ALBRIGHT'S SYNDROME — A GROUP OF CASES CHARACTERIZED BY OSTEITIS FIBROSA DISSEMINATA, AREAS OF PIGMENTATION AND A GONADAL DYSFUNCTION.

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Although the relationship of the parathyroid glands to the decalcification of bone resulting in the disease known as von Recklinghausen's[1] osteitis fibrosa cystica was suspected earlier, it was not until Mandl's[2] successful removal of a parathyroid adenoma in 1925 that the true significance of this relationship was generally recognized. The first clinical diagnosis of this condition in the U. S. A. was made by Dr. Eugene F. DuBois[3] in 1926, the patient being a sea captain named Martel, now famous because he was the first case recognized in this country and because it required seven explorations before the tumor in aberrant parathyroid tissue was finally found in the anterior mediastinum. Barr[4] reported the first proved case in 1929, and suggested the name of hyperparathyroidism. [In 1936 Wilder and Howell[5] were able to collect 135 proved cases from the literature, a large proportion of these coming from the North Atlantic States and twenty-five from the Massachusetts General Hospital in Boston alone. From the Mayo Clinic Wilder could assemble only five proved cases. He suggested that this unusual distribution might be due to differences in the amount of ultraviolet light in different parts of the country. Whatever the true explanation may be, the emphasizing of the irregular distribution of reported cases had the effect of producing an even more careful and intense search for the disease in various large clinics throughout the country. Largely as a result of this there were referred to the Massachusetts General Hospital several patients, who although presenting osteitis fibrosa resembling that of hyperparathyroidism did not fulfill all the criteria for diagnosis of this condition.] Fuller Albright[6] and his co-workers in 1937 thus reported five examples of a bizarre syndrome, some of which had been confused with hyperpara-

*By invitation.

thyroidism and had been subjected to a fruitless operative search for adenomas of the parathyroid. These patients showed a triad of apparently unrelated features, viz: (1) osteitis fibrosa cystica, (2) brown pigmented skin spots, and (3) precocious puberty in females, but not in males.

The literature indicates that at least 12 examples of this syndrome had been previously reported under various titles, the first by Weil[7] in 1922 was designated as "Pubertas Praecox und Knochenbruchigkeit." Cases were also published under the headings of "osteodystrophia fibrosa,"[8] "Von Recklinghausen's Neurofibromatosis"[9] of atypical form, "Xanthomatosis,"[10] "Juvenile Paget's Disease."[11] In 1938 Lichtenstein[12] proposed the name of "polyostotic fibrous dysplasia." Since Albright was the first to establish this syndrome as a clinical entity demarcating it from other accepted osseous disease, and since a simple adequate descriptive term is not available, we prefer to associate this condition with Albright's name. Polyostotic fibrous dysplasia fails to include the skin pigmentation and the precocious puberty in females, features of the syndrome which are just as important as the bone lesions.

Description of Syndrome. Incidence: The syndrome occurs in two forms, (a) the complete, in which the triad of cystic bone disease, pigmented skin spots and precocious puberty in females occurs, and (b) the incomplete form in which one or two of these features is lacking. At the present time a total of 45 instances of this disease has been reported, 31 of the complete, 14 of the incomplete variety. As to the actual incidence of this syndrome it would appear that bizarre outspoken examples of extreme grade with extensive bone lesions, menstruation in the early years of life and huge areas of pigmentation must be undoubtedly of rare occurrence and would almost certainly have been reported. It is quite possible, however, that the incomplete and milder forms may be more frequent than has been generally realized. Of considerable interest is the recent statement of Dr. Albright[13] regarding Lena Medina of Peru, the little girl who gave birth to a child at the age of five. "In answer to an inquiry, Dr. Gerardo Lozada of Pisco, Peru, her attending physician, informed me that she had both the brown spots and bone changes together with precocity."

Age: The disease occurs in the early years of life, symptoms developing in the complete form almost without exception before the

age of ten. In the incomplete form the patients may be in the third or fourth decade or older before the disease manifests itself clinically.

Sex: In the series of 45 cases reported there were 28 females and 17 males.

Symptoms: The disease may have existed in a patient for some years before it is discovered. The first symptom to attract attention is often a *spontaneous fracture* which leads to *X-ray examination* of the bones. The lesions are then seen to be scattered, localized, and multiple, with considerable portions of the skeleton unaffected. This patchy distribution is in sharp contrast to the general decalcification of all osseous tissue found in hyperparathyroidism and osteomalacia and is more like Paget's disease and xanthomatosis. There is a tendency to unilateral involvement. Areas of increased density and fibrocystic changes of varying size, shape, and density frequently occur and pathologic fractures are prone to develop in these latter areas. Although having the appearance of cysts by X-ray these areas actually represent portions of diseased bone filled with fibrous tissue. Precocious bone age and premature union of the epiphyses are often characteristic findings.

To summarize, there are three points which characterize the roentgen examination of the bones of patients with this syndrome. (1) There are areas of increased density representing overgrowth of bone as well as decreased density. (2) There are parts of the skeleton showing normal bone and (3) the epiphyses are rarely if ever involved. *Biopsy* specimens show osteitis fibrosa with an absence of osteoclasts except in those cases which are rapidly progressive.

