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# Oto-Spondylo-Megaepiphyseal Dysplasia (OSMED): Clinical Description of Three Patients Homozygous for a Missense Mutation in the COL11A2 Gene

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We describe a syndrome of midface hypoplasia, non-progressive sensorineural deafness and epiphyseal dysplasia in 3 sibs born to consanguineous parents. Clinical and roentgenographic findings are compatible with a diagnosis of oto-spondylo-megaepiphyseal dysplasia (OSMED). Histologic study of cartilage shows severe osteoarthritis, which may necessitate joint replacements in early adulthood. Ultrastructurally, collagen fibrils are increased in diameter and show aggregation. These findings have not been reported previously and may be diagnostic of OSMED. The affected sibs are homozygous for a COL11A2 missense mutation. We compare the clinical findings in our patients with a group of patients who have a dominantly inherited, non-ocular form of Stickler syndrome due to a COL11A2 splice-site mutation. Both syndromes include midface hypoplasia, epiphyseal dysplasia, and deafness, more pronounced in OSMED. Since mutations affecting the collagen XI genes can obviously result in a spectrum of phenotypes, we performed a literature-search using POSSUM, OSSUM, and the LDDB to identify conditions that might also be caused by mutations in one of the collagen XI genes. A number of conditions matched the search terms in all databases. Of these, Marshall syndrome is very similar to OSMED. Considering these phenotypic similarities and the close association between the COL11A1 and COL11A2 gene products, we propose that Marshall syndrome may be caused by a mutation in COL11A1. We also identify a number of

other conditions that could be caused by mutations in one of the collagen XI genes. *Am. J. Med. Genet.* 70:315-323, 1997.

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**KEY WORDS:** collagen XI; OSMED; Marshall, Stickler

## INTRODUCTION

Oto-spondylo-megaepiphyseal dysplasia (OSMED, MIM 215150) comprises midface hypoplasia, sensorineural deafness, and generalised epiphyseal dysplasia [Giedion et al., 1982; Kääriäinen et al., 1993; Al Gazali and Lytle, 1994]. It has also been called Insley-Astley syndrome, Nance-Sweeney dwarfism, and megaepiphyseal dwarfism [Nance and Sweeney, 1970; Gorlin et al., 1973; Insley and Astley, 1974]. Recently we reported homozygosity for a missense mutation in the COL11A2 gene in 3 sibs with a clinical presentation similar to OSMED [Vikkula et al., 1995]. Here we present detailed clinical descriptions and radiological findings of these 3 patients. Cartilage from one patient was examined by light and electron microscopy. We observed ultrastructural abnormalities that may be unique or even specific for OSMED and that give some important clues to the function of collagen type XI in human articular cartilage. We further identify a number of other conditions that may be caused by mutations in one of the collagen XI genes.

## CLINICAL REPORTS

### Case 1

The eldest female of 6 sibs born to consanguineous (fourth cousin) Dutch parents (Fig. 1). There is no family history of hearing loss. A brother and a sister are similarly affected (cases 2 and 3). Three of the father's sibs have had hip-replacement surgery at approximately age 60 for osteoarthritis. Clinical and roent-

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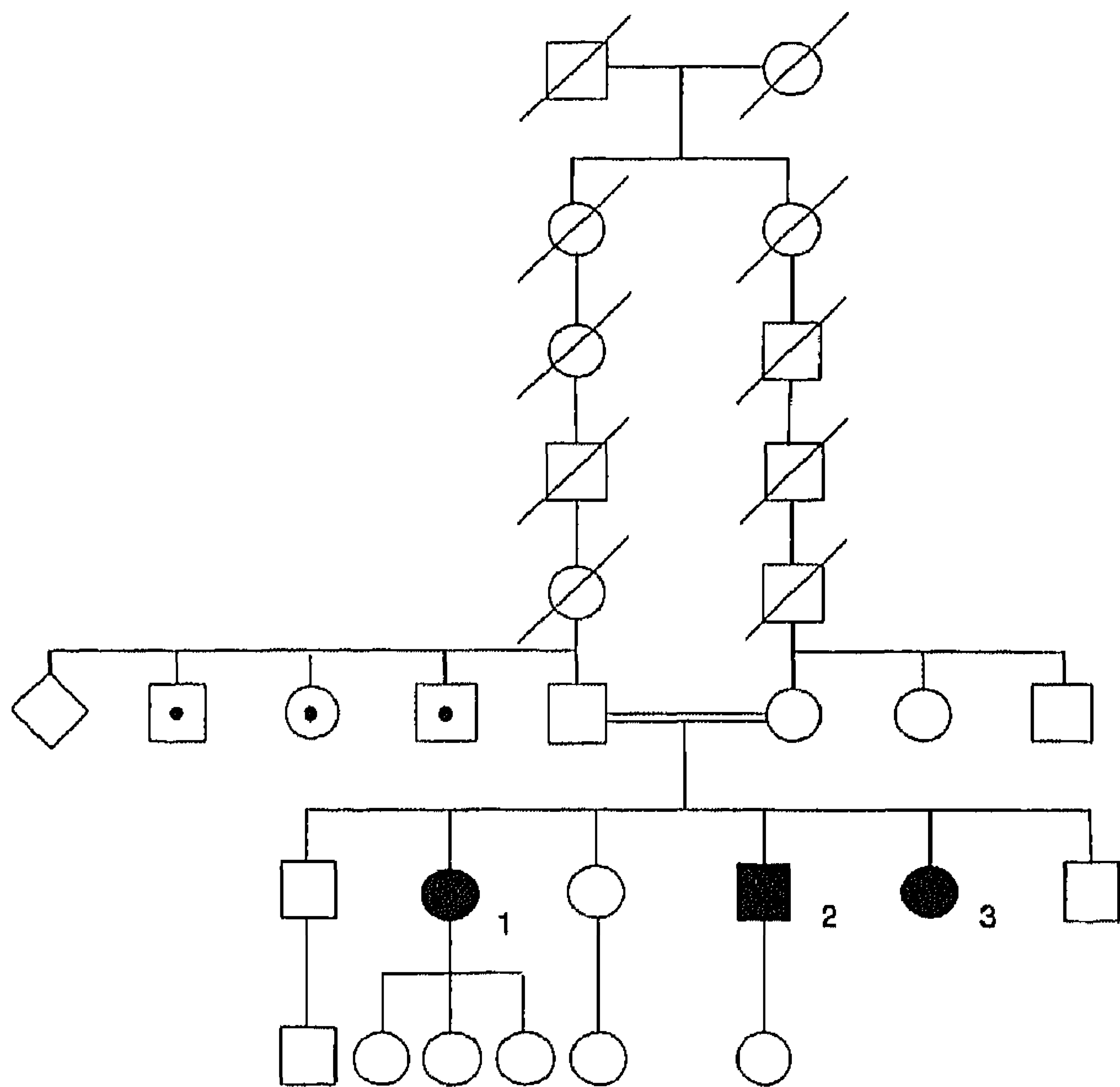


Fig. 1. Pedigree of the family. Dots denote osteoarthritis of hips in middle age, necessitating hip replacement. Shaded symbols indicate cases 1-3 with OSMED.

