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Camurati-Engelmann Disease

Genetics and Clinical Manifestations with a Review of the Literature*

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This syndrome, which usually carries the names of Camurati and Engelmann, was first described by Cockayne in 1920. Its hereditary nature was suggested by Camurati (1922) who reported a father and son both with painful lower extremities which showed cortical thickening and sclerosis of the diaphyses on *x*-ray examination. The single case report of Engelmann in 1929 documented muscular wasting and marked bone involvement. Neuhauser *et al* (1948) subsequently named this rare condition 'progressive diaphyseal dysplasia' emphasizing the progression of the hyperostosis along the shafts of the bones. Subsequently, both sporadic and familial cases have been described.

This report is the result of the authors' unusual opportunity to study extensively a large, cooperative family with 8 affected individuals in 3 generations, representing the largest affected kindred to date. Our observations in this family, together with those from the literature, demonstrate the considerable variability of this autosomal dominant inherited disorder. Clinical and genetic considerations are stressed here, and the radiological manifestations are discussed in greater detail elsewhere (Graham and Sparkes, 1972).

Material, Methods, and Results

Details of the family relationships are presented in the pedigree of Figure 1. Two propositi (IV.1 and IV.12) were discovered independently. Because of the known bone abnormalities in Camurati-Engelmann disease it was elected to screen all available family members by radiological examination. The femurs were selected for this survey, since they were shown by review of the literature to be the most commonly affected bones. Twenty-eight of 35 living members were filmed, with demonstration of 6 additional affected individuals. Individuals in the direct genetic line and hence presumably having the mutant gene received complete skeletal surveys, with only one exception (II.10). Clinical and radiological findings are summarized in Table I. The two propositi are described in detail below.

Case 1. This boy (E.T., IV.1 see Fig.2) had a long history of easy fatiguability, inability to gain weight, and deformities of the extremities. He seemed normal until he began to walk at 15 months, when he was noted to have a waddling gait and to cry frequently when he walked.

He gained only 13 lb between 1 and 6 years, at which time he appeared to be very thin but of normal height. He had marked pronation of his feet. A biopsy from the anterior cortex of the tibia showed 'osteopetrosis', a diagnosis which he carried for several years. At 7 years of age, serum phosphorus and alkaline phosphatase were normal.

A severe genu valgum deformity was noted by his 8th year; this—associated with marked weakness—permitted him to attend school only half time. A 24-hour urine calcium excretion was elevated at 0·185 g. Liver and renal function tests were normal as was a cerebrospinal fluid examination; a serological test for syphilis was negative. He did reasonably well in school until the age of 11 when he left school because of further difficulty in walking. As part of a home study programme, he became skilled as a painter.

At 18 years of age he was a tall, extremely thin youth with little muscle mass but with no muscle paralysis. Movement of the shoulders was limited to 90 degrees of elevation. He had a minimal left thoracic and right lumbar scoliosis. A valgus deformity of 35 degrees in both knees resulted in a 25-cm gap between medial malleoli with the knees together. Flexion contractures of both knees prevented full extension, although they could be fully flexed. Both tibias had 45 degrees of external rotation. Pubic hair and external genitalia were normal male. A grade 2/6 high pitched diastolic heart murmur was heard in the second intercostal space along the left sternal border. Routine blood and urine studies were within normal limits, as were serum calcium, phosphorus, and alkaline phosphatase.

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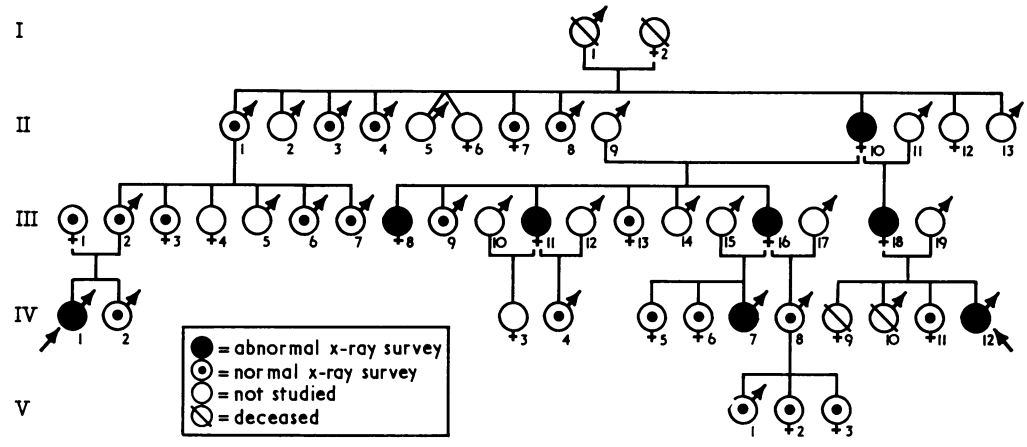

FIG. 1. Family pedigree with results of x-ray surveys. The two propositi (IV.1 and IV.12) are arrowed.

