The surgical management of Dystrophic Epidermolysis Bullosa (excluding the hand)

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SUMMARY. Fifty patients with Dystrophic Epidermolysis Bullosa (DEB) underwent surgery including release of limb, oral, anal, eye and penile contractures and treatment of chronic skin ulceration or skin tumours. Correction of contractures involves extensive release of skin and underlying tissues, with split skin grafting of secondary defects. Specific regions are discussed. Recurrence is inevitable due to ongoing disease; however, functional improvement is obtained for several years. Management of chronic skin ulceration with split skin grafting has failed to produce long term healing, with local flaps successful but limited by the problem of donor site instability. Nine of the 17 patients over 20 years of age developed squamous cell carcinomas (29 lesions), benign hyperkeratosis (9) or malignant melanoma (1) requiring excision and skin grafting or amputation of digits. Local recurrence was infrequent (3 squamous cell carcinomas), with distant metastatic spread occurring in 1 patient.

Dystrophic Epidermolysis Bullosa (DEB) is a heterogeneous disorder characterised by blistering of skin and other epithelial lined structures following minor trauma. The effect of this disease on the patients and their parents is profound, with severe limitation of lifestyle, normal physical activities being impossible due to the marked fragility of their skin. No cure is available for this condition, with surgical treatment providing the major method of symptomatic improvement from their many deformities and skin tumours. We present an overview of the current classification, clinical and diagnostic features of DEB, and report our experience in the surgical management of DEB. The hand, as a complex surgical problem, is considered in a separate publication (Terrill et al., co-submission).

There are over 20 different sub-types of Epidermolysis Bullosa now recognised (Fine et al., 1991). They can be classified into three major groups (Simplex, Junctional and Dystrophic) depending upon the level of blistering within the skin. In DEB the blister forms beneath the lamina densa of the epidermal basement membrane (Fig. 1). Different forms of DEB are encountered, and it is not yet clear whether each form, recognised by its particular mode of inheritance and clinical manifestations, represents a distinct genetic abnormality or whether there is a range of phenotypic expression associated with a more limited number of gene mutations. In general, it is customary to divide DEB into autosomal dominant and recessive types. Of these there may be localised and generalised forms of the disease-the severe recessive form most commonly needing surgery. A rarer, probably distinct sub-type, is the autosomal recessive “inverse” disorder characterised by involvement of the trunk and major flexures rather than acral sites (Gedde-Dahl, 1981). The prevalence of recessive DEB is in the order of 1 in 300000, with dominant DEB in the order of 1 in 50000 (Davison, 1965).

Clinically, DEB is characterised by and differentiated from the simplex and junctional forms by the development of scarring and secondary contractures, milia, and an increased risk of developing skin cancers, especially squamous cell carcinoma, at a young age. Scar contracture in the dystrophic patient is especially marked in the hands and feet but eyes, ears and anus are also commonly involved. Oral mucosal contractures in the autosomal recessive patient may, be severe, limiting mouth and tongue movements, whilst oesophageal blistering may result in the formation of webs and strictures, and abnormalities of motility. Bony prominences and flexural areas are prone to recurrent frictional blistering, resulting in chronic ulceration (Fig. 2). The surgical management of the DEB patient therefore involves the release of severe contractures which limit the ability to carry out tasks of daily living, treatment of areas of chronic ulceration and the surgical excision of skin tumours. Diagnosis of the specific type of DEB can be confusing when relying solely upon the clinical

![Basal Epidermal Cells](image)

