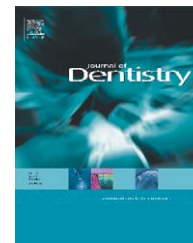


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Systemic disorders and their influence on the development of dental hard tissues: A literature review

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ABSTRACT

Objectives: This report highlights the influence of a number of disorders with systemic physiological effects that impact on the development of dental hard tissues. It focuses in particular, on the pathological effects of systemic conditions with less well recognised, but no less important, impacts on dental development. Such conditions, include cystic fibrosis, HIV/AIDS, leukaemia, Alstrom syndrome, hypophosphatasia, Prader-Willi syndrome, Tricho-dento-osseous syndrome, tuberous sclerosis, familial steroid dehydrogenase deficiency and epidermolysis bullosa. These, along with developmental and environmental causes of enamel and dentine defects, are discussed and the possible aetiology of such effects are proposed. Furthermore, the dental management and long-term dental care of these patients is outlined.

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Conclusions: Enamel and dentine defects can present with a wide spectrum of clinical features and may be caused by a variety of factors occurring throughout tooth development from before birth to adulthood. These may include host traits, genetic factors, immunological responses to cariogenic bacteria, saliva composition, environmental and behavioural factors and systemic diseases. These diseases and their spectrum of clinical manifestations on the organs affected (including the dentition) require an increased knowledge by dental practitioners of the disease processes, aetiology, relevant treatment strategies and prognosis, and must encompass more than simply the management of the dental requirements of the patient. It is important that the impact of the disease and its treatment, particularly in respect of immunosuppression where dental interventions may become life-threatening, is also taken into consideration.

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1. Introduction

Normal dentition develops from the dental lamina originating from a string of epithelial cells in the oral ectoderm during the first months of embryonic development. In each jaw 10 tooth buds corresponding to the deciduous teeth then develop. By the end of the seventh month *in utero* the development of all tooth buds is complete and the formation of their hard tissues

(enamel and dentine) begins. The development of the permanent incisors and premolars is initiated in the fifth month *in utero* and lasts to the tenth month after birth with the development of the permanent molars continuing through the first years of life. More importantly, the developing tooth bud has been shown to be sensitive to a wide range of systemic disturbances and, enamel particularly, is generally unable to recover once it is damaged.¹ Consequently enamel defects can

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be caused by numerous factors occurring throughout the development of the teeth from before birth to adulthood. These may include host traits, genetic factors, immunological responses to cariogenic bacteria, saliva composition, environmental and behavioural factors and systemic diseases.^{2,3}

The extensive variety of factors which can affect the development of hard tissue within the mouth means that defects in enamel and dentine can present with a wide spectrum of clinical features. These may be generalised and seen in many teeth or the whole dentition or localised to one or two teeth. In addition, the defects may affect one surface of the enamel or be evident throughout its full thickness, and may be symmetrical or asymmetrical across the midline of the dentition. Furthermore, defects such as differences from the normal appearance, colour and texture of the tooth, altered translucency and pitting, grooving or missing enamel may result from very different causes including hypomineralisation, growth reduction, hypoplasia or dysplasias and drug treatments.

Systemic disorders which affect the formation and development of dental hard tissue as part of, or secondary to, the disease process may be very complex and have many varying effects on different organs within the individual. They can generally be divided into primary or secondary systemic disorders. Primary disorders are classified as originating or affecting several organs right at the outset of the disease and include genetic, hereditary and developmental diseases. Secondary disorders may be triggered by a particular event such as changes in hormone levels, trauma, onset of a disease and viral infections. These diseases and their spectrum of clinical manifestations on the organs affected (including the dentition) necessitate an increased knowledge by dental practitioners of the disease processes, aetiology, relevant treatment strategies and prognosis, and must encompass more than simply the management of the dental requirements of the patient.

This review focuses on the effect of systemic disease on the incidence and extent of damage in dental hard tissues and on relevant treatment needs of patients.

2. Systemic disorders affecting dental hard tissue development

2.1. Cystic fibrosis

Cystic fibrosis (CF) is the most common lethal autosomal-recessive disease in the Caucasian population.⁴ It is characterised by a severely altered function of the absorbing and secreting epithelia due to abnormal water and electrolyte transport and pH regulation, and stems from a mutation of the cystic fibrosis transmembrane regulator protein (CFTR).^{5,6} These defects result in a chronic disease of the respiratory and gastrointestinal systems, elevated sweat electrolytes, impaired reproductive function, retarded growth and development with delays in dental and skeletal maturation.^{5,7,8} Clinical symptoms of the disease can range from few or no diagnostic symptoms to the full range, although the diagnostic criteria for CF includes a sweat chloride level greater than 60 meq/L and at least two of the following symptoms: chronic

obstructive pulmonary disease, exocrine pancreatic insufficiency or a familial history of CF.⁹

Once diagnosed, most CF sufferers respond well to nutritional therapy of a high calorie, high fat diet including pancreatic enzymes replacement therapy and vitamin supplementation, and infant formulas comprising of protein hydrolysates and medium chain triglycerides used during the first years of life. High sugar foods are often consumed in order to maintain the increased calorific intake needed. Appropriate antibiotics, including penicillins, cephalosporins or trimethoprim-sulfa formulations, are used to combat the respiratory infections associated with CF.^{5,10}

The delays in dental and skeletal maturation observed in CF patients are adequately treated by ensuring an appropriate nutritional intake and are often resolved if survival to the second or third decade of life occurs.⁵ Due to the high sugar containing food consumed by CF patients in order to maintain their elevated calorific and salt intake, it might be assumed that the caries incidence among these patients may be higher. However, the caries incidence has been reported to be lower in CF patients than in an age-matched healthy population, with less dental plaque and gingivitis, though increased enamel defects (opacities) have been observed in CF children.^{8,11,12} It has been suggested that the reduced caries rate may be related to the effects of long-term antibiotic, pancreatic enzyme replacement therapy and patient awareness on the extent of oral microbacteria. In addition, CF is associated with pathological effects on the major salivary glands primarily associated with duct obstruction, and a saliva composition showing elevated levels of calcium, higher mean pH and increased buffering capacity.^{5,13} This higher calcium content and buffering capacity may provide an additional explanation for a reduction of dental caries which favours tooth remineralisation and is consistent with the observed increased prevalence of dental calculus on the teeth.^{5,12,13}

Many CF patients have been reported to present with a higher frequency of enamel hypoplasia (ranging from 5% to 44%) than the healthy population; this may be attributed to the disease itself or be a consequence of treatment.^{11,12,14} Many of the early oral manifestations associated with CF were related to the use of antibiotics, in particular tetracycline therapy, where high incidences of tooth discolouration (24%) and hypoplasia (25%) have been reported.^{8,15} This prompted the use of alternative antibiotics with a resultant reduction in the enamel defects associated with tetracycline therapy. With respect to the other enamel defects observed in patients with CF, it remains unclear which relate to the management of disease and which relate to the disease process itself. Mineral analysis of the enamel of the teeth of CF patients have indicated equivalent levels of zinc and phosphorus but decreased levels of calcium when compared with healthy individuals.^{16,17} In addition, CFTR has been shown to regulate the carbonic acid buffer system which plays a pivotal role in pH regulation within numerous tissues and cells and has been proposed as the main buffering system in developing enamel.^{6,18} The regulation of pH has been shown to be essential for apatite deposition, crystallite growth, proteinase optimisation and function of ameloblasts within the developing enamel. Studies in a transgenic CFTR knockout mouse (CF mouse), proposed as a model for CF in humans,

demonstrated a clear role for CFTR function in pH regulation during the maturation phase of enamel formation, particularly in the mouse incisor.⁶ It was shown that calcium was present in distinct bands within the normal mouse incisor corresponding to areas of neutral pH which were absent from the CF mouse incisors. In addition, normal mouse enamel matrix pH was generally higher and modulated differently than the CF mouse enamel. It has been postulated that a reduced pH results in a lack of calcium influx during enamel maturation and hypomineralisation in CF.⁶

