vice versa. 0 before the figure indicates a deciduous tooth.

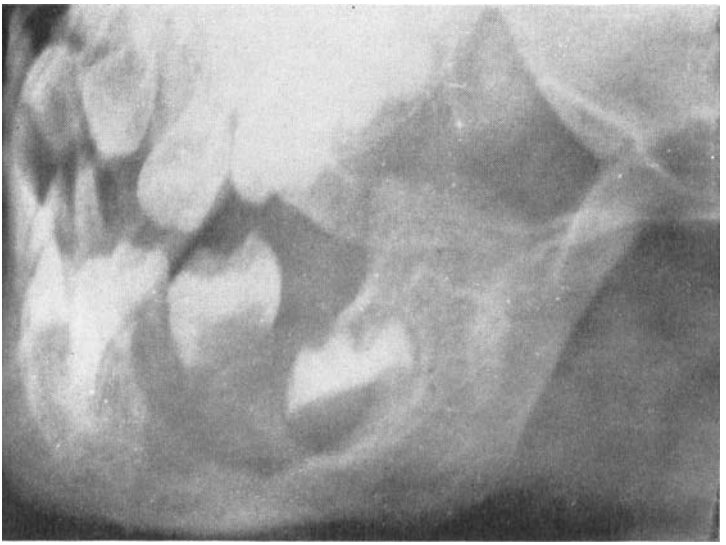

Fig. 3. Case 2. Roentgenogram of the right side of the mandible. Note the radiolucency around the deciduous molars and the first permanent molar.

region of 6— curetted. A histologic examination of a tumor-like mass between the roots of 04 and 05— revealed a focus of Schüller-Christian's disease. During the month of May a bilateral swelling of lymph nodes in the angle region of the mandibular was noticed and biopsy taken.

d. *Radiologic Examinations.* Roentgenogram — of the mandible — revealed a big area of radiolucency extending from the distal part of the second right deciduous molar to beyond the tooth germ of 6— (Fig. 3). Radiolucent areas were also seen in the temporal, and the iliac bones.

e. *Histologic Examination.* At first tissue from a cyst-like cavity of the mandible was examined. "Numerous small pieces of tissue — measuring up to 3—4 mm in diameter — showed 1) a tissue of varying density, rather rich in cells, 2) remnants of cross-striated musculature and 3) connective tissue covered with a well defined, non-hornifying squamous epithelium. The highly cellular tissue showed at some spots dense masses of rather uniform reticulum cells with round or vaguely oval nuclei and rather scarce protoplasma. In the periphery a transition to highly vascular tissue could be seen which formed at some places a regular granulation tissue with numerous plasma cells, histiocytes and especially eosinophilic leucocytes. Partly regions with pronounced reticulum cell proliferation, partly transitions to granulation tissue with pronounced localized eosinophilia have thus been demonstrated. Compared with the clinical information it is most likely that the question is about: Schüller-Christian's disease (1—2 phase)" (signed Dr. G. TEILUM).

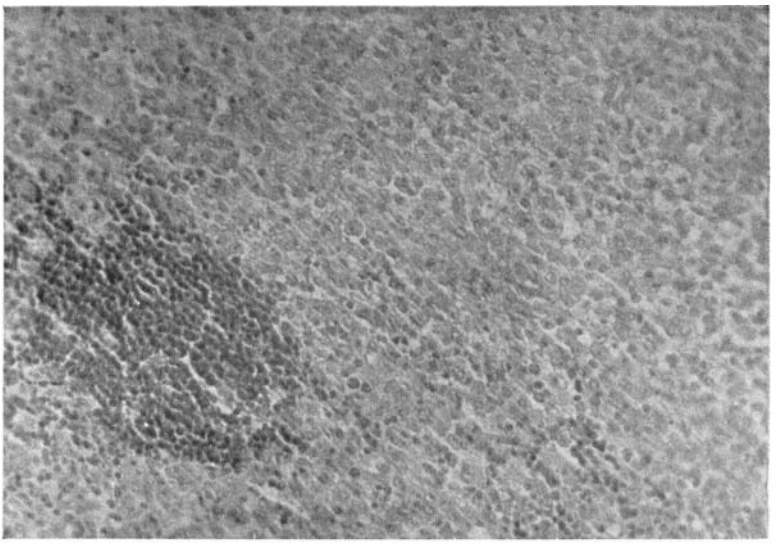

Fig. 4. Case 2. Photomicrograph of tissue from the right angular lymph node. In the left lower corner an "abscess" of eosinophilic leucocytes can be seen. The other large cells are histiocytes. Original magnification: 10 × 12.

