Paparella: Volume I: Basic Sciences and Related Principles

Section 8: General Medical Principles

Chapter 39: Craniofacial Syndromes

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In a text such as this only a few of the more common syndromes of the head and neck can be considered, because their number is legion. Syndromes of deafness are reviewed in detail elsewhere (Konigsmark and Gorlin, 1976). The reader who desires additional information on material presented here or information on syndromes not considered in these pages is referred to comprehensive texts, such as those of Bergsma (1979), Leiber and Olbrich (1981), Gorlin and colleagues (1990), McKusick (1983), Becker (1976), Smith (1982), and Goodman and Gorlin (1977; 1983). The Birth Defects Original Article Series (1969 to present) is an incomparable source of information concerning new and unusual disorders.

Acrocephalosyndactyly

Acrocephalosyndactyly, also called Apert's syndrome, is a rare craniosynostotic syndrome characterized by (1) acrocephaly and (2) syndactyly of the hands and feet. The syndrome was mentioned as early as 1842 by Baumgartner, although eponymic credit is given to Apert for his presentation of the syndrome in 1906. In 1960, Blank established distinct criteria for the syndrome and estimated the incidence to be 1 in 160.000 live births, with an equal distribution between sexes. Because of the high infant mortality rate, he found that the frequency decreased to about 1 in 2.000.000 in the general population. More than 300 cases have been reported.

Most cases of acrocephalosyndactyly are sporadic. Because of the frequently associated mental retardation or unattractive appearance, or both, affected individuals are not likely to contribute to the gene pool - the condition has been shown to have autosomal dominant inheritance. An effect of advanced paternal age has been demonstrated.

The middle third of the face appears flat and underdeveloped, producing a relative mandibular prognathism. The appearance of the nose is quite variable. Hypertelorism, strabismus, and a down-sloping of the palpebral fissures are often noted. The orbits are flattened, and the eyes tend to be proptosed. In some affected infants a horizontal groove extends across the forehead, just above the supraorbital ridges.

The cranium has a characteristic acrocephalic appearance. It is ovoid and brachycephalic, with a high, prominent, steep forehead. The apex of the cranium is located near or anterior to the bregma, the occipital region being flat and in the same vertical plane as the neck. The anterior fontanel may remain patent longer than normal. There is irregular early obliteration of cranial sutures, especially the coronal suture. The cranial base is significantly shortened. A marked accentuation of digital markings is usually observed. Most affected patients have an intelligence distinctly below normal.

The symmetric syndactyly varies in degree from partial cutaneous fusion to a true progressive osseous syndactyly of the metacarpals, metatarsals, and phalanges. When the three middle fingers are completely fused, there is often a common nail that gives the hand the appearance of a mitten (middigital hand mass).

Other skeletal abnormalities have been noted, including aplasia or ankylosis of several joints (especially the elbow, shoulder, and hip) and ankylosis of the cervical vertebrae.

Frequently observed is a high-arched palate with a marked median furrow. Posterior cleft palate or bifid uvula is found in at least 25 per cent of these patients. Associated with a hypoplastic maxilla is relative mandibular prognathism and compression of the upper arcade, which becomes V-shaped, leading to an irregular position of the teeth. Conduction deafness, caused by fixation of the footplate of the stapes, is probably rather common in this disorder.

The condition has been diagnosed prenatally by fetoscopy.

Craniofacial Dysostosis

Craniofacial dysostosis (Crouzon's syndrome) is characterized by (1) premature craniosynostosis, (2) bilateral proptosis as a result of shallow orbits and external strabismus, and (3) midfacial hypoplasia resulting in relative mandibular prognathism with drooping lower lip.

The syndrome is inherited as an autosomal dominant trait with variable expressivity. Sporadic cases (ie, with a negative genetic history, thus representing new mutations) constitute about one-third of the patients.

The facies is easily recognized; it is characterized by marked proptosis as a result of shallow orbits, ocular hypertelorism, exotropia, and a hypoplastic maxilla. This last feature produces a relative mandibular prognathism and short upper lip. The cranium is brachycephalic, with frontal bossing and ridging of the sagittal suture. Roentgenographically, the coronal, sagittal, and lambdoidal sutures are synostosed, often by the third year of life. Increased digital markings are almost always present.

Proptosis is a constant feature. At times there is spontaneous luxation of the globes. Eighty per cent of affected individuals have optic nerve damage. About one-third of patients with Crouzon's syndrome exhibit hearing loss, usually conductive.

