THE MULTIPLE BASAL-CELL NEVI SYNDROME

An Analysis of a Syndrome Consisting of Multiple Nevoid Basal-Cell Carcinoma, Jaw Cysts, Skeletal Anomalies, Medulloblastoma, and Hyporesponsiveness to Parathormone

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THE SYNDROME OF MULTIPLE NEVOID BASAL-cell carcinoma, odontogenic keratocysts, and skeletal anomalies is far more complex and encompassing than was supposed when first described. It involves many organs but principally affects the skin and the endocrine, skeletal, and nervous systems. Because of the publication of several of these cases in 1960 and 1963,[33, 34] one of the authors (R.J.G.) has had numerous communications from individuals telling of their cases and leading us to others heretofore untabulated. Within the past few years, additional information has been added, implicating other body systems. Our present survey would suggest that there are at least 38 reports of this syndrome, involving more than 150 individuals. In addition, at least 10 reports of "familial multiple dentigerous cysts" involving 37 individuals were available for analysis. Moreover, there were 28 reports of single or nonfamilial cases of multiple jaw cysts. The relationship between these entities and the complete syndrome was therefore deemed worthy of investigation.

An attempt to correspond with many of these authors was carried out in an effort to gain additional information concerning family pedigrees and associated anomalies. Such data were obtained from a number of these men, affording us the opportunity to expand our tables. We have had the opportunity to see 4 of the following 6 patients with this syndrome (Cases 1, 3, 5, and 6).

CASE REPORTS

Case 1. The patient, a 12-year-old white boy, was referred for study of multiple jaw cysts. Examination confirmed the presence of numerous radiolucencies in maxilla and mandible. Malocclusion (cross-bite) and mild mandibular prognathism were noted. The palate was high-arched.

Roentgenographic studies showed mild calcification of the falx cerebri. The sella turcica was unusually shallow. There was mild, left lumbar scoliosis and a "generalized demineralization of all vertebrae, radius, ulna and hand bones." Duplication of the posterior segment of the left third rib was also noted. There was also pes planus and mild pectus carinatum. The toes were arachnodactylic. Five pigmented basal-cell nevi were present on the side of the face and scalp above the ear. The 2 largest had white nodules in the center of the pigmented lesions. Additional ones were noted to be developing on the back and chest. The pubic hair pattern was feminine, and the patient exhibited cryptorchism. He had no facial hair.

The patient was obese and round-jowled, with an unusual shape to his forehead. His inter-inner canthal, interpupillary, and inter-outer canthal distances were 40 mm., 75 mm., and 110 mm. respectively.

There was no history of similar anomalies in any member of the family. He was the only child and there were no dead siblings. Buccal smear and chromosomal karyotype were normal.

An Ellsworth-Howard test revealed normal phosphaturic response. Other than an elevated alkaline phosphatase value of 22.6 units, no additional abnormality was found.

Case 2. A specimen removed from 1 of several jaw cysts of a 15-year-old girl was read as "odontogenic keratocyst," and the possibility of the syndrome being present was suggested

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This study was made possible by a grant (DE-1770) in Oral Pathology from the U.S. Public Health Service.

Case 2 was contributed by Dr. John Spink, Moorhead, Minn.; cases 4 and 5, by Dr. F. Schroff, University of Otago Dental School, Dunedin, New Zealand.

Figure 2A and B by courtesy of Dr. J. J. Herzberg.

Figure 4A and B by courtesy of Dr. W. A. Cook;[18] Fig. 4C by permission of *Acta dermat.-venereol.*, 1963.[34]

Received for publication March 4, 1964.

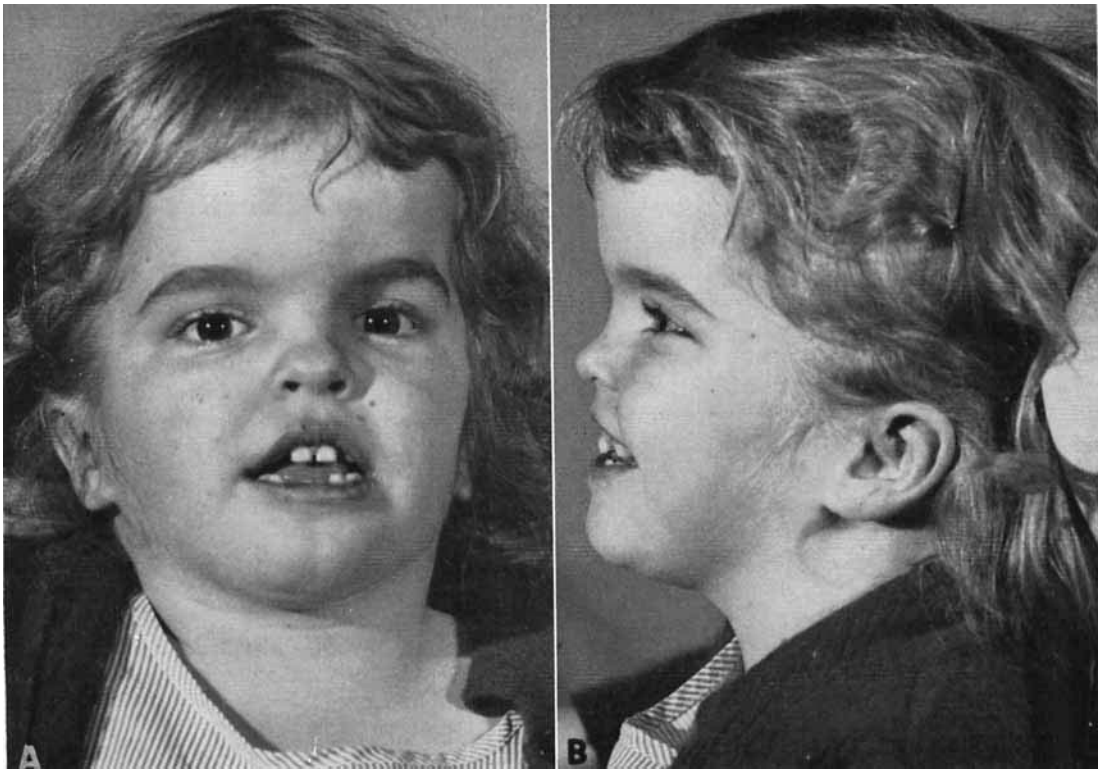


FIG. 1. A and B, Typical facies is characterized by frontal and parietal bossing, ocular hypertelorism, and mild mandibular prognathism. This child's mother and maternal grandmother have the syndrome. The child has bifid rib but has not developed other stigmata to date. (See also Fig. 6A and B.)

to the contributing oral surgeon. Further investigation revealed that no basal-cell nevi were present. Neither were there milia nor palmar dyskeratosis of Mantoux. Complete roentgenographic examination, however, revealed numerous jaw cysts in both maxilla and mandible, dural calcification, frontal and biparietal bossing of the cranium, bifid left third rib, and kyphoscoliosis. There was also mild mental retardation, ocular hypertelorism, and a sunken appearance to the eyes, possibly the result of the marked frontal bossing. She had 1 unaffected male sibling. Further follow-up has been unsuccessful to date.

