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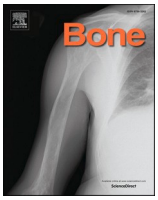

Full Length Article

Osteopetrosis: Discovery and early history of "marble bone disease"☆

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ABSTRACT

Discovery in 1904 of the disorder initially called "marble bones", then in 1926 more appropriately referred to as "osteopetrosis", is attributed to Heinrich E. Albers-Schönberg (1865–1921), the first radiologist. He used the new technique of "Röntgenographie" to report in a young man the radiographic hallmarks of this osteopathy. Clinical descriptions of lethal forms of osteopetrosis had apparently been published earlier by others. In 1926, "osteopetrosis" (stony or petrified bones) replaced "marble bone disease" because the skeletal fragility resembled limestone more than marble. In 1936, despite fewer than 80 reported patients, a fundamental defect in hematopoiesis, secondarily impacting the entire skeleton, was hypothesized. By 1938, the signature histopathological finding of osteopetrosis was recognized – persistence of unresorbed calcified growth plate cartilage. Also, it was apparent that besides lethal autosomal recessive osteopetrosis a less severe form was "handed down directly from generation to generation". In 1965, quantitative, but also qualitative, defects in osteoclasts became apparent. Here, I review the discovery and early understanding of osteopetrosis. Characterization of this disorder commencing at the beginning of the past century would support the aphorism of Sir William Osler (1849–1919): "Clinics Are Laboratories; Laboratories Of The Highest Order". As featured in this special issue of *Bone*, the osteopetroses would prove remarkably informative about the formation and function of the cells responsible for skeletal resorption.

1. The beginning

In 1904, during a medical meeting in Hamburg, Germany, Mr. Heinrich Ernst Albers-Schönberg, a surgeon, described startling findings using a new apparatus and technique that would be called roentgenography. He had performed an "x-ray" to examine a young man who had stepped into a pothole and broken a femur. The radiograph revealed an opaque bone with widened cortices and no trabecular structure or medullary cavity. Also, osteosclerotic rings were apparent perpendicular to the cortex. A roentgenographic survey of his patient's skeleton revealed that the abnormalities were generalized and included additional fractures. A single paragraph from the proceedings of that medical meeting [1] described the key x-ray findings of the new disorder *Marmorknochenerkrankung* (marble bone disease) (Fig. 1). During that same year, 1904, the grand prize at the Louisiana Purchase Exposition (1904–1906) held in St. Louis, USA (Fig. 2) was bestowed upon Albers-Schönberg. The award recognized the superior clarity of his radiographic images. Later, he would also describe the skeletal dysplasia "osteopoikilosis". Tragically, in 1908, malignant lesions attributed to x-ray exposure appeared in his forearms. He lived an additional thirteen years suffering their complications. The life and seminal career of Heinrich E. Albers-Schönberg are currently reported online (https://www.whonamedit.com), briefly described in "A Dictionary of Medical Eponyms" [2], and provided elsewhere (Fig. 3). What Albers-Schönberg reported is captured in the radiograph of a patient with osteopetrosis (OPT) whom I encountered in St. Louis, USA (Fig. 4).

Several publications, including in 1907 another by Albers-Schönberg [4], described his patient's clinical course [5,6] with marble bone disease [7]. At 44 years-of-age, he had suffered multiple fractures since early childhood, and had developed persisting hematological abnormalities with hepatosplenomegaly. The patient died at 49 years-of-age [8]. Albers-Schönberg had encountered likely the autosomal dominant