Oral manifestations include hypoplastic maxilla, a V-shaped palatal arch in contrast to the normal U-shaped form, and dental malocclusion. Cephalometric studies have shown reduction in the height, width, and depth of the pharynx, increased length and thickness of the velum, decreased length of hard palate, and marked reduction in the posterior cranial base. Reduced nasopharyngeal dimensions and reduced patency of the posterior nasal choanae pose the treat of respiratory embarrassment and cor pulmonale, especially in the young child.

Cleidocranial Dysplasia

Accurate descriptions were made by Meckel in 1760. Scheuthauer in 1871, and Marie and Sainton in 1897. Cleidocranial dysplasia is transmitted in an autosomal dominant manner, although in about half the patients is arises spontaneously. More than 800 cases have been reported in literature.

Individuals with this syndrome are short in stature and have long necks and narrow shoulders. The middle third of the face appears small, the nasal bridge is depressed, and the nose is broad at the base. Often, a groove runs over the metopic suture.

The skull is brachycephalic, with marked frontal, parietal, and occipital bossing. Fontanelles and sutures remain open, often for life. Wormian bones are formed through secondary centers of ossification in the suture lines.

The clavicles can be unilaterally or bilaterally aplastic or hypoplastic, generally at their acromial end. Because of this bony defect, patients with the condition can approximate their shoulders in front of the chest.

Other observed bony anomalies include congenital dislocation of the hip, delayed closure of the pubic symphysis, coxa vara or coxa valga, genua valga, scoliosis, kyphosis, and cervical ribs.

Oral manifestations include supernumerary teeth and hypoplastic maxilla. The so-called pseudoanodontia is the result of delayed eruption and impaction of deciduous, permanent, and supernumerary teeth. Probably the most prominent oral manifestation is the number of supernumerary teeth present, which at times simulates a third dentition.

The paranasal sinuses are often underdeveloped or absent. The mastoids are usually not pneumatized because of altered function of the sternocleidomastoid muscles.

A combined orthodontic and surgical approach is taken for correction of the jaw problems.

Mandibulofacial Dysostosis

Mandibulofacial dysostosis is also known as Treacher Collins syndrome and Franceschetti-Zwahlen-Klein syndrome. Treacher Collins (the name is often erroneously hyphenated) described the essential components of the syndrome. Franceschetti and co-workers published extensive reviews of this syndrome during the 1940s, employing the name mandibulofacial dysostosis.

The syndrome has autosomal dominant inheritance with variable expressivity; about 30 per cent represent new mutations. The fathers of these isolated patients tend to be older. About 450 cases have been described to date.

The facial appearance is usually quite characteristic. The down-sloping palpebral fissures, sunken cheek bones, deformed pinnae, receding chin, and large fishlike mouth

present a clinical picture that, once seen, is unforgettable.

The supraorbital ridges are poorly developed, and often there are increased digital markings. The body of the malar bones might be totally absent, but more often they are grossly and symmetrically underdeveloped, with nonfusion of the zygomatic arches. The mastoids are not pneumatized and are frequently sclerotic. The paranasal sinuses are often small and might be completely absent. The lower margin of the orbit is noted to be defective.

The palpebral fissures slope laterally downward, and often (about 75 per cent of patients) there is a coloboma in the outer third of the lower lid. About half of patients have a deficiency of cilia medial to the coloboma.

The pinna is often deformed or microtic, crumpled forward, or misplaced. More than one-third of patients have absence of the external auditory canal or ossicular defects accompanied by deafness. Roentgenographic studies have shown sclerosis of the middle and inner ears, with poor delineation of their structure. Extra ear tags and blind fistulas can occur anywhere between the tragus and the angle of the mouth.

The nasal-frontal angle is usually obliterated, and the bridge of the nose is raised. The nose appears large because of deficient malar development. The nares are often narrow and the alar cartilages hypoplastic.

The mandible is almost always hypoplastic. Roentgenographic studies have shown that the angle is more obtuse than normal and that the ramus can be deficient. The undersurface of the body of the mandible is often pronouncedly concave. The coronoid and condyloid processes are flat or even aplastic. The palate is cleft in about 30 per cent of patients and at least an equal number have palatopharyngeal incompetence. The airway is probably always narrowed, making for difficult intubation and for respiratory complications following surgery.

