WHAT'S NEW IN . . .

Plastic Surgery

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ABSTRACT

The range of casualties treated by the Defence Medical Services in the recent Gulf conflict has reaffirmed the important role of plastic surgery within the military. This review seeks to highlight some areas of recent innovation and improvement within the realms of plastic surgery generally, of which some, such as the introduction of Flammacerium and the availability of skin substitutes, have direct military relevance.

The Treatment Of Burns
Provision of care

In the UK alone, 250,000 people each year suffer some form of burn injury, 175,000 of which attend Accident and Emergency departments, but only 13,000 require admission to hospital. It is estimated that up to 90% of burn injuries are preventable. Although only approximately 1000 cases per year are sufficient to warrant fluid resuscitation, half of whom are under 16 years of age, 300 people per year die from burn injuries, the majority of whom are over the age of 56. Despite improvements in burn wound treatment and reductions in mortality in other age groups, the death rate from burns in those over 56 years of age has remained unchanged worldwide over the last 20 years (1).

Burn wound management in Great Britain suffers from a haphazard provision of services; 30% of adults and 40% of children receiving in-patient treatment for burn injuries do so in non-specialist units (1) Given the unique nature of burn injury in

terms of its varied potential aetiologies (flash, flame, chemical and electrical), its widespread pathophysiological effects such as inhalational injury, loss of epidermal coverage, rhabdomyolysis and propensity for infection and the often devastating psychological, social and cosmetic impact of this form of trauma, specialist care is essential to obtain the best results.

The British Burns Association began a review of burns service provision in 1998, and fuelled by Department of Health support produced the National Burn Care Review (NBCR) (1) in 2001. Within the review there are recommendations for improvements under 8 general headings (Table 1) and two specific areas are highlighted here.

The NBCR commented that the accuracy of assessment of the area and severity of burn injury needed to be improved as incorrect assessment leads to delay and under-treatment in many cases. Conversely, over-treatment may utilise scarce resources inappropriately. It is suggested that attendance on a course such as Emergency Management of Severe Burns (EMSB) could improve the quality of burn assessment by non-specialists and offer guidance in complex areas such as when burns are a form of non-accidental injury in children or the elderly, in the setting of deliberate self harm or in association with drug or alcohol abuse. The introduction of Lund and Browder charts into referring hospital's A&E departments, a dedicated fax referral service of these charts to the regional burns unit and the institution of telemedicine links to allow direct visualisation of the burn injury by specialist burns surgeons before transfer, would all improve burn wound assessment. The NBCR also set out detailed guidelines for onward referral (Appendix 1).

Table 1. Recommendations of the National Burn Care Review with excerpts (in italics) from the Executive Summary.

Uniform National Clinical Management And Referral Guidelines. <i>See Appendix 1.</i>	Critical Care Provision <i>including the establishment of a National Burn Bed Bureau.</i>
In-Patient Provision By Specialists particularly with regards to paediatric burns	Structured Three Tier Burn Care Services. <i>See text for details.</i>
Continuing Care As Part Of The Burn Care Service with improvements in the provision of rehabilitation services	National Networks <i>including urgent implementation of a major incident plan for large numbers of burns either civilian or military</i>
Research And Development including audit and development of an evidence base for burn care	Improved Data Gathering And Information Systems <i>to facilitate burn injury prevention strategies, service planning and monitoring</i>

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Implicit in the changes required for improved burn care management is a reorganisation and rationalisation of the provision of facilities. As burn wounds encompass a wide spectrum of severity, it is inappropriate to equip every burns unit to manage all eventualities, whilst it is appropriate for particular injuries, especially those involving children, to be dealt with by units having specialist expertise and facilities. It is proposed to institute a three tier system of burn care provision (Table 2) with adult and paediatric burn care treated separately. It is envisaged that the most prevalent provision, burn facilities, would refer upwards to burn units and thence onto the regional or supra regional burn centre. It is planned to have three adult and two paediatric burn centres throughout the UK.

Table 2. The proposed three tier system of burn care.

Burn Facilities	Plastic surgery units where personnel are available who have experience of burn management, but no specialist facilities.
Burn Units	Provision of a dedicated ward for burns patients with experienced staff. Not expected to provide 24 hour access to surgical intervention specific to burns
Burn Centres	Equipped and staffed to provide the highest levels of care for the most severely injured. Immediate and 24 hour access to a designated, staffed burns operating theatre

Flammacerium

Ionic silver has been known as a potent antimicrobial agent for years, but its use has been complicated by problems of toxicity and difficulty in application (2) (Table 3).