**Figure 1**—Level of blister formation in the three main types of Epidermolysis Bullosa. (Modified with permission from Eady (1987)).
features, confirmation depending upon the examination of a skin biopsy using electron microscopy and indirect immunofluorescence (Eady and Tidman, 1983; Tidman and Eady, 1990). Electron microscopy will establish the level of blistering within the skin, and demonstrate reduced numbers of anchoring fibrils in the autosomal dominant and recessive localised forms of DEB, and complete absence of these structures in the recessive generalised form (Tidman and Eady, 1985). Indirect immunofluorescence using LH 7.2 monoclonal antibody, which binds to the carboxy terminal region of type VII collagen, a normal constituent of lamina densa and anchoring fibrils (Leigh et al., 1988), shows intense labelling at the epidermal basement membrane in normal skin, and in skin from patients with dominant forms of DEB. In recessive localised DEB there is patchy staining along the epidermal basement membrane, whilst there is complete absence of staining in recessive generalised DEB (Fig. 3) (Heagerty et al., 1986). Prenatal diagnosis of DEB is now possible using these techniques to examine samples of foetal skin at 18 weeks gestation (Eady, 1988; Tidman and Eady, 1990).

Patients

Between 1981 and 1990, fifty patients (26 males and 24 females) with DEB required interventional surgery. The mean age of patients presenting for their first operation was 13.2 years, with a range of 3-42 years. Two patients in this series died (4 %), one of metastatic squamous cell carcinoma, the other due to infection. Thirty percent of patients had a family history of DEB. Of those with a confirmed electron microscopic diagnosis of DEB, 24 (73 %) were generalised recessive and 9 (27 %) localised recessive. Only 3 patients had a provisional diagnosis of autosomal dominant DEB.

Methods and results

A total of 192 operative procedures was carried out. Release of hand contractures was the most frequent operation performed (see Terrill et al., {co-submission}). Thirty-three operations were performed to release contractures of the limbs, oral cavity, anus and other regions (Table 1). Twelve operations were performed for areas of chronic ulceration and 25 for excision of pathological skin lesions. Other procedures performed concomitantly included oesophageal dilatation in 27 patients and teeth extraction in 30 patients.

The foot
A variety of foot deformities may develop as a result of frequent, repeated trauma. Recurrent blistering of the toes results in the formation of a pseudosyndactyly.

with dermal adhesion between adjacent digits, giving a cocoon appearance to the foot. Scar contracture may result in clawing of the toes with either flexion or hyperextension at the metatarsophalangeal joints. Contracture at the ankle joint may result in equinus, plantar or dorsiflexion deformity of the foot. In long standing cases, shortening of extensor tendons, along with destructive bone and joint changes, may develop. Clinically, the patients complain of pain and difficulty with walking due to the abnormal weight bearing. The infant with DEB may present with delay in walking. Foot radiographs show variable degrees of generalised osteoporosis, with destruction, disorganisation and fusion of the tarsal bones and clawing with soft tissue coalition of the toes.

Operative correction involved release of soft tissue dorsiflexion contractures of the ankle and clawing with pseudosyndactyly of the toes, in six patients (Fig. 4). Other operative procedures (2) for marked bone destruction with secondary deformity included a Fowler's arthroplasty for correction of metatarsal head prominence and an astragalectomy to correct an equinovarus deformity of the foot (Fig. 5).

Correction of the pseudosyndactyly was performed by incision of the epidermal cocoon and dissection along the well defined plane between the digits. All toes may be safely released at the same procedure without fear for the vascularity, as the plane of dissection is superficial to the deep cutaneous vascular plexus. When releasing contractures it is advisable to conserve the epidermal cocoon, as its removal will prolong healing and induce the formation of further scar tissue. Release of clawing of the toes was performed by making extensive transverse incisions across the dorsal and/or plantar surface of the toes.