Oculomandibulodyscephaly with Hypotrichosis

Oculomandibulodyscephaly with hypotrichosis, or Hallerman-Streiff-Francois syndrome, consists of (1) dyscephaly, (2) parrot nose, (3) mandibular hypoplasia, (4) proportionate nanism, (5) hypotrichosis, and (6) bilateral congenital cataracts.

There appears to be no genetic basis for this syndrome. At least 150 cases have been reported.

The face is small, with a characteristic beaklike nose, receding chin, and brachycephaly (rarely, scaphoencephaly or microcephaly). Open fontanelles and gaping of the longitudinal and lamboidal sutures are frequent findings.

Ocular anomalies include microphthalmia, blue sclerae, and bilateral congenital cataracts that often rupture spontaneously and resorb. Some patients develop glaucoma. Most patients manifest nystagmus or strabismus.

The nose is thin, pointed, and curved and, combined with the mandibular hypoplasia, gives the individual a parrot-like appearance. Hypotrichosis, especially of the scalp, brows,

and cilia, is a constant feature. Axillary and pubic hair are also scant. Alopecia is most prominent in the frontal and occipital areas.

Other associated findings include osteoporosis, cutaneous atrophy, lordosis or scoliosis, spina bifida, and various congenital heart anomalies.

The most common oral finding is hypoplasia of the mandible, generally accompanied by a "double" cutaneous chin with a central cleft or dimple. Roentgenograms of the temporomandibular joint area show the joint to be displaced approximately 2 cm forward. The palate is high and narrow, and the mouth is usually small. Dental anomalies such as malocclusion and natal teeth commonly occur.

Osteogenesis Imperfecta

Osteogenesis imperfecta is a clinical heterogeneity. Hence, its clinical features depend on the specific type under discussion. Its involvement is often diffuse - not only the skeletal system but the eye, ear, skin, teeth, and blood vessels can be affected. Because of the heterogeneity, the clinical picture can range from an infant with a congenital lethal disorder to an adult with only a slightly increased tendency toward bone fractures, but with dentinogenesis imperfecta.

Diagnosis largely clinical, although exceptions are noted. Although classification of Sillence and associates (1979; 1981) has some problems, it nevertheless should serve as a working basis for discussion.

In those with type I, only about 10 per cent appear to have congenital fractures; most have their first fractures before 5 years of age. Although bone fracture is frequent, bowing and curvature of the long bones and spine are usually mild. Kyphosis with loss of skeletal height occurs with age because of osteopenia of the spine. Otosclerosis with mixed hearing loss is noted with almost 100 per cent frequency by age 50. All affected have blue sclerae. Whereas some families have opalescent dentin, others have normal-appearing teeth. Roentgenograms show characteristic osteopenia and wormian bones in the skull and, if clinical tooth changes (opalescent dentin) are present, reveal the characteristic short tooth roots and obliterated pulp canals and chambers, with constriction at the neck of the teeth. Inheritance is autosomal dominant.

Type II is incompatible with life. It is characterized by extreme bone fragility, huge numbers of intrauterine fractures, especially evident in the ribs, and accordion-like alterations in long bones. Radiographic alterations in addition to beaded ribs and crumpling of long bones include poor ossification of the skull vault and base. Inheritance is probably autosomal dominant, each case representing a new mutation. When more than one sibling is affected, the condition probably resulted form parental gonadal mosaicism.

Type III represents the classic concept of osteogenesis imperfecta. Birth weight and length are often reduced. Hearing impairment is very infrequent. Although the sclerae might be somewhat blue at birth, with age they assume a normal opacity. The affected individual has fractures at birth or early infancy (femora, ribs), marked short stature with progressive deformity of long bones, severe scoliosis, and pectus (in about 50 per cent).

The skull is large, especially in the anteroposterior direction. The forehead is broad and bossed with a temporal bulge, giving the skull a "mushroom" appearance and a triangular facies. Radiographic examination reveals a remarkably thin calvaria and the presence of numerous wormian bones in the occipital area. The long bones, especially those of the legs, are bowed in over 85 per cent of affected individuals. The femora, initially broad, can become thin after puberty. There are often whorled radiodensities in the epiphyses and metaphyses. Fractures appear to decrease in number with age. Laxity of ligaments resulting in habitual dislocation of joints and flatfoot is rather frequent, but it too decreases with age. There is probably considerable genetic heterogeneity, with several different mutations.