Table 3. The potential antimicrobial agents generated by Cerium Nitrate-Silver Sulphadiazine treatment.

Ce 3+	CeSC	AG+	AgSD
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Many of these problems were obviated by the introduction in 1968 of silver sulphadiazine (3) (a sulphadiazine moiety with a single hydrogen substituted by a silver ion). Silver sulphadiazine (SSD) treatment however leaves a soggy, macerated burn wound requiring frequent labour intensive dressing changes. A further modification of SSD occurred with the addition of the rare earth salt cerium nitrate to yield cerium nitrate-silver sulphadiazine (CN-SSD), marketed in Europe as Flammacerium (Solvay Duphar, Netherlands), and available within the United Kingdom on a named patient basis only. It is now the treatment of choice for many burn wounds in the majority of UK burns units.

Since its introduction into burn wound therapy in 1976, CN-SSD has demonstrated improvements in survival rates (4), burn wound bacterial colonisation profiles (5) and healing times (6). The precise mechanism by which these benefits accrue is still undefined but cerium has a wide range of chemical and cellular interactions that may potentially explain these effects.

Cerium interacts avidly with calcium and the cerium effects on calcium dependent systems are numerous. It binds calcium in the eschar (7), potentially reducing transcellular calcium flux, which is implicated in prolongation of the post-mitotic phase of maturation of basal epidermal cells and increasing the numbers of cells in a proliferative phase (8). Displacement of the calcium ion from the cell membrane $\text{Ca}^{2+}/\text{Mg}^{2+}$ ATP-ase pump may also lead to binding and aggregation of adjacent cells, influencing keratinocyte migration and maturation (9). The interaction of cerium with calcium dependant pathways is also responsible for decreased histamine release from granulocytes (10). These changes may have a beneficial effect on wound healing in general and reduction in inflammatory response to injury that could explain some of the effects seen in cerium-treated burns.

An almost universal finding since cerium's introduction is the effect it has on the burn eschar, which is turned into a yellowy-green leathery crust, which acts as a tightly adherent barrier to colonisation (7). This barrier also maintains a moist environment beneath the eschar, previously shown to improve the rates of wound healing (11,12). The eschar usually lifts by about three weeks leaving a non-infected bed free of granulations that will readily accept a split skin graft (13).

Cerium's first proponents, Monafio and Ayyazian, used it in the belief that it had a direct increased antimicrobial action (5); indeed cerium was identified as an antimicrobial as far back as 1894 (14) and was shown to be an effective bacteriostatic against a wide range of bacteria including pseudomonads, staphylococci and *Escherichia coli* in 1947 (15). This antibacterial action is again attributed to cerium's interaction with calcium dependant cellular functions (16). Although mammalian cells are impermeable to cerium, it is readily absorbed by bacterial cells leading to structural damage, binding and inactivation of intracellular proteins, disturbances in calcium metabolism and inhibition of cellular respiration (17).

Although CN-SSD produces four potential antibacterial agents (Table 3), the recent evidence for an enhanced antibacterial activity of SSD by the addition of cerium nitrate is less convincing. Holder showed that cerium generally decreased the bacteriostatic efficacy of silver sulphadiazine, and improved it in only 3 out of 37 cases (18). One study that did demonstrate a synergistic interaction of cerium and silver sulphadiazine showed no inherent antibacterial activity from cerium on its own (19).

It is now widely recognised that cutaneous burn injury may precipitate widespread

immunosuppression (20) and a lipid-protein complex (LPC) has been identified as the toxic agent responsible. The LPC is generated by the effect of thermal energy polymerising several dermal and epidermal skin constituents (21). It is a potent inhibitor of the interleukin-2 dependent immune pathways (22), with a specific diminution of the T-cell mediated response (23). The LPC has been shown to have a hundred fold more immunosuppressive effect than bacterial endotoxin (24). In most civilian burns centres, immunosuppression is limited by early total burn wound excision and closure, thereby physically removing the source of burn toxin. In some situations early total wound excision is impractical because of a lack of resources (including blood and skin coverage products) or the presence of concomitant injuries or co-morbidities that preclude major surgery. In the military environment, wound excision is outside the remit of a deployed Role 3 facility (25). In instances such as these, Flammacerium has been shown to be hugely effective in diminishing the immunosuppressive effects of the in situ burn eschar (Figure 1). Experimentally it has been shown to bind and denature the LPC within the eschar (26) and clinical studies have demonstrated significant improvements in survival following CN-SSD treatment of major burns (27,13). It is likely that this represents the predominant mechanism by which cerium improves outcome after major burn injury.