<table>
<thead>
<tr>
<th>Table 1 Indications for surgery</th>
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<tr>
<td>Patients</td>
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<tr>
<td>Release of contractures:</td>
</tr>
<tr>
<td>Hand</td>
</tr>
<tr>
<td>Lower Limb</td>
</tr>
<tr>
<td>Elbow</td>
</tr>
<tr>
<td>Axilla</td>
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<tr>
<td>Oral</td>
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<tr>
<td>Anal</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Chronic ulceration</td>
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<tr>
<td>Pathological skin lesions</td>
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<tr>
<td>Total</td>
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Fig. 3-Indirect immunofluorescence. (A) Intense labelling of epidermal basement membrane with monoclonal antibody LH 7.2 i~ normal skin. (B) Absence of labelling of epidermal basement membrane in generalised recessive EB.
and distal forefoot, extending into the subcutaneous tissue. In three patients with severe long standing claw toe deformity, division of the shortened long extensor tendons was carried out, with insertion of longitudinal Kirschner wires to help maintain correction during healing. Dorsiflexion contracture of the ankle was released by a single, large transverse dorsal incision. Secondary defects created from release of the contractures were split skin grafted. Split skin grafts were taken from an area of non blistered, unscarred skin usually on the thigh or abdomen, with a hand held knife, using firm pressure and being careful not to place shearing forces on the skin. Grafts were meshed (1 : 1.5), applied and fixed with Histoacryl glue or fine absorbable sutures. The foot was dressed and immobilised in a well padded plaster splint. The first two dressing changes were carried out under anesthetic. Intraoral scarring with the development of microstomia, atrophy of the tongue surface and extensive caries. Operative correction of the claw toes improves the contour of the foot, allowing the patient to wear "trainers" and other commercially available footwear. Pain on walking was reduced in 6 of the 7 patients by correcting the foot's balance, and eliminating areas of abnormal weight bearing. The DEB foot is usually small and short. The patient who underwent a Fowler's arthroplasty developed further difficulty with gait postoperatively due to increased shortening of the foot, with the development of new areas of abnormal weight bearing. In the long term, same degree of recurrence of the deformity is inevitable due to continuation of the disease process, especially on frequently traumatised areas. However, surgery is considered worthwhile by the patient, due to the improvement in symptoms, appearance and lifestyle for several years.
The elbow and axilla

Three operations were performed for release of flexion contractures of the elbow and axilla. Wide incisions were required, extending into subcutaneous tissues with release of muscular contractions in one patient. The secondary defects were split skill grafted.

The oral cavity

Intraoral blistering and scarring may result in microstomia, ankyloglossus, obliteration of the buccal sulci and atrophy of the tongue surface. The teeth are prone to develop early and extensive caries, principally due to inadequate oral hygiene (Fig. 6). Four patients had severe microstomia, limiting eating, teeth cleaning and the ability to carry out dental work and intubation. Release of buccal mucosal contractures was performed by making a deep horizontal incision across the cheek mucosa with release of all tight scar tissue. A meshed skin graft was applied, under a dental stent. This release alone provided an average increase in mouth opening of 2 cm (Fig. 7). Postoperatively, trismus was further overcome and recurrence prevented by the twice daily use of a stack of tongue depressors. The poor state of the teeth does not allow the use of a trismus screw. In one patient, further improvement was achieved by triamcinolone injection of the masseter region. In another patient mouth opening was extremely limited, with a tracheostomy required prior to surgical release. Ankyloglossus, resulting in an inability to protrude the tongue, was corrected in 7 patients by release of the soft tissues at the base of the tongue. A U-shaped incision was made through mucosa and subcutaneous tissues around the tongue base, with division of all tethering fibrous hands, but sparing the sub mandibular ducts. A meshed split skin graft was applied to the secondary defect, with excellent graft take obtained in all patients. The increased tongue protrusion and mobility provided an improvement in speech and mastication. The DEB patients' saliva may be unusually thick and ropy. When combined with a deficient buccal sulcus, constant drooling may result. In 3 patients the tongue tie release was therefore combined with transposition of the submandibular ducts and release of the buccal sulcus.

1 Enbucrilate, manufactured by B. Braun Melsungen AG D-3508 Nelsungen, West Germany.
2 Johnson and Johnson, UK.

The anus

Chronic constipation develops due to poor intake of fibre, resulting in recurrent perianal blistering and fissures from the hard stools, with the long term development of anal stenosis. Four patients required an anal stretch for anal stenosis.

