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Fibrosarcoma complicating polyostotic fibrous dysplasia

William H. Bell, D.D.S., and Edward C. Hinds, D.D.S., M.D.***
Houston, Texas

UNIVERSITY OF TEXAS, DENTAL BRANCH

In 1937 Fuller Albright[1] described a triad of pathologic manifestations which today is known as Albright's syndrome. The triad includes (1) multiple bone lesions which have a tendency to be unilateral, (2) brown pigmented areas of the skin which tend to be on the same side as the bone lesions, and (3) endocrine dysfunction which, in females, is associated with precocious puberty.

The disease had been reported on a number of occasions prior to 1937, but under different names.[3, 10, 12, 14, 17-19, 23, 28, 31, 34, 39] The first report was published in 1922 by Weil[37] under the title "Precocious Puberty and Bone Brittleness." Many reports found in the literature since that time[5, 11, 16, 20-22, 25, 29, 30, 32, 38] refer to the condition as Albright's syndrome; however, the newer name of polyostotic fibrous dysplasia[24] is a more descriptive term and has become more generally accepted.

The cause of the condition is unknown, but the fibrocystic bone lesions are probably the result of altered activity of the specific bone-forming mesenchyme. This concept, proposed by Lichtenstein,[24] does not, however, account for the occurrence of pigmentation, the tendency for the condition to be unilateral, or the endocrine dysfunction. A more likely explanation may be the one hypothesized by Furst and Shapiro,[13] namely, that in fibrous dysplasia there is a hypothalamic lesion in the region of the third ventricle which produces secondary disturbances in the anterior lobe of the pituitary, resulting in abnormal stimulation of its various component trophic hormones.

The condition with which polyostotic fibrous dysplasia is most often confused is hyperparathyroidism. Furst and Shapiro,[13] in their review of seventy-one cases reported in the literature, found that parathyroid exploration had been performed in 18.3 per cent of the cases because of an erroneous diagnosis of hyper-

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parathyroidism. Differential diagnosis is based on the blood chemistry and radiographic findings. In hyperparathyroidism the serum phosphorus is lowered, whereas the serum calcium and alkaline phosphatase are elevated. Roentgenograms show a generalized demineralization of bone. In this condition there is usually no change in the blood chemistry, except occasionally in the more full-blown cases where the alkaline phosphatase may be elevated. Roentgenographically, the bone lesions may be somewhat similar, but they are characterized by expanding lesions which thin or in some cases erode the cortex.

Bell,[2] in describing multiple neurofibromatosis (von Recklinghausen's disease), points out that pigmentation of the skin (café au lait spots) may be present many years before the appearance of the tumors, and it may persist through life as the only sign of the disease. The disease has been shown to be definitely familial and hereditary. Occasionally, there may be deformities of the bones or intraosseous lesions which appear roentgenographically as cysts. These patients usually die of intracranial or intraspinal pressure exerted by one of the nerve tumors in this region or of a neurofibroma undergoing sarcomatous change. Thus, this disease must occasionally be included in the differential diagnosis of polyostotic fibrous dysplasia. Charpentier[4] found mild psychic defects, with a tendecy to depression, in 63 per cent of his patients. Mental retardation and feeblemindedness have been described by numerous other investigators.

The histologic appearance of these bone lesions is that of replacement of the medullary cavity of the affected bones by fibrous tissue in which there may be islands of immature fiber bone or, more rarely, islands of hyaline cartilage. Both endochondral and membranous bones may be involved, the femur, tibia, humerus, radius, and skull being most frequently affected.

In the ninety cases of polyostotic fibrous dysplasia studied by Lichtenstein and Jaffe[25] and reported in 1942, only fifteen of thirty-five males and seventeen of fifty-one females showed any degree of abnormal pigmentation. These areas of increased melanin production may be observed anywhere on the surface of the body, including the oral cavity, but are seen most often on the scalp, face, neck, trunk, and extremities. They may be in the form of small freckles, or they may be diffused over the skin as light brown blotches (café au lait spots).

Treatment is indicated (1) when symptoms are produced by the condition, (2) when there is loss of function, or (3) for esthetic reasons. When treatment is indicated, it will usually consist of either shaving off excess bone for cosmetic reasons or curettage and placement of bone chips to promote osteogenesis. If pathologic fractures should occur, they are treated in the usual manner and are reported to heal well. Irradiation has no place as a modality of treatment. A study by Tanner and Childs[33] suggests that irradiation may be an inciting factor in the development of sarcoma in cases of fibrous dysplasia.

