Gorlin's syndrome

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Introduction

The association of recurrent jaw cysts with multiple naevoid basal cell carcinomata of the skin and certain skeletal abnormalities represents a rare familial syndrome (Gorlin & Goltz, 1960). Straith (1939) was the first to describe the condition when he reported a family of four affected individuals spanning three generations, and exhibiting many of the features which subsequently have proved to be typical of the syndrome. He noted multiple basal cell carcinomata and recurrent 'dentigerous' cysts of both jaws in a 35-year-old female whose father had also suffered from 'epitheliomata' of the face and neck. Her two teenage children subsequently developed similar jaw cysts, and Straith's discovery of calcification of the falx cerebri and parietal dura in one of the children led him to speculate that there might be an underlying disorder of calcium metabolism, although his estimations of serum calcium and phosphate levels were normal. He concluded that the condition represented a 'hereditary embryologic epithelial dysplasia'.

As long ago as 1894, however, Jarisch (1894) described a case of a patient with the full spectrum of dermatological features—basal cell carcinomata, trichoepitheliomata, epithelioma adenoides cysticum and milia. Although no mention was made of the jaws, this patient did have two other common manifestations of the syndrome—scoliosis and mild mental retardation.

During the past twenty years several isolated cases, or short series, have been reported (Binkley and Johnson, 1951; Gross, 1953; Howell and Caro, 1959), but the main work on the condition has been done in Minnesota by Gorlin and his colleagues (Gorlin and Goltz, 1960; Gorlin *et al.*, 1963; Gorlin *et al.*, 1965). Many titles have been given to the syndrome including 'multiple Jaw-cyst Syndrome', 'Naevoid Basal Cell Carcinoma Syndrome' and 'Hereditary Cutaneo-mandibular Polyoncosis' (Pollard & New, 1964) but these are either very unwieldy or else only emphasize one aspect of the complex, and for these reasons the eponymous 'Gorlin's Syndrome' is now most generally used.

Although patients suffering from Gorlin's syndrome present most frequently to dental surgeons, otolaryngologists may encounter cases presenting to them with maxillary or mandibular swelling, or with intraoral drainage of a cyst. Ameloblastic and fibrosarcomatous change may occur in these jaw cysts (Binkley and Johnson, 1951; Howell and Caro,

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1959). In this paper we present a series of seven cases of Gorlin's syndrome from three large London hospitals. One of these cases developed what we believe to be the first occurrence of a squamous cell carcinoma in one such cyst.

Case reports

Case 1

This female patient presented at the age of twelve with bilateral maxillary swellings. Dental X-rays suggested 'dentigenous cysts in both upper canine and premolar regions'. These cysts were removed but unfortunately histological details are not available. Thirteen years later a large cyst related to her left upper canine and premolar teeth was removed, and this was described as being 'lined by squamous epithelium with small areas of calcification and a wall of fibrous tissue'. (Fig. 1). At the age of 33, eight years later, she again presented



FIG. 1.
Wall of odontogenic keratocyst showing uniformly thin lining of stratified squamous keratinizing epithelium, devoid of rete pegs, with an area of calcification. (Case 1)

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with a painful swelling of the left cheek and X-rays revealed a cyst related to her left upper second premolar and first molar and occupying the left maxillary antrum. In addition a polypoid calcified mass was apparent radiologically in the right antrum. The teeth related to the left cyst were removed and a biopsy taken from the wall of the cyst revealed a well differentiated squamous cell carcinoma (Fig. 2). Tissue removed from the right maxillary antrum showed no



FIG. 2.
Well differentiated squamous carcinoma arising from the wall of an odontogenic keratocyst. (Case 1)

evidence of malignancy. Despite a full course of radiotherapy and total maxillectomy, disease still persisted, all specimens of which were squamous cell carcinoma, and the patient died within a year of surgery.*

There were no basal cell naevi on this patient's skin, but she did have small cutaneous pits on both palms—the so called porokeratosis of Mantoux. She had

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well defined supra-orbital ridges and was hyperteloric, and a scar of a cleft lip repair in childhood was present. The palate was intact.