genographic examination of both parents at age 60 did not show overt degenerative joint disease. Case 1 has early-onset sensorineural deafness. Audiological examination at 9 years demonstrated 60 dB bilateral sensorineural hearing loss. Bilateral hearing aids were prescribed. A meniscectomy of the left knee was performed at 22 years for complaints of pain and locking, at which time severe osteoarthritis of the knee was diagnosed. At 30, she visited a rheumatologist for pain in both hips and swelling of both knees. X-ray examination showed dysplastic and severely arthrotic hips and knees and a mild generalised epiphyseal dysplasia, including a mild platyspondyly. Audiological examination again showed a sensorineural hearing loss of 60 dB and a diagnosis of "multiple epiphyseal dysplasia with hearing loss" was made. She was referred to the clinical genetics department at 34 years. She had a striking facial appearance due to midface hypoplasia, anteverted nares with a bulbous nose-tip, and protruding eyes. Mild disproportionate short stature and increased lumbar lordosis were noticed. Short fifth metacarpals and thickened interphalangeal joints were noted (Fig. 2). She wore bilateral hearing aids. Eyesight was excellent. In the following years generalised joint pain developed, particularly of the elbows and hands. The existing complaints slowly increased in severity. Osteoarthritic changes on X-ray examination also showed steady progression. X-ray examination of the spine at 35 years showed irregular vertebral endplates and degenerative changes in the lumbar vertebrae. At 36 years, both hips and one year later both knees were replaced because of severe pain and limitation of motion. Hearing loss remained at 60 dB. At 42, her condition remains relatively stable.



Fig. 2. Left hand of case 1, age 35. Note short fifth metacarpals, flat articular surfaces of phalanges, and epiphyseal dysplasia of metacarpals. Osteophytes are present in the radio-ulnar joint.

### Case 2

A brother of cases 1 and 3. Hearing loss was noted in early childhood. At 7, audiological examination showed a bilateral sensorineural hearing loss of 70 dB. Hearing aids were prescribed. At 15 years, he first complained of pain in both knees. Bacterial arthritis of the left knee was diagnosed and treated by suction-drainage for 4 weeks. At the age of 20 years, osteoarthritis of the right knee was diagnosed by an orthopaedic surgeon. At that time he had no complaints of other joints. At the age of 24 he visited a rheumatologist because of pain in knees and hips. Limitation of motion and flexion contractures in hips and knees were present at that time. Roentgenographic examination showed a mild generalised epiphyseal dysplasia and severe osteoarthritis especially of the hips and knees (Figs. 3-6). A diagnosis of "multiple epiphyseal dysplasia with hearing loss" was made. Because of increasing limitation of motion of the left knee, an arthroscopy was performed when the patient was 26 years old and severe osteoarthritis was diagnosed. In the following year his complaints remained relatively stable apart from increasing lower back pain. At 28 years, this patient was referred to the clinical genetics department together with his sisters. His appearance was similar to that of his sisters (Figs.



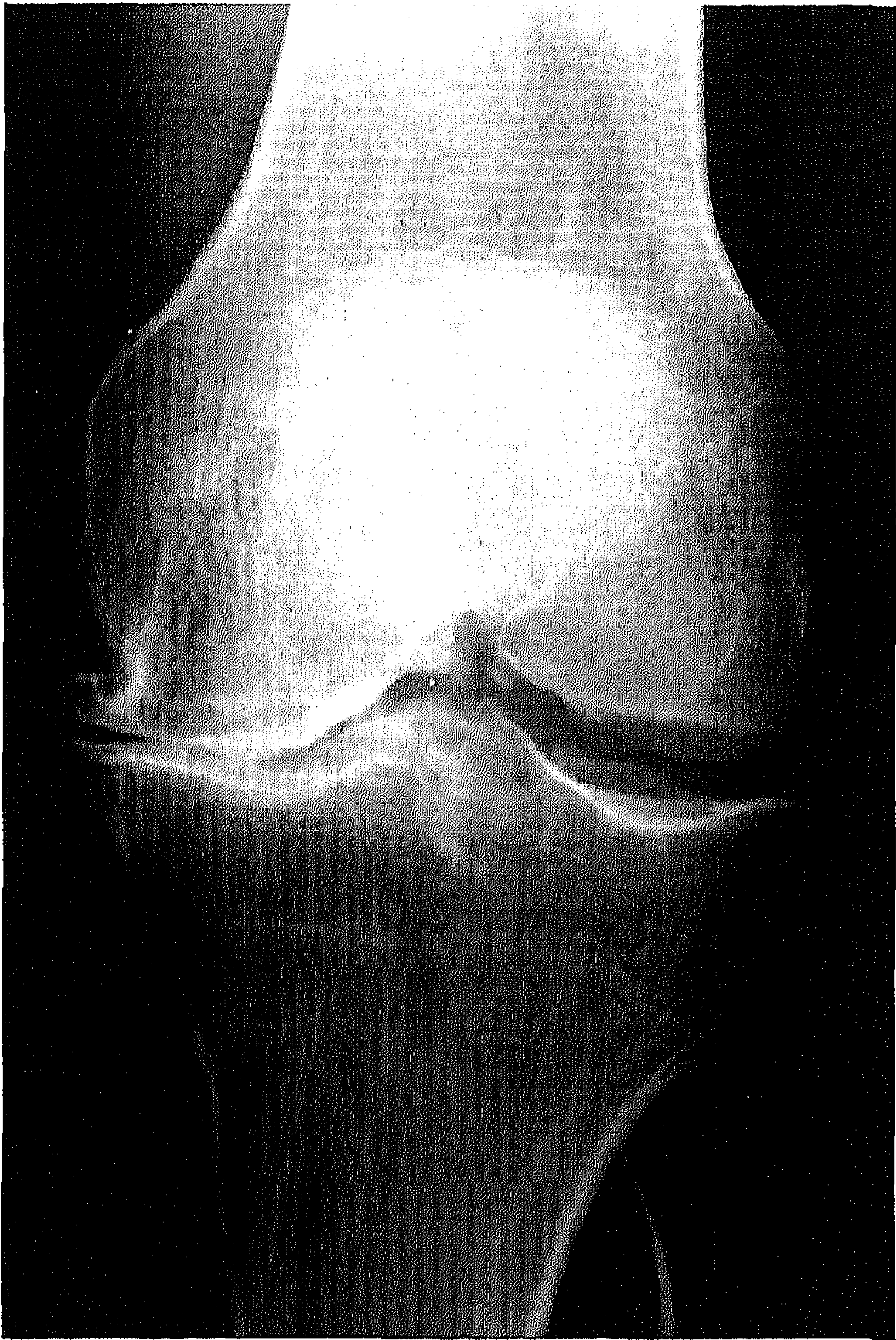


Fig. 3. Right knee of case 2, age 29. Notice the osteophytes, subchondral sclerosis, and obliteration of the lateral articular cavity. Irregular epiphyseal lines are also present.