In these full-blown cases of polyostotic fibrous dysplasia, particularly those showing endocrine changes, the prognosis is probably not as favorable as in the more common cases of the innocuous monostotic form of the disease. Spontaneous regression of bone lesions has been reported, but more frequently these lesions run a progressive course until after puberty or in later years, when they become quiescent.

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In the literature we have found five documented cases of polyostotic fibrous dysplasia in which malignant change has taken place. In all five cases there was a change to osteogenic sarcoma. Two of these cases were reported by Coley and Stewart[6] in 1945, one by Jaffe[20] in 1946, one by Dustin and Ley[9] in 1950, and one by Perkinson and Higinbotham[26] in 1955. Platt,[27] in 1947, reported two cases of sarcoma arising in fibrocystic changes in bone. The cases were not well documented, however, and there is some doubt as to whether there was malignant change of a fibrodysplastic lesion or whether the osteogenic sarcoma was a separate entity. Since 1945 Coley[5] has treated one other patient in whom monostotic fibrous dysplasia underwent malignant change. This was a 21-year-old woman; the disease involved the right humerus and was treated by amputation. At last report, the patient was doing satisfactorily.

Undoubtedly, there have been other cases in which malignant transformation has not been correlated with the previously existing polyostotic fibrous dysplasia. Many other cases have been reported under different titles.

In 1961 Tanner and Childs[33] reported four cases of fibrous dysplasia of the facial bones which presumably underwent sarcomatous change.

CASE REPORT

C.M., a 16-year-old white girl, was first seen at the University of Texas Dental Branch on Sept. 8, 1955, with the chief complaint that she had been told she had a tumor of the palate. About a week prior to this, she had visited her dentsit for the purpose of having a prosthesis made to replace two missing central incisors. The dentist noticed a swelling of the hard palate, took roentgenograms, and told her that she had a tumor. From the University of Texas Dental Branch, she was referred to the M. D. Anderson Hospital and Tumor Institute in Houston, Texas.

Past history

The patient's weight at birth was 10 pounds; delivery was said to have been spontaneous, with no complications. She sat at the age of 6 months, walked at 1 year, and talked at 2 years. She was breast fed for 9 months, and then fed with a bottle until 8 years of age. The history revealed that she had been seen 6 years ago at the Hermann Hospital Clinic in Houston, Texas, because of slowness of speech, nasal twang, and inability to keep up with her class. She had been hoarse since birth and had frequent colds, cough, and nasal stuffiness since early infancy. She complained also of tiring easily, having clumsy movements, and frequently falling down.

Excessive pigmentation on the abdomen and extremities was noted at this time. Roentgenographic examination revealed a multiloculated radiolucency of the right and left body of the mandible (Fig. 1). Cortical defects were present in the lower end of the left femur and the upper end of the left tibia. Roentgenograms of the spine and skull were reported negative.

In November, 1949, the patient was operated on for the removal of these lesions. The affected areas in the mandible were curetted and the defects were electrocoagulated. A curettage of the long bones was also performed and yielded the same brownish gray soft tissue as that removed from the mandible. The pathologist at the Hermann Hospital reported that the prominent feature of all these sections was the large number of multinucleated giant cells present. In these the nuclei were oval, and there was a tendency to group toward the center of the cells. There were approximately fifteen nuclei per giant cell. The stroma was composed of spindle and oval cells, with a whorl-like pattern in some areas. The giant cells were more numerous in the sections of the jaw lesions. The diagnosis was polyostotic fibrous dysplasia or Albright's syndrome.

After the patient's dismissal from the Hermann Hospital, she did very well until the latter part of 1954, when she began complaining of tiring easily and of pain in the neck and shoulders when she read or when she sat for a long time. She stated that she had frequent

