Figure 21.8.8 After initial premaxillary repositioning, patient with bilateral cleft lip and palate undergoing nasal molding. Note two nasal stents added to the plate with an anterior elastomeric chain **(A, B)**. While the elastomeric chain is holding the premaxilla and prolabium down and back, the nasal stents elevate the nasal tip, repositioning the nasal domes towards the midline and elongating the columella **(C–E)**.

Figure 21.8.9 Frontal, profile, and nasal photographs of a patient with bilateral cleft lip and palate who underwent presurgical nasoalveolar molding treatment and primary lip repair. Comparison of before **(A–C)** and after **(D–F)** nasoalveolar molding photographs illustrate reduction of premaxillary asymmetry and protrusion as well as improvement of nasal asymmetry. A satisfactory lip and nasal repair was obtained soon after lip surgery **(G–I)**. Four years after surgery **(J–L)**, the patient maintains excellent lip line, nose/lip relations, nasal symmetry, and projection.
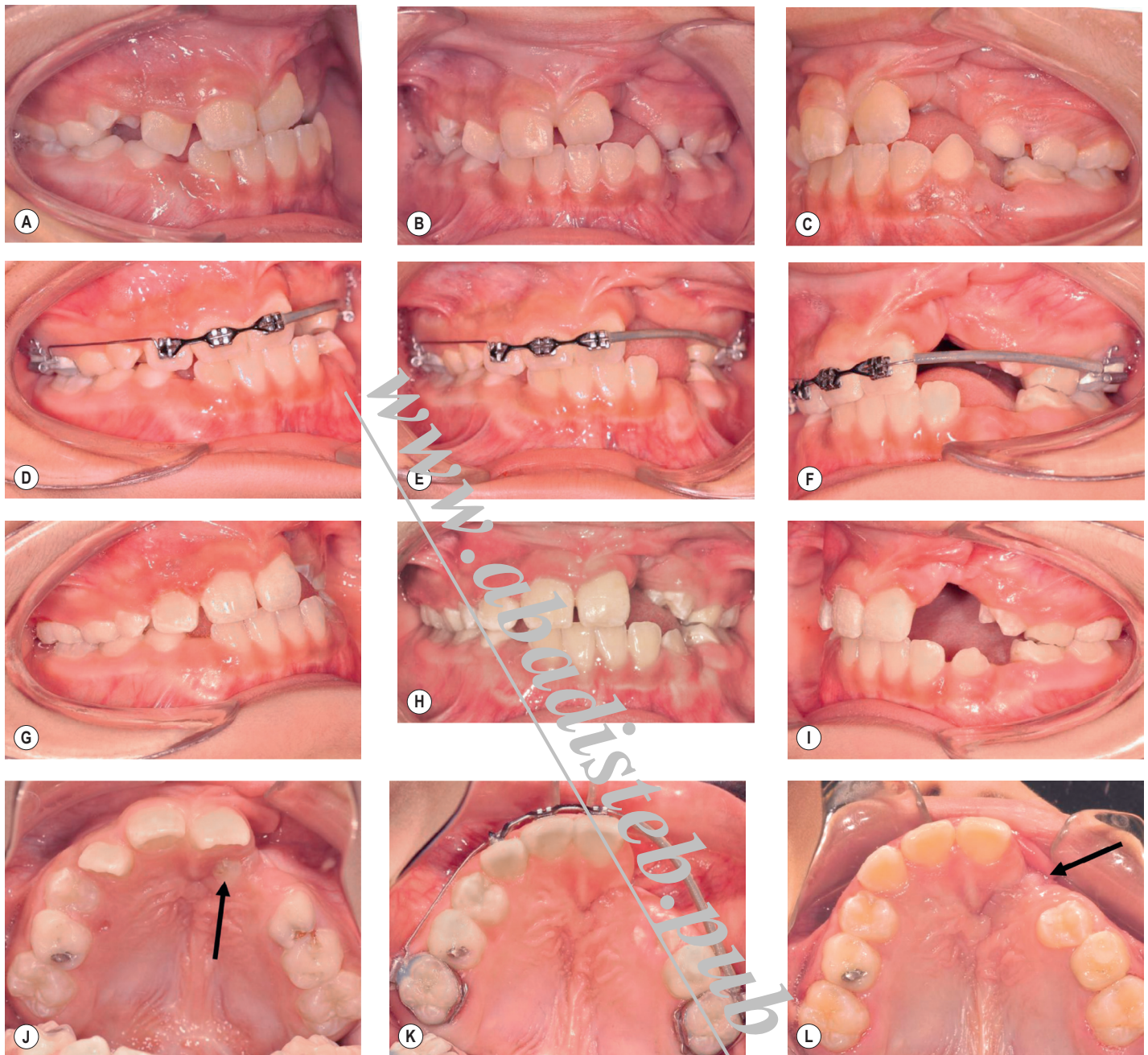
Figure 21.8.10 Long-term follow-up of a patient with unilateral cleft lip and palate treated with presurgical nasoalveolar molding, and only primary lip and palate repair and alveolar bone grafting. Close-up photos of the nose before **(A)** and after **(B)** nasoalveolar molding, and feeding with the nasoalveolar molding prosthesis in place **(C)**. Facial photos before treatment **(D)**, postsurgery at 2 **(E)**, 9 **(F)**, and 16 **(G)** years of age. Note satisfactory outcome with nice lip line and stable nasal symmetry.

Figure 21.8.11 Patient with unilateral cleft lip and palate in the transitional dentition prior to orthodontic preparation for alveolar bone grafting **(A–C)**, after orthodontic treatment **(D–F)**, and after bone graft **(G–I)**. Note alignment of the dental arch with a simple segmental edgewise orthodontic appliance. **(J–L)** Occlusal views at similar stages. Note missing lateral incisor and retained primary canine in the cleft area (arrow) **(J)**. This tooth was extracted prior to surgery. Note aligned arch prior to surgery **(K)**. After surgery, the permanent canine erupted through the bone-grafted area (arrow) **(L)**. **(M–O)** Panoramic radiographs at similar stages: note in the pretreatment radiograph

Comprehensive lower extremity anatomy

Rajiv P. Parikh and Grant M. Kleiber

SYNOPSIS

- Success in lower extremity reconstruction is dependent on a comprehensive understanding of structural and functional anatomy. An anatomic- and defect-specific approach to lower extremity reconstruction enables the surgeon to provide tailored solutions for both the preservation and restoration of a functional limb.
- A comprehensive appreciation for normal lower extremity anatomy and anatomical variants is critical to functional limb salvage when treating lower extremity pathology.
- The reconstructive surgeon may be also be called upon to harvest tissue for transfer from the many potential donor sites in the lower extremity.
- This chapter aims to provide a comprehensive review of the three-dimensional anatomy of the lower extremity to facilitate operative and clinical decision-making.
- A detailed description is given of each region of the lower extremity with respect to skeletal support, musculofascial anatomy, vascularity, lymphatic drainage, peripheral nerves, and skin and soft-tissue elements.
- A broad overview of available soft-tissue donor sites from each region, donor sites for bone grafts, anatomic basis of common lower extremity flaps, surgical approaches to lower extremity recipient vessels, and common points of nerve injury and entrapment are included to provide a clinically relevant discussion for anatomy of the lower extremity as a framework for common challenges in reconstructive surgery.

The gluteal region

Gluteal skeletal structure

The pelvis consists of the two paired hip bones and the midline sacrum, articulating together at the two sacroiliac joints. The hip bones are formed by the fusion of the ilium, pubis, and ischium. These three bony regions of the pelvis coalesce to form the acetabulum. The large thick bony prominences of the pelvis serve as attachments for the muscles of the hip and thigh (Fig. 1.1). These prominences also become clinically relevant in contributing to the formation of pressure ulcers, most commonly over the ischial tuberosity, sacrum, and greater trochanter. Dense ligaments stabilize and distribute the numerous opposing forces acting on the pelvis. The sacrospinous ligament runs from the sacrum to the ischial spine, bounding the greater sciatic foramen. The sacrotuberous ligament attaches the sacrum to the ischial tuberosity and encloses the lesser sciatic foramen. Running from the anterior superior iliac spine (ASIS) to the pubic tubercle is the inguinal ligament. The action of the multiple flexors, extensors, and internal and external rotators on the hip joint serves to stabilize and position the torso during the complex process of ambulation.

Clinical correlation – iliac crest bone graft

The iliac crest serves as a versatile source of autogenous bone graft to reconstruct a variety of defects. Bone grafts can be cortical, cancellous, or corticocancellous in composition. Cortical bone is structurally stable with osteoconductive properties and ideally suited for structural defects requiring immediate mechanical stability. Cancellous bone is osteoinductive, osteogenic, and osteoconductive, undergoes rapid remodeling and vascularization, and is ideally suited for non-unions and bony fusion. Cancellous bone can be obtained between the inner and outer table of the ilium. The anterior and posterior iliac crest are common donor sites for cancellous and corticocancellous bone grafts, with 13 cm^3 and 30 cm^3 average graft volumes available from the anterior and posterior crest, respectively (Fig. 1.2).[1] Anteriorly, bone graft is most commonly harvested from the iliac tubercle, 3–4 cm posterior and parallel to the ASIS to maximize available bone and minimize risk to the lateral femoral cutaneous nerve. The iliac crest lies deep to a musculofascial layer from the external oblique and the iliacus muscle. The ilioinguinal nerve runs along the medial surface of the iliacus muscle and is at risk during harvest from the anterior crest. The anterior iliac crest provides
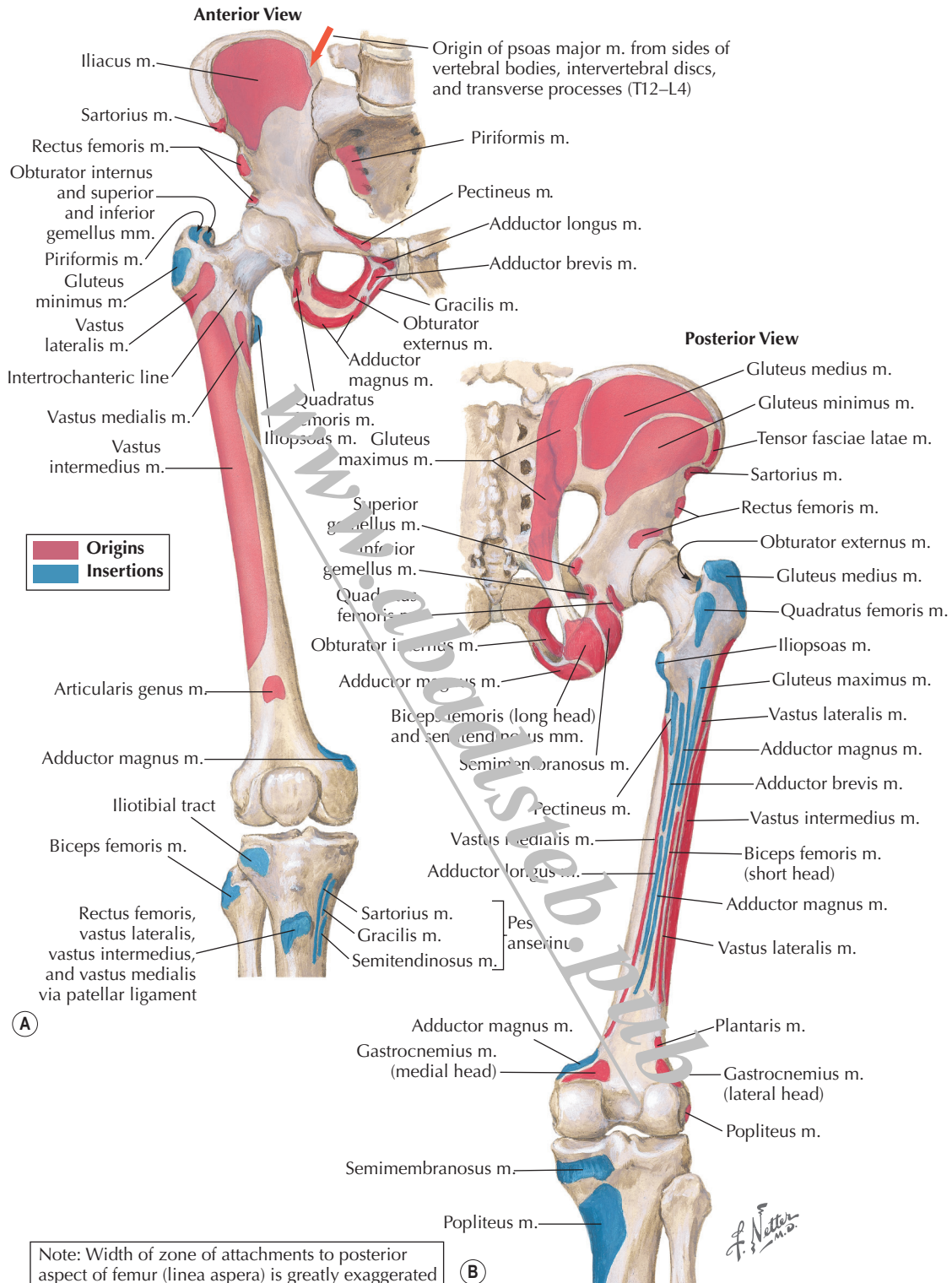
Anterior View

Iliacus m.

Origin of psoas major m. from sides of
vertebral bodies, intervertebral discs,
and transverse processes (T12–L4)

Sartorius m.

Rectus femoris m.

Piriformis m.

Obturator internus
and superior
and inferior
gemellus mm.

Pectineus m.

Adductor longus m.

Piriformis m.

Adductor brevis m.

Gluteus
minimus m.

Gracilis m.

Obturator
externus m.

Vastus
lateralis m.

Adductor
magnus m.

Intertrochanteric line

Quadratus
femoris m.

Vastus medialis m.

Iliopsoas m.   Gluteus
maximus m.

Vastus
intermedius m.

Superior
gemellus m.

inferior
gemellus m.

Quadratus
femoris m.

Origins

Insertions

Obturator internus m.

Adductor magnus m.

Articularis genus m.

Biceps femoris (long head)
and semitendinosus mm.

Semimembranosus m.

Adductor magnus m.

Pectineus m.

Vastus medialis m.

Iliotibial tract

Adductor longus m.

Biceps femoris m.

Rectus femoris,
vastus lateralis,
vastus intermedius,
and vastus medialis
via patellar ligament

Sartorius m.

Gracilis m.

Pes
anserinus

Semitendinosus m.

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Posterior View

Gluteus medius m.

Gluteus minimus m.

Tensor fasciae latae m.

Sartorius m.

Rectus femoris m.

Obturator externus m.

Gluteus medius m.

Quadratus femoris m.

Iliopsoas m.

Gluteus maximus m.

Vastus lateralis m.

Adductor magnus m.

Adductor brevis m.

Vastus intermedius m.

Biceps femoris m.
(short head)

Adductor magnus m.

Vastus lateralis m.

Adductor magnus m.

Plantaris m.

Gastrocnemius m.
(medial head)

Gastrocnemius m.
(lateral head)

Popliteus m.

Semimembranosus m.

Popliteus m.