Further molecular studies using the transgenic CF mouse have clearly shown that the CFTR gene is expressed in developing teeth and other mineralised tissues and is associated with abnormal development of incisors.¹⁹⁻²³ Wright et al.^{22,23} showed that all CF mice had soft, chalky white incisor enamel compared to hard, yellow-brown in normal mice. They exhibited premature degeneration of ameloblasts with increased retention of enamel matrix proteins and a decreased mineralisation of the enamel. Further studies, using energy-dispersive X-ray spectroscopy, demonstrated decreased chloride in the secretory stage CF enamel, with increased iron and potassium and decreased calcium in the CF mature enamel indicating a critical role for CFTR in enamel formation.¹⁹ Gawenis et al.²⁰ concluded that CFTR played a pivotal role in continuously growing incisors but could demonstrate no role for CFTR in the mineralisation of molars or bone in CF mice. They further concluded that the multiple changes in the mineral composition of CF incisors suggested an indirect role for CFTR in several functions such as maintaining the normal salivary environment. Interestingly, they showed that the iron content of CF mouse incisor was markedly reduced, in contrast to the results reported by Arquitt et al.¹⁹ and may explain the differences in pigmentation seen between normal and CF mouse teeth. Differences in the methods employed in taking the measurements may account for some of these discrepancies. Nevertheless, the complexity of the processes and the need for more studies to clarify the role of CFTR in the formation of hard tissues within the mouth are clearly demonstrated.

The complexity of the processes controlling development of the hard tissues in the CF patient emphasises the need for regular and frequent dental care allowing the reduction in the suffering and medical costs associated with treating this disease. In addition, the increased prevalence of enamel defects and calculus accumulation reinforces the need for early involvement of paediatric dentists in the management and long-term care of these patients.

2.2. Human immunodeficiency virus/acquired immune deficiency syndrome

Oral manifestations of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome (AIDS) are, generally, a feature of disease progression and occur in approximately 30-80% of the affected population. Factors which have been shown to predispose patients to oral manifestations include low CD4 T cell levels, high viral load, xerostomia, poor oral hygiene and smoking.²⁴⁻²⁶ Oral lesions can be differentiated as fungal, bacterial or viral infections, neoplasms such as Kaposi's sarcoma and non-specific pre-

sentations such as aphthous ulcerations and salivary gland disease.

Studies investigating the prevalence of oral lesions in HIV/AIDS patients have reported cases of angular cheilitis in approximately 29% of patients, parotid gland bilateral enlargement, erythematous candidiasis and pseudomembranous candidiasis in approximately 18% of patients, and conventional gingivitis in approximately 13% of patients. In addition, herpes simplex virus infections, hairy leukoplakia, recurrent aphthous ulcers and condyloma acuminatum have been seen in up to 6% of patients.^{26,27} Although enamel hypoplasia was seen in 24% of patients in one study, the authors concluded that this could not be attributed specifically to HIV infection, but other factors such as oral hygiene.²⁷ In addition, a study investigating alveolar bone loss in HIV and AIDS patients compared to matched controls concluded that smoking but not HIV status was the primary factor involved in the alveolar bone loss, further emphasising the complexity of assessing the disease and its effects in HIV/AIDS patients.²⁸

Nevertheless, since the advent of highly effective antiretroviral therapies the overall prevalence of oral manifestations in HIV patients decreased significantly from 47.6% to 37.5%, with decreases primarily in hairy leukoplakia and necrotising periodontal disease. No significant decreases were seen in oral candidiasis, aphthous ulcers, herpes simplex virus lesions and Kaposi's sarcoma. However there was an increase in HIV associated salivary gland disease from 1.8% to 5.0% with associated xerostomia and incidence of oral warts.^{25,26}

Xerostomia is a common complaint of HIV patients and can be caused by a number of factors including salivary gland disease, high viral loads, smoking and HIV medications.^{25,29} The change in quantity and quality of saliva may, in turn, lead to increased dental decay and therefore meticulous oral hygiene is critical in reducing and/or preventing oral disease in these patients.

Treatment of oral diseases in HIV/AIDS patients is reportedly very low, adding to the difficulties in accessing information about the management of some of the more common manifestations of the disease and the differentiation of one manifestation from another.^{30,31} Effective dental management, however, is fundamental to the overall care and health of these patients. Significant advances in understanding the pathogenesis and progression of this disease will ultimately lead to improved care of this patient population.

2.3. Leukaemia

Many dental manifestations of leukaemia have been reported, including delayed dental development, hypoplasia, agenesis, V-shaped root and shortened root, taurodontia, mucosal pallor secondary to anaemia, microdontia, odontalgia, ulceration of the palate, gingival bleeding, gingivitis, petechiae and ecchymoses of the hard and soft palate, tongue and tonsils.³²⁻³⁵ In addition, chemotherapy-induced mucositis and infections, including herpes simplex ulcers and oral candidiasis are commonly observed complications of leukaemia in the oral cavity.^{33,34} Gingival hyperplasia secondary to leukaemia cell infiltration and xerostomia caused by chemotherapy are other noteworthy manifestations.³⁴ Pallor, spontaneous haemorrhage, petechiae and ulceration have been described to occur

more frequently in acute than chronic leukemia.³⁵ Gingival hyperplasia is, generally, more common in acute than chronic leukaemia, in adults and in people with “aleukaemia” or “subleukaemic” forms of leukaemia.³⁶ Nonetheless, the development of gingival infiltration is unpredictable, though leukaemia cell gingival infiltrate is not observed in edentulous individuals, suggesting that local irritation and trauma associated with the presence of teeth may play a role in the pathogenesis of this abnormality.³⁶

Conflicting results have been reported on the caries profile of children treated for malignant disease. An increased rate of dental caries has been reported in some studies where more mild opacities were observed in patients receiving combination chemotherapy for malignant disease compared to controls.^{32,37,38} Other studies have reported no difference in dental caries between treated children and their siblings, though significantly more dental anomalies were detected radiographically in the chemotherapy treated group.³⁹ The long-term effects of bone marrow transplantation for leukaemia showed a negative impact on missing or filled permanent teeth (DMFT) index based on multiple post-bone marrow transplantation factors with age as a crucial factor in determining the developmental defect of enamel and root.⁴⁰ This study and others highlight the difficulties for dental practitioners in diagnosing and treating the impact of the disease and its treatment on the development of both deciduous and permanent dentition. It is, therefore, important for a dental practitioner to take into consideration the impact of the disease and its treatment, particularly in respect of immunosuppression where dental interventions may become life-threatening. In general, surgery should be avoided. However dental extractions of carious teeth prior to immunosuppressive therapy may be necessary, as the risks of bacterial infection may outweigh the risks associated with surgical procedures.