The second histologic examination was made on tissue from the probe excision of the swelling angular lymph node: "Section from lymph node (Fig. 4) shows completely broken down structure with remnants of lymphoid tissue. The structure is dominated by a diffuse and densely proliferation of reticulo-histiocytic tissue. At some places the tissue is looser and content of lipoid demonstrated in the cells can be observed. Few leucocytes are to be seen some of which being eosinophilic. In a fibrous vascular tissue at the edge of the lymph node smaller masses of typical foam cells can be seen. Histologic diagnosis: lymph node with diffuse reticulosis and lipoid-phagocytosis; Schüller-Christian's disease (2—3 phase)" (signed Dr. G. TEILUM).

On May 31, the patient was transferred to the children's department, where a new radiologic examination, undertaken July 16, showed increase in size of the radiolucency in the skull, and a new lesion in the sella turcica. Inspite of the local treatment of skin lesion and the roentgenologic treatment of the bone lesion, the patient grew worse and died July 26. The autopsy showed xanthomatosis of the cranial base, the cranial theca, pelvis, thymus, perirenal tissue and pleurae.

2. Third case.

A boy of $3^1/_2$ years was hospitalized at "Dronning Louise's Børnehospital" December 10, 1950, for mandibular osteitis. There was no previous history except fever in connection with eruption of teeth.

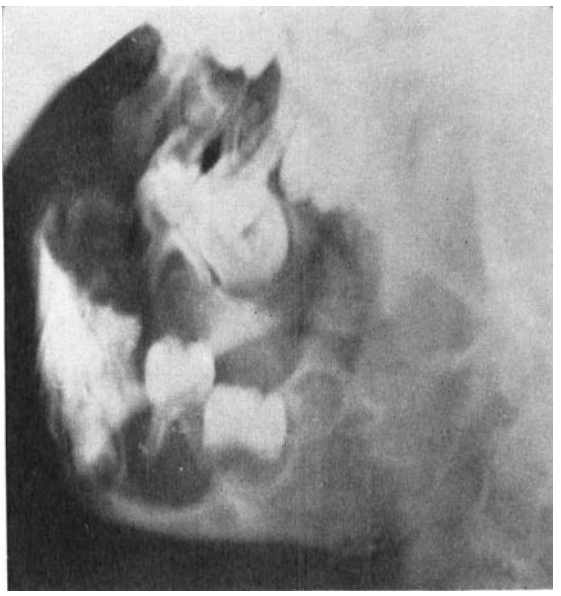

Fig. 5. Case 3. Roentgenogram of the right side of the mandible. Note the radiolucent area corresponding to 05—.

About 6 months prior to hospitalization the patient developed foetid breath and the posterior teeth in mandible and maxilla became loosened. Appetite was lost, the patient refused to take solid food and subsisted mainly on milk.

a. *Clinical examination.* The right parietal region showed an elevation which was about the size of a shilling. On the back, chest, abdomen, and on the scalp a papulous exanthem was noticeable. The lymph nodes at the mandibular angle, axilla and inguen were the size of a pea. There was a pronounced foetid breath, a chronic marginal gingivitis and the posterior teeth showed heavy deposit of calculus.

b. *Laboratory examinations.* On December 11, 1950, the sedimentation rate is: 40; hemoglobin: 85 per cent; white blood cells: 8,480; lymphocytes: 21 per cent; monocytes: 7 per cent; neutrophilic: 66 per cent; and eosinophilic 0 per cent; serum cholesterol: 172 mg per cent.

c. *Dental examination.* December 14, 1950, the examination showed that the mandible and the maxilla were well developed and all the 20 deciduous teeth had erupted. Some carious teeth could be noticed. In the region around the incisors and the cuspid a slight chronic marginal gingivitis was observed, but farther behind in the region around the upper molar a retracted swollen bluish red gingival edge extending about midway on the root of 05 + 05 could be seen. Both teeth were loose and covered with deposits. In the mandible, in the distal side of 04—04 the gingiva showed marked recession. 05—05 were extremely