TABLE I

SUMMARY OF FINDINGS IN THE FAMILY (THE 2 PROPOSITI ARE NOT INCLUDED)

Affected Person	Sex	Age (yr)		History	Physical Examination	Affected Bones by X-ray Examination
		At Onset	At Examination			
M.T.M. (II.10)	F	?	77	Asymptomatic	Normal	Femurs (only bones examined)
M.J. (III.18)	F	?	36	Asymptomatic	Normal	Femurs; tibias; fibulas; L. ulna; R. metacarpal II; skull
E.S. (III.8)	F	5	55	'Polio' age 5; waddling gait; poor leg muscle development; menarche age 17	Height 170 cm; weight 61·5 kg; walks slowly with waddling gait	All long bones; R. clavicle; L. distal phalanx II; skull; mandible
B.M. (III.11)	F	?	50	Asymptomatic	Normal	Femurs; R. tibia; L. middle phalanx V; skull
A.G. (III.16)	F	18	42	Leg aches began age 10	Normal	Femurs; tibias; fibulas; skull
P.G. (IV.7)	M	?	7	Waddling gait; flat feet	Not examined	All long bones; skull

To correct the lower limb deformities, bilateral tibial and fibular osteotomies were performed. The bones had increased vascularity and were softer than expected from their radiological appearance. An uneventful postoperative course was followed by bilateral femoral supracondylar osteotomies. This resulted in a markedly improved alignment of the legs so that subsequently his gait was improved and he was able to return to school.

Histological examination of bone biopsies from the tibias and femurs showed a thickened periosteum without evidence of inflammation. The walls of the small blood vessels were thickened and the bone cortex showed a dense compact structure with normal haversian systems and minimal osteoblastic and osteoclastic activity.

At 20 he had a protein bound iodine of 6·0 μg%, serum vitamin A of 7 units, serum creatine of 0·7 mg%, normal male buccal sex chromatin study, and normal peripheral nerve conductivity, and electromyograms. A biopsy of the right fibular epiphysis showed osteoporotic bone and a normal growth plate with minimal evidence of activity; a muscle biopsy was normal and showed no changes in the blood vessels.

When last seen at age 26 he had progressive hearing difficulty and balance problems. On examination there was total deafness on the right, associated with facial paralysis and considerable decrease of auditory function on the left. Craniotomy was performed with bilateral decompression of the slit-like internal auditory canals, and some improvement was initially noted. There was marked overgrowth of the skull internally, and intracranial pressure was mildly elevated. His orthopaedic status was unchanged.

Complete skeletal surveys were obtained at ages 6, 8, 10, and 18 years. These showed cortical hyperostosis and sclerosis of the diaphyses of all long tubular bones. With advancing age this progressed along the shafts

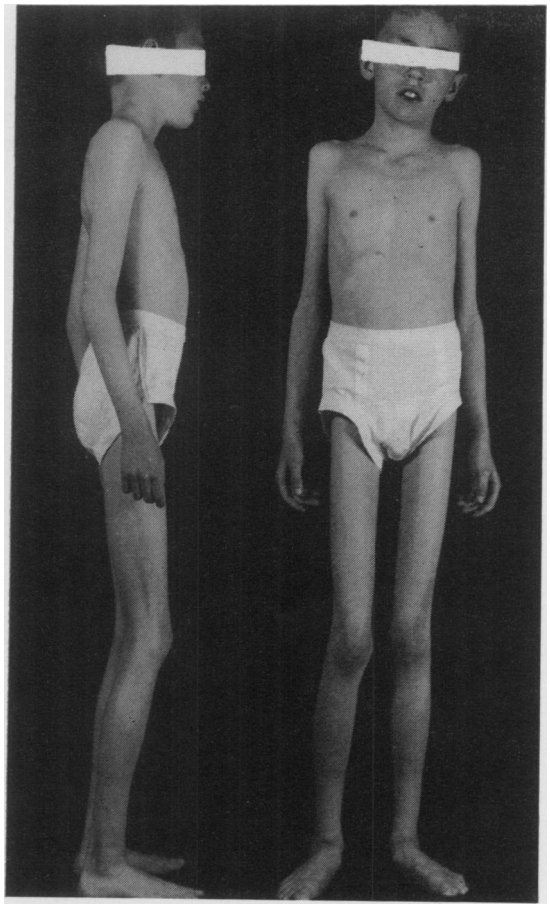

FIG. 2. Case 1 (IV.1) at age 10, showing the general asthenic appearance, the poor muscle mass, pronation of feet, and the characteristic appearance of the limbs.

proximally and distally, but did not involve the metaphyses nor the epiphyses. Transiently there were some short uninvolved areas, especially in the fibulas, which later also became affected. Muscle mass was markedly diminished.

The entire skull base was sclerotic, and the increased density extended particularly into the parietal bones. Initially most of the frontal region was spared, but this subsequently also became thickened. There was a suggestion of increased density of the mandible on last examination at age of 26 years, but the facial bones appeared normal. Skull laminography showed remarkable hyperostosis of the base and vault, with obliteration of diploic spaces and extreme narrowing of the internal auditory canals.

Skeletal maturation was assessed on several occasions. It was lower than average, but within normal limits, at ages 6 and 8 years. At 10 years bone age was slightly retarded, but at age 18 years it was no more than 13½ years which represented a very significant retardation. Fusion of epiphyses was notably delayed.

Case 2. The second propositus, B.J. (IV.12), carried the diagnosis of muscular dystrophy from age 3 to 18 years. He began to walk with a waddling gait at 17 months. He had difficulty in rising from a sitting position. Biopsies early in childhood showed diminished muscle mass. He had always been thin and was the shortest member of his school class. He did not experience the usual pubertal growth spurt. Pubic hair first appeared at age 13, but he had no axillary hair and had not shaved by the age of 18.