The *pigmentation* of the skin occurs in brown patches or spots of varying size, often unilateral, the most frequent site being over the sacrum, buttocks, and upper back. Biopsy shows this to be due to an increase in melanin in the basal layer of the skin. Unilateral bone involvement is apt to be accompanied by pigmented spots on the same side of the body, and bilateral bone disease usually shows bilateral pigmentation, but this is not always so. The amount of pigmentation is roughly proportioned to the degree of skeletal involvement.

The sexual and somatic precocity are present with great regularity in the female, manifested by the early onset of menstruation, secondary sex characteristics and early bone age, and was present in all 16 cases of the complete form of the syndrome thus far reported in

females. In the male this feature is usually absent, puberty coming on at the usual age with little if any evidence of precocity.

Laboratory data: Calcium and phosphorus determinations on the blood show normal values, one of the important diagnostic points in the differentiation from hyperparathyroidism. Calcium excretion may be normal or increased. The blood phosphatase is increased in those cases showing active bone destruction. Blood cholesterol, dextrose tolerance, basal metabolic rate, and excretion of gonadal or estrogenic substances are with few exceptions within normal limits.

Case Reports: Case 1. G. R. A twenty-five-year-old married woman was admitted to the Albany Hospital on June 29, 1936. In November, 1935, she accidentally injured the left forearm. Pain, swelling, and inability to work resulted. An X-ray diagnosis of osteitis fibrosa cystica (von Recklinghausen's disease) was made. The past history revealed a fracture of the right femur in 1930. Physical examination showed a deformity of the left forearm, with swelling over the upper end of the radius, the right femur was bowed and the right leg ¾″ shortened. A small pigmented area of skin was present in the left gluteal region. Skeletal X-rays showed cystic changes principally in the bones of the right leg, the pelvis, left arm and ribs as indicated in the diagram. The characteristic X-ray appearance of these lesions is shown in a film of the right femur. Laboratory data: Urine, blood count, Wassermann and test for Bence-Jones protein were negative. Serum calcium 13.5, 11.5, 10.4. Serum phosphorus 5.2, 7.3. Blood phosphatase 7.4 Bodansky units. Biopsy of rib showed osteitis fibrosa.

Despite the lack of evidence of hyperparathyroidism as indicated by the blood calcium and phosphorus studies, it was felt that parathyroid adenoma could not be excluded. Exploration failed to show tumor. One of the four parathyroids which was approximately twice the size of its fellows was removed. It showed no adenoma on histologic examination. Transient tetany developed which responded readily to calcium administration. We were at a loss to make a satisfactory diagnosis until Dr. Fuller Albright saw the patient (1936) and suggested that she might represent an example of the peculiar syndrome which he was then studying. There was no definite history of sexual precocity, although being of Nordic stock her menses began

at 14 years of age, while those of her mother and sister began at 18 years.

Case 2. C. W. L. An 11-year-old schoolgirl was first seen October 21, 1937. At age 6 right forearm was noticed to be bowed following a fall. At age 8 a neuroma of the optic nerve was removed at the Neurological Institute, New York City. When 10 years old she fell and fractured the left femur. No sexual precocity has been noted. Menstruation is still absent at age eleven. Physical examination showed anterior bowing of right forearm and numerous small pigmented spots scattered over skin of chest and back, arms and legs. Skeletal X-rays showed apparent cystic changes in the distal ends of both femora, the rest of the skeleton being negative. Laboratory data: Urine negative; blood count normal; serum calcium 10.8; serum phosphorus 6.5. Biopsy of skin and bone was refused. Was this an instance of the incomplete form of Albright's syndrome? Sexual precocity was absent. The history of an optic neuroma suggested that this was a case of neuro-fibromatosis of von Recklinghausen—to Dr. Fuller Albright who reviewed the evidence and expressed the opinion that it should not be recorded as an example of his syndrome. Adequate proof of the diagnosis would require biopsy, which unfortunately could not be obtained. Apparent cystic changes in bone may be produced in bone by the neuromas occurring in von Recklinghausen's neurofibromatosis.

A proven case of neurofibromatosis which was studied at the Albany hospital recently showed pigmented skin resembling that seen in Albright's syndrome, but biopsy revealed a plexform neuroma. X-rays of the skeleton were negative.

Case 3. E. M. A 14-year-old schoolboy was seen in April, 1940, complaining of pain in the right hip and a limp while walking, present since 8 years of age. In 1934 he was operated upon in another city and a portion of bone removed from the right femur was said to have shown microscopic evidence of giant cell sarcoma. Since then history of two fractures. Physical examination was negative except for diability of the right hip. Skeletal X-rays showed cystic bony involvement of right femur, right tibia, right fibula, one rib and a right metacarpal and a left metatarsal bone as indicated in the diagram. Laboratory data: Very extensive blood chemistry examinations were all

normal. Serum calcium 9.4; serum phosphorus 3.8; blood phosphatase slightly increased—7.12 Bodansky units.

