

# FIBROUS DYSPLASIA OF BONE

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THE significance of "fibrous dysplasia of bone," a relatively recent addition to medical nomenclature, still remains obscure. The term is used to designate certain specific osseous lesions often subclassified into three main types, depending upon their anatomic distribution and their association with other extraskeletal anomalies. In type I, the monostotic, the lesions are single or multiple but are confined to one bone; in type II, the polyostotic, the lesions involve more than one bone; in type III, the lesions are widely disseminated throughout the entire skeleton, although unilateral preponderance is often seen.

In type III fibrous dysplasia of bone, common accompaniments are cutaneous pigmentation and, especially in females, precocious puberty. Albright and his associates<sup>1</sup> were the first to demonstrate this relationship clearly. Their published report in 1937 stimulated interest in this curious anomaly and led to its recognition as an established clinical entity; thus, the disorder is often referred to as "Albright's brown-spot syndrome." Other descriptive terms have been used, such as "pseudohyperparathyroidism" and "osteitis fibrosa cystica without hyperparathyroidism."

For all three types the current trend, as suggested by Lichtenstein and Jaffe,<sup>2</sup> is toward the use of the general heading, "fibrous dysplasia," since in all three types there is striking roentgenologic and histologic similarity among individual lesions. We shall use this term and shall try to justify its use from the evaluation of our own experiences with the pathologic state it designates.

## CLINICAL STUDY

A survey of our records for the past 25 years disclosed 11 cases in which the clinical, roentgenologic or histologic features were sufficiently characteristic to justify the diagnosis of fibrous dysplasia and also to designate the extent of the disease. Findings in the 11 cases are briefly outlined in the table. There were six additional cases exhibiting the typical microscopic criteria; these were not included in our study since adequate roentgenographic skeletal surveys were not available.

Of the 11 patients considered, 8 had extensive skeletal involvement, in one of whom it was predominantly unilateral. In the remaining three cases the lesions were confined to the femur and tibia of the same side, a strikingly monomelic distribution.

Although 6 of these 11 patients were more than 30 years of age when

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initially seen, 8 had a long-standing history of osseous derangement dating back to childhood, and 6 of them had sustained major fractures.

Of the entire group only one, a 19 year old girl, had a history of precocious puberty. She had a severely rarefied skeleton and at the age of seven years had pubic and axillary hair, accelerated somatic development, and onset of menstruation. No pigmented areas were noted.

Two patients had extensive pigmentation; characteristically this was accompanied by widespread bone disease.

Two of the patients had had hyperthyroidism that had been corrected by subtotal thyroidectomy. The unusual association of fibrous dysplasia and hyperthyroidism has been mentioned in the past by others.<sup>2,3</sup>

Another of the 11 patients had two parathyroid explorations under the erroneous impression that the bone disease might be due to hyperparathyroidism. These operations were performed in the early 1930's prior to the original descriptions by Albright and associates. It can now be fully appreciated that parathyroid tumors are unrelated to this particular malady and hence parathyroid explorations are no longer justified.

### SYMPTOMS AND SIGNS

Because major functional disabilities in fibrous dysplasia arise from skeletal defects, its symptomatology is primarily that of skeletal dysfunction. In types I and II, where the lesions are frequently single and never widely disseminated, there are few, if any, symptoms. The importance of their occurrence is often confined to the diagnosis of an observed roentgenologic defect in one or two bones. We shall confine the remainder of our discussion largely to the disseminated form of the disorder, since it is in this type that the other clinical features appear.

Persistent dull pain in the extremities, particularly the legs, is a frequent complaint of patients with fibrous dysplasia, and was the presenting symptom in more than half of our cases. A pathologic fracture may offer the first indication of the disease. When the lesions are widespread, the fractures are sometimes multiple or recurrent. One of our patients suffered fractures of the sternum, both clavicles, both femora, and nine ribs, in a period of nine years.

Often the onset of symptoms is more insidious. The involved skeletal part may have the appearance of a deformity with obvious local enlargement that is due either to bending or to expansion of the bone. An antecedent history of trauma without a genuine fracture can sometimes be traced in such instances. Actual lengthening of a limb may occur; however, with marked and progressive involvement, shortening of the extremity is more likely. A troublesome limp and gait disturbance may subsequently develop. The osseous changes with the resulting distortions usually progress slowly until skeletal growth terminates with the advent of puberty. At this time there is ordinarily a definite cessation of the pathologic process in the bones. However, the patient may become permanently crippled if both legs have been significantly affected.

