Epidermolysis Bullosa:

An outline for professionals

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EPIDERMOLYSIS BULLOSA: An outline for professionals

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Epidermolysis bullosa is the name given to a group of genetically determined disorders characterised by excessive susceptibility of the skin and mucosae to separate from the underlying tissues following mechanical trauma. The individual diseases vary in their impact from relatively minor disability (eg. limitation of walking distance because of blistering of the feet) to death in infancy[1,2].

Some object to the use of the term for those diseases which fulfil the above criteria but which do not feature true epidermolysis, i.e. lysis of keratinocytes, and would prefer to call these conditions *hereditary mechano-bullous diseases,* rather than epidermolysis bullosa. However, I prefer to continue to use the term *epidermolysis bullosa* in the wider sense, and will do so in this chapter.

There are three broad categories of epidermolysis bullosa: *epidermolysis bullosa simplex, dystrophic epidermolysis bullosa and junctional epidermolysis bullosa*. Within each of these categories, there are several sub-types which are clinically, and probably genetically distinct.

EPIDERMOLYSIS BULLOSA SIMPLEX (EBS)

Definition
A group of inherited disorders characterised by mechanically induced blistering occurring within the epidermis itself as a result of lysis of basal keratinocytes. Because of the characteristic level of cleavage, epidermolysis bullosa simplex is sometimes termed epidermolytic epidermolysis bullosa.

There are several established variants, of which the following are the most important:

- Epidermolysis bullosa simplex Weber-Cockayne type (localized to hands and feet)
- Epidermolysis bullosa simplex Köbner type (generalized)
- Epidermolysis bullosa simplex Dowling-Meara type (Herpetiformis)

There are, in addition, a number of rarer variants that are encountered from time to time:

- Epidermolysis bullosa simplex with muscular dystrophy
- Kallin's syndrome[4]
- Epidermolysis bullosa simplex with mottled pigmentation[5]
- 'Lethal' autosomal recessive epidermolysis bullosa simplex[6]

Aetiology and pathogenesis
The prevalence of the different forms of epidermolysis bullosa simplex has not been systematically studied, and can therefore only be estimated, and probably varies from country to country[7-9]. The prevalence of Weber-Cockayne epidermolysis bullosa simplex is probably 10-20 per million. The Köbner form is rarer, possibly about 2 per million. With increasing experience of clinical and pathological diagnosis of the Dowling-Meara variant, we have gained the impression that the disease is commoner than we had previously imagined, affected neonates being approximately as common as those with either

dystrophic or junctional disease; prevalence is probably in the region of 5-10 per million. The superficial and autosomal recessive types are probably extremely rare, but some of the rare forms may be locally common, for example the Ogna variant, whose prevalence may be as high as 14 per million in Norway[9].

Almost all forms of epidermolysis bullosa simplex are inherited as autosomal dominant traits. There appear to be certain rare forms of that are inherited as autosomal recessive traits, notably epidermolysis bullosa simplex with muscular dystrophy[10], 'lethal' epidermolysis bullosa simplex[6], and there is some evidence that at least occasionally, epidermolysis bullosa simplex localised to the hands and feet may be transmitted as an autosomal recessive trait[11].

Patients with the Weber Cockayne and with the Köbner forms of epidermolysis bullosa simplex almost always have extensive family histories of the condition, and the occurrence of sporadic cases is relatively unusual. As is generally the case with dominantly inherited diseases, severity may vary considerably between affected members of a single family. The majority of cases of epidermolysis bullosa simplex Dowling-Meara appear to be sporadic, but inheritance has been autosomal dominant in all reported familial cases to date[12].

Mutations can be found in about 50% of patients examined in the genes coding for keratins 5 or 14, which are respectively the predominant basic and acidic keratins in the skin[13,14]. These mutations have so far been clustered in six 'hotspots' on the keratin molecules, and it is becoming clear that the site of each hotspot will determine the clinical severity of the resulting disease. Thus the mutations so far identified in the more severe Dowling-Meara form of EBS have all been in the highly conserved regions at the beginning and end of the central rod domain, which are known to be important in the early stages of filament assembly. The mutations identified in the milder Weber-Cockayne and Köbner forms have been in the other 4 hotspots. However, a proportion of EBS patients do not appear to have mutations in keratins 5 or 14, and their mutations are thought likely to be in the genes encoding other basal keratins, such as keratins 15 and 17, or a variety of keratin-associated proteins.

Pathology

The technique of taking biopsies in epidermolysis bullosa is of the greatest importance if the procedure is to provide useful tissue for the pathologist. The biopsy should be taken from clinically unaffected skin. Disruption of the skin should be induced by rubbing the area to be biopsied with a finger or an India rubber for about a minute. There should follow a delay of 5-10 minutes, after which the biopsy should be taken. In our unit, we find that a shave technique provides the best quality material, because artefact is minimal, fixation is rapid, orientation is easier and healing is good. A useful technique is to pass a hypodermic needle in a shallow tangential direction through the biopsy site after local anaesthesia has been achieved, and then to cut along the upper surface of the needle with a scalpel blade.

In all forms of epidermolysis bullosa, routine light microscopy may be misleading. For example, intra-epidermal cleavage in epidermolysis bullosa simplex may appear to be sub-epidermal Epidermolysis bullosa simplex is characterised at the pathological level by true *epidermolysis*, ie. intracellular keratinocyte lysis. At the ultrastructural level, this lysis occurs in the basal keratinocytes[15] in all forms. Epidermolysis bullosa simplex of the generalised and localised types cannot currently be distinguished ultrastructurally. On the other hand, epidermolysis bullosa simplex herpetiformis shows the distinctive feature of tonofibril clumping occurring within basal keratinocytes prior to their lysis[16], though this change cannot always be found easily, particularly in patients with clinical disease that is relatively mild.

Clinical features

Weber-Cockayne type epidermolysis bullosa simplex

This variant of epidermolysis bullosa simplex most characteristically has its onset in early childhood, but very often not until walking is established. In some cases, the condition is not revealed until adolescence or early adult life, when the subject is required to undertake unaccustomed activity, for example a forced march in the army. Those who have Weber-Cockayne EBS often do not consider themselves to have a medical problem, merely an exaggeration of the normal tendency to blister during or after hard walking or running, or after intensive use of the hands.

Rubbing of the feet by footwear is generally the major cause of blisters, and the commonest parts of the feet to be affected are the soles and the junctions between the sole and the sides of the toes or the main part of the foot. A particular feature of all types of EBS is a progressively increased tendency to blister as the environmental temperature rises. So great is this effect that some patients who have marked disability in hot summer weather may have little or none in the winter.

Though it is sometimes implied that epidermolysis bullosa simplex of this type is a relatively trivial disease, some patients experience very substantial disability, mainly because of difficulty in walking. Some individuals may only be able to walk one or two hundred metres on a summer day before painful blistering occurs. Other patients may have problems with manual tasks, and may find it impossible to use hand tools for more than brief periods.

Blisters tend to be small, up to about 2 cm in diameter, and, despite their relatively superficial localization, they are generally tense and may even be haemorrhagic. A particular feature is an erythematous halo around blisters, a characteristic which, in the absence of secondary infection, is generally lacking in other types of epidermolysis bullosa. Nevertheless, secondary infection is common once blisters have ruptured. Though the blisters will heal rapidly in the absence of such secondary infection, the frequent recurrence of provocative trauma at affected sites tends to cause new blisters to occur underneath and at the margins of ones that are in the process of healing. A degree of hyperkeratosis often marks sites of recurrent blistering.

The nails are not usually affected unless subject to considerable trauma such as a heavy object being dropped on to toe nails or toe nails being trodden on. Areas of the body other than the hands and feet are rarely affected. The mouth is almost invariably spared.

Köbner epidermolysis bullosa simplex

Köbner epidermolysis bullosa simplex tends to have an early onset, either during the perinatal period or during the first few months of life. It is not infrequently already present at birth.

In the perinatal period, blistering and erosions occur at sites determined by trauma during delivery and by handling in the nursery. Lesions heal quickly without scarring. Thereafter, the rate of new blister formation tends to slow down, with new lesions only appearing at sites of continuing friction, particularly in the napkin area.

Oral lesions do occur, but tend not to be prominent and only rarely interfere with feeding. Nail involvement is unusual, and when nails are occasionally shed following subungual blistering, they generally regrow without dystrophy.

Rubbing of the skin tends to be the main provocative factor. The blistering tendency is much more apparent in warm weather, to the extent that some patients' problems may be more or less confined to the summer months. As the child starts to crawl, lesions may occur on the knees, feet, elbows and hands. With the onset of walking, the principal problem localises to the feet and ankles, with the hands being the next most frequently affected site. In adults, it is rare for lesions to occur elsewhere, though blisters can be provoked at any site under appropriate provocation.

The blisters are tense and occur at the same sites on the hands and feet as in the localised type of epidermolysis bullosa simplex. Likewise, secondary infection is perhaps the principal complication of the disorder. In the absence of such infection, the blisters heal fairly rapidly without blistering.

Dowling-Meara epidermolysis bullosa simplex[16-19]

Increasing recognition of this disorder is making it clear that this is a commoner type of epidermolysis bullosa simplex than was previously believed. Clinically, it generally causes blistering with an onset in early infancy. There is a great range of severity in individual cases. Blistering may be exceptionally severe during the neonatal period, and these babies can present a devastating picture. Death in the neonatal period is probably not infrequent, and in the past many of these severe cases were probably thought to have lethal junctional EB. In the severe case, blistering may appear to arise quite spontaneously, particularly in a hot environment. Blisters are perhaps even more often haemorrhagic than in other forms of epidermolysis bullosa simplex, and milia may be a transient feature after blisters have healed. It is important to be aware that milia are not pathognomonic of dystrophic forms of epidermolysis bullosa, and that they may occur, albeit rather fleetingly, in all the other forms, but perhaps particularly in Dowling-Meara epidermolysis bullosa simplex.

The hands and feet are the sites of predilection, and blisters at these sites are similar to those seen in other forms of epidermolysis bullosa simplex. However, it is particularly characteristic for blistering on the palms and soles to be succeeded by focal keratoderma, though this is also seen, albeit usually to a lesser degree, in other types of EBS. On occasions, this keratoderma may be very prominent and associated with flexion deformity and loss of function.

A rather characteristic thickening of the nails is also commonly seen in Dowling-Meara EBS. Even in the neonatal period, involvement of the hands and feet is prominent, and is often already associated with nail thickening; this combination can be diagnostically helpful.

Blisters frequently occur at other sites on the face, trunk and limbs, and tend to be disposed in groups with an erythematous border; hence the adjective *herpetiformis*. However, these groups are perhaps more often annular or arcuate than truly herpetiform. Of these other sites, the neck is particularly commonly affected. A major provocative factor appears to be friction from the seams of clothing. However, in this condition, groups of blisters may appear with remarkably little provocation. High environmental temperatures seem to be of great importance in reducing the threshold for blistering. Like other types of epidermolysis bullosa simplex, secondary infection is very common and is perhaps more of a problem in this than any other form of epidermolysis bullosa.

Oral involvement is usually not prominent. However, a proportion of severely affected neonates under the author's care have experienced extreme oropharyngeal blistering with potentially serious interference with feeding. These babies may demonstrate incoordination of swallowing with a tendency to aspirate feeds, and they frequently also demonstrate marked gastro-oesophageal reflux.

Hoarseness of the voice is quite often present, particularly in the more severely affected case; a weak cry may be noticeable in the neonatal period. In the past, laryngeal involvement was considered virtually pathognomonic of the Herlitz type of JEB, but it is now clear that it also occurs regularly in Dowling-Meara EBS.