New cutaneous lesions, oral or otherwise, are often the initial physical finding that leads to a diagnosis of leukaemia and, in particular, in a patient with known myeloproliferative disease, these findings often herald the development of a more aggressive disease with a poorer prognosis. Therefore, it is important for dentists and physicians to recognise mucocutaneous manifestations of systemic malignancies and to provide the necessary care at all stages of the patients' treatment.⁴¹

2.4. Alstrom syndrome

Alstrom syndrome is a rare autosomal recessive inherited disorder characterised by progressive blindness, deafness, early-onset type 2 diabetes mellitus, obesity, and short stature.⁴² The mutated gene, *ALMS1*, which must be inherited from both parents, was identified, though little is known about how this gene causes the disorder.⁴³ There is limited information available on this disorder due largely to its rarity and only one report summarising the oral findings from two cases of Alstrom syndrome from the same family.⁴⁴

In one report the oral findings from two patients aged 14 and 20 years, both with physical and clinical characteristics consistent with Alstrom syndrome, showed the presence of gingivitis with poor oral hygiene. Both had missing or decayed teeth with radiographs revealing vertical and horizontal

alveolar bone loss. In addition, light yellow-brown discoloured enamel bands were observed on the anterior teeth which were characteristic of a moderate form of systemic band-like enamel hypoplasia. Interestingly, this appeared to correlate with tooth development which occurred between 2 and 3 years of age since both siblings showed the same growth lines within the same limited area of the crowns of permanent teeth. This suggests that the enamel hypoplasia was associated with an aetiological factor of the syndrome itself which caused the abnormality at the same age and same stage of tooth formation.

Numerous studies have shown that diabetes mellitus can directly affect the mineralisation and development of bone and teeth with reduced mineralisation and defects in teeth observed in children of diabetic mothers, diabetic adults and in animal studies.^{45–50} Since it has been shown that Alstrom syndrome is associated with early-onset diabetes mellitus, it may be reasonable to postulate that the presence of diabetes mellitus secondary to the syndrome itself may also have an effect on patient dentition.^{42,51} Although the exact mechanism whereby diabetes affects hard tissue development is as yet unclear, there is a suggestion from studies using animal models that diabetes may disrupt the mineral composition in teeth and the normal process of amelogenesis.^{46,47}

Further reports of oral findings from patients with this syndrome are required in order to consolidate the findings to date and to assist dental practitioners in the management of these patients.

2.5. Hypophosphatasia

Hypophosphatasia is an inherited metabolic bone disease that results from a deficiency of the enzyme alkaline phosphatase (ALP) in the bone and serum.^{52–54} It is one of several disorders that resembles osteogenesis imperfecta and is characterised by defective bone and teeth mineralisation with premature loss of dentition. It is caused by abnormalities in the ALP gene leading to the production of inactive ALP protein.^{55–57} Subsequently, several chemicals, including phosphoethanolamine, pyridoxal 5'-phosphate (a form of vitamin B6) and inorganic pyrophosphate, accumulate in the body and are found in large amounts in the blood and urine. It appears that the accumulation of inorganic pyrophosphate is the cause of the characteristic defective calcification of bones seen in infants and children (rickets) and in adults (osteomalacia).^{52,54,55} The severity of hypophosphatasia is variable, ranging from the most severely affected failing to form a skeleton in the womb resulting in stillbirth to mildly affected patients showing only low levels of ALP in the blood with no bone problems. In general, patients are categorised as having perinatal, infantile, childhood or adult hypophosphatasia depending on the severity of the disease and the age at which the bony manifestations are first detected. In addition, odontohypophosphatasia is a disease in which children and adults have only dental, not skeletal, problems, usually involving premature loss of teeth and/or wide pulp chambers that predisposes them to cavities and dental caries.^{52,53,58,59} The clinical forms of this disease tend to have different modes of history and presentation. However, both autosomal recessive and autosomal dominant patterns of inheritance have

been demonstrated for the childhood, adult and odontohypophosphatasia forms.^{52,53,56,57,60}

One of the main characteristics of all forms of hypophosphatasia is the loss of dentition. In particular, premature loss and changes in the deciduous teeth and/or severe dental caries have been reported and remain, along with low levels of ALP, one of the main diagnostic features of hypophosphatasia.^{56,59–61} In general the anterior deciduous teeth are more likely to be affected and the most frequently lost are the incisors. In addition, dental X-rays show reduced alveolar bone and enlarged pulp chambers and root canals.^{62,63} Histological analysis suggests that lack of cementum may be the cause of the premature tooth loss.^{56,59} Comparison of teeth from children with hypophosphatasia with normal controls showed that both acellular and cellular cementum was affected, though no differences were observed in the mineral content of dentin.⁵⁹ Further analysis for the expression of pyrophosphate (an inhibitor of mineralisation) and other enzymes related to pyrophosphate metabolism in pulp and periodontal ligament suggested that mineralisation of cementum was more likely to be under the influence of the inhibitory effect of pyrophosphate than mineralisation of dentin. It has also been reported that dental effects of hypophosphatasia first diagnosed in primary teeth can also be seen in the permanent dentition.⁵⁸ Both histological and radiological changes, with a reduced level of marginal alveolar bone supporting the upper central incisors, large coronal pulp chambers in the molars, abnormal root cementum and dentin resorption and mineralisation disturbances have been observed in a young man with hypophosphatasia.⁵⁸

It is clear that moderate forms of hypophosphatasia are highly variable in their clinical expression, owing in part to allelic heterogeneity but also to other factors that remain undetermined at this time. Nevertheless, the effect of this syndrome on the dentition remains one of the main diagnostic features and emphasises the critical role of the dental practitioner in treating this condition and the need for effective counselling of affected families.

2.6. Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a genetic disorder that occurs in approximately 1 in every 15,000 births and is caused by a dysfunction of the hypothalamus. PWS is now thought to occur through a lack of active genetic material in chromosome 15.⁶⁴ A deletion in part of this chromosome has been shown to occur in about 70% of patients, with another 30% or so of cases thought to occur through receiving both chromosomes from one parent rather than one from each parent.⁶⁴ It affects males and females with equal frequency and all races and ethnicities, and is recognised as the most common genetic cause of obesity. The main features of PWS include infantile hypotonia, mental retardation with behavioural abnormalities, developmental delays, hypogonadism and marked obesity. Patients usually have a short stature, are obese with insatiable appetites and have small hands and feet with tapered digits. They often present with secondary symptoms such as diabetes, somnolence, feeding difficulties, respiratory problems and scoliosis.⁶⁵ The main orofacial features of patients with PWS are a narrow frontal lobe with almond-

shaped eyes often with up-slanting palpebral fissures, strabismus, triangular mouth and prominent forehead.^{66–68}

The major dental findings in PWS patients have been reported to be enamel hypoplasia and rampant caries with delayed eruptions and poor oral hygiene.^{64,66,67,69} Other features which have been reported include micrognathia, xerostomia, hypodontia and supernumerary teeth.^{69,70} Although several studies have reported that the saliva in PWS patients is thick and sticky with a high viscosity and foaminess, no systematic investigations of salivary flow rate, buffering capacity or mineral content of saliva have been performed.^{67,68,70} Nevertheless it is likely that salivary dysfunction accounts for the high prevalence of caries, severe enamel loss and dental erosions. This coupled with consumption of highly acidic drinks, occlusal parafunction and poor toothbrushing habits may predispose PWS patients to increased tooth wear. Normal salivation has been shown to be critical in protecting teeth against the acidic factors that initiate dental erosion through its buffering capacity, clearance by swallowing, pellicle formation, and remineralisation of demineralised enamel.