7 and 8) but his stature was normal compared to the unaffected sibs. Marked midface hypoplasia with slightly protruding eyes and a bulbous nose were noted. The supra-orbital ridges were prominent. Hands and fingers were short with thickened interphalangeal joints. Lumbar lordosis was increased. X-ray examination of the spine showed mild platyspondyly and irregular vertebral endplates (Fig. 6). He wore bilateral hearing aids. Vision was excellent. In the following years his complaints slowly worsened. At 33 years his left hip was replaced and 3 years later his left knee. Tissues obtained at these operations were examined by light and electron microscopy (see below). The sensorineural hearing loss remains constant at 70 dB. His condition is currently stable at the age of 36 years.

### Case 3

The younger sister of cases 1 and 2. Audiological examination at 5 years showed a sensorineural hearing loss of 60 dB. Bilateral hearing aids were prescribed. At 13 years, a meniscectomy of the right knee was performed for complaints of locking. After surgery there was no relief of symptoms. After a fall at 16 years, the patient complained of intermittent pain and swelling in both knees. At the age of 21 years she visited a



Fig. 4. Right humerus of case 2, age 24. Overhanging humeral head with osteophyte formation and irregular humeral epiphysis. Irregular articular surfaces of both the humerus and the glenoid cavity are present.

rheumatologist because of difficulty in walking and pain in both elbows and the right hip. At that time there was limitation of motion in both shoulders, elbows, hips, and knees and flexion contractures of both hips and knees. X-ray examination showed a genera-

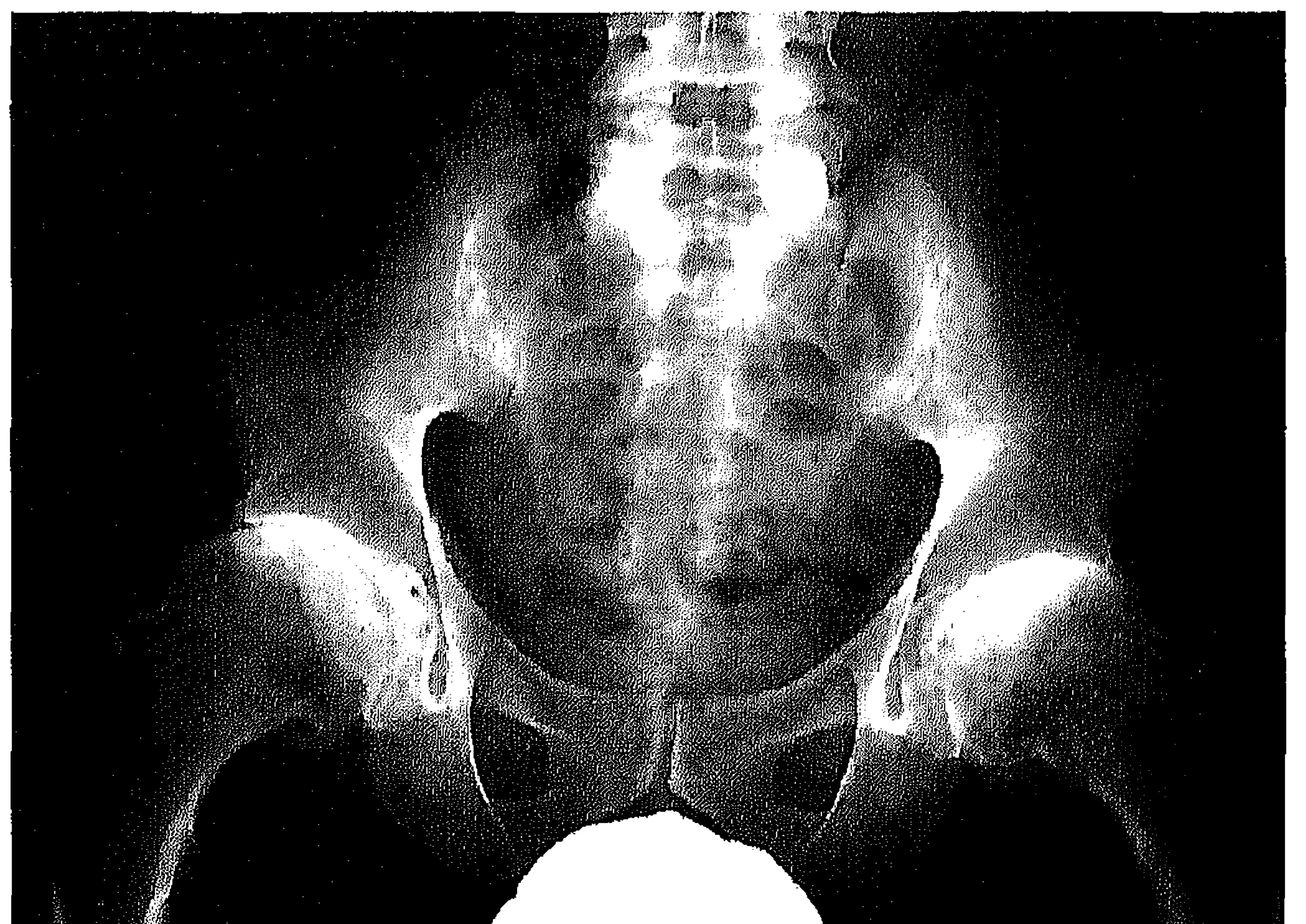


Fig. 5. Pelvis case 2, age 24. Dysplastic femoral heads, subchondral sclerosis of acetabula, and irregular articular cavity.