Cerium does not cross mammalian cell membranes, consequently systemic absorption is minimal (28) and evidence of side effects from cerium treatment limited. A

single case report (29) describing the prolonged treatment of an infant with CN-SSD reported significant amounts of silver within the liver and kidneys and a trace of cerium within the liver. The significance of these findings is unknown. Occasional cases of methaemaglobinaemia after cerium nitrate therapy were reported soon after its introduction (5). It occurred in less than 1% of cases, resolved after withdrawal of the CN-SSD (and did not recur after its reintroduction) and was attributed to bacterial reduction of the nitrate ion rather than any effect of cerium per se. It has not featured in any case series published in the last 20 years.

Conclusions

Burn care services in the United Kingdom need to be reorganised to provide high quality, effective specialist care for a common and often devastating injury. Improvements in burn wound assessment, referral practices and service provision directed by the National Burn Care Review are underway. The introduction of Flammacerium represents a safe and efficacious method of neutralising burn wound toxins in those cases where early excision is either not possible or desirable. It has a significant role to play in stabilising burns in the military environment during evacuation to Role 4 facilities for definitive surgical care.

Skin Substitutes

Early total excision and grafting of burns is the primary method by which bacterial ingress may be limited and systemic immunosuppression avoided. In large surface area burns, however, the paucity of autograft donor sites requires the use of skin substitutes to allow wound excision to achieve the twin goals of improved survival and better restoration of function and cosmetic outcome. Skin substitutes have also been used with increasing frequency to try and heal the indolent ulceration often seen in association with venous hypertension or diabetes.

There are many commercial skin substitutes now available to provide either wound coverage, relying upon the ingrowth of granulation tissue for adhesion (30) or wound closure which restores the epidermal barrier function of skin and becomes incorporated into the healing wound (31). The desirable attributes for the ideal skin substitute are listed in Table 4.

Fig 1. Application of a thick layer of Flammacerium to a burn.

Table 4. Desirable attributes for a skin substitute adapted from Pruitt and Levin (32).

Tissue compatability with little or no antigenicity	Non-Toxic either systemically or locally
Impenetrable to micro-organisms but permeable to water vapour	Rapidly adherent to the wound surface, but allows ingrowth of fibrovascular tissue from wound bed
Malleable to conform to irregular wound shapes, elastic to allow movement over joints and strong enough to resist shear stress	Low cost, easily stored with a long shelf life.

As in many other areas of the body, tissue engineering has found it difficult to reproduce the complex, multilayered functional anatomy that we take for granted. Early skin substitutes are used as dermal substitutes, still requiring some form of split skin graft coverage, whereas newer approaches are using cultured keratinocytes to recreate the epidermal layer. The commonest skin substitutes are discussed below.

Biobrane™

Biobrane™ (Dow Hickam/Bertek Pharmaceuticals, Sugar Land Texas, USA) is a bilaminate membrane of nylon mesh fabric bonded to a thin layer of semi permeable silicone (33). The nylon mesh is coated with peptides derived from porcine collagen to aid wound adherence and fibrovascular ingrowth. As the wound heals, Biobrane separates, and can readily be peeled away from the surface (30). Although originally intended for use on donor sites, it is used most commonly for the treatment of partial thickness wounds in children, where it has been shown to reduce in-patient stay by up to 46 per cent (34). The application of Biobrane requires a 'clean' wound, which usually entails a general anaesthetic debridement and cleaning of the burn before use, adding to the cost of its use.

