Commentary: The sobering truth about tracheal regeneration

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Tracheal replacement to restore functional integrity of a long segmental defect or a complex airway stenosis remains a surgical challenge.1 A variety of surgical techniques have been reported clinically, including transplantation of autologous2 or heterologous3 tissue flaps, direct4,5 or indirect6 cadaveric tracheal allografting, and interposition of a “re-generated” trachea.7

In this issue of the Journal, Fux and colleagues8 from the Karolinska Institute in Stockholm publish a very detailed and well-illustrated long-term follow-up of 3 patients who received a “bioengineered tracheal allograft seeded with bone marrow cells” resulting in numerous complications and finally fatal outcome. These authors from Karolinska institute should be congratulated for their courage. However, the patients involved shouldn’t have undergone this procedure. The devastating outcome after the implantation of a synthetic trachea was fully predictable. In fact, the

See Article page 2525.
bioengineered tracheal allograft seeded with bone marrow cells was nothing more than a plastic tube.8 In 2008, a high-profile paper was published on the first successful regeneration of the trachea.7 In this case report, 2 miracles had occurred: (1) The cells of a donor trachea had been replaced by recipient cells after applying stem cells of the recipient to an enzymatically treated cadaver donor trachea; and (2) The “regenerated” trachea could be used for airway repair without restoration of its blood supply.

The paper attracted much media attention as the first organ that could be regenerated; it was foreseen that other hollow-organ regenerations would quickly follow.9 Indeed, the engineered trachea was seen to be the first step toward other forms of organ regeneration. Classic organ transplantations with their typical side effects due to antirejection medication could then be replaced by growing organs from the body’s own cells.

However, the problem with the tracheal regeneration concept, portrayed as successful, is that it is theoretically impossible. All requirements necessary to consider tracheal regeneration were lacking (Figure 1). More misleading high-profile papers were subsequently published in Lancet as the first “regenerated” synthetic trachea10 and the first “regenerated” cadaver trachea in a child.11 Since 2008, about 20 patients received a “regenerated” trachea in different centers around the world. As could be expected, severe complications arose, with fatal outcomes in the majority of the patients.12 The tracheal replacements were initially published as successful in some patients because of the use of a stent and the omental wrapping, which delayed the inevitable complications (Figure 2).

From the very beginning, we have tried to inform the medical world about this blatant example of scientific deception.13,14 From 2014 onwards, 4 whistleblowers of the Karolinska Institute, and the authors of this current paper in the Journal, joined us in these actions. We had to wait for a reaction from the involved institutions until January 2016, when the scandal was exposed to a wider audience after a 3-hour documentary that was aired on Swedish national television and on BBC. The overwhelming documentary resulted from

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FIGURE 1. Requirements for a regenerated trachea: (1) Mucosal lining; (2) support; (3) vascular supply.

FIGURE 2. Left, nude synthetic trachea: suture lines will never heal, leading to anastomotic breakdown (red circles) with serious complications in the short term. Right, synthetic trachea wrapped with vascularized tissue (eg, omentum): suture lines will not heal. Anastomotic breakdown (red circles) will be delayed by surrounding vascularized tissue. Serious complications will occur in the long term.
top-shelf investigative journalism. Quickly after its broadcasting, board members of the Karolinska Institute, including the secretary-general of the Nobel Committee, had to resign and the paper on the regenerated synthetic trachea was retracted. 15,16

This misleading story on tissue regeneration hasn't come to an end yet. Until now, other papers on the regenerated cadaver trachea still stay afloat. Synthetic tracheas and nonvascularized donor tracheas are destined to fail. They were wrongly used for tracheal replacement and presented as breakthroughs in clinical tracheal tissue engineering.

References

Commentary: Trust but verify—How do we keep the faith?

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In this month’s Journal, Fux and colleagues1 report the first long-term follow-up study of the outcome of synthetic tracheal grafts seeded with bone marrow cells at their institution. Their outcome data contradict previously reported successes with this technique.2-5 Fux and colleagues1 demonstrate that these grafts were not cellularized with site-specific cells and did not become living, functional