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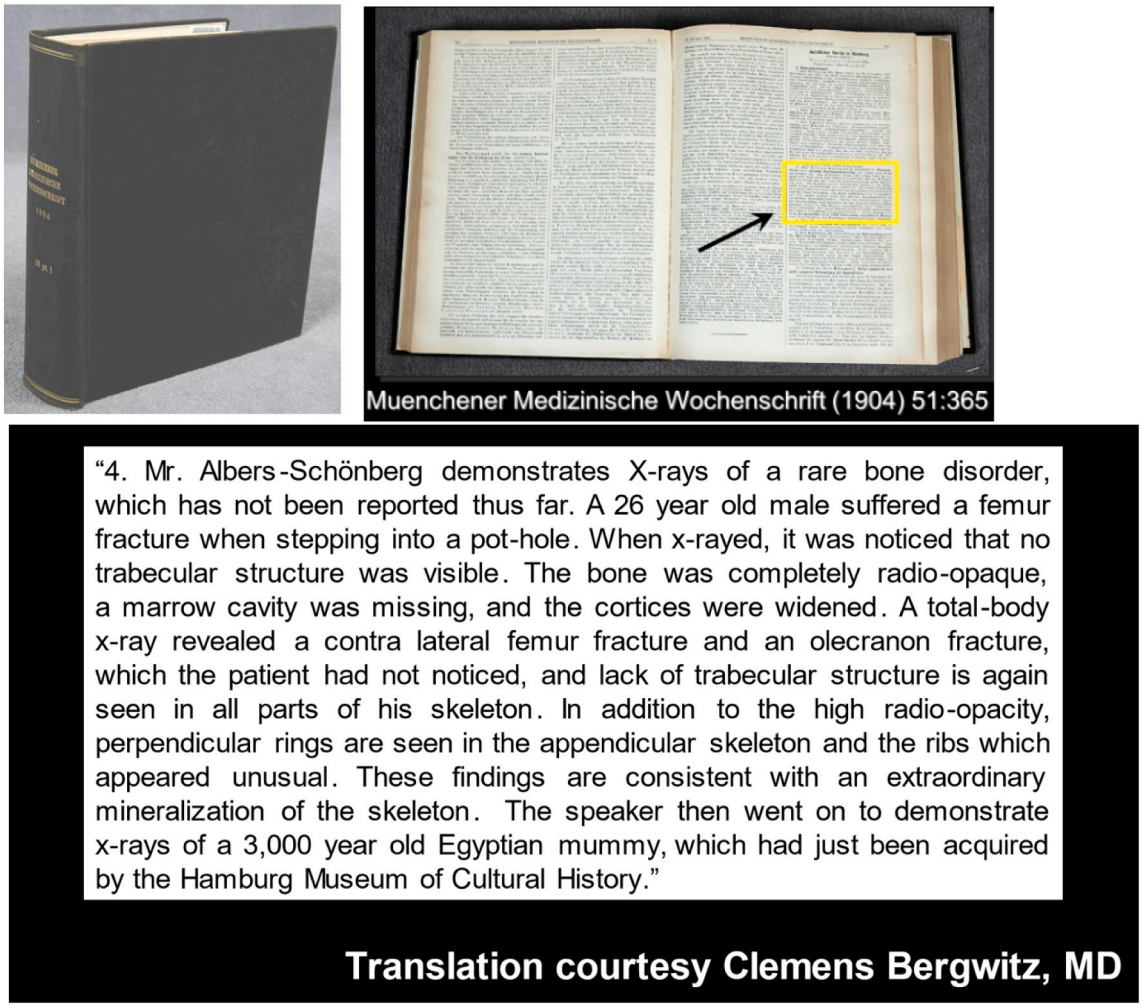


Fig. 1. Albers-Schönberg's Initial Report Concerning Osteopetrosis [1].

Fig. 2. The St. Louis World's Fair in 1904.