Since patient compliance may sometimes be an issue due to the mental and behavioural problems associated with PWS, dental treatment strategies may, through necessity, require a broad based approach to the issues of oral hygiene, diet, and care of teeth. In addition, the generalised caries which leads to almost complete destruction of the teeth may require a prolonged and extensive programme of treatment involving orthodontic, surgical and restorative procedures.^{66,67}

2.7. Tricho-dento-osseous syndrome

Tricho-dento-osseous (TDO) syndrome is a rare, congenital, multisystem disorder belonging to a group of diseases called ectodermal dysplasias, which typically affect the hair, teeth, nails and/or skin and bones. TDO syndrome is characterised by kinky hair, thin and brittle nails, tooth enamel defects, increased thickening and/or denseness (sclerosis) of the calvaria and/or long bones of the arms and legs.^{71–73}

Individuals with TDO syndrome have been shown to exhibit several dental abnormalities that affect both the primary (deciduous) and secondary (permanent) teeth. Several studies have shown that both primary and secondary teeth of these patients can be abnormally prism-shaped with the majority of permanent teeth having an enlarged pulp chamber termed taurodontia.^{74–76} In addition, all the teeth from affected individuals exhibited some degree of decreased enamel thickness compared to control teeth ranging from no enamel to about 60% the thickness of normal teeth.^{75,76} In general, decreased enamel thickness was most severe in the primary teeth with a lesser degree seen in the secondary teeth. Light microscopy and electron microscopy studies of TDO teeth have shown pitting of the enamel surface, extensive enamel hypoplasia with no or limited prism formation. In contrast, dentine appeared structurally normal.^{75,76} Associated with the enamel hypoplasia, several studies have demonstrated hypomineralisation with between 65 and 75% diminution in calcium (hypocalcification) and phosphorus in TDO enamel compared to controls.^{71,75,77} As a result, the tooth

enamel may be abnormally thin, soft, pitted and discoloured with short and open roots leaving the teeth highly prone to dental caries and infection. In some cases, affected individuals also exhibit widely-spaced teeth, absence of teeth, premature or delayed tooth eruption, or secondary teeth which become impacted in the gum. Many individuals lose their teeth early, typically in the second or third decade of life.^{71–73}

Dental abnormalities associated with TDO syndrome may be detected using specialised procedures such as electron microscopy to reveal the extent of enamel hypoplasia and pitting within the enamel, and treated with a variety of techniques. Regular X-rays are important to monitor dental development with respect to premature or delayed tooth eruption, to detect impacted secondary teeth, and to help prevent, detect and/or treat other dental abnormalities. A variety of procedures may be used to restore improperly developed teeth to help prevent decay, abscess formation and/or tooth loss. Artificial teeth or other prosthetic devices may be used to replace lost or absent teeth, with dental surgery or other corrective techniques used to correct other dental abnormalities.

Many of the dental abnormalities and other features associated with TDO probably occur as a result of a genetic defect at the molecular level in common developmental pathways for bone, teeth and hair. Spangler et al.⁷⁵ have postulated that the life cycle or function of the ameloblasts may be particularly affected during the development of the primary and secondary dentition, accounting for the enamel hypoplasia and hypomineralisation seen in TDO patients. Certainly, this syndrome emphasises the need for a broad knowledge of the disease and its affects by dental practitioners and the requirement for further studies, particularly since the dental abnormalities appear to be the most consistent feature in TDO patients.⁷³

2.8. Tuberos sclerosis

Tuberous sclerosis (TSC) is a rare genetic disease that causes benign tumours to grow in the brain and in other vital organs such as kidney, heart, eyes, lung and skin. It affects the nervous system and is associated with epilepsy, mental retardation, angiofibromas, along with skin and oral manifestations. The reported incidence of TSC ranges from 1 in 100,000 to 1 in 1,000,000 individuals, with a varied spectrum of symptoms and mild to severe disabilities.⁷⁸

Several studies have investigated the incidence and extent of enamel pitting in TSC patients and have postulated that numbers of pits, particularly in permanent teeth, may be a helpful adjunct in diagnosing TSC.^{79–82} Mlynarczyk⁸⁰ demonstrated 100% enamel pitting in the adult dentition of TSC patients compared to 7% of a control group using a dental disclosing solution swabbed onto dry teeth. In addition, Lygidakis and Lindenbaum⁷⁹ demonstrated that 71% of persons with TSC and asymptomatic relatives had multiple pits compared to minimal numbers in controls. Although these observations were confirmed in a study by Flanagan et al.⁸³ in which 100% of TSC patients had enamel pitting compared to 65% of relatives and 72% of controls, they suggested that the presence or absence of enamel pits was not a useful screening test for first degree relatives since large and

small pits were seen in all groups, although none of the relatives were shown to carry the TSC gene.

In respect of the dental care of patients with TSC, mental retardation may lead to problems with patient compliance and necessitate the use of deep sedation or general anaesthetic to ease oral examination and evaluation.⁷⁸ This in turn can lead to complications due to the presence in many TSC patients of pulmonary fibrous degeneration, kidney and cardiac lesions. In addition, the high incidence of enamel pits within this population may suggest a higher likelihood of caries development. Therefore periodic preventive measures, along with improved oral hygiene are important in the management and prognosis of these patients.

2.9. Familial steroid dehydrogenase deficiency

This condition arises from a rare autosomal recessive inherited liver disease caused by abnormal bile acid synthesis from cholesterol due to a deficiency in the enzyme 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase which leads to chronic liver disease in childhood as well as malabsorption of fats and fat soluble vitamins.^{84,85} Due to the rarity of this condition and the variability of the phenotype, only one study has reported on the incidence and extent of dental aberrations.⁸⁶ This study showed an increased incidence of numerical (supernumerary) and structural (hypomineralisation and enamel hypoplasia) dental abnormalities linked to the presence of the autosomal inherited liver disease within first cousin-marriages in Saudi Arabia.⁸⁶ Severe dental caries in combination with enamel hypoplasia with four supernumerary permanent tooth buds were observed in one subject at 4 years of age, which by 9 years had increased to 11, along with superficial enamel hypoplasia and general hypomineralisation. Treatment of the liver defect with large doses of chenodeoxycholic acid and Vitamin A did not account for the dental abnormalities, as treatment was started after the dental defects were diagnosed. The presence of supernumerary teeth may therefore result from the same genetic defect as the liver disease, with the observed enamel defects possibly resulting from either accumulating toxic cholesterol metabolites or deficiencies of fat soluble vitamins in early childhood.⁸⁶ This condition represents a new association of dental defects with a genetically inherited syndrome.

2.10. Epidermolysis bullosa

Epidermolysis bullosa (EB) is a diverse, heterogeneous group of conditions characterised by fragility of the skin that results in blisters caused by little or no trauma.^{73,87,88} Three main types have been classified dependent on the histological level of tissue separation: epidermolysis bullosa simplex (EBS) is characterised by discontinuities in the epithelial keratinocyte layer, epidermolysis bullosa junctionalis (EBJ) is characterised by separation within the basement membrane, and, finally epidermolysis bullosa dystrophica (EBD) is characterised by discontinuities in the underlying connective tissue.^{87,88}

The digestive mucosa, including the oral mucosa is one of the most frequently affected regions in this syndrome causing problems with feeding and marked oral fragility. In particular, junctional and dystrophic EB can be associated with marked

soft tissue scarring and alterations in the development of hard and soft tissues of the mouth.^{73,88}