Type IV is the mildest form of osteogenesis imperfecta. Fractures, if they occur at all, are seen during the first few years of life. Some patients have congenital bowing. During adulthood there is a tendency toward progressive kyphoscoliosis. There is no hearing impairment. Some families appear to have dentinogenesis imperfecta, whereas others have normal teeth. Inheritance is autosomal dominant.

Craniometaphyseal Dysplasia and Craniodiaphyseal Dysplasia

Craniometaphyseal Dysplasia

Buried under various designations, such as leontiasis and osteopetrosis, craniometaphyseal dysplasia consists of (1) alterations in the metaphyses of long bones somewhat similar to those seen in metaphyseal dysplasia (Pyle's disease; ie, increased diaphyseal density and widened metaphyses with reduced density) and (2) bony overgrowth of the face and jaws, especially evident in the paranasal areas.

The condition can be transmitted as autosomal recessive but is more often inherited in a dominant manner. Comprehensive reviews include those of Gorlin and co-workers (1969), Beighton and colleagues (1979), and Penchaszadeh and associates (1980).

A head that appears rather large, with an extremely broad and flat nasal bridge, ocular hypertelorism, and open mouth, gives the patient a vacuous expression. The mouth is kept open because of nasal blockage. Blindness resulting from optic atrophy in early infancy is not uncommon in the recessive form. The ocular hypertelorism is a constant finding.

Generalized late motor development is usual in this syndrome. Several patients have shown marked mental retardation, headache, vomiting, and irritability. Facial nerve paralysis and deafness are also common features, presumably the result of overgrowth of the foramina.

Soon after birth the skull exhibits marked thickening and increased density of the vault, with elimination of the diploe, especially in the frontal and occipital areas. The paranasal sinuses are similarly obliterated. The bones of the skull base, the maxilla, and the mandible also become enlarged, thickened, and increased in density.

The long bones, especially the femora, assume an "Erlenmeyer flask" shape in the metaphyseal area. The diaphyseal area is increased in density, with the medullary bone being porotic and lacking the usual trabecular pattern. Similar changes are seen in the metacarpals and phalanges.

The blood count and serum calcium, phosphorus, and alkaline phosphatase determinations are normal and can be used to exclude several entities.

Craniodiaphyseal Dysplasia

What appears to be a different disease, yet having several facets in common with craniometaphyseal dysplasia, is what I call craniodiaphyseal dysplasia. Examples of this condition have been illustrated in the cases of Joseph and coworkers (1958), Stransky (1962), and Macpherson (1974). It is a more severe disorder, producing marked facial distortion and severe mental retardation. The disorder is inherited as an autosomal recessive trait. Nasal obstruction and facial alteration are noticeable within the first few years. Vision fails by the seventh or eight year.

There is marked sclerosis of the calvaria and facial bones, and the paranasal sinuses are overgrown. The ribs are widened and extremely dense, with the clavicles being most severely involved and thickened in the midportions. The vertebrae, for the most part, are not involved. The long bones are straight, with a thin cortex and a remarkably uniform thickness of the shaft. Similar changes are seen in the metacarpals and metatarsals. There is some degree of ballooning of the midportion of the shaft. The cortex is thinner than normal except for the first metacarpal, which shows some osteosclerosis.

Pyknodysostosis

Pyknodysostosis has been defined as a syndrome consisting of (1) short stature, (2) osteopetrosis, (3) partial agenesis of the terminal phalanges of the hands and feet, (4) cranial anomalies, such as persistence of fontanelles and failure of closure of cranial sutures, (5) frontal and occipital bossing, and (6) hypoplasia of the angle of the mandible.

At least 100 cases have been reported to date. It exhibits autosomal recessive inheritance. The consanguinity rate among the parents of the affected patients is about 35 per cent. There is good evidence to suggest that Toulouse-Lautrec had this disease.

Adult height is reduced, usually ranging from 53 to 60 inches. The terminal digits of the fingers and toes are shortened.

The head is rather large because of frontal and occipital bulging, and the chin recedes. A constant finding is agenesis of the angle of the mandible. Facial bones are usually underdeveloped, with pseudoprognathism.

Radiographic changes include dolichocephaly with frontal and occipital bossing. Most cranial sutures and fontanelles remain open, especially the parieto-occipital fontanelles. Wormian bodies are commonly observed.

The frontal sinuses are consistently absent, and the other paranasal sinuses are hypoplastic or missing. The mastoid air cells are often not pneumatized.