Case 3. The patient was a 30-year-old white woman seen in Perth, Australia, for the first time in 1956, for bilateral dentigerous cysts. At that time, multiple basal-cell carcinomas were noted on both eyelids, nose, forehead, chin, and cheeks. They were of several histological types: sclerosing, ulcerating, and pigmented. A cyst was removed from the ovary during a recent pregnancy.

A dermatofibroma was present on the posterior medial aspect of the left knee and in the posterior right axilla.

The patient manifested ocular hypertelorism and biparietal and frontal bossing. Her eyes appeared sunken.

Roentgenographic examination revealed synostosis of the sixth and seventh ribs and calcification of the dura.

She has had 5 children, 2 prematurely. To the best of our knowledge, none has had any anomalies.

Case 4. The patient was a 43-year-old edentulous man with a history of having more than 50 basal-cell carcinomas removed from his face and upper body over the past 20 years. Roentgenographic examination revealed numerous cysts scattered throughout both jaws and a bifid anterior third right rib. The family history appeared to be negative.

Case 5. The patient was a white man, aged 55 years. His medical history dates from December, 1946, when he first presented with an inguinal hernia that was subsequently corrected by operation. He was somewhat mentally retarded. In addition to gynecomastia, the left testis was atrophic, and the right testis was missing. In 1948 he was found to have multiple cysts extending through both the horizontal and vertical ramus of the left

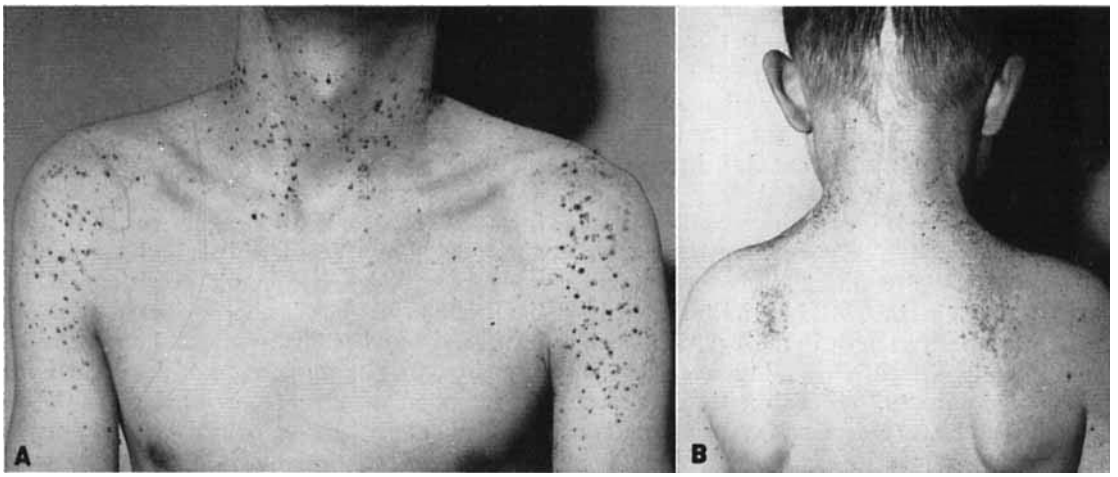


FIG. 2. A, Numerous pigmented basal-cell nevi scattered over neck, upper arms, and trunk. B, Note the scar in nuchal area that was the site for removal of medulloblastoma.

mandible with pathological fracture. Hemisection of the mandible was performed and replaced with an iliac graft.

In the subsequent years he had treatment both by surgery and by radiotherapy for numerous basal-cell carcinomas on the skin of the face, occipital region, shoulder, abdomen, perineum, and thigh. He appeared to have deep pits that were possibly congenital in the upper lip and nasolabial fold. In 1959 additional cysts were observed in the right mandible. These were kept under observation for 2 years and noted to be growing slowly. In 1961 a large cyst was enucleated from the right mandible, and recovery was uneventful. Roentgenographic examination of the chest revealed 3 bifid ribs.

Case 6. This patient was a well-developed 20-year-old white man who was referred for removal of multiple impacted teeth and cysts in the mandible and maxilla. Physical examination at the time of admission to the hospital was essentially within normal limits, with the exception that it was noted that the patient had a rather broad-based nose, hypertelorism, and well-developed supraorbital ridges. There were no motor or sensory abnormalities although it was noted that the patient was mentally retarded. There were a number of small nevi of the chest and back that measured up to 2 to 3 mm. in diameter. Also noted were some defects of the fingernails, possibly an ectodermal dysplasia. The patient had a rather prominent chin although he was not truly prognathic. Radiographic examination disclosed some mild scoliosis and a spina bifida occulta of the first thoracic vertebra and fusion of the spinous processes of the second and third thoracic vertebrae with a narrowing of the interspaces. There also appeared some early hypertrophic changes consistent with arthritis. No other osseous abnormalities were noted.

The results of the laboratory work were as follows: alkaline phosphatase, 4.3 units; calcium, 9.1 mg. per 100 cc.; hemoglobin, 13.3 gm. per 100 cc.; hematocrit, 42%; and white blood cells, 5,200 per cu. mm. with a normal differential.

The oral radiograph disclosed multiple large cystic lesions in the mandible and maxilla. These lesions had considerably displaced teeth but did not include teeth within the lumen. These lesions ranged up to 3×5 cm. in size. At operation the teeth and cysts were removed. The cysts appeared to have a thick gray wall and, on cut section, contained a large amount of keratin. Microscopically the cysts were lined with squamous epithelium and had a well-defined keratin layer on the luminal side. On the basis of these findings, several of the lesions of the chest wall were biopsied and 1 was reported as being nevoid basal-cell carcinoma.

No chromosomal studies have been done as yet. Bifid ribs were absent, and the metacarpals were not shortened. The patient also did not have any palmar dyskeratosis or any ocular defects.

SYSTEMATIC SURVEY

Facies. A characteristic facies (Fig. 1A, B) appears to be part of the syndrome though it is not present in every case. Frontal and temporoparietal bossing is often marked, giving the skull a pagetoid appearance. This, combined with well-developed supraorbital ridges

seen in several cases[33, 40, 49, 97, 102] results in a sunken appearance to the eyes.[11] Internal strabismus may also be present. Broad nasal root is extremely common and may be associated with true ocular hypertelorism (Figs. 1A and 6B) (increased inter-inner canthal, interpupillary, and inter-outer canthal distances) or rarely, dystopia canthorum (increased distance between inner canthi only). Ocular hypertelorism was especially marked in a patient described by Kirsch.[52] Mild mandibular prognathism has been present in most patients personally seen by the authors and in several other documented cases.[45, 47, 52] Tabulation 1 shows the signs and symptoms with their relative frequency.

Skin. In this syndrome, the multiple nevoid basal-cell carcinomas usually appear in childhood or during the second or third decade, but especially around puberty in both exposed and unexposed cutaneous areas. They are usually numerous, appearing as flesh-colored to brownish nodules on the face and trunk (Fig. 2A, B).

