Permacol™: clinical experience with a new biomaterial

Catherine Harper

Permacol™ (Tissue Science Laboratories plc, Aldershot, Hants) is a new biomaterial which combines the strength and permanence of synthetic surgical repair materials with the biocompatibility of natural materials. This article examines the clinical application of Permacol™ in a range of different surgical procedures.

Soft tissue loss or damage can occur for a variety of reasons, including trauma, surgery and disease. Surgeons need repair materials which are biocompatible, non-toxic, easily manipulated, conform well to body surfaces, provide tissue bulk where required, and allow formation of strong new host tissue in the defect with good aesthetic results.

Surgeons continue to rely on autologous tissue (e.g. fascia) which is harvested from a donor site on the patient (Barrington et al, 1998). This has inherent drawbacks including increased theatre time, limited availability and donor site morbidity. Autologous tissue has a limited life span and although it is non-immunogenic, it is still degraded by the body's enzymes and absorbed. Thus, defects repaired in this way may lose strength and form over time. Cadaveric allografts (e.g. AlloDerm®, LifeCell Corp., Suspend®, Mentor) and heterografts from animal tissues (e.g. Surgisis™, Cook Surgical; Peri-Guard®, Bio-Vascular Inc.) are commercially available alternatives that avoid the need for a donor site and are more readily available, although availability of human tissue is organ bank dependent. Some of these products are processed to enhance resistance to biodegradation; however, their permanency is in doubt (Clarke et al, 1996; Ellis and Cousin, 2000).

Synthetic materials have also been used as surgical repair materials. Absorbable materials include polyglactin, polydioxanone and polyglycolic acid (Gadacz et al, 1994; Ghimenton et al, 2000). These elicit only minor local tissue reactions but, by definition, weaken as they dissolve. Non-absorbable materials such as nylon, polyester, polypropylene or polytetrafluoroethane remain strong, but elicit local tissue reactions (Klinge et al, 1999) and run the risk of harbouring infection (Baykal et al, 1999). The risk of long-term rejection of the 'foreign body' or recurrence of the deficit can be high. In operations where continued strength is important, for example in incisional hernia, recurrence within 3 years runs at 43% for patients who had suture repair and 24% who had mesh repair (Luijendijk et al, 2000).

An ideal surgical repair material would offer the surgeon the following characteristics:

- Non-allergenicity
- Strength
- Flexibility
- Permanence
- Potential for incorporation into the host tissue
- Sterility.

Two approaches have been made to create such a material. The first approach is synthetic, where new biomaterials are constructed that meet the above characteristics. The second approach is to start with natural tissue and remove all the elements that are not required (e.g. cellular components) and enhance the elements that are required (e.g. permanence).

DEVELOPMENT OF PERMACOL™

Permacol™ is the culmination of 25 years research and development by scientists at Dundee University, who set out to address the problem of how to produce a permanent biological implant compatible with human tissue.

Dermis has been used in surgical procedures for nearly 90 years; the first cases involved hernia repair and uterine prolapse (Loewe, 1913). Thompson (1960) investigated the histological fate of human autografts used to correct facial defects. Although the epidermis was physically

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removed from the dermal grafts, some cells survived. Hair follicles survived for over 10 weeks and sebaceous glands survived between 1 and 5 years. These were autografts, but if the graft had been from a different (non-autologous) donor then the presence of cells would have evoked an immune response and the tissue would have been rejected. To avoid rejection a non-autologous dermal graft must be devoid of mature cells.

REDUCING COLLAGEN'S ANTIGENICITY

Native collagen has minimal antigenicity when in its undenatured form (Chvapil, 1980). In 1972, Oliver et al demonstrated that porcine dermal autografts, which had been treated to render them cell free, resisted biodegradation for 35 days and achieved a state of permanence. In a paper published in *Nature*, Oliver at al (1975) demonstrated the important role of cross-linking in protecting these dermal autografts from biodegradation and prolonging their survival and permanence following implantation. Collagen autografts and heterografts which were cross-linked using low concentrations of glutaraldehyde underwent the same level of recellularization and revascularization as uncrosslinked allografts (Oliver et al, 1980, 1982). Increased stability was demonstrated by incubating the autografts with bacterial collagenase (Oliver et al, 1976, 1982).