Keratinocyte Culture and Delivery

As most skin substitutes do not regenerate an epidermis, much work has attempted to provide a readily available keratinocyte layer. Clonal growth of keratinocytes has been possible for over 20 years (35,36), with the production of confluent sheets in vitro that may be applied to wounds such as burns (37-39). The ultimate 'take' of such grafts, as with split skin grafts, is dependent upon the vascularity of the wound bed (40) and the ongoing prevention of shear forces. Allogeneic keratinocytes may be cultured and stored in advance of need and autologous keratinocyte sheets are grown 'to order' from a small skin biopsy using a commercially available kit (Epitel-Genzyme Tissue Repair Corporation, Cambridge, Massachusetts, USA) or the facilities available in most university laboratories

(30). Not only is autologous keratinocyte culture costly and time consuming, requiring 3 weeks for viable cells to be ready for grafting, but cultured epithelial autografts are fragile sheets following separation from the substrate, and have an increased susceptibility to infection and contraction prior to application (41). When transplanted, the keratinocytes are undifferentiated, lacking cornified and granular layers, but by 3 weeks a basal lamina is evident. Anchoring fibrils are sparse over the first 6 to 12 months, and elastin expression may take four to five years (42,43). Conversely, allogeneic keratinocyte sheets have been free from acute rejection reactions, but have only a very limited lifespan. Genetic probes have shown survival of allogeneic keratinocytes for only one week when applied to excised tattoo sites although longer survival, up to 6 weeks, has been demonstrated when used on split skin graft donor sites (44,45). It appears that the presence of a native dermis allows growth factor and cytokine secretion to aid engraftment (46), the main use for allogeneic keratinocytes remains as a dressing for chronic open wounds (47) or donor sites (41).

Whilst the addition of fibrin glue to the keratinocyte growth media has improved results whether the cells are applied as a spray or as a confluent sheet, the greatest improvement in engraftment has been noted when the cells are applied to a dermal structure. Research is now underway to develop composite skin substitutes with keratinocyte cultures on the surface of a glycosaminoglycans matrix. Early results have shown acceptable 'take' and basement membrane formation within 9 days of application (48), further addition of fibroblast to the keratinocyte culture yields better basement membrane formation and a thicker epidermal layer. This technique has been used to achieve rapid wound closure in a mouse model (49) and has been recently used successfully when applied to engrafted Integra for the closure of full thickness wounds in burns patients (50).

Transcyte™

Transcyte™ (Advanced Tissue Sciences Inc., La Jolla, California, USA) is a collagen coated nylon mesh seeded with neonatal

fibroblasts. As nylon is not biodegradable, this material cannot act as a dermal substitute. When compared to cryo-preserved allograft as a temporary dermal analogue with subsequent meshed split skin graft closure (51), Transcyte showed equal autograft adherence and take. In a similar, larger multicentre trial with 66 patients, it was noted that, as well as showing good adherence, Transcyte was easier to remove than allograft, resulting in less bleeding (52), and histologically there was little difference between the two, apart from increased granulation tissue in the allograft-treated wounds (48).

It appears that Transcyte has a stimulatory effect on epithelialisation (53). One study of paediatric burns reported that Transcyte treated wounds had a reduced area of skin graft requirement compared to standard topical antimicrobial therapy (54). When compared to silver sulphadiazine treatment of partial thickness burns, Transcyte wounds healed with less hypertrophic scarring (55), and a similar positive effect has been described in the treatment of partial thickness facial burns (56). Although limited studies such as these demonstrate improved results with Transcyte, especially for the treatment of partial thickness burns, its enormous cost (16 times greater than that of Biobrane, which is used for similar indications) is likely to preclude its use in this country.

Alloderm™ and Dermagraft™

Alloderm™ (LifeCell, Woodlands, Texas, USA) is processed human cadaveric skin from which the epidermis and dermal cellular components have been removed prior to cryopreservation in order to avoid a specific immune response (57). Dermagraft™ (Advanced Tissue Sciences Inc., La Jolla, California, USA) is a cryopreserved living dermal structure, manufactured by cultivating neonatal allogeneic fibroblasts on a polymer structure (polyglycolic acid or polyglactin-910) (58). The fibroblasts become confluent within the mesh, secreting growth factors and dermal matrix proteins, thus creating a living dermal structure (59). This remains viable and metabolically active after implantation into the wound, despite cryopreservation (60). Both Alloderm and Dermagraft, as their names might suggest, act as dermal grafts but, with little barrier function, they require split skin grafting, although production of a dermal bed allows ultra-thin cropping of donor grafts. After application of Alloderm, it is repopulated by host cells, revascularised and incorporated into the tissue with good take rates. It reduces the scarring of full-thickness wounds and allows a one-stage grafting procedure (57). Dermagraft functions in a similar manner and has been used more on

chronic unhealed wounds, such as venous ulcers (61,62), than burns. Evidence of improved outcome for Dermagraft over other skin substitutes is currently absent.