Note: Width of zone of attachments to posterior
aspect of femur (linea aspera) is greatly exaggerated

Ⓑ

Figure 1.1 Bony attachments of buttock and thigh muscles. (*Netter illustration from* www.netterimages.com. *Copyright Elsevier Inc. All rights reserved.*)

twice the volume of packed cancellous bone compared to the distal radius or olecranon. Alternatively, tricortical bone grafts can be harvested from the inner and outer table of the anterior ilium and corticocancellous bone grafts can be harvested to include either the inner or outer table. Posteriorly, the bone is thickest and best harvested in the area superior to a line connecting the posterior superior iliac spine (PSIS)

and the apex of the sacroiliac joint. Harvesting from an area approximately 4 cm distal to the PSIS prevents violation of the sacroiliac joint.[2] Unicortical and corticocancellous bone grafts can be obtained from the outer table of the posterior ilium and additional cancellous bone harvested from the inner table of the ilium. The iliac crest can also provide vascularized bone for a variety of composite soft-tissue and bone
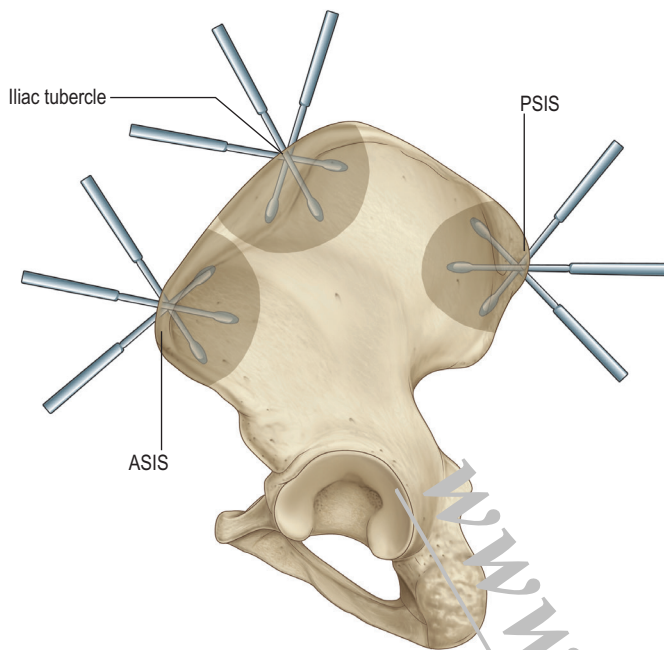
Figure 1.2 Harvest sites for iliac crest bone graft. (*Redrawn from Ebraheim NA, Elgafy H, Xu R. Bone-graft harvesting from iliac and fibular donor sites: techniques and complications.* J Am Acad Orthop Surg. *2001;9(3):210–218.*)

Table 1.1 Mathes–Nahai classification system for muscle vascular supply	
Muscle vascular supply type	**Description**
I	Single vascular pedicle
II	Dominant vascular pedicle and one or more minor pedicles
III	Two dominant pedicles
IV	Segmental vascular pedicles
V	Single dominant vascular pedicle and secondary segmental pedicles

defects. Corticocancellous, vascularized bone can be obtained from the outer cortex of the ilium on the lateral half of the iliac crest, supplied by the ascending branch of the lateral femoral circumflex system.[3] The inner cortex of the ilium, supplied through nutrient branches off the deep circumflex iliac artery, is another common source of vascularized iliac bone.

Gluteal fascial anatomy

The fascial system of the gluteal region and the lower extremity contains various permutations of a nearly continuous superficial fascial and a deep fascial layer. The superficial system is located in the subcutaneous fat. The deep fascial layer is thicker and frequently can be seen as a dual-layered fibrous band. It usually lies directly over the underlying limb musculature and its proper fascia. The superficial fascia of the gluteal region is contiguous with that over the lower back and continues inferiorly into the proximal thigh. The deep fascia covering the gluteal muscles varies in thickness. Over the maximus it is thin, but over the anterior two-thirds of the medius it thickens and forms the gluteal aponeurosis. This is attached to the lateral border of the iliac crest superiorly, and splits anteriorly to enclose the tensor fasciae latae and posteriorly to enclose the gluteus maximus.

Muscles of the buttocks

The gluteus maximus is the largest muscle in the body and lies most superficially in the gluteal region, originating from the posterior gluteal line of the ilium and the dorsal portion of the sacrum (Fig. 1.3). The superficial fibers coalesce into a thick tendinous expansion which contributes to the iliotibial band of the fascia lata, while the deep fibers insert on the gluteal tuberosity of the femur. The gluteus maximus acts as a hip extensor when the hip is in a flexed position. In a standing position, the gluteus maximus dorsally rotates the pelvis and torso, maintaining stability. The vascular supply is primarily derived from the inferior gluteal vessels, which supply the inferior two-thirds of the muscle. The superior gluteal vessels supply the superior portion and the first perforator branch of the profunda femoris contributes to the vascular supply of the muscle laterally. For ease of description, the Mathes–Nahai classification system is used when discussing muscle vascularity (Table 1.1).[4] The gluteus maximus has a type III vascular supply, with two dominant pedicles from the superior and inferior gluteal arteries. Innervation to the gluteus maximus is provided by the inferior gluteal nerve. Underneath the gluteus maximus lie three bursae: the trochanteric, gluteofemoral, and ischiofemoral bursae, which allow frictionless movement over its underlying structures.

The gluteus medius, situated immediately deep to the gluteus maximus, arises from the outer surface of the iliac wing and inserts on the greater trochanter of the femur. It is innervated by the superior gluteal nerve and functions to abduct the hip and medially rotate the femur. Blood supply to this muscle is from the deep branch of the superior gluteal artery and from the trochanteric connection.

The gluteus minimus lies deep to the gluteus medius and arises from the outer surface of the ilium. Its fibers join the aponeurosis of the gluteus medius to insert on the greater trochanter, and the two muscles function together to abduct the hip. The gluteus minimus is innervated by the superior gluteal nerve and receives blood supply from the superior gluteal artery and trochanteric connection. Several small muscles arise from the medial pelvis and insert on the greater trochanter of the femur, functioning collectively to rotate the hip externally. These muscles include piriformis, superior and inferior gemellus, quadratus femoris, obturator internus, and obturator externus.

Gluteal vasculature

The superior gluteal artery (SGA) is the last branch of the posterior trunk of the internal iliac artery. It exits the pelvis through the greater sciatic foramen superior to the piriformis, dividing into two branches (Fig. 1.4). The deep branch runs deep to the gluteus medius, dividing into superior and inferior branches. The superior branch travels laterally to the anterior superior
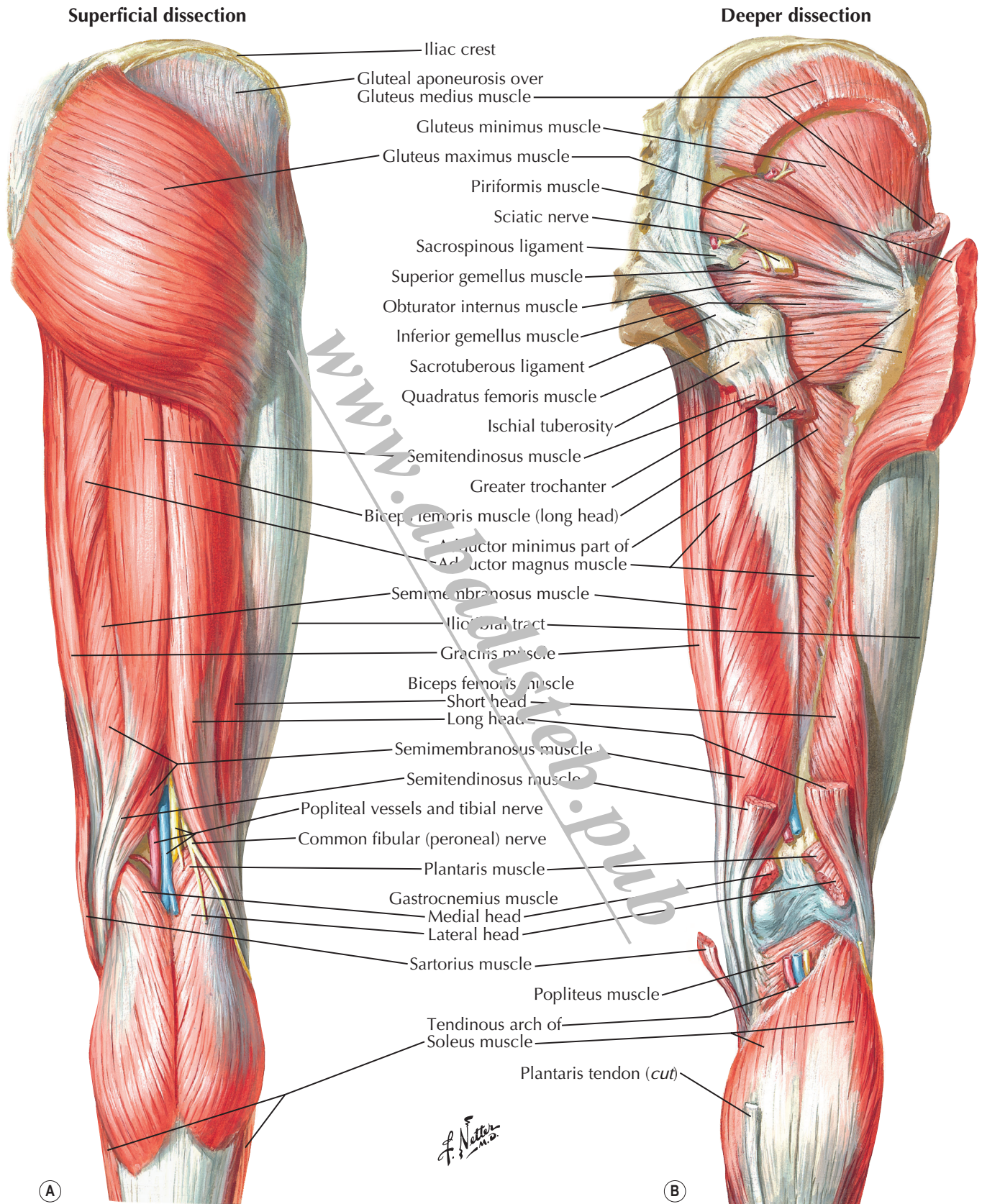
Superficial dissection

Deeper dissection

Iliac crest

Gluteal aponeurosis over
Gluteus medius muscle

Gluteus minimus muscle

Gluteus maximus muscle

Piriformis muscle

Sciatic nerve

Sacrospinous ligament

Superior gemellus muscle

Obturator internus muscle

Inferior gemellus muscle

Sacrotuberous ligament

Quadratus femoris muscle

Ischial tuberosity

Semitendinosus muscle

Greater trochanter

Biceps femoris muscle (long head)

Adductor minimus part of
Adductor magnus muscle

Semimembranosus muscle

Iliotibial tract

Gracilis muscle

Biceps femoris muscle
Short head
Long head

Semimembranosus muscle

Semitendinosus muscle

Popliteal vessels and tibial nerve

Common fibular (peroneal) nerve

Plantaris muscle

Gastrocnemius muscle
Medial head
Lateral head

Sartorius muscle

Popliteus muscle

Tendinous arch of
Soleus muscle

Plantaris tendon (*cut*)

Ⓐ   Ⓑ

Figure 1.3 Muscles of hip and thigh: posterior views. (*Netter illustration from* www.netterimages.com*. Copyright Elsevier Inc. All rights reserved.*)
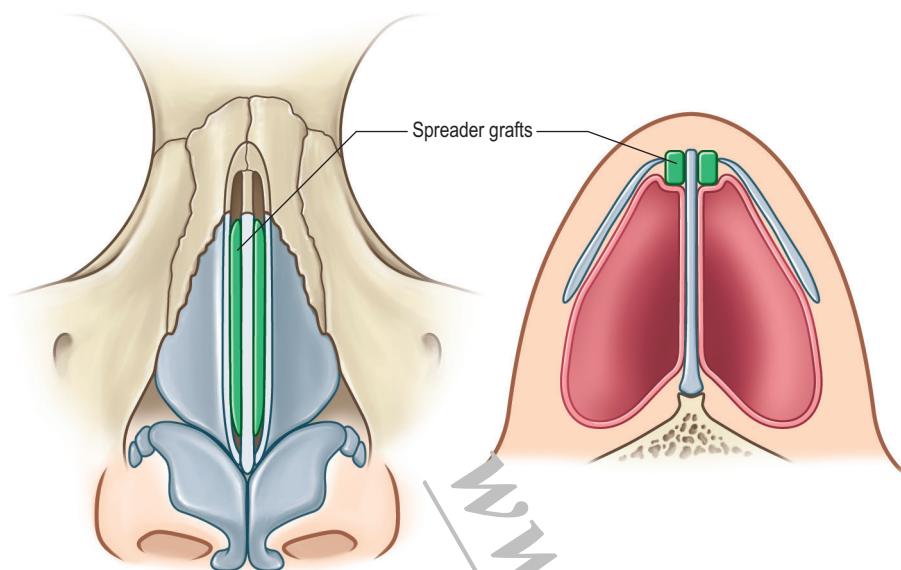
Figure 19.6 Dorsal spreader grafts.

BOX 19.5 **Classification of nasal deviations**

I.   Caudal septal deviation
   a.   Straight septal tilt
   b.   Concave deformity (C-shaped)
   c.   S-shaped deformity
II. Concave dorsal deformity
   a.   C-shaped dorsal deformity
   b.   Reverse C-shaped dorsal deformity
III. Concave/convex dorsal deformity (S-shaped)

present. Correction of septal deviation is key to improving nasal airflow and correcting the deviated nose.

The following principles are used to correct nasal deviation and perform septal reconstruction: (1) exposure of all deviated structures through the open approach; (2) release of all mucoperichondrial attachments to the septum, especially the deviated part; (3) straightening of the septum, and if necessary septal reconstruction, while maintaining a 10 mm or wider caudal and dorsal L-strut; (4) correction of any caudal septal deviation after the posterior septum has been reconstructed; (5) correction of dorsal septal deviations with cartilage grafting and/or scoring techniques; (6) restoration of long-term support with buttressing caudal septal batten or dorsal nasal spreader grafts; (7) if necessary, submucous resection of hypertrophied inferior turbinates; and (8) precisely planned and executed external percutaneous osteotomies.[43–45]

As opposed to septoplasty, where the septal cartilage is scored in an attempt to straighten it, or submucosal resection, where the majority of the septum is removed other than the L-strut, septal reconstruction differs in that only the portion of the septum causing airway obstruction is removed, with the idea that native cartilage is preserved. It is of critical importance to preserve an L-strut of septal cartilage for structural integrity. The technique for septal reconstruction is similar to that for septal cartilage harvest and is discussed later in this chapter.