Griffiths and Shakespeare (1980) prepared human allografts in accordance with the methods of Oliver and co-workers (Oliver et al, 1972, 1975). The authors acted as recipients and 1 month after implantation no inflammatory reaction or immunological rejection was seen. At 12 months the implant showed no sign of clinical or subclinical rejection and was not encapsulated and the whole of the implant was colonized by cells and small blood vessels. After 3 years there was no immune or inflammatory response and no fibrous capsule (Griffiths and Shakespeare, 1982). The implants were colonized by host blood vessels. No collagen resorption was observed.

CROSS-LINKING IN PERMACOL™

Cross-linking with aldehyde has its limitations. A potential problem with long-term aldehyde cross-linked implants is that they may develop the foci of mineralization (calcification) which can then become extensive (McPherson et al 1986). Aldehydes are also cytotoxic at higher levels (Cooke et al 1983). Oliver and Grant experimented with diisocyanate which cross-links collagen fibrils but is non-toxic at high levels and breaks down to urea. Diisocyanate cross-linked porcine dermal grafts were implanted for a period of 2 years in the rat and did not cause mineralization (Oliver, 1987). Owing to its non-toxic nature and the absence of mineralization in long-term implants, diisocyanate was elected as the preferred method of cross-linking to stabilize Permacol™. This is protected by a worldwide patent.

SAFETY STUDIES

The non-toxic nature of Permacol™ has been rigorously demonstrated. It is not cytotoxic or genotoxic (unpublished data, Tissue Science Laboratories plc, 1998). Permacol™ caused no sensitization and is not haemolytic or pyrogenic (unpublished data, Tissue Science Laboratories plc, 1998). All appropriate toxicology has been performed and has proved negative. This is reflected in the regulatory status of Permacol™ which has been approved for use in Europe since 1998 and received clearance from the Food and Drug Administration in February 2000 for use in the USA.

Porcine dermis is the closest to human dermis in structure and appearance (Monteiro-Riviere, 1986; Meyer et al, 1978). Human skin fibroblasts are capable of growing and surviving for at least 7 weeks on intact dermal collagen from pig skin (Oliver et al, 1986).

WHAT IS PERMACOL™?

Permacol™ is a sterile, moist, and tough but flexible sheet of acellular cross-linked porcine dermal collagen and its constituent elastin fibres. Unlike other medical collagen products (e.g. collagen injections and wound dressings), the collagen is maintained in its original three-dimensional form rather than being reconstituted. Permacol™ is non-allergenic, non-toxic and does not elicit a foreign body response (unpublished data, Tissue Science Laboratories plc, 1998). It has a structural architecture very close to human dermis and is readily colonized by host tissue cells and blood vessels (unpublished data, Tissue Science Laboratories plc, 1999).

It is distributed by CR Bard Inc in the UK and the rest of the world, for use in urology and gynaecology applications, under the trade name Pelvicol™.

CLINICAL DEVELOPMENT

Permacol™ has been licensed for permanent implantation into humans since March 1998. Since then over 2000 individual implants have been marketed across Europe. Given the versatil-

ity of Permacol™ a wide variety of studies are underway. Some of the outcomes are shown here.

Ruparelia et al (2000) reported successful repairs of anterior and posterior vaginal prolapse in a group of 47 patients using Pelvicol™. After a follow-up period of 20 months, results showed an aesthetically acceptable implant material that provides firm support to the vaginal repair. Of this group, 78% of women were symptomatically better while 85% were sufficiently satisfied with the procedure to recommend it to others. Patients are being monitored over a 5-year period.