TABULATION 1

Signs & symptoms	*Relative frequency*
Skin	
A_1 Multiple nevoid basal-cell carcinoma	+++
A_2 Palmar dyskeratosis (porokeratosis Mantoux)	++
A_3 Milia; cysts, especially extremities	++
A_4 Fibromas and/or neurofibromas, especially extremities	+
Oral manifestations	
B_1 Multiple jaw cysts	+++
B_2 Mild mandibular prognathism	++
B_3 Fibrosarcoma jaws (?)	+
B_4 Ameloblastoma	+
Skeletal system	
C_1 Rib: bifid, synostosis, partial agenesis, or cervical rudimentary	+++
C_2 Vertebrae: scoliosis, cervical or thoracic fusion	++
C_3 Frontal and biparietal bossing	++
C_4 Shortened metacarpals	++
C_5 Deformed chest	+
Central nervous system	
D_1 Mental retardation, variable; schizophrenia	++
D_2 Congenital hydrocephalus	++
D_3 Calcification dura (falx, tentorium), choroid	++
D_4 Agenesis corpus callosum (?)	+
D_5 Medulloblastoma	+
Eye	
E_1 Congenital blindness, coloboma choroid and optic nerve	+
E_2 Dystopia canthorum, hypertelorism	++
E_3 Strabismus, internal	+
E_4 Chalazion	+
Genitals	
F_1 Pelvic calcification (?)	++
F_2 Ovarian fibroma	++
F_3 Infantile genitals, female pubic-hair pattern and scanty facial hair in male patients	+
Other findings	
G_1 Hyporesponsiveness to parathormone	+++
G_2 Autosomal dominant inheritance pattern	+++

In his survey, Maddox[64] found the nevoid form of basal-cell carcinoma to constitute about 0.4% of all cases of basal-cell carcinoma and/or epithelioma adenoides cysticum. The basal-cell nevus has been considered to differ from the basal-cell carcinoma, largely in its appearance at a young age and its occurrence in cutaneous areas not exposed to sunlight.

The basal-cell nevus exhibits a wide diversity of histopathological appearance, the spectrum ranging from that of a benign adnexal tumor to trichoepithelioma to a typical aggressive ulcerating basal-cell carcinoma. The histogenesis of the basal-cell nevus has not been determined but it probably arises from the primary epithelial germ that gives rise to both the cutaneous basal-cell layer and the adnexal structures. It is probable that all cutaneous structures contain both equipotential and pluripotential cells[25, 68] and, hence, may give rise to any of the spectrum of skin tumors (Fig. 3A, B, C).

Maddox[64] divided the skin tumors into 5 classes and estimated their frequency: solid (72%), adenoid (27%), cystic (19%), morphea-like (17%), and superficial (6%). About one third of the patients exhibited 2 or more types. When compared with a control series of basal-cell cancers the tumors seen in the syndrome appeared to be more often associated with an inflammatory infiltrate and with minute calcification but were otherwise indistinguishable.

Cysts of the skin vary in size from minute milia,[13, 14, 33, 47] common to the face, to those 1 to 2 cm. in size, more often found on the extremities.[97] Howell[46] suggested that chalazion was seen in several of his patients. Comedones have also been stated to be common.[15, 57]

A characteristic palmar-plantar dyskeratosis, described as a porokeratosis of Mantoux, has been noted in several patients.[14, 34, 46, 106] These are punctate lesions, the central core of which falls out, leaving a well-circumscribed, rather purplish depression.

Other skin anomalies have included supernumerary nipples,[24] hyperhidrosis and acrocyanosis,[18] and telangiectasia.[103]

Skeletal Anomalies. Skeletal anomalies are common, being present in probably 75% of individuals affected with the syndrome. The

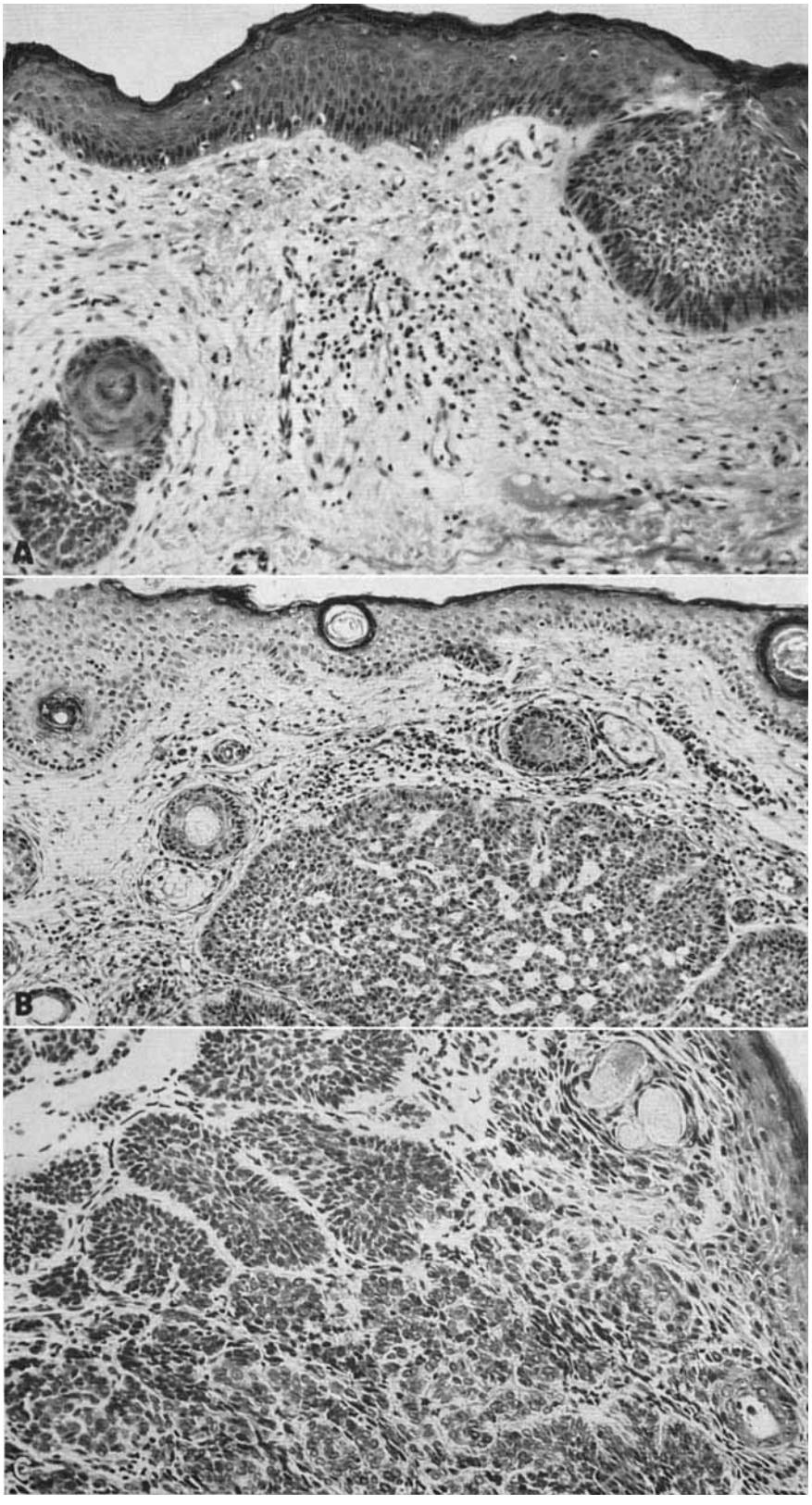


FIG. 3. A, B, and C, **Photomicrographs of spectrum of skin tumors.** Note the origin of these multiple basal-cell nevi from both basal layer of epidermis and hair follicles. Note also trichoepitheliomatous and adenoid patterns.