Inferior outfracture/limited submucous resection

The turbinates exist as three or four bilateral extensions from the lateral nasal cavity. The inferior turbinate consists of highly vascular mucoperiosteum covering a thin semicircular conchal bone.[47] It is involved in regulation of filtration and humidification of inspired air. In combination with the internal nasal valve, the anterior extent of the inferior turbinate can be responsible for up to two-thirds of the upper airway resistance.[17,48] Posteriorly, the inferior turbinate diverges away from the nasal septum, allowing for reduced upper airway resistance in this area.[17,49]

Inferior turbinoplasty is performed in patients with nasal airway obstruction secondary to inferior turbinate hypertrophy that is refractory to medical management. We prefer a more conservative surgical approach to correct inferior turbinate hypertrophy, as we have found it to be effective with low morbidity.[50] Overly aggressive surgical management may be complicated by bleeding, mucosal crusting and desiccation, ciliary dysfunction, chronic infection, malodorous nasal drainage, or atrophic rhinitis.[17] In most cases, inferior turbinoplasty with outfracture of the inferior turbinate and, in some cases, limited submucous resection, is adequate to achieve significant improvement (Fig. 19.7).[50]

After removal of the previously placed oxymetazoline-soaked cottonoid pledgets, the inferior turbinates are inspected after vasoconstriction of the overlying mucosa has occurred. In cases of inferior turbinate mucosal hypertrophy, a long Vienna speculum is used to outfracture the inferior turbinates.[50] In cases of inferior turbinate bony hypertrophy, limited submucous resection of the inferior turbinate is indicated.[50] Outfracture is performed so that the entire inferior turbinate is microfractured laterally to open the nasal cavity. Limited submucous resection is performed using needle point electrocautery to incise the inferior border of the anterior 1–2 cm of the inferior turbinate down to the conchal bone. A Cottle elevator is used to develop a medially based submucoperichondrial flap to expose the portion of the conchal bone to be resected. Takahashi forceps are used to sharply resect the bone from the anterior third of the turbinate. The mucoperichondrial flap is replaced down over the cut edge of the
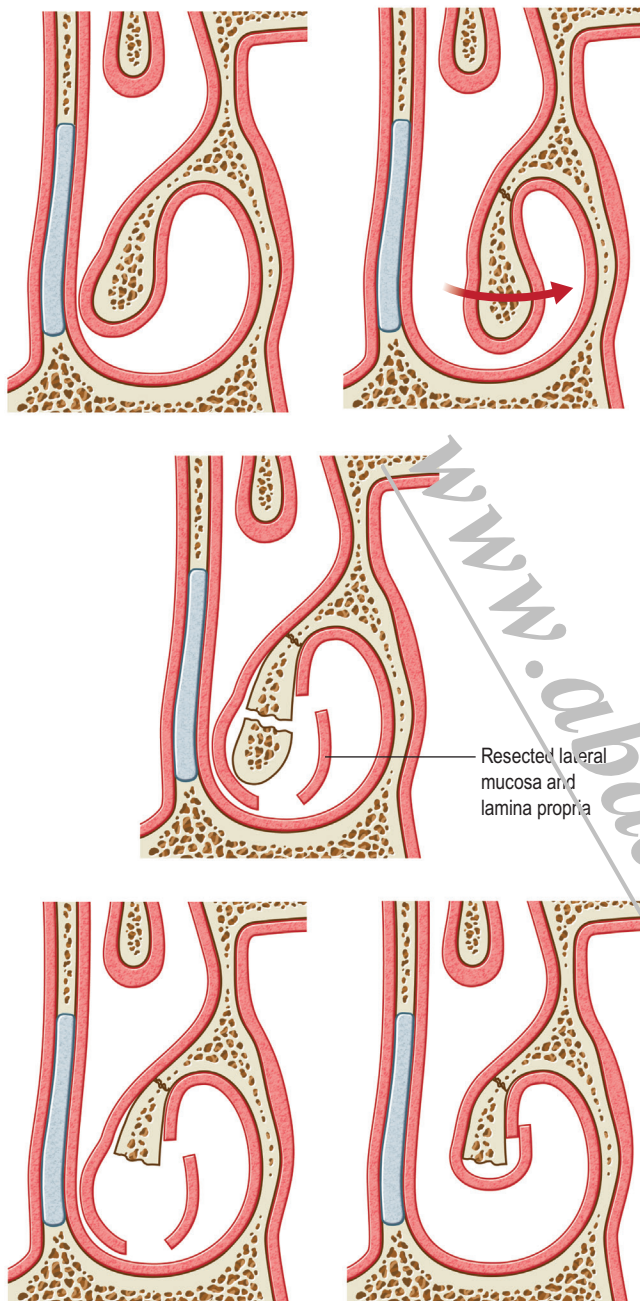
of tip projection due to disruption of ligamentous support and increased skin undermining.[67] As such, we commonly employ columellar strut graft and nasal tip suturing techniques to maintain nasal tip support during open rhinoplasty.

Cephalic trim

Cephalic trim is commonly performed with the bulbous or boxy tip (Fig. 19.14).[68] Paradomal fullness is secondary to prominence of the cephalic border of the middle and lateral crura of the lower lateral cartilages. Cephalic trim of this area reduces paradomal fullness and helps to define the tip and narrow the distance between the tip-defining points. An alar rim strip of at least 5–6 mm is preserved for adequate support of the external valve. Cephalic trim should be used judiciously. In some cases in which the quality of the lower lateral cartilages is poor, cephalic trim will further weaken the cartilages despite preserving a 5–6 mm alar rim strip, leading to alar rim collapse. In these cases, use of a lower lateral crural turnover flap is a better option to improve tip definition while preserving structural support.[69] Calipers should be used to accurately measure the alar rim strip. The excised cartilage can also be used as a source of autogenous grafts.

A lower lateral crural turnover flap is another useful technique to address paradomal fullness while providing additional support to the lower lateral cartilages.[69] It is beneficial for deformities, weakness, and collapse of the lower lateral crura and can also be used to improve lower lateral crural strength during tip reshaping. However, there must be sufficient lower lateral crura to leave a 5 mm alar rim strip. It can be used in combination with other external valve and alar rim supporting techniques.

Columellar strut graft

An intercrural columellar strut graft is used to maintain or increase nasal tip projection and aids in unifying the nasal tip.[70–72] It can be either floating or fixed (Fig. 19.15). A floating columellar strut graft is used more commonly to maintain tip projection and is positioned between the medial crura and rests in the soft tissues 2–3 mm anterior to the anterior nasal spine. A fixed columellar strut graft is used to increase tip projection and is positioned between the medial crura and rests on the maxilla. The columellar strut graft is typically fashioned from septal cartilage to measure 3 × 25 mm. A double hook is placed with a hook in the vestibular apex of each lower lateral cartilage. Upward traction is placed, and scissors are used to dissect a pocket between the medial crura down towards the anterior nasal spine. A 2–3-mm pad of soft tissue is preserved over the nasal spine to keep the graft from moving back and forth over the nasal spine with lip movements.[73] The columellar strut graft is placed in the pocket. With the tip-defining points held at the same level, a 5-0 PDS suture is used to stabilize the medial crura to the columellar strut graft, followed by several additional 5-0 PDS sutures to unify the nasal tip complex. The columellar strut graft is then trimmed as necessary.

Septal extension grafts

The septal extension graft is a versatile graft that effectively controls tip projection and rotation, whereas a columellar strut

Figure 19.7 Inferior turbinate outfracture and submucous resection.

Resected lateral mucosa and lamina propria

conchal bone; no suturing is necessary as this will adhere to the raw surface. Replacement of the flap will avoid postoperative hemorrhage or crusting.

The nasal tip

A graduated approach to nasal tip surgery requires a combination of techniques including the cephalic trim, the use of a columellar strut graft, nasal tip suturing, and nasal tip grafting. Application of these techniques will help to correct tip deformities and improve tip shape while minimizing deformities secondary to loss of support. In addition, compared with the closed approach, the open approach may cause mild loss

Harvesting autologous grafting material

The trend over recent decades in rhinoplasty has shifted away from ablative techniques involving over-reducing the osseo-cartilaginous framework to conserving the native anatomy and augmentation of deficient areas to correct contour deformities and restore structural support. As such, certain situations require harvest of autologous cartilage for graft material. Autologous grafts are preferential to homografts and alloplastic implants because of their high biocompatibility and low risk of infection and extrusion.[51] Their disadvantages include donor site morbidity, graft resorption, and unavailability of sufficient quantities for graft material.[41] Autologous cartilage grafts are most commonly obtained from septal, ear, and costal cartilage. Other donor sites for autologous grafts include calvarial and nasal bone, and the olecranon process of the ulna.[51] Concerns regarding donor site morbidity, graft availability, and graft resorption will necessitate the use of homologous or alloplastic implants.[52] Recently, temporal fascia grafts have found utility as an autologous graft material in rhinoplasty for camouflage or as composite grafts such as diced cartilage grafts wrapped in temporal fascia. Temporal fascia can be harvested with minimal donor site morbidity and an inconspicuous scar located in the temporal scalp.[53–55]

Septal cartilage

Septal cartilage is the primary choice for autogenous grafts in rhinoplasty. It can be used in all areas including tip grafts, dorsal onlay grafts, columellar strut grafts, and nasal spreader grafts.[53] It is easily harvested, leaves minimal donor site morbidity, and is available in the operative field. Septal cartilage harvest is performed as previously described for septal reconstruction.

Open rhinoplasty allows for ease of septal cartilage harvest with improved exposure and visualization. Septal cartilage harvest is performed only after component dorsal hump reduction is complete as it is essential to preserve an L-strut that is at least 10 mm for nasal support. However, this width will depend on the strength of the septal cartilage, and in many instances a width of 15 mm or more may be required to ensure long-term support. Dorsal reduction of the septum after septal cartilage harvest may leave an L-strut that is too narrow to provide adequate nasal support. Septal cartilage harvest is performed after the lower and upper lateral cartilages have been separated from the quadrangular cartilage. A No. 15 blade scalpel is used to score the mucoperichondrium of the septal angle, and then a Cottle elevator is used to develop the submucoperichondrial pocket on both sides of the septum (Fig. 19.8). Once in the correct plane, the denuded septal cartilage has a gray–blue hue, the septal cartilage has a gritty texture, and there should be little resistance elevating the mucoperichondrium off of the septal cartilage until the dissection reaches the osseocartilaginous junction between the quadrangular cartilage and the vomer. Dissection of the submucoperichondrial pocket is done towards the floor of the nasal cavity to the maxillary crest and posteriorly to the vomer (Fig. 19.9). During development of the submucoperichondrial pockets, care is taken to avoid perforations of the mucosa. Unilateral mucosal perforations generally do not cause any problems. However, bilateral opposing mucosal perforations should be repaired with 5-0 chromic gut sutures to prevent formation of a septal perforation postoperatively. A dorsal and caudal L-strut is created using a No. 15 blade scalpel to incise the septal cartilage parallel to the dorsal edge of the septum from the perpendicular plate of the ethmoid and is curved to parallel the caudal edge of the septum (Fig. 19.10). This incision is then continued posteriorly and parallel to the caudal edge of the septum until the crest of the maxilla. A Cottle elevator is then used to elevate the septal cartilage from the maxillary crest and vomer, liberating the septal cartilage. Any bony septal deviation of the perpendicular plate of the
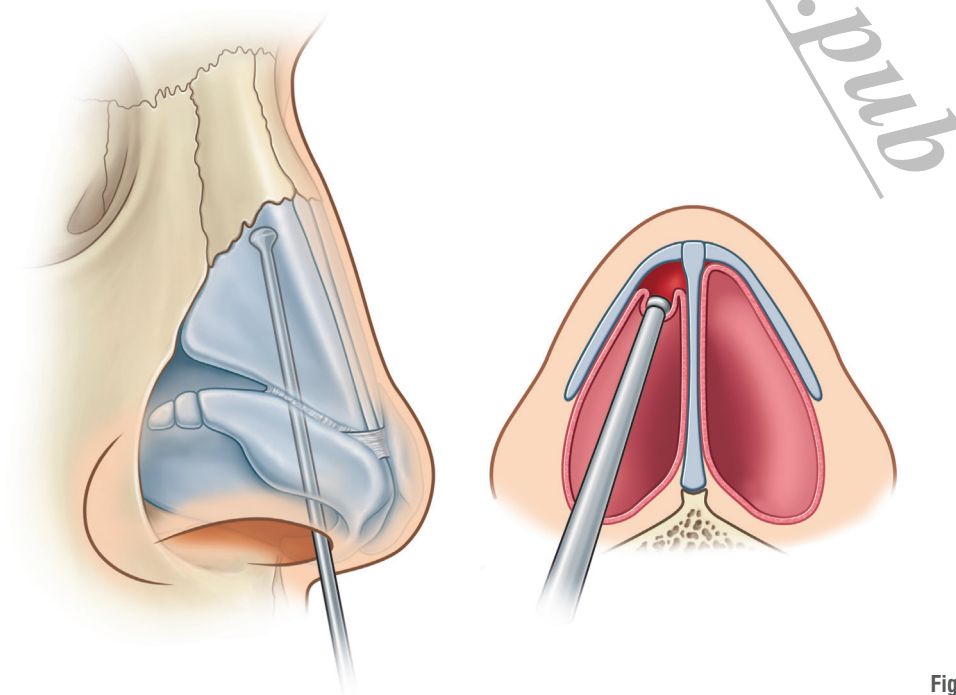

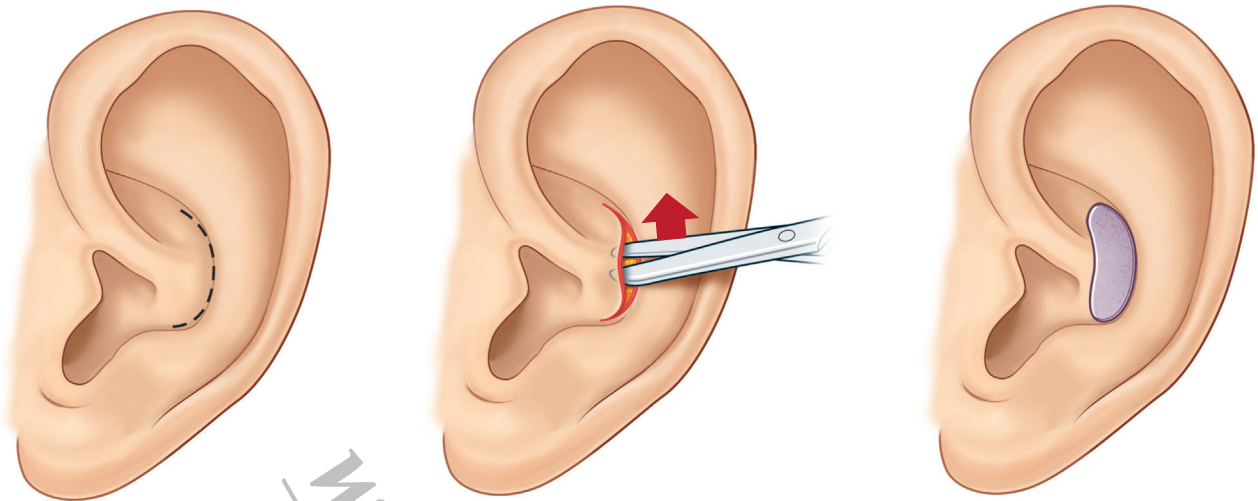**Figure 19.8** Submucoperichondrial dissection.

Figure 19.11 Harvesting ear cartilage.

inferiorly at the incisura intertragica, preventing donor site deformity. The outlined ear cartilage is then incised using a No. 15 blade scalpel, and fine dissecting scissors are again used to dissect the anterior auricular skin off of the anterior aspect of the conchal cartilage in the subperichondrial plane. Once the desired amount of cartilage has been dissected away from the anterior and posterior auricular skin it is excised with a No. 15 blade scalpel. Hemostasis is obtained and the incision is closed with a 5-0 plain gut running suture, followed by placement of a tie-over petroleum gauze bolster as previously described.

Costal cartilage

Costal cartilage provides abundant autogenous graft material. It can be used for tip grafts, columellar strut grafts, nasal spreader grafts, alar cartilage grafts, and dorsal onlay grafts. Given the size, amount, and intrinsic qualities, costal cartilage lends itself well to use as a dorsal onlay graft and where structural support is required. It can be carved into any shape. However, allowing at least 30 minutes to pass prior to carving allows initial warping to occur, minimizing late deformity.[60] In addition, utilizing centrally over peripherally located cartilage may help to minimize late deformity.[60,61] Some authors advocate the use of internal stabilization of costal cartilage grafts with Kirschner wire to prevent warping, but this can be associated with long-term complications, including extrusion of the Kirschner wire.[62]

Various authors[63–66] have described harvesting costal cartilage from different ribs, but it is our preference to harvest the 9th rib because it is straight medially and provides 4–5 cm of autogenous graft material (Fig. 19.12). The 9th rib is a floating rib and can be located by palpation. A 2-cm incision is made on the anterolateral aspect of the chest wall. Since the skin overlying the rib is mobile in this area, a long segment of rib can be harvested through this relatively small incision. The perichondrium is lightly scored and is dissected away from the underlying rib cartilage using both a dental elevator and a Joseph elevator. When freeing the cartilage away from the deep perichondrium, care is taken to avoid damaging the parietal pleura and creating a pneumothorax. After the amount

of cartilage needed is determined, it is harvested by incising through the rib using a No. 15 blade scalpel. Slightly more cartilage should be harvested than what is needed because cartilage is lost secondary to carving. Hemostasis is obtained, and the perichondrium is closed using 3-0 Vicryl. The wound is closed in layers using 4-0 Vicryl followed by a 5-0 Monocryl intradermal suture. Injection of 0.25% bupivacaine into the donor site for postoperative pain control is followed by application of Steri-Strips (3 M, St. Paul, MN).

