Surgical pathology of the mouth and jaws

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6. Genetic, metabolic and other non-neoplastic bone diseases

Craniofacial defects - surgical considerations

Many developmental defects such as cleft lip and palate, branchial arch defects, craniostenoses or supernumerary teeth are genetic traits. However, the family history is informative in relatively few of these patients. Most arise by new gene mutations and only then become potentially heritable. There are also chromosomal defects of which the most common is Down's syndrome (trisomy 21), which is not usually heritable.

Other conditions such as the Pierre Robin anomaly probably have an entirely environmental cause. Here, it appears that the developing fetus is unable to extend the neck due to deficiency of amniotic fluid. As a result the tongue does not descend from between the developing palatal shelves and prevents them from fusing in the midline. Failure of the fetal neck to extend also causes the developing chin to press on to the sternum. Gross mandibular hypoplasia with consequent obstruction of the airway are the results. However, it is important to note that, in such congenital defects, growth potential is normal. If early nursing difficulties can be overcome, mandibular growth will ultimately catch up and, as there is no intrinsic shortage of palatal tissue, anatomical repair of the cleft palate can often be achieved without detriment to subsequent maxillary growth.

For many of these conditions, any distinction between a genetic or environmental aetiology is academic. Once the condition has become established, management depends more on appreciation of the scope of the primary defect than on its aetiology. For example, in hemifacial microsomia the intrinsic defect is probably confined to structures arising from the mandibular arch. Early surgery to the young mandible should therefore encourage normal growth of the maxilla, thus avoiding developmental defects which are predominantly secondary to the mandibular asymmetry.

In many conditions, knowledge of the growth potential of various parts of the developing facial skeleton is incomplete, and clinical findings have often been distorted by the effects of earlier surgery. The best example is in the study of the growth of the maxilla in cleft lip and palate patients. It is only comparatively recently that sufficient sound evidence has accumulated to establish that the middle third of the face in unoperated clefts has a normal growth potential in all dimensions. Nevertheless, gross cosmetic defects should usually be repaired early in life, but the timing and nature of such surgery should be such as to minimize damage which lessens the intrinsic growth potential.

In this text, only the more common craniofacial defects can be considered as examples of what may be susceptible to surgical improvement.

Facial clefts and associated anomalies

Cleft lip with or without cleft palate

The overal incidence is about 1 per 1000 Caucasian live births, only 0.4 per 1000 births in Afro-Americans, but in Japan reaches 1.7 per 1000 births. In general, males are more frequently affected. Isolated cleft lip may be unilateral or bilateral; when unilateral, 70% are on the left side. Eighty-five per cent of bilateral cleft lips and 70% of unilateral cleft lips are associated with complete clefts of the hard and soft palate.

Isolated cleft palate

This appears to be a separate entity with an incidence of approximately 1 per 2000 live births in Caucasians and Afro-Americans. There is a 2:1 female predominance for complete palatal clefts, but an equal sex incidence of clefts of the soft palate only. Bifid uvula (an incomplete form of cleft palate) is present in 1:80 Caucasians and may be associated with a submucous palatal cleft in which there is imperfect muscle union across the velum but an intact mucosal surface. Often there is an associated notch in the posterior hard palate.

Because of the different patterns and associations of cleft lip and palate, it has been difficult to analyse the patterns of inheritance. However, there clearly is a strong familial influence. The risk of having a cleft is much higher if a parent or sibling is affected (Table 6.1)

Table 6.1 Risk levels for clefts for those with affected relatives (After Tolorava, 1972)

	Cleft lip and/or palate	*Isolated cleft palate*
Normal parents		
One affected sibling	4%	3.5%
One affected parent		
No affected siblings	4%	3.5%
One affected sibling	12%	10%
Both parents affected		
No affected siblings	35%	25%
One affected sibling	45%	40%.

Associated anomalies. The association of congenital lower lip pits with cleft lip and palate is strong and due to an autosomal dominant gene showing 80% penetrance. Other rare associated anomalies are talipes equinovarus, syndactyly and various eye defects, but there is a great variety of craniofacial syndromes where clefting is a feature, as Gorlin et al (1971) have described.

The Pierre Robin anomaly (cleft palate, micrognathia and glossoptosis) is probably quite different from other clefting conditions in aetiology and management. As discussed earlier, there is no inherent lack of tissues in this condition; growth can catch up if early nursing difficulties can be overcome.

Surgical aspects of cleft lip and/or palate

Until relatively recently it was believed that maxillary hypoplasia in all three planes was an intrinsic feature of clefts. However, studies on unoperated clefts have shown that they have an almost normal growth potential (Ortiz-Monasterio et al, 1956; Mars and Houston, 1990). Without early surgery, facial and dental development are normal. It seems, therefore, that postnatal surgery to close the cleft lip and palate defect inhibits subsequent growth. Two factors are important. First, in developing vomerine flaps to close the hard palate, the vomerine growth centre is irrevocably damaged, inhibiting downward and forward development of the maxilla. Secondly, the surgery itself results in extensive scar formation which also inhibits growth. von Langenbeck or Wardill-type flaps in the palate leave bare areas to granulate and scarring can restrict subsequent transverse growth. Dissection in the anterior floor of the nose for lip closure inhibits subsequent alveolar growth, often resulting in infra-occlusion. The timing and planing of procedures to limit these problems is therefore critical.

One approach has been to delay hard palate closure until 8 or 9 years of age when a considerable amount of maxillary growth has taken place. As a consequence, growth inhibition and distortion could be minimized. Hotz and Gnoinski (1979) adopted this regimen and used a modified Widmaier procedure for the anatomical closure of the soft palate only (Perko, 1979). The extensive hard palate fistula could be obturated with an appliance until hard palate closure was carried out at 8 years. Hotz and Gnoinski (1979) are among the few cleft teams who have kept meticulous records. They have followed up their patients carefully, and convincingly shown excellent results in terms of facial growth and dental occlusion. However, some controversy persists as to the ultimate quality of their patients' speech; this may be acceptable in the more guttural Germanic languages but is less acceptable for English.