In type III, the skull is frequently the site of a major localization of the

TABLE  
Analysis of 11 Cases Diagnosed as Fibrous Dysplasia of Bone

Case No.	Age (yr.)	Sex	Duration (Known Years)	Skeletal Involvement	Presenting Complaint or Problem	Pigmentation	Ca-P	Phosphate	Biopsy	Fractures	Remarks
1	31	M	23½	Wide-spread	Leg pains. Facial asymmetry.	Extensive	Normal	4.25	None	14	Parathyroid exploration (twice).
2	37	M	31	Extensive	Pain left leg with bowing.	None	Normal	7.6	Yes	8	Lesions predominantly left-sided (femur, tibia, ilium, 2 tarsal and one metatarsal bones and 10th rib). Skull and 10th dorsal vertebra implicated bilaterally.
3	57	F	Noted in routine chest film in 1941.	Extensive	Symptoms of hyperthyroidism for 8 yr.	None	Normal	5.3	Yes	None	Thyroidectomy.
4	48	M	36	Extensive	Bilateral blindness 3 weeks' duration.	None	Normal	12.0	None	3	At age of 12 yr. difficulty breathing through left nostril. Overgrowth of all bones left side of face and forehead.
5	27	F	4	Left tibia and femur	Pain in left leg.	None	Normal	2.4	Yes	1	

FIBROUS DYSPLASIA

TABLE -- (Continued)

Case No.	Age (yr.)	Sex	Duration (Known Years)	Skeletal Involvement	Presenting Complaint or Problem	Pigmentation	Ca-P	Phosphatase	Biopsy	Fractures	Remarks
6	18	F	16	Extensive	Pain in right leg.	None	Normal	15.4	Yes	5	
7	26	F	5	Right tibia and femur	Recurring pain right knee and leg.	None			Yes	None	
8	60	F	Over 50	Extensive bilateral	Soreness and pain both legs.	None	Normal	12.5	Yes	1	Vertebral involvement since childhood with marked kyphosis. Thyroidectomy 5 yr. previously.
9	33	F	21	Right tibia and femur	Tiredness, irritable colon.	None	Normal	1.5	None	1	Pathologic fracture of right femur at age of 12 yr.
10	18	F	18	Extensive	Obesity.	Present	Normal	14.1	None	None	Marked asymmetry of head present since birth.
11	19	F	14	Extensive	Pain in right arm, at side of pelvis, and right ribs.	None	Normal	5.2	None	8	Menses and secondary sex characteristics appeared at age of 7 yr.

disturbance. When the skull becomes involved, the cranial tables usually reveal sclerosis and thickening as well as areas of rarefaction. This is in striking contrast to the events in hyperparathyroidism in which cranial thickening is not observed. Facial asymmetry may develop, due to unilateral bony overgrowth; frequently it is the only visible stigma of the disease. Occasionally, grotesque and hideous deformities are produced, and these probably account for most examples of so-called leontiasis ossea. Involvement of the roof of the orbit may result in considerable downward displacement of the eyeball and is a rare cause of unilateral exophthalmos. Disease of the sphenoid wings may lead to compression of one or both optic nerves with consequent optic atrophy and blindness. This was the presenting problem in one of our cases (case 4). The patient, a 48 year old man, had noted the onset of bilateral blindness three weeks prior to examination. However, the history revealed that at the age of 12 years he had begun to have difficulty in breathing through the left nostril (thickening of left nasal bones) and showed progressive facial asymmetry. He had sustained two femoral fractures during childhood. Widespread skeletal involvement was revealed at the time of initial examination.

Similar morbid processes may result in varying degrees of deafness caused by encroachment upon the auditory apparatus.

Of interest is the case reported by Neller<sup>4</sup> in which the patient was operated upon, for, presumably, an infected cyst of the scalp. The lesion proved to be a herniation of the meninges through a cranial osseous defect produced by fibrous dysplasia.

**Pigmentation:** Cutaneous pigmentation is the most common extraskeletal manifestation of this condition. Lichtenstein and Jaffe<sup>2</sup> in 1942 reported an incidence of 35 per cent. In our review of about 100 cases reported since then, 63 per cent of the patients exhibited this abnormality. The higher incidence may be partly due to a more careful scrutiny by examiners as a result of their increased awareness of the clinical relevance of pigmentation. Jaffe<sup>5</sup> emphasized how readily these colored patches can be overlooked unless a meticulous examination, particularly of the scalp, is carried out. These flat spots are yellowish or yellowish-brown in color (*café-au-lait*), and reflect accumulations of abnormal amounts of melanin in the basal cells of the epidermis. The pigmented area may consist of a small uniform patch or it may cover a very extensive field. The edges are typically serrated and have been described by Albright as "irregular as the coast of Maine when compared to the coast of California."