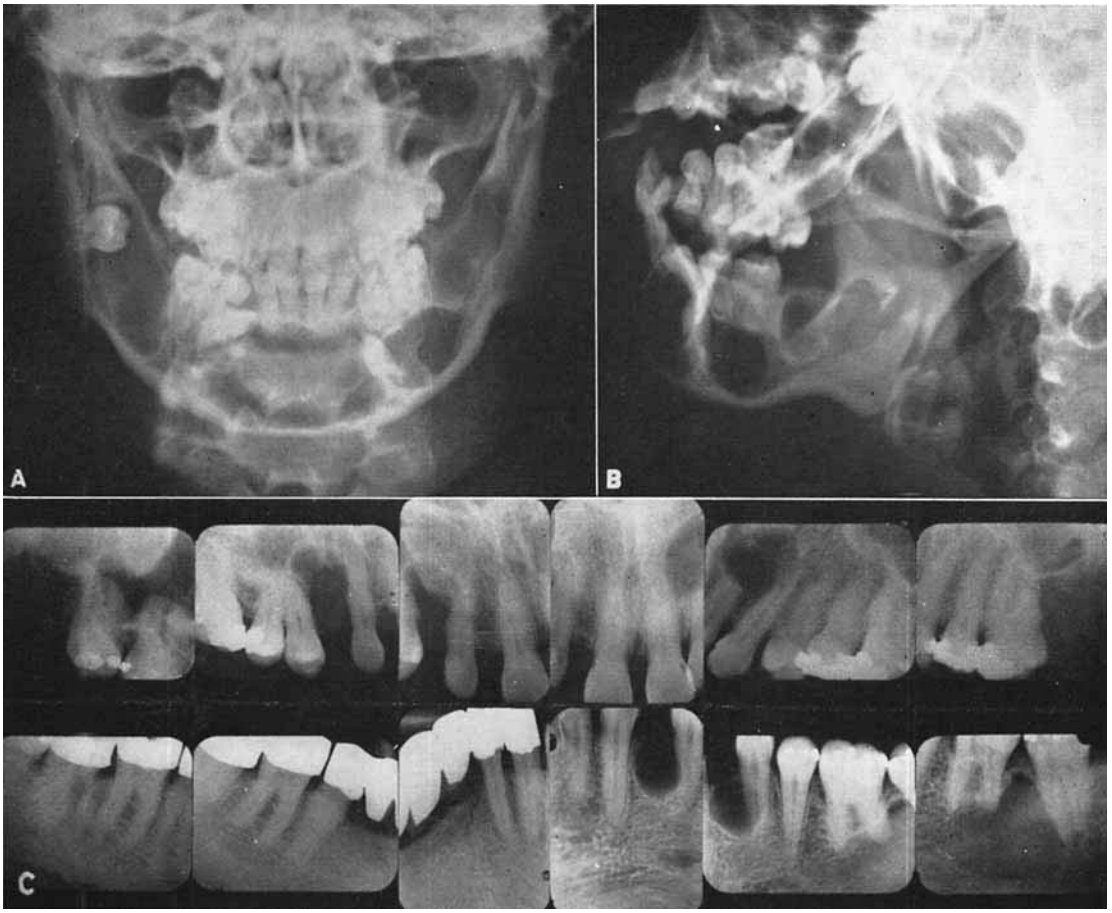


FIG. 4. A, B, and C, Multiple cysts scattered throughout both jaws.

most common anomaly is bifurcated rib (Fig. 6A). Bifurcation may involve several ribs and may be bilateral. Other costal anomalies include synostosis, partial agenesis posteriorly, and cervical rudimentary ribs. Pes planus[19] (Case 1 of this paper) and a defective clavicle[64] have also been seen.

Kyphoscoliosis has been observed by a number of investigators.[11, 15, 33, 50] Cervical and/or thoracic vertebral fusion has also been noted occasionally and, in the case of Eisenbud et al.,[24] resulted in their diagnosis of Klippel-Feil syndrome. Deformed chest has also been described but possibly is the result of kyphoscoliosis.

Shortened metacarpals, especially the fourth, were seen by Gorlin et al.,[34] Block and Clendenning,[10] and Holland.[45] In the case of Block and Clendenning,[10] shortening of the fourth metacarpal was so marked as to suggest pseudohypoparathyroidism. Lausecker[59] noted polydactyly and bizarre thumb formation, and Davidson[19] noted an extra metatarsal. Arachnodactyly was described by Boyer and Martin,[11] Shear,[94] Gorlin et al.,[34] and Maddox.[64]

Frontal bossing has already been mentioned. It is usually combined with biparietal bossing, producing a head circumference in adults of approximately 60 cm. or more. Facial asymmetry was described by Jablonska.[49] Broadened nasal root is seen in at least one fourth of these patients[8, 11, 33, 34, 36, 47] and may exist without increased distance between inner canthi or without increased distance between the pupils.

It has been argued that costal anomalies commonly occur not associated with the syndrome. Etter[26] found the incidence of presumably isolated bifid rib, rudimentary rib, and synostosis of ribs to be 6.2, 2.0, and 2.6 respectively per 1,000 live births. Ashbury et al.,[3] in examination of more than 22,000 United States Army inductees, found an incidence of 3.0, 1.2, and 1.0 per 1,000 men. These figures would make a fortuitous associ-

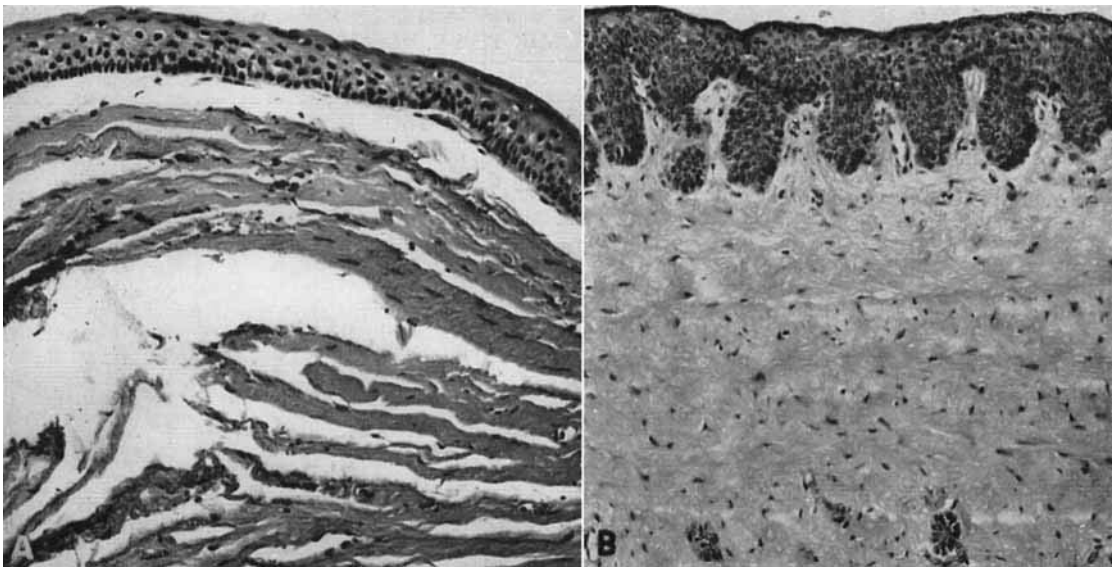


FIG. 5. Photomicrographs of odontogenic keratocysts. A, Note the uniform thickness of epithelium covered by a thin layer of keratin. B, Note the proliferation of the basal layer, simulating adnexal development in embryonal skin.