Physical examination at age 18 showed him to be thin and pale with the appearance of a 12-year old boy. There was marked diaphoresis of hands and feet. Only a few pubic hairs and facial down were present. Dentition was good as were peripheral pulses. The left testis was descended but was small and soft; the right testis could not be palpated. He walked with a wide-based waddling gait. Deep tendon reflexes were hyperactive. Body proportions showed: height, 156 cm; arm span, 156 cm; and pubis to floor measurement of 83 cm. Marked lumbar lordosis, genu valgum with external rotation of the tibias, and flat feet were present. Muscle development was poor and there was non-tender thickening of the shafts of the long bones. He had loss of full flexion at the shoulders while abduction was complete. Internal rotation of the shoulders was limited to 30 degrees bilaterally. There was a 10-degree lack of full extension of the left elbow. Pronation and supination were grossly limited bilaterally. There was a 25-degree flexion contracture at the hips, and a 10-degree valgus at the right knee and 5 degrees at the left. The knees lacked 10 degrees of full extension bilaterally. There was a severe lordosis attributed to rotation of the pelvis secondary to the hip flexion contracture.

At age 18 a routine haematological and urine examination were normal. However, a urinary gonadotrophin excretion test showed none detectable.

Skeletal survey at age 18 years revealed virtually identical distribution and degree of long tubular bone abnormalities to those noted in case 1 at the same age (Figs. 3 and 4). However, the skull was not as extensively involved, with almost complete sparing of the calvarium (Fig. 5). As in case 1, the shoulders, thorax, spine, pelvis, hands, and feet were entirely normal. Bone age was determined to be no more than 12½ years, a very marked retardation.

Other Family Members

Clinical and Radiological Findings. On survey of the family, 6 additional cases of Camurati-Engelmann disease were discovered (see Table I and Fig. 1). The degree of skeletal abnormality ranged from the most severe in a 55-year-old woman (III.8), in whom it was especially noteworthy that her mandible was markedly involved, to milder but obvious long bone hyperostosis and sclerosis in her 3 younger sisters. The most common complaint was leg aches, but 3 radiologically affected

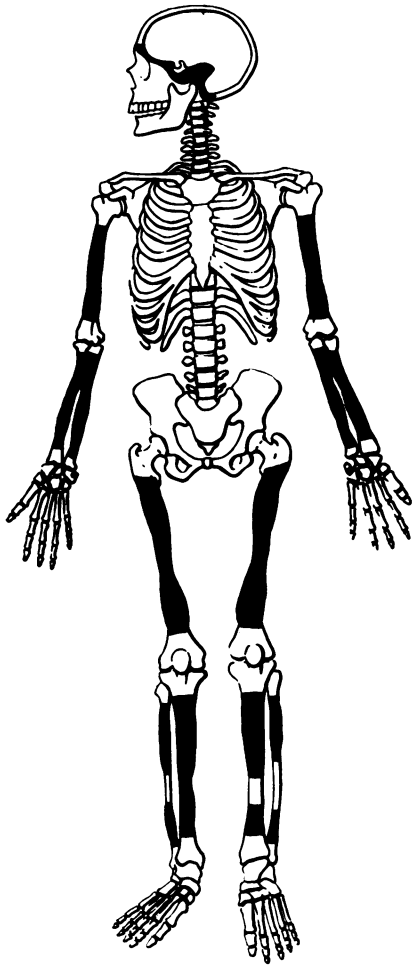

FIG. 3. This schematic drawing of the skeleton shows the affected bones in case 2 (IV.12) at 18 years of age. Only short segments of the leg bones are uninvolved.

family members were entirely asymptomatic. Four were normal on routine physical examinations. One affected individual (II.10), due to lack of full cooperation, only allowed filming of her pelvis through the upper tibias-fibulas; her femurs were typically involved.

One additional family member (II.6) had a very strong history suggestive of Camurati-Engelmann disease, but she refused *x*-ray screening and physical examination and is not included as an affected member of the family. Both male ancestors (II.1 and III.2) in the direct genetic line to the affected propositus (IV.1) showed considerably more 'bone sclerosis' than matched individuals of their age and activity level; however, with negative histories and without other physical manifestations, these were ultimately assigned to the negative findings category. Because of this apparent two generation 'skip' of the manifest disorder to propositus IV.1, his mother (III.1) was filmed in greater detail. However, her skeleton appeared entirely normal.

In general, those family members who showed more severe clinical alterations also had more extensive radiological bone abnormalities, while asymptomatic persons demonstrated relatively minimal changes.

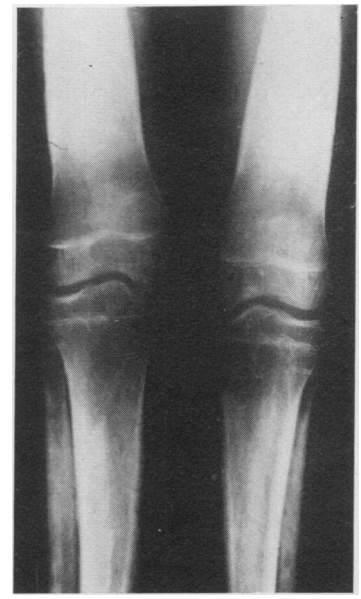

FIG. 4. Lower extremity radiograph of case 2 at 18 years of age. The severe hyperostosis and widening of the diaphyses with sparing of metaphyses and epiphyses in evident; the musculature is sparse.

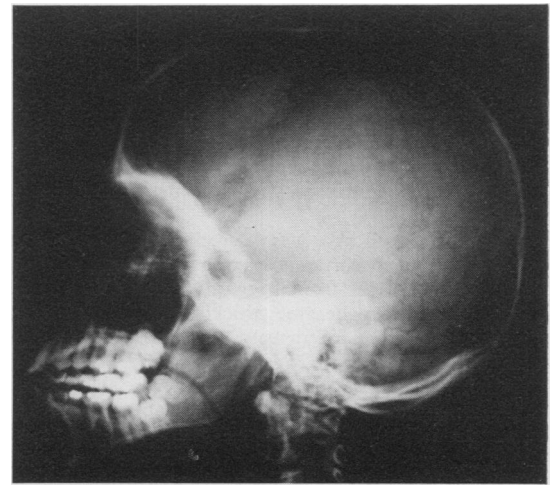

FIG. 5. Skull film of case 2 reveals marked sclerosis of the base and floor of the anterior fossa, sparing the face, mandible, and calvarium.