Another approach has been adopted in Norway, where all cleft surgery for the entire country is undertaken by two small teams that have become, as a result, very experienced. A more traditional approach has been adopted and the hard and soft palates together are closed before 18 months, using conventional von Langenbeck-type procedures. Nevertheless, results have been excellent and osteotomy procedures to correct subsequent growth deficiencies have rarely been required. This suggests that extesive experience and very gentle handling of the tissues can minimize the secondary growth defects consequent on the primary surgery. However, the genetic pool may be different in Norway and palatal clefts there may be less severe than elsewhere in Europe and America.

Another approach has been developed by Precious and Delaire (1993) in France, where it is argued that for harmonious balanced growth in the cleft lip and palate subject it is necessary, at the time of lip repair and, later, at the time of palate repair, to mobilize widely all the associated muscles from their anomalous insertions and restore them to their normal anatomical arrangement. Only under the influence of normal muscle function can the face and jaws develop normally, as described by Markus et al (1993).

Although there have been advances in the repair of palatal clefts since the days when it was performed without benefit of anaesthesia, it cannot be said that there is any consensus about the most satisfactory technique. Moreover, the evaluation of current techniques is by no means satisfactory, as Roberts et al (1991) have confirmed. The only conclusion that can be drawn is that all surgery results in some scar tissue and that scar tissue does not grow. Therefore, all surgery in cleft lip and palate patients should be kept to a minimum, but a convincing case seems to have been made for Delaire's muscle mobilization technique and late closure of the hard palate.

Lateral facial clefts

An extensive variety of lateral facial clefts with associated anomalies of the ear, eyelids and malars have been described. Their association with other defects such as polydactyly, syndactyly or absence of digits has led to the suggestion that these deformities result from persistent amniotic bands. The most useful classification of these cleft is that of Tessier (1976).

Hemifacial microsomia (Goldenhar syndrome, oculoauriculovertebral dysplasia, first and second branchial arch syndrome)

This group of conditions has not been shown to possess any significant familial predisposition. They appear once in approximately 3000 live births, with an equal sex ratio. In the majority (70%) the condition is unilateral but, when bilateral, is always asymmetrical. Seven per cent of cases are associated with a cleft lip and palate. The defects may vary from slight to severe when they extend well beyond the mandible and can include defects of the auricle, middle ear, malar, maxilla, squamous temporal bone and related soft tissues including muscles of mastication and parotid gland. Rarely, there are facial palsy, unilateral coloboma and epibulbar dermoids. Anomalies of the cervical spine and ribs are also seen. Poswillo (1973) has suggested, from animal and clinical studies, that rupture of the stapedial arterial system in the 35-day fetus results in focal necrosis of tissues in the vicinity of the developing mandibular ramus. The expanding haematoma is unselective in its effects, and clinical cases vary in severity according to the degree of primary destruction and the capacity of the tissues to effect compensatory repair.

Surgical aspects

The skeletal tissues are not only defective or absent, but the soft tissues which comprise the functional matrix are also affected. Thus treatment planning should take account of any lack of functioning muscle, as it will lead to atrophy of any bone grafts used to augment the facial skeleton. However, when some functional muscle is present, serial bone grafting may prevent the onset of secondary deformities. Indeed, costochondral bone grafts have sometimes been seen to grow under the influence of the functional matrix. When there is little functioning soft tissue, it is necessary to introduce new hard and soft tissue into the area to facilitate facial reconstruction. Currently, microvascular surgery is being used for this purpose.

Down's syndrome (mongolism; trisomy 21)

Down's syndrome is the most common autosomal chromosome abnormality and also the most common of the clinically recognizable categories of mental handicap. Down's syndrome has an incidence of approximately 1 in 700 live births and accounts for about one-third of severely mentally handicapped children. The trisomic mongol is usually born of an older mother and the risk rises to 1 in 100 at 45 years of age. The translocation type is born to a younger mother; in about 50% this defect is inherited from a parent, usually the mother. The risk to these mothers of having a further Down's syndrome baby is 1 in 3-6.

All Down's syndrome children are mentally subnormal to some degree, but usually amiable and cooperative. Congenital cardiac defects are found in up to 50%. The main types are atrial septal defect, mitral valve prolapse or, less often, atrioventricular canal and vetricular spetal defect. About one-third die in the first few years of life from heart disease. There are typically also multiple immunological defects to that infections of the skin, gastrointestinal and respiratory tracts are common, especially in institutionalized patients. However, infective endocarditis does not appear to be unusually frequent. The risk of acute leukaemia (usually acute lymphoblastic) in Down's syndrome is 20 times greater than in the general population. Though life expectancy has been greatly extended by cardiac surgery and control of infections, premature ageing is characteristic and like those with Alzheimer's disease, there is reduplication of the amyloid gene in Down's syndrome.

There are many oral abnormalities: the most obvious is an open-mouth posture. The tongue is frequently abnormally large, protrusive and fissured. The circumvallate papillae enlarge, but filiform papillae may be absent. The lips tend to be thick, dry and fissured and there is a poor anterior oral seal. Anterior open bite, to whicha strong tongue thrust contributes, posterior crossbite and other types of malocclusion are common. The maxilla and malars are small, the mandible is somewhat protrusive and class III malocclusion is common. The palate often appears high, with horizontal palatal shelves, but a short palate is more characteristic. About 0.5% have a cleft palate and there is also a high incidence of bifid uvula and cleft lip. Tooth formation and eruption are retarded. Up to 30% have morphological abnormalities of both dentitions, particularly short, small crowns and roots.

There is also severe early onset of periodontal disease, and lower anterior teeth, in particular, are usually lost early. By contrast, caries incidence is usually low in both dentitions.

Down's children are generally more easily managed than many other mentally handicapped patients. Dental treatment can usually be carried out under local anaesthesia with sedation of necessary.

General anaesthesia needs to be carried out by a specialist because of the frequency of cardiac defects and respiratory disease. Intubation may be difficult because of the hypoplastic midface; congenital respiratory tract anomalies may be associated and there is abnormal susceptibility to chest infections. Anaemia, a risk of atlanto-axial subluxation when extending the neck, and possible hepatitis B carriage are other hazards. Despite these difficulties, improvement in the facial appearance by maxillofacial reconstruction and plastic surgery may be considered.