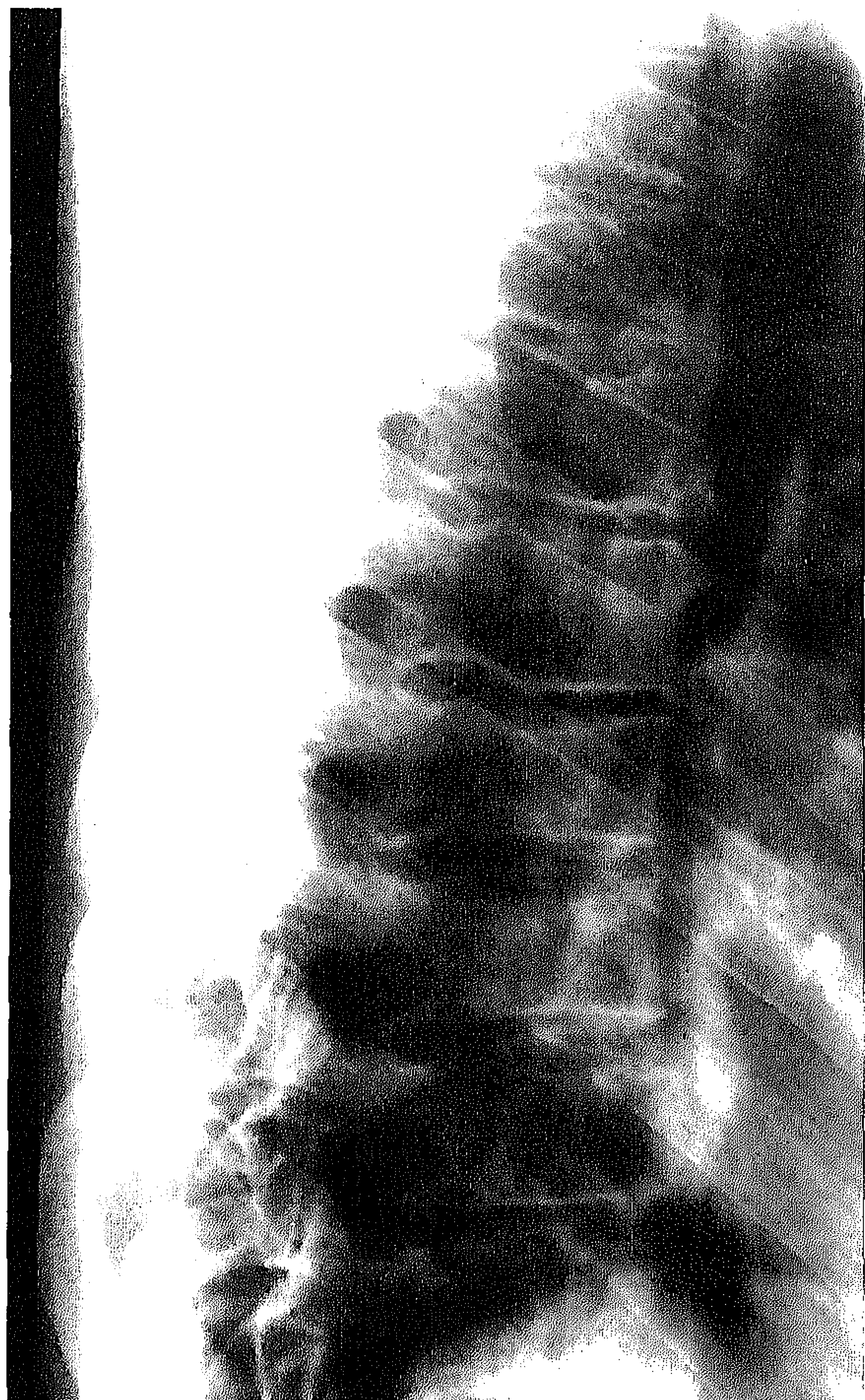


Fig. 6. Thoracic spine of case 2, age 24 years. Absence of normal thoracic kyphosis. Irregular vertebral endplates and mild platyspondyly.



Fig. 7. Case 2, age 29 years. Midface hypoplasia with upturned nose and prominent supra-orbital ridge.

lised epiphyseal dysplasia, severe osteoarthritis of the knees, and beginning osteoarthritis of the cervical and lumbar spine and both hips, as well as platyspondyly, degenerative changes of the entire vertebral column, and a slight thoracic scoliosis (concave to the right). A bilateral sensorineural hearing loss of 75 dB was noted. A diagnosis of "multiple epiphyseal dysplasia with hearing loss" was made. In the following years she also developed osteoarthritis of both ankles and feet. At 24 years, an exostosis of the right first cuneiform bone was removed. At that time the surgeon stated that he considered the exostosis to be a sequel of the osteoarthritic changes in the joint. At 26 years she was referred to the department of clinical genetics. Upon examination she had a striking appearance due to midface hypoplasia with prominent supra-orbital ridges, protruding eyes, and a slightly bulbous nose. Hands and fingers were short and interphalangeal joints were thickened. Moderate disproportionate shortness of stature and increased lumbar lordosis were present. She wore bilateral hearing aids. Vision was described as excellent. In the following years her complaints slowly worsened. At 27 years, arthroscopy of the right knee showed "severe osteoarthritis of all compartments." One year later the right hip and knee were replaced, followed by the left hip and knee after another year. Subsequently the left

radial head was resected and the left ulnar nerve transposed because of increasing complaints of pain in the left elbow and ulnar nerve area. The same operation was performed on the right side the following year. Audiological examination at that time showed a conductive loss of 20 dB on the left side, superimposed upon the sensorineural loss, which remained constant at 75 dB. At 32 years the left shoulder joint was replaced. Since this last joint replacement she has developed pain of the right wrist and of the cervical spine.

## LIGHT AND ELECTRON MICROSCOPIC EXAMINATION

### Materials and Methods

Cartilage was obtained from the femoral head, femoral condyles, and the tibial plateau at the time of total hip and knee replacement in case 2. Control cartilage was obtained from unrelated patients undergoing hip and knee replacement for secondary (i.e., non-hereditary) osteoarthritis. Prior to fixation the femoral head was sectioned in 1 cm thick slices using a water cooled saw. Tissues were fixed in 0.1 M phosphate buffered (pH 7.4) 4% formaldehyde for light microscopy or