Discussion

Since its initial description half a century ago, Camurati-Engelmann disease has become a well-defined clinical entity. Its most striking characteristic is the diaphyseal dysplasia of the bones, but poor muscle development and retarded maturation are also seen in the more severely affected persons. It is often inherited in an autosomal dominant pattern, but several sporadic cases have been reported. Our evaluation of a large family in which this disorder occurs underscores the autosomal dominant inheritance and the marked variability of phenotypic manifestations of the mutant gene. An earlier report (Clawson and Loop, 1964) emphasized the orthopaedic aspects of the disorder in our propositus E.T. (IV.1).

Twenty-eight family members had an *x*-ray screening examination of the femurs, and 8 family members (including the 2 propositi) were detected with bone changes indicative of this syndrome. The detailed findings of these affected individuals are found in Table I and their relationships are noted in the pedigree. In addition, one of the family members (II.6), who did not have *x*-ray examinations, had symptoms suggestive of this disorder.

Examination of the pedigree in Fig. 1 reveals 2 propositi. The first (IV.1) was said to have a negative family history when initially seen, and *x*-ray examination of other family members was not undertaken at that time. Subsequent to this, the second propositus (IV.12) was seen independently. An extensive family pedigree indicated that the two propositi were indeed second cousins. Thus, the present family was ascertained because two affected individuals had severe manifestations, including muscle weakness, leg pain, and retarded sexual maturation. Three others (III.8, III.16, and IV.7) had mild symptoms or signs and 3 more (II.10, III.18, and III.11) were detected only by radiological study. This illustrates the importance of this valuable diagnostic tool in giving genetic counselling to relatives of patients with Camurati-Engelmann disease. However, it is of interest that a severely affected individual (IV.1) had asymptomatic parents and grandparents who showed no definite radiological abnormalities. Because of the rarity of this disorder and the close relationship of the two propositi, it seems very likely that the gene was present in the father (III.2) and the grandfather (II.1) of case 1 (IV.1). If this conclusion is correct, it emphasizes the wide variable expressivity of the mutant gene and indicates that a normal *x*-ray examination may not rule out the presence of the mutant gene. It also suggests that one great grandparent (I.1 or I.2) probably had the gene. It is of interest that the severest manifestations are in the most recent generation, a pattern suggestive of anticipation.

Review of the Literature. With gradual accumulation of new information and development of a better understanding of the disease spectrum of this relatively rare disorder, it has become clear that some case reports in the literature do not represent Camurati-Engelmann disease. Conversely, a few have been published under other titles. We have critically evaluated as many of the reported cases as possible, emphasizing familial occurrences.

Confirmed affected families, except our own, are summarized in Table II (pp. 78–81). These 20 families still include at least one which is questionable (Ramon and Buchner, 1966), because of the childhood mandibular changes and the lack of early muscular abnormality. It is interesting that the propositus in the family of Trunk, Newman, and Davis (1969) has been reported on 3 previous occasions (Riley and Schwachman, 1943; Neuhauser *et al*, 1948; Jackson, Hanelin, and Albright, 1954) as a sporadic case, but these were before his recent parenthood. McKusick (1966) noted that restudy of the sporadic case presented by Singleton *et al* (1956) showed 3 affected generations, but this was not detailed and the family is not included in Table II. Lennon, Schechter, and Hornabrook (1961) also noted that Roth in 1957 reported an affected 18-year-old youth whose father and 14-year-old brother were similarly affected; this family is not included in Table II because we have not been able to evaluate the original article. The unusual family of Favreau *et al* (1963) was eliminated because the condition is probably not Camurati-Engelmann disease.

We have been able to confirm 33 reports of sporadic cases including 20 affected males and 21 affected females.* In general there do not appear to be significant phenotypic differences between familial and sporadic cases. However, as might be

* Cockayne, 1920; Engelmann, 1929; Fritsch, 1933; Riley and Schwachman, 1943; Neuhauser *et al*, 1948; Sear, 1948; Wiedemann, 1948; Michaelis, 1949; Bingold, 1950; Stronge and McDowell, 1950; Gillespie, and Mussey, 1951; LeBien and Heilman, 1951; Gulledge and White, 1951; Lavine and Koven, 1952; Anderson, 1953; Chipps, Penner, and Travis, 1954; Jackson *et al*, 1954; Perassi, 1954; Weingraber, 1954; Griffiths, 1956; Singleton *et al*, 1956; Stewart and Cole, 1956; Mikity and Jacobson, 1958; Girdany, 1959; Patz and van Heerden, 1960; Fairbank, 1951; Cohan *et al*, 1962; Neumann, 1962; Dell'Acqua, Ruberti, and Piffanelli, 1963; Ioppolo and Marino, 1964; Pizon, 1964; Mottram and Hill, 1965; Galimberti, 1966; McKusick, 1966; Gulati, Bhardwaj, and Vyas, 1967; Royer *et al*, 1967; Shetty, Khandige, and Varadaran, 1968; Nelson and Scott, 1969; Allen *et al*, 1970.