Skull X-rays— Calcification of the falx cerebri and areas of increased radiodensity in the frontal and parietal regions are present. The pituitary foss is bridged over. (Figs. 3, 4).

Chest X-ray— A bifid left fourth rib is present.

Family History—Negative.

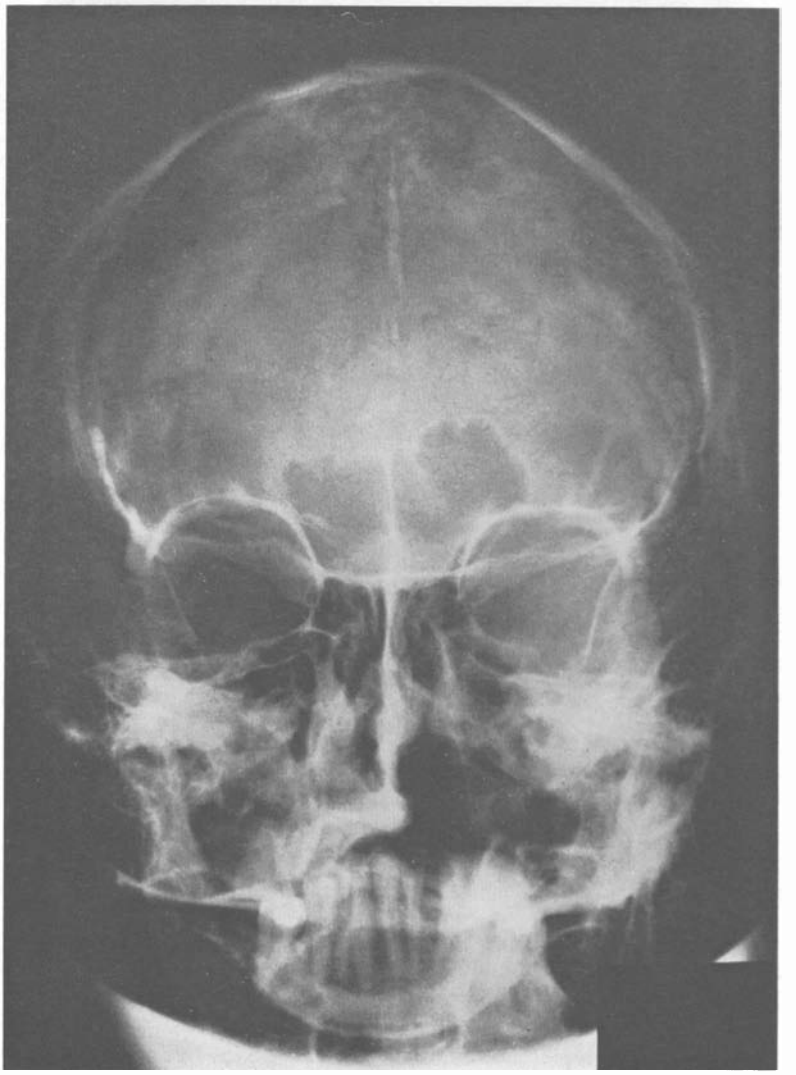


FIG. 3.

Skull X-ray (Case 1) showing calcification of the falx cerebri and diffuse mottling in the parietal regions. A left maxillectomy has been performed.

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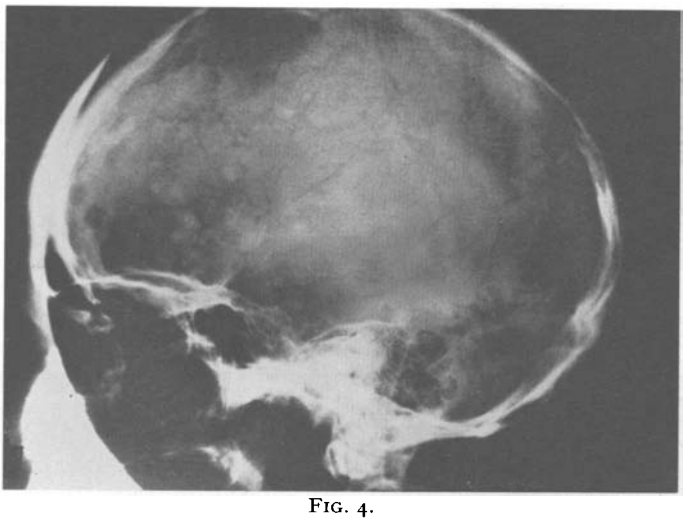


FIG. 4.
Lateral skull X-Ray illustrating dural calcification in the frontoparietal regions and a bridged-over sella turnica.

