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A new technique using cultured epithelial sheets for the management of epistaxis associated with hereditary haemorrhagic telangiectasia

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Abstract

A new technique for the treatment of severe epistaxis associated with hereditary haemorrhagic telangiectasia is described. The nasal septum and inferior turbinates, surgically denuded of respiratory epithelium, were grafted using autografts of cultured epithelial sheets derived from buccal epithelium. All patients upon whom this technique has been used have shown considerable lessening in the frequency and severity of their epistaxes although two patients received grafts on two occasions, in each case approximately three months apart. It is postulated that a nasal lining of stratified squamous epithelium is likely to be more resistant to trauma than the normal respiratory type, and this is supported by the observation that bleeds very seldom occur from the oral cavity in this syndrome.

Key words: Epistaxis; Telangiectasia, hereditary haemorrhagic; Epithelial cells, autologous, cultured; Transplantation; autologous

Introduction

A new technique is described using autografts of cultured epithelial sheets derived from buccal epithelium which were used to graft the nasal septum and inferior turbinates after surgical removal of the respiratory epithelium in patients suffering from hereditary haemorrhagic telangiectasia (HHT).

Patients and methods

Three patients have been treated in this fashion, all of whom had undergone many operations in an attempt to improve their symptoms including silver nitrate and electro-cautery, and elevation of the septal mucosa, all of which produced little or no long-term benefit. There were two men, aged 47 and 48, and one woman aged 64. All had developed septal perforations due to previous treatments, and had had very troublesome symptoms for ten years before our intervention.

Technique

A 5 millimeter square biopsy of buccal epithelium, harvested under a local anaesthetic, was used to provide the epithelial cells for culture, the laboratory requiring receipt of this for processing within four hours of harvesting. Sheets of stratified squamous epithelium, principally the germinal layer of the epidermis, were then grown on 25 square centimetre (cm^2) flasks according to previously described and now established techniques (Green *et al.*, 1979; Fabre and Cullen, 1989; Premachandran *et al.*, 1990). When confluent, the primary culture was dispensed into a single cell suspension and secondary cultures then were produced in 75 cm^2 flasks. Two or three epithelial sheets from these secondary cultures were required for each procedure and it generally took three weeks to produce a sufficient area of graft. Once the graft becomes confluent it remains stable and suitable for insertion for approximately five days.

Following the administration of a general anaesthetic, the nasal cavity was packed with cotton wool soaked in 5 per cent cocaine for ten minutes and the sub-mucoperichondrial space infiltrated with lignocaine 2 per cent and 1 in 80 000 adrenalin in order to reduce haemorrhage. Adequate exposure was obtained using a Killian's nasal speculum and the nasal mucosa was removed from the septum and inferior turbinates with the very gentle use of a Joseph rasp which leaves the perichondrium of the cartilage intact. In this situation, the oval fine cross serrated file ended or fine toothed (1 millimeter) pattern of rasp (Downs Surgical catalogue numbers HM 160-01-R and HM 160-04-X respectively) are preferable to the coarser designs so that troublesome haemorrhage may be avoided.