Integra™

Integra artificial skin (Integra Life Science Corporation, Plainsboro, New Jersey, USA) is currently the most widely accepted synthetic skin substitute to be developed for use in burns patients. It has a bilaminar structure of cross-linked bovine collagen and glycosaminoglycans, with a silicone membrane coating on one side providing 'epidermal' function, and a pore size of 70–200 µm in order to allow optimal migration of host endothelial cells and fibroblasts. Following application to a freshly excised wound, the collagen layer becomes integrated into the wound to form a vascular 'neodermis' over approximately three weeks. Once the neodermis is formed the protective silicone layer can be removed and an ultra-thin split skin graft applied.

The first large scale trial (63) of Integra (149 cases in 106 patients) reported median take rates of 85% for Integra and 95% in the controls treated with split skin grafts. These results were comparable to using allograft. This trial also reported subjective improvements in cosmesis, particularly at the donor sites, attributed to the harvesting of ultra-thin (0.15 mm) autografts. Donor sites healed four days quicker and with less hypertrophic scarring than standard donor sites.

One large series reported on the use of Integra over a 10 year period (64) with a mean graft take of over 80%, no cases of severe hypertrophic scarring formation and 93% of patients with only minimal (or absent) hypertrophic scarring. All patients with joint involvement achieved excellent function and areas grafted with Integra in paediatric burns were able to grow with the child. Subjectively, the areas grafted with artificial skin were felt to be cosmetically superior to those where only autograft was used, although in no instances was it felt to be identical to normal skin. Biopsies taken at two year follow up showed gradual remodelling of the dermal component resembling papillary and reticular dermis, but no rete ridges. There was no evidence of an immune reaction or scarring (65).

As the use of Integra requires an interval of three weeks before split skin grafting, it has been proposed that this time could be used to generate a cultured epidermal autograft from a skin biopsy, thereby reducing the need for autograft donor sites. Orgill *et al* showed successful take of cultured epithelial autografts onto a pre-grafted Integra-like material in a porcine model (66), with the wounds showing nearly complete confluence of the cultured epidermal autograft at seven days,

compared to controls where there was poor take of cultured epidermal autografts onto freshly excised full-thickness wounds. Current research is focusing on modifying the collagen / glycosaminoglycan matrix through the incorporation of peptides (67) and antibiotics (68) and cultured autologous keratinocytes which can produce a surface epithelium when seeded into Integra and grafted onto athymic mice (69). The seeded material exhibited good wound adherence, complete healing and minor wound contraction, and has the potential to reconstitute a functional, elastic and durable human skin (30).

Integra has an important role in immediate wound cover following early excision in patients with insufficient autograft, providing readily available dermal coverage without the inherent cross infection risks of allograft. It provides improved elasticity and cosmesis at the recipient site compared to ultra-thin split skin grafting alone, with a reduced donor site morbidity, quicker healing and less scarring from the ultra thin grafts compared to a standard thickness one. Donor sites can be re-cropped more often. There are however disadvantages to the use of this product. It is relatively expensive when compared with cadaveric allograft skin from skin banks, and there is a high initial failure rate whilst learning to use the product. Half the burns units in the UK are using skin substitutes, all of whom have experience of Integra whilst use of these other synthetic skins is much less prominent (70).

Apligraf™

Apligraf™ (Organogenesis Inc., Canton, Massachusetts, USA and Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA) is marketed as 'living skin equivalent' and is a combination of bovine collagen gel seeded with living neonatal allogeneic fibroblasts with an overlying cornified epidermal layer of neonatal allogeneic keratinocytes. It is the most sophisticated commercially available skin substitute and also the most expensive, as it is the only product that has been engineered to mimic both layers of the human skin from a single application. Studies using Apligraf for chronic unhealed wounds such as venous and diabetic ulcers have shown significant benefit over compression therapy to gain complete wound closure at eight weeks (71), although DNA studies have demonstrated the persistence of allogeneic keratinocytes in only 2 out of 8 biopsies at one month post-grafting and in no biopsies one month later (72). A randomised trial to assess the potential benefits of using Apligraf applied over meshed split thickness autografts to improve the cosmetic and functional

outcome showed no difference in the take of the autograft. Pigmentation, pliability, and vascularity of the skin graft in the Apligraf-treated group were significantly better than the control group (73).