Case 2

This female presented at the age of 23 with a cyst in the right side of her mandible. The cyst was removed, but accurate details are not available. By the age of 34 she had multiple basal cell carcinomata on her forehead, and these were treated by radiotherapy. Seven years later she was found to have a large cyst at the right angle of the mandible which had so thinned the bone that a spontaneous fracture occurred. The cyst was removed and a full dental clearance carried out. Histology of the lining indicated it to be squamous epithelium.

During the following years she had treatment, by excision, curettage or radiotherapy for numerous basal cell carcinomata of the shoulders, back, abdomen, inguinal regions and face, in particular the forehead, eyebrows and naso-buccal groove. During this period three further jaw cysts required excision. One involved the body and ramus of the left side of the mandible, and the others the right and left maxillae.

Skull X-ray— Calcification of the falx and tentorium is present and there is thickening of the occipital bone below the external occipital protuberance.

Chest X-ray— Marked cervicodorsal scoliosis is present. The posterior end of the third right rib is expanded and there appear to be vestigial remains of the rib below this.

Pelvis X-ray— There are cystic areas in the floor of the right acetabulum suggestive of polyostotic fibrous dysplasia.

Case 3 (Son of Case 2)

From the age of 8 he has been under dental care for multiple jaw cysts involving predominantly the maxillae and on one occasion the mandible. He is

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at present 18 years old and as yet has no evidence of basal cell carcinomata. He has genital hypoplasia and in infancy a congenital cataract was removed.

Skull X-ray— The skull is large with a poorly defined pituitary fossa.

Chest X-ray— Multiple congenital rib anomalies are present, involving the right fourth rib and the left second and fourth ribs. There is spina bifida of C_7.

Case 4

When this patient was 12 he was first seen with painless swelling of the left lower jaw, radiological examination of which revealed three cysts in the left body of the mandible. These were examined and the lining membranes scrutinized histologically, confirming stratified squamous epithelium in all cases, keratinizing in two and non-keratinizing in the third.

Ten years later he developed a swelling of the left cheek due to a large cyst related to the upper third molar which was being displaced laterally. The cyst occupied the posterior half of the maxillary antrum and appeared to be expanding the posterior wall of the maxilla. Secondary infection occurred in this cyst producing a marked systemic upset, trismus and cervical lymphadenopathy. A smaller comparable cyst was noted in relation to the upper right third molar. The left sided cyst was removed and reported as an odontogenic keratocyst with a wall of fibrous tissue lined with parakeratinised stratified squamous epithelium. Six months later the right maxillary cyst, by now almost filling the antrum, expanding the post-antral wall and displacing the third molar, was also removed. The histological picture was again 'odontogenic keratocyst'.

At the age of 6 several 'cysts' had been removed from the skin of the hand and eyelids and in his teens a clinically diagnosed basal cell carcinoma was excised from the left lower eyelid. Unfortunately we have been unable to trace the histology of these lesions.

Skull X-ray— Normal.

Chest X-ray— Bifid and splayed anterior ends of the ribs on both sides are present with fusion of the left third and fourth ribs posteriorly and in the axilla. (Fig. 5)

Family History—Negative.

Case 5

This girl was first seen at the age of 8 years, with cystic areas associated with delayed eruption of her right upper incisors, and both lower canine teeth. The cyst linings showed the characteristic features of odontogenic keratocysts—thin stratified squamous epithelium with an absence of rete pegs. This patient subsequently developed more cysts of both upper and lower jaws, in particular two large cysts of the maxillae extending into the antra, producing expansion of the lateral walls and displacing the second and third molars on each side upwards and backwards. These were both removed and proven histologically to be odontogenic keratocysts.