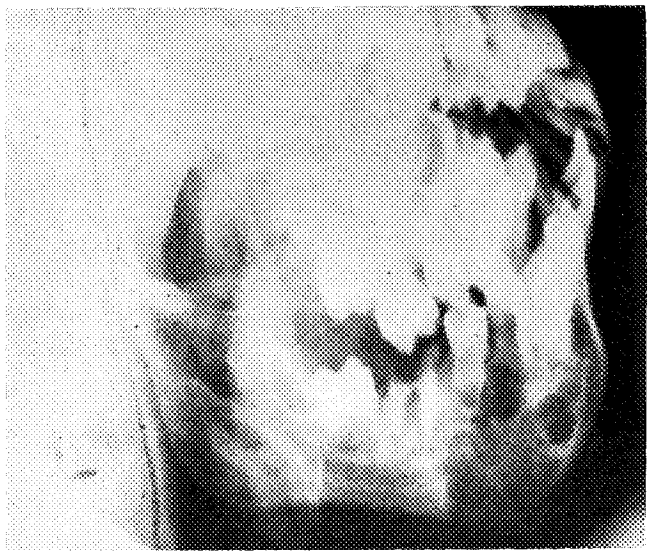

Fig. 1. Feb. 14, 1949. Multiloculated radiolucency of left body of mandible.

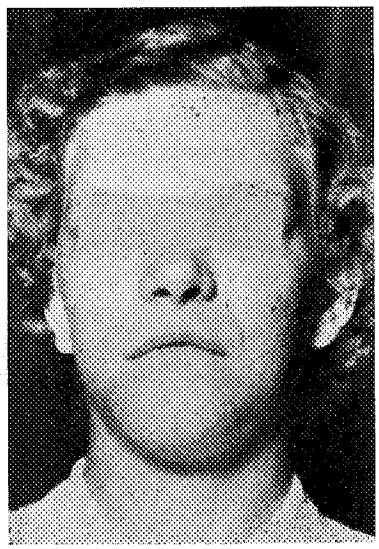

Fig. 2. Sept. 7, 1955. Leonine facial appearance with generalized melanosis.

episodes of sinusitis with colds during the winter and that the previous year she had bronchial pneumonia. Menstruation began at the age of 14, and periods occurred regularly every 28 days until June, 1955, when they came every 21 days. With the exception of a tonsillectomy in 1949, there was nothing else remarkable about the past history.

Family history

The patient's mother, father, one brother, and two sisters were all living and well. Her maternal grandmother died of asthma and hypertension, and her maternal grandfather died of cancer of the colon. The family history was negative otherwise.

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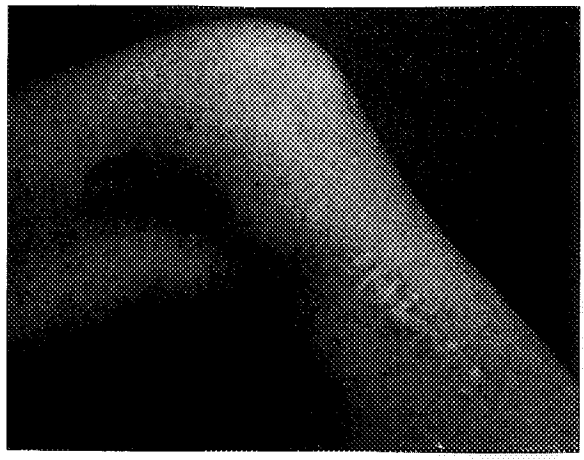


Fig. 3. Jan. 29, 1957. Left leg, showing generalized melanosis, café au lait spot, and scar from excision of tibial lesion in 1949.

Physical examination

When first seen at M. D. Anderson Hospital and Tumor Institute, this 16-year-old hyposthenic, white girl (Fig. 2) weighed 125 pounds and was 5 feet 8 inches tall. There was a slight asymmetry of the face due to prominence of the right zygoma and right symphysis region. The skull was dome shaped, and the eyes appeared to be wide set; the facial appearance was that of leontiasis ossea. The supraorbital ridges appeared very prominent. There were several small subcutaneous nodules on the chest, abdomen, buttocks, and extremities. These were very small, the largest being 0.5 cm. in diameter. Large areas of brownish pigmentation (café au lait spots) were also present on the extremities (Fig. 3).

Intraoral examination revealed an overgrowth of the right maxilla (Fig. 4), smooth and nontender, covering about two thirds of the hard palate and extending from past the midline of the left side to the upper right buccal sulcus. There was gross malocclusion, with the teeth on the right side widely spread and not occluding with the lower teeth. The roots of several of the anterior teeth had become exposed to the oral cavity. There was a prominent band of scar tissue located in the lower right buccal sulcus, where a previous operation had been performed.

With the exception of a scar on the medial aspect of the left leg, nothing else remarkable was revealed by the physical examination.