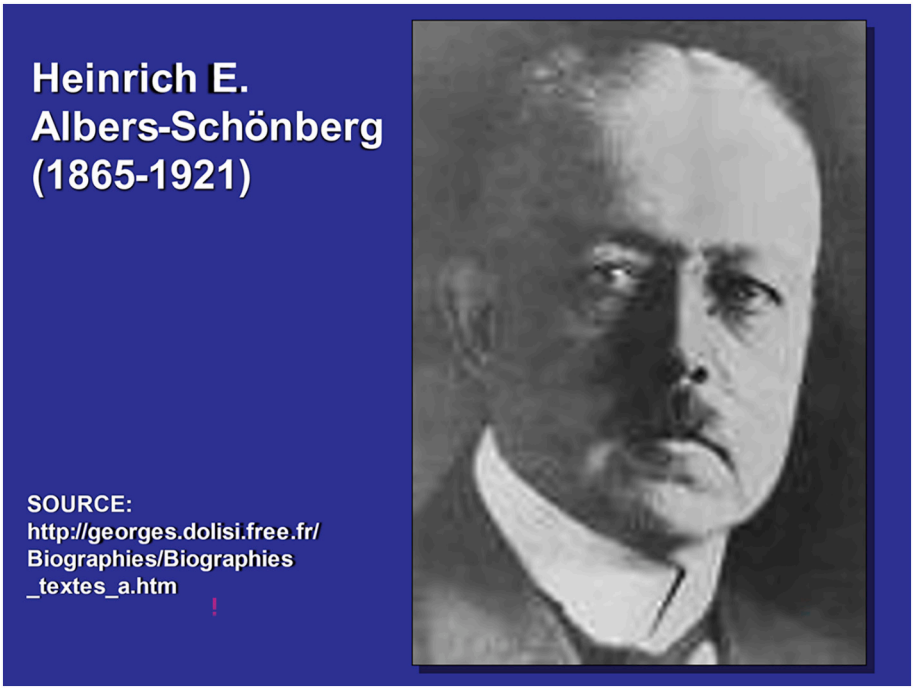


Fig. 3. The First Radiologist And Discoverer Of Osteopetrosis.

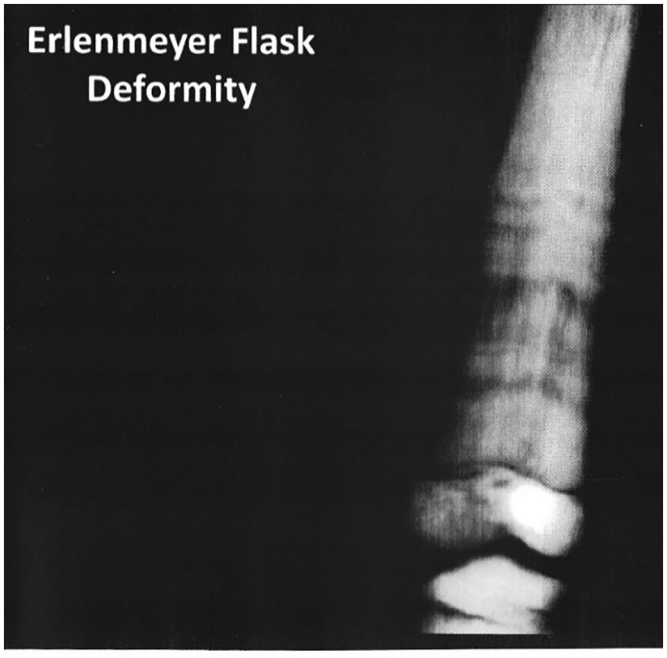


Fig. 4. Classic Radiographic Features of Albers-Schönberg's Disease.
This radiograph of a distal femur shows the changes of osteopetrosis reported in 1904 by Albers-Schönberg: [1] skeletal opacity, absence of trabecular structure as well as the medullary cavity, and impaired bone modeling later called "Erlenmeyer flask deformity" [3]. The "rings" of osteosclerosis perpendicular to the bone surface are striking, reminiscent of the "zebra lines" caused by anti-resorptive treatment when given intermittently to children with osteogenesis imperfecta, and suggest cyclical disease activity.

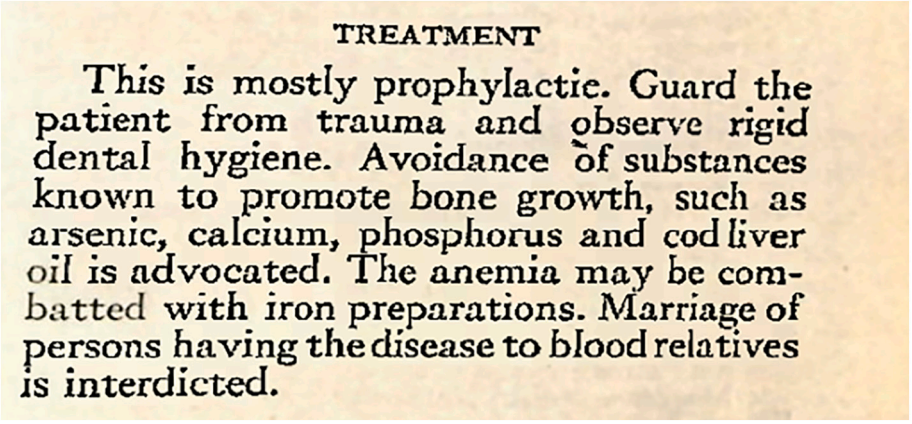
"benign" form of OPT, which 97 years later would be explained by heterozygosity for pathogenic variants of *CLCN7*, the gene that encodes chloride channel 7 necessary for osteoclasts to acidify their resorption lacuna and thereby dissolve bone mineral. In 2001 also in Hamburg, Germany, U. Kornak and colleagues discovered that bi-allelic loss-of-function mutations of *CLCN7* caused autosomal recessive OPT [9], and DNA from patients followed in St. Louis and elsewhere enabled E. Cleiren et al [10] in Antwerp, Belgium to discover that heterozygous *CLCN7* mutations explained autosomal dominant OPT. Now, "Albers-Schönberg disease" [11] should no longer be called "type II autosomal dominant osteopetrosis" [12], because "type I autosomal dominant osteopetrosis" does not reflect failed osteoclast action but is instead LRP5 and LRP6 high bone mass from increased Wnt/β-catenin signaling and bone formation by osteoblasts [13]. The term Albers-Schönberg disease continues to denote, eponymically, autosomal dominant OPT [14].