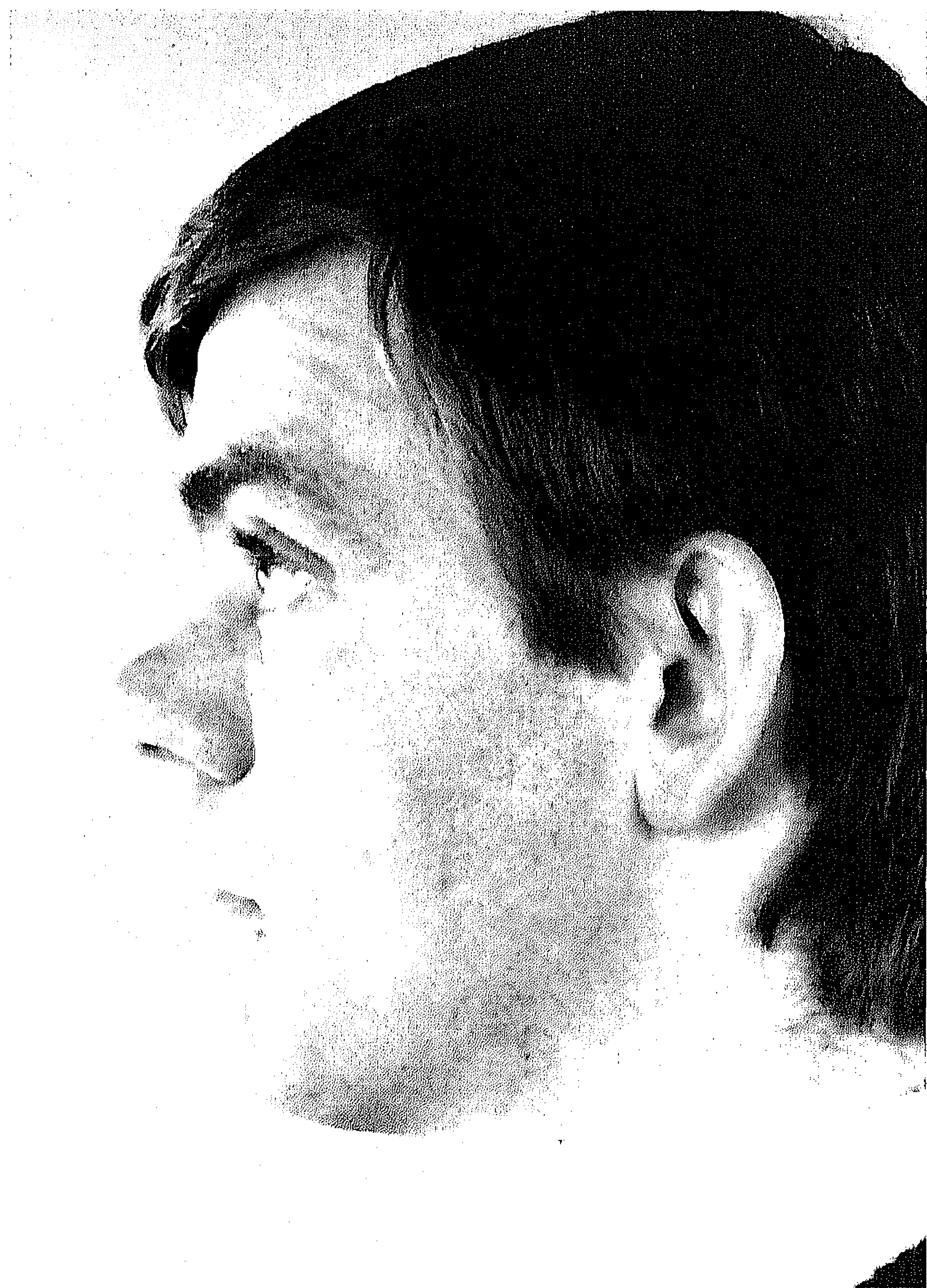


Fig. 8. Case 2, age 29 years. Same as in Figure 7; bulbous nose and flat nasal bridge. Somewhat coarse facies.

in 0.1 M phosphate buffered 1% glutaraldehyde and 1.25% paraformaldehyde for electron microscopy. After fixation the tissues were decalcified in a 0.1 M phosphate buffered (pH 7.4) 10% ethylenediamine tetraacetate (EDTA)-solution.

The slices from the femoral head were embedded in paraffin and the tissues of the knee in polymethylmethacrylate. After sectioning, samples were stained with hematoxylin/eosin and Alcian blue. Samples intended for electron microscopic examination were post-fixed in phosphate-buffered 1%  $\text{OsO}_4$ -solution, embedded in Epon 812, thin sectioned, counterstained with lead citrate and uranylacetate, and examined in a Philips EM 301 transmission electron microscope. Collagen fiber diameters were measured using a micrometer with an accuracy of 0.1 mm on photographs at a magnification of  $\times 45,000$ . Fiber diameters were measured in the superficial cartilage layers where proteoglycans were absent and in the deeper layers where the cartilage matrix still contained proteoglycans. In each area 50 fibril diameters were measured.

## RESULTS

### Light Microscopy

The gross appearance of the joint surfaces in case 2 strongly resembled that of a joint from a patient with

secondary osteoarthritis. Large areas were abraded, leading to exposure of the subchondral bone. Osteophytes were present at the joint margins. Light microscopy also showed extensive abrasion of cartilage. There was fibrillation of the superficial cartilage layers and diminished Alcian blue staining of the superficial layers (Fig. 9A). Throughout the cartilage there were zones of necrosis with clustering of the chondrocytes. Examination in polarized light showed fibrillation of matrix collagens in all cartilage layers (Fig. 9B,C).

Multiple tide marks were present in the zone of transition from calcified to non-calcified cartilage. Zones of fibrous erosion in the calcified cartilage were noticed. The observed apposition of woven bone in the erosions was strongly suggestive of reactive bone formation due to erosion of the subchondral bone (Fig. 9D,E). Cartilage remnants in the subchondral bone suggested a process of reactive bone formation moving towards the joint surface. The pathological changes observed by light microscopy were quantitatively and qualitatively similar to those observed in a control sample. The observed changes were identical in both joint surfaces.

### Electron Microscopy

Light microscopic examination showed no differences between OSMED and control osteoarthritic cartilage. However, electron microscopic examination did show important differences. In the basal regions of the osteoarthritic cartilage the matrix was intact and contained collagen fibrils and proteoglycans. In the superficial layers of the osteoarthritic cartilage there were two populations of collagen fibrils: relatively thick bundles with a mean diameter of  $79.66 \pm 11.45$  nm and thin bundles with a diameter of  $23.25 \pm 5.34$  nm. In the basal regions of the cartilage obtained from case 2 with OSMED, extremely thick collagen fibers were found (mean diameter  $148.99$  nm  $\pm 30.14$ ). In cross-section these appeared as slightly irregular, round bundles. When sectioned parallel to the long axis of the bundles, these extremely thick bundles were found to consist of aggregated thinner fibrils (Fig. 9H). Collagen fibrils in the control osteoarthritic cartilage were thinner and more regular (mean diameter  $83.11 \pm 14.03$  nm). Aggregation of fibrils was absent in the control (Fig. 9J). In the superficial layers of the OSMED cartilage, collagen fibers were not aggregated. No proteoglycans were attached to them. Mean fiber diameter was  $33.80 \pm 6.24$  nm; fibers were also more regularly shaped than in the basal region. In conclusion, the fiber population in the OSMED cartilage is different from that in control cartilage. In control osteoarthritic cartilage there are two fibril populations: one of thin ( $<25$  nm) and one of thick (80 nm) fibers. These do not show aggregation. In OSMED cartilage, both in basal and in superficial layers one population of fibers measuring approximately 35 nm is present. In the basal cartilage layers, these are aggregated into bundles measuring in excess of 140 nm (Fig. 10). OSMED cartilage also shows a disorganized matrix when compared to control cartilage. The normally ordered arrangement of fibers, as seen in the control cartilage, is absent.