**Skeletal Precocity:** In many cases there is hastening both of skeletal growth and of maturation; occasionally skeletal maturity occurs without sexual precocity. The aberration results in a child's becoming exceedingly tall for his age and manifesting epiphysial development far in advance of the chronologic age. However, these persons ordinarily reveal a premature arrest of growth and may eventually appear of shorter stature than average because of the accelerated ossification and fusion of the epiphyses.

**Sexual Precocity:** This is noted in 20 to 30 per cent of all cases. The incidence of sexual precocity has probably been overestimated because of the

spectacular nature of the symptoms as compared with those due to skeletal anomalies or pigmentation.

The early puberty is almost invariably seen in females; however, several instances of its occurrence in males are on record.<sup>6, 7</sup> Its etiology is unknown. Stimulation of the hypothalamus by pressure from an adjacent fibrodysplastic lesion has been suggested as a cause. The scant autopsy material available fails to shed any light on the problem. From a purely functional standpoint, it appears to be an early "awakening" of the pituitary.

**Blood Chemical Findings:** An elevated alkaline phosphatase concentration is the only repeatedly abnormal laboratory finding and in some, it too is normal. The concentration tends to parallel roughly the degree of skeletal rarefaction. Blood calcium and phosphorus determinations and urinary and fecal calcium excretions are characteristically within normal range; these contrast with the deviations usually encountered in hyperparathyroidism.

### Roentgenologic Findings

The lesions in all three types of fibrous dysplasia present a fairly typical roentgenographic appearance. If a number of bones are involved, the roentgenographic evidence is so unmistakable that the diagnosis can be made on this basis alone. In no other pathologic entity is there as decided a tendency towards monomelic and unilateral skeletal involvement. Even when both sides are extensively involved, there usually, though not always, is a predominance of the lesions in one side of the body. Curiously, the pigmentation shows a similar tendency to homolateralization.

The histologic features of bony lesions in fibrous dysplasia may account in part for the roentgenologic appearance of the lesions. The lesions consist essentially of masses of fibrous tissue in which are found numerous scattered spicules of metaplastic bone. While this cellular mass is often seen beneath the periosteum, the commonest site is in the medullary portion of the bone. The latter results in resorption and thinning of the cortex from within with a concurrent outward expansion as mentioned earlier. Bowing and fractures can readily occur through these weakened areas. On the other hand, considerable ossification of the connective-tissue substratum may take place, and on the roentgenogram this may be observable as a homogeneous density, described as a "ground-glass" or "smudged" appearance.

The following roentgenographic features have been considered valuable diagnostic criteria:<sup>5, 8-10</sup>

- (1) A well-demarcated radiolucent area within a bone.
- (2) Usual localization of the lesion in the diaphysis when a long bone is attacked.
- (3) Presence of normal osseous fabric between lesions.
- (4) "Smudged" or "ground-glass" appearance due to intrinsic calcification. Usually observed in the medullary portion of the affected long bones.
- (5) Ridge formation and trabeculation suggesting cystic changes and often producing a multilocular appearance. (Actually, cyst formation seldom occurs and when found it is the result of focal degeneration of, or hemorrhage into, the fibrodysplastic tissue.)

- (6) Broadening or expansion of the cortex with frequent marked deformities.
- (7) Absence of periosteal reaction except in the presence of a pathologic fracture.
- (8) Osteosclerotic skull lesions (besides rarefaction) with consequent disfigurement.
- (9) Frequently accelerated osseous growth in childhood with early epiphysial closure and resulting dwarfism or deficient stature.
- (10) Pathologic fractures with frequent shortening and gross distortion of bone.

### ETIOLOGY AND HISTOPATHOLOGY

According to Lichtenstein and Jaffe,<sup>2</sup> the histologic peculiarity of polyostotic fibrous dysplasia seems to be a "disturbed function or development of the bone forming mesenchyme" which normally is the origin of the myeloid or fatty marrow. This dysfunction results in the substitution of the osseous medulla by a peculiar cellular aggregate consisting primarily of connective tissue frequently arranged in interlacing bundles and whorls. Within this fibrous tissue are varying numbers of trabeculae of partly calcified, newly formed, primitive bone. Islands of cartilage can be seen in some of the sections. Groups of multinuclear giant cells closely resembling osteoclasts are often noted in the neighborhood of blood vessels or of hemorrhages. Microscopic study reveals that bone trabeculae and the adult cartilage are formed by the direct metaplasia of the undifferentiated fibrous or mesenchymal (reticuloendothelial) tissue. Mature collagenous connective tissue can be seen to form by enlargement and collagenous transformation of pre-existing and newly formed reticular fibrils.

