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The Arrest of Christ: Autotransplantation from Miracle to Medical Procedure

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Abstract

During the arrest of Christ, one of his disciples, Simon Peter, cut off the ear of a servant of Caiaphas. Christ put the ear back, a miracle and the first recorded autotransplantation. Currently, autotransplantation is an established procedure in reconstructive dental and bone surgery. Autotransplantation of splenic fragments can retain spleen function after splenectomy. Following pancreatectomy for chronic pancreatitis or benign or malignant diseases of the pancreas, islet autotransplantation can prevent diabetes. Autotransplantation of hematopoietic stem cells enables reconstitution of hematopoiesis after intense chemo and/or radiotherapy for leukemia and lymphoma. The development of biomedical technology to generate induced pluripotent stem cells, gene editing with CRISPR Cas, and *in vitro* organoid cultures opens the possibility to treat a wide array of inborn and acquired diseases by autotransplantation.

Introduction

The Temptation of St. Anthony (1500-1510) is an altarpiece by Jheronimus Bosch. Colorful altarpieces were closed during the Lenten period, the 40 days' penitential preparation for Eastern, or just during the final week before Eastern, the Holy Week. For that reason, the reverse side of the wings often were painted in grey (grisaille) depicting scenes from the last week of the life of Jesus. The scene painted on the left wing, The Arrest of Christ, depicts the moments when Jesus was arrested in the garden of Gethsemane. On the foreground, Simon Peter swings his sword with the clear intention to attack Malchus, a servant of the high priest Caiaphas, who had ordered the arrest of Jesus. The relevant passage in the Gospel of John (18:10-11) reads: "then Simon Peter having a sword drew it, and cut off his right ear. The servant's name was Malchus" [1]. It is impossible to know whether this event actually happened, although it has been argued that early Christians probably would not have made up stories which would depict them as violent. The interpretation of Bosch of this Biblical event is slightly different because from the positioning of Simon Peter and the way Malchus turns his head (see Figure 1), it is virtually impossible to cut off the right ear. The Gospel of Luke (22:50-51) describes Jesus' response to this act of Simon Peter: "Jesus answered, "No more of this!"

Figure 1: Fragment of The Arrest of Christ, reverse side of left outer panel of The Temptation of St. Anthony (1500-1510) by Jheronimus Bosch. Museu Nacional de Arte Antiga, Lisbon, Portugal. https://upload.wikimedia.org/wikipedia/commons/9/9e/Jheronimus_Bosch_001_exterior_01.jpg Assessed December 24, 2019.

And he touched the man's ear and healed him" [2].

Above biblical event could be considered as the first recorded autotransplantation. During the following centuries, anecdotal references to transplantation and autotransplantation were classified as myths and miracles [3]. Autotransplantation of

skin flaps for reconstruction of missing noses was practiced already in the 16th century [4]. Renal transplants in humans initially were performed using pig and goat donor kidneys [5], followed by using monkey kidneys [6]. These forms of transplantation are termed xenotransplantation, and, although technically successful, the kidneys lasted no longer than just a few days at best and all patients died soon afterwards. The first medical documented (successful) kidney transplantation was performed in 1954 in identical twins [7]. Liver, heart and pancreas transplants followed by the 1960s, and lung and intestinal organs in the 1980s [8,9]. Rejection, based on histo-incompatibility between donor and recipient turned out to be the major obstacle for lasting success [10]. Improvements in immunosuppressive treatment and matching of donor and recipient HLA have dramatically improved success rates [11,12]. The price to pay for immunosuppression is increased infection and malignancy risk, but identical donor organs, even matched donors, are scarce. The availability of a donor kidney from an identical twin is truly exceptional [7], even HLA-identical siblings are rare. Transplantation across histocompatibility barriers therefore requires immunosuppression with the inherent risk of infections and secondary malignancies. In autotransplantation, defined as transplantation (or repositioning) of organs or tissues in the same individual, the donor and recipient are the same person and therefore histo-compatible.

Autotransplantation of skin, hair and teeth

Autotransplantation of teeth is part of reconstructive oral surgery in case of unevenly distributed agenesis, missing lower premolars, missing or lost incisors, as well for repositioning of ectopic teeth [13-15]. Other bony elements can be used for autografting to repair complex bone fractures, for fractures that would pose a health risk, or which do not heal properly [16,17]. Autologous bone transplantation is osteoinductive and osteogenic (meaning that osteoblasts originating from the graft material contribute to new bone growth), as well as osteoconductive [18,19].

Autologous hair transplantation techniques are used for treatment of vitiligo [20] and alopecia [21], as well as for cosmetic reasons [22]. The outcome of skin transplantation for treatment of burn wounds would benefit from autologous skin. The major problem is that autologous skin needs to be pre-cultured and rapid healing of burn wounds is critical to relieving morbidity and reduce mortality [23]. It has been shown that autologous skin cell suspensions combined with hydrocolloid dressings accelerated epithelialization and improved healing [24].