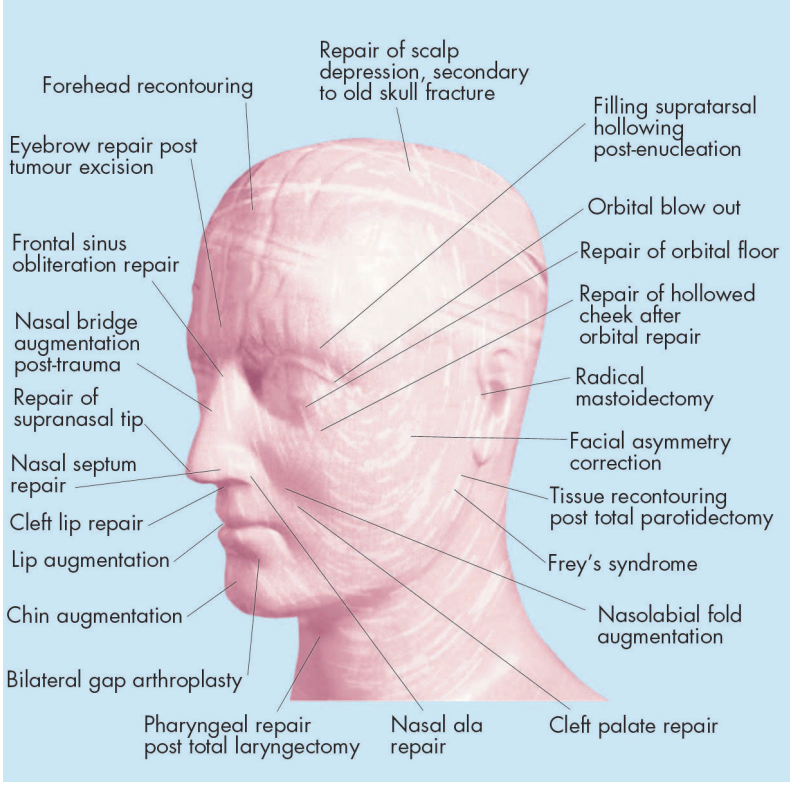

Figure 1. Sites of Permacol™ implantation in the head and neck.

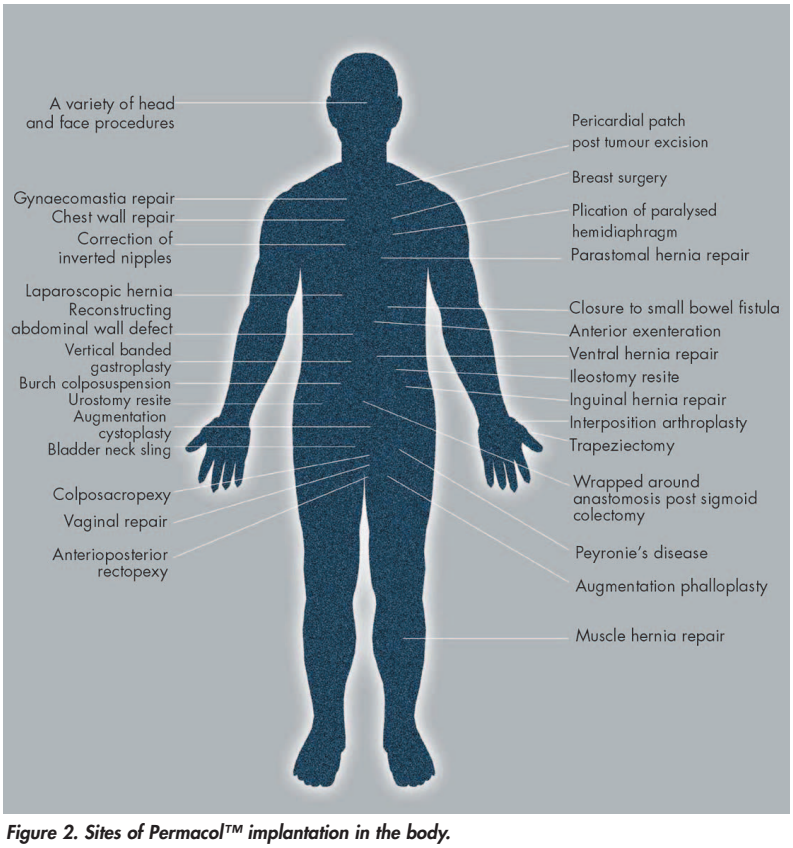

Figure 2. Sites of Permacol™ implantation in the body.

Long strips of Pelvicol™ have been successfully used as suburethral slings to treat female urinary stress incontinence in 20 patients (Barrington and Edwards, 2000). The procedures were performed as a day case and the success rate was excellent. Longer term results are awaited.

Pelvicol™ was used to correct penile curvature in Peyronie's disease (Lloyd and Hetherington, 2000). The plication or excision of the normal tunica albuginea to correct penile curvature in Peyronie's disease produces unacceptable penile shortening in some patients. Pelvicol™ was used as a graft following plaque excision and became integrated into the surrounding tissues, supporting local angiogenesis. The authors concluded that although the procedure takes longer than a standard Nesbitt procedure, the advantage of preserving penile length and function is a worthy clinical outcome.

Pelvicol™ has been used in cystoplasty for mixed and urge incontinence where ileocystoplasty was not possible because of bowel disease or previous surgery (Speakman, 2000). The technique avoids the potential problems of bowel segments. Symptomatically all patients improved. Follow-up cystoscopy showed excellent re-epithelialization of the bladder. Surgically the method was straightforward and saved theatre and hospital time. Longer term results are awaited.