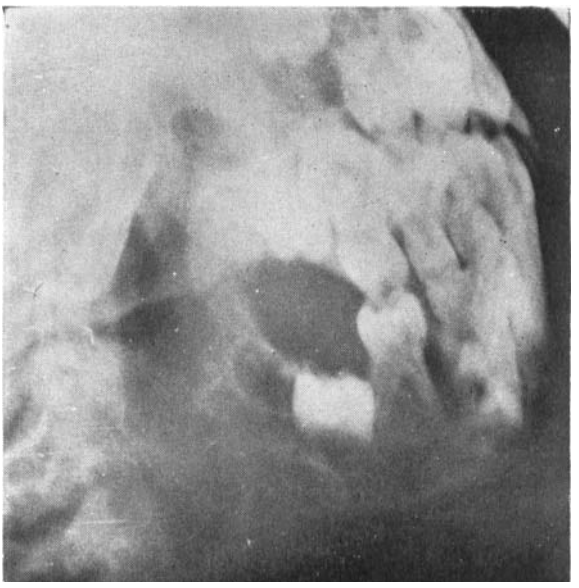

Fig. 6. Case 3. Roentgenogram of the left side of the mandible. Note the radiolucent area around the deciduous molars and the first permanent molar.

oose. Due to ulceration the mesial half of the crown of the lower right first molar was exposed and the whole region was covered with yellowish grey foetid deposits. The gingiva around —05 had markedly receded, and the first molar was covered with a bluish red gingival swelling. Like on the right side the teeth in the left half of the mandible showed large amounts of deposits. None of the deciduous molars showed clinical signs of resorption of the roots.

In order to avoid a large extraction wound, 6— was not extracted although the chances for its normal development were not favorable. 05—05 were removed. Upon the extraction all the area between 6— and 04— appeared as a deep cavity the size of a hazel nut. Both deciduous molars together with a small amount of curetted tissue from the alveolus of 05— were examined histologically.

d. *Radiologic examinations.* On December 14, 1950 the radiologic examination of the skull showed several sharp rounded radiolucent areas localized partly in the anterior and partly in the posterior parts of the parietal bone. (Fig. 11 A.) These extended all the way through the cranial wall, and the biggest measured $3^1/_2 \times 2$ cm. On December 18, the radiologic examination of the mandible showed big cystic radiolucency localized around 6—, 05— (Fig. 5) and —05 and —06 (Fig. 6). There seemed to be no sign of second premolars; the germs of the second molars were distinguishable and a beginning calcification of the cuspids was noticed. A radiologic examination of the maxilla showed a pronounced resorption of the marginal bone tissue around

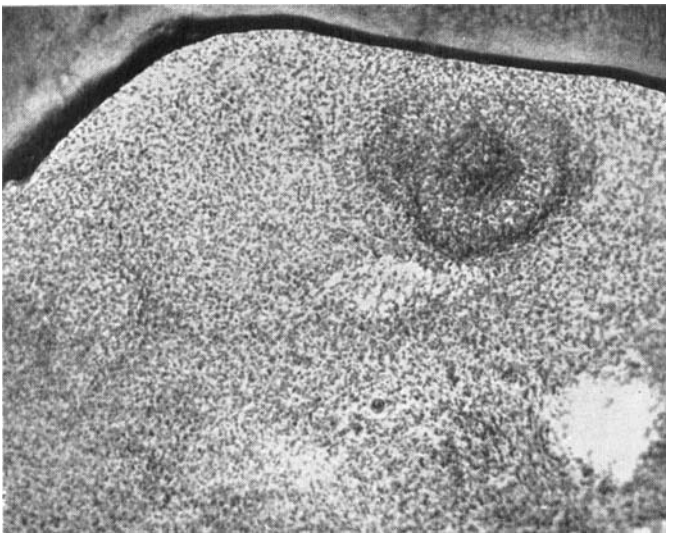

Fig. 7. Case 3. Photomicrograph of the interradicular area of —05. The abscess like formation is an accumulation of eosinophilic leucocytes. Original magnification: 10 × 4.

05 + 05. A radiologic examination of the thorax showed nothing abnormal in the lung regions or at the cardial shadow. However, areas of radiolucency, increase of width and partial destruction of the bone similar to that seen in the skull was seen in four ribs in the ileum and the upper part of the femur.