TABLE II

FAMILIAL CASES FROM THE LITERATURE (EXCLUDING CLAWSON AND LOOP, 1964)

Author	Sex	Age (yr)		Relationship	Symptoms	Physical Findings	Affected Bones	Comments
		At Onset	At Diagnosis					
Camurati (1922)	M	Birth	7	Propositus	Leg pains; broad-based gait	Poor muscle development; fusiform swelling below knees	Femurs; tibias; fibulas	Eight more family members in 4 generations had suggestive history and physical findings
	M	Birth	55	Father	Childhood leg pains; broad-based gait	Poor muscle development; fusiform swelling below knees	Femurs; tibias; fibulas	
Feddema (1949)	F	—	50	Proposita	—	—	Tibias	
	F	—	47	Sister	—	—	Tibias	
	F	—	56	Sister	—	—	Tibias	
	F	—	53	Sister	—	—	Tibias	
Ribbing (1949)	F	17	21	Proposita	Forehead headaches; leg pain	Fusiform thickening of legs	Tibias; L. fibula; skull (?)	Cortical and cancellous osteosclerosis on biopsy
	F	—	26	Sister	—	—	Femurs; L. tibia	
	M	23	31	Brother	—	—	L. tibia	Normal angiography —left leg
	F	26	39	Sister	Leg pain	—	L. femur; tibias; R. radius	
	M	—	—	Father	Unexplained leg pains	—	—	
Paul (1953)	M	19	31	Propositus	Otosclerosis; leg pain	—	Femurs; tibias; fibulas; R. radius	Chronic osteoperiostitis; sclerotic on biopsy
	M	—	1	Son	Walking difficulty	—	Most long bones	
	M	—	35	Brother	Left ear deafness	—	L. femur; tibias; L. ulna	
	M	—	—	Father	—	—	Long bones	Discovered later (personal communication from Dr Paul)
Ortolani and Castagnari (1953)	F	—	6	Proposita	Easily fatigued; pain in limbs; abnormal gait	Poor muscle development; lordosis	All major long bones	
	M	—	19	Brother	None	—	Femurs; tibias; fibulas	Not progressive
Jammes *et al* (1956)	M	—	19	Propositus	Widebased gait	Thickened extremities	Long bones; skull	*X*-ray survey of mother and 8 sibs was negative
	F	—	16	Sister	Widebased gait; delayed menses	Thickened humeri	Femurs; skull; humeri	
	M	—	55	Father	Widebased gait	—	Femurs; humeri	

TABLE II—*continued*

Author	Sex	Age (yr)		Relationship	Symptoms	Physical Findings	Affected Bones	Comments
		At Onset	At Diagnosis					
Girdany (1959)	M	—	5	Propositus (case 4)	'Peculiar gait'	Poor muscle development	'Skeleton'	
	F	—	9	Sister	Thin	—	'Entire skeleton'	
	M	—	—	Father	—	—	Tibias; skull	
	M	—	3½	Propositus (case 1)	Waddling gait; muscle pain; tired easily	Poor muscle development	All long bones; skull	Initially diagnosed as muscular dystrophy
	F	—	1½	Sister	Waddling gait	Small muscle mass	Long bones; skull	
	F	—	33	Mother	Asymptomatic	Normal	All long bones; skull	
	M	14	21	Maternal uncle	Weak	Normal	'Entire skeleton'	
	M	—	30	Maternal uncle	Asymptomatic	Normal	Tibias	
	F	—	57	Maternal grandmother	Asymptomatic	—	'Throughout skeleton'	
Goerke (1960)	F	4	19	Proposita	Unusual gait	Hypoplastic muscles; thin limbs	All long bones	
	M	—	47	Father	'Healthy'	—	Femurs; tibias; fibulas	
	M	—	—	Paternal uncle	Unusual gait; weak	—	—	No radiographs
	M	—	—	Brother	Unusual gait, weak	Thickened forearms	—	No radiographs
Thelen (1961)	F	—	21	Proposita	Thin; unusual gait; menarche age 20	Hypoplastic muscles	All long bones; skull	*X*-ray survey of 2 sibs was negative
	M	—	51	Father	Thin; decreased hearing	—	All long bones; skull; mandible	
Bedogni (1962)	F	27	28	Proposita	Leg pain	Decreased muscle mass; enlarged long bones	Femurs; tibias; fibulas; skull; mandible	Diffuse dense osteopathy; sister had similar *x*-ray changes
Dell'Acqua *et al* (1963)	F	21	21	Proposita	Leg pain	Hyper-reflexia	R. tibia	One normal child said to have 'positive' radiological findings
	F	—	48	Sister	None	—	?	
Wetzel (1964)	M	Childhood	28	Proposita	Unusual gait; decreased hearing; facial paralysis; leg pain	Slight muscle hypoplasia; large skull	All long bones; skull; mandible	
	F	—	57	Mother	Unusual gait; decreased hearing; facial paralysis; leg pain; easily fatigued	Muscle hypoplasia; large skull; long extremities	All long bones; skull; mandible	
	M	—	26	Brother	Unusual gait	Large skull	All long bones; skull	
	M	—	—	Maternal grandfather	Typical 'sailor's gait'	—		