Several evaluations are underway in the UK including a 200-patient inguinal hernia trial comparing Permacol™ with standard techniques. Other ongoing clinical studies involve rotator cuff repair, interposition arthroplasty, breast recontouring following malignant lumpectomy and laparoscopic hernia repair.

This paper documents 140 of these surgical procedures across 8 specialties.

CLINICAL APPLICATIONS OF PERMACOL™

The aim of the study was to demonstrate the wide clinical applications of Permacol™ surgical implant and to determine user satisfaction with the material.

Methods

Surgeons in the UK with an interest in the assessment of new surgical repair materials were recruited to participate in this open assessment of Permacol™. The material was provided free of charge, along with a case report form to record data, but no other financial assistance was provided. The surgical use of Permacol™ was left to the surgeon's discretion. On completion of the surgery, a case report form was completed and, where appropriate, long-term follow-up data were recorded.

General data

Eighty-two surgeons from 71 different UK hospitals participated in the study. The surgical disciplines in which Permacol™ was implanted were: ear, nose and throat, plastic, general, urology, gynaecology, maxillofacial, cardiothoracic and orthopaedic.

A total of 60 different surgical procedures were undertaken and these are described diagramatically in *Figures 1* and *2*. Exactly half of the procedures were on the head and neck and half on the rest of the body. The study included 140 patients aged between 4 and 93 years. There were 60 males and 80 females.

Results

Manipulation and handling: Permacol™ was supplied in a variety of sizes and in two thicknesses (0.75 mm and 1.5 mm). In the 140 reported cases, 77 patients received the 1.5 mm thick material and 63 patients the 0.75 mm thick material. Surgeons shaped the material to suit the operation in 99 (70.7%) of the procedures. In 68 (48.6%) procedures strength was considered important and, in the remaining 72 (51.4%) procedures, tissue replacement was considered more important.

The surgeons' assessment of ease of use is described in *Figure 3*.

Long-term follow-up: At the surgeons' discretion, long-term follow-up was completed. Permacol™ has been implanted in patients for a duration of between 10 and 33 months. Of the 140 cases documented here, 32% of procedures were performed 24 months ago or more, and in 94% of cases, Permacol™ has been implanted for 12 months or more.

In total, longer follow-up information was provided for 42 patients. No evidence of allergenicity, immunological rejection or hyper-/hypopigmentation was reported for any patient. Wound contraction was absent in 34 (81%) patients with 6 (14.3%) recording no comment. Two procedures were recorded as showing wound contraction (use of Permacol™ as a plug in a foot ulcer and its use as a filler in nasal augmentation post trauma). No adverse medical events attributable to the implant were reported in any of the 140 patients, although four cases of postoperative infection were reported.

Overall assessment at follow-up: The surgeons stated that the product met their expectations in 34 (81%) of the cases. Reasons for failing to meet expectations were: too early to tell in four cases, resistant to suture in two cases, and not thick enough/not thin enough in one case each. In 39 of 42 cases, surgeons said that they would use Permacol™ again, with two surgeons waiting for longer follow-up and one making no comment.

Global assessment: The overall performance of Permacol™ was rated by surgeons as shown in *Figure 4*. On a scale of 10, where 1 = poor and 10 = excellent, the overall mean (+/-standard deviation) assessment of Permacol™ surgical implant was 8.0 (+/- 1.4).

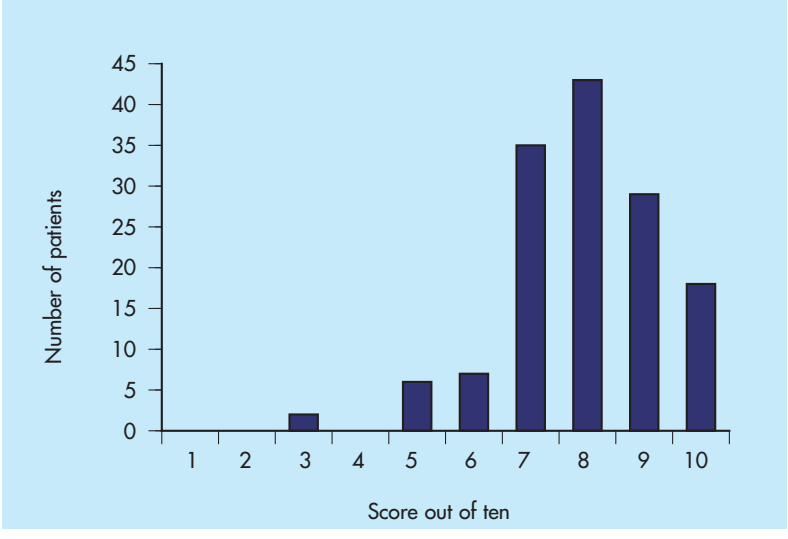

Figure 3. Overall ease of use as assessed by surgeons.