She was free of cutaneous lesions at the age of 18. She then emigrated to

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Australia and on returning recently on holiday to Britain she confessed to having had several "skin cancers" excised from her face during the preceding year.

Skull X-ray— A very shallow pituitary fossa is present.

Chest X-ray— There is a bifid anterior end of the second right rib and there is also an anomaly of T_2/T_3 suggesting fusion of the bodies, spina bifida, and replacement of the spinous processes by a single process overlying T_3. There is slight scoliosis. (Fig. 6).

Family History—Negative.

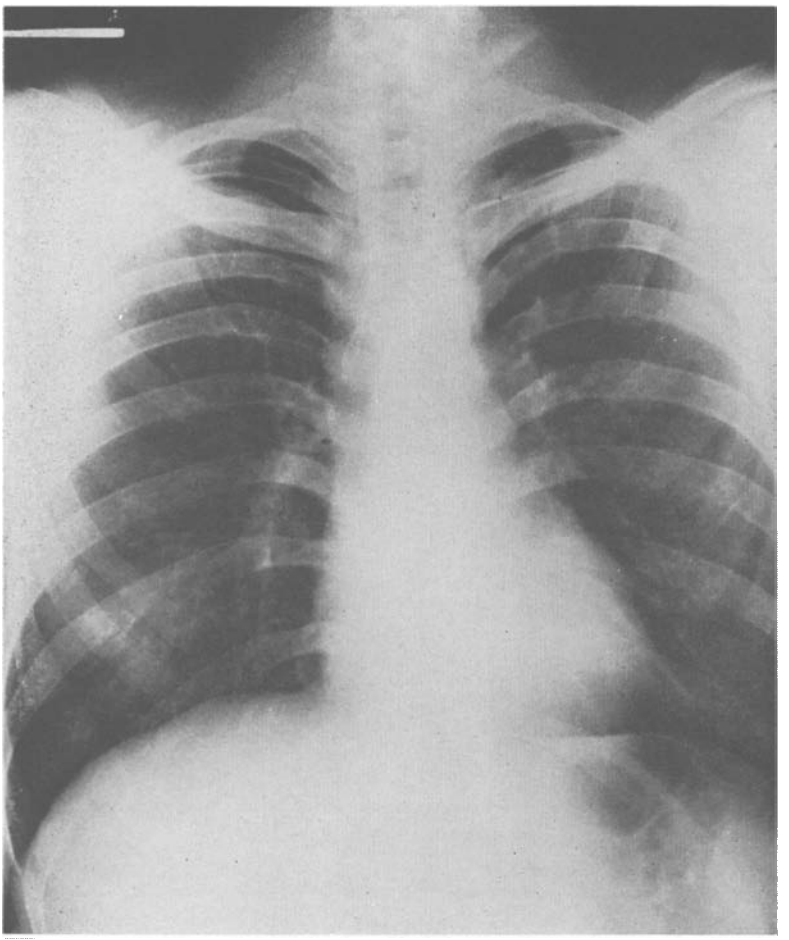


FIG. 5.

Chest X-Ray (Case 4). Bifid and splayed anterior ends of ribs on both sides.