There is increased radiopacity of all bones, but especially of the long bones, spine, and skull base. The increased bone density is responsible for multiple fractures in these patients,

but this peculiarity tends to disappear after puberty. The terminal digits of the fingers and toes are markedly hypoplastic, exhibiting fragmentation of the head with preservation of the bases, underdevelopment of the unguiculate processes, or narrowing of the ends of otherwise normal terminal phalanges. Some patients exhibit upper airway obstruction with cor pulmonale. Fracture of the mandible can complicate tooth extraction.

Orofaciodigital Syndrome I

The orofaciodigital syndrome, type I, of (1) multiple hyperplastic frenula, (2) multilobulated tongue, (3) dystopia canthorum, (4) hypoplasia of nasal alar cartilages, (5) median cleft of the upper lip, (6) asymmetric cleft palate, (7) various digital malformations, and (8) mild mental retardation was first defined by Papillon-Leage and Psaume in 1954. Similar cases had been reported earlier under various names. At least 200 cases have been published.

The syndrome is inherited as an X-linked dominant trait limited to females and lethal in males (Fuhrmann et al, 1966; Gorlin, 1968; Melnick and Shields, 1975).

The facies is characteristic, presenting lateral displacement of the inner canthi, malar hypoplasia, hypoplasia of the alar cartilages, and broad nasal root. The upper lip is short, presenting a pseudocleft in the midline in about 35 per cent of patients.

Evanescent milia of the face and ear are common, but they disappear before 3 years of age. Dryness, or alopecia of the scalp (or both) is present in about 30 per cent of affected individuals.

Several digital malformations, such as brachydactyly, clinodactyly, and syndactyly, have been noted in 50 to 70 per cent of patients. Toe malformations are less common and include unilateral hallucal polysyndactyly, variable syndactyly, and brachydactyly. Roentgenograms of the hands and feet reveal the short tubular bones to be shorter and thicker than normal, with some degree of osteoporosis. The cranial base angle (nasion-sella-basion) is increased, being about 140 degrees (normal value, 131 degrees).

About 40 per cent of patients are mildly mentally retarded (IQ, 70 to 90). Rarely, mental retardation is severe, and there may be hydrocephalus or porencephaly.

Oral manifestations include a thick, hyperplastic, upper central frenum that, in part, eradicates the mucobuccal fold in the area. The frenum also extends through the upper lip beyond the vermilion border, producing a small midline "cleft". Lateral clefts of the palate are produced by bilateral grooves arising from the maxillary buccal frenula. The palate is then divided into an anterior segment (behind the canines) and two posterior processes. The soft palate presents a complete asymmetric cleft in about 35 per cent of patients.

The lower mucobuccal fold in about 75 per cent of patients is traversed by thick, fibrous bands, especially in the region of the lower lateral incisors, which can produce grooving of the alveolar process and, by extension, bifurcation, trifurcation, or tetrafurcation of the tongue.

About 40 per cent of patients have a small, whitish choristoma between the lobes of the divided tongue. This mass is formed by fibrous connective tissue, adipose tissue, a few striated muscle fibers and, rarely, cartilage. Perhaps 10 per cent of patients have ankyloglossia.

Agenesis of the mandibular lateral incisors and supernumerary teeth have been documented in about 20 per cent of affected individuals.

Polycystic kidney has been reported in 15 per cent (Connacher, 1987).

A somewhat similar syndrome (type II, Mohr's syndrome) is inherited as an autosomal recessive trait. People with this disorder have bilateral polysyndactyly of the halluces and manual hexadactyly (Gustavson et al, 1971; Pfeiffer et al, 1972; Annerén et al, 1984).

Cleft Palate, Small Dysplastic Mandible, and Glossoptosis

The combination of cleft palate, small dysplastic mandible, and glossoptosis, Robin's sequence, was recognized as early as 1822 by St. Hilaire. The syndrome is named after Robin (1923), and the corrective procedure is named for Douglas (1946), but the condition and its treatment were both thoroughly described by Shukowsky in 1911.

It can be an isolated triad or part of many other syndromal disorders (Gorlin et al, 1990). During the tenth to twelfth week in utero the maxilla grows rapidly and, by the fourth to fifth month, the disparity between the upper and the lower jaws is quite apparent. Cohen (1976) pointed out that Robin's sequence can be a component of many syndromes. It has also been suggested that about 30 per cent of infants with Robin's sequence have Stickler's syndrome.