Malignant Melanoma

Melanoma is a neoplasm arising from melanocytes and is always malignant. It is most commonly found on the skin, but can occur within the eyeball, below nail plates and within any mucous membranes such as the intraoral and intestinal mucosa. Over recent decades the incidence of melanoma has significantly increased (74), and this is likely to reflect changing habits of social sun exposure, which has been identified as the primary causative factor. Notable exceptions do occur, as the incidence of melanoma is actually decreasing in Australia following an aggressive public awareness campaign known as 'Slip, Slap, Slop' in light of their excess melanoma incidence (75). The current incidence for malignant melanoma within the UK is 10 per 100,000 (76), whereas that for Auckland in New Zealand is 70 per 100,000 (77), almost certainly reflecting environmental and climatic differences.

Given the increasing incidence of this cancer, which continues to have an appreciable associated mortality rate (78) and three recent publications (79-81) examining the progression of staging and management of this condition, it is perhaps now prudent to examine the current evidence and latest guidelines for the management of cutaneous melanoma. The highlights of the recent joint report of the British Association of Dermatologists and the Melanoma Study Group (79), are described below.

Diagnosis and Documentation

Diagnosis relies on the identification of major and minor indicators. Major indicators are a change in size, irregular shape or irregular pigmentation, whilst minor indicators are a maximal diameter greater than 7 mm, inflammation, bleeding and a change in sensation. The presence of any major or three minor features implies a suspicious pigmented lesion, which should be further assessed. This diagnostic method however, is unhelpful in the diagnosis of amelanotic melanoma. Aside from the features used as diagnostic indicators, the presence of ulceration, further pigmented lesions, lymphadenopathy or hepatomegaly should be recorded.

Genetic Testing

There is insufficient evidence to support genetic testing unless more than three family members are affected, but counselling by a clinical geneticist would be appropriate in situations where two to

three melanomas arise within a family.

Screening and Surveillance

There are two groups to be considered. Group 1 are those with a previous melanoma, or very large numbers of pigmented lesions, some of which have atypical features, which have an 8-10x risk of melanoma development. Group 2 are patients with a Giant Congenital Naevus, defined as greater than 20cm diameter or 5% of the total body surface area, which have a hundred fold increased risk of developing melanoma. It was proposed that patients in group 1 be taught to self examine and report suspicious changes, whereas those within group 2 should have long term expert follow-up and possibly undergo genetic counselling if 3 or more family members are affected with melanoma change.

Biopsy and Definitive Treatment

Incisional biopsy is rarely recommended other than in the case of suspected lentigo maligna arising on the face. In all other cases full thickness excision with a 2-5 mm margin is recommended. Consequent upon the histology report and confirmation of the diagnosis, definitive further wide local excision should be undertaken, the margins dependent on the depth of invasion of the tumour (Table 5).

Table 5. Margins for wide local excision of proven malignant melanoma.

In situ	Histological clearance
<1mm	1cm
1-2mm	1-2cm
2.1-4mm	2-3cm
>4mm	2-3cm

Staging

Patients should be staged according to the American Joint Committee on Cancer (AJCC) system and all patients at Stage 2B and higher should undergo chest X-ray and liver ultrasound or CT of chest, abdomen +/- pelvis in addition to Full Blood Count, Liver Function and Lactate Dehydrogenase estimation. Controversy exists over these UK recommendations for staging as it suggests that sentinel lymph node biopsy (SLNB) only be used within specialist cancer centres in contradiction of both the AJCC guidelines and the World Health Organisation, which mandates SLNB as standard of care (82). The role of SLNB is discussed in more detail below.

Adjuvant treatment

There is no proven adjuvant therapy. Interferon is offered in the USA and is available from specialist centres within the UK but is of unproven long-term benefit (83,84).

The AJCC Guidelines

The AJCC paper (80) was published in

2001 with a companion publication (81) explaining the validation of the staging system by analysis of prognostic factors. Data was obtained from 13 cancer centres across Europe and US, involving 30,450 patients. After close scrutiny 17,600 patients were found to have complete clinical and pathological follow-up information, 73% of which had >5 year records, 49% >10 years, and 14% >20 years. Their published Tumour, Node, Metastasis (TNM) staging system* incorporates a number of recent amendments taking into account factors such as microscopic nodal metastasis (the information received from intra-operative SLNB), and the worse prognosis of ulcerated tumours.