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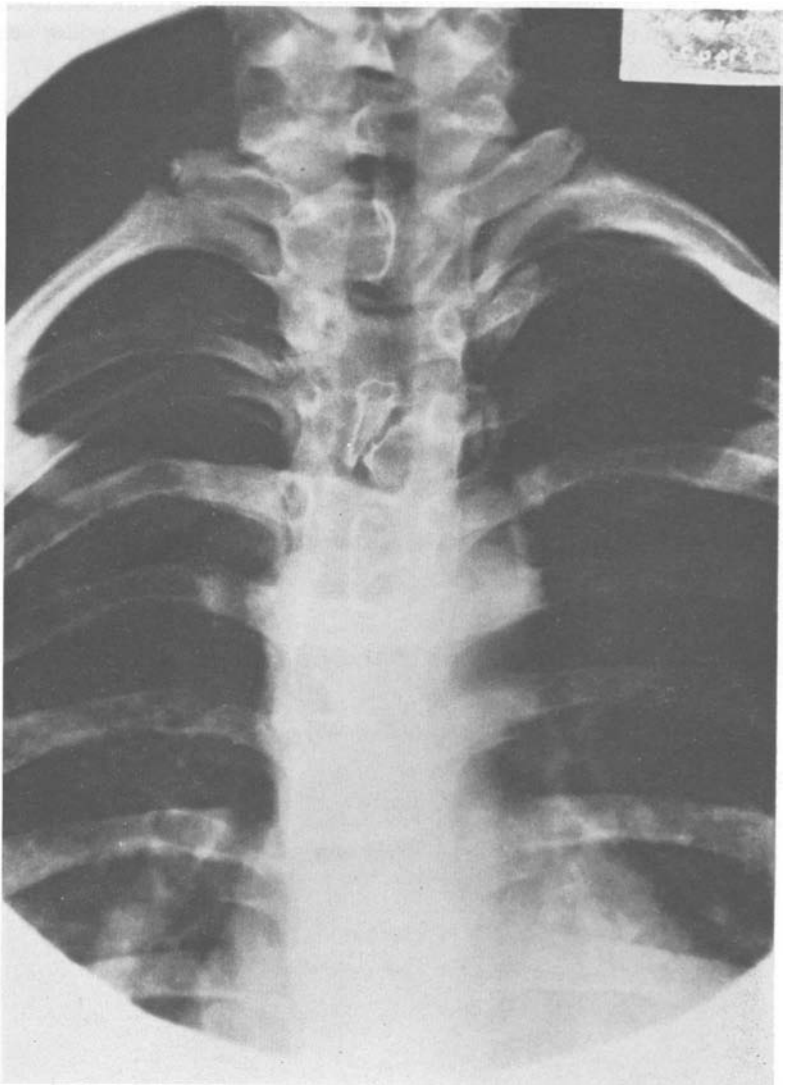


FIG. 6.

Fusion of vertebral bodies of T_2/T_3 and replacement of spinous processes by a single process. Spina bifida is present.

Case 6

This boy was born in 1961 and from the age of 18 months to the present, he has had numerous cysts, all odontogenic keratocysts, removed from both upper and lower jaws, the most recent of which in relation to the right upper

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third molar displaced that tooth up into the maxillary antrum. There are no cutaneous abnormalities, though at present he is only 13 years old.

Chest X-ray— Normal.

Skull X-ray— Not available.

Family History—His father had a history of multiple jaw cysts and a baby sister died of medulloblastoma.

Case 7

This teenage boy presented in 1967 when cysts were removed from both sides of his mandible. Later the same year he developed a painless fluctuant swelling, about the size of an orange, of the left cheek. Sinus X-rays showed a large cyst completely filling the maxillary antrum and displacing his second premolar up to the roof of the antrum (Fig. 7). At operation this cyst was found