The eye

Recurrent blistering of the eye and lid results in blepharitis, corneal erosions and scarring, symblepharon and ectropion. Two patients underwent surgical correction of eye deformities. One patient with ectropion and conjunctival exposure underwent a postauricular Wolfe graft to the lower eyelid, with complete correction of the ectropion maintained. The second patient with symblepharon (conjunctival adhesion) underwent a z-plasty to release the conjunctival tethering (Fig. 8); however, early recurrence occurred post correction, more severely than pre-operatively. Twenty-nine patients had a past history of recurrent corneal erosions and blepharitis. These are best treated with regular eye toilets and antibiotic eye ointment during acute periods.
Figure 7-Microstomia; (A) Preoperatively. (B) Six years post release of mucal mucosal and split skin grafting

Figure 8—Symblepharon.

The penis

Two patients developed phimosis of the penis. The first patient underwent a circumcision, which we felt was unsatisfactory as it left the glans exposed, predisposing to the possible later development of urethral stenosis. The second patient with phimosis therefore underwent a simple dorsal split of the foreskin, thus maintaining its protection to the glans and urethra. Adhesions of the meatus occur but do not usually result in functional impairment.

Chronic ulceration

Chronic ulceration develops after repeated minor trauma to pressure points and flexural areas, especially around the elbow, neck and spine. Ten areas were treated with split skin grafts. Good graft take was achieved initially; however, recurrent ulceration developed within 12 months due to further trauma and blistering of the region. In one patient bilateral scapula flaps were carried out to treat bilateral areas of chronic ulceration overlying the acromion. Sustained healing of the areas occurred; however, the donor sites have developed problems with intermittent ulceration along the suture line, one area requiring a latissimus dorsi rotation flap to distribute skin tension further (Fig. 9).
Surgical Management of Dystrophic Epidermolysis Bullosa

Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>EB type</th>
<th>Pathology</th>
<th>Site(S)</th>
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<tbody>
<tr>
<td>1</td>
<td>30 F</td>
<td>AR,G</td>
<td>SCC</td>
<td>Knee</td>
</tr>
<tr>
<td>2</td>
<td>24 M</td>
<td>AR,G</td>
<td>SCC</td>
<td>Legs</td>
</tr>
<tr>
<td>3</td>
<td>41 M</td>
<td>AR,G</td>
<td>SCC</td>
<td>Forearms</td>
</tr>
<tr>
<td>4</td>
<td>34 M</td>
<td>AD</td>
<td>SCC</td>
<td>Knee</td>
</tr>
<tr>
<td>5</td>
<td>29 M</td>
<td>AR,G</td>
<td>SCC</td>
<td>Knee</td>
</tr>
<tr>
<td>6</td>
<td>24 F</td>
<td>AR,G</td>
<td>SCC</td>
<td>Hands, forearms, Legs, feet</td>
</tr>
<tr>
<td>7</td>
<td>22 M</td>
<td>AR,G</td>
<td>SCC</td>
<td>Hand</td>
</tr>
<tr>
<td>8</td>
<td>24 F</td>
<td>AR,L</td>
<td>Melanoma</td>
<td>Back</td>
</tr>
<tr>
<td>9</td>
<td>44 F</td>
<td>AR,G</td>
<td>SCC</td>
<td>Hand, forearm</td>
</tr>
</tbody>
</table>

* Cases 1-6 and 9 reported in McGrath et al. (1991b).

Skin lesions

Nine patients (5 males, 4 females) underwent 25 operations, to remove 29 squamous cell carcinomas (SCC), 9 benign hyperkeratotic (HK) lesions, 1 malignant melanoma and bilateral metastatic SCC of the axillary lymph nodes (Table 2). The average age of patients presenting with skin tumours was 26 years, with a range of 22-44 years. Eight of the 17 patients (47%) in our series, over 20 years of age, have developed SCC. The mean follow-up of patients with SCC was 2.9 years, with a range of 6 months-6 years.