If there is concern for pneumothorax during costal cartilage harvest, the wound is filled with saline and positive pressure ventilation can be performed by the anesthesia provider to ensure that there are no gas bubbles escaping from the chest cavity. If the parietal pleura has been violated, the tip of a red rubber catheter is inserted into the defect and a 3-0 Vicryl purse-string suture is performed around the catheter. The anesthesia provider performs a Valsalva maneuver while suction is applied to the red rubber catheter. As the catheter is withdrawn, the purse-string suture is tied to seal the parietal pleural defect, followed by wound closure. An upright chest X-ray should be performed postoperatively to confirm resolution of the pneumothorax.

Temporal fascia

The anterior limit of the incision is made in line with the tragus (Fig. 19.13).[53–55] A posteriorly pointing, V-shaped incision is used as this gives the widest exposure for the subcutaneous dissection. The incision is approximately 5 cm in craniocaudal dimension and spans approximately 2.5 cm in anteroposterior dimension. The skin of the scalp is infiltrated with 5 mL of 1% lidocaine with epinephrine. The skin is incised down through the temporoparietal fascia to expose the deep temporal fascia. A needle tip electrocautery is used to dissect the areolar tissues off the superficial surface of the deep temporal fascia. An attempt should be made to harvest the largest piece of temporal fascia possible. This involves incising the temporal fascia close to the temporalis muscle's attachments to the skull periosteum superiorly and posteriorly and where it begins to divide into deep and superficial layers anteriorly. The temporal fascia should be harvested inferiorly to the level of the ear.
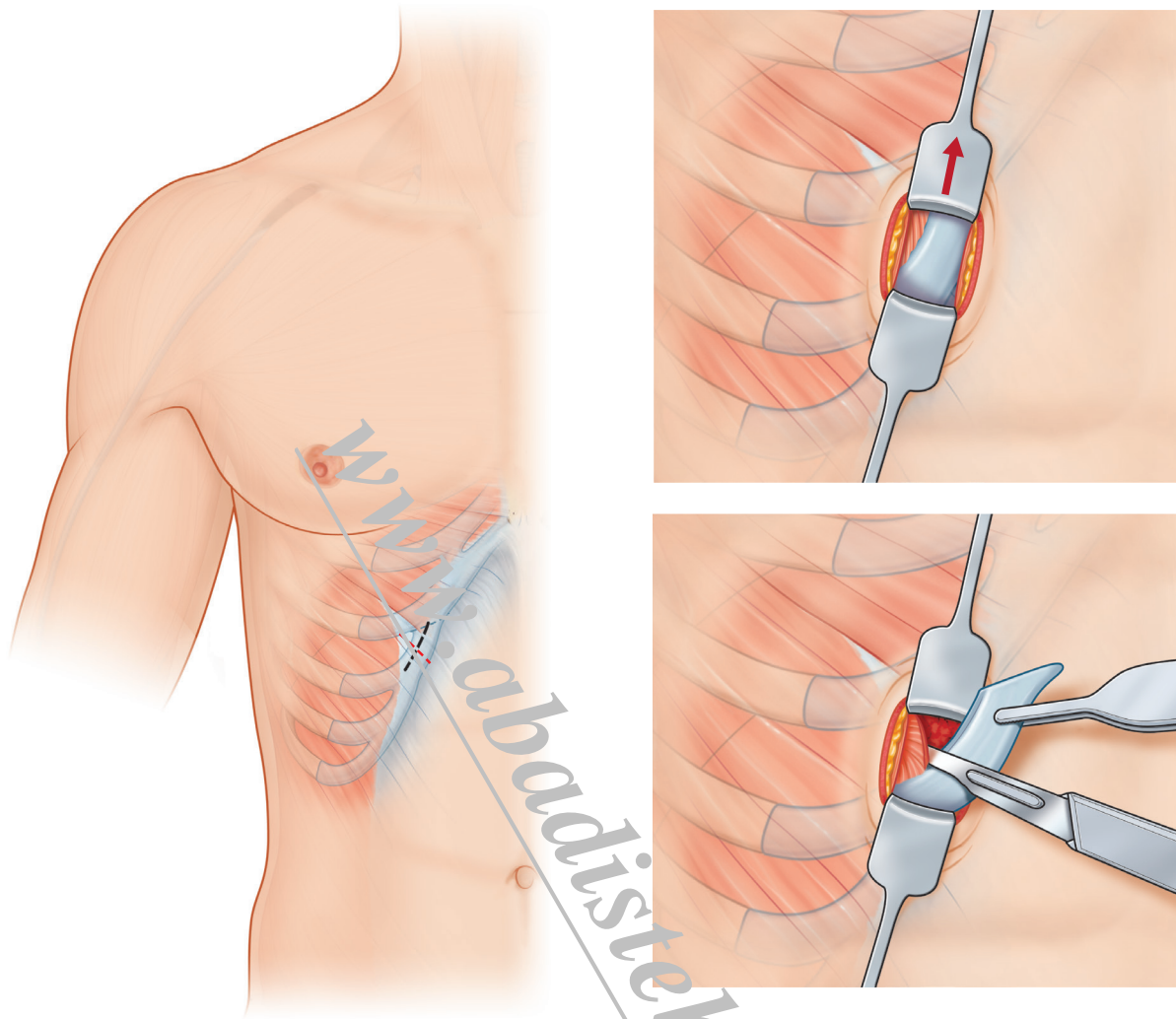
Figure 19.12 Harvesting costal cartilage.

Figure 19.13 Harvest of temporal fascia.

Although this area is about 8×6cm in dimension, temporal fascia contracts significantly and this generally yields a temporal fascia graft that is about 5×4cm in dimension. The deep temporal fascia is incised with the needle tip electrocautery and then swept off the underlying temporalis muscle. Muscle fibers should not be harvested with the temporal fascia graft. Hemostasis is obtained, and the skin is closed in layers with 3-0 Vicryl inverted deep dermal sutures followed by a running 4-0 chromic gut suture.
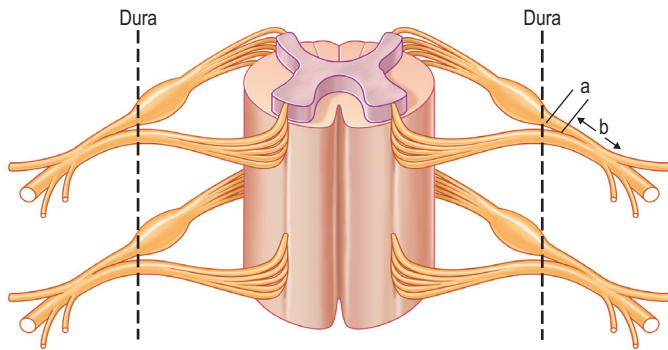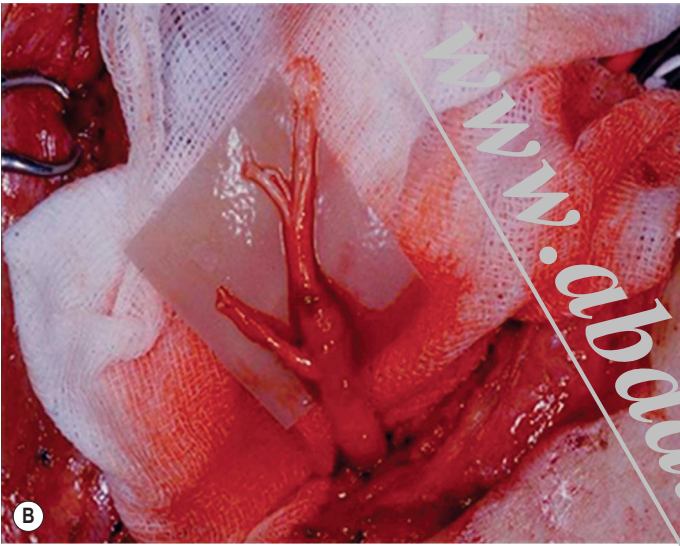
Figure 23.2 (A) The drawing shows that the postganglionic root is part "a"; the postganglionic spinal nerve is part "b" from the anatomy point of view; **(B)** an avulsion C7 (distal stump) during dissection.

Level II injury: inside the (scalene) muscle; it is postganglionic spinal nerve injury, located at the interscalene space proximal to the suprascapular nerve; pure level II injury is around 8%.

Level III injury: pre- and retroclavicular; it includes trunks and divisions; pure level III injury is about 5%.

Level IV injury: infraclavicular; including cords and terminal branches injury proximal to the axillary fossa; the second most commonly encountered injury, about 17%.

There are some relationships among the levels of injury:

1. An extended-level injury on the same nerve is frequently observed: for instance, C7 injury from the root level down to the interscalene space (level I and II injury).

2. A combined-level injury on different nerves is common: for instance, C5 and C6 spinal nerve rupture injury (level II) accompanied with C7–T1 root avulsion (level I).

3. A skip-level injury is rare: for instance, a longitudinal skip-level injury in which C5 and C7 are injured (avulsion or rupture) but C6 is intact; a horizontal skip-level injury in which level I and level III are injured, but level II is grossly intact.

4. Level IV injuries are usually isolated, and rarely show upward extension.

The term "supraclavicular BPI" will cover a large zone of injury, including level I, II, or III lesions.

Preoperative differentiation of supra- (level I–III) vs. infraclavicular (level IV) injury is important to avoid long incisions, unnecessary dissection and tissue damage, prolonged operative time, increased postoperative morbidity, and large scars [42] (Table 23.3). With the help of imaging studies and preoperative clinical evaluation, it is not difficult to diagnosis a level I lesion. However, when the injuries are incomplete, differential diagnosis becomes difficult.

Patterns of brachial plexus injury

There are two types of characteristic lesions seen in BPI: avulsion and rupture. Both are traction injuries but with different characteristics. Avulsion refers to the nerve being torn from its attachment (proximal avulsion occurs at the spinal cord, distal avulsion at the muscle or bone edge). Rupture is a nerve injury involving a traction force on an incompletely divided nerve, causing a complete division with irregular proximal and distal ends. In avulsion injury, only one disrupted end with a coiled spring-like appearance can be seen in the operative field in the acute stage (Figs. 23.3A & 23.4A), or a fusiform pattern (glioma) in the chronic stage (Figs. 23.3B & 23.4B). If a surgeon attempts to locate the other disrupted end, a second operative wound is usually required. However, in rupture injury the two nerve ends can be visualized in the same operative wound in the acute stage (Fig. 23.3C), or within a big neuroma noted in the chronic stage.

Root avulsion is very common in BPI due to its weak supporting structures consisting of dura and dentate ligaments. A novel approach of performing spinal cord implantation with or without nerve graft[43–45] showed unsatisfactory clinical results. This implies that in avulsion injury only one end (distal end) is available, while the other (proximal) end is absent or unsuitable for repair. "Root injury" is an obscure term which may mean avulsion from the cord (true avulsion), or rupture or stretch at rootlets or roots. Root avulsion in BPI is usually accompanied by dura tearing and a cerebrospinal fluid leak with cyst formation, called pseudomeningocele. However, in some cases the root can be avulsed at its origin with an intact dura cone (called "avulsion *in situ*"). The nerve root may remain inside the spinal canal or at the dural orifice, giving a grossly normal appearance or loosening with curvature of the spinal nerve at the time of surgical intervention despite established paralysis. Most often, however, the entire avulsed root, including ventral, dorsal roots, and ganglia, retracts and migrates downward to the interscalene or preclavicular region (Fig. 23.2B).

Pathophysiology and degree of nerve injury

Timing of nerve exploration is dependent upon the degree of nerve injury. The degree of peripheral nerve injury can be classified into neuropraxia, axonotmesis, and neurotmesis (Seddon classification[46]) or grade 1–5 injury (Sunderland classification[45]). Seddon's axonotmesis or Sunderland's second-degree injury starts to have wallerian degeneration

Table 23.3 Differentiatial diagnosis (DD) between supra- and infraclavicular BPI with incomplete paralysis of shoulder and elbow

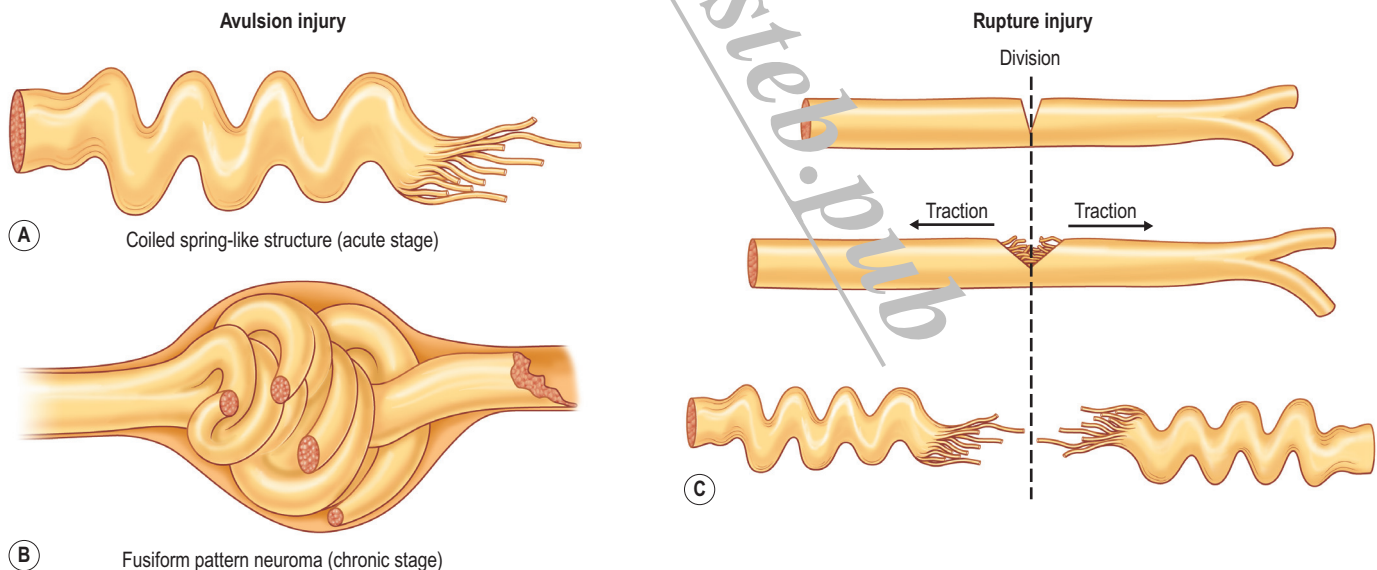| Condition	Supraclavicular BPI	Infraclavicular BPI	DD
Isolated axillary nerve injury	Impossible	Yes	No need to DD
Isolated musculocutaneous nerve injury	Impossible	Yes	No need to DD
Shoulder dislocation		Yes	No need to DD
InfraclavicularTinel's sign (+)	+ (due to nerve regeneration)	+	**Need to DD**
Muscle strength examination			
(A) When supraspinatus (M0), serratus anterior (M0)	Yes	Impossible	No need to DD
(B) When supraspinatus (M>3), serratus anterior (M>3)	Impossible	Yes	No need to DD
(C) When supraspinatus (M<2), serratus anterior (M<2)	?	?	**Need to DD**
(C-1) when C-PM (M>3), teres major (M>3), LD (M>3)		Yes	**No need to DD**
(C-2) when C-PM (M<2), teres major (M>3), LD (M>3)	High possible level III		
(C-3) when C-PM (M<2), TM (M<2), LD (M<2)	High possible level II–III		
Condition			
Scapular fracture		Potential lesion	
Imaging studies	Important for level I	Not important	
EMG, NCV	important	important	
C-PM, Clavicular part of pectoralis major muscle; EMG, electromyography; LD, latissimus dorsi; NCV, nerve conduction velocity.			