Prognosis

Generally, the prognosis in EBS is good, particularly in the common Weber-Cockayne type, the great majority of patients having a normal life expectancy. However, disability can be significant, patients' choices of career, housing, employment and leisure activity being constrained by limitations on the distance they can walk. While the Dowling-Meara type of EBS can undoubtedly be lethal in early infancy, the blistering tendency tends to improve with time, and some adults who had problems with the condition as children later become more or less free from any evidence of the disease. However, other adults remain substantially disabled by Dowling-Meara EBS throughout their lives[20], particularly as a result of persisting blistering of the hand and feet, and palmar and plantar keratoderma.

Differential diagnosis

The principal problem in diagnosis of the commoner varieties of EBS is to distinguish them clinically from other forms of EB, though this is, in the main, only a problem in the neonatal period. Immunohistochemistry and electron microscopy of appropriate skin biopsies usually allow differentiation, but experience is required for reliable interpretation.

In the neonate, EB may be confused with any of the following: incontinentia pigmenti, miliaria crystallina, bullous ichthyosiform erythroderma, bullous impetigo or staphylococcal scalded skin syndrome, the EEC, AEC and Rapp-Hodgkin forms of ectodermal dysplasia (which all feature lip and /or palatal clefting), neonatal or congenital varicella and herpes simplex, neonatal pemphigus or pemphigid gestationis, infantile pemphigoid and cutis aplasia. In adults, pachyonychia congenita will need to be considered, particularly in Dowling-Meara EBS where palmar and plantar hyperkeratosis and nail thickening may both be prominent.

Treatment

In Weber-Cockayne and Köbner epidermolysis bullosa simplex, the long family association with the disease, combined with an awareness both of the provoking influences and the limitations of available therapy, make it fairly unusual for patients to seek medical assistance. When they do, the most useful contribution one can make is to provide advice about suitable footwear, general care of the feet and genetic counselling.

Fresh blisters should be drained after puncturing them with a sterile disposable needle, as they tend to extend if left alone. Where blisters tend to refill after simple puncturing, a small V-shaped incision with a pair of sharp sterile scissors may be more effective in ensuring decompression of the blister. If the patient finds compression painful after lancing the blister, aspiration can be performed using a fine gauge needle and syringe. The blister roof should be left *in situ*. It is often useful to bathe blistered feet and hands in warm water containing potassium permanganate at a dilution of about 1:8000. The ideal dressing for erosions and blisters in patients with epidermolysis bullosa simplex have yet to be invented, and none of the currently available products seems very precisely to fit these patients' requirements. Patients and their parents generally make up their own minds about the dressing materials that most suit their own needs, and the dermatologist's job is really to ensure, firstly that they are properly informed about the range of different types of dressing available, and, secondly, that they are able to secure a supply of their chosen dressings as economically as possible.

Because of the frequent occurrence of secondary bacterial infection, patients often like to use topical antimicrobial applications. However, we lack the ideal topical antimicrobial agent to protect these patient from secondary bacterial infections, and the regular use of any particular preparation tends to be associated with the development of bacterial resistance to the antimicrobial employed. We therefore tend to prefer to concentrate on physical cleansing and the use of potassium permanganate soaks as described above. If anything is to be applied to individual lesions, we prefer an antiseptic to an antibiotic,

but we discourage patients from using either. Of those preparations that are currently available, the least unsuitable would include 1.5% hydrogen peroxide cream (*Hioxyl,* Quinoderm, Oldham, UK), 10% povidone-iodine aqueous solution or ointment (*Betadine,* Napp, Cambridge, UK) and 0.5% cetrimide cream (*Cetavlex,* Care, Wilmslow, UK). The application of cornflour to eroded areas in EBS may be particularly helpful in drying the lesions and appears to hasten healing. Where blistering is predominantly on the feet, this may be applied directly into the socks before they are put on. Cornflour used in this way may also reduce the occurrence of new friction induced blisters.

It is important to provide children with epidermolysis bullosa simplex with footwear which allows them the maximum mobility while providing the best possible protection for their feet. Many children can wear 'off the peg' shoes if these incorporate appropriate design features. Ideally, these shoes are made of very soft leather, with the minimum number of internal seams. There should be plenty of room for the toes, in both the horizontal and vertical planes. Both the uppers and the insock should be made of permeable leather, in order to keep the foot as cool and dry as possible, and the inside of the sole should have a shape which is as anatomically appropriate as possible. Few 'off the peg' shoes fulfil these criteria, other than certain lines of *Elefanten* shoes (UK Agents: Intershoe Ltd, Stockton on Tees) which we have found more or less ideal. Socks should be absorbent and should therefore contain a high proportion of cotton. They should also provide additional cushioning; the towelling type of sport sock is ideal. It is sometimes useful for the patient to wear two pairs of socks as this helps to reduce friction.

A small proportion of babies and young children with köbner epidermolysis bullosa simplex, and a larger proportion with Dowling-Meara epidermolysis bullosa simplex may be very fragile, and they will need protective measures as described under dystrophic epidermolysis bullosa. However, it is very important to avoid the use of heavy dressings which may increase the skin surface temperature and therefore the rate of blistering. In children with Dowling-Meara epidermolysis bullosa simplex it seems especially important to check that clothing does not have rough internal seams, and that it fits loosely, especially at the neck, wrists and ankles.

Avoidance of high environmental temperatures whenever possible is a helpful measure, and it is especially important to keep affected infants cool. We use an air-conditioned cubicle for these infants during any admission to hospital, and we arrange for severely affected infants to be provided with a portable air-conditioning unit for use at home in the early years.

Topical application of 10% glutaraldehyde and 10% aluminium chloride hexahydrate haveboth been advocated for the soles of patients with Weber-Cockayne EBS[21,22], but neither have proven useful for the majority of patients.

A useful response of Dowling Meara EBS to the oral 5HT-2 antagonists pipamperone and cyproheptadine has been reported[23], but we have given cyproheptadine to several affected children with minimal benefit.

The author has occasionally used short courses of oral prednisolone to reduce blistering temporarily in Dowling-Meara EBS. The effectiveness of oral corticosteroid therapy in Weber-Cockayne was documented many years ago[24]. The use of such treatment may be worth considering as a short-term measure when symptoms are particularly distressing in any form of EBS.

Neonates severely affected with Dowling-Meara EBS have required nasogastric feeding for a period which may last several months.

Rarer types of epidermolysis bullosa simplex

Epidermolysis bullosa simplex with muscular dystrophy
This is a rare form of autosomal recessive EBS which is now know to reflect mutations in the gene coding for plectin (PLEC1), a cytoskeleton-membrane anchoring protein. Generalized blistering is of early onset, and the clinical features tend to be rather similar to those seen in junctional EB, with prominent periungual blistering, nail loss, atrophic scarring, dental enamel hypoplasia and occasional laryngeal blistering. The development of progressive muscular dystrophy, which may occur anywhere between the first year and the fourth decade of life, reflects the important role of plectin in skeletal muscle as well as skin.

Epidermolysis bullosa simplex superficialis[3]
A group of patients has been described in which blistering occurs just below the stratum corneum; inheritance was autosomal dominant. Despite the superficial level of cleavage, peeling of the skin was not noted; the patients reported generalised blistering and, frequently, the development of superficial erosions and crusting without prepeding blisters. Patients were also liable to a variable degree to milia, atrophic scarring, nail dystrophy, and oral and ocular involvement.

Kallin's syndrome[4]
This syndrome was described in 2 sisters, in whom it was thought likely to have been transmitted as an autosomal recessive trait. It featured blistering of the hands and feet, occasionally haemorrhagic, occurring mainly in the summer, essentially identical to those seen in patients with Weber-Cockayne EBS. However, these children also had hypodontia associated with a dental enamel dysplasia, increased curvature or thickening of the nails, and diffuse alopecia without scarring. One of the sisters had been discovered to be totally deaf in one ear when she was 5 years old.

Epidermolysis bullosa simplex with mottled pigmentation[25-27]
This condition has now been described by several authors, and is likely to be transmitted by an autosomal dominant gene. Affected individuals have lifelong, mechanically induced blistering, essentially indistinguishable from Köbner EBS, healing without scarring or atrophy. The mucosae are generally not affected. The blistering becomes less prominent with increasing age, and may even disappear. Pigmentary abnormalities are the main distinguishing feature of the disorder, and take the form of well-demarcated pigmented macules 2-5mm in diameter, most profuse on the trunk and the proximal limbs, which may be present from very early in life and whose appearance does not seem to be a direct result of blistering. In several case, there may be a mixture of hyper- and hypo-pigmented macules. Another fairly regular feature has been the development of small warty palmo-plantar keratoses measuring 2-5mm across.

'Lethal' autosomal recessive epidermolysis bullosa simplex[6]
This disorder has been described in a single Sudanese family in which it appeared to be inherited as an autosomal recessive trait. Generalised blistering healed without scarring. Anaemia was common and most affected individuals died in early childhood. The cause of death was likely to have been laryngeal involvement resulting in upper airways obstruction.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

Definition
A group of inherited disorders characterised by mechanically induced blistering occurring immediately below the lamina densa of the basement membrane zone.

Because of the characteristic level of cleavage, dystrophic epidermolysis bullosa is sometimes termed *dermolytic* epidermolysis bullosa. These disorders derive the name *dystrophic* from the tendency of the blisters to heal with atrophic scarring.

Aetiology and pathogenesis
Dystrophic epidermolysis bullosa may be inherited as an autosomal dominant or an autosomal recessive trait. In general, it tends to be most severe when inherited as a recessive, and mildest when inherited as a dominant, but there is considerable clinical overlap. In sporadic cases, it is therefore imprudent to guess the mode of inheritance on clinical grounds alone. In the great majority of cases of dominant dystrophic epidermolysis bullosa, there is a clear family history, suggesting a low rate of new mutations. Most sporadic cases of dystrophic epidermolysis bullosa seem to be of recessive type, even where clinically mild.

There are few data to indicate the prevalence of DEB. In Norway the prevalence of dominant DEB has been estimated to be 1.4 per million[9] . In England an estimated prevalence for all recessive types of EB was 3 per million[28], of which most were probably cases of DEB. A more recent estimated prevalence from Scotland was 21.4 per million for all types of dystrophic EB[7].

Linkage and mutational analysis have demonstrated the likelihood that all types of dystrophic EB reflect mutations in the gene for type VII collagen (known as COL7A1)[30,31], which has been localised to the short arm of chromosome 3 at the 3p21.1 locus[32]. Type

VII collagen is a major component of anchoring fibrils[33-34]. It is a large molecule (approximately 1000kDa), which is synthesised and secreted by keratinocytes. Structurally, it comprises a homotrimer of 3 a1(VII) chains which associate to form a triple helix. The molecule has 3 domains: a central triple helical domain consisting of (Gly-X-Y) repeats and 2 non-helical globular domains termed NC-1 and NC-2. Type VII procollagen molecules associate via their carboxy- terminals, following which the NC-2 domains are cleaved off. The resulting type VII collagen molecules further condense to form anchoring fibrils.

It is becoming clear in dystrophic EB that the type of mutation or mutations present in the type VII collagen gene will be increasingly able to predict the clinical severity and prognosis of that individual's disease[35]. There is evidence that the most severe forms of recessive dystrophic EB reflect mutations that result in premature termination of translation and in truncated a1(VII) chains[36-38], while alterations of the NC-2 domain cause milder recessively transmitted disease not manifest in heterozygotes[39]. Dominantly transmitted disease may generally reflect mutations affecting the triple helical domain[31].