The teeth of affected individuals have been shown to have thin enamel with localised or generalised enamel hypoplasia and defects such as pitting and furrowing, which in turn can predispose EB patients to an increased incidence of dental caries. Minor enamel defects have been shown to occur in all EB subtypes, with the most substantial occurring in the EBJ subgroup.^{87–90} All patients with EDJ have been reported to present with defects in enamel, whereas the prevalence of defects in EBS and EBD was similar to that of the control population (27%), suggesting that the mechanism causing damage to enamel may be very different between the three subtypes.⁸⁸ In addition, Wright et al.⁸⁸ reported that the incidence of dental caries was increased in patients with EBJ and EBD. Studies into the chemical composition of enamel from EB patients, in terms of mineral content, carbonate content, protein content and amino acid composition, have reported essentially normal enamel chemistry in EBD patients whereas EBJ enamel contained a significantly reduced mineral per volume content, which resulted in enamel hypoplasia.^{87,89} The high caries incidence in EBD patients may be related to other factors such as compromised oral hygiene, whereas in EBJ patients the enamel is developmentally compromised and associated with the genetic basis of the disease. In contrast, other workers have reported minor enamel defects in all three EB subtypes with a slight reduction (10%) in mineral content in some EBJ and EBD teeth.⁹⁰ Overall no difference between mean mineral content of EB teeth and normal controls was observed, although marked alterations in the enamel structure, such as prismatic structure and orientation and surface pitting, was observed in EBJ teeth. It has been suggested that the genetic defect in EBJ accounted for the alterations in the structure of enamel whilst leaving the mineralisation process essentially intact. Given the systemic involvement of some EB subtypes, it is perhaps not surprising that some of the enamel defects seen in the three subtypes may be caused as a direct result of the molecular defect, whereas others are caused by mechanisms secondary to the disease process.

Due to the fragility of the oral mucosa and the increased susceptibility to dental caries, the dental management of these patients requires special care.^{73,91} Palliative and preventative treatment is important to prevent destruction and subsequent loss of dentition and may be sufficient for the majority of EB patients. More aggressive dental intervention and therapies may be necessary for the most severely affected patients to maintain oral health with frequent follow up visits and good hygiene and dietary advice essential.

2.11. Other developmental and environmental causes of enamel defects

Osteogenesis imperfecta (OI) is a relatively common inherited connective tissue disorder resulting in skeletal dysplasia and characterised by bone fragility and fractures. Other tissues including ligaments, tendons, fascia, skin, eyes, ears and teeth, are also affected in OI. Most cases result from mutations in genes responsible for the production of type I collagen and the phenotypic presentation varies from mild to lethal. The most commonly observed dental abnormalities in OI include

dentinogenesis imperfecta (DI) and malocclusion.⁹² DI, where teeth are discoloured, translucent and brittle, can occur in isolation as an autosomal dominant familial trait as well as a component of OA. Hereditary dentine disorders, DI and dentine dysplasia (DD), are characterised by abnormal dentine structure affecting either the primary, or both the primary and secondary, teeth.⁹³ Currently DI has been divided into three subtypes, and DD into two. DI Type I is associated with OI, whereas type II is not. DI types II and III and DD type II are associated with mutations in dentine sialophosphoprotein (DSPP).^{93,94} A recent study on Norwegian adults with OI found that they had twice as many missing teeth as the general population and higher numbers of endodontically treated teeth, although their daily oral health habits were good and they visited the dentist regularly.⁹⁵

Recommended treatment involves the removal of the sources of pain or infection, aesthetic improvement and protection of the posterior teeth from wear, using crowns, overdentures and dental implants. It is believed that where early diagnosis is made, and good treatment provided, excellent aesthetic and functional outcomes can be achieved.⁹⁴

The literature on amelogenesis imperfecta (AI) has been reviewed recently.⁹⁶ AI primarily affects amelogenesis. The authors found that in case reports of AI aberrations were documented in the eruption process, crown morphology, pulp-dentine, and in the number of teeth. Additionally, calculus was commonly found, and gingival conditions and oral hygiene were often reported as poor.⁹⁶

Molar incisor hypomineralisation (MIH) is a common developmental condition resulting in enamel defects in the first permanent molars and incisors and presents at the eruption of those teeth. A rapid breakdown in the tooth structure may occur and therefore early diagnosis is important in limiting symptoms. Enamel hypomineralisation causes marked reduction in the elastic modulus of enamel, due primarily to an increase in the thickness of the protein layers between apatite crystals and, as a consequence, leads to impaired dental function.⁹⁷ A recent review of the literature by Willmott et al.⁹⁸ suggested that affected teeth indicated a systemic cause in the prenatal, perinatal or postnatal periods. At present the aetiology remains unclear, however, a number of possible causes have been suggested by several studies on children with MIH, including upper respiratory tract infections, asthma, pneumonia, otitis media, antibiotics, dioxins in maternal milk, tonsillitis and tonsillectomy, and exanthematous fevers of childhood.^{99–101} Many of these illnesses may produce hypoxia, hypocalcaemia or pyrexia in either the child or the mother.¹⁰⁰ The reviewers concluded that there was little evidence to support any treatment option over another, with restorations using adhesive intra-coronal to extra-coronal restorations and, in severe cases, extractions of the first molars allowing the second molars to come forward, all proving effective. They did suggest that little improvement was achieved with microabrasion in anterior teeth, and that direct or indirect composite resin restorations may be appropriate in some children. It has been suggested that for children with repeated illnesses in the first years of life, and for those with opacities on erupted molars or incisors, it is useful to increase

the frequency of dental check-ups during the period of erupting first permanent molars.¹⁰²

The possible environmental causes of enamel defects have been reviewed by Brook et al.² by comparing an ancient (Romano-Briton) and modern British population. They used the same examiners and index and concluded that episodes of systemic illness and general debilitating factors can lead to enamel defects. In addition they reported that 68.4% of 1518 London schoolchildren had enamel defects in their permanent dentition, with 10.5% having 10 or more teeth affected, 67.2% with opacities and 14.6% with hypoplasia. A study in low birth weight children by the same authors showed significantly more enamel defects relating to major health problems, including mineral and vitamin deficiencies, low blood oxygen and ventilation requirement, occurring during the neonatal period.

Other factors which may cause enamel defects include cerebral palsy, mental retardation or hearing defects.¹⁰³ Developmental hypoplastic enamel defects occur with greater frequency in the primary teeth of children with cerebral palsy, mental retardation or sensorineural conditions. This is in accordance with data from the study in children which showed that all the children with cerebral palsy had enamel defects.² Many of the syndromes reported above are associated with features of mental retardation suggesting that mental conditions secondary to the syndrome itself may be the cause of some of the enamel defects observed. In children in particular, further research to ascertain whether the causes of dental defects occurred intra-uterio, pre- or postnatally is required.

3. Conclusion

Enamel has a protective role on the tooth – loss of enamel exposes the sensitive dentine underneath. Once damaged, enamel is generally unable to recover. Enamel and dentine defects can present with a wide spectrum of clinical features and may be caused by a variety of factors occurring throughout tooth development from before birth to adulthood. These may include host traits, genetic factors, immunological responses to cariogenic bacteria, environmental and behavioural factors, and saliva composition. Tooth enamel and/or dentine are also affected by systemic diseases such as cystic fibrosis, HIV/AIDS, leukaemia, Alstrom syndrome, hypophosphatasia, Prader-Willi syndrome, Tricho-dento-osseous syndrome, tuberous sclerosis, familial steroid dehydrogenase deficiency and epidermolysis bullosa.

Systemic disease may arise from exogenous factors, including viral infections (e.g. HIV/AIDS), bacterial infections, and environmental factors (or stress) but can also be the result of endogenous genetic abnormalities (e.g. cystic fibrosis). The nature and severity of the disease itself as well as other factors often determine the extent of the damage to enamel and dentine. It is important for the dental practitioner to understand the nature of the underlying disease and the potential adverse effects that any therapy may incur.