Avulsion injury

(A) Coiled spring-like structure (acute stage)

(B) Fusiform pattern neuroma (chronic stage)

Rupture injury

Division

Traction   Traction

(C)

Figure 23.3 The drawing shows the mechanism of avulsion **(A,B)** vs. rupture **(C)** injury.

at proximal and distal stumps. Seddon's neurotmesis or Sunderland's third- to fifth-degree injury has the potential for aberrant reinnervation after nerve regeneration. In Sunderland's fourth- or fifth-degree injuries, only nerve repair can succeed in restoring continuity, but in first-, second- or third-degree injuries, spontaneous recovery, complete and incomplete, may occur.

Timing of brachial plexus exploration

There are five possible time points for brachial plexus exploration and repair:

1. Immediate repair or repair within days or weeks
2. Early repair within a month
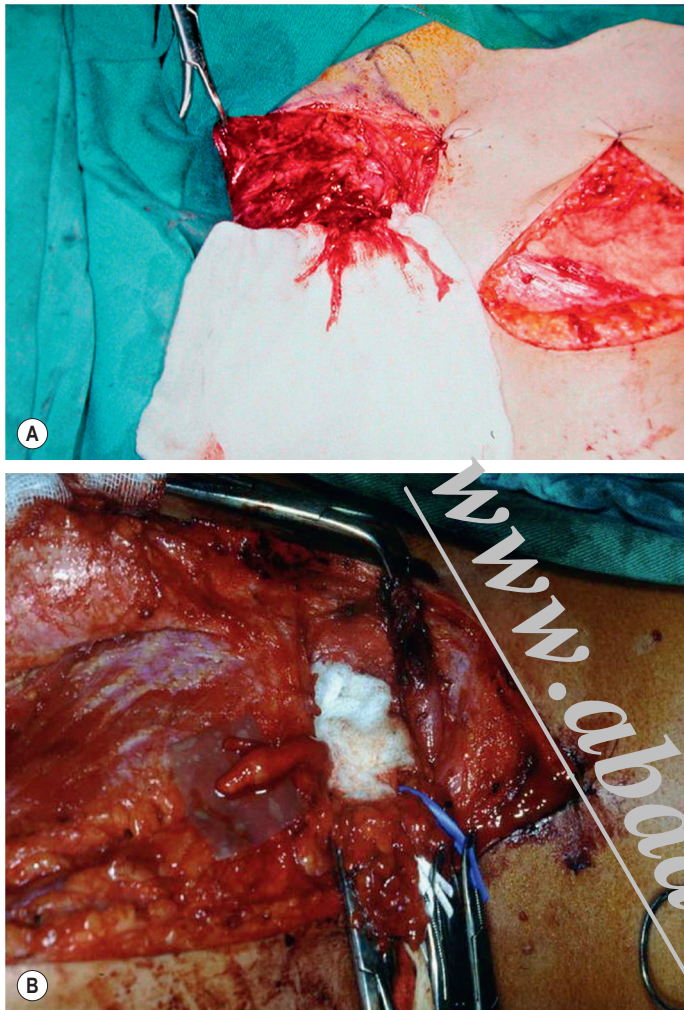3. Delayed early repair within 3–5 months

Figure 23.4 (A) Coiled spring-like structure with irregularity of stumps of C5 and C6 avulsion (acute stage); **(B)** fusiform pattern neuroma (or glioma) of the distal C7 stump (chronic stage) during dissection.

4. Late repair more than 6 months
5. Chronic repair more than one year

There is rarely an argument for immediate exploration after penetrating injury by sharp objects for direct nerve repair. Some surgeons also advocate exploration of the BPI as early as possible[47,48] for adult closed BPI for its advantages, including easy diagnosis of root avulsion and avoidance of difficult dissection through scarring. However, such early exploration is not recommended by most brachial plexus surgeons.[31,33,37] In cases of closed BPI, the degree and extent of injury are difficult to judge soon after injury and are often underestimated. The benefits of waiting usually outweigh the advantages of early surgery.[41]

Clinical evaluation

Etiology of adult brachial plexus injury

BPI may be caused by trauma (open or closed type), compression, tumor, infection, inflammation, toxins, and other etiologies.

Patient history

Patient history should include mechanism of injury, conscious level at the time of trauma, associated injury (such as head injury, fracture, open wound, chest injury, vascular injury), kinds of previous surgical intervention (such as chest intubation, cervical spine surgery), and characteristics of pain. This information helps to determine the degree and extent of injury and the need for surgical intervention. Mechanism of injury (e.g., upward or downward traction and with or without rotation) is not easily detected due to the patient's loss of consciousness or amnesia for the accident. A history of shoulder dislocation or glenoid fracture may have a high incidence of level IV injury, whereas a history of cervical spine injury or fracture may cause a level I root injury. Artery rupture and repair imply the site of nerve injury. For instance, arm traction by rolling machine or conveyor belt often causes an open wound in the axilla, extensive ecchymosis around the shoulder and chest (due to rupture of axillary vessels), and level IV BPI. Segmental thrombosis of the subclavian artery is usually associated with C8–T1 root injury. History of rib fracture and chest intubation may preclude intercostal nerve transfer because of a higher failure rate.[49] Extreme causalgia with or without a phantom limb is often seen in cases of root avulsion in lower-root (C8–T1) avulsion as they contain the richest sympathetic fibers. The pain character, like an electric shooting, continues for short duration for seconds, followed by spontaneous relief and recurrence. Extreme causalgia is also a major factor for poor outcome due to poor rehabilitation. Sometimes a partial Brown–Sequard syndrome (hemitransection of the spinal cord with ipsilateral upper motor neuron lesion below the level of lesion, and contralateral abnormal sensation to pain and temperature which may not be at the same level) is also noted in the level I injury.[50]

Preoperative evaluation and diagnosis

Most adult BPIs are closed injuries. Accurate assessment of the extent and severity of the injury in closed BPI is difficult. Clinical evaluation is still essential and is the most important step in establishing the diagnosis of site and degree of injury, and determining the treatment and prognosis. A brachial plexus chart (left and right formats, Fig. 23.5) outlining the possible injury should be completed before definite brachial plexus surgery. This chart is filled at the initial examination, usually performed at 2 months after injury. The chart is also useful for follow-up evaluations allowing comparison of clinical pictures.
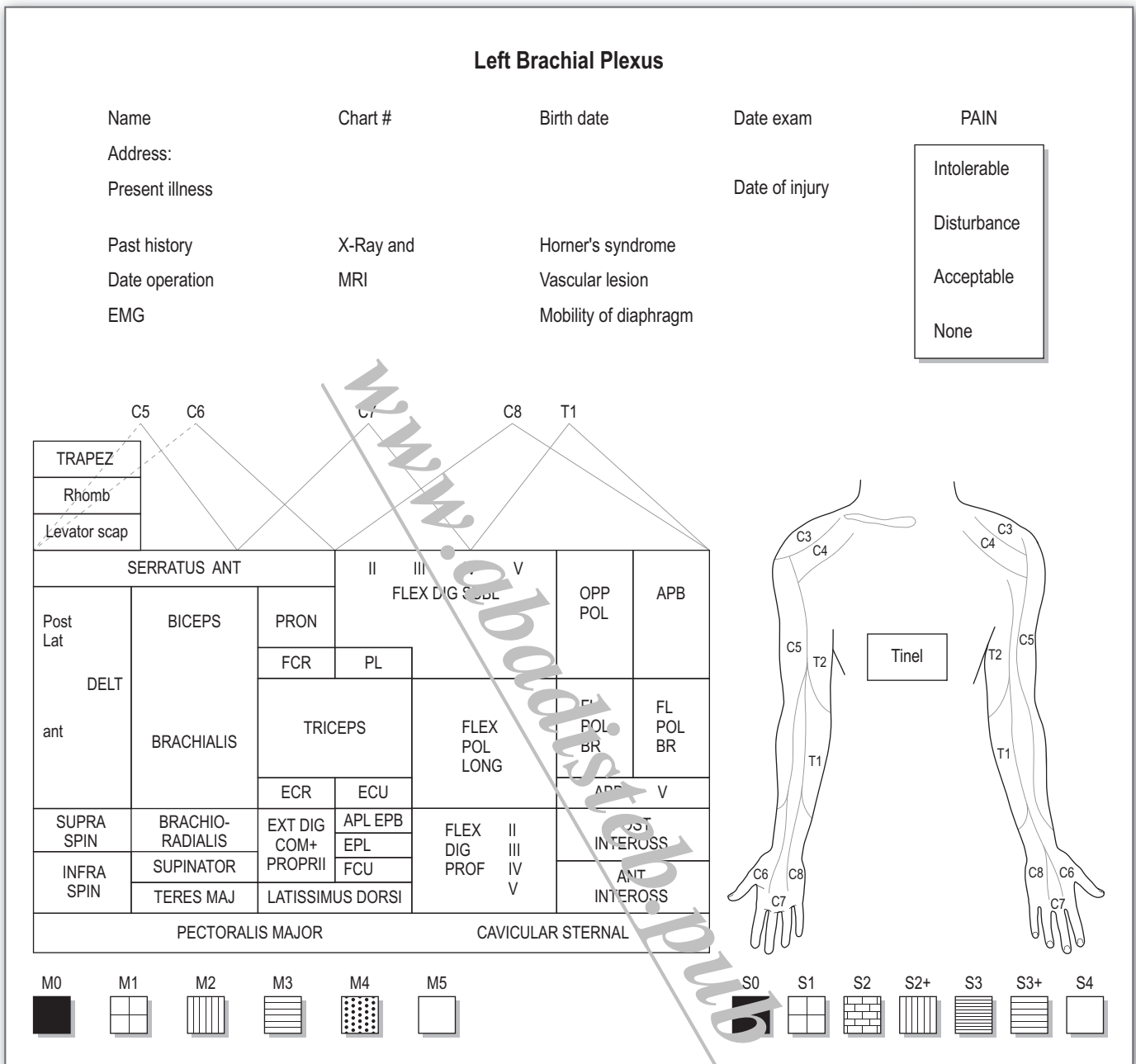
Motor examination

Muscle-by-muscle examination should be completed in a distal-to-proximal fashion and recorded, using the British Medical Research Council (MRC) scale (M0–5).[51] We have modified the motor evaluation system, adding more detailed differentiation: M5, strength against four fingers (examiner) resistance; M4, against one finger, resistance for longer than 30 seconds; and M3, against gravity (Table 23.4). M4 is recognized as useful muscle strength. The action of each muscle should be examined separately in relation to the movement of a single joint. Although there is no single muscle innervated by a single spinal nerve, some muscle palsy can give specific information related to the level of the injury. For instance:

1. Diaphragm palsy implies C4 and very proximal C5 (level I) injury.
2. The levator scapulae muscle lies anterior to the trapezius muscle in the neck, and can be more easily detected than the rhomboid muscles, which are covered by the trapezius muscle. Both levator scapulae and rhomboid muscles are innervated by the same nerve (dorsal scapular nerve, or C4 and C5). Preservation of its function in upper plexus or total plexus injury may imply C5 is a rupture injury (level II) with an available proximal stump.

3. Serratus anterior muscle: The long thoracic nerve has two portions: the upper portion originating from C5 and C6, and the lower portion from C7. The upper portion is responsible for scapular protraction, and the lower portion is important for scapular stabilization.[52] Positive anterior traction of the scapula (shoulder protraction test) shows that at least C5 is ruptured after branching to the long thoracic nerve, so the proximal C5 is available for transfer. Scapular winging is observed only when the lower portion is denervated, but isolated C7 root avulsion is rarely seen in adult BPI. In pure
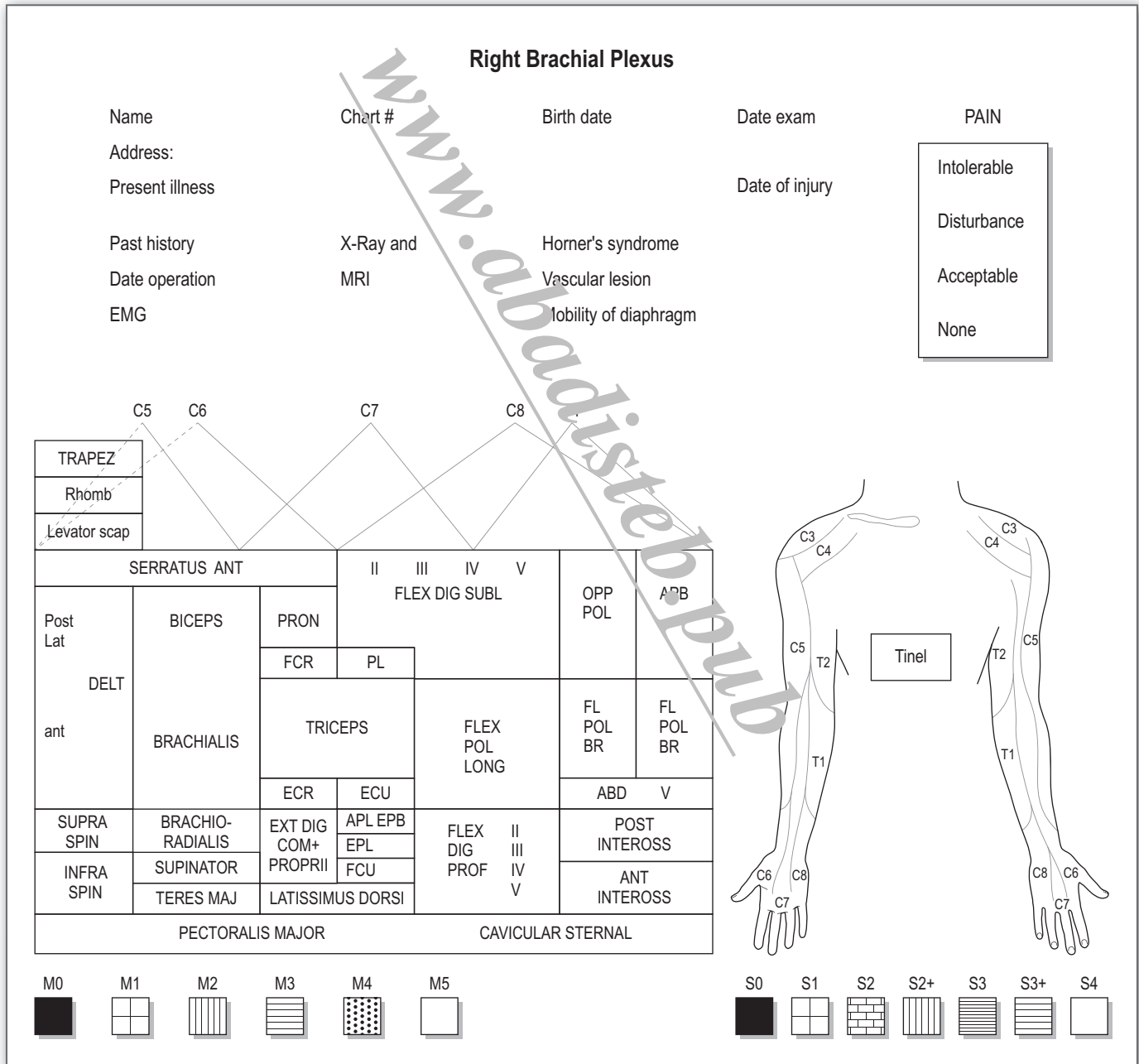
Figure 23.5 Special charts for evaluation of the brachial plexus injured patient, **(A)** for the right and **(B)** for the left upper limb.