Autotransplantation of internal organs

Organ	Indication	
Skin, hair, teeth	Reconstructive and cosmetic surgery	
Spleen	Preservation of splenic function after traumatic spleen rupture	Splenic fragments are transplanted
Kidney	To relief the pain of kidney injuries, shortening of ureters in case of kidney stones, loin pain hematuria syndrome, Nutcracker syndrome	Kidney is repositioned
Parathyroid	(Now outdated) parathyroid autotransplantation after total thyroidectomy.	
Liver	Advanced hepatic alveolar echinococcosis; advanced cholangiocarcinoma	ex vivo liver resection and autotransplantation
Pancreatic islet	Nonmalignant and malignant indications for pancreatectomy	
Heart	Following ex vivo surgical resection	

Table 1: Autotransplantation of organs and tissues.

Autotransplantation of organs and tissues is performed for a variety of clinical indications (Table 1). Traumatic rupture of the spleen, splenic abscesses in case of tuberculosis and radical surgical clearance of adjacent tumors, all are indications for total splenectomy [25,26]. Furthermore, there are a number of diseases leading to splenomegaly, including sickle cell anemia and thrombocytopenic conditions, which benefit from splenectomy [26]. Major post-operative risk of splenectomy is Overwhelming Post Splenectomy Infection (OPSI), most often due to a *Streptococcus pneumoniae* sepsis. Prophylactic antibiotics and adequate vaccination can reduce these risks but do not compensate for other splenic functions. In case of splenectomy for trauma, autotransplantation (of part of the spleen) can be performed [27,28] which restores the functional lymphoid compartment of the spleen and improves the response to vaccination [29,30]. Kidney autotransplantation, involving the repositioning of the kidney, is being performed for various indications such as renal vessel pathologies, ureteral avulsion, urothelial malignancy, and renal trauma [31,32]. Parathyroid autotransplantation during total thyroidectomy has been advocated in order to prevent postoperative hypocalcemia and/or hypoparathyroidism [33,34]. In a retrospective study it was shown that 1) these complications

are rare and 2) parathyroid autotransplantation had no significant effect in further reducing these complication [35] and therefore this advice has been abandoned [36].

Ex vivo liver resection and subsequent autotransplantation is used in treatment of advanced hepatic alveolar echinococcosis and advanced cholangiocarcinoma [37,38]. In patients with chronic pancreatitis and severe (abdominal) pain, total pancreatectomy is performed followed by islet autotransplantation to prevent the development of diabetes [39,40]. Islet autotransplantation is also performed in case of total pancreatectomy for benign or malignant diseases of the pancreas [41,42]. Cardiac autotransplantation is performed as part of the surgical resection of malignant [43] or complex benign tumors of the heart [44]. Cardiac autotransplantation involves explantation of the heart after which ex-vivo tumor resection is performed, damaged tissue reconstructed and the heart reimplanted [45]. Autotransplantation also is involved in coronary artery bypass surgery. Autologous blood vessels are used for grafting mostly the internal thoracic artery, the radial artery, and saphenous vein in that order [46,47].

Autologous transplantation of cells

Next to organs, also (mixtures of) cells are used for autologous transplantation. Autologous blood transfusion is a common procedure during elective surgical procedures. It can be based on preoperative autologous blood donation, acute normovolemic hemodilution, or intraoperative and postoperative autotransfusion of recovered blood lost during surgery [48,49]. Apart from strictly medical reasons for autologous blood transfusion, it is also used as a form of doping in high performance athletes such as cyclists and long-distance runners [50]. Because of improved detection methods for erythropoietin, athletes have reverted back to blood doping, although this form of doping now also can be detected [51]. Autologous blood transfusion is effective because in a controlled setting with recreational athletes, VO_2max and performance as measured with treadmill running performance tests improved by 17% and 15%, respectively [52].