A number of enamel and dentine defects occur as a result of the primary disease itself requiring the dental practitioner to have a broad based knowledge of the disease process and its

effects in order to ensure the best possible dental care of the individual patient. The disease process, aetiology, patient's current condition and relevant treatment strategies (especially with regards to immunosuppressed patients where the dental interventions themselves may potentially be life-threatening) will affect prognosis and must be carefully weighed before treatment plans are initiated.

The timing and nature of the stimuli which causes enamel defects may be very different between the various diseases or conditions; however the end result may be very similar as far as each individual patient and the dental practitioner is concerned.

In cystic fibrosis patients, for example, due to the increased prevalence of enamel defects and calculus accumulation, early dental intervention is important in the long-term care of these patients. Hypophosphatasia can present during the perinatal, infantile, childhood or adult stages. One of the main diagnostic features of hypophosphatasia, is the loss of dentition, probably due to the lack of cementum. Dental effects of hypophosphatasia first diagnosed in primary teeth are usually also evident in the permanent dentition, necessitating early dental intervention and counselling. Early long-term dental intervention is also important in individuals with Tricho-dento-osseous syndrome, where dental abnormalities affect both primary and secondary teeth, often resulting in the loss of dentition during the second or third decade of life. In Prader-Willi syndrome, a complex genetic multisystem sporadic disorder which presents during childhood and proceeds into adulthood, early dental consultation and long-term orthodontic, surgical and restorative procedures are usually necessary due to the almost complete destruction of the teeth which result from generalised caries.

It has been estimated that 30–80% of HIV/AIDS patients suffer with oral lesions, including fungal, bacterial or viral infections, neoplasms such as Kaposi's sarcoma and non-specific presentations such as aphthous ulcerations and salivary gland disease. Although in many cases improved oral hygiene reduces and/or prevents oral disease, effective dental management remains an essential part of the overall care and health of HIV/AIDS patients. The need for improved oral hygiene is also an important aspect of the dental care of patients with tuberous sclerosis, a rare genetic disease that causes benign tumours to grow in the brain and in other vital organs, often associated with enamel pitting.

Many other systemic conditions, which have not been discussed in detail here, are known to affect enamel. The hypocalcification type of Amelogenesis imperfecta, an autosomal dominant condition, results in incomplete enamel mineralisation. The X-linked hypoplastic type on the other hand results in enamel hypoplasia, which is nevertheless of normal composition. Chronic bilirubin encephalopathy may also cause enamel hypoplasia and green staining of the enamel. Erythropoietic porphyria results in porphyrin deposition in the body including in tooth enamel where the deposits appear red and fluorescent). Celiac disease results in enamel demineralisation.

Many difficulties arise from the variety of terminology and indices used to measure dental damage often making comparisons between different studies difficult, adding to the complexities of assessment and treatment. Nevertheless,

the availability of many new technologies in dental management, restorative care and assessment now make treatment of individual patients both more rewarding and complete than previously possible.

REFERENCES

- Levine RS, Turner EP, Dobbing J. Deciduous teeth contain histories of developmental disturbances. *Early Human Development* 1979;3:211–20.
- Brook AH, Fearn JM, Smith JM. Environmental causes of enamel defects. *Ciba Foundation Symposium* 1997;205:212–21. discussion 21–5.
- Shuler CF. Inherited risks for susceptibility to dental caries. *Journal of Dental Education* 2001;65:1038–45.
- Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. *Science* 1992;256:774–9.
- Fernald GW, Roberts MW, Boat TF. Cystic fibrosis: a current review. *Pediatric Dentistry* 1990;12:72–8.
- Sui W, Boyd C, Wright JT. Altered pH regulation during enamel development in the cystic fibrosis mouse incisor. *Journal of Dental Research* 2003;82:388–92.
- Mahaney MC, McCoy KS. Developmental delays and pulmonary disease severity in cystic fibrosis. *Human Biology* 1986;58:445–60.
- Primosch RE. Tetracycline discoloration, enamel defects, and dental caries in patients with cystic fibrosis. *Oral Surgery Oral Medicine Oral Pathology* 1980;50:301–8.
- Wood RE, Boat TF, Doershuk CF. Cystic fibrosis. *American Review of Respiratory Disease* 1976;113:833–78.
- Wood R. Determinants of survival in cystic fibrosis. *CF Club Abstracts* 1985;26:69.
- Kinirons MJ. Dental health of patients suffering from cystic fibrosis in Northern Ireland. *Community Dental Health* 1989;6:113–20.
- Narang A, Maguire A, Nunn JH, Bush A. Oral health and related factors in cystic fibrosis and other chronic respiratory disorders. *Archives of Disease in Childhood* 2003;88:702–7.
- Kinirons MJ. Increased salivary buffering in association with a low caries experience in children suffering from cystic fibrosis. *Journal of Dental Research* 1983;62:815–7.
- Jagels AE, Sweeney EA. Oral health of patients with cystic fibrosis and their siblings. *Journal of Dental Research* 1976;55:991–6.
- Kinirons MJ. The effect of antibiotic therapy on the oral health of cystic fibrosis children. *International Journal of Paediatric Dentistry* 1992;2:139–43.
- Cua FT. Zinc in teeth from children with and without cystic fibrosis. *Biological Trace Element Research* 1991;29:229–37.
- Cua FT. Calcium and phosphorous in teeth from children with and without cystic fibrosis. *Biological Trace Element Research* 1991;30:277–89.
- Smith CE. Cellular and chemical events during enamel maturation. *Critical Reviews in Oral Biology and Medicine* 1998;9:128–61.
- Arquitt CK, Boyd C, Wright JT. Cystic fibrosis transmembrane regulator gene (CFTR) is associated with abnormal enamel formation. *Journal of Dental Research* 2002;81:492–6.
- Gawenis LR, Spencer P, Hillman LS, Harline MC, Morris JS, Clarke LL. Mineral content of calcified tissues in cystic fibrosis mice. *Biological Trace Element Research* 2001;83:69–81.
- Sui W, Boyd C, Wright J. Expression of the CFTR gene in different tissues of mice (abstract). *Journal of Dental Research* 2001;80:634.
- Wright JT, Hall KI, Grubb BR. Enamel mineral composition of normal and cystic fibrosis transgenic mice. *Advances in Dental Research* 1996;10:270–4. discussion 75.
- Wright JT, Kiefer CL, Hall KI, Grubb BR. Abnormal enamel development in a cystic fibrosis transgenic mouse model. *Journal of Dental Research* 1996;75:966–73.
- Arendorf TM, Bredekamp B, Cloete CA, Sauer G. Oral manifestations of HIV infection in 600 South African patients. *Journal of Oral Pathology and Medicine* 1998;27:176–9.
- Patton LL, McKaig R, Strauss R, Rogers D, Eron Jr JJ. Changing prevalence of oral manifestations of human immunodeficiency virus in the era of protease inhibitor therapy. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 2000;89:299–304.
- Tappuni AR, Fleming GJ. The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: a UK study. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 2001;92:623–8.
- Magalhaes MG, Bueno DF, Serra E, Goncalves R. Oral manifestations of HIV positive children. *Journal of Clinical Pediatric Dentistry* 2001;25:103–6.
- Persson RE, Hollender LG, Persson GR. Alveolar bone levels in AIDS and HIV seropositive patients and in control subjects. *Journal of Periodontology* 1998;69:1056–61.
- Younai FS, Marcus M, Freed JR, Coulter ID, Cunningham W, Der-Martirosian C, et al. Self-reported oral dryness and HIV disease in a national sample of patients receiving medical care. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 2001;92:629–36.
- Lausten LL, Ferguson BL, Barker BF, Cobb CM. Oral Kaposi sarcoma associated with severe alveolar bone loss: case report and review of the literature. *Journal of Periodontology* 2003;74:1668–75.
- Mascarenhas AK, Smith SR. Factors associated with utilization of care for oral lesions in HIV disease. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 1999;87:708–13.
- Cho SY, Cheng AC, Cheng MC. Oral care for children with leukaemia. *Hong Kong Medical Journal* 2000;6:203–8.
- Kaste SC, Hopkins KP, Jones D, Crom D, Greenwald CA, Santana VM. Dental abnormalities in children treated for acute lymphoblastic leukemia. *Leukemia* 1997;11:792–6.
- Minicucci EM, Lopes LF, Crocchi AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. *Leukemia Research* 2003;27:45–50.
- Weckx LL, Hidal LB, Marcucci G. Oral manifestations of leukemia. *Ear Nose and Throat Journal* 1990;69:341–2. 45–6.
- Dreizen S, McCredie KB, Keating MJ, Luna MA. Malignant gingival and skin “infiltrates” in adult leukemia. *Oral Surgery Oral Medicine Oral Pathology* 1983;55:572–9.
- Kinirons MJ, Fleming P, Boyd D. Dental caries experience of children in remission from acute lymphoblastic leukaemia in relation to the duration of treatment and the period of time in remission. *International Journal of Paediatric Dentistry* 1995;5:169–72.
- Pajari U, Lanning M, Larmas M. Prevalence and location of enamel opacities in children after anti-neoplastic therapy. *Community Dentistry and Oral Epidemiology* 1988;16:222–6.
- Nunn JH, Welbury RR, Gordon PH, Kernahan J, Craft AW. Dental caries and dental anomalies in children treated by chemotherapy for malignant disease: a study in the north of England. *International Journal of Paediatric Dentistry* 1991;1:131–5.
- Uderzo C, Fraschini D, Balduzzi A, Galimberti S, Arrigo C, Biagi E, et al. Long-term effects of bone marrow transplantation on dental status in children with leukaemia. *Bone Marrow Transplantation* 1997;20:865–9.
- Collard MM, Hunter ML. Oral and dental care in acute lymphoblastic leukaemia: a survey of United Kingdom