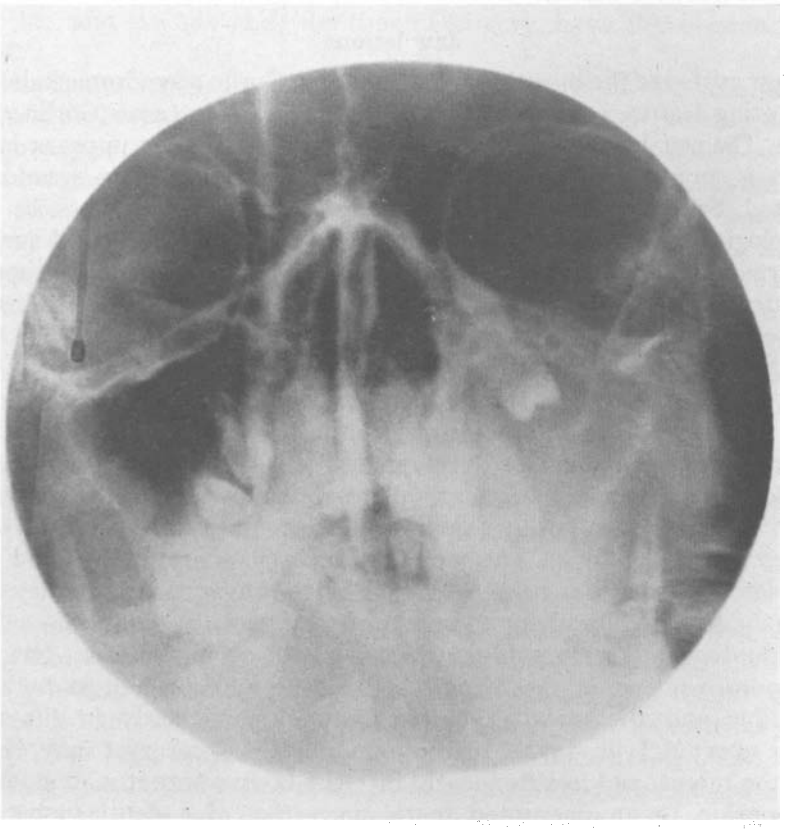


FIG. 7.

Sinus X-Rays (Case 7). Opaque left antrum due to an odontogenic keratocyst with displacement of two teeth into the antrum. The second premolar has been displaced up to the floor of the orbit, which was eroded. A smaller cyst with lesser displacement of two teeth has occurred on the right. Note also calcification of the falx.

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to reach the medial wall of the antrum and to have eroded the floor of the orbit, exposing the extraocular muscles.

Since then numerous cysts have been removed from his jaws, and all exhibit similar histological features. The lining is of thick stratified squamous epithelium devoid of rete pegs.

He has no cutaneous stigmata. He is mentally rather dull and has gonadal hypoplasia.

Skull X-ray— This showed a small bridged pituitary fossa with a very thick dorsum sellae and calcified falx.

Chest X-ray— This revealed bifid anterior ends of the third and fourth right and third left ribs, and suggested a slight degree of fusion of T_1 and T_2 with some spina bifida.

Family History—His mother had a partial mandibulectomy in Jamaica several years previously for multiple jaw cysts.

Jaw lesions

Jaw cysts are the most frequent finding in Gorlin's syndrome being the presenting feature in more than half of Gorlin's own cases (Gorlin *et al.*, 1965). The usual complaint is of swelling of the jaw, either upper or lower, which is more often painful than not as the cyst becomes secondarily infected. Spontaneous intra-oral drainage occurs in some cases, as does pathological fracture of the mandible. Alternatively the dental surgeon may suspect the presence of a cyst, when he finds incomplete dentition in a patient who has never had an extraction, and an X-ray examination may confirm that a cyst is present.

The cysts are of the variety known as odontogenic keratocysts. This term is used to describe those lesions previously classified as primordial cysts, the newer term alluding to the actual form of the cyst rather than implying anything about its development. It is thought that these lesions develop from the degenerating stellate reticulum before the process of tooth formation, and thus the cyst replaces the corresponding tooth (Killey and Kay, 1972). The fact that such cysts are often found with complete dentition has been explained by the suggestion that they arise from the stellate reticulum of supernumerary teeth.

Odontogenic keratocysts may occur anywhere in the jaws, but they are more common in the mandible than the maxilla, and in both the mandible and the maxilla are encountered particularly in the third molar area (McIvor, 1972). In the mandible the keratocyst may extend into the ramus, and less frequently into the body where it may assume a relationship to an unerupted tooth suggestive of a dentigenous cyst, but as Killey and Kay (1972) point out, this is not a true dentigenous relationship. An unerupted tooth may be grossly displaced from its normal site, particularly in the upper jaw where it may be found in the roof of the antrum (Fig. 7). Dilaceration of the roots of already erupted teeth

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may result from pressure from such an expanding cyst. Cysts involving the ramus of the mandible may achieve considerable size before swelling becomes obvious to the patient, and pathological fracture thus becomes a risk, as in our Case 2.