Laboratory findings were negative, with the exception of the blood chemistry which showed an elevated alkaline phosphatase (3.5).

Roentgenographic findings

There was a rather sharply defined multiloculated radiolucency throughout the right mandible (Fig. 5) from the anterior margin of the second molar across the midline to the position of the cuspid. This cystlike defect was largest in the region of the premolar, where there was a circular radiolucency sharply defined by a slender zone of increased density measuring 2 cm. in diameter. The process involved the alveolar margin throughout and, in the area of maximal involvement, extended practically across the mandible to involve the entire width of the bone except for the cortex.

Similar multilocular radiolucencies involved the right upper alveolar process and extended across the midline to the plane of the cuspid. The central portion of the alveolar process and its teeth were absent. The lesion in the bone (Fig. 6) was apparently expanding and had perforated the right nares; the associated thickening of bone had encroached upon the lower two thirds of the right maxillary antrum. In this area there was some increase in density of the expanded bone.

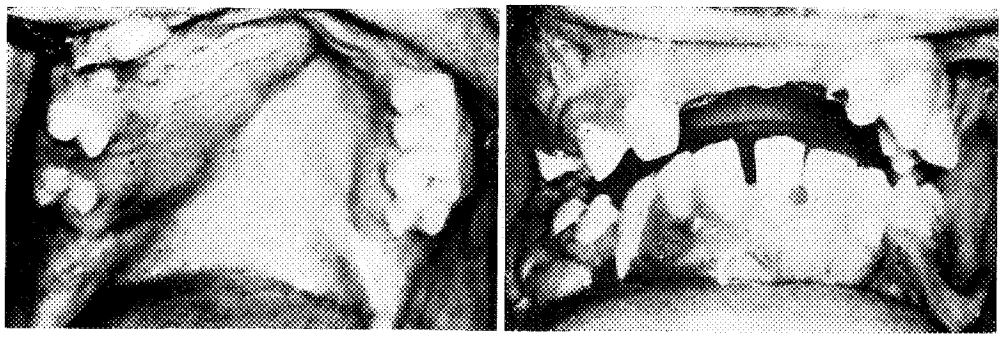


Fig. 4. Sept. 12, 1955. *A*, Overgrowth of right maxilla. *B*, Malocclusion of teeth.

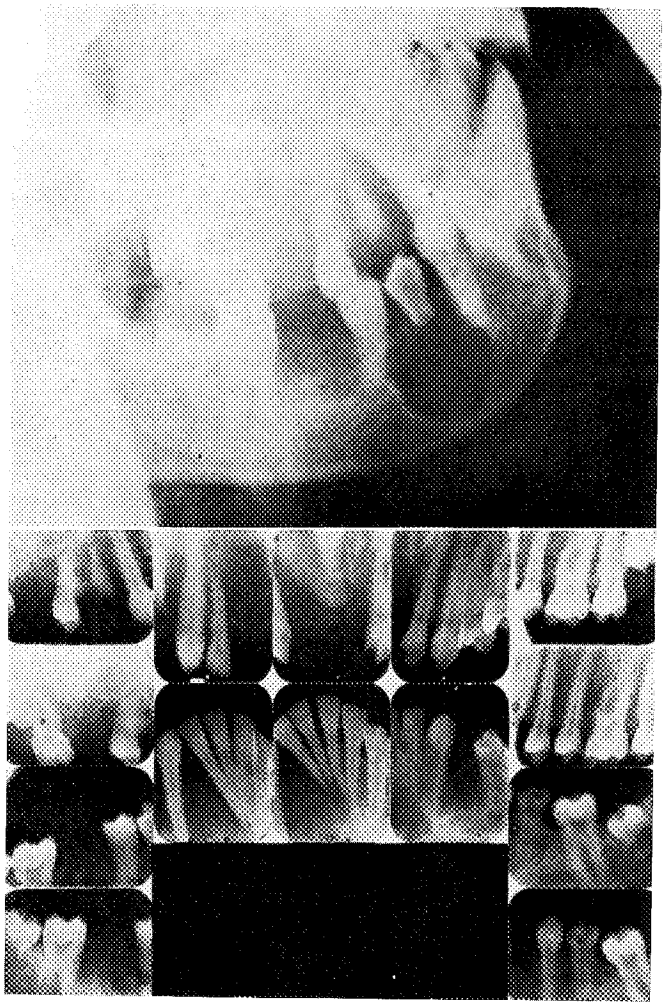
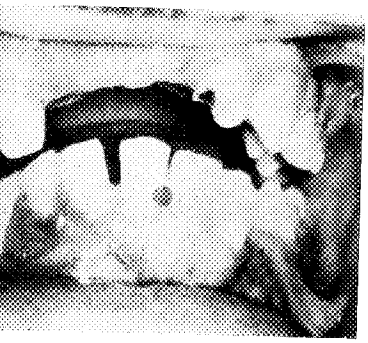
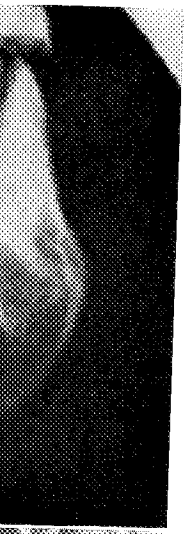
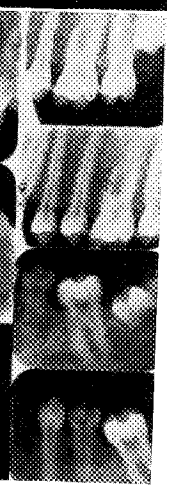