Clefts of lip or palate should be treated as in any other child. When adolescence is reached, assessment in conjunction with parents or guardians, for orthognathic surgery should be carried out. Many have an anterior open bite with poor facial muscle tone and a large tongue. These require bimaxillary surgery with advancement and impaction of the posterior maxilla and reduction of the mandible. Frequently, tongue reduction is also needed and sometimes also reduction of the lower lip to improve lip posture and seal. In severe cases it is also possible to carry out canthal surgery to improve the mongoloid slant of the palpebral fissures.

Down's syndrome children accept such treatment with few difficulties and the benefits from the improvement in their appearance are very encouraging.

Psychological aspects of remedial surgery

Surgical reconstruction of many genetic or other developmental jaw defects is not a practical proposition because of the technical difficulties and stress on the child of multiple operations. In addition, associated mental defect has generally been considered to be a contraindication to surgery. However, there is not a move towards cosmetic surgery for those with mild mental defect. In the case of Down's syndrome, the most common of such disorders, it appears that removal of the facial stigma leads to a considerable improvement in the children's performance and in their ability to integrate with their normal peers. Absence of insight or self-awareness should not necessarily, therefore, be thought to be an essential concomitant of mental defect, and anything that can be done to enable these children to integrate into 'normal' society will optimize their subsequent development.

Osteogenesis imperfecta (brittle bone syndrome)

Osteogenesis imperfecta is characterized by abnormal fragility of bones and is usually inherited as an autosomal dominant trait. The underlying defect is in type I collagen formation, but at least five subtypes are recognized. In addition to those with poisitive family histories, sporadic cases due to new mutations are relatively common.

Typical features are that the bones are capable of growing to their normal length but are abnormally thin and weak. Multiple fractures follow minimal or unnoted trauma and the most severe form (type II - autosomal recessive) is lethal as a result of multiple fracutres *in utero* and almost complete failure of ossification of the skull.

About 80% of cases are type I. They suffer multiple fractures in childhood and usually therefore become grossly deformed. The thin sclerate appear blue and there is hearing loss due to overgrowth of soft spongy bone round the oval window or to fractures of the auditory ossicles. Joints are frequently also hypermobile and the aortic valves are thin. The teeth are abnormally translucent with weak attachment of the enamel to the dentine (dentinogenesis imperfecta), particularly in type IV.

The long bones typically have slender shafts but normal epiphyses, giving them a trumpet-like shape. Fracture healing is not delayed but usually leads to distortion of the bones and there is frequently excessive callus formation which can rarely undergo sarcomatous change.

Microscopy

Bone is both inadequate in amount and typically woven in character. Osteoblasts are sometimes excessively numerous.

Management

Though the long bones are fragile and care must be taken when carrying out extractions, fractures of the jaws are uncommon. Management of dentinogenesis imperfecta, when present, depends on specialized restorative procedures.

Osteopetrosis (marble bone disease)

Osteopetrosis is a genetically heterogeneous group of disorders characterized by defective osteoclast function. As a consequence there is failure of normal bone modelling, formation of abnormally dense bone with loss of differentiation between cortical and cancellous types and complete or almost complete obliteration of medullary spaces. The two main forms are a milder, usually dominant type with bone defects as the main manifestations, and a severe, usually recessive, type with anaemia or pancytopenia, widespread extramedullary haemopoiesis, and neurological complications of the bone disease. Blindness, deafness and facial palsy or trigeminal nerve pain result from cranial nerve compression by overgrowth of bone. There may also be multiple dental defects. The bones, though abnormally dense, are weak and fracture readily; osteomyelitis is a recognized complication as a result of the impaired blood supply. Craniofacial abnormalities in severe osteopetrosis include frontal bossing and exophthalmos.

Microscopy

In mild cases there may be an attempt to form normal lamellar bone, but the medullary cavity is replaced by bone containing minute marrow spaces and little or no haemopoietic tissue. Younai et al (1988) have described three distinct patterns of bone abnormality in a severely affected mandible. These comprised a tortuous pattern of lamellar bone trabeculae, amorphous globular areas and an osteophytic pattern. Osteoclasts were numerous but appeared to be inactive.

Management

The dominant type is compatible with normal survival with only occasional effects such as those described. Symptoms may even be absent and the abnormalities discovered only by chance on routine radiography. Intermediate forms are characterized by rickets-like skeletal disease and renal tubular acidosis. In the most severe, recessive type, haemopoiesis is so much impaired that death in childhood from anaemia, haemorrhage or infection is usual, but bone marrow transplantation can be life-saving.

The chief risk from dental surgery and particularly extractions is that of osteomyelitis, which can also follow dental infections. Long-term antibiotic treatment, sequestrotomy and hyperbaric oxygen may be required.

Hypophosphatasia

Severe (infantile) hypophosphatasia is recessively inherited, but the milder adult form may be due to a dominant trait. The typical biochemical abnormalities are a low plasma alkaline phosphatase level and a high phosphoethanolamine level in the urine (Fallon et al, 1984).

Infantile hypophosphatasia may be lethal due to hypercalcaemia and renal failure. In childhood hypophosphatasia, the main features are rickets-like skeletal disease leading to short-limbed dwarfism. Radiographically, the ends of the long bones are ragged or invisible and there is failure of mineralization of wide areas of the skull. Early synostosis of cranial sutures can lead to oxycephaly and exophthalmos. Adults with hypophosphatasia have frequent fractures and may have rickets-life deformities. However, premature exfoliation of deciduous teeth due to failure of cementum formation is sometimes the only clinical abnormality. These teeth may have abnormally large pulp chambers and hypoplastic enamel defects. Permanent teeth are less frequently shed spontaneously.

Cleidocranial dysplasia

This rare autosomal dominant disorder is characterized by defective formation of the clavicles, delayed closure of the fontanelles, but the presence of multiple Wormian bones, and retrusion of the maxilla. Partial or complete absence of clavicles may allow patients to bring the shoulders together in front of the chest.