- children's cancer study group centres. *International Journal of Paediatric Dentistry* 2001;11:347–51.
42. Goldstein JL, Fialkow PJ. The Alstrom syndrome. Report of three cases with further delineation of the clinical, pathophysiological, and genetic aspects of the disorder. *Medicine* 1973;52:53–71.
 43. Collin GB, Marshall JD, Cardon LR, Nishina PM. Homozygosity mapping at Alstrom syndrome to chromosome 2p. *Human Molecular Genetics* 1997;6:213–9.
 44. Koray F, Dörter C, Benderli Y, Satman I, Yilmaz T, Dinccag N, et al. Alstrom syndrome: a case report. *Journal of Oral Science* 2001;43:221–4.
 45. Albrecht M, Takats R, Fosse G, Sapi Z, Banoczy J. Dental enamel hardness tests in diabetics. *Fogorvosi Szemle* 1991;84:363–6.
 46. Atar M, Atar-Zwillenberg DR, Verry P, Spornitz UM. Defective enamel ultrastructure in diabetic rodents. *International Journal of Paediatric Dentistry* 2004;14:301–7.
 47. Atar M, Davis GR, Verry P, Wong FS. Enamel mineral concentration in diabetic rodents. *European Archives of Paediatric Dentistry* 2007;8:195–200.
 48. Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. *Diabetes/Metabolism Research and Reviews* 2004;20:196–204.
 49. Noren JG. Microscopic study of enamel defects in deciduous teeth of infants of diabetic mothers. *Acta Odontologica Scandinavica* 1984;42:153–6.
 50. Schwartz AV. Diabetes mellitus: does it affect bone? *Calcified Tissue International* 2003;73:515–9.
 51. Boor R, Herwig J, Schrezenmeier J, Pontz BF, Schonberger W. Familial insulin resistant diabetes associated with acanthosis nigricans, polycystic ovaries, hypogonadism, pigmentary retinopathy, labyrinthine deafness, and mental retardation. *American Journal of Medical Genetics* 1993;45:649–53.
 52. Chapple IL. Hypophosphatasia: dental aspects and mode of inheritance. *Journal of Clinical Periodontology* 1993;20:615–22.
 53. Herasse M, Spentchian M, Taillandier A, Keppler-Noreuil K, Florito AN, Bergoffen J, et al. Molecular study of three cases of odontohypophosphatasia resulting from heterozygosity for mutations in the tissue non-specific alkaline phosphatase gene. *Journal of Medical Genetics* 2003;40:605–9.
 54. Whyte MP. Hypophosphatasia and the role of alkaline phosphatase in skeletal mineralization. *Endocrine Reviews* 1994;15:439–61.
 55. Henthorn PS, Raducha M, Fedde KN, Lafferty MA, Whyte MP. Different missense mutations at the tissue-nonspecific alkaline phosphatase gene locus in autosomal recessively inherited forms of mild and severe hypophosphatasia. *Proceedings of the National Academy of Sciences of the United States of America* 1992;89:9924–8.
 56. Hu JC, Plaetke R, Mornet E, Zhang C, Sun X, Thomas HF, et al. Characterization of a family with dominant hypophosphatasia. *European Journal of Oral Sciences* 2000;108:189–94.
 57. Taillandier A, Sallinen SL, Brun-Heath I, De Mazancourt P, Serre JL, Mornet E. Childhood hypophosphatasia due to a de novo missense mutation in the tissue-nonspecific alkaline phosphatase gene. *Journal of Clinical Endocrinology and Metabolism* 2005;90:2436–9.
 58. Olsson A, Matsson L, Blomquist HK, Larsson A, Sjodin B. Hypophosphatasia affecting the permanent dentition. *Journal of Oral Pathology and Medicine* 1996;25:343–7.
 59. van den Bos T, Handoko G, Niehof A, Ryan LM, Coburn SP, Whyte MP, et al. Cementum and dentin in hypophosphatasia. *Journal of Dental Research* 2005;84:1021–5.
 60. Whyte MP, Teitelbaum SL, Murphy WA, Bergfeld MA, Avioli LV. Adult hypophosphatasia. Clinical, laboratory, and genetic investigation of a large kindred with review of the literature. *Medicine* 1979;58:329–47.
 61. Ramer M, Basta R, Fisher K. Childhood hypophosphatasia. A case report. *New York State Dental Journal* 1997;63:36–9.
 62. Beumer III J, Trowbridge HO, Silverman Jr S, Eisenberg E. Childhood hypophosphatasia and the premature loss of teeth. A clinical and laboratory study of seven cases. *Oral Surgery Oral Medicine Oral Pathology* 1973;35:631–40.
 63. Brittain JM, Oldenburg TR, Burkes Jr EJ. Odontohypophosphatasia: report of two cases. *ASDC Journal of Dentistry for Children* 1976;43:106–11.
 64. Anavi Y, Mintz SM. Prader-Labhart-Willi syndrome. *Annals of Dentistry* 1990;49:26–9.
 65. Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics* 1993;91:398–402.
 66. Banks PA, Bradley JC, Smith A. Prader-Willi syndrome—a case report of the multidisciplinary management of the orofacial problems. *British Journal of Orthodontics* 1996;23:299–304.
 67. Bazopoulou-Kyrkanidou E, Papagiannoulis L. Prader-Willi syndrome: report of a case with special emphasis on oral problems. *Journal of Clinical Pediatric Dentistry* 1992;17:37–40.
 68. Young W, Khan F, Brandt R, Savage N, Razek AA, Huang Q. Syndromes with salivary dysfunction predispose to tooth wear: Case reports of congenital dysfunction of major salivary glands, Prader-Willi, congenital rubella, and Sjogren's syndromes. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 2001;92:38–48.
 69. Salako NO, Ghafouri HM. Oral findings in a child with Prader-Labhart-Willi syndrome. *Quintessence International* 1995;26:339–41.
 70. Wood R, Nortje C, Schikerling L. Dental evidence aids diagnosis of Prader-Willi syndrome. *Ontario Dentist* 1987;64:25–9.
 71. Seow WK. Trichodontoosseous (TDO) syndrome: case report and literature review. *Pediatric Dentistry* 1993;15:355–61.
 72. Shapiro SD, Quattromani FL, Jorgenson RJ, Young RS. Tricho-dento-osseous syndrome: heterogeneity or clinical variability. *American Journal of Medical Genetics* 1983;16:225–36.
 73. Wright JT, Fine JD. Hereditary epidermolysis bullosa. *Seminars in Dermatology* 1994;13:102–7.
 74. Seow WK, Lai PY. Association of taurodontism with hypodontia: a controlled study. *Pediatric Dentistry* 1989;11:214–9.
 75. Spangler GS, Hall KI, Kula K, Hart TC, Wright JT. Enamel structure and composition in the tricho-dento-osseous syndrome. *Connective Tissue Research* 1998;39:165–75. discussion 87–94.
 76. Wright JT, Roberts MW, Wilson AR, Kudhail R. Tricho-dento-osseous syndrome. Features of the hair and teeth. *Oral Surgery Oral Medicine Oral Pathology* 1994;77:487–93.
 77. Melnick M, Shields ED, El-Kafrawy AH. Tricho-dento-osseous syndrome: a scanning electron microscopic analysis. *Clinical Genetics* 1977;12:17–27.
 78. Cutando A, Gil JA, Lopez J. Oral health management implications in patients with tuberous sclerosis. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics* 2000;90:430–5.
 79. Lygidakis NA, Lindenbaum RH. Pitted enamel hypoplasia in tuberous sclerosis patients and first-degree relatives. *Clinical Genetics* 1987;32:216–21.
 80. Mlynarczyk G. Enamel pitting. A common sign of tuberous sclerosis. *Annals of the New York Academy of Sciences* 1991;615:367–9.