Pathology

Dystrophic epidermolysis bullosa is the clinical reflection of defective attachment of the basement membrane to the underlying dermis, manifest at the ultrastructural level by reduced numbers of morphologically abnormal anchoring fibrils[40]. The monoclonal antibody LH 7:2 binds to the basement membrane zone in normal skin, but not in severe recessive dystrophic epidermolysis bullosa. It is now clear that this antibody binds to the NC-1 domain of type VII collagen. While there is generally no binding at all in severe recessive dystrophic epidermolysis bullosa, binding is often weakly present in milder recessive dystrophic epidermolysis bullosa, but is normal in dominant dystrophic epidermolysis bullosa[41-45].

Clinical features

There is very wide variation in the severity of the dystrophic epidermolysis bullosa in different patients, reflecting the many different mutations that may affect the type VII collagen gene. At its least severe, dystrophic epidermolysis bullosa can allow an almost normal quality and length of life, while at its most severe, it may cause major handicap and a relatively brief and painful life.

Skin

The clinical hallmark of dystrophic epidermolysis bullosa is the tendency for blistered areas to heal with atrophic scarring and the development of contractures. While the presence of milia in recently healed areas is highly characteristic of dystrophic forms of EB, milia may more transiently be seen in other types of EB.

In the past, attempts were made to subdivide dystrophic epidermolysis bullosa into a number of distinct subtypes. Such efforts were in practice hampered by the considerable

degree of overlap observed between different subtypes, and it is the writer's view that an obsession with precise categorisation of the individual case is generally unnecessary and unhelpful. It is all too easy for an academic preoccupation with classification to distract from the more urgent and important matter of providing care and advice to patient and family. In the individual case it is sufficient for the purpose of clinical management to establish that the patient has a dystrophic form of the disease. Beyond this, the most important issue is whether it has been transmitted as an autosomal dominant or recessive trait, for the purposes of genetic counselling and prenatal diagnosis. However, apart from the wide variability in the severity of the different clinical manifestations of dystrophic EB in individual patients, it is possible to recognise a pattern of cutaneous disease in a minority of cases in which the trunk and proximal flexural areas are predominantly affected, in contrast to the more usual predilection for peripheral areas. In patients with this 'inverse' pattern[46,47], the hands tend to be less severely affected, but the non-cutaneous aspects of the disease are generally just as troublesome.

Blistering in dystrophic epidermolysis bullosa tends to be provoked predominantly by knocks and blows to the skin rather than by rubbing as is the case in epidermolysis bullosa simplex. Blisters in dystrophic epidermolysis bullosa therefore occur most frequently at skin sites where knocks and blows are common, such as the dorsa of the hands and feet, and the elbows and knees. However, persistent rubbing of the skin does also predispose to blistering, especially rubbing by clothing and bedding such as occurs around the neck, the waist, groins, hips and the lumbosacral area. Another prominent cause of blistering and ulceration is the attachment of anything adherent to the skin, such as adhesive tapes; this feature has great practical importance in initial clinical recognition of the disease in the neonate and in management of the patient. However, in the longer term, perhaps the most important provocative factor of all is excoriation by the patient of healing or recently healed areas of skin.

The blisters may vary considerably in size, and some patients may develop blisters that exceed 10 cms in diameter. The blisters tend to be rather flaccid, and are filled with either clear or blood-stained fluid. Healing of previously unblistered sites is generally fairly rapid. Crops of milia are common following initial re-epithelialisation, but where an area is not subject to further blistering, the milia disappear after a few months. Discernible scarring is unusual following a single episode of blistering in a particular area, and generally only follows recurrent blistering. Blistering is much more easily provoked in areas that have previously been blistered, particularly when scarring has occurred. Healing areas tend to itch, and when the patient scratches, further blistering is likely to follow. This can establish a cycle of blistering, itching and reblistering, the situation being made ever worse by the decreasing quality of healing and the increasing ease with which reblistering therefore occurs. Scarring is often not apparent after a particular area of skin has only been blistered once, but becomes progressively more apparent the more often blistering occurs.

In the great majority of cases, blisters or, more often, erosions are present at or very shortly after birth. Rather commonly, an extensive eroded area is present at birth on one

or both lower legs, usually on the dorsum and lateral aspect of the foot and on the medial and anterior aspect of the shin. This type of lesion almost certainly evolves *in utero* as a result of the fetus rubbing the one leg against the other. When unilateral and in the absence of other lesions suggestive of epidermolysis bullosa, the significance of this type of lesion may not be appreciated. Such congenital absence of the skin on the lower leg is not specific for any particular type of EB[48]. These areas usually heal fairly rapidly, though the resulting scarring frequently leads to some deformity, particularly to upward displacement of the great toe, and to diminished growth of the foot.

New blisters develop less frequently with increasing age. It is unclear whether this is because of a genuinely decreased tendency of the skin to blister or is simply a reflection of more effective avoidance of trauma by older patients. In patients who are more severely affected, this trend is often counterbalanced by the steadily increasing fragility of skin that has been repeatedly ulcerated in the past, and which becomes atrophic and as delicate as tissue paper. Whereas previously ulcerated areas would usually heal rapidly, these atrophic areas may now break down so frequently that they never seem to heal. The neck, axillae, elbows, hands, hips, knees and ankles seem to be among the most troublesome sites from this point of view. Nevertheless, most patients who survive into adult life may nevertheless enjoy a gradual improvement in the quality of scarred areas alongside a greater resistance of the skin to the development of new blisters. In those with mild dystrophic EB, scarring can almost disappear in adult life, leading to a remarkable improvement in the appearance for example of the hands.

Patients with dystrophic EB quite frequently develop areas of dark macular pigmentation rather characteristic irregular borders which may show histological features resembling malignant melanoma[49]. True malignant melanoma has been reported but is probably rare[50].

The most sinister late complication of dystrophic epidermolysis bullosa is the tendency for epitheliomas, predominantly squamous carcinomas, to develop in recurrently ulcerated and scarred areas, particularly over bony prominences on the limbs50-57. The incidence of these tumours reaches its peak in the third and fourth decades. Tragically, patients are very often unaware of this danger and may therefore fail to bring such lesions to medical attention in good time. As a result, death from metastatic disease is frequent in some series[58]. Squamous carcinoma is a major cause of death in patients with severe dystrophic EB that survive into adult life.

Albopapuloid dystrophic EB

The term 'albopapuloid' was first used by Pasini[59] to describe the ivory-white papules he observed in 2 patients with dystrophic EB. These lesions are generally small and multiple, but may coalesce to form plaques up to about 4cm in diameter. They are most often seen on the trunk, especially the lower back, but they have also occurred at other sites. Although it was initially believed that lesions of this type were specific to a particular autosomal dominant variant of dystrophic EB, it now seems more likely that they are

non-specific though they tend to be seen most often in older children and adults with relatively mild dystrophic EB. They have been reported in otherwise unremarkable cases of recessively inherited dystrophic EB[60], and in both pretibial EB[61] and EB pruriginosa[62].

Epidermolysis bullosa pruriginosa[62,63]

There appears to be a fairly distinctive clinical variant of dystrophic EB in which the predominant features are pruriginous papules or lichenified plaques, associated with scarring. Lesions occur mostly on the limbs, particularly on the shins, but may also be seen on the trunk. Itching is often marked. Finger and toe nail dystrophy is very common, with thickening or loss of the nail plate. Because intact blisters are rarely seen, the fact that the patient has dystrophic EB can easily be overlooked. Mucosal lesions tend to be absent. Where familial cases have occurred, inheritance has generally been autosomal dominant.

Pretibial epidermolysis bullosa[61,64-66]

In this variant of dystrophic EB, blistering and scarring are predominantly frequently exclusively located on the shins. There may be associated toenail dystrophy.

Transient bullous dermolysis[67-70]

A subgroup of infants with dystrophic EB can be defined on the basis of abundant amounts of type VII collagen found intra-epidermally on immunocytochemistry. These infants have a relatively good prognosis, with most enjoying virtual resolution of their disease by the end of the first year of life, though initially blistering may be severe, even fatal[71]. It appears likely that there is a transient abnormality of handling of type VII collagen in these cases. The intra-epidermal type VII collagen may disappear within a few weeks of birth, so that it is important to take skin biopsies within the first 2 weeks of life if this variant of dystrophic EB is to be recognised.

It is important to be aware that sparse deposits of intra-epidermal type VII collagen may be found quite commonly in all forms of dystrophic EB as long as the disease is active, if sufficiently sensitive methods are used, perhaps in up to a third of cases, but this finding probably has little significance[72].

Hands

Cutaneous scarring in dystrophic epidermolysis bullosa may lead to a variety of complications, particularly to joint contractures, and to fusion of the fingers and toes. Progressive hand deformity is common in patients who blister readily. When digital fusion is going to develop, one can usually detect the earliest signs of the process within the first year of life. By this age, one can also usually gain some idea of the likely speed of its progression. The process of fusion seems to occur rather insidiously in the apices of the interdigital spaces, where careful examination will generally reveal small fissures. Occasionally, accidental trauma will lead to denudement of skin on the opposing aspects of more than one finger. If the fingers are opposed during healing, they may become fused within hours. Children with severe dystrophic EB are always at risk of acute loss of

the entire skin cover of one or more fingers or of an entire hand, an injury known as 'degloving'. This is especially likely to happen when a small child stumbles whilst holding an adult's hand. The adult holds on tightly to prevent the child from falling only to remove the skin from much of the hand; it requires no imagination to realise how distressing such an event will be both to child and adult.

Surprisingly good hand function may be retained despite marked digital fusion, so long as opposition of index finger and thumb is retained. More disabling is the development of flexion contraction of the hand, due to fibrosis of the skin on the palmar aspects of the fingers and hand.

Nails
Subungual blisters are common, and are generally followed by partial or complete separation of the nail plate. The nail will usually regrow normally after his has occurred on one or two occasions, but repeated nail loss will lead to the development first of nail dystrophy and, then, permanent nail loss. In the very mildest cases of dystrophic epidermolysis bullosa, nail dystrophy may be an important diagnostic aid, particularly dystrophy of the great toe nails.

Upper gastrointestinal tract
Blistering of the oral, pharyngeal and oesophageal mucosa is common in dystrophic epidermolysis bullosa, and may lead to a number of problems73-76, of which the most important are:

a. pain, leading to reduced nutritional intake,

b. progressive contraction of the mouth,

c. progressive fixation of the tongue,

d. dental caries due to oral infection and impaired dental hygiene,

e. oesophageal dysmotility and strictures/webs[77-80]

f. gastro-oesophageal reflux

Dysphagia is a rather common complication of dystrophic epidermolysis bullosa, particularly of severe recessively transmitted disease, but it can occasionally be seen in patients in whom skin involvement is relatively trivial. Many factors contribute to this dysphagia, and although great emphasis has been placed on the the role of oesophageal strictures in causing dysphagia, these are not their only, nor perhaps even their most important cause. Major contributions are made by problems in the mouth, particularly by submucous fibrosis in the oral cavity, contraction of the oral and pharyngeal openings, and by fixation of the tongue. In addition, the teeth are often very poor and many may have been extracted. Extremely painful erosions are frequently present in the mouth and pharynx. Combinations of these problems cause patients great difficulties in chewing and swallowing normal food. Eating is often painful, slow and exhausting, so that only

relatively small quantities of food can be coped with at any meal.

Gastro-oesophageal reflux, both symptomatic and asymptomatic, is exceedingly common in children with dystrophic EB, from early infancy. It is probable that such reflux would contribute substantially to dysphagia by aggravating oral, pharyngeal and oesophageal ulceration, by increasing dental decay, and by accelerating oesophageal stricture formation. Gastro-oesophageal reflux is an additional reason why children with dystrophic EB may restrict their nutritional intake. We have a patient who has a laryngeal stricture which we believe is the consequence of recurrent aspiration of gastric acid; he now has a tracheostomy.