Cleidocranial dysplasia is a cause of delayed or, ofen, failure of eruption of permanent teeth. The latter frequently remain embedded in the jaw and are associated with multiple supernumerary teeth. Cyst formation round these embedded teeth is common, but unless this happens there is no justification for wholesale removal of buried teeth as this leads to gross atrophy of the jaws. However, surgery is required when teeth erupt late in life under a denture.

Marfan's syndrome

Marfan's syndrom is a relatively common defect of collagen formation inherited as an autosomal dominant trait. Typical features are a tall, slender body habitus with arachnodactyly, dislocation of the lens and cardiovascular defects. The underlying defects include unstable crosslinkage and increased solubility of the collagen molecule or other defects in type I collagen. This leads to weakness of many important connective tissue structure such as joint capsules or the media of arteries.

Clinically, there is wide variation in expression of Marfan's syndrome. In addition to the typical body habitus, about 50% of patients have mild to severe ectopia lentis and up to 90% of patients have mitral valve prolapse and regurgitation, and an enhanced susceptibility to infective endocarditis. Aortic dilatation and regurgitation are less common but more serious, and the main cause of shortened expectation of life is aortic dissection. Aortic and mitral valve dysfunction may be associated with hypermobile joints in some of these patients.

The palatal vault is high and hypermobility can lead to recurrent subluxation of the temporomandibular joint. Cleft palate or bifid uvula may be associated in some cases. Prognathism and malocclusion are common. Cardiovascular disease can affect the management of the patient when surgery is required.

Sickle cell disease and the thalassaemias

Sickle cell disease and the thalassaemias are genetically determined haemolytic diseases in which bone abnormalities can result from bone marrow hyperplasia or, in sickle cell anaemia, from bone infarction.

Sickle cell anaemia

Sickle cell anaemia mainly affects people of African, Afro-Caribbean, Indian, Mediterranean or Middle Eastern origin. There are estimated to be about 5000 persons in Britain who have sickle cell anaemia (homozygotes), but many more with sickle cell trait (heterozygotes).

In homozygotes, formation of abnormal haemoglobin (HbS) brings the risk of haemolysis, anaemia and other effects. In heterozygotes, sufficient normal haemoglobin (HbA) is formed to allow normal life with only rare complications.

The complications arise from the polymerization of deoxygenated HbS which is less soluble than HbA, and forms long fibres. These deform the red cells into the characteristic sickle shapes and cause them to be readily haemolysed. Haemolysis causes chronic anaemia with a haemoglobin level around 8 g/dL. Nevetheless patients, under normal circumstances, typically feel well, as HbS releases its oxygen content to the tissues more readily than HbA, and are in a steady state which does not require treatment.

Exacerbation of sickling causes increased blood viscosity and blocking of capillaries. Factors which precipitate sickling include (a) hypoxia from poorly conducted anaesthesia or chest infections, (b) dehydration, and (c) infection, acidosis and fever. Infections (occasionally dental) can not merely precipitate painful crises, but these patients are also abnormally susceptible to infection, particularly pneumococcal or meningococcal.

Sickle cell crises are of three main types:

1. Painful crises caused by blockage of blood vessels and bone marrow infarcts.

2. Anaemic crises due to marrow aplasia. They require immediate transfusion.

3. Sequestration crises probably due to extensive sickling, particularly in the viscera. An acute chest syndrome, characterized by pain, fever and leucocytosis, is the most common cause of death.

Painful crises can affect the jaws, particularly the mandible, and mimic acute osteomyelitis. Bone infarcts form foci susceptible to infection and salmonella osteomyelitis is a recognized hazard in these patients. Infarcts in the jaws may mimic toothache or

osteomyelitis. Rarely, the true nature of a crisis with jaw infarction may not be recognized and biopsy has to be carried out. The oral mucosa may also be pale or yellowish due to haemolytic jaundice.

Radiography

Abnormalities result from expansion of the haemopoietic marrow causing thickening but apparent osteoporosis of the bones of the skull. In severe cases, the changes resemble those of thalassaemia. Bone infarcts may appear relatively radiolucent at first, but become sclerotic. Rarely, jaw lesions can be the sole radiographic manifestation of the disease. Sclerotic areas in the skull or jaws may be seen in radiographs as a result of earlier infarcts.

Microscopy

Biopsy is only likely to be carried out under unusual circumstances such as unexplained jaw pain or radiographic changes. Typical features of a bone infarct are erythrocytic haemopoiesis, sickled erythrocytes and haemosiderin-filled macrophages.

Management

Tests for the sickling trait should be carried out particularly in those of Afro-Caribbean origin, if general anaesthesia is anticipated. If the haemoglobin is less than 10 g/dL, then the patient is probably a homozygote with sickle cell disease.

In those with sickle cell trait, the main precaution is that general anaesthesia, if unavoidable, should be carried out with full oxygenation. Occasionally, crises may be precipitated by dental infections such as acute pericoronitis. Regular dental care and prompt antibiotic treatment of infections are therefore necessary for these patients.

Painful bone infarcts should be treated with non-steroidal anti-inflammatory analgesics and fluid intake should be increased (at least 3 litres/day for adults). Admission to hospital is required for severe painful crises not responsive to simple analgesics.

Rigorous routine dental care is necessary because of the susceptibility to infection. General anaesthesia, if utterly unavoidable, should be carried out in hospital where precautions include exchange transfusions to raise the HbA level, rehydration and avoidance of hypoxia and acidosis if anaesthesia has to be given.

The thalassaemias

Bone disease in the thalassaemias is also due to bone marrow hyperplasia. The alpha-thalassaemias mainly affect Asians, Africans and Afro-Caribbeans, while the beta-thalassaemias mainly affect the Mediterranean littoral, such as Greece (thalassaemia: literally, sea in the blood). Alpha- and beta-thalassaemias result from inadequate synthesis of alpha and beta globin chains of haemoglobin. The imbalance between the production of the globin chains means that the normal chains are present in the red cells in relative excess and tend to precipitate out. In homozygous thalassaemia, haemolysis can therefore result.