A number of criticisms of the UK guidelines have been voiced, some of which concern the discrepancy between the AJCC and UK recommendations including the discrepancy over SLNB (85-87). In addition the UK paper refers to a group of patients with a 0.75 mm Breslow thickness for whom a 5 mm excision margin is adequate, however AJCC uses a 1mm limit instead of 0.75 mm. The recommendation of a 2-3cm excision margin for tumours 2.1-4mm deep gives no guidance as to which margin to aim for, particularly in light of evidence suggesting a wider margin confers no long-term survival benefit (88).

Sentinel lymph node biopsy

Selective lymphadenectomy was first described by Cabanas in 1970 as part of the treatment of penile cancer. Its use in melanoma was pioneered by Morton in the late 1980s, he subsequently developed a technique, now known as triple therapy, and currently the method most commonly used for the identification of the sentinel node (89).

Sentinel node biopsy takes place at the same time as wide local excision of the melanoma after initial excision and confirmation of the pathological diagnosis. Prior to transfer to the operating theatre, the patient receives an intradermal injection of a radio labelled isotope, usually technetium 99, in the area surrounding the previous excision scar. Subsequent assessment by a gamma camera identifies the area in which the sentinel node (the one with the highest gamma count) is to be found as this may not be obvious, particularly in the case of midline truncal disease which may identify sentinel nodes in more than one lymphatic basin. More than one sentinel node within a single basin may also be identified. The second and third parts of the technique both take place in theatre. The wide local excision is marked out and an injection of blue dye, such as 'patent v', is given intradermally within the area for excision (Figure 2), this is then taken up in the

* The complete AJCC TNM classification is not included here but the interested reader is referred to Reference 80.

lymphatics and transported to the lymph drainage basin and hence the sentinel node. Before beginning the lymphadenectomy, the draining lymph node basin is swept with a hand held gamma-detection system to more precisely identify the location of the sentinel node, constituting the second part of the technique. During lymph node dissection the sentinel lymph node can be seen to have taken up the blue dye and is the final part of the triple therapy technique.

Fig 2. Four injections of vital blue dye around the previous excision scar (dotted line) within the proposed wide local excision margin (solid ellipse).

Historically, American surgeons have performed regional lymphadenectomy, or block dissections, for melanoma much more commonly than their British counterparts, which is likely to explain the relative resistance to SLNB in the UK as an unnecessary escalation in management. The nodal status of a melanoma patient, however, is a requirement to be accurately staged according to the AJCC - as it is impossible to clinically diagnose micrometastasis without SLNB. Several studies have examined sentinel node biopsy in melanoma, and all give similar results. In general, SLNB is positive in 20% of cases and in those in whom completion lymphadenectomy is performed - as is usual - one fifth have nodal disease beyond the sentinel node (90). The reported false negative rates are 3-5% (91).

Specific consideration of the indications for SLNB have been made for two particular groups, namely thick and thin melanomas. In patients with thin melanomas (<1mm), the likelihood of metastasis is very small and consequently the risks and complications associated with surgery, although small, may outweigh the benefit gained, except where specific indications are present such as a positive deep margin on initial biopsy, ulceration, histological regression or Clark Level 4 or 5 tumour (92). It was presumed

that in patients with thick melanomas (>4mm) there would be no survival advantage in obtaining lymph node assessment. However, in a recent paper specifically addressing this question, only one third of patients had a positive sentinel node, and of these, half had no further evidence of spread. Follow-up out to three years showed survival rates of 80% for sentinel node negative patients compared to 60% for sentinel node positive ones ($p=0.006$) and the author concluded that sentinel node status was a strong independent prognostic factor for survival, and recommended its use in this group of patients (93).

From published literature and personal experience, the current guidelines for sentinel lymph node biopsy in melanoma should include all patients with disease >1mm, and in addition those with disease <1mm but with any of the following; positive deep margin on initial biopsy, histological regression, Clark level four or five or ulceration.

Conclusion

The classification of Malignant Melanoma is still predominantly based upon Breslow thickness, although the demarcations of depth of invasion have been revised. In addition there are several factors, including ulceration and nodal status, which are now known to be of significant prognostic relevance. Sentinel node biopsy should be carried out routinely in all but uncomplicated, thin melanomas.