Fig. 5. Sept. 12, 1955. *A*, Roentgenogram of right mandible. *B*, Periapical roentgenograms showing separation of teeth.

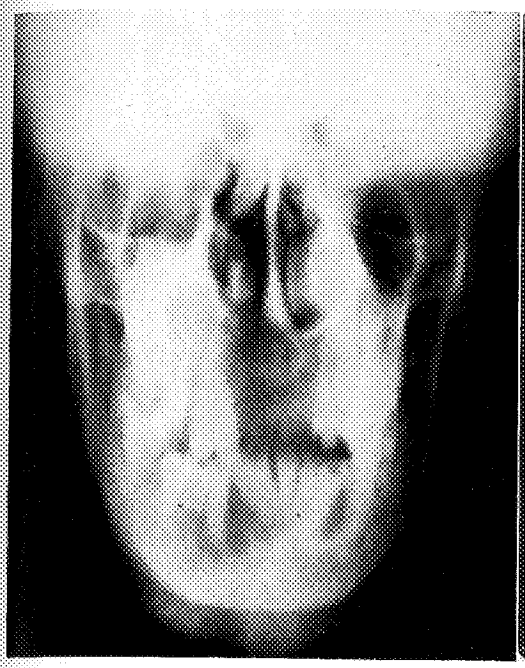


B, Malocclusion of teeth.





B, Periapical roentgenograms



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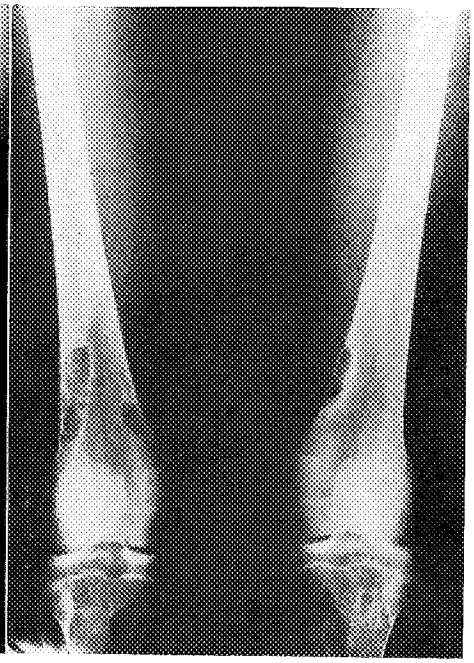


Fig. 7

Fig. 6. Sept. 12, 1955. Tomogram outlining extent of maxillary lesion.
Fig. 7. Sept. 12, 1955. Roentgenographic appearance of long-bone defects.

Films of the skull showed no abnormalities in the calvarium except for a flattening of the outer table in the upper parietal region, predominantly on the right side but extending about 2 cm. across the midline.

Bone survey. In the lower end of the femora and the upper end of the tibia, there were classic cortical defects (Fig. 7), ranging from 2 to 6 cm. in length. They were scalloped in contour and had sharply defined, slender margins of increased density and were located in the cortex.