The severity of the disease depends on the numbers of alpha or beta globin genes affected, but in simplified terms the diseases are thalassaemia minor in heterozygotes and thalassaemia major in homozygotes.

Thalassaemia minor is characterized by mild but persistent microcytic anaemia (Hb over 9 g/dL), but is otherwise asymptomatic, apart sometimes from splenomegaly.

Thalassaemia major (usually homozygous beta-thalassaemia) is characterized by severe hypochromic, microcytic anaemia, great enlargement of liver and spleen and skeletal abnormalities due to marrow hyperplasia. The results are failure to thrive and early death if repeated blood transfusions are not given.

Radiography

The diploic spaces of the skull are enlarged and there is thinning of the cortex with a 'hair on end' appearance. The maxillae may also be expanded, causing severe malocclusion. The zygomatic bones are pushed outwards and the nasal bridge depressed in severe cases.

Management

Regular transfusions prevent the development of bony deformities, but lead to progressive deposition of iron in the tissues. In those that survive, therefore, haemosiderosis can lead to dysfunction of glands and other organs. Typical complications include diabetes mellitus, hepatic cirrhosis and cardiac failure in early life. A Sjögren-like syndrome can result from iron deposition in the salivary glands.

Desferrioxamine, a chelating agent, may lessen the effects of the iron overload and folic acid treatment may ameliorate the haemolytic anaemia.

Other genetic disorders affecting the jaws

Garner's syndrome is discussed in Chapter 5, the Gorlin-Goltz syndrome in Chapter 3 and cherubism below.

Fibro-osseous lesions

Fibro-osseous lesions range from fibrous dysplasia to the well-circumscribed lesions of ossifying or cementifying fibroma. Apparently, intermediate variants have features of both types of lesions, but this is a controversial area where the diagnosis must take into account clinical and radiographic as well as the microscopic findings.

Fibrous dysplasia

Typical monostotic fibrous dysplasia is characterized by focal but poorly circumscribed fibro-osseous replacement of an area of bone to form a swelling that starts in childhood but is likely to undergo arrest with maturation of the skeleton. The jaws are the most frequently affected site in the head and neck region, but overall these represent only 20-25% of cases,

as the ribs and femur are considerably more frequently involved. Males and females are almost equally often affected.

Polyostotic fibrous dysplasia is relatively rare and is characterized by histologically similar lesions affecting several or many bones. Females are affected in the ratio of 3 to 1 male, and some show precocious puberty.

Albright's syndrome comprises polyostotic fibrous dysplasia, skin pigmentation and sexual precocity. Lesions are typically unilateral or segmental in distribution.

The aetiology of fibrous dysplasia is unknown. Unlike cherubism, which frequently has a similar natural history, there is no evidence of any genetic component.

Clinically, monostotic fibrous dysplasia is mainly seen in young adults, usually in their 20s, while polyostotic fibrous dysplasia is more frequently seen in childhood. The lesion typically forms a painless, smoothly rounded swelling in the maxilla more often than the mandible. The mass may be large enough to cause disturbance of function in some sites; malocclusion, for example, can result from displacement of teeth. Though the fibro-osseous mass weakens the bone, pathological fracture of the jaws is rare but relatively common in long bones.

Polyostotic fibrous dysplasia involves the head and neck region in up to 50% of cases. A jaw lesion may be the most conspicuous feature and the patient may appear to have monostotic disease. In a young girl, in particular, a search for other skeletal lesions and pigmentation may be appropriate. Skin pigmentation consists of tan to brown macules, 1 cm or more across, with an irregular outline. Pigmentation frequently overlies affected bones but has a predilection for the back of the neck, trunk, buttocks or thighs. Though any skin area can be affected, pigmentation of the oral mucosa is very rare.

Radiography

Most characteristic is an area of lessened radiopacity, with a fine orange-peel texture which merges imperceptibly with the surrounding normal bone. The outer surface may have an eggshell thin cortex of expanded normal bone. However, a variety of appearances can be seen and depend on the state of ossification of the lesion. Predominantly fibrous lesions may mimic cysts or cystic tumours. More heavily ossified lesions may have a pagetoid pattern or a patchily sclerotic appearance.

Microscopy

The typical appearance is of loose cellular fibrous tissue in which there are evenly distributed trabeculae of woven bone. The trabeculae tend to be slender and arcuate or branched but very variable in shape. Osteoblasts are scattered throughout the substance of the trabeculae. This may contrast with the more conspicuous osteoblastic rimming seen in ossifying fibroma, where, in addition, the bone is typically lamellar rather than woven. However, lamellar bone or calcified spherules can also be seen in fibrous dysplasia. The types and amount of bone vary considerably from case to case, but more important is the lack of

definable borders where the trabeculae of fibrous dysplasia merge imperceptibly into the surrounding normal bone.

In addition to the mainly trabecular pattern of fibrous dysplasia, there may be myxoid areas or small foci of giant cells scattered in the fibrous stroma. These giant cells are not in such compact masses as those of giant cell lesions.

Management

There is nothing as yet to suggest that different patterns of bone formation are of any value in predicting the behaviour of the lesion or its response to treatment. The natural history is of steady progression until (very approximately) skeletal maturity is reached, when most lesions become static. Though the time of arrest is variable and doubt has been expressed as to whether this happens in all cases, there are undoubtedly numerous cases which have been followed up for sufficient periods to confirm spontaneous arrest. Moreover, unlike some benign tumours, there appear to have been no cases of untreated elderly patients with actively proliferating fibrous dysplasia.

The chief concern is usually therefore largely cosmetic or to ameliorate serious interference with function. There is also a small possibility of sarcomatous change which is more frequent in polyostotic disease and typically develops in early adult life. Ebata et al (1992) were able to identify 89 reported cases: the majority (61%) were osteosarcomas. The tendency to malignant change in fibrous dysplasia appears to be related to the disease itself, as only a minority (approximately 30%) of the reported cases had received radiation treatment.