2. The early progress

Actually, several reports prior to 1904 provided clinical and post-mortem descriptions concerning what were surely instances of "malignant" autosomal recessive OPT, but at the time considered leukemias or "pseudoleukemias" [8]. Malignant OPT was characterized radiographically in 1914 by P. Sick [15]. In 1923, a patient's family history obtained by Alexander [16], and similarly by others, supported autosomal recessive inheritance [17]. At the time, the "clubbing" of the long bones frequently had OPT mistakenly considered a type of rickets [18].

In 1926, R.G. Karshner [17] at Children's Hospital, Los Angeles, USA suggested that the term "osteopetrosis" (stony or petrified bones) better characterized the skeletal phenotype than "marble bone disease" because the osteopetrotic skeleton was more like limestone than marble. He described four patients and elegantly detailed the multisystemic complications and emphasized the unique radiographic findings of OPT, including the rings or transverse bands of osteosclerosis at long bone ends that suggested cyclical disease activity [17]. Karshner clarified that the available studies "present no resemblance whatever [for rickets] on the roentgenogram" [17]. His recommendations for treating OPT are presented in Fig. 5.

In 1934, R.W.B. Ellis [18] superbly reviewed the progress made in understanding OPT. During the 30 years after Albers-Schönberg's first report, fewer than 40 people with the disorder had been reported. Nevertheless, by then, the radiographic features of the skeleton were


TREATMENT

This is mostly prophylactic. Guard the patient from trauma and observe rigid dental hygiene. Avoidance of substances known to promote bone growth, such as arsenic, calcium, phosphorus and cod liver oil is advocated. The anemia may be combatted with iron preparations. Marriage of persons having the disease to blood relatives is interdicted.

Fig. 5. R.G. Karshner's Treatment For Osteopetrosis in 1926 [17].

considered characteristic, including what we now call the "bone-within-bone" finding sometimes seen in the carpals and elsewhere [18]. As Karshner [17] had suggested, "osteopetrosis" was now being used to affirm the skeleton's brittleness [18]. At the time, the prevailing pathogenesis for OPT [18] favored the 1930 hypothesis of J. Dupont [19] implicating parathyroid overactivity. Others postulated an epiphysitis. Ellis offered "most likely . . . the condition is inherited as a Mendelian recessive disorder". He considered that among the principal complications of OPT the excessive bone growth could compromise hematopoiesis due to progressive reduction of the marrow cavity leading to extramedullary blood formation, and injure the nervous system at the skull base causing hydrocephalus and optic atrophy due to dense bone, and narrowed cranial foramina leading to facial and ocular palsies and nystagmus [18].

In 1936, H. Wortis at Bellevue Hospital in New York, USA determined that fewer than 80 patients with OPT had been reported, and like Ellis provided an excellent overview [7]. He too considered "the characteristic evidence of this disease is the Röentgen demonstration of the overgrowth of the skeletal portion of the bone at the expense of the medullary cavity". Bone thickening would also explain the narrowed optic foramina [7]. Nevertheless, the cause of OPT was unknown; "It does, however, show a striking familial tendency and is occasionally hereditary. Parental consanguinity is apparently a factor." Furthermore, "evidently osteopetrosis is a disturbance of the endosteal and endochondral bone metabolism – the periosteum nearly always remains intact. There may be associated evidence of active or old rickets." [7] Interestingly, Wortis remarked that "it has been suggested that osteopetrosis is not a disease of the bony system with secondary compensatory changes in the more primitive blood-forming organizations but a disease entity involving the entire hematopoietic system" [7]. Hence, reviewed in this special issue of *Bone*, the defects of marrow-derived osteoclasts support and refine this hypothesis from 1936.