February 8, 1951, an examination of the left parietal bone showed enlargement of the previous lesion and a new bigger area of radiolucency (Fig. 11 B). March 17, 1951, a renewed radiologic examination showed no changes in the size of destructions of the skull. But the radiolucency around the 05 + 05 had expanded interradicularly up till the apical third of the roots. In the mandible the cystic elucidations seemed to extend still farther forwards, thus threatening the 04—04 and the germs of the first premolars.

At hospitalization December 10, 1950, no abdominal organ tumor, no exophthalmus or diabetes insipidus had been proved.

e. *Histologic examination. α.* Sternal puncture taken December 16, 1950, shows "marrow with increased erythropoiesis and shifting to the left. The finding was unspecific, and there was no sign of lipoidosis, myelomatosis or leukemia. The changes corresponded on the whole to an infectious-toxic marrow irritation" (signed Dr. S. Petri).

β. Granulation tissue taken from the dental alveolus December 19, 1950. "Two small tissue particles were examined: one showed a mucous membrane with subacute-subchronic inflammation and some eosinophilia in the connective tissue. The other piece of tissue was rich in cells, of which some showed a transition to cells being more polygonal and

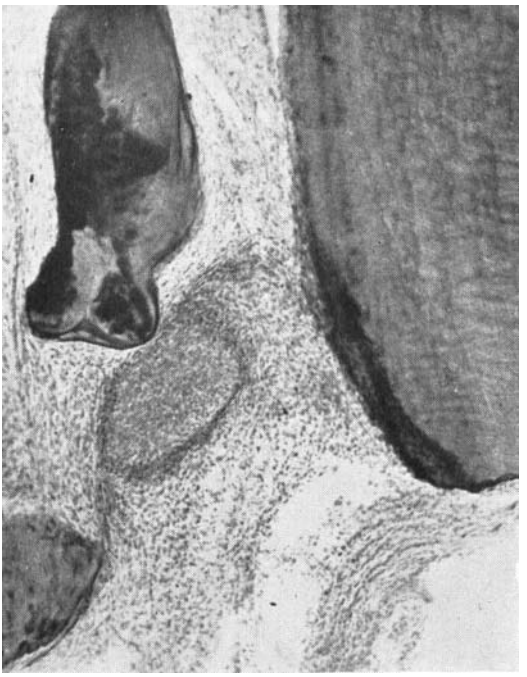

Fig. 8. Case 3. Photomicrographs of the apex from 05—. Note the abscess-like accumulation of eosinophilic leucocytes in relation to denticle in the pulp. Original magnification: 10 × 4.

pale, probably containing lipoid. The tissue was moderately filled with vessels and at some spots it contained many eosinophilic leucocytes. There did not seem to be any necrosis, only a slight, fresh bleeding. From the histologic evaluation several diagnostical possibilities were probable: 1) formation of older granulation tissue with eosinophilia, 2) fibroma rich in cells (possibly fibrous epulis) with eosinophilia, 3) eosinophilic granuloma or 4) Schüller-Christian's disease. Although the histologic changes did not seem to be fully developed, the appearance of the present stroma cells and the rather pronounced eosinophilia suggested the latter diagnosis" (signed Dr. S. PETRI).

γ. 05—05, extracted December 19, 1950. The teeth were decalcified in nitric acid (5 %), embedded in "Geigy's pro-celloidine", sectioned in series and stained with hematoxylin-eosin. Despite the extraction some adherent tissue had been retained on the surface of the roots. Most of the normal periodontal connective tissue and bone tissue had disappeared and had been replaced by a diffused reticulo-histiocytic tissue consisting of large polygonal cells. Everywhere in this stroma numerous eosinophilic leucocytes with polymorph nuclei could be seen, sometimes in a form so concentrated that it appeared like an abscess (Fig. 7 and 8). Fig. 9 shows a detail of the interradicular region of —05,