There is no evidence that the small intestine is affected and malabsorption is not a problem.

Constipation
Chronic constipation is a common complication of dystrophic EB. It is caused principally by anal fissuring, which leads to painful defaecation and therefore to faecal retention, faecal soiling and overflow, and to constipation[75,81]. The tendency to constipation is aggravated by a low dietary fibre intake[80,82]. It seems probable that these patients' tendency to take food in frequent small quantities, rather than in discrete meals of reasonable size, leads to a degree of disordered intestinal peristalsis, which will tend to aggravate the constipation still further. The tendency to chronic constipation is frequently compounded by sub-optimal fluid intake, administration of oral iron supplements and generalised apathy

These problems are frequently underestimated, but frequently have a major impact on patients' quality of life. Besides causing great discomfort, they frequently exert a substantial adverse effect on the patients' nutritional status, principally because of secondary anorexia. Any decrease in appetite is critical in these patients since their dietary intake is already almost invariably low. A frequent and undesirable consequence of constipation is that it presence often discourages oral administration of iron.

Teeth
Rapidly progressive caries is a regular feature in patients with severe dystrophic EB. It results from chronic intraoral infection and gum disease, a high sucrose intake and the absence of the normal physical cleansing effect of food due to the diet being more or less liquid. The situation is made worse in severe dystrophic epidermolysis bullosa by the loss of the gingivobuccal sulci, causing residual food remaining applied to the buccal surfaces of the teeth for long periods, and by the loss of the normal cleansing of the teeth because of fixation and shrinkage of the tongue83. There is no evidence of a dental enamel defect84.

Eyes [85-87]
Conjunctival bullae occur quite frequently in patients with severe dystrophic epidermolysis bullosa, and lead to conjunctival ulceration and painful corneal erosions.

These may result in conjunctival and corneal scarring, and symblepharon, and may threaten vision in the longer-term, both directly and indirectly, by interfering with tear film stability and tear production.

Genito-urinary tract

A few boys will develop phimosis, and scarring of the external genitalia in a girl led to diversion of the urine into a distended vagina and into the uterus[88]. Children of both sexes may very occasionally develop strictures of the urethral meatus, resulting in urinary retention[89]. We have seen temporary but recurrent obstruction of the urethral meatus in boys lead to urine tracking under the epithelium of the glans.

Kidneys[90]

Chronic post-infectious glomerulonephritis, considered likely to be a complication of secondary streptococcal skin infection, has been reported in a 10 year old child with severe dystrophic EB. Nephrotic syndrome secondary to renal amyloidosis has also been recorded in a 17 year old.

Anaemia

Anaemia is a problem in most patients with severe dystrophic epidermolysis bullosa. Investigations demonstrate haematological features both of iron deficiency and of decreased red cell iron utilisation ('anaemia of chronic disease'). The iron deficiency probably reflects both chronic blood loss from skin, mouth, oesophagus and anal canal, and poor iron intake.

Heart

There have been several reports of fatal dilated cardiomyopathy in children with severe dystrophic epidermolysis bullosa[91-3]. In one of these, the cause was suspected to have been secondary haemochromatosis following multiple blood transfusions[92]. A role for selenium deficiency has also been proposed[93].

Nutritional problems[82,94,95]

The malnutrition which occurs in severe DEB is a consequence of a combination of decreased nutritional intake and increased requirements. Intake is reduced for a variety of reasons, including oropharyngeal ulceration, fibrosis leading to restricted opening of the mouth, tethering of the tongue, oesophageal dysmotility and strictures, and secondary anorexia due to chronic constipation, resulting from anal fissures and faecal retention. Requirements are increased as a result of loss of blood and plasma from denuded epithelium, skin infection and continuous wound healing.

Children with severe dystrophic EB on unsupplemented diets tend to consume inadequate amounts of iron, zinc, magnesium, calcium, vitamins, protein, energy and fibre, and are shorter and thinner than normal controls. Laboratory investigations indicate deficient levels of selected micro-nutrients, notably plasma iron and zinc, and vitamins A and B6. The malnutrition that results exerts a major detrimental impact on growth, wound healing, resistance to infection, quality of life and mortality. Those who survive into adult life frequently demonstrate short stature, cachexia and delayed sexual maturation.

Growth

Children with more severe dystrophic epidermolysis bullosa tend to grow poorly. A decrease in linear growth velocity is usually preceded by an inadequate rate of weight gain, implying that the growth effect is secondary to inadequate nutrition. Anaemia probably also makes a significant contribution.

Prognosis

There is an extraordinary variation in prognosis in dystrophic EB. Patients with the mildest clinical presentations will enjoy early cessation of blistering, occasionally even in the first year of life. On the other hand, more severely affected individuals will experience increasing malnutrition, increasing anaemia, and progressively increasing disability due to interference with joint mobility. While it is now relatively rare in good centres for children with dystrophic EB to die in infancy, death towards the end of the first decade remains a threat to the most severely affected. The final cause of death in these cases is very frequently overwhelming sepsis, probably mainly a reflection of deteriorating nutritional status. There is some correlation between the amount of type VII collagen seen immunohistochemically at the basement membrane and the prognosis, complete absent suggesting a worse outlook. The good prognostic significance of abundant intraepipermal type VII collagen has already been highlighted.

Differential diagnosis

Differential diagnosis is normally only a problem during the neonatal period. The principal conditions that require consideration at this time include 'sucking blisters', congenital herpes simplex, the various causes of cutis aplasia congenita, incontinentia pigmenti, focal dermal hypoplasia, bullous ichthyosiform erythroderma, transplacental herpes gestationis and pemphigus vulgaris, miliaria crystallina, bullous impetigo and staphylococcal scalded skin syndrome.

During the neonatal period, it is unwise to attempt to distinguish the various types of epidermolysis bullosa clinically. The later appearance of milia is indicative of dystrophic epidermolysis bullosa, though small numbers of milia can undoubtedly be seen from time to time in non-dystrophic types.

Early diagnostic biopsy is important, but considerable skill is required in interpretation of results, and such biopsies may be of limited value in centres unaccustomed to handling them. The technique of taking a biopsy in epidermolysis bullosa is discussed above. In our unit, all specimens are examined immunohistochemically with LH7.2 antibody (for collagen VII) and GB3 antibody (for laminin 5), and ultrastructurally to identify the level of splitting and to examine the various structures normally present in the basement membrane zone.

Treatment[1,2,96,97]

We will generally keep new babies with epidermolysis bullosa in hospital until the clinical situation is stable and the parents feel confident enough to take over in their own home. There is of course a great deal to be done while the child is in hospital in addition to the basic skin care. Precise diagnosis has to be made, and much time needs to be spent with parents explaining the nature of their child's problems and its care. Feeding and nutritional problems have to be overcome. Before the child's departure from hospital, contact must be made with community nursing and medical staff, and local social services. The genetic implications need to be clarified with the parents, and the risks to further offspring must be delineated as far as possible at this stage. The availability of the means to prevent the birth of a similar child must be explained to parents; it is the clear responsibility of the child's doctors to do so whatever their personal views. It is advisable, lest the issue subsequently be neglected, to do this during the affected child's first admission.

Subsequently, in our unit we generally review the more mildly affect patients in the out-patient clinic, but we would arrange brief admissions for multidisciplinary review for the more severely affected.

a. Skin care.

Skin care in patients with epidermolysis bullosa must incorporate the twin objectives of protection against trauma and provision of optimal conditions for healing of blisters and erosions, in such a way as to minimise disability. A third objective is surveillance for epidermal neoplasia in adult patients.

Neonates

The skin of neonates with epidermolysis bullosa may be extraordinarily sensitive, even to 'normal' handling. Infants transferred to our unit frequently have erosions on each side of the trunk where they have been picked up earlier. Sometimes there are 5 on each side, one for each of a nurse's or midwife's fingers. Therefore, special handling techniques are required. In addition, where possible, it is now the authors' preference for neonates with EB to undergo initial assessment by a clinical nurse specialist at the unit where they were born to avoid unnecessary trauma from transfer at this critical stage.

Unless for reasons such as prematurity babies with EB should not be nursed in an incubator as the heat and humidity can encourage further blistering. The cord clamp should be removed and replaced with a ligature to avoid damaging the skin. Name bands should not be used since they easily blister the skin of the wrist or ankle. Babies with epidermolysis bullosa should not be nursed naked. Such babies are usually uncomfortable, irritable and restless; they will therefore generally do themselves considerable harm, for example by rubbing together their legs, and their lesions heal relatively slowly. Babies wearing the correct dressings are usually more comfortable and are to some extent shielded from external mechanical trauma, particularly that which is self-induced. Once dressings are in place, the baby is clothed in soft clothing, turned inside out to avoid

rubbing from seams, which provides added protection during handling. When picking up the baby, the hands should not be pushed underneath, but the baby should first be rolled away, and then allowed to roll back on to the hands and lifted. No child with epidermolysis bullosa of any age should ever be lifted under the arms. There is a danger that parents will be discouraged from handling their baby; it is however important for them to do so, and handling should be encouraged once the correct techniques have been learnt.

We change dressings as necessary. We like to drain new blisters after puncturing them with a sterile disposable needle, as they will often extend if left intact; the blister roof is left in situ. After bathing in warm water, the baby is patted, rather than rubbed dry, with a soft but non-fluffy sheet or towel.

We currently employ the following dressing techniques: Following bathing, erosions are covered with Mepitel dressings (Mölnlycke). Mepitel comprises a silicone mesh, which although "sticky" to the touch, is easily removed from the wound, with pain or trauma. Aquacel (Convatec), a hydrofibre dressing can be applied over the Mepitel in very moist areas. A secondary dressing is applied over the Mepitel, e.g. Mepilex (Mölnlycke) or Mepliex Transfer (Mölnlycke). Mepliex has a similar silicone surface and, hence the same stickiness as Mepitel, but also has a foam backing providing absorption from exudative erosions as well as a degree of protective cushioning. Mepilex Transfer has a thinner layer of foam than the Mepilex and is useful for sites such as axillae where a conforming dressing is required. Both Mepilex and Mepilex Transfer are designed to be used as a primary wound dressing, but in the author's experience these have a tendency to adhere to the wounds in those with a severe form of epidermolysis bullosa and need to be used a s secondary dressings in conjunction with Mepitel. Alternative secondary dressings include Release (Johnson and Johnson, Slough, UK), Avance (SSL) and Lyofoam (SSL). The above dressings are secured by a suitable conforming bandage, e.g, K Band (Parema), and or a tubular stretch bandage such as Tubifast (SSL). The great advantage of Mepitel and Mepilex is that they need only to be changed once or twice a week, saving time for the carers and reducing the pain for the child, whilst allowing healing to take place. The secondary dressing overlying the Mepitel can still be changed daily if there is any exudate. Previous application of any cream or ointment appears to reduce the efficiency of MepitelR. However, we have found it very satisfactory to apply creams or ointments over the MepitelR when this is necessary, eg topical corticosteroids to reduce pruritus (see below).

The use of these dressings is generally associated with a good rate of re-epithelialization, probably reflecting both their occlusive and protective properties. However, they are not used soley to encourage healing of blistered areas; they are also useful for protection in any area, whether affected or not, which is liable to blistering. Parents should be encouraged to learn these techniques and to use them after they take the baby home.

Mepiform (Mölnlycke) is invaluable for securing intravenous cannulae, as its adhesive

properties hold the cannula in place, but in contrast to adherent tapes, removal does not cause any damage to the skin.