Left Brachial Plexus

Name   Chart #   Birth date   Date exam   PAIN

Address:

Present illness   Date of injury

| Intolerable |
| Disturbance |
| Acceptable |
| None |

Past history   X-Ray and   Horner's syndrome

Date operation   MRI   Vascular lesion

EMG   Mobility of diaphragm

C5   C6   C7   C8   T1

TRAPEZ
Rhomb
Levator scap

SERRATUS ANT   II   III   V   OPP POL   APB
FLEX DIG SUBL

Post Lat   BICEPS   PRON   FCR   PL

DELT   FCR   PL

ant   BRACHIALIS   TRICEPS   FLEX POL LONG   FL POL BR   FL POL BR

ECR   ECU   V

SUPRA SPIN   BRACHIO-RADIALIS   EXT DIG COM+ PROPRII   APL EPB / EPL / FCU   FLEX DIG PROF   II III IV V   POST INTEROSS

INFRA SPIN   SUPINATOR   ANT INTEROSS

TERES MAJ   LATISSIMUS DORSI

PECTORALIS MAJOR   CAVICULAR STERNAL

Tinel

C3 C4   C3 C4
C5 T2   T2 C5
T1   T1
C6 C8   C8 C6
C7   C7

M0 M1 M2 M3 M4 M5   S0 S1 S2 S2+ S3 S3+ S4

B

Figure 23.5 cont'd

C5–6 level I injury, the lower part of the muscle is still functional. The result of spinal accessory nerve transfer to the suprascapular nerve is much superior in the reconstruction of total root avulsion.

4. Clavicular and sternal portions of the pectoralis major muscle: The major pectoral muscle can be separated into two parts: clavicular and sternal parts. The clavicular part is innervated by upper and middle trunks or its divisions (lateral pectoral nerve), while the sternal part is innervated by the lower trunk (medial pectoral nerve).

An incomplete or complete paralysis of the clavicular part of the pectoralis major muscle may imply at least level III or more proximal lesion.[42]

Sensory examination

Sensory evaluation should include sensory tests and elicitation of a Tinel's sign. Sensibility tests include pain and temperature appreciation, static and moving two-point discrimination, constant touch, and vibration. However,

Figure 28.10 Case example of a patient who received a right TRAM flap in the setting of preoperative radiation therapy with contralateral reduction and subsequent nipple–areolar reconstruction. **(A)** Preoperative defect with planned contralateral reduction. **(B)** Intraoperative markings. **(C)** Patient at 4 months' postoperative from initial surgery showing planned nipple reconstruction and fat grafting for improved contour. **(D)** Final reconstructive outcome 11 months' postoperative.

Hints and tips

1. Preoperatively, carefully select patients who will benefit from this procedure and who understand both the benefits and risks involved.

2. As the goal is to obtain a symmetrical reconstruction, the contralateral breast must be addressed and may involve a breast reduction that can be safely done at the same time. The benefit is that less tissue is transferred with the TRAM flap, thus reducing the risks of fat necrosis. If the contralateral breast needs only a mastopexy, this is typically done secondarily.

3. Carefully assess the mastectomy site in the patients undergoing an immediate reconstruction. First, the vascularity of the mastectomy flaps is assessed, and any compromised flaps are excised and adjustments made with a larger TRAM flap skin island. Second, the mastectomy pocket generally needs to be adjusted due to wide resection at the site of the IMF and laterally.

4. In patients undergoing delayed reconstruction, the mastectomy scar is excised and the skin flaps are elevated off the pectoralis major muscle to recreate the mastectomy pocket. The skin below the mastectomy scar is usually excised down to the IMF, as it is generally too tight to accommodate the flap. Consequently, a TRAM flap with a larger skin island is required in delayed reconstruction. The "Bikini Inset" may also be considered as an option for delayed TRAM flap inset in the previously irradiated breast.

5. The pedicled TRAM flap is elevated as described above and a medial subcutaneous tunnel is made connecting the mastectomy site with the abdominal dissection, which minimally encroaches into the IMF of the side being reconstructed. Generally, the tunnel is big enough to allow a hand to traverse, and thus the pedicled flap can be introduced into the cavity with minimal trauma. For safe passage through the tunnel, the TRAM flap should be pushed rather than pulled.

6. Zone 3 of the TRAM is brought superiorly and can be affixed to the chest wall with an absorbable suture.

7. It is helpful to make the TRAM flap slightly bigger than the opposite side, to allow for muscle atrophy. If it is still too large at the time of nipple–areolar reconstruction, liposuction can be performed to obtain better symmetry.

8. A final assessment is made of the mastectomy flap vascularity, excising any tissue with questionable vascularity. The final de-epithelialization of the flap is performed and the inset completed. SPY technology (Novadaq Corp., Bonita Springs, FL), if available, may be helpful to evaluate compromised skin.

(Continued)

Hints and tips—cont'd

9. The suturing of a thicker mastectomy flap to the edge of a de-epithelialized TRAM flap may lead to an uneven repair with an overriding of the mastectomy flap and relative depression of the TRAM flap. To avoid this uneven repair, the use of a suturing technique that starts deep and takes a vertical mattress bite of the de-epithelialized side of the flap and a more superficial horizontal mattress of the surrounding mastectomy flap, results in a more even repair and better result.

10. Great care needs to be taken in repairing the abdominal wall using mesh as described above. The mesh is inlaid into the defect created by muscle harvest and attached to the conjoint tendon laterally and linea alba medially. The rectus fascia is then advanced with a running polypropylene suture, thereby covering up a significant part of the mesh and providing a strong repair and restoring the normal muscle tension of the remaining abdominal wall muscles. Even if the fascial defect can be closed primarily, mesh is still used as it provides a stronger repair, a reduced likelihood of hernia, and minimal displacement of the umbilicus. Care should be taken to ensure that the polypropylene mesh is

inset with the direction of stretch in a vertical orientation and that the repair is not "too tight", as this can cause considerable discomfort postoperatively that is difficult to treat.

11. Drains are inserted at both the mastectomy site (usually one drain) and at the abdominal donor site (usually two drains – one on each lower abdomen).

12. The use of long-lasting local anesthesia agents delivered by an On-Q pump (I-Flow Corporation, Irvine, CA) can help with postoperative pain.

13. Overall satisfaction: in the authors' experience, patients undergoing pedicled TRAM flap surgery (both unilateral and bilateral) tend to relate minimal interference with daily activities and report a satisfaction score of 8.3 out of 10, with most stating that they would have the surgery again.[19,30] Others, including Moscona *et al*., report that a total of 75% of women were satisfied with the operation, 73% declared high satisfaction, and only 12% were dissatisfied with the results.[31] Also, Veiga *et al*. similarly found a generic increase in health-related quality of life after TRAM breast reconstruction.[32]

29

Breast reconstruction with the latissimus dorsi flap

Dennis C. Hammond

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Introduction

Breast reconstruction has undergone a transformation over the past 40 years. Techniques in soft tissue management and improvements in tissue expander and implant design have advanced to the point where the subtle and artistic forms that define the female breast can be preserved and even improved upon after mastectomy. Central to the development of these techniques, and in particular, the management of soft tissue, has been the description and subsequent refinement of the latissimus dorsi musculocutaneous flap (LDMF). This chapter will outline the basics of latissimus dorsi flap breast reconstruction and describe in detail how the flap can be used to obtain outstanding results in both immediate and delayed breast reconstruction after mastectomy.

Operative strategy

To understand the important role the latissimus flap has played in helping define the current results and expectations associated with modern breast reconstruction, it is helpful to organize the goals inherent in achieving an aesthetic result.

- Volume – One of the most powerful visual criteria that defines breast beauty is volume. The creation of proportional and symmetric breast volume is paramount when performing breast reconstruction. Volumes that either fall short of aesthetic or conversely exceed the desired amount can adversely affect the quality of the result, particularly when any degree of asymmetry is created.
- Skin envelope – To accommodate a desired volume, it is imperative that a proportional skin envelope be either preserved or reconstructed. Failure to create a skin envelope of either adequate surface area or shape will adversely affect the final result as the volume of the reconstructed breast will fall short of ideal.
- Contour – An aesthetic breast presents smooth and even contours across the medial, superior and lateral borders that flow away from the chest wall. Any element of sudden contour change or sharp step-off appears artificial and can be a hallmark of an unsatisfactory breast reconstruction.
- NAC – The nipple–areola complex (NAC) presents as a defining element of an aesthetic breast. When absent, a breast mound can be perfectly reconstructed; however, the missing NAC is immediately noticed. The addition of a symmetrically placed NAC of the proper size and shape that preserves symmetry enhances the quality of the aesthetic result in a very significant manner.
- Symmetry – Central to any successful breast reconstruction is the creation of symmetry in every aspect of breast appearance. This includes the position of the breast footprint, volume, shape, inframammary fold location, breast base diameter, projection and position of the NAC. Each of these aesthetic elements can be properly reconstructed; however, if symmetry with the opposite breast is lacking, the quality of the result is adversely affected.

The great advantage afforded by the addition of the LDMF is that each of these elements of an aesthetic breast can be reconstructed using the skin, fat and muscle of the flap to add missing volume, replace missing skin, soften peripheral contours, create a reconstructed breast that can accommodate the addition of a significant amount of volume, and provide appropriate symmetry. Additionally, secondary to the thickness of the dermis on the back, using the skin island of the flap to reconstruct the NAC results in the most reliable and long-lasting projection of the reconstructed nipple of any technique currently described. Such results are often lacking when using traditional techniques based on thin mastectomy skin flaps. While the technical versatility of the LDMF is of great advantage, perhaps even more important is the reliability of the vascular supply to the flap. Due to the robust thoracodorsal pedicle that supplies the flap, it is very unusual to experience any degree of ischemia in either the muscle, skin or fat of the flap, even in patients with complex medical conditions such as diabetes, connective tissue disease, or even in patients who smoke. The dissection of the flap is straightforward and the anatomy is constant, which facilitates easy elevation and rotation of the flap into the mastectomy defect. Taken together, all of these factors combine to make the LDMF an excellent option for patients seeking either immediate or delayed breast reconstruction.

Anatomy

The latissimus is one of several muscles that cover the upper portion of the back[5] (Fig. 29.1). Of these muscles, it is the largest and takes origin from the medial thoracolumbar fascia, posterior iliac crest, and lateral fibers of the external oblique before inserting via a thick tendon into the intertubercular groove of the humerus. The anterior border of the muscle defines the posterior border of the axilla. The superior border of the muscle takes origin from under lower medial origin of the trapezius before coursing over the tip of the scapula. As the muscle passes into the axilla, there is a variable fusion of muscle fibers with those of the teres major that must be correctly identified and released to allow proper access to the axilla.

The dominant vascular pedicle to the LDMF is the thoracodorsal artery, which is a branch of the subscapular artery, which comes off the axillary artery[6,7] (Fig. 29.2). The thoracodorsal artery gives off an important serratus branch approximately 10 cm below the tendinous insertion of the muscle. This branch can maintain vascular viability of the flap via reversal of flow when the thoracodorsal pedicle has been previously ligated.[8] A secondary blood supply is provided by perforators off the posterior intercostal arteries laterally and the lumbar arteries medially. These perforators enter the under surface of the muscle directly from the chest wall in the mid-substance of the muscle and must be directly controlled during flap elevation. Within the substance of the muscle, the thoracodorsal artery then bifurcates into a transverse and a lateral branch that then extensively arborizes within the muscle, passing multiple perforators to the overlying skin and fat. The venous return parallels the artery as two evenly spaced comitantes before emptying into the axillary vein.

The innervation to the latissimus muscle comes from the C6 to C8 ventral nerve roots that coalesce into a well-defined thoracodorsal nerve. The nerve enters the muscle separately from the vascular pedicle and can be positively identified by pinching the substance of the nerve and observing the intense contraction that results in the muscle. Once the nerve enters the muscle, several different portions of the muscle are innervated independently, which has led some surgeons to adopt a partial muscle harvest strategy when using the LDMF and yet still leave behind functional muscle mass.[9]

Patient marking

The marking sequence in LDMF breast reconstruction is important as it identifies the specific landmarks that guide the surgical procedure (Videos 29.1 ▶ & 29.2 ▶). This marking procedure is performed preoperatively with the patient standing comfortably with the arms at the sides. Initially the midline is marked along with the palpable tip of the scapula. A line is drawn from the posterior border of the axilla curving medially across the tip of the scapula. This represents the upper border of the latissimus muscle. The estimated inferior margin of the trapezius is drawn as it covers the superomedial corner of the latissimus muscle. With the arm raised up over the head, the anterior border of the muscle is marked by identifying the edge of the muscle in the axilla and drawing this landmark inferiorly toward the iliac crest. The origin of the muscle from the thoracolumbar fascia is drawn estimating this to be 2–3 cm off the midline and this muscle origin is followed as it curves inferolaterally along the iliac crest. In this fashion, the surface area of the latissimus muscle is outlined in such a way that the skin island can now be centered

Tissue engineering

Ramin Shayan and Karl-Anton Harms

Introduction

The field of tissue engineering embodies, like few other areas of scientific endeavor, the principles, aspirations, and the techniques of plastic surgery. However, the "boom time" promises of the early "frontier" tissue engineers and their pioneering endeavors have not been matched, to date, by real-world solutions that translated into useful outcomes for plastic surgery patients.

Unfortunately, the fortunes of the tissue engineering sector closely matched those of the turn of the century "tech bubble"; and in the wake of a historic stock market correction, suffered a similar collapse. What has been less well-described, however, have been some of the factors that created the "perfect storm" that made this course inevitable. Similarly neglected has been a discussion of the fact that this collapse led to a re-evaluation and a quiet re-birth of tissue engineering, which has now begun to take shape from the ashes of the collapse. Studying the factors that contributed to this collapse will reveal key lessons that may be used to ensure the success of tissue engineering Mark-II, and the longevity of plastic surgery in general.

From the early 2000s implosion of the tissue engineering sector have emerged a series of modified aims and realities that may loosely be termed as a "re-invention". The dreams and hype of the 1980s and 90s were unable to be matched by the fundamental science capabilities of the time and the desired translation into solutions to supersede then-available conventional plastic surgical solutions did not eventuate. As a result, the role of today's plastic surgeons at the cutting edge of the field was diminished and the leadership mantle was instead taken on by cellular and molecular biologists and translational science entrepreneurs.

As plastic surgeons, therefore, we must ask ourselves whether we are willing to now invest in our trainees and craft group, in order to in-build the fundamental science capability to remain conversant in the burgeoning scientific fields now required to engage in a "new wave" of tissue engineering. Are we willing to go back and learn from the problems that led to the crash of nearly 20 years ago and are we willing to apply the attitudinal changes required to make a real contribution and to drive the program? Or are we instead willing only to be passive consumers of products designed by biological engineers and biologists without our clinical input?

One truth that is certain is that given the cost, time, and expertise required to undertake meaningful science in the 2020s, a field that calls itself "tissue engineering" cannot exist independently of commercially viable products and imperative nor of the timelines and stringencies required to deliver them. Half a century on, we explore tissue engineering as a parable for plastic surgeons over-promising and under-delivering, and examine the lessons that must be incorporated into plastic surgery if we are to remain a viable and independent specialty into the next century. We examine some highs and lows of tissue engineering in plastic surgery and ask what might become of the field in future years. If we are to remain in the tissue engineering game for the next 50 years, there are two elements we must adopt overall:

1. *Focus*: Plastic surgeons must play to their clinical and personal strengths; and
2. *Commitment*: Plastic surgeons must invest in the skill sets and people to continue to evolve.

Plastic surgery principles in tissue engineering and the first 40 years

Plastic surgery seeks to restore or enhance the function and/or form of body tissues and organs of patients afflicted by congenital or developmental anomalies, or by a physical insult. The congenital or developmental anomaly may be either a sporadic or inherited genetic program mishap, or an acquired perturbation in utero. It may more recently be considered to include an ostensibly undisturbed genetic program that is inconsistent with the identity or perceptions of the patient's self.

A physical insult that disrupts the patient's tissues or organs may result either from the physical environment due to an external injurious force or agent; or due to a planned intervention by doctors seeking to combat a pathological condition such as malignancy, benign unwanted tissue growth or pathologic infective processes. From the dawn of surgery, the legendary figure of Sushruta who worked in India between the years 600–1000 BCE,[1] anatomical examination and research have been a cornerstone of the surgical techniques applied to patients treated for punitive nasal amputations administered as punishment for adultery.

Sushruta identified the fact that a more thorough understanding of underlying science was required to inform application to patients:

[A]nyone wishing to acquire a thorough knowledge of anatomy must prepare a dead body and carefully observe and examine all its parts.