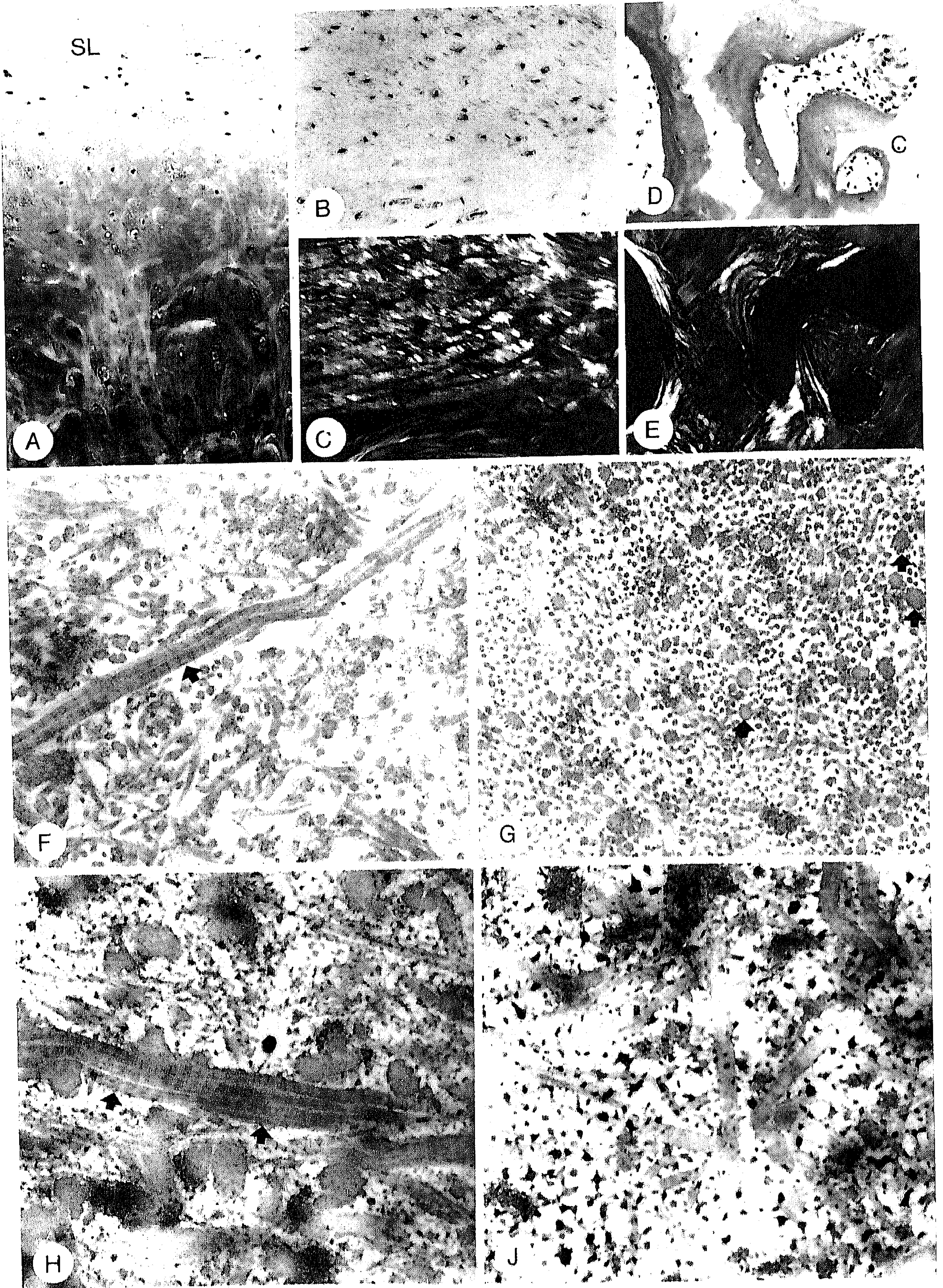


Fig. 9.



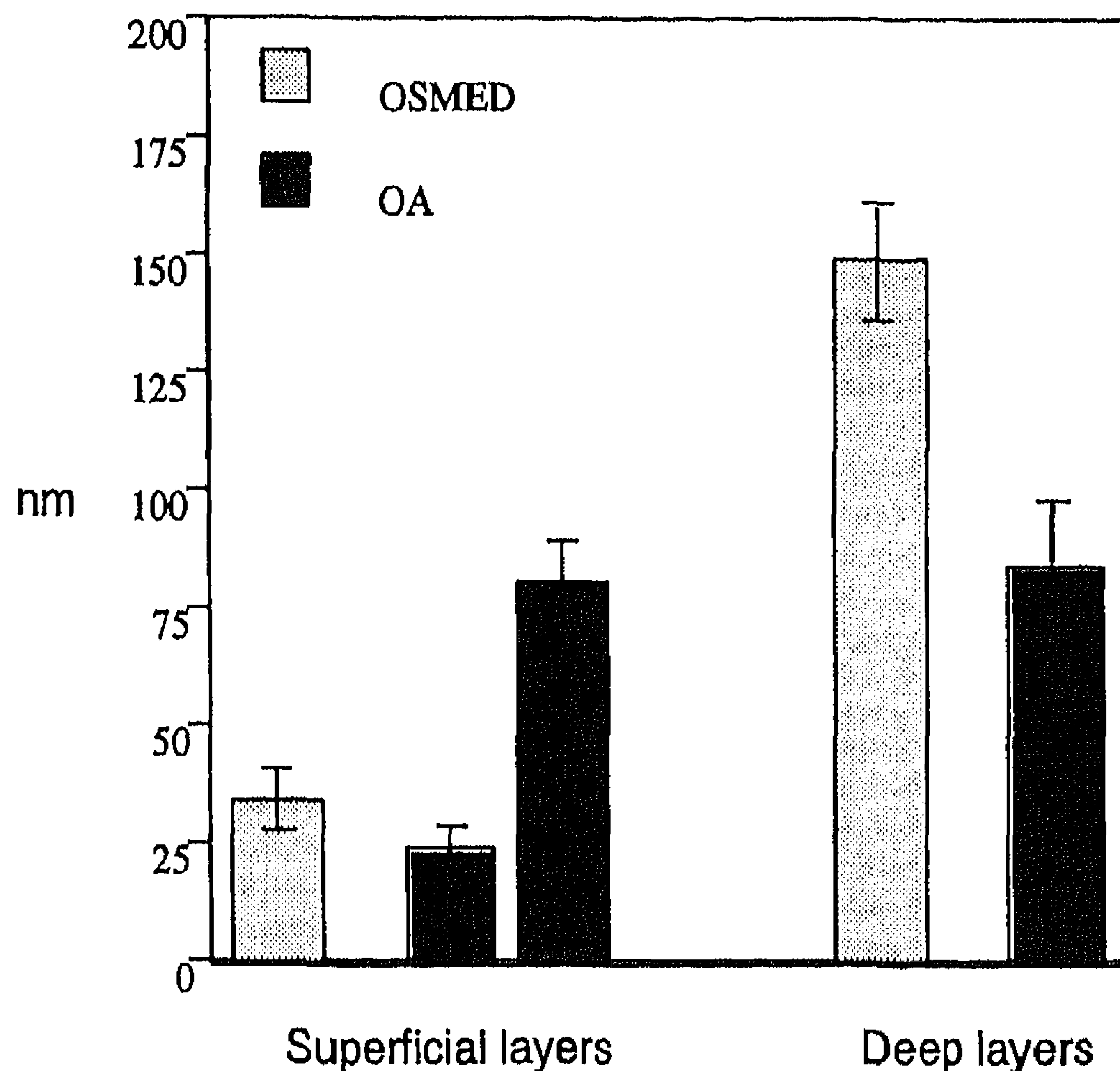


Fig. 10. Graphic representation of fiber diameters in OSMED and control (OA) cartilage. Error bars:  $\pm 1$  SD.

### DISCUSSION

These three patients have an identical condition, characterised by generalised epiphyseal dysplasia, sensorineural deafness, and midface hypoplasia. The epiphyseal dysplasia causes severe osteoarthritis starting in early teenage years and necessitates joint replacement in early adulthood. The deafness is non-progressive with a nearly constant loss over a wide frequency range (Fig. 11). The midface hypoplasia does not appear to lessen during adulthood. Light microscopic examination of hyaline cartilage showed severe osteoarthritis; electron microscopy demonstrated an increase in collagen fibril diameter and aggregation of collagen fibrils in the basal cartilage regions. These new ultrastructural findings offer some clues to the pathogenesis of OSMED and the function of collagen type XI in normal human articular cartilage.