ation in this syndrome highly unlikely. Skeletal anomalies such as these are often clinically overlooked and only discovered when sought. Therefore, their incidence in the syndrome, though high, would probably be even greater if a thorough roentgenologic survey were given to each patient having the syndrome.

Central Nervous System. Mild mental retardation and schizophrenia have been described.[8, 10, 33, 50] Binkley and Johnson[8] reported partial agenesis of the corpus callosum found at autopsy but this has not been confirmed to date by other case reports. Lamellar calcification of the dura in the parietal region, falx, tentorium, and/or choroid is a frequent finding but has frequently been overlooked and its actual frequency is probably far higher than that reported.

Congenital hydrocephalus was noted by Gorlin et al.,[34] Gross,[36] Schamberg,[88] and Mad-

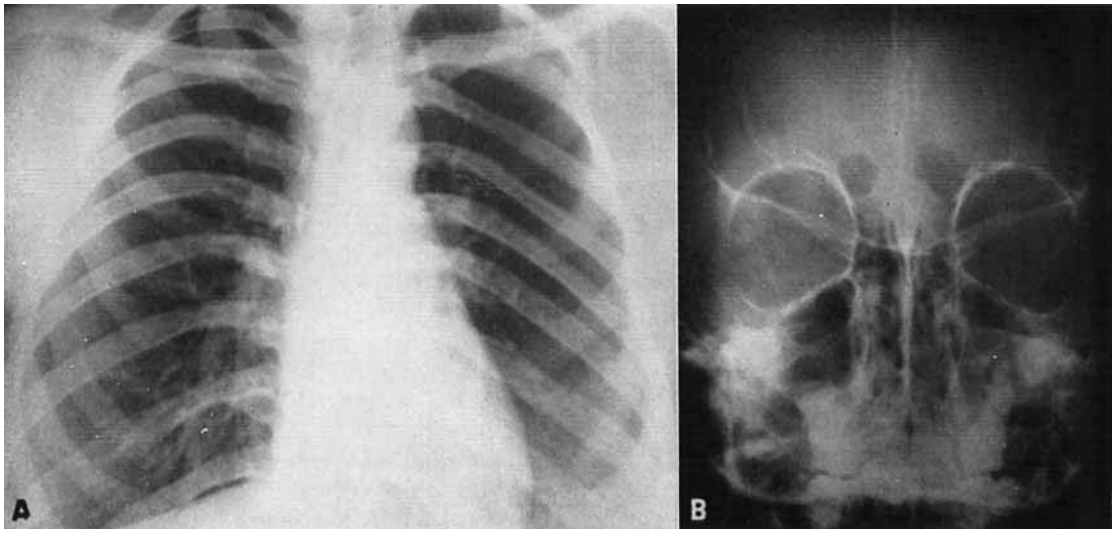


FIG. 6. A, Bifurcation of ribs and scoliosis are common findings. B, Note the mild ocular hypertelorism and ectopic calcification of falx cerebri. (See also Fig. 1A and B.)

TABLE 1

MULTIPLE BASAL-CELL NEVI SYNDROME*

Author	Signs & symptoms†																							
	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4	C_1	C_2	C_3	C_4	C_5	D_1	D_2	D_3	D_4	D_5	E_1	E_2	E_3	F_1	F_2	F_3	G_1
Jarisch[60]	+	0	0	0	0	0	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0
Straith[99]	+	0	+	0	+	0	0	0	0	0	+	0	0	0	0	+	0	0	0	0	0	0	0	0	0
Binkley & Johnson[8]	+	0	0	+	+	+	+	0	+	0	0	0	0	+	0	0	+	0	0	0	0	0	+	0	0
Carney[15]	+	0	+	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eisenbud et al.[24]	0	0	0	0	+	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lausecker[59]	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Calnan[14]	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gross[36]																									
Schamberg[88]	+	+	+	0	+	0	0	0	+	0	+	0	+	0	+	0	0	0	0	+	0	0	0	0	0
Lehnert[60]	+	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kirsch[62]	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Boyer & Martin[11]	+	0	0	0	+	+	0	0	+	+	+	0	+	+	0	0	0	0	0	0	0	0	0	+	0
Howell & Caro[47]	+	0	+	0	+	0	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Thoma[104]	+	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gorlin & Goltz[33]																									
Gorlin et al.[34]	+	+	+	0	+	+	0	0	+	+	+	+	0	+	+	+	0	0	+	+	0	0	+	0	+
Hermans et al.[40]	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0	0	0
McKelvey et al.[67]	+	0	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oliver[74]	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0
Rebello & Savatard[83]	+	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Thies et al.[103]	+	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clarkson & Wilson[17]	+	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ward[107]	+	+	0	0	+	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Jablonska[49]	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0
Kraus & Vortel[57]	+	0	+	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Davidson[19]	+	+	0	0	+	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0
Maddox[64]‡	+	0	0	+	+	0	0	+	+	+	+	0	0	0	0	+	+	0	0	0	0	0	0	+	0
Block & Clendenning[10]	+	+	0	0	+	0	0	0	+	+	0	+	0	+	0	+	0	0	0	+	+	+	+	0	+
Herzberg & Wiskemann[42]	+	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0
Cook[18]	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0
Lande[68]	+	0	0	0	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Shear[94]	+	0	0	0	+	0	0	0	+	0	+	0	0	0	0	0	0	+	0	+	0	0	0	0	0
Marascalco[65]	+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pedlar[76]	0	0	0	0	+	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Holland[45]	+	0	0	0	+	+	0	0	0	+	+	0	0	0	0	+	0	0	0	+	0	0	0	0	0
Summerly[101]	+	0	+	0	+	+	0	0	+	+	+	0	0	+	0	+	0	0	0	0	0	0	0	0	0
Rasmussen[82]	+	0	+	0	+	0	0	0	+	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
Pres. study	+	0	0	0	+	+	0	0	+	+	+	0	+	0	0	+	0	0	0	+	0	0	0	0	0

*Some of these data have been furnished in recent personal communications to one of the authors (R.J.G.).
‡The salivary gland tumor in this case was seen by one of the authors (R.J.G.) who interpreted it as an atypical

dox[64] and may be responsible for the frontal and biparietal bossing.