Sushruta, 600-1000 BCE[2]

Later, Italian surgeon Gaspare Tagliacozzi examined the anatomy of executed prisoners in order to learn the anatomy that would form the basis of his famous adaptations of the earlier version of reconstructive rhinoplasty that he performed to treat nasal injuries acquired in duels.[1]

Tagliacozzi neatly summarized the aspirations of plastic surgery, which can also encompass the fundamental aims of tissue engineering:

We restore, rebuild and make whole those parts which nature hath given, but which fortune has taken away. Not so much that it may delight the eye but that it might buoy up the spirit, and help the mind of the afflicted.

Gaspare Tagliacozzi

The first evolution of plastic surgery – random pattern and pedicle flaps and the culture of better solutions

Since its inception, plastic surgery has necessarily required an inquisitive and pioneering mindset. Throughout the clinical practice of plastic surgery and more recently in the modern post-war era of plastic surgery, the practice has involved the surgeon experimenting through observation and trial and error with the limits of blood supply and tissue endurance.[3,4]

From the first early-20th century theaters of war, through the 1940s, the founders of modern plastic surgery recognized the experimental nature of their revolutionary work. The "experimental" nature of the work of New Zealander Sir Harold Gillies (Fig. 18.1) and his cousin Sir Archibald McIndoe, aided by Thomas Kilner, Rainsford Mowlem, and a host of other pioneers, earned their patients the moniker "The Guinea Pig Club".[5] The implication was that the prevailing treatments of debridement, amputation, and dressing wounds to heal by secondary intention could be extended to enhance the functional and aesthetic outcomes for wounded servicemen through observational experimentation and brinksmanship that would push the boundaries of what was then possible. The results were wound closure of defects that would once have necessitated amputation or crippling disfigurement of the face or limbs that would render a normal existence impossible. This

Figure 18.1 Sir Harold Gillies (1882–1960). A pioneer of facial reconstruction and pushing the boundaries of what was possible at the time. Sir Harold and colleagues took on the difficult reconstructive challenges of the airmen survivors of the RAF and disfiguring and functionally impairing scarring.

represented a great evolution in surgical management that would spurn several generations of innovation and would eventually lead to the concept of tissue engineering.

Within three decades the limitations of random pattern and tubed pedicle flaps would become apparent and would stimulate the next great evolution in wound management.[6] The pedicle flaps would necessitate 6 or more months of hospitalization and an extensive series of surgical procedures that were both resource-intensive and personally and physically taxing on the patient.[6] Again, a generation of pioneering iconoclasts were called upon to move the specialty of plastic surgery into a new age.

The second evolution of plastic surgery – microsurgery and the precedent for better solutions

In Boston, USA, Dr Joe Murray successfully transplanted a kidney between humans in 1954 and received the Nobel Prize in Physiology or Medicine in 1990.[7] Also in the US, Dr Harry Bunke reported the first experimental replantation surgery of a rabbit ear in 1964, followed by the first primate digital replantation (toe to hand transfer) in 1966 and human tissue transfer of omentum to scalp in 1969.[8] In Melbourne, Australia, Professor G. Ian Taylor mapped the blood vascular supply of the human body in the morgue of his local hospital, and in 1971 performed the first composite fasciocutaneous free tissue transfer when he transferred a groin free flap to an open ankle fracture (Fig. 18.2)[9] The "angiosome concept" described the entire body in vascular territories that could be utilized to transfer tissue from almost any donor site.[4,6] In 1976, also in Melbourne, Taylor's cross-town rival Dr Bernard O'Brien (see
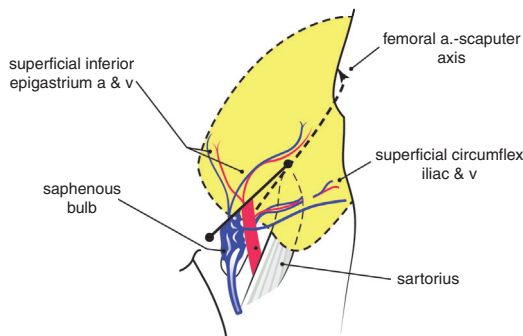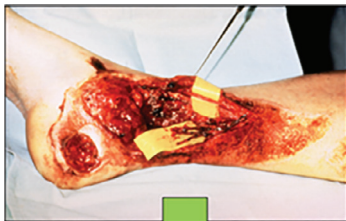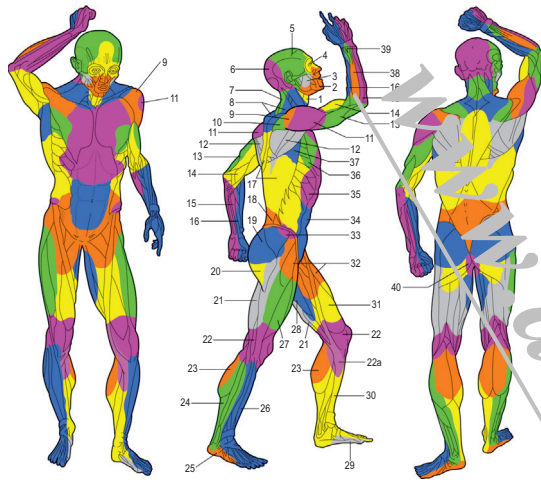
Fig. 18.2) described the use of microsurgery for the restoration of the physiology of the lymphatic system in the form of lymphatico-venous anastomosis surgery,[10] and later, in the form of free vascularized lymph node transfer.[11]

What had once been the stuff of science-fiction had now become clinical reality, and the coming decades would see the institution of the research performed by these and other visionary surgeons to create hundreds of variations of autologous free tissue transfer of 3D blocks of vascularized tissue for all manner of clinical applications. Microsurgery transformed the capability of plastic surgeons to treat congenital or developmental anomalies, and the physical insults acquired during the course of cancer treatment or in trauma in all areas of the human body. Finally, French surgeons performed the first composite tissue allotransplantation (CTA) of a hand in 1998,[12] and in 2005,[13] the first partial face transplantation to a living recipient. The first full face transplant was performed in 2010 in Spain, and since that time the technical exercise has been replaced by the more subjective art of clinical judgment of appropriate recipients. This has become the focus of CTA surgeons world-wide.[14]

Open fractures and ungraftable soft-tissue defects in the limbs could be salvaged; and tissues could be transferred to cover critical exposures of underlying organs in abdominal, pelvic, cranial and chest wall defects, in which locoregional options were not available. Congenital hand deformities could be treated using free toe transfers, and genitalia, breasts, and the previously untreatable areas of the head and neck – such as jaws, laryngopharynx, and base of skull – could be reconstructed in ways that could previously only have been imagined. What had once been possible in many months, if at all, was now possible overnight (Fig. 18.3). Plastic surgery had learned to transfer entire faces and hands from donor to recipient – two areas emblematic of human identity and function.

Microsurgery made it possible to achieve a superior outcome in a matter of hours. Here a free fibular flap is made into a neo-mandible and a second free flap is used to cover the external skin of the chin in a significant soft-tissue defect resulting from a p16-negative squamous cell carcinoma of the cutaneous chin.

Virtually overnight, an area of human endeavor had been created that would revolutionize the practice of reconstructive surgery, but which could be readily taught and learned to the extent that, today, microsurgery is a fundamental tool in the algorithm known as the "reconstructive ladder" of plastic surgery. Essentially, the success of microsurgery had been driven by a vast and worldwide unmet clinical need for the solution. It boasted the great attributes that modern companies seek; scalability and transferability of techniques. The requirements were core knowledge about the vascular anatomy of the body, training by experienced technicians, a relatively modest initial outlay to furnish a microsurgery unit with microscopes, a set of reusable instruments and micro-sutures. These giant steps had been accomplished by all of the pioneers and thanks to excellent international clinical fellowships and courses, microsurgery had been disseminated successfully to the four corners of the globe.

The third evolution of plastic surgery: tissue engineering, the answer beyond surgery

It was due in no small part to the amazing success of microsurgery that plastic surgery was able to take on the mantle
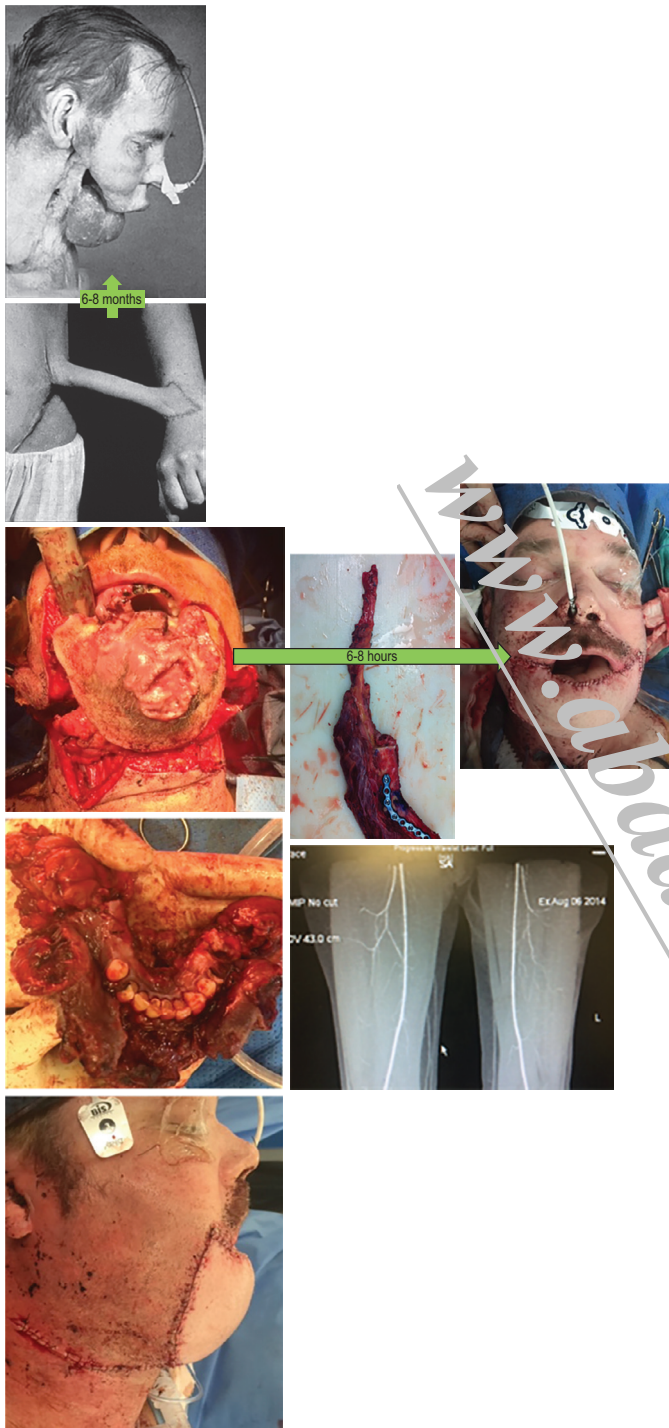

Figure 18.2 The quest to transfer tissues around the body led to the characterization of all of the "angiosomes" of the human body.

Figure 18.3 Jaw reconstruction that had once been achieved through painstaking pedicled flap surgery was now possible in a matter of hours.

as a significant contributor to human health. Microsurgery demonstrated the fact that plastic surgery could be a nimble and innovative specialty that could readily evolve and adapt to clinical needs. But where to from here?

Plastic surgery had managed to capture the public and, therefore, the funding bodies' imagination for some years and to open a new frontier of human endeavor. Funding bodies such as the national hospital systems in some jurisdictions, and public research funding organizations and philanthropic

donors in others, had funded research into microsurgery with good returns in human health metrics to the community.

If free flaps inherently involved "robbing Peter to pay Paul",[15] surely then, the final frontier for plastic surgeons was to achieve their goal of restoring form and function to tissues and organs that make up the organism and person as a whole –*without* paying the price of "robbing" the body of a donor tissue (Fig. 18.4). For plastic surgery researchers taking this next step – particularly for patients in whom there was a paucity of donor sites or in whom the donor site trade-off was not acceptable – the next evolution, or at very least the next iteration, was needed.

In the 1990s, Langer and Vacanti[16] encapsulated the discipline that had arisen from such noble and lofty aims as:

A new interdisciplinary field, tissue engineering, applies principles of biology and engineering to develop functional biological substitutes to restore, maintain or improve function in damaged tissue and diseased organs.

The dream of plastic surgeons was to create "off-the-shelf" body parts that could be utilized for patients in whom the donor sites were either non-existent or costly (Fig. 18.5). In addition to "bulk filler" soft-tissue reconstruction, niche areas of unmet need also existed in more nuanced areas such as nerve and limb regeneration and inspired inquisitive minds to explore an exciting field of scientific endeavor.

The 1960s saw an emerging focus on biomaterials and engineering driven by the post-war challenges that drove a race toward global technological supremacy. A new substance that integrated the structural integrity of cross-linked polymer chains with an ability to absorb fluid, called hydrogels, had been developed at that time and was first applied to contact lenses and by the pharmaceutical industry for drug testing.[17]

During the following decade the specialties of engineering and surgery combined when a like-minded engineer and surgeon described a coral-like structure that provided the structural integrity under greater force requirements that hydrogels lacked.[18] In the late 1970s to early 1980s, burgeoning ink-jet technology was soon adapted for delivery of cultured cells in a 2D printed cell layer.[19] In 1985 the term "tissue engineering" was introduced by Y.C. Fung,[20] giving rise, between the years of 1987 and 1992, to a rapid expansion in biotech companies that could loosely be termed the "first biotech boom".[17] The epicentre of this boom was at the Massachusetts Institute of Technology (MIT) and Harvard University precincts in the US, and, to a lesser extent, other multidisciplinary institutions that sought to become the leading commercial translational institutions. At that time, the make-up of the fledgling tissue engineering sector was predominantly (90%) academic, with makeshift spin-outs and start-ups combining due to a strong investment appetite (90% private),[17,21] without the governance and regulatory structures that are evident internationally today.

Europe and the UK were off to a slower start than was seen in the US, due to a more conservative investment risk appetite, a greater proportion of public funding that boasted higher funding hurdles, and a larger oversight role of more dominant government bodies on companies (e.g., the National Health Service in the UK) and on their products.[21] In Japan much of the early cell work was only in the setting of state hospitals

Figure 18.4 A young man enjoys a coffee and reads a text message using a finger constructed from a toe, following a four-finger amputation. He pays the price of a missing toe, a significant deterrent for many patients – "robbing Peter to pay Paul".

Figure 18.5 The dream of tissue engineers in plastic surgery: "off the shelf" body parts.
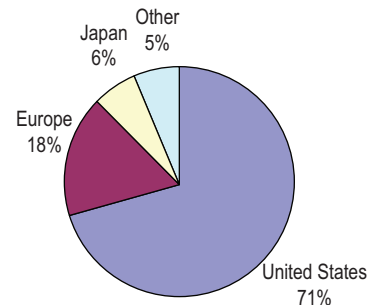

Figure 18.6 Graphical representation of the intellectual property filed in early tissue engineering by country, 1980–2001 (N = 567). *(Source: Viola J, Lal B, Grad O. The Emergence of Tissue Engineering as a Research Field. Alexandria, VA: National Science Foundation; 2003.)*

and academic centers, with no state scientists permitted to transition to also work in industry until 1998.[21] This environment resulted in relatively slower approvals and a smaller number of large firms dominating the landscape and no start-ups to speak of; with a chief focus on exploiting already-approved products.[21] Key regulatory changes in 2014 allowed cell cultivation outside hospitals and increased research speed and encouraged firms to develop their own products.[22] This more supportive environment lead to a boom in nano-technology and the description of induced pluripotent stem cells (iPS)-related and stem cell products that would penetrate more deeply into the tissue engineering field, eventually giving rise to the cell-based therapeutics fields.[23]

In Australia, the 1980s saw the O'Brien Institute transition from pursuits that had helped to play a key role in the development of microsurgery[24] (particularly with regard to the lymphatic system[10,11]), toward a "vascular-loop" cell chamber-based tissue engineering focus.[25] This transition would result in a key highlighting of the microenvironment and importance of tissue nutrition to the overall success of tissue engineering.[25] Nevertheless, despite increasing interest globally, the majority of the intellectual property relating to tissue engineering continued to emanate from the US (Fig. 18.6).[21] A strong private investment appetite in the early 1990s continued to drive interest in the new field of tissue engineering, in which new opportunities to marry technology and reconstructive surgery fuelled the hope that the next generation of rebuilding human bodies was nigh.[12,21,26]

The fall of tissue engineering Mark-I

During the latter part of the 1990s, the frenetic tissue engineering sector began to show signs of a "bubble market".[12,21,27] Issues started to appear in the translation of expanding media hype into rigorous experimental ideas, high-quality science, and eventually working solutions.[12,21,26,27] A major sticking point in the tissue engineering model related to the inherent commercially unviable practice of using and handling living cells that were, by definition, hard to come by and to maintain; and which were marred in regulatory and ethical complexity.[26,27] These factors led to poor commercial viability and inability of companies to achieve sufficient scale, and to a low rate of FDA and other regulatory approvals.[28]

The consequence was low doctor and payer adoption of the proposed new technologies over conventional methods, reduced demand, higher costs, and diminished product recognition. US insurance providers were reluctant to pay for these unproven technologies, further eroding care-provider acceptance and inhibiting the efficacy of product marketing and broader integration into the health system.[?]