Dyspnea and periodic cyanotic attacks associated with retraction of the sternum and ribs are evident during the inspiratory phase of respiration, especially when the infant is in the supine position. The difficulty is usually noted at birth. Complications include respiratory obstruction with resultant hypoxia, vomiting, and aspiration pneumonia. Death may occur. If the infant survives the initial period, subsequent mandibular growth catches up so that a normal profile is achieved by 4 to 6 years of age.

Pruzansky (1969) described the mandible as having a foreshortened body with a characteristic ratio of the ramus to the mandibular body length. Presumably, the primary defect lies in the dysplastic growth of the mandible. This prevents the normal descent of the tongue from between the palatal shelves. The palate is characteristically U-shaped (Hanson and Smith, 1975).

The symmetric lack of lower jaw growth prevents adequate support of lingual musculature, allowing the tongue to fall downward and backward (glossoptosis). This obstructs the epiglottis, permitting egress of air but preventing inhalation (similar to the action of a ball valve). Nasopharyngeal tubes can ensure adequate relief of the airway obstruction if correctly positioned and maintained.

Cleft Lip-Palate and Paramedian Sinuses of Lower Lip

The syndrome of cleft lip-palate and paramedian sinuses of the lower lip, also known as van der Woude's syndrome, has been recognized for more than 100 years. Extensive surveys have been carried out by Červenka and associates (1967), Janku (1980), Rintala and Ranta (1980), Shprintzen and colleagues (1980), Burdick (1985), and Schinzel and Kläusler (1986).

The syndrome is transmitted in an autosomal dominant manner with 95 per cent penetrance. It is seen with a frequency of about 1 in 35.000 to 100.000 live births, and affects both sexes equally. The syndrome occurs in about 1 to 2 per cent of patients with facial clefts. Affected individuals have a 22 to 40 per cent chance of having an affected child with a cleft with or without lip pits.

Usually bilateral, symmetrically located depressions are observed on the vermilion portion of the lower lip. The fistulas can be as large as 3 or more mm in diameter or so small as to barely permit the introduction of a hair probe. The pits can be circular or present as transverse slits. Rarely, they are located at the apex of nipple-like elevations. The depressions represent blind sinuses that have descended through the orbicularis oris muscles to a depth of 0.5 to 2.5 cm and that communicate with underlying minor salivary glands through their secretory ducts. These fistulas often transport a viscid saliva to the surface, either spontaneously or on pressure.

The pits can be an isolated finding (about 33 per cent of patients), associated with cleft lip-palate (about 33 per cent), or associated with cleft palate or submucous cleft palate (about 33 per cent). When associated with lip-palate clefts, the clefts are bilateral in more than 80 per cent of patients.

A few cases have been reported in which there was only a single pit. Adhesions between the maxilla and mandible and filiform ankyloblepharon have also been noted (Shaw and Simpson, 1980).

Warbick (1952) suggested that the congenital lip pits arise from persistence of embryonal sulci that are normally present in the mandibular arch of the 5- to 6-mm embryo, but that disappear by the 10- to 16-mm stage.

Associated anomalies of the extremities have included talipes equinovarus, syndactyly, and popliteal pterygia. Congenital lip pits have also been seen in association with the orofaciodigital syndrome (Gorlin et al, 1976).

Multiple Mucosal Neuromas, Pheochromocytoma, and Medullary Carcinoma of the Thyroid

The syndrome of multiple mucosal neuromas, medullary carcinoma of the thyroid, and pheochromocytoma, also called multiple endocrine neoplasia, type 2B, has autosomal dominant inheritance (Gorlin and Mirkin, 1972; Gorlin et al, 1990; Carney et al, 1978).

The mucosal neuromas principally involve the lips and anterior tongue, although commissural, buccal, gingival, nasal, conjunctival, and laryngeal lesions have been described. Labial involvement produces a "blubbery" appearance. The oral and labial component appears first and often is evident during the first few years of life. Microscopically the mucosal nodules consist of myelinated and unmyelinated axons, hyperplastic neurilemmal cells, and associated collagen fibers, a picture similar to that seen in amputation neuromas. Ganglioneuromatosis can involve the gastrointestinal tract, salivary glands, pancreas, gallbladder, upper respiratory tract, and urinary bladder.

Numerous white, medullated nerve fibers traverse the cornea to anastomose in the pupillary area. They can easily be seen by slit lamp examination. The upper eyelid is often thickened and everted.