Since these pathologic oddities are seen so frequently in early childhood, Lichtenstein and Jaffe<sup>2</sup> envisioned a congenital basis for the anomaly.

Valls, Polak and Schajowicz,<sup>11</sup> using special stains for embryonal tissue, were able to confirm Lichtenstein's earlier observations. They emphasized that the presence of large cartilaginous masses growing in plain mesenchyme was strong evidence favoring the congenital origin of this dysplastic tissue. These masses, however, were only observed in the polyostotic form of the disease, which they accepted as a real dysplasia. The absence of the cartilaginous masses from the monostotic or solitary type cast doubt on the latter's congenital origin and on the possibility of an etiology common to the polyostotic form. The authors asserted that monostotic lesions may correspond to the final cicatricial stages of inflammation or traumatic processes. They admitted that the problem of etiology is a difficult one and at the present time is not settled.

Schlumberger,<sup>12</sup> after a review of 67 cases of monostotic fibrous dysplasia studied at the Armed Forces Institute of Pathology, concluded that the lesions of the polyostotic and monostotic forms of the disease are produced by different etiologic factors. He expressed the belief that many monostotic lesions probably represent an abnormal response to bone injury. He was unable to find islands of cartilage in any case of his series except in connection with healing pathologic fractures.

As the most logical etiologic mechanism, Albright postulated that the disease is a dysfunction of the central nervous system primarily localized in the region

of the hypothalamus. In his view such a disturbance would best explain widespread and seemingly unrelated lesions which involve simultaneously the skin, the skeleton, and the endocrine glands.

## DIFFERENTIAL DIAGNOSIS

### A. Polyostotic form:

1. The importance of the exclusion of hyperparathyroidism in the differential diagnosis has already been mentioned; convincing proof is offered by the relatively high percentage of unnecessary explorations for parathyroid adenomata in cases subsequently diagnosed as fibrous dysplasia.

The differentiation between the two disorders is not usually difficult to make. When precocious puberty and extensive skin pigmentations are present there should be no uncertainty. In incomplete forms of the disorder it is well to remember that hyperparathyroidism is rare in childhood, in which fibrous dysplasia usually becomes manifest. In the latter ailment there usually is no constitutional symptomatology; the patients ordinarily feel well except for the skeletal disabilities. In hyperparathyroidism patients are frequently distressed with severe muscular weakness, digestive disturbances, and renal lithiasis and nephrocalcinosis which often result in renal failure.

The skeletal system in parathyroid disease may show widespread osteoporosis without osteosclerosis. Resorption of the periodontal lamina dura is common. In fibrous dysplasia the osseous defects are spotty in character with roentgenologically normal bone between them. The thickening of cranial tables with cephalic asymmetries, the condensation of the long bones with the resulting "ground-glass" appearance in association with a consistently noninvolved lamina dura are features never noted with parathyroid hyperfunction.

Finally the characteristic hypercalcemia and hypophosphatemia with negative calcium balance of hyperparathyroidism contrast with the normal values seen in fibrous dysplasia.

2. Skeletal enchondromatosis (dyschondroplasia or Ollier's disease) begins early in life and is associated with dwarfism and exceptionally may be predominantly unilateral thus resembling fibrous dysplasia. However, in cases of skeletal enchondromatosis there is a characteristic involvement of the bones of the hands and feet by cartilaginous exostosis giving rise to a typical punched-out appearance with bulging of the contours visible on the roentgenograms. Since only bones ossified in cartilage are affected in Ollier's disease, rarefaction of the skull is extremely rare. Disturbances of the epiphyses are a prominent finding in cases of skeletal enchondromatosis, and are not observed in those of fibrodysplastic anomalies. Sexual precocity and cutaneous pigmentation are additional factors helpful in the differentiation since they are never identified with Ollier's disease. The latter's distinctive histologic picture, which is basically hyaline cartilage, should settle any remaining diagnostic indecision.

3. Hand-Schüller-Christian disease (lipoid granulomatosis) is sometimes mistaken for fibrous dysplasia when skull roentgenograms reveal radiolucent areas. Distinguishing points are the frequent occurrence of diabetes insipidus



and abnormally high blood cholesterol levels and the absence of osteosclerosis, cutaneous pigmentation and sexual precocity in the xanthomatous bony disorder as compared to polyostotic fibrous dysplasia. Occasionally a biopsy becomes necessary for differentiation; the presence of an abundant number of foam cells establishes the presence of xanthomatosis.