81. Sampson JR, Attwood D, al Mughery AS, Reid JS. Pitted enamel hypoplasia in tuberous sclerosis. *Clinical Genetics* 1992;**42**:50–2.
82. Weits-Binnerts JJ, Hoff M, van Grunsven MF. Dental pits in deciduous teeth, an early sign in tuberous sclerosis. *Lancet* 1982;**2**:1344.
83. Flanagan N, O'Connor WJ, McCartan B, Miller S, McMenamin J, Watson R. Developmental enamel defects in tuberous sclerosis: a clinical genetic marker? *Journal of Medical Genetics* 1997;**34**:637–9.
84. Clayton PT, Leonard JV, Lawson AM, Setchell KD, Andersson S, Egestad B, et al. Familial giant cell hepatitis associated with synthesis of 3 beta, 7 alpha-dihydroxy-and 3 beta, 7 alpha, 12 alpha-trihydroxy-5-cholenoic acids. *Journal of Clinical Investigation* 1987;**79**:1031–8.
85. Ichimiya H, Nazer H, Gunasekaran T, Clayton P, Sjovall J. Treatment of chronic liver disease caused by 3 beta-hydroxy-delta 5-C27-steroid dehydrogenase deficiency with chenodeoxycholic acid. *Archives of Disease in Childhood* 1990;**65**:1121–4.
86. Lyngstadaas SP, Crossner CJ, Nazer H, Thrane PS, Nordbo H. Severe dental aberrations in familial steroid dehydrogenase deficiency: a new association. *Clinical Genetics* 1996;**49**:249–54.
87. Kirkham J, Robinson C, Strafford SM, Shore RC, Bonass WA, Brookes SJ, et al. The chemical composition of tooth enamel in junctional epidermolysis bullosa. *Archives of Oral Biology* 2000;**45**:377–86.
88. Wright JT, Fine JD, Johnson L. Hereditary epidermolysis bullosa: oral manifestations and dental management. *Pediatric Dentistry* 1993;**15**:242–8.
89. Kirkham J, Robinson C, Strafford SM, Shore RC, Bonass WA, Brookes SJ, et al. The chemical composition of tooth enamel in recessive dystrophic epidermolysis bullosa: significance with respect to dental caries. *Journal of Dental Research* 1996;**75**:1672–8.
90. Wright JT, Hall KI, Deaton TG, Fine JD. Structural and compositional alteration of tooth enamel in hereditary epidermolysis bullosa. *Connective Tissue Research* 1996;**34**:271–9.
91. Serrano Martinez C, Silvestre Donat F, Bagan Sebastian J, Penarrocha Diago M, Alio Sanz J. Hereditary epidermolysis bullosa. Dental management of three cases. *Medicina Oral* 2001;**6**.
92. Huber MA. Osteogenesis imperfect. *Oral Surgery Oral Medicine Oral Pathology Oral radiology and Oral Endodontics* 2007;**103**:314–20.
93. Hart PS, Hart TC. Disorders of human dentin. *Cells Tissues and Organs* 2007;**186**:70–7.
94. Barron MJ, McDonnell ST, MacKie I, Dixon MJ. Hereditary dentine disorders: dentinogenesis imperfecta and dentine dysplasia. *Orphanet Journal of Rare Diseases* 2008;**3**:31.
95. Saeves R, Lande Wekre L, Ambjornsen E, Axelsson S, Nordgarden H, Storhaug K. Oral findings in adults with osteogenesis imperfecta. *Specialist Care in Dentistry* 2009;**29**:102–8.
96. Poulsen S, Gjorup H, Haubek D, Haukali G, Hintze H, Lovschall H, Errboe M. Amelogenesis imperfecta—a systematic literature review of associated dental and orofacial abnormalities and their impact on patients. *Acta Odontologica Scandinavica* 2008;**66**:193–9.
97. Xie ZH, Swain MV, Swadener G, Munroe P, Hoffman M. Effect of microstructure upon elastic behaviour of human tooth enamel. *Journal of Biomechanics* 2009;**42**: 1075–80.
98. Willmott NS, Bryan RAE, Duggal MS. Molar-incisor-hypomineralisation: a literature review. *European Archive of Paediatric Dentistry* 2008;**9**:172–9.
99. Muratbegovic A, Markovic N, Ganibegovic Selimovic M. Molar incisor hypomineralisation in Bosnia and Herzegovina: aetiology and clinical consequences in medium caries activity population. *European Archive of Paediatric Dentistry* 2007;**8**:189–94.
100. Lygidakis NA, Dimou G, Marinou D. Molar-incisor-hypomineralisation (MIH). A retrospective clinical study in Greek children. II. Possible medical aetiological factors. *European Archive of Paediatric Dentistry* 2008;**9**: 207–17.
101. Chawla N, Messer LB, Silva M. Clinical studies on molar-incisor-hypomineralisation. Part 1. Distribution and putative associations. *European Archive of Paediatric Dentistry* 2008;**9**:180–90.
102. Weerheijm KL. Molar incisor hypomineralisation (MIH). *European Journal of Paediatric Dentistry* 2003;**4**:114–20.
103. Bhat M, Nelson KB. Developmental enamel defects in primary teeth in children with cerebral palsy, mental retardation, or hearing defects: a review. *Advances in Dental Research* 1989;**3**:132–42.