Medullary carcinoma of the thyroid, usually bilateral, a tumor derived from cells from the ultimobranchial body, elaborates amyloid, calcitonin, and various active neuroendocrine polypeptides. Originally these cells probably migrated into the ultimobranchial body from the neural crest. The tumor can appear as early as the 14th year but, in most cases, becomes manifest before the 35th year. In roughly 15 per cent of patients it has metastasized, causing death. Total thyroidectomy must be carried out in very early childhood to avoid eventual metastasis (Jones and Sisson, 1983).

The pheochromocytoma can produce weakness, choking and flushing, pounding headache, hypertension, palpitation, profuse sweating, and intractable diarrhea. The attacks can last from minutes to hours and can terminate in shock or death. The tumors are often (approximately 60 per cent) bilateral. They might be evident as early as puberty but usually occur before the fourth decade. The tumors are rarely malignant, but they are potentially lethal, because of their cardiovascular effects, resulting in death in 15 per cent of patients.

Some patients have severe disturbance of gut motility, megacolon, and others have neurofibromatous lesions of Auerbach's and Meissner's plexuses. Most patients have a marfanoid or asthenic build resulting from muscle wasting, loose joints, and pes cavus.

Gardner's Syndrome

Gardner's syndrome was first extensively described by Gardner and co-workers in 1953. It has autosomal dominant inheritance with full penetrance and variable expressivity. Its frequency in the US has been estimated to be about 1 in 7500 population. Most investigators agree that Gardner's syndrome and familial polyposis of the colon represent two extremes of a single disease.

Epidermoid inclusion cysts of the skin represent one of the most frequent manifestations of the syndrome. They can be present on the face, trunk, and extremities, usually appearing after puberty. Fibromas and desmoid tumors of the skin, or mesentery, or both, as well as lipomas and lipofibromas, occur in 15 to 20 per cent of patients. Postoperative dense adhesion bands are commonly noted.

The characteristic feature of the syndrome is the presence of polyposis of the colon and rectum, with a marked tendency to malignant degeneration. Less often are polyps or

adenocarcinomas of the stomach or periampullary area of the duodenum, adenomas and adenocarcinomas of the adrenals and thyroid, carcinoma of the bladder, and various sarcomas. The polyps can be present before puberty. Adenocarcinoma of the colon occurs in 50 per cent of untreated patients by the age of 35 years.

Multiple osteomas might be found in the calvaria and facial skeleton. The osteomas generally precede the appearance of intestinal polyposis. The frontal bone, maxilla, and mandible are most frequently involved. Histologically, the bone shows a mature appearance and well-developed haversian system. Long bones can also be the site of osteomas, but these are small and may mimic osteomyelitis.

Roentgenologically, in addition to the polyposis of the large bowel, the most striking feature is osteomas of the skull. Radiopaque, diffuse areas can be seen throughout the calvaria, especially in the frontal and temporoparietal region. The maxilla and the mandible are also involved not only with osteomas but with odontomas and diffuse bone densities (Ida et al, 1981; Cohen, 1982). The osteomas expand and can obliterate the paranasal sinuses. They are especially common in the sphenoid and ethmoid sinuses.

Nevoid Basal Cell Carcinoma Syndrome

The major components of the nevoid basal cell carcinoma syndrome, also called Gorlin's syndrome, are (1) multiple basal cell carcinomas, (2) cysts of the jaws, (3) vertebra and rib anomalies, chiefly splayed and bifid rib, (4) calcification of the falx cerebri, and (5) calcified bilateral ovarian fibromas. Gorlin (1987) extensively reviewed the syndrome.

The nevoid basal cell carcinomas, present in about 50 per cent of patients, generally appear in childhood or at puberty and involve the nose, eyelids, cheeks, trunk, arms, and neck. They are flesh-colored to pale brown. Microscopically they cover the wide spectrum of basal cell and adnexal carcinomas - superficial, multicentric, pigmented, adenoid, and solid (Rayner et al, 1977). Milia are often intermixed with the skin carcinomas. Palmar pits are found in about 5- per cent of patients.

Bifurcation or splaying, or both, can involve more than one rib and be bilateral. A shortened fourth metacarpal, bridging of the sella, calcification of the falx cerebri, spina bifida occulta in the cervicothoracic area, and kyphoscoliosis are also frequent findings. Small multiple bone densities and radiolucencies are noted in the hands, ribs, and innominate bones.

Various associated eye anomalies have been reported, including congenital cataract, glaucoma, and coloboma of the chorioid and optic nerve.