Surgery

In Oct. 27, 1955, the patient was given a general endotracheal anesthetic, and an operation was undertaken to curette the lesions of the mandible and maxilla. An incision was made over the crest of the alveolar ridge from the region of the lower right second premolar to the left second premolar. The lower right and left central incisors, lateral incisors, right and left cuspids, and right first premolar were extracted. The mucoperiosteum was reflected buccally and lingually, exposing the areas of fibrous tissue, which were easily curetted. The appearance of these lesions was that of a grayish white, gritty fibrous tissue. There was extensive bleeding in all curetted areas, but this was controlled with pressure packs and Gelfoam. The defects were filled with autogenous bone chips which had been taken previously from the patient's iliac crest. On Oct. 29, 1955, the fibrous tissue was curetted from the maxilla, and the defect was filled with autogenous bone chips.

Pathology report

The specimen from the mandible consisted of multiple fragments of a brownish red, firm, fibrous tissue. The sections (Fig. 8) showed a fibroblastic growth, arranged in a somewhat whorling or interlacing pattern, mixed with a prominent number of multinucleated giant cells. The giant cells showed abundant eosinophilic cytoplasm and numerous round, moderately hyperchromatic nuclei. The matrix was composed of spindle-shaped cells of the fibroblastic

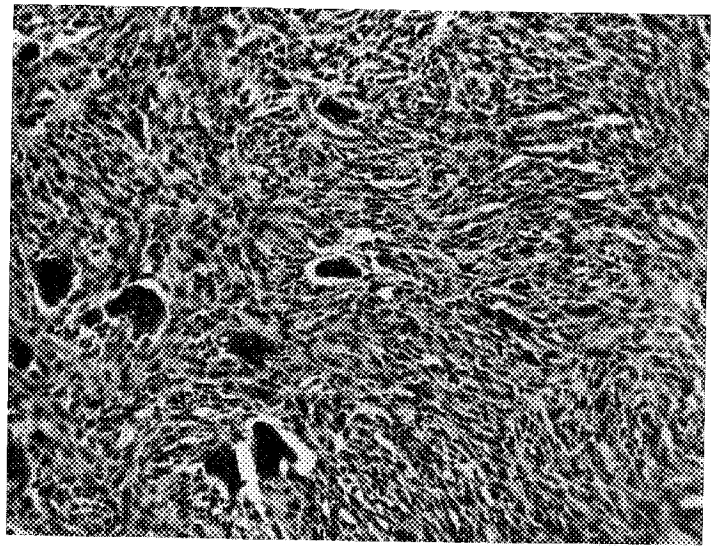


Fig. 8. Photomicrograph showing fibroblastic growth in whorling pattern with multinucleated giant cells.

type and, in some areas, interstitial hemorrhage and histiocytes containing hemosiderin. The pathologic diagnosis was fibrous dysplasia with giant-cell formation.

Sections of the specimen removed from the maxilla were similar in histologic appearance to the specimens removed from the mandible and long bones in 1949.

Postoperative follow-up

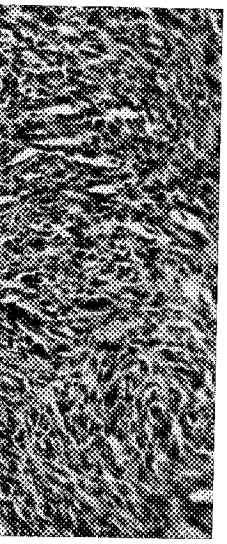
The postoperative course was uneventful. On April 26, 1956 a roentgenogram of the mandible (Fig. 9) revealed increased density and filling-in of the mandibular cystlike areas with new bone. By June 28, 1956, there was roentgenographic evidence of remodeling in the anterior maxilla. There was no indication of disease progression in either the mandible or the maxilla.

In January, 1956, the patient noticed some pain in the middle thoracic area. An open biopsy of this mass was performed in the perivertebral region and was reported by the pathologist as showing fibrosarcoma. There was slight tenderness at the lower portion of the mass. The tumor was slightly larger than an egg, adherent, and soft. There was some hypalgesia of the paraumbilical region on the left from D8 to D11. The deep tendon reflexes were active bilaterally and equally. The right knee jerk showed little increase. There was a questionable bilateral Babinski reflex. The other neurologic examination findings were within normal limits.