Older infants and toddlers

Over the months that follow birth, dressing methods need to accommodate the child's increasing need for mobility and play. However, as the child becomes more mobile, the risk of external trauma from falls and knocks becomes a greater factor, at least initially. Later, as the child gradually learns to become more careful, the risk of mechanical trauma again diminishes. Sadly, toddlers are notoriously careless, and certain sites tend to become recurrently traumatized. In dystrophic epidermolysis bullosa, these sites become permanently scarred, a problem because such areas are less resistant to subsequent trauma than unscarred areas. The sites that are at special risk in the toddler are the elbows, wrists, hands, knees, shins, ankles and feet. Many parents elect to use protective dressings to cushion these sites. An appropriate technique is to use LyofoamR (SSL) on intact skin, or Mepilex at an eroded area, over which is applied Tubifast (SSL) an elasticized viscose tubular bandage. TubipadR (SSL), a foam-lined tubular bandage, on the areas that require protection. Alternatively, materials such as quilting can be sewn inside commercially bought clothing in order to protect at-risk areas.

The ideal dressing for erosions and blisters in patients with epidermolysis bullosa beyond infancy has yet to be invented. None of the currently available products seems very precisely to fit these patients' requirements although in the authors' experience, Mepitel and Mepilex used as described above, provides a comfortable dressing which encourages re-epithelialisation of broken skin. Patients and their parents generally make up their own minds about the dressing materials that most suit their own needs, and the dermatologist's job is really to ensure firstly that they are properly informed about the range of different types of dressing available, and, secondly, that they are able to secure a supply of their chosen dressings as economically as possible. There can be little question that relatively occlusive dressings are more effective in accelerating healing[98,99].

Clearly, avoidance of trauma is an important facet of treatment of these children. It is extremely difficult however for parents to get the balance right between what could be regarded as appropriate avoidance of trauma and overprotection of the developing child. Children with epidermolysis bullosa should be brought up as normally as possible, in order to maximise their physical, manipulative and social skills. They gradually themselves learn to take extra care, and to avoid situations in which trauma is likely to occur. Older children with epidermolysis bullosa learn to stand back when other children scuffle. However, during the toddler phase, they tend to be rather careless, and may need someone on hand to patch them up after tumbles. In order to give them the best chance of taking part in normal activities, the emphasis should be on the provision of protective dressings and clothing, rather than on the avoidance of all remotely physical activities.

It is particularly important to provide children with epidermolysis bullosa with footwear which allows them the maximum mobility while providing the best possible protection for their feet. Ideally, their shoes will be made of very soft leather, with the minimum number of internal seams. There should be plenty of room for the toes, in both horizontal and vertical planes. Both the uppers and the insock should be made of permeable leather, in order to keep the foot as cool and dry as possible, and the inside of the sole should have a shape which is as anatomically appropriate as possible. In practice, few 'off-the-peg' shoes fulfill these criteria. However, certain lines of Elefanten® shoes (UK Agents: Intershoe Ltd, Eveline House, Preston Farm Business Park, Stockton on Tees. Tel. 01642-677222) appear to be more or less ideal. Some children will have misshapen feet due to early damage and subsequent scarring with contraction. They will require tailor-made shoes, which will similarly need to incorporate the features listed above; Schein® shoes have been recommended by some orthotists, and are available from Salt and Son Ltd, Saltair House, Lord St., Birmingham B7 4DS, UK. Tel. 0121-359-5123). In order to protect the toes from damage often caused by other children stepping on them, it is helpful to incorporate a protective toe-cap into tailor made shoes, or to adapt 'off-the-peg' shoes.

Socks should be absorbent and should therefore contain a high proportion of cotton. Wearing 2 pairs of socks can help to reduce friction. Socks should provide additional cushioning for the foot; the toweling type of sport sock is ideal. Other clothing needs to be chosen carefully. Before purchase, all items should be inspected to check that they do not have rough internal seams, and that they fit loosely, especially at the neck, wrists and ankles. In the UK, a good range of suitable clothes is available from sources that specialise in clothing for those with skin diseases, such as Cotton-On (Monmouth Place, Bath BA1 2NP Tel: 01225-461155).

Older children and adults

The great majority of patients with epidermolysis bullosa find that new blisters develop less frequently with increasing age. It appears probable that there is a genuinely decreased tendency of the skin to blister, coupled with more effective avoidance of trauma by older patients. In the case of patients with severe dystrophic epidermolysis bullosa, this gradual improvement is sometimes counterbalanced by the steadily increasing fragility of skin which has been repeatedly ulcerated in the past, and which may locally be atrophic and exceedingly delicate. These areas may break down so readily that they never heal for long. The neck, back, axillae, hips, knees and ankles seem to be among the most troublesome sites from this point of view. It is tempting to consider skin grafting such areas, but this has proved to be of limited value in ensuring permanent healing in this situation50. Similarly, cultured keratinocytes from normal human skin have failed to produce lasting benefit[100].

Adults with dystrophic EB need to be aware of the need for constant surveillance of their skin for the development of squamous carcinoma. It is exceedingly unusual for such lesions to occur in the pre-adolescent. Sadly, it is not uncommon for patients with epidermolysis bullosa to become disenchanted with the medical profession; such patients

may fail to ask for help with an unfamiliar skin lesion, and they are often not aware of the risk of malignancy. Even if they do seek medical advice, their doctor may also be ignorant of this important and potentially lethal complication. It is of the greatest importance that all patients with dystrophic epidermolysis bullosa be fully educated in relation to this risk, and that they should report promptly any unusual skin lesion, particularly nodules, or ulcers or crusted lesions which seem particularly unwilling to heal. They should be carefully examined at least once yearly, though this can be difficult to do in an out-patient setting because all dressings have to be removed; it may therefore be more convenient for patients to be admitted briefly for this purpose.

b. topical anti-microbials

Secondary bacterial infection is a constant problem in blistered and eroded areas, and it frequently delays healing. Great caution must be exercised in the use of topical antibacterial agents in epidermolysis bullosa because of the twin risks of induction of bacterial resistance, and of adverse effects that may either be systemic as a result of their percutaneous absorption, or local, usually in the form of interference with healing.

One of the first reports of *Staphylococcus aureus* resistant to mupirocin related to a patient with epidermolysis bullosa[101]. Whereas at one time the use of this agent was advocated[102], it soon became clear that such an approach would inevitably be complicated by the induction of resistant *Staphylococcus aureus*[103].

The potentially serious hazards of systemic absorption of topical antibacterials should not be underestimated in patients with epidermolysis bullosa, particularly when they are used in children. We have seen children with impaired hearing in whom we strongly suspect past ototoxicity from ill-advised applications of bacitracin, polymyxin, neomycin or gentamicin, to extensive areas of de-epithelialised skin under partially occlusive dressings. Chlorhexidine is potentially neurotoxic, and povidone-iodine may be thyrotoxic.

For these reasons, the use of topical antimicrobial agents should in our view not be routine, and should generally be avoided wherever possible. We still lack the ideal topical antibacterial agent to protect these patients from the secondary bacterial infections that tend to be such a problem for them. Of those preparations that are currently available, the least unsuitable appear to be 1.5% hydrogen peroxide cream (*Hioxyl*, Quinoderm, Oldham, UK) and 1% silver sulphadiazine cream (*Flamazine*, Smith & Nephew, Romford, UK).

Some patients apply various natural substances to ulcerated areas with the aim of accelerating healing. These include honey[104] and sucrose[105], which may discourage micro-organisms by providing a hyperosmolar environment. Unfortunately, the beneficial or other effects of such agents have very rarely been the subject of scientific evaluation and it is therefore difficult to comment upon their value.

c. other topical and systemic therapy

Over the years a number of systemic agents have been reported to have beneficial effects in dystrophic epidermolysis bullosa; the principal claims for such agents have been

reduced blistering rates and accelerated healing.

(i) phenytoin, protease inhibitors, retinoids and tetracyclines
Early ultrastructural studies of recessive dystrophic epidermolysis bullosa suggested that collagen breakdown in the papillary dermis might contribute to the development of blisters. The subsequent observation that skin fibroblasts cultured from patients synthesise increased amounts of a structurally altered collagenase appeared to strengthen this view and provided the rationale for the therapeutic use of phenytoin, as this agent appeared able to reduce this collagenase production *in vitro*. After early reports of clinical benefit from oral phenytoin[106], a larger multi-centre controlled trial failed to confirm this impression of therapeutic benefit[107], and phenytoin is no longer widely used. We were always extremely anxious about its use in infants because of its significant adverse effects, which include megaloblastic anaemia, lymphoma, encephalopathy and choreoathetosis.

Following the demonstration that retinoids are able to inhibit collagenase activity in vitro, there was interest in their possible therapeutic value in recessive dystrophic epidermolysis bullosa. However, these drugs have not to date turned out to be helpful in practice[108], and if they are given in high dose may lead to increased skin fragility.

Tetracyclines have also been shown to inhibit collagenase, and minocycline has been reported to have decreased the rate of blistering in severe dystrophic EB[109]. Similarly, topical protease inhibitors have been reported to have been helpful in reducing blistering rates[110].

Increased protease activity in dystrophic EB is currently regarded as a secondary phenomenon, and none of the above agents has proved to be of consistent therapeutic value in clinical practice.

(ii) corticosteroids
In the past, many patients with severe dystrophic EB were treated with oral corticosteroids[111], and this therapy did appear to lead to genuinely decreased blistering rates. However, the current consensus is that the longer term toxicity of this form of treatment outweighs any benefits, and it is generally avoided. Its use has been considered in specific situations, such as for a few months after restorative hand surgery, or after oesophageal dilatation for dysphagia, but there is no evidence that patients have enjoyed worthwhile degrees of benefit from this intervention.

On the other hand, it appears to us that topical corticosteroids can be of great value in the treatment of pruritus in healing and healed areas. Dealing with the substantial pruritus experienced by many patients not only enhances patients' comfort but has the important benefit of averting damaging excoriation and reblistering. This approach requires considerable judgement in terms of selection of an appropriate potency of topical corticosteroid for the individual patient depending on age, extent of area to be treated, and response to treatment. We have used highly potent preparations intermittently without the development by patients of worrying adverse effects. However, the optimum method of using topical corticosteroids in this situation has yet to be established.

(iii) vitamin E

Over the years, there has been interest in the possible value of vitamin E as a treatment for dystrophic epidermolysis bullosa, but little objective evidence of benefit.

d. prevention and treatment of complications
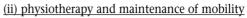
(i) digital fusion and contracture

In our view, corrective surgery should be undertaken as soon as the function of the hand is signicantly impaired[112,113]. Function is mainly compromised by flexion and by fusion of the first interdigital web. Ideally, only one hand should be operated upon at one time. The surgical procedure involves firstly separating the fused digits, and then releasing any contractures as completely as possible. Split-skin grafts are then sewn into place in the resulting defects along the separated surfaces and on the palmar aspect of previously flexed joints. Where the hand is almost completely encased, the whole extremity may be more conveniently 'degloved' before proceeding to separate the fingers completely and release the contractures.

Kirschner wires are sometimes used to maintain extension during the immediate post-operative period, and are particularly valuable in maintaining complete separation between thumb and index finger. It is however of great importance to splint the hand in a flat position, with all joints extended as fully as possible between plaster-of-Paris slabs on the front and back of the hand. The dressings are changed under general anaesthesia at 1-2 weeks and at about 4 weeks.

While this type of surgical procedure is technically relatively straightforward, the benefit may be limited by rapid recurrence of flexion deformity and digital fusion. For this reason, it is essential to use early post-operative hand splintage in an attempt to maintain extension and separation of the fingers. Traditionally, hard acrylic splints have been employed; these are generally made by taking an impression in dental alginate at the second dressing change. We now prefer a new type of splint that is easier and cheaper to produce, more comfortable to wear and easier to replace when necessary. These splints are made of a thin and light thermoplastic material, with silicone rubber inserts between the digits[114]. After surgery, children initially wear the splints continuously for three months, then for decreasing periods during the day, until after 6 months they wear them only at night.