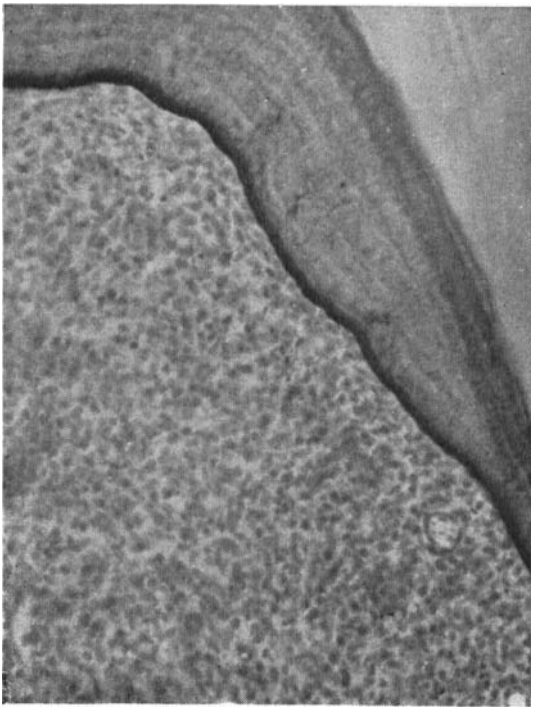

Fig. 9. Case 3. Photomicrograph of the interradicular area of —05. The periodontal tissue has been replaced by histiocytes among which eosinophilic leucocytes are interspersed. Original magnification: 10 × 4.

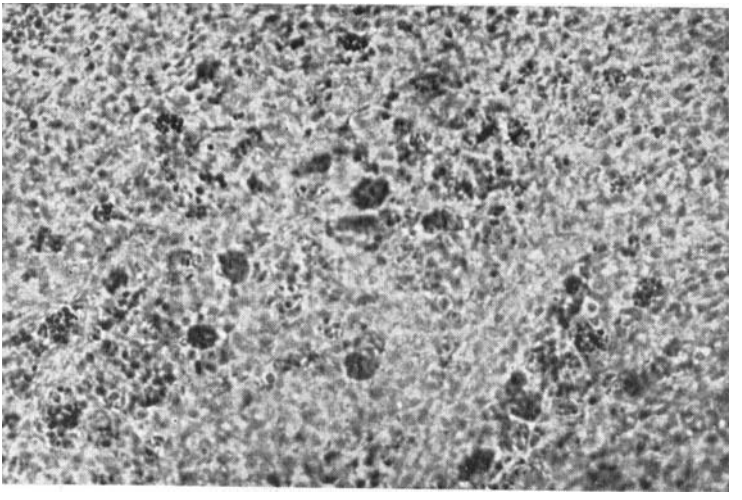

Fig. 10. Case 3. Photomicrograph of interradicular area of —05. Note the giant cells phagocytosing fragments of eosinophilic leucocytes. Original magnification: 10 × 12.

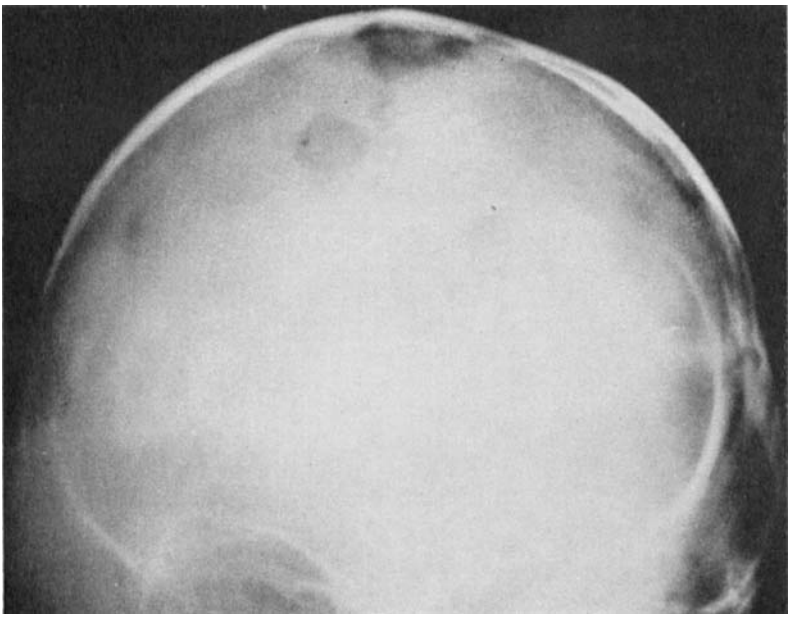

Fig. 11 A.