Treatment for fibrous dysplasia, when indicated, should be resection. However, this is only justifiable for disfiguring lesions or those which seriously interfere with function. Recurrence usually within two or three years may be expected in up to 30% of cases, largely because of the difficulty of defining the extent of and completely eradicating the disease. Occasionally, fibrous dysplasia involves the orbital region and can cause proptosis and, rarely, blindness. In such cases, early radical excision and reconstruction is required. This may be undertaken via a transcranial approach planned on three-dimensional CT reconstruction of the region.

If sarcomatous change develops, wide radical excision is indicated, as for other sarcomas.

Cherubism

Cherubism is an autosomal dominant disease (formerly known as *familial fibrous dysplasia*) with variable expressivity. Due to weaker penetrance of the trait in females, the disorder is approximately twice as common in males. Like other genetic diseases, many non-familial cases appear as a result of new mutations.

The characteristic abnormalities are multiple, symmetrical pseudocystic masses in the jaws. These form in infancy or childhood and give the face an excessively chubby or, less

frequently, a so-called cherubic appearance. Partial or complete resolution of the lesions with skeletal maturation is the general rule.

Clinically, the onset is typically between the ages of 6 months and 7 years and symmetrical mandibular swelling is the characteristic manifestation. Radiographic changes may be seen considerably earlier than the swelling of the jaws. The time of the onset of clinically evident disease and the rapidity of progress of the lesions are both variable.

Frequently, only the mandible, particularly the region of the angles, is involved. Maxillary involvement is usually associated with widespread mandibular disease and is seen in about 65% of cases. Extensive maxillary lesions cause the eyes to appear to be turned heavenward; this together with the plumpness of the face, is the cause of these patients being likened to cherubs. The appearance of the eyes is due to such factors as the maxillary masses pushing the floors of the orbits and eyes upwards, with the result that the sclera below the pupils becomes exposed. Expansion of the maxillae may also cause stretching of the skin and some retraction of the lower lids; rarely, the infra-orbital ridges may be destroyed and support for the lower lid is weakened.

The alveolar ridges are expanded and the mandibular swelling may sometimes be so gross lingually as to interfere with speech, swallowing or even breathing. Maxillary involvement can cause the palate to become an inverted V shape. Teeth are frequently displaced and may be loosened.

Despite the lack of inflammation, there is frequently cervical lymphadenopathy, due to reactive hyperplasia and fibrosis.

Radiography

The defects are usually more extensive than is clinically apparent. The angles of the mandible are bilaterally involved and the process extends towards the coronoid notch and sometimes also forwards along a considerable part of the body of the mandible. The appearances resemble multilocular cysts as a result of fine bony septa extending into the soft tissue masses. Progressive expansion of the latter reduces the bony cortices to eggshell thickness.

Maxillary involvement is shown by diffuse rarefaction of the bone, but spread of the soft tissue masses can cause opacity of the sinuses. A distinctive radiographic sign described by Cornelius and McClendon (1969) is exposure of the posterior part of the hard palate in lateral skull films, as a result of forward displacement of the teeth. In severe cases, upward bulging of the orbital floor and destruction of part of the infra-orbital ridges may be seen. Even after complete clinical resolution of the facial swelling, bone defects may be evident radiographically.

Microscopy

The soft tissue masses consist of highly cellular and vascular fibrous tissue containing many giant cells. The fibrous tissue may be loose and relatively delicate in some areas but

dense in others. Blood vessels are numerous and are typically surrounded by a cuff of eosinophilic fibrin-like material.

The giant cells have variable numbers of nuclei and may be in compact foci or scattered. There may also be small irregular bone trabeculae of which some are probably metaplastic, but others are remnants of normal bone undergoing resorption. Occasionally, epithelial remnants of teeth whose development has been aborted by the disease may be seen.

A limited biopsy of cherubism tissue may be indistinguishable microscopically from some areas of fibrous dysplasia, but overall the many giant cells and scanty bone of cherubism are in contrast with the pattern of bone trabeculae but scanty giant cells which are typical of fibrous dysplasia. More important are the clinical presentation and distinctive radiographic features. In particular, the early onset and symmetrical distribution of the lesions distinguish cherubism from fibrous dysplasia and from other giant cell lesions. A positive family history helps to confirm the diagnosis.

Management

Most cases can be allowed to progress to spontaneous resolution and the parents reassured accordingly. Exceptionally, treatment may be necessary for extensive lesions which interfere with function or are disfiguring. Surgery is the only feasible method of treatment, as the possible complications of radiotherapy in a child preclude its use. Treatment, ranging from conservative curettage, repeated as necessary, to more aggressive resection and filling the void with autogenous bone chips, has been advocated from time to time. Nevertheless, radical or conservative surgery are equally likely to be followed by recurrence and further bone destruction if carried out while the disease is still active. Any surgery should be delayed, if possible until the disease is becoming quiescent in adolescence. However, by this time, treatment may be less necessary. Moreover, residual bone lesions persisting after clinical resolution of the disease should not be interfered with as this may provoke renewed activity. Though it has been suggested that extraction of related teeth may halt jaw expansion, extractions in a case reported by Ireland and Eveson (1988) led to fungation of the giant cell tissue through the socket, despite complete clinical regression of the disease. Control of the soft tissue proliferation could be achieved only by covering it with a mucoperiosteal flap.

Paget's disease of bone

The clinical and pathological features of Paget's disease of bone (osteitis deformans) were first described in detail by Sir James Paget in 1877 (Paget, 1877).

Paget's disease is characterized by the onset in later life of anarchic osteoclastic and osteoblastic activity leading to distortion and weakening of bones. One or many bones may be affected, but though the cranium is relatively common site, the maxillofacial skeleton is infrequently and the mandible very rarely involved.

Paget's disease is common, particularly if asymptomatic cases are included. The detection rate rises with the age of the population sample and on radiographic rather than clinical signs of the disease. In a survey of over 13000 persons, Barker et al (19770 found radiographic signs of the disease in 7-8% in people aged over 55 years in several adjacent

towns in Lancashire, and an average prevalence of 5% in other counties. There was a considerably higher prevalence in men (6.2%) than women (3.9%). Smith (1992), from reported data, suggested that 0.75 million people have Paget's disease in Britain and that 5% (150000) of them have substantial disability.