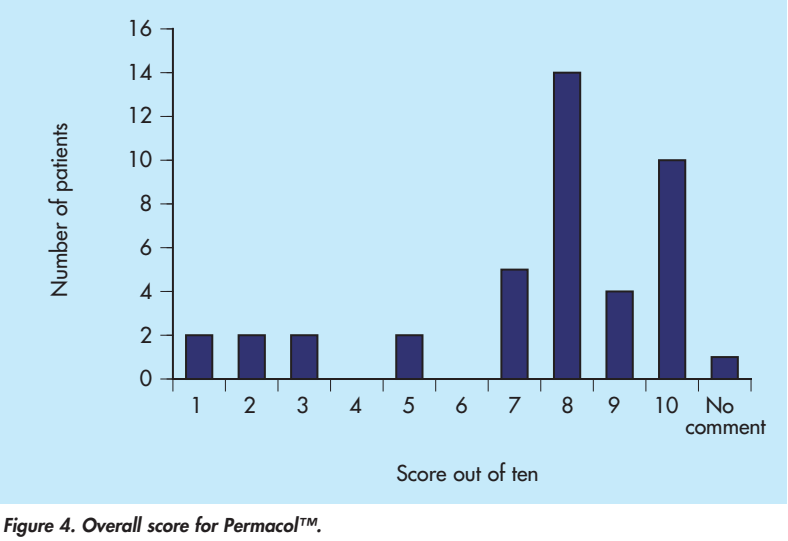

Figure 4. Overall score for Permacol™.

Case reports

This section outlines two cases where Permacol™ has been used and gives a brief overview of the surgeons' experiences.

Cheek augmentation: A 58-year-old female presented with a hollowed cheek resulting from an uncorrected depressed infraorbital rim fracture. The surgeon performed a submuscular dissection of the left cheek through an infraorbital incision. Permacol™ was inserted in layers to build up cheek contour (*Figure 5*). The surgeon found that Permacol™ was easy to manipulate and scored 9/10 for ease of use.

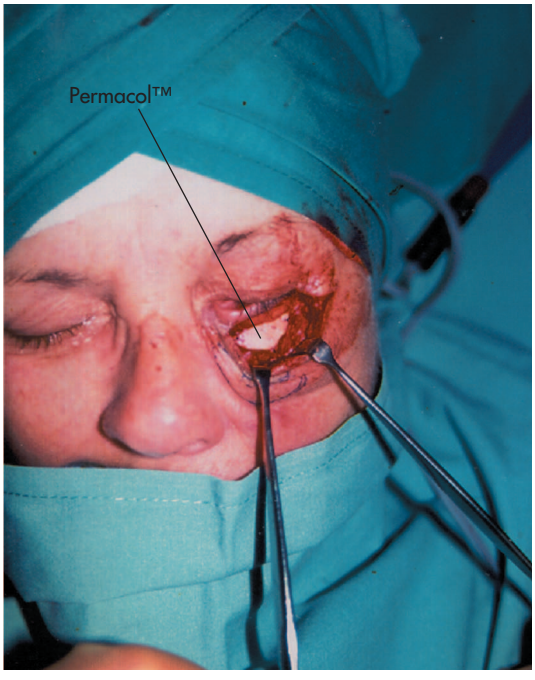

Figure 5. A 58-year-old female presented with a hollowed cheek resulting from an uncorrected depressed infraorbital rim fracture. Permacol™ was inserted in layers to build up cheek contour.