TABLE II—*continued*

Author	Sex	Age (yr)		Relationship	Symptoms	Physical Findings	Affected Bones	Comments
		At Onset	At Diagnosis					
Ruelle and Dubois (1964)	F	16	28	Proposita	Painful arm and legs; easily fatigued; poor secondary sex characteristics; puberty 16 years	Hypotrophic muscles	Long bones; skull	Dense haversian canals; active osteoblasts; 2 normal brothers (clinical examination)
	F	2	6	Daughter	Pain in legs; weak	—	Long bones; skull	
Stirpe (1965)	M	?40	40	Propositus	Weak muscles; exophthalmos; convergence problem	—	Long bones; skull; mandible; clavicles; pelvis	
	F	34	67	Mother	Weak muscles; exophthalmos; convergence problem	—	—	No radiographs
	F	—	10	Daughter	Convergence problem	—	Femur (slight)	
	F	30	43	Sister	Aesthenia; exophthalmos; convergence problem	—	Long bones (except fibula); skull	
	F	—	36	Sister	Headaches	—	Skull (only bone examined)	
Massé and Parenti (1966)	M	—	39	Propositus	Exophthalmos	Scoliosis-dorsal lumbar; large arms and legs	Long bones; some short tubular bones; skull; mandible	Normal chromosomes; sister and sister's daughter said to be affected (by *x*-ray and clinical findings)
	M	—	—	Father	—	Symmetric enlargement of arms and legs		
Ramon and Buchner (1966)	M	39	40	Propositus	Paresthesia left arm and left leg (recent onset)	Muscle wasting on left but good on right; prominent mandible; 'short' limbs	Long bones; skull; mandible; vertebrae	
	M	—	10	Son	Asymptomatic	Good muscle development 'manly jaw'	Long bones; metacarpals, skull; mandible; pelvis	
	F	—	14	Daughter	Asymptomatic	Good muscle development enlarged mandible	Long bones; metacarpals, skull; pelvis	
Anczykowa *et al* (1967)	F	5	13	Proposita	Leg pains; unsteady gait; underweight; poor appetite	Generalized muscular atrophy; scanty adipose tissue	Skull	Bone biopsy—blurred systemic (haversian) bone; thickened blood vessel walls. Muscle biopsy—thickened blood vessel walls; abundant adipose tissue
	M	5	12	Brother	Lower leg pains; 'duck-like' gait	Physically the same	Femurs; tibias; humeri; skull	Biopsy the same
	F	5	8	Sister	'Duck-like' gait	Physically the same	Skull	Biopsy the same
	M	—	55	Father	Unsteady gait	—	—	
	M	—	15	Paternal cousin	Unsteady gait	—	—	
	F	—	30	Paternal aunt	Unsteady gait	—	—	

TABLE II—*continued*

Author	Sex	Age (yr)		Relationship	Symptoms	Physical Findings	Affected Bones	Comments
		At Onset	At Diagnosis					
Trunk *et al* (1969)	M	3	4	Propositus	Delayed onset of walking; easy fatigability; muscle weakness; delayed development of secondary sex characteristics; aching pain in arms and legs; headaches; blurred vision; hearing loss	Decreased muscle mass; lordosis	Long bones; some short tubuler bones; skull; mandible; pelvis (slight); vertebrae; clavicles	Biopsy—sclerosis of cortical and cancellous bone; unevenly distributed haversian systems; prominent osseous lamellae; pseudomosaic pattern; vessel walls
	M	2	3	Son	Waddling gait	Wasting of hips and legs	Long bones	Thickened vessel walls
	M	—	1½	Son	Generalized underdevelopment; poor growth and weight gain		Long bones	Thickened vessel walls
Allen *et al* (1970)	M	1½	9	Propositus	Peculiar gait; thigh bone pain; knee pain; muscle weakness	Waddling gait; thickened bones; poor muscle mass	All long bones	Bone biopsy—thickened and sclerotic cortex; no osteoclasts; good response to steroids
	M	Boyhood	Adult	Father	Wide based waddling gait	—	—	Diagnosis confirmed by *x*-ray
	F	—	—	Paternal grandmother		—	—	Diagnosis confirmed by *x*-ray; 8 other family members affected from history; pedigree compatible with autosomal dominant inheritance

expected, the latter are generally rather severe examples of Camurati-Engelmann disease corresponding closely to the propositi of the familial cases. In most instances of single case reports, relatives were not examined, so that a familial occurrence could not be excluded; also the possibility that the sporadic cases represent new mutations has to be considered.

Some nonfamilial patients demonstrated unusually rapid progression of markedly widespread disease, and these reports are questioned (Schönfeld, 1955; Cohen and States, 1956; Stegman and Peterson, 1957; Nelson and Scott, 1969). We have not attempted the difficult reclassification of this small osteosclerotic group but it is doubted that few if any are truly Camurati-Engelmann disease. Several others are easily reclassified into the 'craniometaphyseal dysplasia' category, for example the case of Gvozdanovic (1950), and are not included in our list of cases.

The familial or hereditary nature of this disorder has often been overlooked in the past and it is said to be nonhereditary in several current textbooks. As illustrated in our present family, a negative family history is no assurance that other family members are not affected. This does not rule out the possibility that the sporadic cases are different from the familial cases although they have the same phenotypic manifestations. However, the 21 affected families, including our own, clearly indicate a strong familial or hereditary aspect of this problem in some instances.

The family studies also demonstrate the considerable variability of the manifestations of apparently the same gene within a family. Because of this and because of the essentially typical but minimal findings in the cases of Ribbing (1949) and Paul (1953), these should be included within the Camurati-Engelmann disease complex.

Examination of the familial instances from the literature indicates 4 families with 1 generation affected, 14 families in which 2 generations are

affected, and 2 families in which 3 generations are affected. These patterns suggest a dominant form of inheritance and the presence of father to son transmission in some families rules out the possibility of X-linkage and indicates autosomal dominant inheritance. Further, the finding of a nearly equal sex distribution with 31 males and 30 females affected in the reported families gives additional support to this latter interpretation.