Autologous transplantation of hematopoietic stem cells is being used for rescue of hematopoiesis after myeloablative therapy for malignancies and reconstitution of the immune system following intense therapy in autoimmune diseases. The four phases of autologous hematopoietic stem cell transplantation include: a) harvesting, purification and cryopreservation of autologous hematopoietic progenitor cells; b) administration of high-dose therapy for the underlying disease in the form of chemotherapy and/or radiotherapy; this phase is called conditioning or preparative regimen; c) thawing and infusion of the autologous cells; and the last phase d) reconstitution of hematopoiesis. During phase d, vigorous supportive care including prophylactic antibiotics, transfusion of blood components, and other measures is required [53-55]. Initially, hematopoietic stem cells were derived from bone marrow [56,57], but currently this has largely been replaced by blood derived stem cells. Normally, blood contains only very few $CD34^+$ stem cells, but these numbers can be greatly expanded by administration of Granulocyte-Colony Stimulating Factor (G-CSF). Standard is a 5-day regimen of G-SCF, but addition of the reversible CXCR4 antagonist AMD3100 greatly improves stem cell mobilization [58-60]. Quite unexpectedly, the combination of AMD3100 and sildenafil also is a very potent (no pun intended) way to mobilize peripheral $CD34^+$ stem cells [61]. The minimum dose of $CD34^+$ cells for a successful autologous stem cell transplantation is 2 x 10^6 cells/kg recipient body weight, but ≥ 4–6 x 10^6 cells/kg is considered optimal [62,63].

Autologous stem cell transplantation is most often used in the treatment of leukemia and lymphoma, in particular multiple myeloma [64] and both Hodgkin's and non-Hodgkin's lymphoma [65,66] (Figure 2). Autologous stem cell transplantation is also used in treatment of patients with recurrence of high-risk solid tumors that may respond to intensive chemo- or radio-therapy, including neuroblastoma, soft tissue sarcoma/Ewing, and germinal tumors [67-69]. Autoimmune diseases are also being treated with autologous stem cell transplantation [70,71]. The underlying principle is that existing lymphocyte subsets are eliminated by intense therapy, after which repopulation of the immune system can take place, with establishment of self-tolerance. Multiple sclerosis and systemic sclerosis are the autoimmune diseases most treated with autologous stem cell transplantation in Europe [72,73], but also a variety of other systemic and organ-specific autoimmune diseases [74-76].

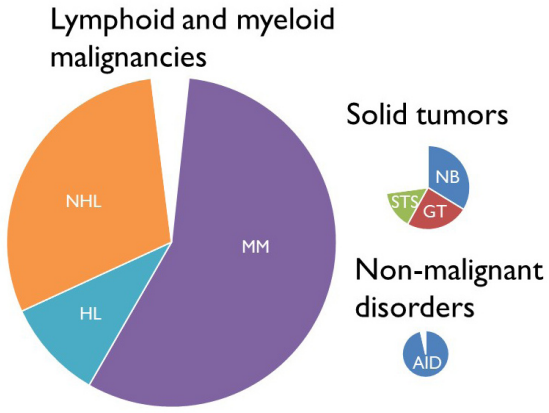

Figure 2: Autologous stem cell transplantations in Europe in 2018. MM, multiple myeloma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NB, neuroblastoma; STS, Soft tissue sarcoma/Ewing; GT, Germinal tumors; AID, Autoimmune diseases. The open parts of the pie represent other indications. Pies and pie parts are proportional to the number of patients treated. Data derived from reference [77]. Data from the Center for International Blood & Marrow Transplant Research CIBMTR indicate that also worldwide the major indications for autologous hematopoietic stem cell transplantation are MM, NHL, and HL [78].

Induced Pluripotent Stem Cells for autotransplantation

The main reason to prefer autotransplantation over allotransplantation is to minimize the risk for attack and rejection by the recipient's immune system. For a great number of diseases an inherited or acquired genetic defect or functional impairment makes autotransplantation impossible. Induced Pluripotent Stem Cells (iPSC) [79,80] could offer an alternative. Autologous iPSC-based therapy for genetic diseases becomes possible because the disease-causing gene defect can be repaired *in vitro* using CRISPR–Cas9 technology [81]. Neural [82], intestinal [83], kidney [84], lung [85,86], and cardiac [87] organoids have been grown which offer exciting new possibilities for disease modeling, drug discovery, and ultimately new treatment modalities for diseases like Hischprung disease, cystic fibrosis, and surfactant deficiency [81]. During generation of iPSCs and subsequent differentiation and long-term culture to generate organoids, mutations could arise. Indeed, it has been shown that especially in mitochondrial DNA, nonsynonymous mutations can arise which encode neoantigens that can elicit an immune response [88,89]. The prospects of iPSC based organoid autotransplantation are good, but these, and other potential limitations, should be considered.

Epilogue

Autotransplantation of organs and (stem)cells has become an established procedure in the treatment of a number of diseases. Novel biomedical technologies such as induced pluripotent stem cells, gene repair with CRISPR Cas, and 2D and 3D organoid cultures will further expand the therapeutic potential of autotransplantation. Strictly speaking, the attachment of the cut off ear of Malchus is not autotransplantation. Replantation is the term for reattaching a severed limb (or ear), so that term probably is more appropriate for the scene depicted in the Arrest of Christ (Figure 1). It was the last recorded miracle of Jesus, but the first recorded medical procedure of this type.

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