In 1938, A.M. Nussey in Birmingham, England advanced understanding of the heritable nature of OPT recognizing there were "seven families embracing twenty-six affected individuals in whom the disease was handed down directly from generation to generation. . . . and it is safer to assume that there is also a type of osteopetrosis which is handed down as a simple dominant." [8] He added "race does not appear to be a factor". Nussey emphasized that an important clue to understanding the pathogenesis for OPT was the growing impression that there is "a disturbance in endochondral formation of bone which allows the cartilaginous bone to persist." [8]

In 1948, some ten years later, H.A.T. Fairbank described OPT thusly: "a rare developmental error the chief characteristic of which is excessive radiographic density of most or all the bones of the skeleton" [20]. Furthermore, "a distinct familial tendency is displayed and the disease is occasionally inherited . . ." [20], also citing the report from 1936 by C.N. McPeak [21]. Consanguinity had been recognized as an etiologic factor, and patients had been encountered of all ages. Then, in his classic 1951 "Atlas Of General Affectations Of The Skeleton", H.A.T. Fairbank illustrated the radiographic features of OPT ranging from "severe" to "benign" [22].

In 1965, C.E. Dent, J.M. Smellie, and L. Watson [23] in London, England reported that many cases of OPT had now been described, and at intervals good review articles had sequentially appeared from McCune and Bradley (1934) [11], Higinbotham and Alexander (1941) [24], Pines and Lederer (1947) [25], Seigman and Kilby (1950) [26], Kneal and Sante (1951) [27], and Hasenhuttl (1962) [28]. Dent and colleagues concluded that most of the bone abnormalities could be related to a quantitative deficiency of osteoclasts seen histologically by Kneal and Sante [27], Piatt, Erhard, and Arj [29], and Engfeldt, Fajers, Lodin, and Pehrson [30], yet perhaps also involve a qualitative defect of these cells. Furthermore, Dent and colleagues [23] concluded that osteoclast inaction was revealed during growth by the persisting calcified cartilage formed early in the chain of events of endochondral bone formation as there was failure of remodeling of the bone. As a consequence, little or no medullary space forms, metaphyses show a characteristic club shape, and foramina, such as those through which the cranial nerves pass, fail to enlarge.

In 1976, R. Wynne-Davies and T.J. Fairbank [31] indicated that apparently OPT had been encountered in 1880, as recognized by Newman [32] as well as by Arce and Arce [33], both in 1964. Other names for OPT (from the German *Marmorknochen* and *Marmorskelett*) had included osteopetrosis generalisata, marble bones, Albers-Schönberg's disease, chalky bones, osteosclerotic anemia, congenital osteosclerosis, and osteosclerosis fragilitas generalisata.

In 1977, the brief review of OPT provided by R. Loria-Cortés et al. [34], reporting a high prevalence of malignant OPT in Costa Rica, indicated 69 patients with OPT had been reported by 1934 [11], 203 by 1955 [35], and 300 by 1966 [14]. Also in 1977, P. Beighton and colleagues in South Africa [36], in a summary entitled "A Review of the Osteopetroses", described the OPTs as "a group of conditions which are characterized by varying combinations of bony sclerosis and modeling defects," and "a number of separate conditions" for which "diagnostic accuracy is crucial". They concluded that due to "the complexity of the terminology, it is not surprising that there has been considerable confusion . . . concerning this group of conditions" [36].

What follows in this special issue of *Bone* aims to diminish confusion concerning OPT. Here is an overview of the remarkable progress in delineating and now understanding the OPTs that followed the early progress described herein. This came largely by discovering the genetic bases of the OPTs and understanding how they compromise the cells that resorb the skeleton.

CRediT authorship contribution statement

Michael P. Whyte, M.D. is the only author.

Disclosures

None.

Declaration of competing interest

None.

Data availability

No data were used for the research described in the article.

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