Unfortunately, these operations often need to be repeated from time to time. It may be necessary to relieve similar flexion contractures at other joints, especially in the feet, at the knees, hips and in the axillae.

It is perhaps surprising that skin autografts can be so easily and successfully undertaken in patients with dystrophic epidermolysis bullosa. Attempts to grow therapeutically useful autologous keratinocyte sheets *in vitro* from patients with dystrophic epidermolysis bullosa have been frustrated by the tendency of the cells to separate from one another in culture.

(ii) physiotherapy and maintenance of mobility

Physiotherapy probably has little part to play in the treatment of established flexion contractures, but is useful for the maintenance of mobility, which should have the effect of slowing down the progression of such contractures, and, in children, the encouragement of normal motor development. Reasonable levels of physical activity should be encouraged, particularly in the case of children, who may mistakenly be immobilised by well-meaning parents or doctors. Patients should be reviewed regularly with full assessment of all joint ranges of movement, muscle power gross and fine motor abilities and, in children, motor development[115]. Home exercises should be initiated for specific joints as soon as limitation of movement is detected at review. In addition, daily prone lying, and mouth and tongue exercises are recommended for all patients to delay soft tissue shortening and adherence. Patients with contractures may benfeit from active exercises in a hydrotherapy pool, and, in some patients, passive 'stretches' may also be beneficial, though these need to be done with great care to avoid skin trauma. Splintage with suitable materials may be a useful additional approach.

Osteoporosis

Osteoporosis is a frequent finding in severe EB, although the mechanism for this is not well understood. Limited weight bearing and mobility, possibly in addition to reduced dietary intake of calcium and vitamin D, have been suggested to play a role but this has not been substantiated. Bone pain is a common finding in these patients and crush fractures may also arise. Nutrition should be optimized and supplemental calcium and vitamin D given. In the authors' unit, a number of children who are symptomatic with bone pain or who have evidence of crush fractures, have received intravenous bisphosphonates. This therapy has resulted in rapid and significant improvements in symptoms and mobility, although the longer term effect on bone turnover has yet to be established.

(iii) nail problems

Thickened, dystrophic finger and toe nails may be extremely unsightly; in the case of toe nails, they may interfere with wearing shoes. Such nails should be permanently removed surgically.

(iv) dysphagia and nutrition[116,117]

Babies who are being bottle-fed require the softest available teats (generally those designed for premature infants). The opening can be enlarged by use of a hot needle to make feeding easier. We particularly like the Haberman® teat which is long enough to ensure that the plastic neck of the bottle does not come into contact with the nose. This teat has the additional benefit of incorporating a valve that ensures easy delivery of feed without the need for the baby to suck hard; as a result babies with severe oral ulceration can often succeed in feeding with this teat rather than having to be fed by nasogastric tube. Some babies find it easier to take milk from a spoon than from a bottle.

Overcoming the combination of nutritional problems presented by many patients with

dystrophic EB can prove exceedingly difficult. Some patients with dysphagia find it helpful to have their food liquidised, but others never accept this, unless they have been fed nothing else from infancy. However, apart from making it easier for the patient to eat, liquidising the diet may help prevent further damage to the pharynx and oesophagus, and may reduce the frequency of the episodes of acute dysphagia they often experience. However, liquidising food usually involves increasing its fluid content and therefore its bulk. If water or gravy is used for this purpose, the calorific value of the food will be reduced, whereas this effect can be minimised by the use of milk or soup. The process may make food blander and less appetising. Sieving food should be avoided as it removes fibre, which is retained if food is liquidised.

Many patients' diets are heavily dependent upon milk. This dependence upon milk should not be discouraged, but such a diet may be far from complete from a nutritional point of view, and will tend to be short on fibre and iron content. High fibre foods should be encouraged, yet they tend to have a lower calorie content, and usually require more effort to eat than foods with a low fibre content.

We do not encourage the addition of dextrose polymer to the diet as this will merely increase the calorie intake, without improving overall nutrition. Though sucrose provides a highly effective means of increasing the patient's calorie intake, we like to restrict high sucrose foods, such as chocolate, to meal-times, in order to minimise their harmful effect on the teeth.

Our own experience suggests that the best approach is to inform parents and patients of the nutritional properties of different foods, and to encourage them to focus on those that provide nutrition in its most concentrated and best balanced form. The aim is a well-balanced diet with a higher than normal content of protein, vitamins and minerals. The emphasis is on foods of soft, manageable consistency, with an attractive appearance and flavour.

Patients should be encouraged to take their food in discrete meals, rather than be eating small quantities continuously throughout the day. However, many children with epidermolysis bullosa will not be able to eat enough at only three meals, mainly because they find the process of eating both painful and tiring. A system of 3 or 4 main meals per day, plus 2-3 snacks, will often be more appropriate. It is often a good idea to put a limit on the time allowed to each meal or snack to prevent one meal from overlapping with the next.

The first 2 years of life are probably critical to the nutritional status of children with epidermolysis bullosa, and great efforts need to be directed towards improving nutrition during this period.

Since few patients do succeed in achieving even a normal nutritional intake, vitamin and mineral supplements are advisable. We generally give a complete vitamin supplement such as *Ketovite* (Paines & Byrne Ltd, Greenford, UK), a liquid iron supplement such as *Sytron* (Parke-Davis & Co Ltd, Eastleigh, UK), or one in the form of granules that can be

dispersed in food, such as *Feospan* (Smith, Kline & French Laboratories Ltd, Welwyn Garden City, UK), and a zinc supplement such as *Z-Span* (Smith, Kline & French), which also takes the form of granules that can be dispersed in food.

Many children with severe dystrophic epidermolysis bullosa intermittently experience periods when they cannot eat at all, due either to pain in the mouth or throat, or to obstruction in the pharynx or oesophagus. If they are also unable to drink, it may be necessary to give fluid intravenously. A short admission for intravenous fluid administration allows for 'rest', and seems to accelerate recovery. Nasogastric feeding can be used to provide longer periods of rest with full nutritional support. Nebulised budesenide or a short course of oral dexamethasone may also provide more rapid resolution of dysphagia due to pharyngeal blistering and oedema.

If swallowing difficulties become more constant, it may occasionally be beneficial to release the buccal mucosa, to allow fuller opening of the mouth. Dribbling can be improved at the same time by transplantation of the submandibular ducts back into the tonsillar fossa [50]. Improved access to the mouth is sometimes necessary for anaesthesia and dental work, but because these procedures also mobilise the tongue, they have the additional benefit of making it much easier for the patient to masticate, swallow and talk. Mouth opening can also be improved by exercises.

Improvements in dietary intake using conventional oral supplements are rarely sustained in patients with dysphagia and more invasive procedures such as naso-gastric feeding frequently need to be be considered [82,118]. Although insertion of a nasogastric tube does not require surgery, problems arise with placement, day-to-day management and disfigurement [116]. It is therefore best reserved for short-term use.

Oral verapamil administration has been advocated to alleviate oesophageal dysmotility and spasm [119]. Our experience has been that any improvement is short-lived, and that verapamil will generally exacerbate the constipation which is already a major problem in most patients.

Surgical approaches which have been taken include balloon dilatation of the oesophagus[118] or endoscopy and oesophageal bougienage[119]. In the authors' unit, balloon dilatations are performed under radiological screening and usually result in significant alleviation of dysphagia, although improvement may be short-lived and repeat dilation after several months may be necessary. Intraoperative deaths due to rupture of the oesophagus have been reported, even from centers familiar with this type of intervention. More radical procedures have included oesophageal reconstruction by reversed gastric tube [121], resection and end-to-end oesophageal anastomosis [122] and colon transplant [123]. Favourable results at 5-year follow-up have been reported [124], but the numbers of patients so treated has been small, and the associated risks are substantial.

We have now inserted gastrostomies in over 60 children with dystrophic, some of whom have now been receiving feeding by gastrostomy for over 8 years [125]. We prefer to insert a gastrostomy button device primarily, using an open operative technique. We particularly favour the Mic-Key® device (Medical Innovations Corp, Draper, Utah 84020, USA).

Although it has generally been recommended that button devices be inserted only after a tract has formed from a previous gastrostomy, primary insertion offers certain advantages in DEB. It avoids an extra general anaesthetic; furthermore, button devices are small and unobtrusive, and therefore aesthetically much more acceptable, particularly to older children. Although percutaneous endoscopic gastrostomy insertion is now widely regarded as the procedure of choice in childhood, our experience has been that the endoscope causes substantial shearing damage in the oropharynx and oesophagus. We therefore now consider this technique to be contraindicated in dystrophic EB.

In most cases, it proves most convenient to deliver gastrostomy feeds overnight, over a period of about 8 hours, using a pump. We favour a nutrient-dense, fibre-containing feed. With a gastrostomy, significant weight gains can be obtained. Additional benefits have been prevention of constipation, and the ease with which medicines and nutritional supplements such as iron can be given when the child has a gastrostomy.

Nutrient requirements increase markedly during adolescence because of rapid growth and the virtual doubling of body mass. Furthermore, if growth throughout childhood has been impaired, nutrition during adolescence should allow for catch-up growth. Since most adults with severe dystrophic EB demonstrate delayed sexual maturation and short stature, it is critical that these patients' nutrition is optimal at the onset of adolescence.

We have found that younger children accept the procedure more readily than the adolescents. Older children are more aware of body image, and adolescent girls, in particular, may be alarmed by a sudden increase in weight. Psychological factors should be taken into account before surgery, with a psychologist and play specialist included in discussions.

Complications of gastrostomy are few, but include leakage around the device, enureseis because of nocturnal fluid administration and gastro-oesophageal reflux.

The effect of long term gastrostomy feeding on oral intakes in dystrophic EB is as yet unknown. It is our policy to encourage oral intake when possible, and we hope that at least some patients will be able to manage without a gastrostomy in adult life.

Gastrostomy insertion, where indicated, in conjunction with oesophageal dilatation should be considered in preference to more invasive surgical procedures in children with DEB in whom dysphagia compromises nutritional intake. Gastrostomy feeding can permit catch-up growth in children with growth failure, and offers further benefits which include amelioration of constipation and improved compliance with vitamin and mineral supplementation. Feeding by this route should not be considered exclusively for children who demonstrate growth failure. It can greatly alleviate the stresses associated with feeding children who are still just managing to maintain growth, but are not likely to continue to do so in the future, particularly at adolescence.

(v) gastro-oesophageal reflux
One needs to maintain a high level of vigilance for symptoms of gastro-oesophageal reflux in young children with dystrophic EB. It is the authors' practice to treat

prophylactically in children with severe EB, even if asymptomatic, to minimize damage to the oesophageal mucosa and reduce the risk of resultant stricture formation. Ranitidine (2-4mg/kg/dose twice daily) is generally given in conjunction with domperidone (0.2-0.4mg/kg/dose threee to six times daily). If symptoms are severe, a pH study may be useful to delineate the extent of the problem

(vi) constipation
Low fibre intake is a contributory factor to constipation in dystrophic EB. Unfortunately, the oral and oesophageal problems of severely affected patients preclude the consumption of increased amounts of dietary fibre in the form of conventional foods (high-fibre cereals and breads, fruit and vegetables). Studies suggest that the fibre-containing liquid enteral formulas which have been commercially produced in recent years can improve gastro-intestinal tolerance and function and reduce laxative use [126]. They have provided us with a new approach to the prevention and therapy of constipation in children with dystrophic EB, and one that should be preferred to the long-term use of laxatives.