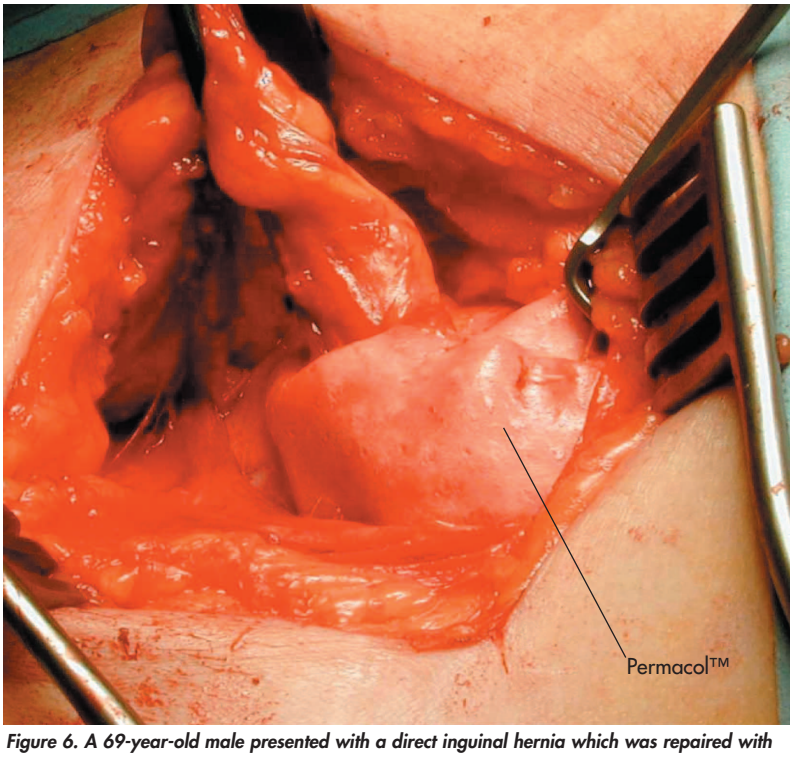

Figure 6. A 69-year-old male presented with a direct inguinal hernia which was repaired with Permacol™.

Inguinal hernia repair: A 69-year-old male presented with a direct inguinal hernia. Permacol™ was used in the repair, being cut to shape and easy to manipulate (*Figure 6*). The surgeon scored 9/10 for the procedure overall.

FUTURE RESEARCH

Permacol™ has been demonstrated to be a highly versatile surgical repair material that offers the ideal range of attributes, namely: natural, strong, biocompatible, and permanent. The technology has wide potential. The implant material can be presented in a range of different physical forms (e.g. in a milled form as a permanent collagen injection or in a highly perforated form as a chronic wound therapy). Given its biocompatibility, Permacol™ also has the potential to be used as a matrix in which to grow cells for autologous implantation.

Finally, the Permacol™ technology, whereby animal tissues are rendered safe for implantation in man and are not degraded over time, could also be applied to other tissues (e.g. blood vessels, ligaments). Tissue Science Laboratories plc, the manufacturers of Permacol™, have received a number of government grants to support their active research and development activities in these areas.

CONCLUSIONS

From the data presented, it can be seen that Permacol™ has a wide spectrum of surgical applications. Applications requiring a permanent strong repair (e.g. hernia and orbital floor repairs) were successfully achieved with Permacol™, as were applications where tissue replacement/recontouring was required (e.g. nasal bridge augmentation post trauma, Peyronie's disease).

Permacol™ has a number of unique properties, namely: it is a natural, safe, non-allergenic, flexible and strong biological matrix that is readily incorporated into host tissue and effects a permanent repair. In the hands of the surgeons taking part in this study it was generally regarded as easy to use, handle and manipulate. After long-term follow-up, the surgeons continued to record high levels of satisfaction with Permacol™.

New improved materials are relatively uncommon. Permacol™ appears to offer the

strength and permanence of synthetic surgical repair materials with the biocompatibility and safety profile of natural materials. Additional studies are in progress to further demonstrate the cost-effectiveness of Permacol™ in soft tissue repair. **HM**

Figure 5 *was provided courtesy of Mr H Henderson, Consultant Plastic Surgeon, Leicester Royal Infirmary*
Conflict of interest: Dr C Harper is employed by and has shares in Tissue Science Laboratories plc who manufacture Permacol™.

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KEY POINTS

- Soft tissue loss, damage or weakness can occur for a variety of reasons, including trauma, surgery and disease.
- Permacol™ is a new biomaterial made from acellular cross-linked porcine dermal collagen and its constituent elastin fibres.
- Permacol™ is licensed for permanent implantation into humans. It is distributed for use in urology and gynaecology applications under the trade name Pelvicol™.
- Unique patented cross-linking renders Permacol™ resistant to biodegradation and absorption thus providing a permanent repair.
- One hundred and forty implantation procedures have been successfully performed using Permacol™ throughout the body. Follow-up data revealed no evidence of allergenicity, immunological rejection or absorption was reported for any patient.
- New improved materials are relatively uncommon. Permacol™ combines the strength and permanence of synthetic surgical repair materials with the biocompatibility of natural materials.
- The technology has wide potential and could be applied to other tissues.