One of the more fascinating facets of the syndrome is medulloblastoma (Fig. 7). The occurrence was first pointed out by Herzberg and Wiskemann.[42] This present survey would indicate at least 4 cases.[18, 39, 42, 94] It would seem most likely that medulloblastoma was not heretofore recognized as a manifestation of the syndrome, since the affected child usually died of the tumor prior to the development of the rest of the syndrome. It is not inconceivable that more cases might be uncovered if family pedigrees were more carefully analyzed for the cause of death of "unaffected" siblings.

There seems to be some reason to believe that the behavior of the "medulloblastoma" in this syndrome is somewhat unusual. Some patients have survived.[16] A sibling of 1 patient whose other sibling had medulloblastoma died of "epileptiform seizures." This child may also have had this tumor but autopsy was not performed.[16]

Eye. Congenital blindness due to cataract, glaucoma, and/or coloboma of the choroid

Other findings
...
...
...
Sm. stature, epicanthus
Supernumerary nipple
Polydactyly, bizarre thumbs
...
...
...
...
Deaf, arachnodactyly, high-arched palate, lge. ears, sunken eyes
...
Polyuria
Syndactyly, calcified thyroid masses
Hyperhidrosis, acrocyanosis
...
...
...
Telangiectasis, nevi
Syndactyly toes
Cataracts, cleft lip & palate
Facial asymmetry
...
Inguinal hernia, high-arched palate, flat feet, extra metatarsal, prox. phalanx toes small
Deformed clavicle, keloid, atypical mucoepid. ca. salivary gl., saddle nose, enlgd. fr. sinus, syndactyly 2d & 3d toes, 5th toe missing
Hallux valgus, renal calculi
...
...
...
Congen. cataract, arachnodactyly
...
Only 1 kidney
Confluent eyebrows
Deformed scapula, cleft lip, ovarian cyst, metast. melanoma ?, L-shaped kidney, aberrant renal arteries, malrotation lge. bowel
Sprengel's deformity scapula
Flat feet, high-arched palate, obesity, exophthalmos, arachnodactyly toes, broad nose, shallow sella

†See Tabulation 1 for explanation.
acinic cell carcinoma of parotid salivary gland.

and optic nerve has been recorded by Gorlin et al.,[34] Oliver,[74] and Shear.[93]

Hermans et al.[40] thought the eye changes, which he described as "dysgenesis neuroblastica gliomatose," were so characteristic as to be classified as a fifth type of phakomatosis.

Internal strabismus was seen by Gorlin et al.,[34] Jablonska,[49] and Block and Clendenning.[10] Epicanthal fold has also been noted.[15]

Endocrine System. Gorlin et al.,[34] in 1963, suggested that the shortened metacarpals and calcifications in various parts of the body might signify abnormal calcium and/or phosphorus excretion. Block and Clendenning[10] almost simultaneously published findings that demonstrated an almost complete lack of end-organ response to parathormone, almost no phosphorus diuresis being experienced. This finding has been substantiated in our and other laboratories.

Ovarian fibromas with ovarian or uterine calcification have been noted by a number of authors;[8, 10, 34] occurrences are not likely due to chance.

Furthermore, other workers,[11, 19, 64] as well as the present authors, have reported that several male patients have manifested hypogonadism. They have had cryptorchism, female pubic-hair pattern, and scanty facial hair.

Oral Anomalies. Jaw cysts appear to be a constant feature (Fig. 4A, B, C). They have been classified as primordial cysts or odontogenic keratocysts (Fig. 5A, B). Often appearing initially during the first decade of life, they have been the chief source of complaint in about half the cases due to swelling of the jaws, dull pain, or drainage of the cysts intraorally. They are scattered throughout both jaws. They vary in size from microscopic to several centimeters in diameter, occasionally being so large as to produce a pathological fracture.

If the cysts arise during the stage at which tooth root formation is progressing, the

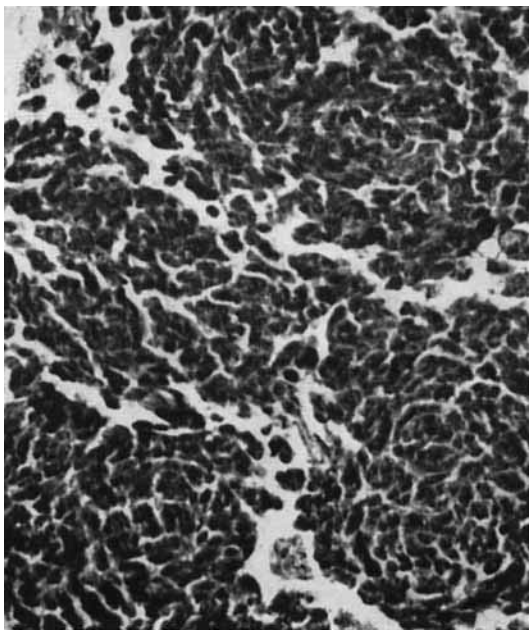
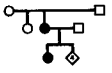
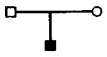


FIG. 7. Photomicrograph of medulloblastoma removed from sibling of patient with the syndrome.

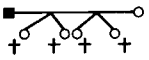
2. 1939 99



3. 1951 8

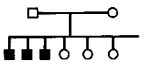


4. 1952 15



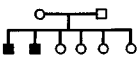
6. 1952 59

7. 1953 14



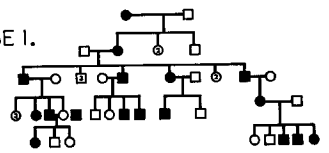
9. 1955 60

10. 1956 52



11. 1958 11

CASE 1.

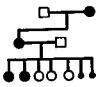


CASE 2.

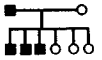
CASE 3.

12. 1959 47 64

CASES 3-5.

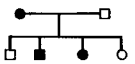


14. 1960 33
1963 34



16. 1960 67

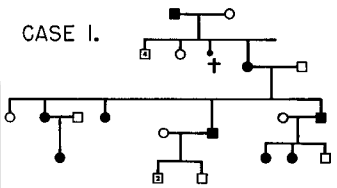
17. 1960 74



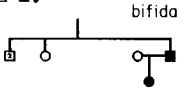
19. 1960 103

20. 1960 17

CASE 1.

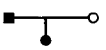


CASE 2. †spina bifida

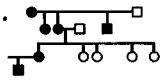


21. 1960 107

CASE 2.



CASES 6-9.



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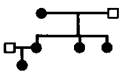
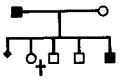


25. 1962 64

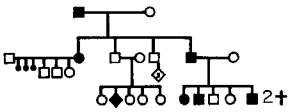
CASE 1.

CASE 2.

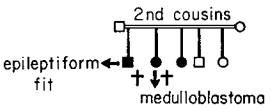
26. 1963 10



27. 1963 42



28. 1963 18

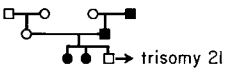


30. 1963 94

31. 1963 65

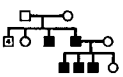
CASE 1.

CASE 2.



34. 1963 101

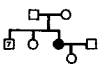
CASE 1.



CASE 2.