Barker (1984) noted that in the USA the prevalence of Paget's disease ranged from 1.2% to 2.6% for black nd 0.9% to 3.9% for white persons over 55 years of age, and that the prevalence was low in many European countries, notably Sweden where it was only 0.4%. These variations appear to be compatible with an environmental influence such as a slow virus, superimposed on a genetic factor conferring susceptibility. A genetic component has been confirmed by Sofaer et al (1983), who found that in 13.8% of 463 patients there was a family history of the disease and in them the mean age of onset was earlier (approximately 54 years) than in sporadic cases (57 years).

In addition to a possible genetic factor, intranuclear inclusions are visible by electron microscopy in bone and other cells of Paget's disease. Immunofluorescence and *in situ* hybridization studies show these inclusions to be compatible with a paramyxovirus, such as the measles or respiratory syncytial virus which can be shown in both osteoblasts and osteoclasts. The most recently proposed candidate is the canine distemper virus, but the evidence for Paget's disease being due to a slow virus remains incomplete.

Clinical features

As noter earlier, Paget's disease is a disease of old age. It is polyostotic in approximately 90% of cases, though frequently localized to a single site initially. The bones chiefly affected (in declining order of frequency) are the lumbar vertebrae, sacrum, skull, femur, tibia, clavicle, humerous and ribs. When the skull is involved, the cranial bones, particularly the calvarium, are considerably more frequently affected than the facial skeleton and the mandible is exceptionally rarely involved.

The effects depend on the bones affected but, in general, they become thickened and larger but weaker. As a result, long bones become distorted by the stresses put on them. Increased vascularity of diseased bones may cause the overlying skin to feel warm and bone pain can be severe.

In the case of Paget's disease of the vault of the skull, the bone becomes thickened and enlarged until it may bulge forward over the face. Differentiation of the inner and outer plates is progressively lost and the diploic space becomes obliterated until ultimately a section of the skull appears grossly uniform but porous. Involvement of the temporal bone can cause deafness. Other neurological effects are compression of the VIIIth and occasionally of the optic nerve.

Involvement of the maxilla causes bulging of the central third of the face. Gross thickening of the alveolar ridges causes them to become enlarged, broad and rounded and the teeth may become spaced. Similar effects can rarely be seen in the mandible.

Paget's disease usually remains active for 3-5 years and then may become virtually static. Bone pain is often the most troublesome feature, but widespread disease can cause

high-output heart failure due to the excessive vascularity of many bones producing, in effect, an arteriovenous shunt.

Radiography

Paget's disease of the vault of the skull shows well-defined, irregular areas of abnormal radiolucency ('osteoporosis circumscripta') in the early stages. This is followed by sclerosis which is patchy at first but spreads to produce the typical cottonwool appearance.

In the jaws, the normal trabecular pattern is lost and, as in the calvarium, areas of radiolucency are followed by the development of cottonwool opacities. In the early stages, loss of the lamina dura and resorption of periapical bone may mimic infection. Later there is typically gross craggy hypercementosis and bony ankylosis.

Microscopy

The characteristic features are anarchic, apparently uncontrolled, alternating resorptive and appositional activity of bone cells with osteoclastic activity predominating at first. The result is a pattern of scalloped areas of resorption, replaced in turn by irregular, basophilic reversal lines giving a jigsaw puzzle-like ('mosaic') pattern, when apposition follows. In the active stages, rimming of the bone by numerous osteoclasts and osteoblasts is conspicuous. The osteoclasts are frequently abnormally large with an excessive number of nuclei. Later, these cells become scanty but the jigsaw puzzle pattern of reversal lines persists. In addition, the bone marrow is replaced by highly vascular, loose connective tissue and in widespread disease extramedullary haemopoiesis may result.

Biochemistry

Blood calcium and phosphate levels are typically normal, but the alkaline phosphatase levels are higher than in any other disease and can be as high as 700 u/L. Hypercalcaemia can result from the patient having become immobile or bedridden. Urinary hydroxyproline levels are raised during active, resorptive phases.

Management

Treatment is not indicated for asymptomatic cases. Aspirin or other anti-inflammatory analgesics may be effective for pain. In more severe cases, calcitonin can be given particularly for bone pain, to lessen any neurological complications or for hypercalcaemia. Though effective for these purposes, calcitonin is unlikely to improve the skeletal lesions and formation of neutralizing antibodies may limit its benefits. Salcatonin is less immunogenic, but does not remove the risk. Biphosphonates, particularly disodium etidronate, are adsorbed on the hydroxyapatite crystals to slow their growth and resorption. The rate of bone turnover is slowed as a consequence and the biochemical abnormalities usually return to normal. Toxic effects of biphosphonates include nausea and diarrhoea: in high doses they may worsen bone pain and increase the risk of fractures.

Giant cell tumours in areas of Paget's disease occasionally develop in the skull or facial skeleton. Their behaviour is similar to that of central giant cell granulomas and they

also respond to conservative curettage. Sarcoma in Paget's disease is well recognized, with an estimated incidence of 0.1-1%, but there are few authenticated cases involving the jaws. Both giant cell lesions and sarcomas develop much later in life than in otherwise normal persons.

Oral complications include difficulty with dentures and bleeding or infection of the bone, particularly as a result of attempted extraction of grossly hypercementosed teeth.

Hyperparathyroidism

Hyperparathyroidism can be primary or secondary and results from overproduction of parathyroid hormone. This raises the blood calcium level, partly by bone resorption, but there is also increased calcium absorption from the gut and renal reabsorption. Bone resorption may not therefore be seen in early cases and significant bone lesions are now rarely seen in hyperparathyroidism.

Approximately 80% of cases of primary disease are due to a parathyroid adenoma, while the remainder are due to hyperplasia or, more rarely, carcinoma of the gland. Even more rarely, hyperparathyroidism can be a manifestation of the multiple endocrine neoplasia syndromes, either type I or II.

Secondary hyperparathyroidism is a reaction to a persistent hypocalcaemia due to chronic renal failure or prolonged renal dialysis, or rarely to malabsorption.