OSMED comprises midface hypoplasia, sensorineural deafness, and generalized epiphyseal dysplasia with broad epiphyses and metaphyseal flare [Nance and Sweeney, 1970; Gorlin et al., 1973; Insley and Astley, 1974; Giedion et al., 1982; Kääriäinen et al., 1993; Al Gazali and Lytle, 1994]. Early osteoarthritis can be a component manifestation, as can joint contractures and mild platyspondyly. Deafness is non-progressive. Except for cleft palate, the clinical findings in the pres-

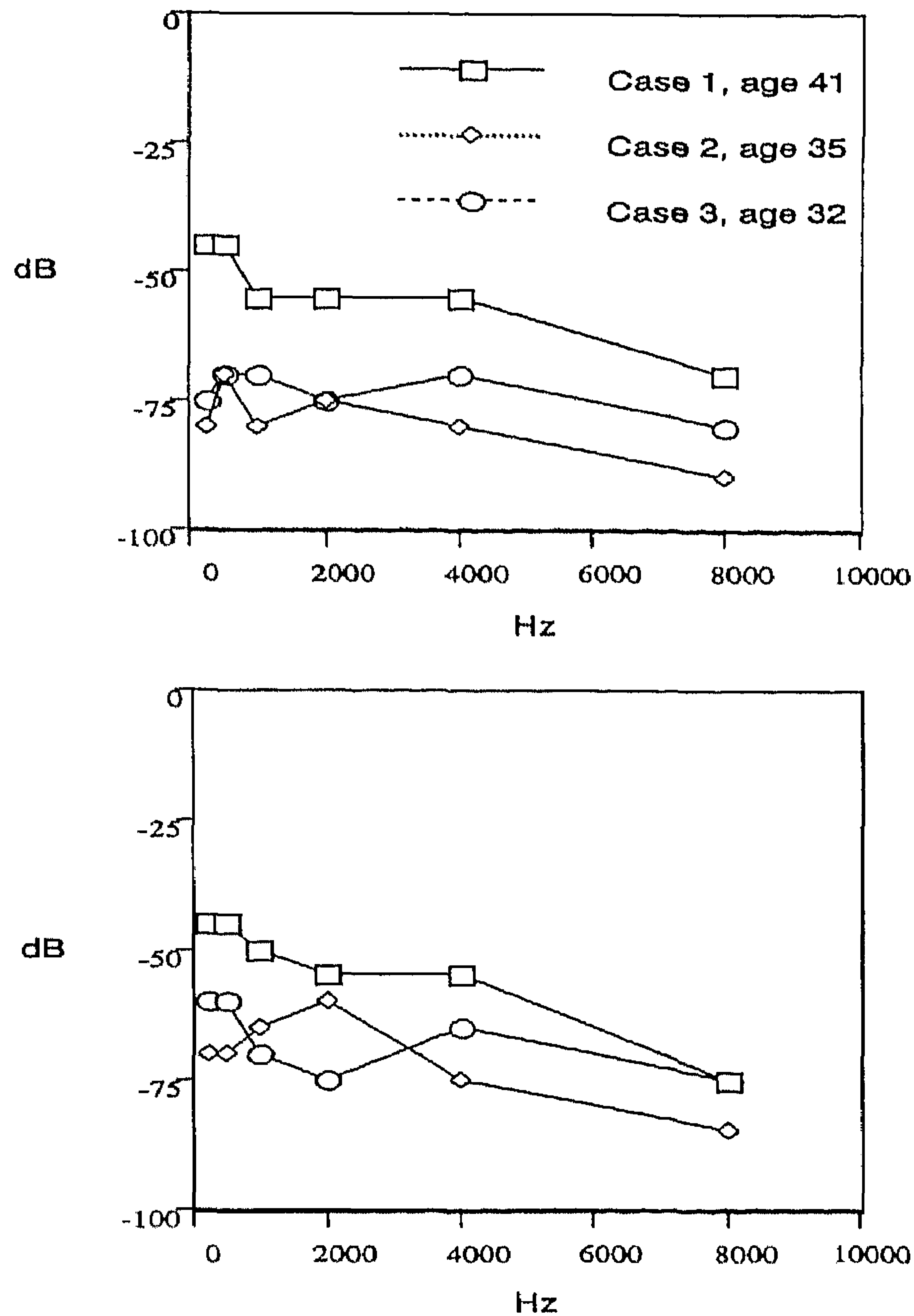


Fig. 11. Compound audiogram for cases 1-3, left ear (top panel) and right ear (bottom panel).

ent patients were identical to those previously reported in OSMED. Clinical and radiological findings are listed in Table I. Case 1 of Kääriäinen et al. [1993] was excluded because of the absence of any vertebral anomalies, the absence of joint enlargements and the atypical facies (upslanting palpebral fissures and epicanthic folds). Case C of Giedion et al. [1982] was excluded because of the absence of the facial anomalies that were present in all other patients in our selection. We have recently shown that the condition in this family is linked to COL11A2 and is caused by a missense mutation leading to a glycine to arginine substitution within the triple helical region of  $\alpha 2(\text{XI})$  collagen [Vikkula et al., 1995]. Only one other pathogenetic mutation in type XI collagen has been reported in humans. A Dutch

Fig. 9. **A:** Light microscopy. Appearance of relatively unaffected part of cartilage from tibial plateau of case 2. Note inhomogeneous distribution of collagen fibrils coursing from basal to superficial layers (fibrillation) and superficial loss of Alcian Blue staining (PAS-Alcian Blue staining in polarized light). SL: superficial layer. **B:** Chondrocytes in relatively intact central part of OSMED cartilage. **C:** Same location but viewed in polarized light, showing fibrillation of cartilage. **D:** Layer of transition from OSMED cartilage (C) to subchondral bone. Penetration of cartilage by fibro-vascular tissue and replacement of cartilage by plexiform bone. **E:** Same as in D, but viewed in polarized light. **A-E:** magnification  $\times 140$ . Appearance of control cartilage was identical. **F-J:** Electron microscopy. Superficial (F, G) and deep (H, J) matrix from OSMED (F, H) and control osteoarthritic cartilage (G, J). Note aggregation of collagen fibers into thick bundles in OSMED cartilage (arrows in F and H). In the superficial layers of control osteoarthritic cartilage two bundle-types can be discerned, relatively thick bundles (arrows in G, J) and relatively thin bundles. Only a single type of fiber is present in the superficial layers of the OSMED cartilage. Note presence of proteoglycans (black particles) in association with collagen fibrils in control cartilage (J) and relative absence of these particles in OSMED (H). **F-J:** magnification =  $\times 45,000$ .



TABLE I. Comparison of Clinical and Radiological Findings in OSMED and Non-Ocular Stickler Syndrome

	OSMED <sup>a</sup>	Non-ocular Stickler syndrome <sup>b</sup>
Clinical		
Midface hypoplasia <sup>c</sup>	17/17	15/15
Anteverted nares	17/17	15/15
Pierre-Robin sequence	5/15	4/15
Isolated cleft palate	7/11	2/15 <sup>d</sup>
Perceptive hearing loss	12/17	6/15
Conductive hearing loss	0/17	1/15
Mixed hearing loss	4/17	5/15
High myopia	0/17	0/10
Short stature	17/17	1/15
Increased lumbar lordosis	12/17	0/15
Short hands & fingers	17/17	1/15
Prominent IP-joints	13/17	0/15
Contractures	15/17	0/15
Joint pain	12/14	8/15
Radiological		
Epiphyseal dysplasia	15/15	+ <sup>e</sup>
Wide flat epiphyses	15/15	ND <sup>f</sup>
Metaphyseal flaring	12/15	ND
Mild vertebral dysplasia	17/17	+ <sup>f</sup>
Fusion of carpalia	6/15	ND
Large carpalia	8/14	ND
Short metacarpals	15/15	2/16
Large tarsal bones	4/11	ND
Early osteoarthritis	4/6	4/8

<sup>a</sup>OSMED cases: cases 1–3 this report; cases 1–3 of Al Gazali and Lytle [1994]; cases A, B, and D of Giedion et al. [1982]; patient of Gorlin et al. [1973]; cases 2 and 3 of Kääriäinen et al. [1993]; cases 1 and 2 of Miny and Lenz [1985], cases 1 and 2 of Insley and Astley [1974]; case of Nance and Sweeney [1970].