The range of age of onset seems quite variable depending upon the means of ascertainment; by history alone some individuals would appear never to be affected, while radiological studies show positive findings in various age groups.

Six familial instances (Ribbing, 1949; Paul, 1953; Bedogni, 1962; Ruelle and Dubois, 1964; Anczykowa, Bernasowska-Knapczykowa, and Zamorska, 1967; Trunk *et al*, 1969; Allen *et al*, 1970) have had bone biopsies and there appear to be no obvious distinguishing features in these familial cases compared to the biopsies from sporadic cases.

The Nature of the Syndrome. As often happens with new syndromes the most severe and classical forms are first identified and subsequently milder variants are later recognized. That Camurati-Engelmann disease can have considerable variability in the severity of signs and symptoms is well illustrated by our family study. From early infancy the most severely affected persons had leg pain associated with a waddling gait, poor muscle mass, and easy fatigability. Delayed puberty and deformed joints with decreased joint mobility may also be a part of the severe form of this syndrome. Mildly affected persons in the families of severely affected persons may be detected only by *x*-ray examination. Radiological abnormalities vary both in severity and in distribution.

Other reports also indicate this wide variability of signs and symptoms in affected persons. This is especially well seen in the larger reviews (Griffiths, 1956; Lennon *et al*, 1961; Rubin, 1964). The possible 'endocrine aspect' was first recognized in the report of Cockayne (1920) in which Parkes Weber noted this possibility, and it has also been further commented upon by others (Neuhauser *et al*, 1948; Patz and van Heerden, 1960; Lennon *et al*, 1961). Whether the retarded bone maturation and delayed puberty in our probands is due to an endocrine imbalance is not clear.

Because clinical manifestations show considerable variability, the radiological criteria for diagnosis as noted by Neuhauser *et al* (1948) still remain very helpful in making a specific diagnosis. These include: usually symmetrical skeletal distribution; fusiform enlargement of the diaphyses of the long bones; thickening of the cortex by endosteal and periosteal accretion of mottled new bone without recognizable trabecular pattern; abrupt demarcation of the lesion with loss of normal trabeculation, the involved cortex being irregularly dense; progression of the lesion along the long axis of the bone in both proximal and distal directions with gradual alteration of previously normal bone; soft tissue changes similar to those of underdevelopment of muscles and malnutrition; and normal epiphyses and metaphyses. Neuhauser's suggestion that there is 'elongation of the extremities relative to the size of the child' is not supported by our family study and survey of the literature. The extremities appear elongated because of extreme thinness, but are normal or shorter in length when compared to these bones in normal sibs of the patients.

Although these bony abnormalities are only part of the syndrome, they appear to represent the most specific and constant manifestation. Involvement of the femurs and tibias seems to be most common. However, most tubular bones, as well as the skull, have been affected. Because one cannot be certain that all the described cases represent Camurati-Engelmann disease, it is not entirely possible to be certain that some of the more unusual findings are part of the syndrome. Nevertheless, based upon our acceptance of certain cases, the following appear to be some of the uncommon regions of bone involvement: pelvis (Sear, 1948; Anderson, 1953); mandible (Chipps *et al*, 1954; Wetzel, 1964; Ramon and Buchner, 1966); clavicle (Sear, 1948); and ribs, metacarpals, phalanges, and spine (Mottram and Hill, 1965).

There are relatively few other conditions to consider in a differential diagnosis of Camurati-Engelmann disease and their radiological differentiation is discussed elsewhere (Graham and Sparkes, 1972). However, a large number of conditions have been previously considered in the differential diagnosis, including Paget's disease, familial metaphyseal dysplasia, leontiasis ossea with generalized bone changes, hyperostosis generalizata with pachydermia, osteopetrosis, melorheostosis, renal osteodystrophy, fibrous dysplasia, Caffey's disease (infantile cortical hyperostosis), fluorosis, heavy metal poisoning, myelosclerosis, osteoblastic carcinomatosis, Garre's osteomyelitis, Brodie's abscess, osteoid osteoma, hypervitaminosis A, congenital lues, osteomyeloreticulosis, osteopoecilia (spotted bones), and epiphyseal dysplasia (Sear, 1948; Cohen and States, 1956; Griffiths, 1956; Lennon *et al*, 1961; Ruelle and Dubois, 1964; Wetzel, 1964; Ramon and Buchner, 1966). With

appropriate evaluation of the patient, these disorders can be readily excluded.

Also contributing to the confusion is the large number of synonyms which have been given this disorder: periostitis hyperplastica, symmetric sclerotic hyperosteosis, progressive diaphyseal dysplasia, hereditary multiple diaphyseal sclerosis, osteopathia hyperostotica (sclerotisans) multiplex infantilis, polyostotic infantile sclerosis, and hereditary symmetric osteitis. Numerous synonyms for a given disorder can lead to considerable confusion and we therefore hesitate to suggest a change in present terminology. When possible, it is best to identify a disease by descriptive terminology which includes its primary aspects or etiological mechanism. With the present disorder we favour Camurati-Englemann disease because the aetiology is not known and because it may involve tissues other than bone, acknowledging that the diaphyseal dysplasia is the most specific and constant finding.

Aetiology and Mechanism of the Disease. The aetiology and the mechanism for production of this disorder are not known. Autosomal dominant inheritance seems most likely. Since genes control the formation of proteins and this is a dominant disorder, the defective protein would most likely be nonenzymatic in nature or, if it is an enzyme defect, the mutation would probably lead to increased enzyme activity. With our current understanding of the disorder there is no evidence to implicate a specific protein. Furthermore, it is not clear which tissues in the body are primarily affected and which may represent secondary effects from a still unrecognized primary defect.