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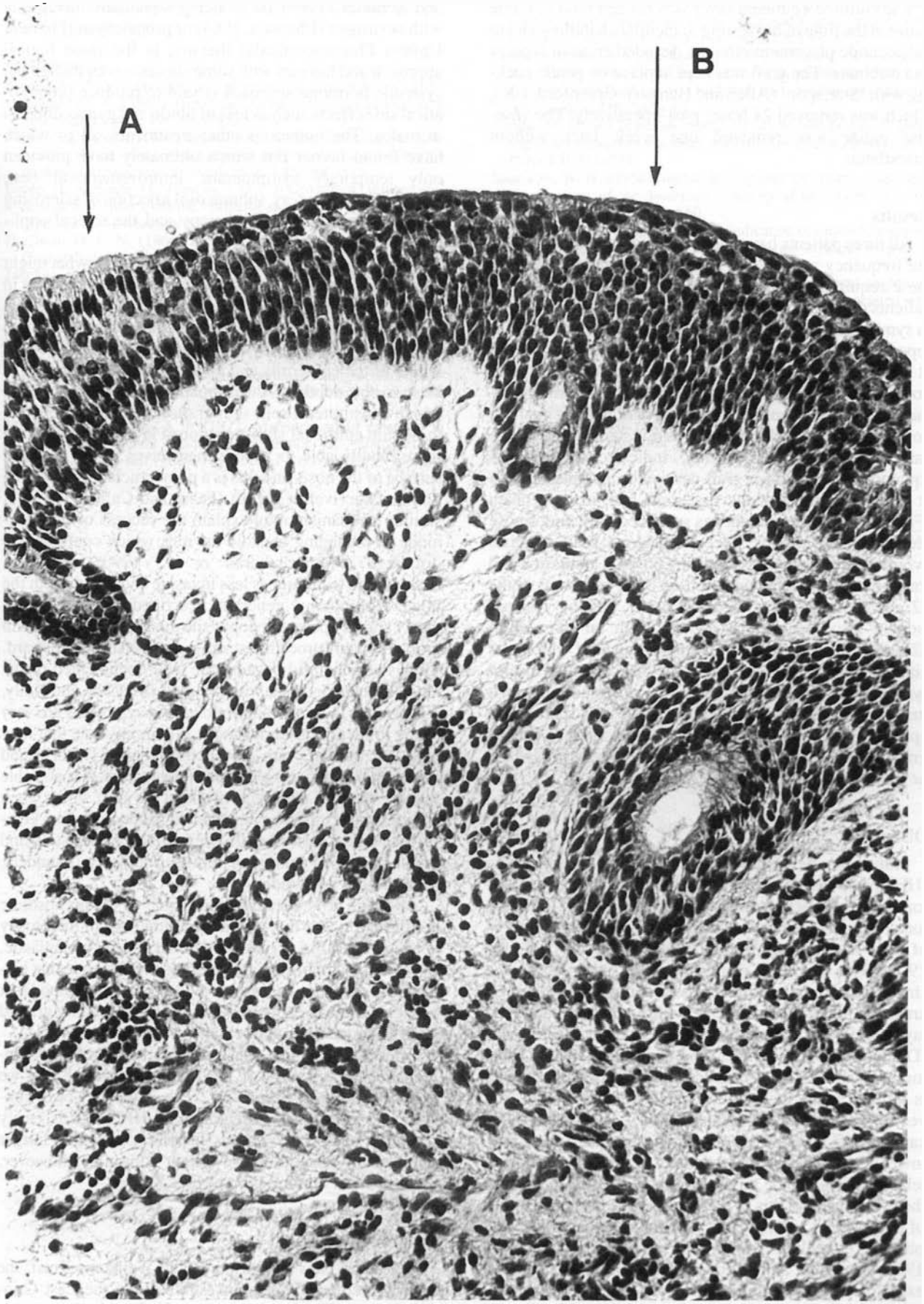

FIG. 1

Biopsy from the nasal septum three months after grafting with cultured epithelium. Both respiratory (labelled A) and squamous (labelled B) epithelium are present.

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The cultured epithelial layer was backed onto vaseline gauze at the time of harvesting to facilitate handling and to aid accurate placement onto the denuded areas of septum and turbinate. The graft was kept in place by gentle packing with 'Sterispon' (Allen and Hanbury, Greenford, UK), which was removed 24 hours post-operatively. The vaseline gauze was removed one week later without anaesthetic.

Results

All three patients have shown considerable lessening in the frequency and severity of epistaxes, although two of these required the insertion of two grafts. In these two patients the initial graft failed to produce an improvement in symptoms and therefore in each case the procedure was repeated 12 weeks after the first. A nasal mucosal biopsy at one of these second grafting procedures demonstrated both buccal and respiratory epithelium in the same specimen. Although it must be conceded that, in this situation, no particular intracellular features nor staining technique can, with absolute reliability, indicate whether this squamous epithelium is graft derived or metaplastic, it is at least plausible that the first graft had, in part, taken (Fig. 1). This latter patient has sustained only minor nose bleeds for 24 months since the second graft and has avoided the major bleeds requiring hospital admission and transfusion which had occurred on three occasions in the 12 months preceding the first graft. The 64-year-old woman also received two grafts with an interval of 12 weeks between the two, the most recent of which was nine months ago. Since then she has obtained useful symptomatic improvement and has not required transfusion. The third patient has continued to sustain trivial epistaxes on a daily basis in the 18 months following grafting but has not sustained the major bleeds with which he had suffered pre-operatively.