Fig. 11. Case 3. Frontal roentgenograms taken A: December 14, 1950, and B: February 8, 1951. Note the enlargement of the lesion after only two months.

where the histiocytes fill in completely the place of the former periodontal connective tissue. There are no foam cells to be seen on either 05— or —05. Everywhere in the pathologic tissue giant cells could be observed evidently derived from the histiocytes. At certain areas giant cells were phagocytosing fragments of eosinophilic leucocytes (Fig. 10). In the cementum and superficially in the dentine areas of resorption were seen on both deciduous teeth.

δ. Biopsy of the skin taken February 21, 1951. "The skin surface is delicately scalloped, covered with a medium thick layer of normal epidermis. Subepithelially, in the connective tissue papillae and in the subpapillary stratum proliferation of cells similar to connective tissue cells could be seen. Further reticular elements, numerous eosinophilic leucocytes and some lymphocytes were observed. In some areas the changes had attacked the epidermis where a pronounced infiltration of eosinophilic leucocytes, necrosis, and ulceration could be noticed. In other sections some of the bigger, proliferating cells seemed to contain lipoid. The histopathologic findings corresponded to the changes observed in the skin in Schüller-Christian's disease resp. Letterer-Siwe's disease, resp. eosinophilic granuloma" (signed Dr. S. PETRI).

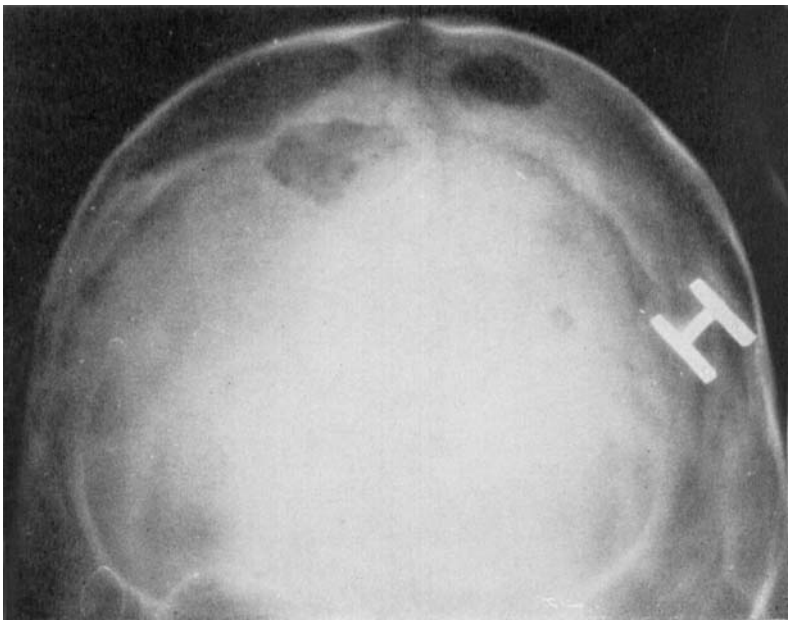

Fig. 11 B.

January 17, 1951, 310 mg ACTH was given during 9 days without visible effect. During the treatment the patient developed mumps and serum was given together with a blood transfusion. Immediately after the seponeration of the ACTH the patient had an attack of cramps, but recovered in 24 hours, but showed a strong diuresis indicating a diabetes insipidus. Gradually he recovered, the diuresis going down to about 1 l. in 24 hours, and after receiving 3 blood transfusions he was sent home on March 4, 1951. At the check-up March 17, 1951, the patient felt perfectly well; he drank about $1^1/_2$ l. milk during the day and the diuresis was about 1 l. during 24 hours (see the comments on the radiologic examination March 17, 1951, — Fig. 11 A and B). He was referred to ambulant radiologic treatment at the Finsen Institute.

X. Discussion.

The aim of the present work has been to investigate whether the manifestation of the process in cases of eosinophilic bone granuloma and Schüller-Christian's disease follows the same pattern in the jaws as in other parts of the body. When comparing

the three cases described above and considering their likely pathogenic correlation it appears that they are different phases of the same disease.

Case no. 1 is a type of eosinophilic bone granuloma appearing only in the mandible. Its solitary manifestation in the mandible and its lack of symptoms separate it from the following two cases. The similarity of the roentgenograms and especially of the histologic picture with the two other cases entitles, however, to consider the eosinophilic bone granuloma as being related to the Schüller-Christian's disease. The term of eosinophilic bone granuloma must be maintained as a clinical concept, if by this is understood an inflammatory histiocytosis only (SCHROFF, 1948).

