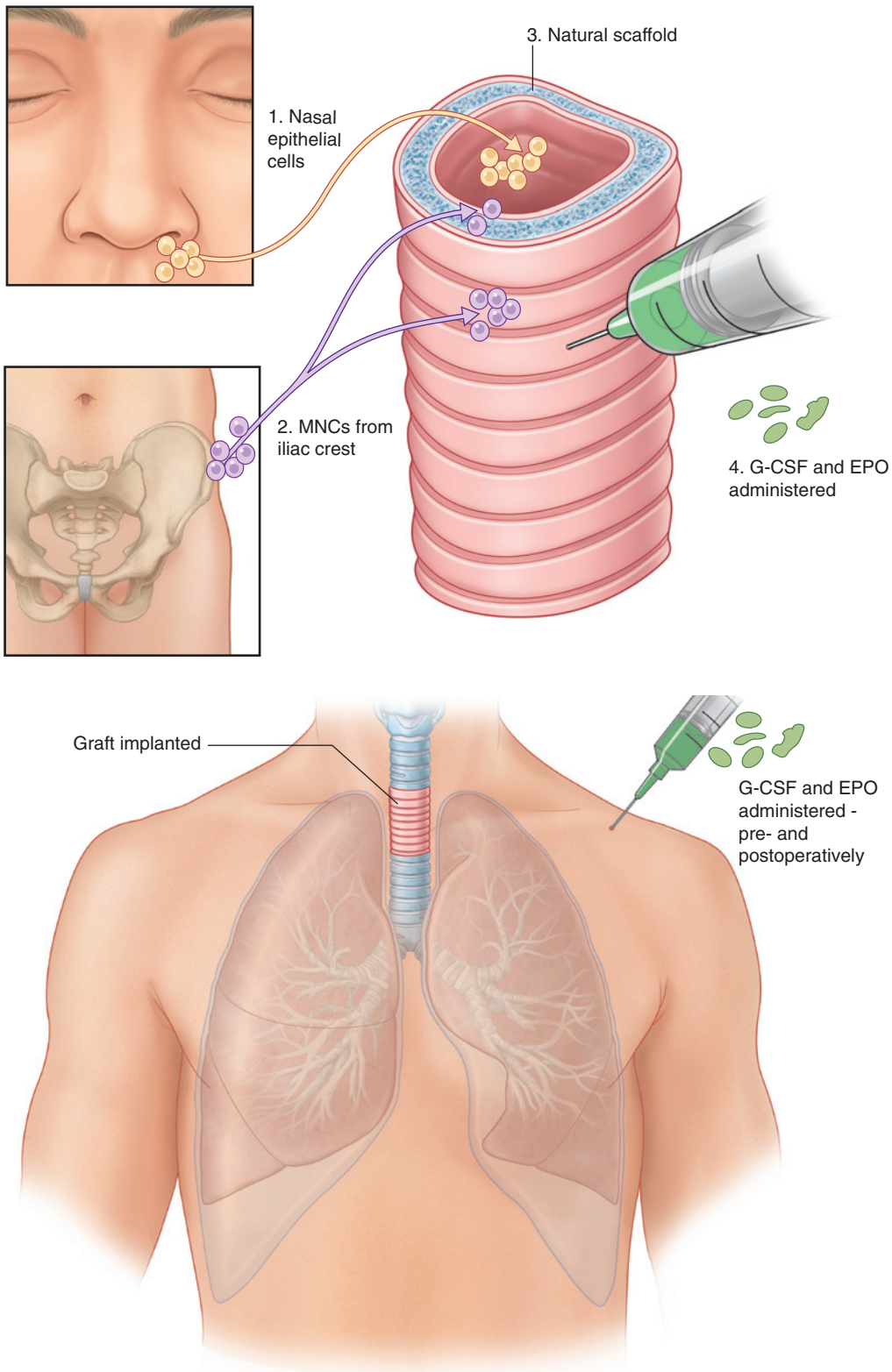

Figure 6.2 Stem cell–based tissue engineered tracheal replacement. (1) Autologous epithelial cells were obtained from a nasal biopsy and seeded onto the internal surface of the decellularized donor scaffold. (2) Autologous mesenchymal stem cells, obtained from the mononuclear fraction of a bone-marrow biopsy, were differentiated into chondrocytes. (3) A decellularized tracheal tube was seeded with these cells in a bioreactor. Granulocyte-colony stimulating factor (G-CSF) and topical human recombinant erythropoietin (EPO) were injected into the scaffold. (4) After 96 h in the bioreactor, the graft was implanted clinically. In the initial report in 2008, the authors did not make use of vascularized tissue to wrap around the construct.[71] However, all trachea reconstructions so far treated with this strategy failed due to instability of the construct.