Discussion

Although hereditary haemorrhagic telangiectasia (HHT) was first described by Gamen Sutton in 1864 (Sutton, 1864) and Benjamin Guy Babington in 1865 (Babington, 1865), its eponymous title is accorded to the authors of three later papers (Rendu, 1896; Osler, 1901; Weber, 1907). The condition results from the inheritance of a single autosomal dominant gene producing localized areas of thin-walled capillaries with only an endothelial layer, and other areas of dilated arterioles and capillaries (Dolowitz, 1953; Kindler and Tiedman, 1956). What mural elastic and muscular tissue does exist is sparse and is thought to be incapable of effective constriction of a vessel when damaged (Jahnke, 1970). Although bleeds can occur from these lesions within the gastro-intestinal, lower respiratory and urinary tracts, severe epistaxes from telangiectasia on the nasal septum and turbinates typify the syndrome and this is attributed to the close proximity of the vascular anomalies to the thin pseudostratified respiratory epithelium within the nasal cavity (Harrison, 1964; McCabe and Kelly, 1972). This arrangement explains why conventional methods of epistaxis control are not only ineffective, but may even provoke further haemorrhage. It is also why nasal lining modifying therapy, either replacement with a split skin graft (Letterman and Schurter, 1964) or inducing squamous metaplasia with oestrogen (Harrison, 1964) or progestogen (Provera, Upjohn Pharmaceuticals) therapy, is the most logical approach and has met with some success, even though the systemic hormone approach is said to produce problematical side effects such as loss of libido and gynaecomastia in males. The numerous other treatments, all of which have found favour but which ultimately have provided only temporary symptomatic improvement at best, include electrocautery, submucosal injection of sclerosing agents, cryosurgery, radiotherapy and the topical application of coagulants.

The technique that we describe differs from what might appear to be the analogous septodermoplasty technique in several important respects. Firstly, the grafted cells inserted into the nose when they are a confluent sheet constitute largely the germinal layer of the epidermis and not the whole of the epidermis and part of the dermis (usually at least to the depth of the subpapillary vascular plexus) which constitutes a split skin graft. Potentially, therefore, these thin epithelial sheets produced in the laboratory are more readily able to appose themselves to the denuded surface of the nose, and this is a point crucial for the nutrition and survival of a graft (Fabre and Cullen, 1989). A similar mechanism may explain the success of our technique in managing mastoid cavities which continuously discharge (Premachandran *et al.*, 1990). Secondly, because this technique is less invasive and avoids both the bilateral rhinotomy generally described for septodermoplasty and any potential donor site morbidity of a split skin graft, revision procedures are far more straightforward. This is very helpful because the well-documented recurrence of telangiectasia within a graft (McCabe and Kelly, 1972) tends to imply that troublesome symptoms are very likely to recur with time, and it is certainly true that they tend to worsen with advancing years. Thirdly, and although this remains a matter of conjecture, it is possible that, by virtue of the buccal origin of the graft which when fully matured might be expected to produce far less keratin than a skin derived graft, the troublesome crusting and odour described following septodermoplasty (Saunders, 1968) might be avoided.

Although it is virtually impossible to obtain absolute confirmation that the squamous epithelium in the biopsy specimen (see Fig. 1) is graft derived and not metaplastic, as far as the authors are aware this is the first time that histological evidence has been provided of the likelihood that nasal respiratory epithelium has been replaced by grafted stratified squamous epithelium.

Effective treatment that provides sustained improvement in the epistaxes of HHT remains elusive and we believe that the technique that we describe may be of considerable value in the treatment of HHT and is easily repeated should symptoms persist or recur. Larger numbers of patients and a longer follow-up, however, would permit confirmation of this.

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