Clinically, the diagnosis is made in the majority of patients from biochemical screening, either as a chance finding or for the investigation of gastrointestinal symptoms, renal stones, hypertension, fluid retention, stiffness or other musculoskeletal symptoms or psychiatric disorders. In the elderly, symptoms of hypercalcaemia are more common and cause dehydration, with thirst and nocturia, anorexia, vomiting or constipation, and confusion or depression. In secondary hyperparathyroidism, bone disease is common but renal stones relatively uncommon.

Localized bone lesions ('osteitis fibrosa cystica') can cause pain, deformity or pathological fractures. However, jaw lesions, a well-recognized feature in the past, can be painless or cause localized swellings. Rarely, jaw lesions have been the first sign of the disease. Even more rarely, hyperparathyroidism can give rise to a soft tissue lesion similar both clinically and microscopically to a giant cell epulis.

Hyperparathyroidism can cause lethal renal damage. Accurate diagnosis of a giant cell lesion of the jaw is therefore essential. Hyperparathyroidism should particularly be suspected in a patient of a middle age or over. In such patients, blood biochemistry and possibly parathormone assay must be carried out. In doubtful cases, this may be supplemented by a skeletal survey, starting with the fingers.

In patients with carcinoma of the breast or lung there may be bone metastases which can mimic Paget's disease radiographically. However, in carcinoma of the lung the biochemical findings can also be similar to those of primary hyperparathyroidism. A chest radiograph may therefore be required.

Secondary hyperparathyroidism may be seen in a child: in such a case the history of renal disease will suggest the diagnosis. Rarely, a jaw lesion due to secondary hyperparathyroidism may be an early sign of rejection of a kidney graft.

Radiography

The most characteristic change is generalized osteoporosis. Localized bone lesions appear as moderately well-defined, cyst-like areas often with a multiloculated pattern. These may be associated with other bone lesions such as resorption and tufting of the terminal phalanges, or cyst-like areas of bone resorption in the cranial vault or long bones. Disappearance of the lamina dura of the teeth is inconstant and an unreliable sign. The nature of the jaw lesions is unlikely to be recognized until after microscopy.

Microscopy

The bone lesions appear grossly as soft, livid masses which are typically brown due to altered blood (brown tumours). Microscopicatlly, they are non-specific giant cell lesions which can be distinguished from giant cell granulomas of the jaws only by blood chemistry. Some lesions consist predominantly of fibrous tissue.

Management

Blood for calcium levels must be taken from a fasting patient and, to avoid venous stasis, without a tourniquet. The level should be related to the serum albumin level and venepuncture may need to be repeated several times as elevation of serum calcium may only be intermittent. The reference range for albumin-adjusted serum calcium is 2.20-2.65 mmol/L, but 2.20-2.70 mmol/L for women aged over 69 years. Hypophophataemia is frequently but inconstantly associated. Alkaline phosphatase levels are raised in proportion to the extent of the bone disease. Immunoassay of parathormone is sometimes necessary, but the levels in hyperparathyroidism overlap with the normal range and the level is also raised in renal failure.

Other causes of hypercalcaemia must be excluded, particularly the considerably more common hypercalcaemia secondary to tumours of the lungs, breast and other sites, or myeloma. The biochemical findings are the same of those of hyperparathyroidism, but the hypercalcaemia usually responds to corticosteroids. Other possible causes of hypercalcaemia include sarcoidosis, thyrotoxicosis, immobility and milk-alkali syndrome. However, these should not cause confusion in a patient with a giant cell lesion of the jaw.

In primary hyperparathyroidism, removal of the parathyroid adenoma is curative, though the tumor may be difficult to find. This is the required treatment for those with bone lesions and particularly for those with renal complications of the disease. For those without symptoms, where hypercalcaemia has been a chance finding, prolonged follow-up shows an unexpectedly favourable outcome without surgery.

For those with secondary hyperparathyroidism, treatment of the underlying renal disease, and if possible a renal transplant, is necessary.

Idiopathic osteosclerosis (solitary bone islands)

These foci of abnormal bone density have been thought in the past to result from chronic inflammation (Chapter 2).

Massive osteolysis (phantom bone disease)

Massive osteolysis is a rare disease which sometimes affects the maxillofacial bones. Frederiksen et al (1983) reviewed 14 cases and added another. The cause is unknown and no genetic or biochemical abnormalities have been found.

The onset can be at any age, but appears to be most frequent in young adults. When the maxillofacial bones are affected, the mandible appears to be first and most severely affected and the first symptoms are usually loosening and exfoliation of teeth or there may be spontaneous fracture of the mandible.

Radiography

Early signs may be subcortical foci of radiolucency with indistinct margins. These coalesce and involve the cortex. The mandible can be progressively resorbed along its whole length from the alveolar ridge downwards, until only the lower border and the ramus remains, but even these may disappear. Heffez et al (1983) reviewed 43 earlier cases and reported, in a 13-year-old boy, resorption of the mandible from condyle to symphysis, the posterior zygomatic arch, the hyoid bone, the lower thirds of the pterygoid plates, the mastoid tip, the occipital bone and the lateral aspect of the middle cranial fossa. Nine months later the maxilla and other bones, including the cervical vertebrae, were affected.

Microscopy

The main features are dilated vascular channels, active osteoclastic resorption at the interface with normal bone and fibrous tissue proliferation.

Management

Massive osteolysis may have to be distinguished from haemangioma of the jaws or the osteolysis that occasionally complicates systemic sclerosis. No reliably effective treatment for idiopathic osteolysis is known, but the disease may be self-limiting. Frederiksen et al (1983) replaced the lost mandibular tissue with a rib graft, but this too was almost completely resorbed and had to be removed. Two years later the disease was still active. By contrast, in the patient reported by Heffez et al (1983) with more extensive disease, a CT scan taken a year after presentation showed stabilization and partial recalcification of osteolytic foci in the mandible and vertebrae. A short course of radiotherapy had been given, but it is not clear whether it was of any benefit.

Management is therefore essentially palliative with regular CT scanning to check progress and treatment of complications as they arise.