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Appendix

National Burn Injury Referral Guidelines

It has been traditional to use the size of skin injury following a burn injury as the single criterion to guide referral. This approach has often been criticised as overly simplistic. Consideration of other important factors has proved difficult as quantification of these is unclear or impossible.

It has been recognised that practical clarification is needed and the British Burn Association by way of the Committee of the National Burn Care Review wish to propose the following guidance. Such guidance is not to be viewed as rigid instruction but used to help highlight some of the important features of burn injury that are known to predict a complex clinical course. It is proposed that burn injuries be referred to appropriate burn care hospitals based on the injury complexity for assessment and management.

Complex

A burn injury is more likely to be complex if associated with the following criteria:

Age	Under 5yrs or over 60yrs
Site involvement (with dermal or full thickness loss)	Face or hands or perineum or feet Or Any flexure particularly the neck or axilla Or Any circumferential dermal or full thickness burn of the limbs, torso or neck
Inhalation injury monoxide poisoning	Any significant such injury, excluding pure carbon
Mechanism of injury	Chemical injury (>5% TBSA) Exposure to ionizing radiation injury High pressure steam injury High tension electrical injury Hydrofluoric acid injury (>1% TBSA) Suspicion of non-accidental burn injury; adult or paediatric

A complex burn is also suggested by one involving:

Size of skin injury (with dermal or full thickness loss)	Paediatric (under 16yrs old) >5% TBSA Or Adult (16yrs or over) >10% TBSA
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A burn injury may also be deemed complex if it occurs alongside:

Existing conditions eg	Cardiac limitation and/or MI within 5yrs Respiratory limitation of exercise Diabetes Pregnancy Immuno-suppression for any reason Hepatic impairment; cirrhosis
Associated injuries	Crush injuries Fractures Head injury Penetrating injuries

Associated injuries, such as those listed, complicate any burn injury and may make it complex. However the range of presenting problems must be carefully considered and the most compelling injury dealt with first, according to clinical need. This may, in some circumstances, delay any referral for the burn injury to be dealt with. In such instances as regards burn management should always be sought.

A complex non-burn would include:

Inhalation injury	any significant such injury with no cutaneous burn, excluding pure carbon monoxide poisoning
Vesiculobullous disorders eg	any over 5% TSBA epidermolysis bullosa staphylococcal scalded skin syndrome (Ritter's) Stevens-Johnson syndrome Toxic epidermal necrolysis (Lyell's)

*All injuries deemed to be **complex** need referral to the local Burn Centre or Burn Unit.*

The criteria listed above put the patient at risk of a complex injury. While some are absolute others such as age <5 or >60 years, co-existing medical problems, associated head injury, fractures, burns to the face, hands, feet are open to interpretation if the burn is not more than 5% TBSA and has no area of deep burn. Under these circumstances the burn may be treated locally in an A&E Department provided it is reviewed within 24 hours by an experienced A&E clinician, and referred to the burns service if there is doubt about the extent or severity of the injury. A&E Departments are advised to discuss these types of cases with their local burns service on initial presentation, if there is any uncertainty about the nature, severity or the significance of each of the criteria.

Non Complex

All burn injuries felt not to be complex may be referred for assessment and admission according to the skin surface area involved.

Size of skin injury	Paediatric (under 16yrs old) 2% to 5% TBSA if dermal or any smaller injury if full thickness loss. Adult (16yrs or over) 5% to 10% TBSA if dermal or any smaller injury if full thickness loss.
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*All **non-complex** injuries referrals should be made to a local Plastic Surgery Unit (Burn Facility).*

Other injuries, not meeting the criteria laid out above, are often suitable for care in an A&E Department or in the community.

Non-acute referrals

Injuries that may require referral from A&E, GP, Practise Nurse or District Nurse in the post acute phase include:

Wound healing	Any wound unhealed at 14 days post injury
Complications	Any significant infection, septic episode or suggestion of a Toxic Shock-like illness.
Rehabilitation	Any healed wound where the scarring suggests there will be: A significant aesthetic impact and/or psychological disturbance
disturbance	The need to consider skin camouflage A significant functional limitation The need to consider pressure therapy or other forms of scar modification The need to consider surgical reconstruction

In the opinion of the National Burn Care Review Committee and the British Burn Association, there is no justification for injuries requiring hospital admission to be dealt with outside this system.

British Burn Association
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