<sup>b</sup>Non-ocular Stickler syndrome: Brunner et al., 1994.

<sup>c</sup>More pronounced in OSMED.

<sup>d</sup>Submucous cleft.

<sup>e</sup>Not systematically analysed in all cases, but present in 8 individuals who had X-ray examination because of joint pain.

<sup>f</sup>Severe in the recessive OSMED cases and much milder in the dominant COL11A2 linked non-ocular form of Stickler syndrome.

<sup>g</sup>ND: No data.

family with a dominantly inherited non-ocular form of Stickler syndrome was found to have a splice-site mutation causing an in-frame deletion of 18 amino acids in the triple-helical region of  $\alpha 2(XI)$  collagen [Vikkula et al., 1995]. In contrast to conditions that are due to mutations in the type II collagen gene, high myopia and vitreoretinal degeneration are not present in these two kindreds with abnormal type XI collagen. This is surprising, since type II and type XI collagen are in close association in cartilage [Keene et al., 1995]. The absence of ocular findings in the recessive and the dominant kindreds can be explained by the absence of the  $\alpha 2$ -chain of collagen type XI in the mammalian vitreous, where it is replaced by the  $\alpha 2$ -chain of collagen type V. This arrangement has been demonstrated for the bovine vitreous [Mayne et al., 1993], but comparable data are not yet available on humans.

The clinical picture of OSMED and the non-ocular Stickler syndrome is remarkably similar (Table I). Both have midface hypoplasia, sensorineural deafness, and epiphyseal dysplasia. In OSMED the epiphyseal dysplasia is more severe and leads to osteoarthritis in early adulthood. The midface hypoplasia of OSMED is also more striking than that observed in cases of non-

ocular Stickler syndrome. Joint contractures and short hands with stubby fingers are also more prominent in OSMED. Short fifth metacarpals have been observed in both the dominant and the recessive kindreds [Brunner et al., 1994]. In general, OSMED can be considered as a clinically more severe autosomal recessive variant of the autosomal dominantly inherited non-ocular Stickler syndrome. This is consistent with the previous assignment of OSMED and Stickler syndromes to a single chondrodysplasia "family" [Spranger, 1985].

Mutations of the different collagen XI genes probably result in a spectrum of phenotypes in humans. Animal studies have given further clues to the function of type XI collagen in cartilage formation and to the phenotypic effects of mutations in these genes [Li et al., 1995]. Collagen type XI is likely to be important in limiting collagen fibril diameter [Vikkula et al., 1995]. This view is consistent with the results of the electron microscopic examination of the cartilage obtained from case 2. There, no fibers with a diameter less than 25 nm were seen. Mean fiber diameter was more than 30 nm in the superficial layers and there were aggregates of collagen fibers in the basal layers measuring in excess of 140 nm (Fig. 3). Regulation of fiber diameter is thought to be effected by the globular N-terminal domain of collagen type XI, which is not subject to post-translational modification [Wu and Eyre, 1995]. By projecting away from the fibril, it prevents the addition of extra collagen type II fibrils in a process known as steric hindrance. Lack of steric hindrance due to abnormal collagen type XI molecules could explain the observed increase in type II fibril diameter. This is entirely consistent with the observation of Keene et al. [1995] that type XI collagen is preferentially associated with thin fibers in cartilage. However, the disappearance of the fiber population measuring 80 nm in diameter from the superficial layers of OSMED cartilage is puzzling, since it cannot be explained from the reported association of collagen type XI with thin fibrils. Our findings suggest that the absence of normal  $\alpha 2(XI)$  collagen chains interferes with the normal regulation of collagen fibril diameter in cartilage, both of thicker and of thinner fibril types. The disorganized appearance of the cartilage in OSMED also strongly supports a role for collagen type XI in establishing and perhaps maintaining normal cartilage architecture, both in joint surfaces and in the growth plate.

Because of the close association between types II, IX, and XI collagen, mutations in type XI collagen genes may be expected to have phenotypic consequences similar (but not identical) to those of mutations in type II collagen genes. Moreover, the  $\alpha 3$  chain of collagen XI is encoded by the COL2A1 gene [Morris and Bachinger, 1987]. A human COL11A1 mutation might therefore share certain characteristics with the Stickler-Kniest family of bone dysplasias [Spranger, 1985]. This hypothesis is supported by the phenotype associated with the dominant COL11A2 mutation which shares a number of characteristics with classical (COL2A1-linked) Stickler syndrome. Phenotypes associated with COL11A1 mutations most likely will include ocular findings since the  $\alpha 1$ -chain of collagen XI is present in



the mammalian vitreous [Mayne et al., 1993]. In order to identify further conditions that may be caused by mutations in one of the type XI collagen genes, we searched the POSSUM database [Bankier et al., 1994] using epiphyseal dysplasia, midface hypoplasia, and deafness as search terms. An identical search in the OSSUM [Bankier et al., 1989] and LDDDB [Winter et al., 1984] databases did not provide additional insights. The Marshall syndrome [Marshall, 1958; Ruppert et al., 1970; Keith et al., 1972; Zellweger et al., 1974; O'Donnell et al., 1976; Nguyen et al., 1988; Stratton et al., 1991] appeared to be most similar to OSMED. It is possible that the Marshall phenotype is caused by a mutation in COL11A1, as the  $\alpha 1$ -chain of collagen XI is present in the vitreous [Mayne et al., 1993]. The finding of a mutation in COL11A1 would provide a biological basis for splitting the Marshall-Stickler group into distinct entities [Aymé and Preus, 1984].

There are a number of reports of other conditions that share clinical similarities with both OSMED and Marshall syndrome and could also be caused by mutations in one of the collagen type XI genes [Pfeiffer et al., 1973; Beighton et al., 1978; Farag et al., 1987; McDermot et al., 1987; Bonaventure et al., 1992].

Other conditions that also have midface hypoplasia, but are phenotypically distinct from either the OSMED or Stickler syndromes, are probably due to mutations affecting other cartilage expressed genes. Atelosteogenesis types 1 and 3 show clear midface hypoplasia but are radiologically and clinically distinct from either OSMED or Stickler syndrome [Maroteaux et al., 1982; Stern et al., 1990]. SPONASTRIME dysplasia [Fanconi et al., 1983] also has midface hypoplasia but it lacks deafness, myopia, or a generalised epiphyseal dysplasia.

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