Comment: A knowledge of this syndrome is of paramount importance in the differential diagnosis of hyperparathyroidism. No less than 19 cases have been explored without finding an adenoma of the parathyroids, and three of these patients were subjected to two operations in a vain search for tumor. The mistake will not be made if one remembers that blood calcium and phosphorus values are normal and the distribution of bone lesions "spotty" in Albright's syndrome. Pigmented spots on the skin and a history of sexual precocity should at once arouse suspicion of this condition. Atypical neurofibromatosis with its skin pigmentation may resemble this syndrome and there are still some writers who believe that Albright's syndrome is no more than an atypical form of von Recklinghausen's disease. Case 2 of our series illustrates the similarity of the two conditions. Biopsies, however, have never shown neurofibromas in Albright's syndrome. Various other conditions which have been mentioned as the cause of the syndrome can be readily excluded. Thus Paget's disease is unlikely, because the age of onset is much later and biopsies tend to disprove it. Ollier's disease (unilateral dyschondroplasia) may be dismissed because the lesions are not confined to cartilaginous bone. Xanthomatosis is not to be considered since biopsies do not show the typical foam cells and the blood cholesterol is normal (one exception). Multiple hemagiomas of bone recently reported by Pierson, Farber, and Howard may produce widespread osteolytic lesions of the skeleton, but are readily differentiated by biopsy as well as by other features. One need mention only to exclude the various other conditions advanced as of etiologic importance, since no proof has been offered that they are the causative factors in producing this syndrome, viz., dysfunction of the adrenal, ovary, pituitary, testis, pineal and thymus.

Albright has tried to explain the etiology on a single embryonic defect involving the hypothalamic area. It seems more probable that a multiple congenital defect involving several systems is the explanation.

Prognosis must be guarded, as the progress of the disease is variable, but disability from recurring fractures is not unlikely in active cases seen in childhood. There is no known effective treatment. Radiation of bones, pituitary and parathyroids has been tried without success.

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DISCUSSION.

DR. WALTER S. MCCLELLAN (Saratoga Springs, N. Y.): I will take two minutes, if I may, to say just a personal word regarding Captain Martel and to pay my respects to him as a hero in medicine. I think that without question those of us who had the exceptional opportunity of working with Captain Martel in the early years of the study of this condition look back on that as a remarkable experience. We saw this man, who in the prime of his life stood at a height of six feet one inch and whom we could imagine guiding the transports across the water during the last war, and who in the course of eight years had shrunk to a stature of only five feet six, exhibiting, as Dr. Gorham has pointed out, the frequent fractures, the studies of which brought him into prominence with the finding of a high serum calcium on the wards of Bellevue Hospital. Preceding that time he had been in the Marine Hospital and many others.

The thing I do feel about Captain Martel is his splendid coöperation over the remaining period of his life, during which I would without question say that in the field of hyperparathyroidism his case probably would sum up to a greater volume of hospital records than any other.

It is with regret that all of us who worked with him, not alone our group in Bellevue, but the group in Boston, Alb, Bauer, Albright, and others, took so long to find the offending tumor which was finally removed from deep down in the mediastium, only too late to save his life because of the irreparable damage which had been done to the kidneys.

One point in relation to the subject under discussion. I would like to ask Dr. Gorham if there are any changes in the neuromuscular sensitivity. In Captain Martel there was a very much reduced nerve muscle sensitivity in contrast to that found in tetany.

DR. MAURICE FREMONT-SMITH (Boston, Mass.): I have been very much interested in Dr. Gorham's paper, especially because I have been privileged to see a few of these cases in Dr. Albright's clinic. I would like to emphasize a few of the points that Dr. Gorham made, one that this is not an endocrine disease, because it is not a generalized bone disease. Dr. Albright is always pointing out that in hyperparathyroidism, being endocrine disease, all the bones are affected, some to one degree, some to another. In this disease it is a spotty disease. It is interesting that the distribution of the lesions follows, as it were, a branch and then twigs. If an arm is involved one or two fingers may be involved, and if one or two fingers are involved they will be involved down to the extremities; all the points of those fingers will be involved and no other fingers.

Dr. Albright, therefore, feels that this is in the nature of some neurogenic disorder, not an endocrine disorder.

Then a word about the brown spots. You may remember in the Case 2 that Dr. Gorham showed there was a brown spot, and the case he said was probably not Albright's disease. In that case the brown spot had two characteristics. It was smooth in its outline. In Albright's disease, in contrast to von Recklinghausen's disease, the brown spots are quite irregular, like the map of a state, in outline. The other characteristic in von Recklinghausen's disease, the brown spots

follow a radial direction, a nerve direction, radially, whereas in Albright's disease the brown spots are apt to be simply placed up against the spine on one side or the other, without any of that radial direction and are very apt to occur on the side of the bone lesions.

I have heard Dr. Albright say that he thought that possibly any bone cyst, single bone cyst, might be an incomplete evidence of this disease.

DR. L. W. GORHAM (Albany, N. Y.): In answer to Dr. McClellan, I would say that so far as I know no studies have been made on neuromuscular sensitivity. They were not made in our cases.