On Jan. 24, 1957, a myelographic examination of the spinal cord was negative. The spinal-fluid protein, however, was increased to 80 mg. per cent and the serum calcium to 11.9 mg. per cent. An operation was performed in an attempt to remove the lesion. It could not be completely removed, however, since it had spread deeply between the fifth, sixth, and seventh ribs at their posterior extremities and had destroyed the transverse processes and posterior spines of the appropriate vertebrae.

Pathology report

The histologic structure (Fig. 10) showed a definitely malignant and infiltrating sarcoma, which was fibrous in many parts with areas of myxomatous transformation. In some parts, there was margination of fibrotic tissues of a reactive type along the outer aspects of the tumor, with incorporation of pre-existent muscle fibers into the growth pattern. A definitive nerve



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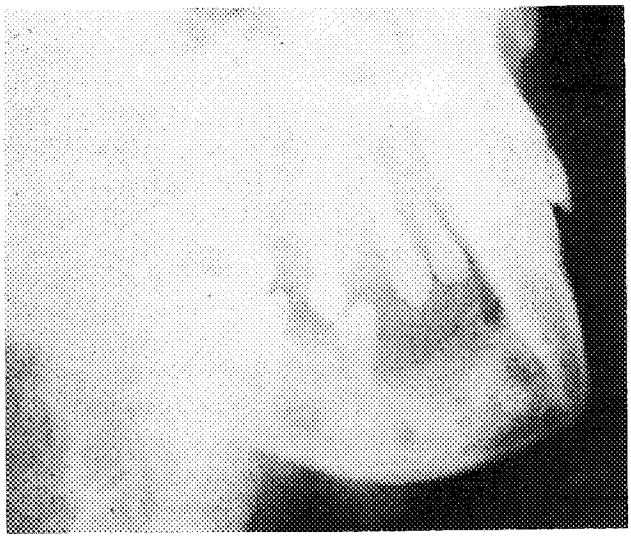

Fig. 9. April 26, 1956. Postoperative result after enucleation of mandibular lesions and placement of bone chips.

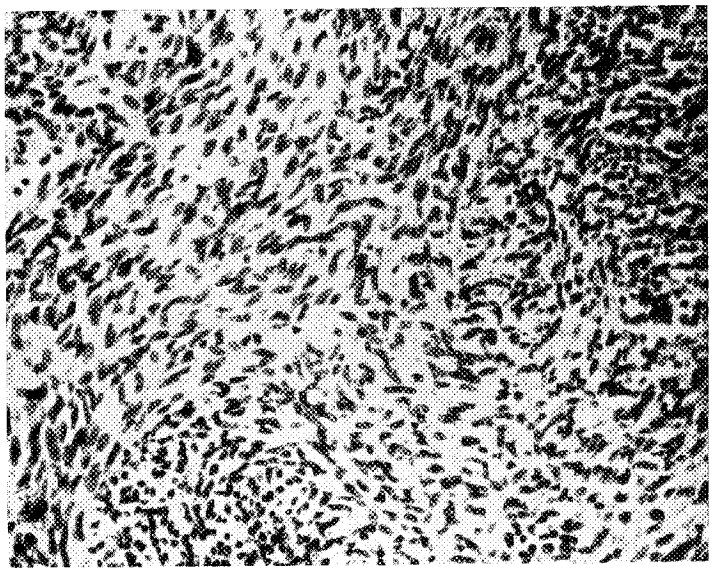

Fig. 10. High-power photomicrograph of myxofibrosarcoma.

origin could not be assigned on the basis of histologic structure, but such an origin was considered possible if not probable. The diagnosis was myxofibrosarcoma, Grade II (consistent with nerve origin).

The patient did very poorly following the operation. Her downhill course was characterized by loss of weight, pain, and a large, very rapidly growing recurrence of the tumor in the operative site. By the end of March, 1957, she had become paralyzed from the waist down. On June 1, 1957, she was seized with convulsions, became comatose, and died.

DISCUSSION

The preceding case shows the difficulty encountered in stereotyping this condition. The patient lacked one of the classic signs of polyostotic fibrous dysplasia, namely, precocious puberty. (Menstruation began at age 14.) Also, the pigmentation was in the form of generalized melanosis, with no tendency to be unilateral.

Oral melanotic pigmentation was not present in this case. It has been mentioned only twice in the literature,[15, 36] but it may be more frequent than reported.