4. Neurofibromatosis with skin pigmentation frequently exhibits rarefied osseous areas and consequently assumes importance in the differential diagnosis. However, in neurofibromatosis the defects of bone are not extensive and fail to reveal sclerosis. They are usually restricted to certain regions of the skeleton, such as the upper end of tibiae and lower ends of femurs. The pigmented areas have smooth edges as compared to the irregular margins commonly discernible in fibrous dysplasia.

5. Multiple myeloma may at times have to be strongly considered. This more ominous state is almost never seen in patients less than the age of 40 years. The following distinguishing traits are commonly recognized: elevated serum protein and calcium levels, Bence Jones proteinuria, plasma cells in the peripheral blood and a characteristic marrow histology. Renal calculi, renal dysfunction, and anemia are commonly associated serum findings. Alkaline phosphatase is usually normal.

6. In sarcoidosis the osseous lesions are usually confined to the hands and feet. The frequently accompanying granulomatous patches involving the skin, lymph nodes, parotid glands, uveal tract, and lungs, the hyperproteinemia and hyperglobulinemia and the palsies of the seventh and other cranial nerves should clarify the diagnosis. Occasionally, when these features are missing a biopsy is required to differentiate sarcoidosis from fibrous dysplasia.

7. Paget's disease, granulosa-cell tumors of the ovaries with precocious puberty, and metastatic bone malignancies rarely cause any confusion and deserve only passing mention.

### **B. Monostotic form:**

Until a clarification of the etiology of monostotic fibrous dysplasia is definitely achieved, it would probably be wise to consider it a milder grade of the polyostotic form, as Lichtenstein originally suggested. The lesion or lesions of this type of fibrous dysplasia are much more difficult to identify on clinical and roentgenologic grounds alone than are those of the polyostotic type.

It is interesting to note that of the 67 monostotic cases reported by Schlumberger<sup>12</sup> in 1946, the correct diagnosis was not given once in the roentgenographic report before the histologic studies were completed. In only 19 cases was the lesion recognized as fibrous dysplasia by the pathologists who submitted the specimens to the Armed Forces Institute of Pathology.

Of the long list of solitary lesions that are apt to cause diagnostic difficulties, simple cysts, giant-cell tumors and nonosteogenic fibromas are among the commonest.

Solitary bone cysts characteristically occur in the metaphysis of long bones, particularly the humerus, femur, and tibia, in contrast to fibrodysplastic tissue which is prone to develop in the diaphysis. The cysts produce resorption with

expansion of the bone and thinning of the cortex, but the osseous condensation seen in the other condition is always lacking.

Giant-cell tumors are ordinarily found in an older person; they tend to be located close to the epiphyses and produce a multicystic, trabeculated appearance in the roentgenogram, as if the mass were composed of large bubbles. There is no intrinsic calcification demonstrable. Moreover, these tumors exhibit a strikingly favorable response to irradiation.

Nonosteogenic fibromata possess no distinguishing features except for the absence of thickening of bone.

Usually a tissue biopsy is essential to ascertain the true nature of these monostotic lesions.

### PROGNOSIS AND TREATMENT

The outlook for the great majority of patients with fibrous dysplasia of bone is very good and their life expectancy is normal. A few die of their disease, but these patients are those who have been burdened with extensive skeletal disease from an early age and, especially those with significant endocrine dysfunction. Considerable slowing and actual arrest of the morbid osseous processes ordinarily occurs with the advent of skeletal maturity.

Therapy in this disorder calls for a great deal of individualization. Only those areas causing or apt to cause trouble require attention. These are often located in the upper end of the femurs and in the long bones generally. Thorough curettage of the unhealthy tissue and filling of the resulting cavity with autogenous bone chips is an effective method of eradicating the disease locally and strengthening the osseous structure. The entire lesion should be resected; otherwise, its recurrence after absorption of the grafted chips is to be anticipated.

If a bone has undergone one or more fractures or is in danger of fracturing, the introduction of a large graft may be particularly helpful. Nonoperative therapy, such as braces and corsets, is also indicated for support or correction of deformities. Patients should be cautioned as to the proper use of the involved skeletal part in order to prevent fractures.

### SUMMARY

1. Some of the clinical, roentgenographic, and histologic features of fibrous dysplasia of bone are presented as a basis for a review of the subject of fibrous dysplasia with special emphasis on its diagnosis and differentiation from other osteolytic diseases, particularly hyperparathyroidism.

2. Some of the present thoughts on the controversial issue of the etiology of the monostotic variant and its relationship to the polyostotic form are briefly discussed.

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