Children with megarectum or fecal impaction, demonstrable on abdominal X-ray, should have their bowel emptied before the introduction of a fibre-containing feed. This is not only humane, since it removes the necessity for the child to pass the accumulation of large, dry stools, but it also allows the increased fibre to take effect quickly and so encourages future compliance. If faecal impaction is present, commonly associated with faecal overflow, initial clearance can be achieved by administration of sodium picosulphate solution (Picolax®, Nordic, Middlesex, UK), or a polyethylene glycol-electrolyte solution (Klean-Prep®, Norgine, Oxford, UK) [127]. Unfortunately, most children are defeated by the large volumes of solution that need to be drunk and a naso-gastric tube often needs to be passed unless the patient already has a gastrostomy. The naso-gastric tube used must be as soft and of as narrow a gauge as possible, and fixed with a non-adhesive dressing. The procedure also requires hospitalisation of the patient for up to 2-3 days. A less invasive and faster method that can be employed in cases of less severe impaction, is the use of oral sodium picosulphate such as Picolax® (Nordic, Middlesex, UK) or sodium picosulphate elixir. The prior application of topical local anaesthetic makes the procedure much less unpleasant for the patient.

Because of the great improvements in constipation that we have regularly observed through gastrostomy feeding, we now regard intractable constipation in its own right as a reasonable indication for gastrostomy insertion. Parents who were previously reluctant to give iron supplements, because of aggravation of constipation, are now happy to do so via the gastrostomy.

If children remain constipated despite taking adequate volumes of EnrichR, it is important to check radiologically that faecal impaction is not present; its treatment has been discussed above. If it is absent, the child can be prescribed a faecal softener such as lactulose (Duphalac®, Duphar Laboratories, Southampton, UK) (1-5 years: 5ml bd; 5-10years: 10ml bd), which has the additional benefit of increasing bulk, or docusate sodium (Dioctyl

Paediatric Syrup®, Medo Pharmaceuticals, Chesham, UK) (6mths-2 years: 12.5mg tds; 2-12 years: 25 mg tds). It may in addition be worthwhile to encourage daily defaecation by the regular oral administration of use of senna (Senokot 2-6 years 2.5-5.0 ml nocte; >6years 5-10ml nocte) for a period of a few months. The senna dose should then be progressively reduced. The routine administration of liquid paraffin is in our view contraindicated because of the real risk of its entry into the respiratory tract in these patients.

If constipation persists despite these measures, and where anal pain on attempted defaecation is marked, it may be worth considering an anal stretch under general anaesthesia.

(vii) anaesthesia
Despite the delicacy of the oral and pharyngeal mucosa, and anxieties about acute laryngeal obstruction if blistering of the larynx were to occur following intubation, general anaesthesia has proved to be fairly straightforward in patients with epidermolysis bullosa, if certain precautions are taken[120,128,129].

All those involved in handling these children before, during and after surgery must be made aware of the extreme vulnerability of their skin. Patients must be moved about with great care. Trolleys and operating table should be well padded so that pressure on the skin is kept to a minimum. No-one should lean on the patient during the operation. Plenty of non-adherent soft gauze padding such as MelolinR roll should separate blood pressure cuffs and tourniquets from the skin. Domestic Clingfilm® is very useful to place under the child to reduce shearing forces and to prevent adherence; it is also valuable as a temporary covering for eroded areas when dressings are removed. Sticky tapes and other adhesive materials, such as those used to attach ECG electrodes, must be avoided as the skin will come away when they are removed. Mepiform has proved very valuable for securing devices such as intravenous cannulae, as its adhesive properties hold the device securely but, in contrast to adherent tapes, removal does not cause any damage to the skin. Non-adhesive elasticated netting, conforming bandages, and sutures if necessary, may also be useful. Heart rate is probably best monitored by the use of pulse oximetry. The eyes should be carefully closed and covered with Vaseline gauze® or Geliperm®.

General anaesthesia is to be preferred to extensive local anaesthesia, because the latter may cause blistering. To avoid undue facial manipulation, intubation is generally preferable, and an uncuffed tracheal tube should be selected, a size smaller than one would normally use. The tracheal tube and laryngoscope blade should be well lubricated. The tube should be fixed using ribbon gauze. All tubing should be padded, and where it touches the lips or skin, Vaseline gauze® should be interposed. Occasionally, limitation of mouth opening or dental problems may make intubation difficult; in such cases, and for short procedures, inhalational anaesthesia can be maintained by means of a face mask, which should have a soft air cushion separated from the skin by Vaseline gauze®. Vaseline gauze® should also be placed against the patient's skin where the underside of the jaw is held by the anaesthetist. Oropharyngeal airways should not be used.

The author is unaware of any reported cases in which laryngeal or tracheal obstruction has occurred following intubation in patients with dystrophic epidermolysis bullosa.

(viii) pain
There can be no doubt that patients of all ages with EB experience a great deal of pain, predominantly from cutaneous ulceration, particularly at times of dressings changes, from oropharyngeal ulceration, and from anal fissures, particularly at the time of defaecation. Pain from the skin can be minimised by the choice of the most appropriate dressings; Mepitel® is extremely valuable from the point of view as daily changes are unnecessary. Similarly, pain from the oropharynx can be reduced by provision of a gastrostomy in selected cases, and pain on defaecation can be minimised by keeping the faeces soft.

Drugs like paracetamol (15 mg/kg), codeine (0-5-1 mg/kg), dihydrocodeine (0.5 -1 mg/kg) and morphine (200-500mg/kg) are often helpful if given orally in anticipation of the pain predictably associated with dressings changes.

Recently we have found amitriptyline [McQuay et al, 1997] very promising in the management of the chronic pain suffered by many of the children under our care with severe dystrophic EB. Reduction of this pain can improve quality of life substantially, an improvement that can be manifest in enhanced mobility or better performance at school for example. The appropriate dose for this purpose is about 0.5 mg/kg at night.

(ix) anaemia
Patients with more severe dystrophic epidermolysis bullosa almost invariably become anaemic within a few years of life. Investigations generally demonstrate haematological features both of iron deficiency and of decreased red cell iron utilisation ('anaemia of chronic disease')[130]. The iron deficiency probably reflects both chronic blood loss from skin, mouth, oesophagus and anal canal, and poor iron intake.

Where there is evidence of iron deficiency, probably best indicated by a low mean cell volume (MCV), administration of iron supplements is appropriate, but it is generally found that iron therapy alone is of limited value in relieving the anaemia because of decreased red cell iron utilisation. It may therefore become necessary for some patients to have frequent blood transfusions in an attempt to control their profound anaemia, but this approach is both uncomfortable and associated with significant hazards which include infection and iron overload. In practice, transfusion is reserved for those patients who are substantially disabled by their anaemia and for patients undergoing surgical procedures. It has been our policy not to transfuse unless the anaemia is causing significant symptoms or handicap; in these relatively immobile individuals, transfusion is therefore rarely necessary until haemoglobin levels fall below 7 g/dL. It must be borne in mind that iron overload may become a problem if transfusions are given more often than every 6-8 weeks over prolonged periods. Every effort should be made to improve the patient's general condition, with particular attention to nutrition and to care of the skin, as these measures may reduce the frequency at which transfusion is required.

The majority live with long-term anaemia which causes adverse effects that are likely to include anorexia, lethargy, malaise, delayed wound healing and oesophageal webbing.

More effective therapy of chronic anaemia in patients with EB may lead to very worthwhile improvements in quality of life. It is hoped that improved general nutrition will be helpful in preventing anaemia, and it may turn out that there will be a role for human recombinant erythropoietin.

(x) teeth

While the teeth are usually structurally normal in dystrophic epidermolysis bullosa, they are prone to severe caries. Appropriate dental care includes improvements in the diet, improved cleaning of the teeth, the regular use of an antiseptic mouthwash after meals to clean away as much of the residual food as possible, and oral fluoride supplements in areas where it is not adequately present in tap water[131]. It may be ueful to use an electric toothbrush such as the Braun Oral-B Plaque Remover®.

In dystrophic epidermolysis bullosa, a conservative approach to dental therapy should be adopted, rather than wholesale extraction as has occasionally been recommended. Those who propose this approach argue that the patients do not require teeth as their diet is more or less liquid. The possession of teeth is helpful in giving the patients a more normal facial appearance, since dentures are not tolerated. Furthermore, we have gained the impression that shrinkage of the mouth is accelerated by dental extractions.

Undoubtedly, extraction is sometimes the only practical option for severely carious teeth, because of the difficulty of doing conservative dental work through these patients' very restricted oral opening. Where extraction is necessary, healing is rapid. Patients may be unable to eat for 24-48 hours after dental extraction because of unavoidable oropharyngeal trauma. For this reason, we like to insert a nasogastric tube in patients who do not already have a gastrostomy. The nasogastric tube is best secured by wrapping it around an elasticated bandage which is then passed around the head. Feeding should be provided via the tube until the patient is able to take drink and food comfortably.

(xi) dribbling

Dribbling often occurs in children with severe dystrophic EB, mainly due to obliteration of the lingual and inferior gingivo-buccal sulci. This has been successfully corrected by surgical relocation of the submandibular salivary ducts to the base of the tongue[73].

(xii) eyes

The use of lubricants such as simple eye ointment BP (10% liquid paraffin, wool fat 10%, in yellow soft paraffin) is valuable when patients have bullae or erosions, and in patients who experience recurrent lesions, we recommend its use nightly on a prophylactic basis. Topical corticosteroids without preservative may be indicated in the acute phase of ulceration, but their use should not be prolonged unless it is possible to monitor intra-ocular pressure.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

Definition

A group of inherited disorders characterized by mechanically induced blistering occurring within the basement membrane at the level of the lamina lucida.

Aetiology and pathogenesis

Because most affected individuals die early in life, the incidence of junctional EB is particularly difficult to ascertain. From our experience of neonates referred to our unit, we estimate that the incidence of new cases is approximately the same as for dystrophic EB ad is therefore likely to be around 20 per million births. A recent estimate of prevalence in Scotland - presumably exclusively of surviving patients - was 0.4 per million[7].

It has been known for some time that basement membrane zone binding of the monoclonal antibody GB3 is absent or greatly reduced in junctional epidermolysis bullosa, with some evidence of an inverse relationship between severity and the degree of binding[132,133]. This antibody was found to recognise a lamina lucida protein originally designated as BM600 and was subsequently renamed as nicein[134]. A basement membrane protein called kalinin was isolated at about the same time[135], and both proteins were subsequently shown to be identical[136]. Several variants of the laminin molecule have since been identified, all of which have been shown comprise 3 polypeptide chains, known as A, B1 and B2. Nicein/kalinin, whose A, B1 and B2 chains are designated as a3, b3 and g2, has itself been redesignated as laminin 5[137]. It now seems likely that most cases of junctional EB will be reflections of mutations in the gene encoding the a3, b3 and g2 chains of nicein/kalinin, known as LAMA3, LAMB3 and LAMC2 respectively, but it seems very likely that mutations in other genes encoding lamina lucida proteins such as BPAG2 and b4-integrin (BTGB4) will also play a part[31,138].

To date, all types of junctional epidermolysis bullosa have been transmitted as autosomal recessive traits[139].

Pathology

In junctional epidermolysis bullosa, separation of the epithelium occurs through the lamina lucida, between the lamina densa of the basement membrane and the basal keratinocytes. In most cases there is an abnormality of the structures known as hemidesmosomes, which appear to have a role in bonding these two structures; these tend to be absent, or reduced in number and hypoplastic, lacking sub-basal dense plates[140]. However, in some patients these structures appear to normal both structurally and numerically[141]. Immunohistochemical staining with GB3 antibody is absent or reduced[142].