The discovery of the bone lesions in 1949 during a routine examination is very typical of the condition. Skeletal expansion was so gradual that the patient did not notice the progressive deformity. In 1955 the expanding palatal lesion (Fig. 4) was discovered during a routine dental examination. Since the disease has an indefinite progression, the patient with such a lesion should be closely followed and checked every 6 to 8 months.

It is interesting to note the lack of development of the lower right first premolar (Fig. 5). When first examined, it would appear that this represents root resorption, due possibly to pressure from an ameloblastoma or a multilocular cyst. However, when the roentgenogram taken in 1949 is examined, we see that the root of this tooth never fully developed. From this we conclude that the tooth's development was prevented by the production of pathologic tissue which took the place of the area destined to be the apical end of the tooth.

The two conditions from which the case had to be differentiated were hyperparathyroidism and neurofibromatosis of Recklinghausen. The former was ruled out by the normal blood chemistry and the lack of generalized skeletal decalcification. The latter, however, remains a point in question.

In 1944, Thannhauser[35] attempted to show that fibrous dysplasia was not a separate entity but was related by its clinical and histologic features to neurofibromatosis of Recklinghausen. Jaffe,[21] in 1945, refuted this hypothesis and described the distinctive appearance of the skin lesions in each disease. He described the pigmentation of fibrous dysplasia as having an "irregular, smeary appearance," while those in neurofibromatosis were "sharper, somewhat less irregular in outline and predilecting the trunk." The fibrosarcoma in our case was interpreted by the pathologist as being neurogenic in origin, which would seem to add some credence to Thannhauser's hypothesis. Roentgenograms of the spine taken in 1949 and 1955, however, were negative, indicating one of two different possibilities. The first is that two separate entities were present, the fibrosarcoma developing independently of the polyostotic fibrous dysplasia. The chance of a malignant degeneration of fibrous dysplasia in this case is unlikely in view of the previous negative roentgenographic reports of the site from which the fibrosarcoma developed. The second possibility is that the condition represented a case of multiple neurofibromatosis with malignant degeneration.

Café au lait spots may precede by years the appearance of the characteristic cutaneous or subcutaneous nodules. The pigmentation is not symmetrical and does not follow the distribution of nerve roots. In this case the melanosis was generalized and not distributed along nerve roots.

Whorls of spindle cells, when present in fibrous tissue (Fig. 8), are thought by some pathologists to be indicative of neurofibromatous origin. This cellular

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tous origin. This cellular

pattern, however, is also present in some cases of monostotic and polyostotic fibrous dysplasia.

Courvoisier[7] found fifty-three instances of malignant transformation in 800 cases of neurofibroma; fifteen were classified as pure sarcoma and the rest as myxo- and fibrosarcoma. It is interesting to note that the malignant lesion in this case was a myxofibrosarcoma. It should also be noted that the patient showed mental retardation with a tendency toward depression, a trait described by many as occurring in these patients.

When the clinical appearance, roentgenograms, and histologic specimens of the patient are considered, polyostotic fibrous dysplasia would seem to be the most likely explanation. However, if the clinical progress and malignant transformation are considered, a diagnosis of multiple neurofibromatosis would seem more tenable.

Reported results of treatment of these lesions by placement of bone chips have been varied. In this case, the mandibular lesions that occurred in 1949 were merely curetted out and their bases were cauterized. Six years later there was roentgenographic evidence of recurrence of the lesions (Fig. 5).

Because of the age of this patient when seen in 1955, it was thought that the condition in the facial bones would progress still further to produce marked deformity. They would probably become self-limited sometime during the latter part of puberty.

The patient had the typical leonine appearance seen in the more bizarre cases of polyostotic fibrous dysplasia or Paget's disease, slight facial asymmetry, and gross deformity of the hard palate. It was thought that curettage and placement of bone chips might stem the progress of the condition by stimulation of osteogenesis and might also prevent further facial deformity. The results obtained seem to bear out the original belief.

SUMMARY AND CONCLUSIONS

A short review of the literature on polyostotic fibrous dysplasia has been presented, and a case history has been reported.

When a diagnosis is being sought, it is essential to use all of the sources of information at our disposal: (1) roentgenograms of long bones and the affected bones, (2) histologic examination of soft tissue or bone lesions, (3) thorough blood chemistry studies, and (4) a careful history and physical examination. Occasionally, even after all of these tests are carried out, we are at a loss to affix a definite name to the condition.

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