Tissue engineered products fabricated by lab bench-scale processes remained prohibitively expensive and impractical with cost per product based on cost of cultivation, storage, transport in precise conditions of living cells far outstripping the budget available and the solutions that they had been intended to supersede.[26–29] The lack of cost-effective production and distribution made tissue engineered solutions resource-intensive and of variable reproducibility and quality compared with more established treatments.[26] Unfortunately, the result of poor competitiveness of tissue engineered solutions further contributed to the costs of production and many early firms became bankrupted, thus breaking continuity of any breakthroughs and developments that they might have made.[21,26,27] Finally, investors lost patience with tissue engineering companies as they struggled to translate good ideas into real profits, eventually ceasing to fund the relatively speculative ventures behind the tech and biotech bubbles; and with them the relatively smaller tissue engineering industry.[27] Whilst 1992 and 1998 saw minor corrections of the biotech sector, the major correction seen in 2000 would spell the end of many of the listed tissue engineering companies.[27,28] The total capital value of tissue engineering companies dropped by a staggering 90%, from a total value of US$2.5 billion in 2000, to US$300 million two years later[21] (Fig. 18.7).
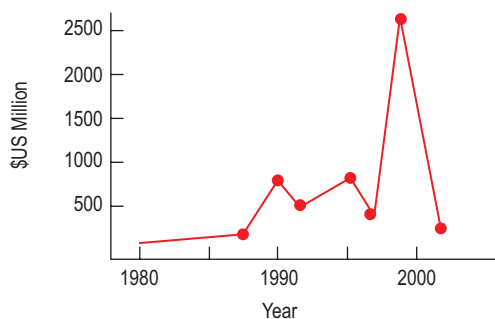

Figure 18.7 Market value of tissue engineering firms 1980–2002, showing the crash around the turn of the century.

At the time of the collapse of the tissue engineering sector, 89 firms in 15 countries, employing 2600 full-time equivalent roles in research and development, were destroyed.[21] Work in skin and cartilage structural biology had represented over 50% of tissue engineering and comprised over 800 FTE roles; however, at the time, the entire industry was yet to produce a single profitable product despite over US$4.5 billion research and development funds having been invested.[21,27–30] Twenty products were in FDA trials; six of these were abandoned or failed. A total of four of these original 20 products were eventually approved, however, none of these managed to achieve commercial success, and no successful product portfolio was generated. As a result, by mid 2002, few of the early tissue engineering firms remained commercially viable and the industry had officially collapsed.[30]

Issues that led to the collapse of the early tissue engineering sector

After having promised so much, the collapse of the tissue engineering market had left the sector in tatters. In order to understand the reasons behind the rise and fall, one must examine the global environment more broadly. Bouyed by unbridled optimism and unrealized expectation on behalf of both society and investors, the failure to create workable products led to disappointment and disaffection after a handful of years.[27]

Unfortunately, the science capability at the time did not match the aspirations of the public and the increasingly expansive media outlets of the day. Insufficient thought had been given to a path to market and practical clinical application of the tissue engineering experimental models.[26,31] There was insufficient business and industry expertise built into the largely academic ventures that in turn led to less emphasis on planning and governance; and slower and less direct passage through regulatory pathways.[32]

Insufficient forethought in the areas of target product profile and product differentiation from then gold-standard treatments as well as poor process management and manufacturing quality assurance, meant that any progress made within the early funding rounds were not channelled into meaningful returns on investment.[31,32] The public's imagination was captured not only by block-buster science fiction movies and iconic television series, but it was also fanned by the headlines such as Dolly the sheep, cloned from adult stem cells in the UK, and the famous images of the Vacanti mouse, which boasted a bovine cartilage ear scaffold implanted beneath the back skin of an immunocompromised mouse (Fig. 18.8).[17,27,30,32] Unfortunately, much like the fate of the tissue engineering sector in the 1990s, the once bold ear scaffold of the Vacanti ear construct quietly involuted into an amorphous ball of scar tissue on the back of a nude mouse.[17,32]

Tissue engineering Mark-II – focusing on the old domains and new paradigms

It was recognized after the fact that the clinical solutions provided by tissue engineering had not lived up to the hope promised by early breakthroughs in the field.[26] Having enjoyed the spoils of success, made possible by the successful pioneers of microsurgery, the field of plastic surgery became, to an extent,

Figure 18.8 A cartilaginous ear scaffold implanted beneath the dorsal skin of a nude mouse. An image of what is generally known as the "Vacanti mouse", after creators Charles A. Vacanti and Joseph P. Vacanti, became famous globally after it was published on magazine covers and featured in news reports in 1997. *(Courtesy of Dr. Joseph P. Vacanti and the Laboratory for Tissue Engineering and Organ Fabrication, Massachusetts General Hospital, Boston, MA.)*

Table 18.1 Characteristics required for a tissue engineering scaffold

Characteristic	Rationale
Biocompatible	Generate appropriate host immune response
Biodegradable	Absorption rate compatible with tissue regeneration rate
Surface area/ characteristics	Suitable surface topography and biochemical characteristics to promote cell adherence and biology
Porosity	Porous structure, of adequate dimensions to facilitate cellular and vascular ingress
Structural integrity	Adequate strength to tolerate physical forces and preserve cellular integrity
Mechanical resilience	Sufficient elasticity to endure deformity without structural compromise long term

a victim of its own success. As microsurgery became mainstream, and expertise in microvascular free tissue transfer continued to become more widely available, the case for an unmet clinical need driving the field was, in fact, diminished.

There was, however, a strong case for being able to generate products that could either augment the natural processes required to heal or regenerate, provide the same nature of reconstruction or tissue regeneration without a costly donor site, and to do so without the requirement for the high level of training and resources inherent in the practice of plastic surgery.[33] In order to construct soft tissue from simple cells, supporting substrates of tissues would be required and constituent cells would need to be supported or adapted for utility in forming a replacement organ or tissue (Table 18.1).

Following the correction in the biotech bubble, there was a pruning of the original ambitions held by plastic surgeons and a realization that the field had to get "back to basics". Tissue engineering as a field began to fragment and diverged into components that would:

1. Support or enhance the formation of new tissue by harnessing the natural developmental or healing processes; or
2. Provide delivery of therapeutics on the micro-scale: regenerative medicine.

The basics of plastic surgery are today that surgeons reconstruct the following tissue types relating to form and function:

1. Skin and integument first and foremost as a barrier against the external environment
2. Structural support of bone in the craniofacial regions and limbs
3. Functional transfers of nerve and muscle to restore motor deficits
4. Physiology of vascular and lymphatic systems, including immune response
5. The great tracts: alimentary, respiratory, and urogenital

Within the sub-component of plastic surgery tissue engineering, then, we should focus on these same clinical tasks and diseases. Just as the transition was made from macro- to micro-surgery, we need to consider how we may utilize micro-material and therapeutic interventions to manipulate and tailor cells and tissue processes, rather than focussing exclusively on the fabrication of cellular masses of tissue that externally resembled an idealized model of an organ.[33] The same intellectual transition made by our predecessors may be made to cross the boundaries of our physical limitations as surgeons to go "beyond surgery into the sub-cellular realm, whilst not losing our clinical objectives and perspective, nor our creativity and patient-centric focus".[21]

The lessons derived from the adversity of the challenges faced during the early endeavors of plastic surgery tissue engineers has paved the way for future triumphs in the field. In order to share in these objectives we must first embrace the quest of becoming conversant in science and investing in our people, as well as funding the research programs that are required. Iain Whitaker, of the Reconstructive Surgery and Regenerative Medicine Research Group (Recon Regen), in Swansea, UK, wrote in 2017: "Although tissue-engineered solutions hold great promise, we must be realistic in that contemporary tissue-engineered constructs implanted into immune-competent animal models … undergo inflammation, fibrosis, foreign body reaction, and degradation."[34] Tissue engineers had dreamed big, but a reality check had come in form of a bursting of the aspirations to create a complete "organ on a shelf".[26,35] Many tissue engineering solutions turned out to be inferior to the analogue plastic surgery solutions that they were intended to improve upon.[26–29] The constraints of the complexity of a multidimensional relationship between the tissue microenvironment and each cellular and subcellular element that makes up a tissue had not been realized.[27–31,35]

From 2003, however, a re-think prompted by the crash led to a pivot toward molecular sciences, scaffold and spheroid technology, cellular bioprinting and drug and device testing.[21] This adaptation has seen many who had gained valuable experience from the first iteration of tissue engineering re-emerge with greater experience and a new vision.[35] Some pioneering founders reinvent themselves, taking valuable lessons to start new companies. Many abandoned long-term organ goals, instead seeking to design more short-term profitable products such as for the cosmetic and drug testing industries.

The 2010s saw a shift toward more simplified products and devices that were designed to be more scalable and to have a clearer regulatory and commercial pathway that improved the likelihood of enhanced time to market.[21,31] That decade saw the first profitable tissue engineering products emerge and the generation of value for investors and solutions for patients.

Subcomponents of tissues that would allow neovascularization over previously ungraftable wound beds – such as Integra[36] and Biodegradable Temporizing Matrix (BTM)[37] – have transformed the key areas of complex 3D defect reconstruction.[35]

Modern tissue engineering – the TERM for progress

Regenerative medicine has been said to be a field that "centres on the restoration and regeneration of components of damaged tissue"; while tissue engineering is an "application of regenerative medicine that seeks to create functional tissue components and whole organs" in order to "restore biological function".[26,38] The previous demarcation of regenerative medicine being the preserve of the physician or cell biology scientist; while tissue engineering is the domain of the surgeon and the material engineer[15] has now been somewhat blurred by the overall advancement of our understanding of both the molecular science and technologies inherent to both components of the combined regenerative sciences.[26]

While tissue engineering may focus on the arrangement and delivery/implantation of the structural components of a tissue with or without constituent cells, potentially enhanced in their functional or replicative functions by bioactive accompaniments,[38] regenerative medicine may be mediated via often systemic modulation and harnesses pre-existing regenerative processes.[35,38]

Much attention has been paid in tissue engineering to the method of physical assembly of the structural elements of the construct,[39] in particular, focussing on the 3D adaptations of the original 2D bioprinting pioneered in the 1980s, and the printing itself may include printing of the scaffold, the cellular components or a combination of each.[15,35] In contrast, regenerative medicine is primarily aimed at the enhancement of natural healing using promoting agents or processes such as cell, gene or immune therapy, as well as nutritional approaches. The integration of these disciplines, which may in their application be highly complementary, has been captured by the acronym TERM – Tissue Engineering and Regenerative Medicine.[26]

Modern tissue regeneration science now involves a complex interplay of the disciplines of biomaterial engineering (involving nanomaterial and structural science)[39,40] with adequate nutrient supply (vascularization[41]) and waste eradication systems (venous and lymphatic systems[42]), micro-environmental optimization (largely driven and maintained by the stem cell niche) and cellular molecular biology.[42,43] The molecular biology itself involves expertise in developmental biology and genetics and gene editing, chemistry, biophysics and an "omics" capacity, in order to optimize the cellular components of the engineered/regenerated tissues.[44] Finally, in order to complete the process of translation from "bench to bedside", adequate attention is needed in the process management and manufacturing; as well as to the business, fundraising, regulatory, and clinical strategy and pathways (Fig. 18.9).[31]

Cell biology and cell signaling – a complex interplay of individual fields of expertise

Cellular biology and the signaling pathways are integral to both arms of TERM.[26] In regenerative medicine, the cells may be the modulators of the tissue repair and may be stimulated to this role either *in vitro* and then introduced or re-introduced to the patient in order to enhance their tissue growth or repair.[15] In tissue engineering, the cells may be introduced alone or in concert with a structural matrix that seeks to replicate the macro-structure, if not the function, of the extracellular matrix.[15,26,35] Gene editing technology (CRISPR – clustered
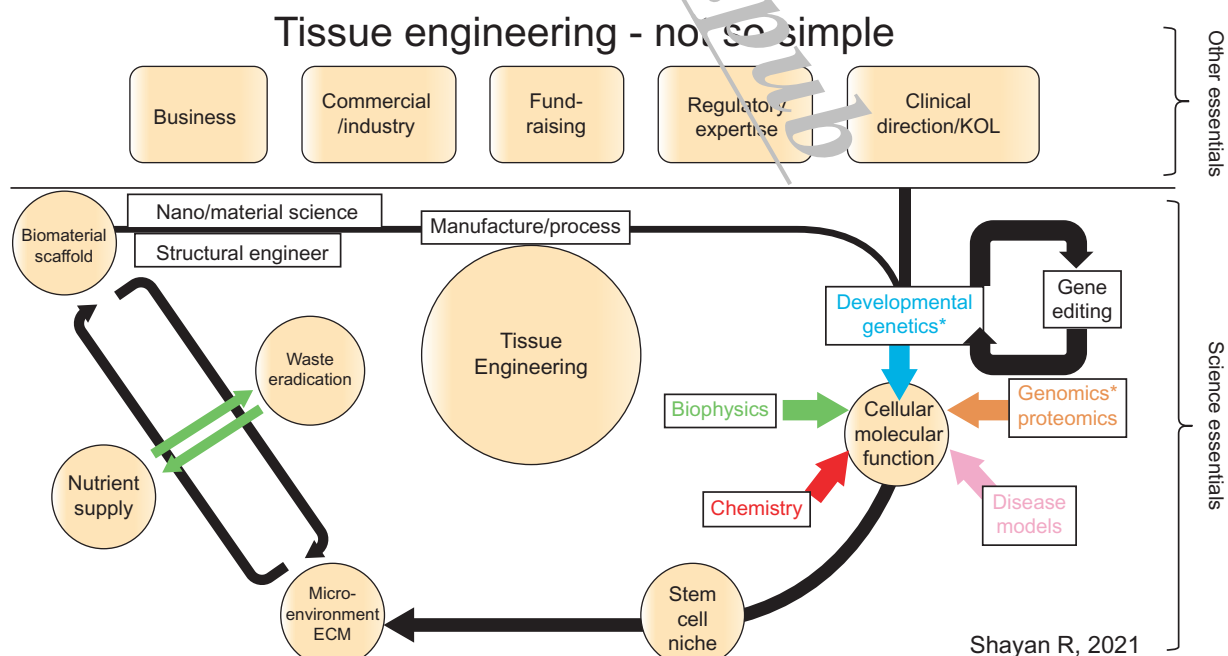

Figure 18.9 Pictorial schematic of the integrated subdisciplines of modern tissue engineering and regenerative medicine. ECM, Extracellular matrix; KOL, Key Opinion Leader.