The jaws, more often the mandible, show numerous cysts that vary in size from microscopic to several centimeters. These are lined by a uniform layer of keratinized or parakeratinized stratified squamous epithelium (odontogenic keratocysts). They have a 50 per cent recurrence rate following surgical removal. Cleft lip or palate (or both) occurs with greater than chance frequency.

Among the more frequent findings are bilateral multicentric calcified ovarian fibromas. Cardiac fibromas have also been noted (Little, 1979; Gorlin, 1987).

Most patients have increased head circumference from childhood. Medulloblastoma has been reported in several instances, and, in some families, a sibling of an affected individual was reported to have died in early childhood of medulloblastoma.

The syndrome exhibits autosomal dominant inheritance, with high penetrance and variable expressivity.

Peutz-Jeghers Syndrome

The most important component of Peutz-Jeghers syndrome is polyposis of the gastrointestinal tract. The polyps are hamartomatous in origin. The following sites, in order of frequency, are involved: jejunum, ileum, large bowel, rectum, stomach, duodenum, appendix.

Polyps can produce intussusception and occasionally lead to severe intestinal obstruction and death. The age of onset cannot be precisely determined, but generally there is a history of gastrointestinal problems before the third decade of life.

There is some evidence that the polyps are premalignant in perhaps 1 to 2 per cent of patients (Perzin and Bridge, 1982), but not all investigators agree (Linos et al, 1981). The sites of the adenocarcinomas are mainly the gastric antral region and duodenum. Some patients have polyps of the bladder, nose, cervix, and bronchi, but this is unusual.

Fifty per cent of affected individuals exhibit discrete, brown to bluish black macules of the skin, chiefly around the oral, nasal, and orbital orifices. The number of pigmented spots varies among patients. Pigmentation of the extremities can also be found.

The lips, especially the lower lip, and the buccal mucosa are involved with pigmented macules in about 98 per cent of patients; the gingiva and palate are involved less frequently. The melanotic spots are larger than those on the skin. The cutaneous pigmented macules tend to fade after puberty, but the intraoral pigmentation is more stable.

Multiple, small, bilateral gonadal tumors causing sexual precocity (granulosa-theca cell-derived, but growing in a Sertoli cell pattern, sex cord tumor with annular tubules) have been noted in several patients with the syndrome, both males and females. There can be an increased incidence of breast neoplasms in those with this syndrome. Adenoma malignum of the uterine cervix has also been reported.

Hypohydrotic Ectodermal Dysplasia

The major components of hypohydrotic ectodermal dysplasia are (1) hypodontia, (2) hypotrichosis, and (3) hypohidrosis. Principally affected are structures of ectodermal origin.

The syndrome is usually transmitted as an X-linked recessive trait, but at least 40 females have manifested the complete syndrome. The increased parental consanguinity in these cases suggests autosomal recessive inheritance and illustrates the genetic heterogeneity of this syndrome (Gorlin et al, 1970). Dominant hidrotic forms of ectodermal dysplasia represent different syndromes from the one considered here.

The facies is quite characteristic - different affected individuals looking enough alike to be considered brothers. The skull resembles an inverted triangle. Marked frontal bossing, depressed nasal bridge (simulating the saddle nose of congenital syphilis), protuberant lips, and obliquely inserted ears are the most prominent facial features. Female heterozygotes of the X-linked recessive form often exhibit such features as reduced sweat pore counts, and hypodontia and minor stigmata such as sparse scalp hair and patchy distribution of body hair. Carrier detection is possible in about 75 per cent of patients.

The syndrome might not be manifested until the second year of life and, because the physical features are not so apparent, the child can present with a "fever of unknown origin". The inability to sweat, because of marked aplasia of the eccrine sweat glands, results in intolerance to heat, with severe hyperpyrexia. The skin is soft and thin, presenting severe dryness because of the absence of sebaceous glands. Eczema and asthma are common. Linear wrinkles are seen about the eyes and mouth. Small hyperkeratotic plaques are frequently noted on the palms and soles. At birth the body is devoid of lanugo hair; after puberty the beard is generally normal, but axillary and pubic hair are scant. The scalp hair is generally blond, fine, stiff, and short. The eyelashes and especially the eyebrows are often entirely missing. The fingernails and toenails are usually normal or slightly spoon-shaped.

The most striking oral finding is hypodontia or, in several cases, anodontia. The few teeth that might be present are often retarded in eruption and have a conical crown form.

The condition can be diagnosed prenatally by skin biopsy.