Junctional EB with pyloric atresia appears to be a distinct subtype in which GB3 staining is normal or only slightly reduced despite typical ultrastructural findings of a lamina lucida split and absent or hypoplastic hemidesmosomes[143].

Exactly what is happening pathologically in the larynx is uncertain, but blistering on the

edges of the cords is probably followed by the development of granulations, and eventually in at least some cases by squamous metaplasia and the development of mucous retention cysts[144].

The pathological basis for the profound failure to thrive observed in many babies remains unclear.

Clinical features

Previously junctional epidermolysis bullosa was more usually known as epidermolysis bullosa letalis. However, although junctional epidermolysis bullosa is undoubtedly more likely than the other categories of epidermolysis bullosa to result in death in infancy, a number of children do survive, some for a few years, and others into adult life, occasionally with relatively little handicap. Because of the regular occurrence of such survivors, the term epidermolysis bullosa 'letalis' is usually now avoided. Although not yet adequately differentiated, it seems clear that there are several distinct varieties of junctional epidermolysis bullosa. From the clinician's point of view it is currently practical to consider there to be 3 broad groups of patients:

i)   Herlitz junctional EB
ii) Non-Herlitz junctional EB
iii) Junctional EB with pyloric atresia

There are almost certainly intermediate types in addition.

(i) Lethal junctional epidermolysis bullosa (Herlitz)[145]
In the great majority of cases, blistering is present at birth or develops within the first few days of life. Despite the likelihood of an early lethal outcome, the initial lesions may be deceptively mild. It is always a mistake to try to guess the type of epidermolysis bullosa or the prognosis on clinical grounds alone in the neonate, as there is little correlation between initial severity and outcome, either in terms of life expectancy or ultimate degree of handicap.

In the infant, the sites of blistering are essentially the same as in other types of epidermolysis bullosa. Subungual and mucosal blisters are equally typical and frequent in junctional epidermolysis bullosa as they are in dystrophic epidermolysis bullosa. Initially, healing is rapid, and milia are not infrequent though they are not as numerous nor persistent as in dystrophic epidermolysis bullosa. Scarring is not a prominent feature as it is in dystrophic epidermolysis bullosa, but slightly atrophic areas are a not infrequent sequel to previous blistering. In the absence of profound scar formation, digital fusion and hand and foot deformity do not occur.

As time passes, healing tends to become more and more sluggish, and by the second year of life, if the child survives, the disease is often typified by the development of gradually extending areas of chronic ulceration. These are perhaps most characteristically seen around the mouth and nose. The development of excessive granulation tissue in these non-healing areas is a peculiarity of junctional epidermolysis bullosa, and is perhaps most

obvious in association with smaller ulcerations. Obstruction of the nares by granulation tissue is rather characteristic[146]. Whereas dystrophic EB is rarely associated with scalp lesions, the scalp is quite often affected in junctional EB. Chronic paronychia with nail loss is a frequent feature, with the nail being replaced by excessive granulation tissue, often leading to a drum-stick appearance of the tips of the fingers and toes.

The mouth and pharynx are affected, often severely, causing substantial pain and difficulty with feeding, but erosive lesions at these sites is not complicated by oral submucous fibrosis, nor by pharyngeal and oesophageal strictures. However, the early appearance of profound failure to thrive is a regular and very distinctive feature of lethal junctional epidermolysis bullosa. The development of this complication of the disease has ominous significance for the infant as it tends to fail to respond to any attempt at correction, including the use of nasogastric hyperalimentation.

The disease is also serious because of its tendency to affect the larynx[144,147]. Many babies with junctional epidermolysis bullosa become hoarse very early in life; indeed the appearance of this symptom seems to be one of the few relatively reliable features that allow a clinical distinction to be made between junctional and dystrophic epidermolysis bullosa in the first weeks of life, though one needs to be aware that it is also frequently present in Dowling-Meara EB simplex. Hoarseness is usually followed by recurrent bouts of stridor, each of which carries a serious risk of fatal asphyxiation.

As in severe dystrophic epidermolysis bullosa, a degree of anaemia is common. In some cases this is severe. As in dystrophic epidermolysis bullosa, the pattern is a mixture of iron deficiency anaemia and anaemia of chronic disease.

As in dystrophic epidermolysis bullosa, anal fissuring, faecal retention and constipation are common.

Ocular disease similar to that described in dystrophic epidermolysis bullosa may occur[148].

Involvement of the bladder and urethra appears to be an occasional complication of junctional EB in surviving children, almost certainly secondary to direct involvement of the epithelium by the disease.

Rapid dental degeneration is the rule. Dental enamel hypoplasia appears to be common in junctional epidermolysis bullosa[149,150], and the resulting development of caries is accelerated by the dietary preference of affected children for foods and drinks with a high sucrose content.

(ii) Non- Herlitz junctional epidermolysis bullosa[151,152]
The early clinical course of individuals with this type of epidermolysis bullosa seems to be rather similar to that of children with lethal junctional epidermolysis bullosa, though the development of excessive granulation tissue, growth failure and anaemia is less prominent. The patient survives through early childhood, with a gradually decreasing tendency to develop new blisters. Non-healing areas may remain a life-long problem for such patients. Areas of previous blistering show a variable degree of atrophy, and both

nail dystrophy and scarring alopecia are prominent sequelae of previous blistering and ulceration.

Distinction of the 'lethal' and 'benign' types of junctional epidermolysis bullosa is complicated by the reported death in early infancy of some of the siblings of patients with the clinically 'benign' type. Many of the non-cutaneous features are qualitatively very similar, including involvement of the teeth, eyes, bladder and urethra[153,154].

(iii) junctional epidermolysis bullosa with pyloric atresia[155]
Congenital pyloric atresia occurs in a small but significant number of infants with junctional epidermolysis bullosa, and the combination appears to be indicate a distinct disorder, with a generally poor prognosis. Involvement of the genitourinary tract appears to be particularly frequent156.

Prognosis
Death in the first 2 years of life is usual in the lethal form of junctional EB, but is not invariable. The cause of death is generally either acute respiratory obstruction due to laryngeal involvement or overwhelming sepsis consequent upon malnutrition. Conversely, survival into adult life is usual not invariable in the benign form. Death in infancy is generally to be anticipated in the pyloric atresia-associated variant, but there have been occasional survivors[156,161].

There is a general tendency for the prognosis to be better the less reduced is immunohistochemical staining with GB3 antibody, except in the case of the junctional EB-pyloric atresia variant in which the outlook is usually, but not invariably poor.

Differential diagnosis
The problem of differential diagnosis in the neonatal period is discussed under dystrophic epidermolysis bullosa (p00). The laryngo-onycho-cutaneous syndrome is a very rare condition that has certain clinical similarities with junctional EB[162].

Treatment
As in other forms of epidermolysis bullosa, specific treatment is not available, and there is no evidence that patients benefit from the administration of any systemic therapy other than nutritional supplements.

General skin care, pain control and the management of complications such as constipation, malnutrition, ocular disease and anaemia are essentially the same as in the case of dystrophic epidermolysis bullosa, though we would hesitate to place a gastrostomy in a patient with junctional EB.

Patients with junctional epidermolysis bullosa usually tolerate a less liquid diet and, because there is much less mucosal scarring, the teeth are more accessible to the dentist. A normal conservative approach to dental treatment is therefore both more necessary and feasible.

Autologous epidermal grafts have been successfully used for the treatment of chronic facial ulceration in junctional epidermolysis bullosa[163].

We have found that humidification of the inspired air is valuable in babies with sub acute stridor. We believe that the onset of acute laryngeal obstruction in these cases is possibly more likely to reflect the development of granulations on the vocal cords than intact blisters, and we therefore treat more intense stridor by inhalation of nebulised racemic adrenaline (racepinephrine, Vaponephrin®, 0.5 ml in 2ml Normal saline [limited supplies available from Fisons Pharmaceuticals, Loughborough, UK, for named patients]), and corticosteroids, such as beclomethasone dipropionate, 100 mcg (Becotide® suspension, Allen & Hanburys, Greenford, UK), both as often as 2 hourly. Although we are keen to know the precise cause of the obstruction, we do not routinely undertake laryngoscopy because this would require that we be prepared if necessary both to intubate the patient acutely, and to undertake tracheostomy later. It is our view that tracheostomies are too difficult to maintain in babies with junctional epidermolysis bullosa because of the ulceration that occurs at the insertion of the tube and along the line of the ties used to hold it in place.

Because some children will survive, we believe that surgical treatment of pyloric atresia in the junctional EB-pyloric atresia variant is justified.

DebRA Australia Inc

(National Dystrophic Epidermolysis Bullosa research Association of Australia) Incorporated

DebRA Australia and its member State branches are associations formed by patients with epidermolysis bullosa, and parents of affected children. The association exists to help those with all forms of epidermolysis bullosa. It provides support, regular meetings, information and newsletters, and very effectively promotes the interests of those with epidermolysis bullosa at all levels. It provides information to professionals involved in the care of individuals with epidermolysis bullosa, and creates helpful links between patients and professionals. It provides awareness of epidermolysis bullosa to the general community which raises funds for improved services and support as well as research. For contact details and additional information about DebRA Australia please visit our website: www.debra.org.au

Information and resources for professionals in Australia

New South Wales

Multidisciplinary EB Clinic (outpatients dept),
Sydney Children's Hospital, Randwick,
Tel 02-93821470.
Clinics held on the last Friday of each month.
Advance appointments essential.

A/Prof Dédée Murrell, Head, Dept of Dermatology,
St George Hospital, Kogarah, Sydney.
Tel 02-9350-2088.
Clinics for adults with EB first Friday of each month.
email d.murrell@unsw.edu.au

Queensland

Multidisciplinary EB Clinic (outpatients dept),
Royal Children's Hospital, Brisbane,
Clinics held 3 to 4 times a year depending on numbers.
Advance appointments essential.
Clinic Coordinator: Project Officer Jenny Berkman
Queensland Clinical Genetics Service
Tel 07- 36361686.
email: Jenny_Berkman@health.qld.gov.au

Victoria

Multidisciplinary EB Clinic
Royal Children's Hospital Melbourne
Dept of Dermatology
Tel 03-9345 5510
Clinics held quarterly - appointments essential

South Australia

Women's and Children's Hospital North Adelaide
Tel 08-8161 7000

Western Australia

Princess Margaret Hospital for Children
Tel 08-9340 8222

Online

Professional forums are also available online at:
www.debra-international.org

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dEBra

Information and resources for professionals in Australia

New South Wales

Multidisciplinary EB Clinic (outpatients dept),
Sydney Children's Hospital, Randwick,
Tel 02-93821470.
Clinics held on the last Friday of each month.
Advance appointments essential.

A/Prof Dédée Murrell, Head, Dept of Dermatology,
St George Hospital, Kogarah, Sydney.
Tel 02-9350-2088.
Clinics for adults with EB first Friday of each month.
email d.murrell@unsw.edu.au

Queensland

Multidisciplinary EB Clinic (outpatients dept),
Royal Children's Hospital, Brisbane,
Clinics held 3 to 4 times a year depending on numbers.
Advance appointments essential.
Clinic Coordinator: Project Officer Jenny Berkman
Queensland Clinical Genetics Service
Tel 07- 36361686.
email: Jenny_Berkman@health.qld.gov.au

Victoria

Multidisciplinary EB Clinic
Royal Children's Hospital Melbourne
Dept of Dermatology
Tel 03-9345 5510
Clinics held quarterly - appointments essential

South Australia

Women's and Children's Hospital North Adelaide
Tel 08-8161 7000

Western Australia

Princess Margaret Hospital for Children
Tel 08-9340 8222

Online

Professional forums are also available online at:
www.debra-international.org