The odontogenic keratocyst is so named because of the presence within its lumen of keratin which closely resembles cholesteatoma, and which, in the absence of infection, is not offensive. The lining is of stratified squamous epithelium and exhibits a characteristic microscopic appearance (Shear, 1960). It is uniformly thin with a notable absence of rete pegs, and a superficial layer of keratin or parakeratin. Calcification may be present within the wall (Fig. 1). It is very difficult to keep this thin membrane intact during surgical removal, and the frequent recurrence of odontogenic keratocysts may be due to small fragments of the sacs being left behind. Small satellite microcysts which have budded off the main sac, and are missed at the time of surgery, have also been incriminated.

Neoplastic change in odontogenic keratocysts occurring outside the complex of Gorlin's syndrome is well documented, and the commonest malignancy is squamous cell carcinoma (Gardner, 1969). When odontogenic keratocysts occur as part of Gorlin's syndrome, malignant change is rare. Ameloblastoma might be expected to occur in a cyst reputedly derived from the enamel epithelium, and several authors have indeed recorded cases of this tumour (Thoma, 1959; Gorlin *et al.*, 1963; Block and Clendenning, 1963). Two cases of fibrosarcoma have been encountered (Binkley and Johnson, 1951; Howell and Caro, 1959), though that described by Binkley and Johnson was almost certainly a consequence of radiotherapy to previous jaw cysts. Shapiro (1970) described a tumour 'difficult to recognise as either carcinoma or fibrosarcoma' and this too followed a previous course of superficial x-ray treatment. Our Case 1 would appear to be the first unequivocal squamous cell carcinoma in an odontogenic keratocyst in a patient with Gorlin's syndrome.

Skin manifestations

The most characteristic cutaneous feature in Gorlin's syndrome is the occurrence of multiple basal cell naevi. These may occur in childhood, but it is more common for them to appear later in life than the jaw cysts, in the third and fourth decades (Anderson *et al.*, 1967). As many as 3,000 lesions have been counted in one individual (Anderson and Cook, 1966) and their distribution is not confined to areas chronically exposed to the sun. Though they are most commonly seen on the skin of the nose, eyelids and cheeks, they also frequently involve the chest, abdomen, back and limbs. These features—multiplicity, age of onset and distribution—help distinguish basal cell naevi from the more usual basal cell carcinomas. The lesions vary from small pigmented papules or nodules to ulcerating

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and infiltrating basal cell carcinomas. Microscopically there is a spectrum ranging from epithelioma adenoides cysticum (Gross, 1953) and trichoepithelioma to frank basal cell carcinoma (Jarisch, 1894). One may expect to see the complete range of appearances in different parts of the same patient.

Because they appear later in life than the jaw cysts, and because of the variable expressivity of this feature of the syndrome noted by Anderson *et al.* (1967), basal cell naevi are not noted in all the patients in this series. Of the four cases with no naevi, three are still under twenty and one might reasonably expect lesions to appear in at least some of these patients in the next ten to twenty years. Gorlin *et al.* (1965) have pointed out that the basal cell carcinoma is the cutaneous analogue of the ameloblastoma.

Certain other cutaneous abnormalities may be noted in Gorlin's syndrome. Palmar-plantar dyskeratosis of Mantoux describes a pitting of the palms of the hands and soles of the feet caused by a central plug of keratin falling out leaving a slightly umbilicated appearance. Ward (1960), Pollard and New (1964), and Gorlin *et al.* (1965) all noted this feature which was observed in our Case 1. Milia, skin cysts, and cutaneous fibromata may also occur. (Jarisch, 1894; Straith, 1939).

Skeletal anomalies

Costal and vertebral abnormalities are an almost constant finding in patients with Gorlin's syndrome. Of our seven cases, only one had a normal chest X-ray. Ribs may be bifid, or have splayed anterior ends. They may be short, broad, vestigial or synostozed. Cervical ribs may occur. In our series the second, third and fourth ribs were most commonly involved. Kyphoscoliosis has frequently been described (Jarisch, 1894) as has some degree of intervertebral fusion and spina bifida. These anomalies, like those of the ribs, appear to be more common in the upper thoracic and lower cervical segments. Three of our seven cases were found to have spina bifida with fusion of vertebral bodies between T_1, and T_2 and T_2 and T_3 in two of these cases. (Fig. 6).