Case no. 2 shows multiple bone lesions and cutaneous affections. According to HENSCHEN, 1939, it has to be considered as type 4 among the different manifestations of the Schüller-Christian's disease. It is very similar to case no. 4 of ENGELBRETH-HOLM et alii, 1944, where also exophthalmus and diabetes insipidus were lacking. Characteristic for our case no. 2 is that the first histologic examination shows changes like in 2—3 phase with commencing lipoid phagocytosis. This development backs up the present conception of the Schüller-Christian's disease as being a primary histiocytosis with secondary deposits of lipoid.

Case no. 3 reminds more of Schüller-Christian's disease clinically as the patient develops a diabetes insipidus in the course of the period of illness besides the multiple bone lesions and changes in the skin. In that respect the case reminds also of ENGELBRETH-HOLM et alii's case no. 5 and according to HENSCHEN's classification it will become a type no. 3 of Schüller-Christian's disease. The extensive histologic examination has not shown typical foam cells, but only presumably cells containing lipoid, so the case must be characterized as being in the 2—3 phase. By the histologic examination of two deciduous molars tissue has been demonstrated like in case of a granulomatous phase, replacing the tissue normally surrounding the teeth. In contradistinction to MEŽL and ŠKORPIL, 1947, nobody has succeeded in proving eosinophilic granulomas in the pulp connective tissue itself; only in the apical foramen an accumulation like an abscess of eosinophilic leucocytes has been ascertained (Fig. 8). The cases often mentioned in the literature of loose teeth in connection with Schüller-Christian's disease may be explained by the fact that collagenous fibers (the Sharpey fibers) keeping the teeth in place

in the alveolus are destroyed together with the alveolar bone and are replaced by histiocytic eosinophilic granulation tissue.

The prognosis of case no. 3 is much better now than at an earlier stage of the disease. It is difficult to explain this change for the better; the most effective treatment up to the present moment of Schüller-Christian's disease is X-ray radiation and by this method some amazing results have been obtained. *E. g.* RADDING, 1935, describes a case where a 3-year-old child with several bone defects, exophthalmus and diabetes insipidus had roentgenographic treatment and improved in such a way that within 8 years a complete recalcification of the defect bone regions took place. Radding's roentgenograms of the mandibular defects of the different stages of the healing are most illustrative.

As mentioned before it often happens with patients with Schüller-Christian's disease that they consult their dentists for a pronounced gingivitis or loosening of teeth. An excellent example of this is case no. 3, where the disease commenced by halitosis and loosening of the posterior upper and lower deciduous molars. In case no. 2 the patient was at first hospitalized for general dermatitis and the correct diagnosis was not made until a roentgenogram of a loosened tooth led to a general roentgenographic examination of all the bones. Although it is not a common disease the dentists and physicians should not overlook this disease in cases of very slow healing of extraction wounds or loose teeth in children. There may be the first symptoms of a more general disease.

XI. Summary.

In the introduction the history and terminology of the eosinophilic bone granuloma are mentioned. Previous examinations concerning occurrence, clinic, roentgenology, histology, cutaneous and visceral complications are dealt with. Previously published cases of eosinophilic bone granuloma localized in the jaws are mentioned in table 1 and in connection herewith a case of solitary eosinophilic bone granuloma is described in the lower jaw of a 14-year-old boy. Histologically, numerous histiocytes and a heavy infiltration of eosinophilic leucocytes are noticeable.

In the next chapter the connection between the eosinophilic bone granuloma and Schüller-Christian's disease and Letterer-Siwe's disease is mentioned, and the two last mentioned diseases

are dealt with briefly. In table 2 previously published cases of Schüller-Christian's disease with localization in the jaws are listed. Two cases ($1^1/_2$ year and $3^1/_2$ year boys) of Schüller-Christian's disease without the typical triad are described. There are defects in the jaws and the histologic examination of the biopsy material shows pictures demonstrating the relation with the eosinophilic bone granuloma.

Moreover, two deciduous molars from a case of Schüller-Christian's disease were examined histologically. Histiocytic eosinophilic granulation tissue was seen to have replaced the normal periodontal tissue and alveolar bone. Finally, it is pointed out that the dentist may be the first to make the diagnosis of Schüller-Christian's disease.

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