The clinical appearance of the SCC was extremely variable, ranging from the clinically obvious tumours, to the relatively innocuous area of hyperkeratosis occurring within a region of chronic ulceration or scarring (Fig. 10). All primary SCC developed in the extremities, at or distal to the elbow or knee. Four patients have developed multiple SCC, one patient to date with 12, two patients with 3 SCC, and another with 2. In our series, local recurrence has developed in only 3 of the 29 SCC excised (Cases 2 and 9), those tumours being very extensive with invasion down to muscle or bone at presentation (Figs 10A, 11). The development of a malignant melanoma by Case 8 is of interest, but may be incidental.

Cases 1-8 underwent excision and skin grafting of 29 lesions, with Case 6 also requiring partial amputation of the index finger, for an SCC of the fingertip. Primary closure of the defect is not usually possible as the lesions are frequently extensive with ill defined margins and the surrounding skin light. Case 9 underwent excision and skin grafting of a benign HK of the right hand in 1983 and an SCC in 1985. During this period she also developed cervical dysplasia, treated with laser therapy. She represented...
in 1989 with an extensive SCC of her right hand which required a transmetacarpal amputation. Simultaneous excision and skin grafting of an SCC of her left forearm was performed (Fig. 11). Subsequently she developed bilateral metastatic axillary lymphadenopathy, for which she underwent axillary clearance.

Figure 10


Figure 11

Squamous cell carcinomas of the right hand and left forearm.

Satellite nodules of SCC due to lymphatic spread developed along both forearms, which were treated with surgery and radiotherapy, the latter appearing to be of little benefit. Her disease progressed rapidly and she died within 6 months of initial diagnosis of the SCC of her right hand.

The histological appearances of the tumours were variable. Most were well differentiated, extensively keratinising squamous cell carcinomas. Two were of the verrucous subtype and two were so poorly differentiated that their epithelial nature could only be determined initially by the use of immuno- cytochemistry (McGrath et al., 1991a). Examination of further material in each case eventually demonstrated foci of origin from the overlying squamous epithelium. A poorly differentiated, angiosarcomatous SCC was diagnosed in Case 9, who developed widespread metastatic disease.

The anaesthetic
During surgery special care must be taken to avoid skin trauma. Intravenous access is frequently difficult to procure, with use of the brachial and external jugular veins most likely. Intravenous cannulae should be held in place with vaseline impregnated gauze and a crepe bandage. The patient can be monitored via a pulse oximeter carefully clipped to a digit. Blood pressure can be measured using a well padded sphygmomanometer cuff. Most surgery is performed under general anaesthesia, usually with endotracheal intubation. Endotracheal tubes should be well lubricated and held in place with non adherent tapes. Facial masks may be used for short anaesthetics, liberally covered with vaseline gauze and held gently, the underside of the jaw protected with vaseline gauze to prevent facial blistering from the anaesthetist's fingers. In over 380 anaesthetics given at St Thomas' Hospital no major problems have been encountered with this technique, especially in terms of the previous concern of postoperative laryngeal blistering with airway obstruction (Wilson, 1959). In the literature, no major complications have been reported with anaesthesia in the DEB patient, with minor blistering occurring in 6% of anasthesics (James and Walk, 1982). In recovery, we have found it useful to have a family member in attendance to reassure the patients and help protect them from injuring themselves on the bed and surrounds as they awake from the anaesthetic.

Discussion

Recurrent blistering in patients with DEB results in the formation of scar tissue and secondary contractures. Severe disability may result, impairing further their limited ability to carry out tasks of daily living. Interventional surgery with release of contractures allows a significant improvement in lifestyle, as well as improved self esteem and a feeling of normality. The severity of the disease between individuals is extremely variable, with same children requiring corrective surgery by 3 years of age, whilst others maintain good function into their teenage years. Surgery should be considered early before the development of secondary joint or musculotendinous contractures and bone destruction. If severe contractures have developed, release of tendons, ligaments and bony arthroplasties may be required. Surgery may need to be repeated several years later if recurrence has developed due to ongoing disease.