CASE 3.

CASE 4.



35. 1963 82

pressure engendered may result in bending or dilaceration of the adjacent roots.

Microscopically, the uninfected cyst is often lined by a rather uniform layer of stratified squamous epithelium that, in turn, is covered by a thin uniform layer of keratin. This type of cyst has been designated as primordial by Shear[93] and as a keratocyst by Philipsen.[78] Some cysts exhibit budding, reminiscent of embryonal skin, and it is likely that some tendency exists for the transformation of these cysts to ameloblastoma, as may be seen from the cases of Davidson,[19] Maddox,[64] Thoma,[104] and Gorlin et al.[34] It is, however, uncertain at this time whether these represent true ameloblastoma or merely proliferated odontogenic rests of Malassez.

Recurrence of the curetted cysts is common, possibly from adjacent microcysts. These were nicely illustrated by Thoma and Blumenthal[105] and resulted in their term "polycystoma."

High-arched palate has been seen in their patients by Boyer and Martin,[11] Davidson,[19] and by the present authors.

Other Findings. It is difficult to evaluate the miscellaneous findings, since many have been recorded but a single time. These have included: keloid,[64] supernumerary nipple,[24] polydactyly,[59] arachnodactyly,[11, 94] syndactyly,[17, 34, 64] oligodactyly,[64] acrocyanosis,[40] hyperhidrosis,[40] inguinal hernia,[19] congenital cataract,[94] deformed clavicle,[64] pes planus,[19] deformed scapula,[101] cleft lip,[101] kidney malformations,[76, 101] and malrotation of bowel.[101]

Most may be chance associations; but before we exclude their significance, future investigators should note their presence or absence.

Heredity. The genetic pedigrees of 25 families exhibiting the syndrome clearly demonstrate that it is inherited as an autosomal dominant trait as originally suggested by Gorlin and Goltz.[33] Penetrance appears to be marked and expressivity to be variable. The contention that the syndrome is inherited as an X-linked dominant trait, as stated by Block and Clendenning[10] is certainly not valid. With such a pattern, the syndrome should be transmitted to all the daughters but to none of the sons of an affected man, and this is clearly not the case, as shown by the reports of Howell and Caro,[47] Maddox,[64] Herzberg and Wiskemann,[42] Lehnert,[60] Oliver,[74] and Ward[107] (Fig. 8).

Another point made by Block and Clendenning[10] was the predilection for the female sex. This does not seem to be true when larger series are examined. Examination of Fig. 8 reveals that at least 62 females and 57 males were affected. The only case to date exhibiting consanguinity is that of Shear[94] and this may well be fortuitous.

In addition to the 10 reports of multiple dentigerous cysts in which there was evidence of a family pedigree (Fig. 9), there are several in which no mention was made of other family members being affected. Several explanations may be valid: new mutation, hence no family history; phenocopy; inadequate investigation of family; incomplete penetrance of gene; failure of expressivity of gene; or illegitimacy. These cases would include those reported by Bennett,[4] Boyko et al.,[12] Caldwell and Thompson,[13] Catania,[16] Dechaume et al.,[20] Dillon,[21] Droege,[22] Frech,[28] Gerke,[30] Grellier,[35] Hauer,[37] Heidsieck,[38] Hern,[41] Hewer,[43] Kallenberger,[51] Knight and Manley,[54, 55] Kostečka,[56] Limberg,[61] Mayrhofer,[66] Offenhauer,[72] Pekarsky,[77] Philipsen,[78] Radden and Janes,[81] Seeman,[90] Shear,[93] Shlefstein,[95] Starup,[97] Stea,[98] Talley,[102] and Worth.[111]

Personal communication with several of these authors was recently attempted to gain additional information. Good evidence of negative family history was obtained in the cases of Folkins,[27] Knight and Manley,[54, 55] Rushton,[85] and Starup.[97]

Moreover, several of these patients with multiple dentigerous cysts had associated anomalies that are worthy of note: Boyko et al.,[12] broad forehead; Caldwell and Thompson,[13] woolly-hair appearance of skull, punched out areas in femurs and hand bones, calcification of falx; Catania,[16] obesity; Dillon,[21] macular choroiditis; Limberg,[61] ocular

FIG. 8. (opposite page). Genetic pedigrees in nevoid basal-cell carcinoma syndrome. In 20 additional cases the family history was described as "unknown" or "negative." They were the cases of Jarisch,[50] Eisenbud et al.,[24] Calnan,[14] Gross[36] and Schamberg,[88] Thoma and Blumenthal,[105] Gorlin and Goltz[33] and Gorlin et al.[34] (Cases 1 and 2), Hermans et al.,[40] Rebello and Savatard,[83] Jablonska,[49] Kraus and Vortel,[57] Davidson,[19] Maddox[64] (Cases 3, 4, 5, 10, and 11), Lande,[58] Pedlar,[76] and Holland.[45] The symbols used in the pedigrees indicate the following: open symbols, unaffected individuals; solid symbols, affected individuals; large square, male adult; large circle, female adult; small square, male child; small circle, female child; small open square with number, number of unaffected male children; small open circle with number, number of unaffected female children; smallest circle or square, miscarriage or abortion in which the sex of the fetus was known; diamond, sex unknown; cross, dead.

