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EDITORIAL

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Lessons from transplantation and future perspectives

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Abstract Organ transplantation is now a routine treatment for a number of chronic kidney, heart, lung, and liver diseases. We have accumulated much knowledge about these treatments in the respective disciplines, and it seems appropriate to reflect on some general "across-the-border" lessons that may be important for medicine as a whole. The natural history of several diseases has been extended; however, we have also learned much about temporary organ replacement, with the possibility of treating and, perhaps, also preventing some diseases in ways that were not possible in the past. This study explores the phenomenon of temporary organ replacement, whereby organs that are in danger of losing their function may recover in quiescence. It raises the question of whether there might be a common, underlying mechanism – such as apoptosis – for some very different diseases. Pharmacological interventions designed to modulate apoptosis are being developed that will hopefully reduce the amount of time needed for organs to recover their function. We have learned some lessons, but are there more possibilities that need to be explored?

Key words Transplantation, lessons · Lessons, transplantation

Organ transplantation is now a routine treatment for a number of chronic kidney, heart, lung, and liver diseases, and the benefit is great for the patients involved. We have accumulated much knowledge about these treatments in the respective disciplines, and it seems appropriate to reflect on some general "across-the-border" lessons that may be important for medicine as a whole.

Each organ has, apart from its own individual function, a vital role in the organism as a whole. Thus, when the function of an organ declines, the entire organism eventually dies. Many organs could recover if we could temporary replace their vital roles. The chances for recovery would be even better in an otherwise intact organism rather than in one severely suffering from failure of that specific organ. For this reason, temporary organ replacement therapy should be encouraged using either artificial devices or auxiliary transplantations.

When dialysis became a routine treatment, the natural history of several kidney diseases changed. The temporary replacement of a kidney has allowed most cases of acute tubular necrosis to recover spontaneously; it has also made it possible to treat and cure a number of other renal diseases. The recovery of native kidney function after the cessation of kidney graft function has also been observed [12]. We learn even more about kidney diseases when we observe recurrence of the disease in the graft or de novo appearance.

In the case of severe heart failure, ventricular assist devices have been used as a bridge to transplantation in several centers [13, 18, 28]. They have also been shown to facilitate recovery in end-stage organ failure [10], making transplantation possible. Weaning from assist devices without transplantation has been reported sporadically [13, 17, 22, 27, 28]. Recently, weaning from mechanical support after complete recovery was demonstrated in 15 patients with idiopathic dilated cardio-

myopathy [M. Loebe, personal communication]. When the organs are given the necessary time to recover (in this case, anywhere from a few months to a year), severe heart failure can even be cured, and heart transplantation is no longer necessary.

In the case of a deterioration in lung function, extracorporeal membrane oxygenation (ECMO) can only be done for a few days. If this is not sufficient time for recovery, lung transplantation will be necessary. In some cases of single lung transplantation, the remaining weakened native lung has been observed to regain function over time when relieved of the full burden of respiration [A. Haverich, personal communication]. In young people with acute respiratory distress syndrome (ARDS), it is best to remove the smaller left lung, perform a temporary single lung transplantation, wait 1–2 months for regeneration of the remaining native right lung, and then remove the graft and stop the immunosuppression. Temporary heterotopic lung transplantation has been done in dogs, providing effective gas exchange and supporting both oxygenation and ventilation [7].

In liver transplantation there have been a few reports of a temporary liver graft being removed after recovery of the native liver in some types of fulminant disease [3, 11, 14]. In a multicenter European study, 30 patients with fulminant hepatic failure due to hepatitis A and B, paracetamol overdoses, ecstasy, hepatotoxic drugs, autoimmune hepatitis, pre-eclampsia and other unknown causes were given an auxiliary partial orthotopic liver transplantation (APOLT). There was subsequent regeneration of the native liver and 19 patients survived, including 13 without immunosuppression [6]. In such cases, the graft will either atrophy or be removed. In a recent report, the procedure was done in a 3-year-old boy [29]. Artificial liver support devices that allow blood or plasma to circulate in devices with liver cell lines of human hepatoblastoma or of porcine origin are being developed [4, 21, 25, 35]. Conditionally immortalized hepatocytes were recently shown to be effective in supporting life during acute liver insufficiency in animal experiments [23].

However anecdotally, these cases are a further inspiration to develop artificial devices or techniques for cellular transplantation for temporary use. Different organs require varying amounts of time for recovery after acute nonfunction. The resumption of normal kidney function after oliguric acute tubular necrosis may take anywhere from a few days to a month, and sometimes 2 months or more [9]. Assist devices for hearts can be used for months to years, allowing the heart sufficient time to recover. Hepatic regeneration after APOLT is reported to take place within 3–4 weeks [29]. ECMO is generally only done for 2–7 days in adults, although longer periods have been reported [15, 30]; in children, it may be continued for 2 weeks. Since recovery from ARDS takes $1^1/_2$–2 months, transplantation is essential.

At a time when there is such a discrepancy between the need for, and the supply of, available donor organs for transplantation, it is clearly worth exploring the aforementioned procedures, as well as developing cell lines for extracorporeal use or for repopulation of the diseased organ. This would provide a much-needed alternative for the 40%–50% of patients who undergo heart transplantation due to cardiomyopathy [5], the 6%–10% who receive liver transplants because of fulminant hepatic failure [15], and the smaller percentage of lung transplant recipients who have ARDS, not to mention patients diagnosed as having other diseases. The patients would benefit by avoiding the long-term immunosuppression necessary after transplantation, more patients could be treated despite the shortage of available organs, and society would benefit from fewer costly, long-term procedures. There have been a few reports in the literature on the reuse of transplanted organs [8, 20], and this might even be developed into a new kind of domino auxiliary transplantation.

In islet transplantation, protecting the newly transplanted islets from exhaustion by maintaining an absolutely normal blood sugar is imperative until the islets have established themselves in the liver [19]. This is also the underlying reason for trying to avoid insulin dependent diabetes mellitus in relatives of diabetics by pretreating them with insulin, thereby protecting the β-cells [16].

The time it takes a kidney, heart, lung, or liver to recover from organ failure is different from the time it takes for the organ to be rejected after organ transplantation. This suggests that immunology may not play as large a role as other mechanisms. The question then arises: are we dealing with a number of specific diseases, or is there a common, underlying mechanism in these very different cases? Might there be some cellular or subcellular mechanism that is exhausted, and could that be reversed under the right therapy?

Apoptosis, or programmed cell death, plays a role in the pathogenesis and treatment of many diseases [1], including end-stage heart failure [31, 32], acute lung injury [24], and fulminant liver disease [26]. Pharmacological interventions designed to modulate apoptosis are being developed [2] and, if applied to these diseases, they could reduce the amount of time needed for the recovery of organ function.

The liver has an enormous potential for recovery. The kidney also has a unique potential for structural and functional recovery. Recently, experiments were conducted that were able to accelerate this recovery with a number of growth factors. The repair processes included epithelial proliferation, differentiation, and apoptosis [33, 34].

It is exciting to observe an extension of the natural history of some diseases with a possibility for recovery in stead of certain death as observed formerly. It gives one the opportunity to study, treat, and perhaps also prevent some diseases in ways that were not possible in the past. We have learned some lessons, but there are, no doubt, more avenues to explore in the future. Perhaps we should focus our attention on techniques that will allow failing organs to recover in quiescence.

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