MSCs and with autologous nasal epithelial cells.[71,72] At eight months, the patient developed a ventral collapse within the proximal graft. It could be that ischemia was, at least partly, responsible for this complication, due to the absence of a well-defined vascular pedicle enclosing the scaffold.[72,73]

The same group reported the first use of synthetic scaffold for tracheal repair in 2011. Their patient suffered from a main bronchus defect after the resection of a recurrent cancer of the upper airway.[74] The authors used a bioartificial nanocomposite scaffold that they seeded with bone-marrow derived autologous mononuclear cells (MNCs) in a bioreactor. An asymptomatic, tumor-free outcome was initially reported. However, in a follow-up Editorial, it appeared that multiple complications arose.[75]

Elliott *et al* also used a decellularized tracheal tube that was seeded with bone marrow–derived MNCs and autologous epithelial patches. TGF-beta was added to induce chondrocyte differentiation. Recombinant erythropoietin was used to saturate the construct intra-operatively and post-operatively, to promote angiogenesis.[76]

Zopf *et al* used a bioresorbable polycaprolactone-splint obtained by 3-D rapid prototyping technology to treat a segmental bronchial collapse. Bronchoscopy demonstrated a patent airway in expiration after one year follow-up.[77]

THE CARDIOVASCULAR SYSTEM

In 1919, Guthrie stated that for repairing a blood vessel, "*an implanted segment only needs to temporarily restore mechanical continuity, serving as a scaffolding bridge for the ingrowth of tissue from the host.*"[78] Although tissue engineering-based principles seem appealing to create the trachea, stability and vascularization of the construct remain the hurdlestones. The defining characteristics of regenerative cardiovascular implants have not strayed from that statement, but have taken it one step further: the tissue-engineered implant not only restores continuity and serves as a scaffold for tissue migration, it also has the ability to degrade, leaving remaining neotissue to integrate in the host.[1]

VASCULAR GRAFTS

In a NEJM report in 2001, Shin'oka *et al* described a tissue-engineering approach to treat occlusion of the right intermediate pulmonary artery in a 4-year-old patient.[79] They used autologous venous-wall cells that were seeded on a tube composed of poly-caprolactone-polyglycolic-acid, reinforced with woven PGA. They reported a patent transplanted vessel after a 7-month follow-up.

In a multicenter study, McAllister *et al* reported the use of a tissue-engineered autologous vascular graft to create a vascular access for hemodialysis in ten patients in need of an AV-fistula but without having appropriate veins.[80] They cultivated confluent sheets of autologous fibroblasts and their deposed extracellular matrix and seeded them around a stainless steel mandrel. After the vessel was taken off the mandrel, endothelial cells were seeded into the lumen. The patency rate was 60% at 6 months, equal to the patency rate of natural AV-fistulae.

In another clinical protocol, Hibino *et al* used autologous bone-marrow mononuclear cells seeded on a biodegradable scaffold of PGA and ε-caprolactone/L-lactide to create a cavopulmonary conduit; 5 out of 25 patients developed a thrombosis or stenosis of the graft. There was no reported aneurysm or graft rupture.[81]

Olausson *et al* used a decellularization procedure on a donor iliac vein and re-seeded it with endothelial and smooth muscle cells derived from bone marrow of the recipient. This procedure was used in a 10-year-old patient with portal vein thrombosis. This first construct failed after 1 year due to mechanical obstruction by tissue from the mesocolon, but a similar second procedure led to normal portal blood flow.[82]

CELL THERAPY FOR MYOCARDIUM

Vrtovec *et al* reported a 5-year follow-up of patients treated with intracoronary CD34+ stem-cell transplantation in non-ischemic dilated cardiomyopathy.[83] Their study revealed that transplantation might be associated with improved ventricular function, exercise tolerance and long-term survival.

Bolli *et al* reported in the *Lancet* in 2011 the early functional results of a phase-1 trial using cardiac stem cells isolated from autologous atrial appendages in patients with ischemic cardiomyopathy. Their approach led to enhanced function following myocardial infarction and failure of coronary stents.[84]

HEART VALVES

Mechanical valves[85] offer exceptional durability coupled with a considerable risk of thrombogenesis. Biological valves do not need anticoagulation, but have a limited life span. The concept of tissue engineering is based on the repopulation of biological decellularized scaffolds with autologous cells, creating an immune-privileged heart valve resistant to degeneration and with the potential to grow.

In 2006, Cebotari *et al* reported the clinical implantation of a decellularized human allogenic pulmonary heart valve, which was re-seeded with mononuclear cells isolated from human blood, including the EPC-fraction. Enzymatic treatment with trypsin/EDTA converted pulmonary valves in a cell-free scaffold with 98% reduction of DNA-content. Histology revealed a well-preserved 3-D network of collagen fibers in extracellular matrix. They reported 3.5 years of follow-up in two patients aged 13 and 11. Postoperatively, a mild pulmonary regurgitation was documented in both children, however no signs of valve degeneration were observed. They showed that, in contrast to conventional homograft and xenografts, decellularized fresh allograft valves exhibited the potential to remodel and grow accordingly to the somatic growth of the child.[86]

The same authors treated 131 patients with decellularized pulmonary homografts from 2005 to 2015. Because of the observation of spontaneous recellularization by several groups, they implanted non-seeded valves. They demonstrated promising superior results related to durability of the constructs, e.g. related to freedom of explantation, development of relevant gradients, compared to cryopreserved pulmonary homografts and bovine jugular vein conduits.[87]

CONCLUSION

Plastic and reconstructive surgeons must embrace tissue engineering and regenerative medicine. We have the soft tissue handling and knowledge about remodelation.