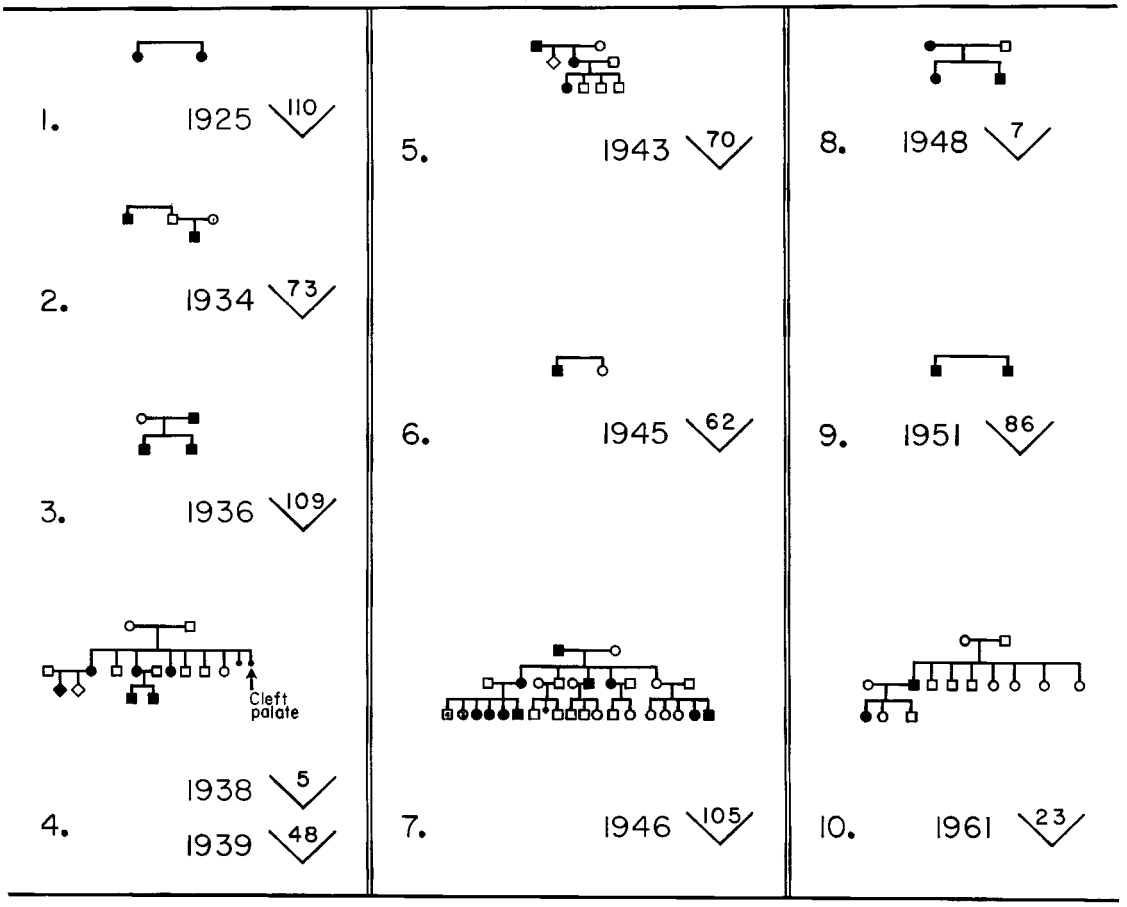


FIG. 9. Genetic pedigrees in cases of multiple dentigerous cysts. See Fig. 8 for explanation of symbols.

hypertelorism, epicanthus, depressed nasal bridge; MacGregor,[62, 63] mild mental retardation, frontal bossing; Oliver,[73] multiple septic skin eruptions; and Sprawson,[96] mild mental deficiency. The reader will note the descriptive similarity of several of these findings to those seen in the multiple basal-cell nevi syndrome. That these cases represent an incomplete form of the syndrome is further suggested by our case 2. The patient, while having numerous signs of the syndrome, lacked the basal-cell nevi components.

Beyrent[6] revealed that his patients did not have bifid rib. Knight,[53] Hewer,[44] Sharland,[92] and Gerke[31] stated that their patients had neither skeletal anomalies nor cutaneous neoplasia.

Several of these patients or individuals in the same families have been reported by, or seen by, several authors (Beyrent,[5] Weidman and Besancon,[108] Gross,[36] Schamberg,[88] Ivy,[48] Wigginton,[109] and Rushton[85]), and others seem quite likely related. For example, affected members of a branch of a family seen in Massachusetts by Thoma and Blumenthal[105] moved to Michigan, and several reports of the syndrome have been made from this area.

DISCUSSION

The designation of multiple basal-cell nevi syndrome is admittedly not a good one, but a description of the manifold signs exhibited in this syndrome becomes unwieldy. Ultimately, the inborn error in developmental metabolism will be discovered and we shall then have a better designation for this symptom-complex.

There appear to be striking analogies between the cutaneous and jaw lesions (Fig. 10). For example, the jaw cysts correspond to the cutaneous milia, and the adnexal skin tumors have their analogue in the mural proliferations seen in some of the jaw cysts. Furthermore, the ameloblastoma is the counterpart of the cutaneous basal-cell carcinoma. Do

these lesions have a further analogue in the medulloblastoma that apparently is a component of the syndrome? Another aspect worthy of consideration is the peculiar behavior of the brain tumor in the syndrome. Was the salivary gland tumor reported in 1 patient by Maddox[64] part of the syndrome? Since we are dealing with so few cases involving these facets of the syndrome, we cannot reach any conclusion. No doubt other cases will be revealed when "unaffected" siblings of affected patients are examined. A reverse approach, that is, the analysis of a large series of patients with medulloblastoma, is also greatly needed.

The failure of the kidneys to respond to administered parathormone, a frequent finding, is a most interesting phenomenon and may eventually provide the key to the biochemical defect that is the basis for the syndrome. The metabolic defect acts over a considerable period of development—during the early embryologic period—to produce bizarre rib anomalies, and extends into mature adult life with continued formation of skin tumors and jaw cysts.

No one component of the syndrome is present in all patients, i.e., there is variable expressivity of the several facets. Some are more common, e.g., skin tumors, jaw cysts, skeletal anomalies, and hyporesponsiveness to parathormone. However, other aspects may be more subtle and have heretofore been overlooked.

Not included in the analysis of this syndrome are the following cases: the patient described by Allington[1] had basal-cell nevi, jaw cysts, a "benign breast tumor," and a thyroglossal cyst, but none of these anomalies was documented. The cases of Scarff and Thomson[87] and Worth[112] were not sufficiently well documented to be certain that they were true cysts. The case of multiple basal-cell carcinomas in a 5-year-old child appeared to be an example of the syndrome.[89] Frontal bossing, ocular hypertelorism, and thymoma were noted, but no mention was made of other anomalies. A recent attempt at follow-up has not been successful. The child described by Rodin[84] appears to have had multiple nevoid basal-cell nevi, but no further study was carried out.

SUMMARY

1. More than 35 cases of a syndrome have been analyzed, the chief components of which are: multiple basal-cell nevi, jaw cysts, skeletal anomalies, hyporesponsiveness to parathormone, a characteristic facies, and, conceivably, medulloblastoma. Analysis of the families of these probands has revealed more than 150 cases of the syndrome.

2. Numerous reported cases of multiple jaw cysts have been analyzed and it seems likely that these may represent additional cases of the syndrome.

3. The syndrome, as well as the case of multiple jaw cysts, is inherited as an autosomal dominant trait. The opinion that the syndrome is inherited on an X-linked dominant basis is not borne out.

4. The incidence of medulloblastoma is probably higher than indicated as it appears to be fatal at an age prior to the appearance of the other components of the syndrome. The behavior of the brain tumor in this symptom complex needs further investigation.

5. Several male patients with the syndrome have exhibited eunuchoid traits, such as female pubic-hair pattern and the absence of facial hair. Several female patients have had ovarian fibroma with ovarian or uterine calcification.

6. Analogies between the cutaneous and oral lesions have been discussed.

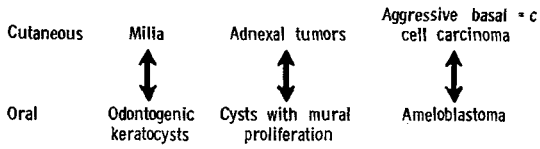


FIG. 10. Analogous lesions in skin and jaws.

ADDENDUM

Since our paper was submitted for publication, several additional papers related to the syndrome have come to the authors' attention.

Of special interest among these papers are the observations of Clendenning et al.[115] regarding the finding of lymphatic cysts of the mesentery of the small intestines and the occurrence of ovarian fibroma. Ovarian fibroma also was noted by Bazex et al.[113] Pollard and New[118] observed medially hooking scapulae.

Recently, one of the authors (J.J.W.) observed, in a patient with several cutaneous basal-cell carcinomas, a 1.×1.×1.-cm. lesion of the anterior gingiva, which microscopically could not be differentiated from cutaneous basal-cell carcinoma!

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