Release of foot and toe contractures relieves pressure from abnormal weight bearing surfaces, providing excellent symptomatic improvement for the patient. Release of the pseudosyndactyly allows the purchase of normal footwear and it is of psychological benefit to the patient to observe a "normal" foot with five toes.

Secondary to the problem of intraoral blistering and its sequelae is poor nutritional intake. This may be compounded further by oesophageal strictures with dysphagia, malabsorption, and chronic blood and protein loss through open blisters. In severely affected patients this results in a state of chronic malnutrition, anaemia, hypoalbuminaemia, reduced immunocompetence and constipation. Most DEB patients have height and weights in the lower 10th centile for their age (Tanner and Whitehouse charts, 1976), with haemoglobin levels of less than 10g/dl, associated with protein, iron folate and zinc deficiencies. Thus dietary advice and supplementation is helpful perioperatively to aid in wound healing. Correction of microstomia, ankyloglossus and excessive dribbling has not been previously reported in cases of DEB. Improvement in mastication secondary to these procedures allows the patient's diet to be adjusted to obtain optimal nutrition, minimising further growth retardation, anaemia, and disturbance of wound healing.

Chronic ulceration is a difficult problem in these patients. In our experience a split skin graft applied to the area will result in short term healing of the area; however, over the following 12 months the area will inevitably break down again due to recurrent trauma atrophicalcianakes scalp flaps performed. One patient produced sustained healing of the areas; however, due to the overall tightness of the patient's skin, the sutured wounds of the donor site were unstable, requiring further surgery to distribute tension. At present, trials are being carried out at our institution to consider the role of cultured allograft skin in the healing of these troublesome areas. Carter (1988) reported 3 cases with chronic facial erosions and junctional EB treated with cultured autologous keratinocyte grafts. Complete re-epithelialisation was obtained in 2 of these 3 patients.

In DEB, squamous cell carcinomas typically develop at a younger age than in the general population and are frequently multiple. A 2:1 male predominance for the development of SC has been reported in DEB patients (Goldberg et al., 1988); however, in Oursers and that reported by Reed et al. (1975a), equal numbers of males and females have developed malignant skin lesions. All patients in OUT series developed SCC involving the distal limbs, the areas most frequently traumatised and consequently, the regions of most severe scarring. It has been postulated that the increased risk of developing SCC in these patients is related to chronic wound ulceration and tissue stress, a similar feature to that previously described by Marjolin in 1828. For patients over 20 years of age constant observation must be maintained by patient and physician to detect early any area suggestive of malignant change, as suggested by a non-healing ulcer, of ten covered by a crust and heaped up scale. Biopsy of any suspicious area is essential. Wide excision and skin grafting is the treatment of choice for malignant skin lesions, as local skin tightness precludes the use of direct closure. The use of irradiation has been reported in several cases; however, its use has been associated with local tumour recurrence and non-healing of the irradiated bed (Wechsler et al., 1970). Systemic chemotherapy has been used infrequently in patients with metastatic disease, with a partial response observed without undue toxicity (Lentz et al., 1990).
At present there is no cure for DEB. Medications such as steroids, Vitamin E, and phenytoin have been tried but discarded over the years due to ineffectiveness or side effects related to high dosage levels (Atherton, 1990). Of interest was a menopausal woman in our series with severe recessive DER, the blistering occurring in a cyclical pattern with her menses. No hormonal abnormality was detected. However, the introduction of a Progesterone only contraceptive pill has markedly reduced her degree of blistering. Similar changes have previously been reported in a woman who underwent a hysterectomy (Matsuoka and Safai, 1980).

Interventional surgery for the correction of contractures provides a worthwhile improvement in symptoms, function, and appearance for several years. Split skin grafting areas of chronic ulceration has failed to produce log term healing, with 10cal flaps successful but limited by donor site instability. Patients over 20 years of age must be closely observed for the development of skin cancers. A high index of suspicion must be maintained, with early biopsy of any area of chronic ulceration, hyperkeratosis or frankly malignant lesions.

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References


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