Studies aimed at the aetiology of this disorder have not been revealing. Most routine laboratory studies are within normal limits. Much attention has been directed towards the boney abnormality. Bone biopsies all appear to show essentially the same changes, which include an altered cortex with progressive active bone resorption as well as deposition. The changes are generally considered to be nonspecific and result from resorption with subsequent remodelling of the bone (Riley and Schwachman, 1943; Ribbing, 1949; Bingold, 1950; Gulledge and White, 1951; Paul, 1953; Chipps *et al*, 1954; Griffiths, 1956; Singleton *et al*, 1956; Mikity and Jacobson, 1958; Rubin, 1964; Trunk *et al*, 1969). However, Allen *et al* (1970) were particularly impressed by the apparent absence of osteoclasts with definite evidence of decreased bone resorption; in one patient a good clinical response to steroid treatment was associated with increased bone resorption and histological evidence of osteon formation with secondary remodelling. The vascular thickening which has been observed in some cases (Singleton *et al*, 1956; Bedogni, 1962; Ioppolo and Marino, 1964; Anczykowa *et al*, 1967; Trunk *et al*, 1969) is provocative and might be related to the localization of the boney changes to the diaphysis, because of its relatively limited vascularization (Singleton *et al*, 1956).

Necropsy of one alleged case (Cohen and States, 1956) showed very dense bone at the base of the skull and no air sinuses in the frontal or ethmoid region at about 7 years of age. The ribs were normal, but the cortex of these bones was moderately thickened, although smooth. All long bones showed marked thickening in the region of the diaphysis. There was narrowing of the medullary cavity. The metatarsals and metacarpals were also involved. The membranous bones of the skull showed the same histological changes as did the diaphyses of the long bones. There was disappearance of the compact bone structure with its replacement by cancellous bone of an abnormal pattern. Active remodelling processes were present in all sections and only rudimentary haversian systems were seen. The periosteum showed increased accretion and resorption. The recently deposited subperiosteal new bone showed resorptive lacunae, as well as lightly stained seams indicating accretion. The periosteum was especially thickened in the cambial layer where multiple layers of osteoblasts were found.

Thus, the gross and histological findings, particularly of the bones, do not specifically identify the basic problem, although the observed vascular changes perhaps could be related to some of the nonosseous abnormalities in muscle and in endocrine function.

Genetic Aspects. It is not certain that the sporadic and familial cases represent the same disorder, but there is insufficient clinical, radiological, or laboratory evidence to indicate that they are different. The family studies are most suggestive of an autosomal dominant trait. The lack of family studies in the sporadic cases do not give insight into the possibility of their representing phenocopies or perhaps new mutations. Further, it is not entirely clear whether all familial cases represent the same basic disorder or may be genocopies.

The variability observed in our family as well as in the reported familial cases is typical of dominant disorders. The reason for this variability is generally unknown, but one has to consider at least

the following possibilities: multiple normal isoalleles; multiple mutant alleles at the same locus causing the disease; the presence of different nonallelic modifiers; and environmental modifiers, which are of particular interest because they could offer important clues to treatment of this disorder.

Review of the literature suggest that Caucasian persons have most commonly been affected, but this may reflect a limited geographic interest in these disorders. However, Negroes (Girdany, 1959), a Filipino (Gulledge and Winter, 1951), a Jew (Lennon *et al*, 1961), and an Indian (Shetty *et al*, 1968), have also been found to be affected.

Chromosome studies have been undertaken in 3 instances (Ioppolo and Marino, 1964; Galimberti, 1966; Trunk *et al*, 1969) and have been normal.

Therapy. Relatively few attempts at systemic treatment have been tried in these patients. Oestrogen and testosterone therapy produced no effect in one instance (Griffiths, 1956). There has been some suggestion that muscle weakness may improve with exercise, but this may be related to the general problem of the progressive or nonprogressive nature of Camurati-Engelmann disease. Several studies have documented that the osseous changes may be progressive into adulthood (Ribbing, 1949; Jackson *et al*, 1954; Griffiths, 1956; Wetzel, 1964; Mottram and Hill, 1965; Trunk *et al*, 1969). Studies showed minimal progression of bone lesions in one adult patient (Mikity and Jacobson, 1958). The progression may be related to the general severity of the problem in a given instance. The earlier reported treatment of patient E.T. (Clawson and Loop, 1964) indicates that surgical therapy may be a reasonable approach to some boney deformities. The usual analgesics have been generally unsuccessful in significantly alleviating the curious leg aches.

Two recent reports (Royer *et al*, 1967; Allen *et al*, 1970) have indicated a good symptomatic response to corticosteroid treatment in four patients. One child (Royer *et al*, 1967) even seemed to show normalization of *x*-ray bone changes, while pre- and post-treatment bone biopsies in another (Allen *et al*, 1970) demonstrated increased bone resorption and histological evidence of osteon formation with secondary remodelling, changes more towards normal. At present there seems to be no explanation for the response to steroids, but as the authors indicate these results suggest that steroids deserve further clinical trials in the treatment of this disease.

Summary

Clinical and radiological investigations of a large family with Camurati-Engelmann disease demonstrate the wide variability in expression of the manifestations, suggest that the familial distribution is most compatible with an autosomal dominant disorder, and show radiological examination to probably be the best current diagnostic aid in determining the presence of the disorder. Familial and sporadic cases from the literature are critically reviewed to assess diagnostic accuracy based on both clinical and radiological findings. Current understanding of the genetics of Camurati-Engelmann disease, the histology of affected bones, and possible therapies are also considered.

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