Hypertelorism, dolicephaly and frontoparietal bossing may give a characteristic "pagetoid" facial appearance. Some degree of prognathism may be present. Straith (1939) first noted that the pituitary fossa may be malformed and this has been endorsed many times since. Four out of our seven cases had an abnormality of the sella, either shallow and poorly defined, or bridged over. One of the most interesting findings on skull radiography may be calcification of the dura, particularly of the falx and tentorium. Pollard and New (1964) point out that the lameller configuration of the calcification in Gorlin's syndrome is reminiscent of that seen in certain disorders of calcium metabolism, such as hypervitaminosis D and the Fanconi syndrome and distinct from the pattern

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of dural calcification which occurs in 6–9 per cent of normal subjects. (Fig. 3). The mottled appearance in Fig. 4 is due to dural calcification over the parietal lobes.

When Straith (1939) first observed this abnormal calcification, he wondered whether some disorder of calcium metabolism might underly the condition. This has been further questioned by Block and Clendenning (1963) who noted that one of their patients had shortened fourth metacarpals, an observation which led these authors to explore a possible realtionship between Gorlin's syndrome and pseudohypoparathyroidism. They found this patient and one other to have a decreased phosphorus diuresis following intravenous infusion of parathyroid hormone (Ellsworth-Howard test). Block and Clendenning concluded that Gorlin's syndrome might be a variant of pseudohypoparathyroidism. Serum phosphorus, calcium and alkaline phosphatase in their and other investigations have been consistently normal.

Our Case 2 had a cystic appearance of the right acetabulum suggestive of polyostotic fibrous dysplasia.

Of the less common features of the syndrome the most fascinating is the occurrence in certain subjects, or a sibling, of medulloblastoma. Gorlin *et al.* (1965) in their extensive survey came across four cases of medulloblastoma in patients with the syndrome. Our Case 6 had a baby sister who died of this tumour, and it seems possible that she and others like her who succumb at an early age might well have gone on to develop other stigmata of the syndrome. An analysis of all cases of medulloblastoma and their families might well reveal further cases of hitherto unsuspected Gorlin's syndrome. Agenesis of the corpus callosum, a postmortem finding in Binkley and Johnson's (1951) case has not subsequently been confirmed Many sufferers are of low intelligence, sometimes exhibiting frankly schizoid characteristics.

Other Findings

Numerous other less frequently occurring findings have been recorded, the relevance of which to the syndrome are hard to evaluate. Of those which appear to have a more than fortuitous association we include genital hypoplasia—in two of our cases, and congenital cataract in Case 3. A variety of eye disorders have been noted, including congenital cataract, glaucoma, coloboma and internal strabismus. (Oliver, 1960).

Case 1 in our series had a cleft lip repaired in infancy, an association noted also by Gorlin.

Syndactyly and polydactyly have been described in particular by Anderson *et al.* (1967) but none of our cases exhibited these features.

One of our series had radiological features of polyostotic fibrous dysplasia of the acetabulum. Such a finding has not been previously described and its significance is not certain.

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Mode of inheritance

Anderson *et al.* (1967) conclude that the syndrome is transmitted by a dominant mode of inheritance and is determined by a highly penetrant autosomal gene of variable expressivity. They stress that the jaw cysts, the basal cell naevi and the porokeratotis are age-dependent, the average age of appearance of the cysts being 15 years, and of the naevi, 19 years. The skeletal anomalies are congenital and not age-dependent. Chromosome studies have not, as yet, revealed any significant changes. Gorlin implies that the most important clue to the nature of the disorder may be the decreased phosphaturic effect observed by Block and Clendenning (1963). Perhaps it is this biochemical defect which is genetically determined and which underlies the development of the other anomalies. Not all workers have been able, however, to confirm Block and Clendenning's findings.

Summary

The uncommon familial syndrome of multiple odontogenic keratocysts, basal cell naevi and skeletal anomalies is reviewed, and seven cases are described, including one patient who developed squamous cell carcinoma in a previous odontogenic keratocyst of the maxilla.

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