Fighting 50 Years of Failure

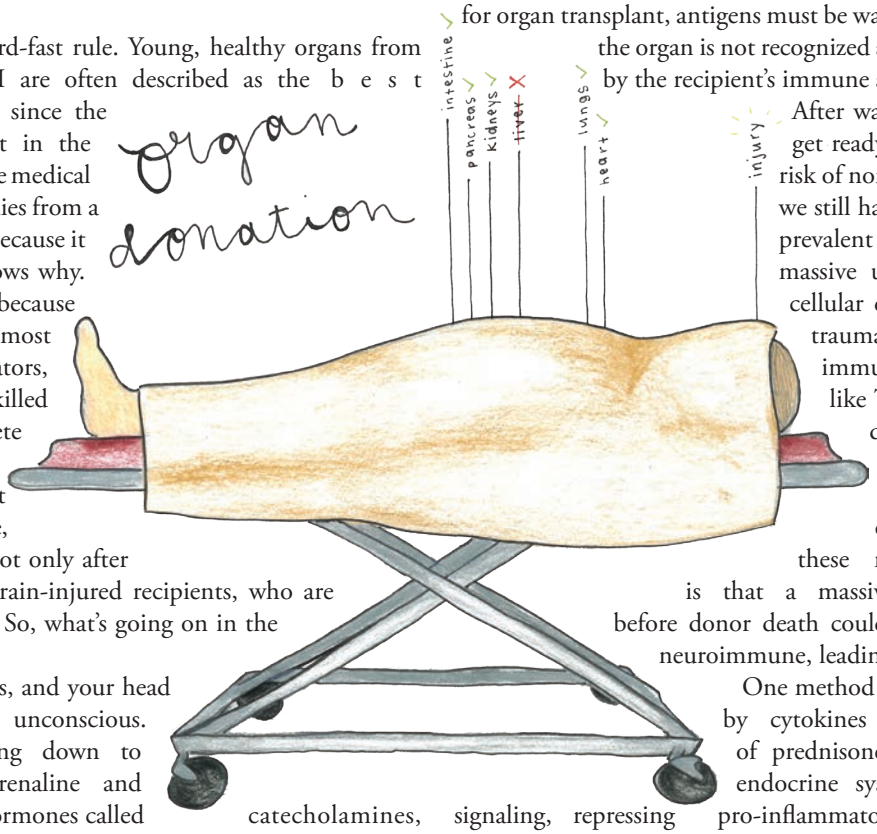
Liver Transplant Failure after Traumatic Brain Injury

Written by Zoe Swann
Illustrated by Claire Hoy

Every day, 30 people die before they can receive life-saving organs (i.e., 11,000 people every year), according to Donate Life America. Organ shortage is increasingly found to be one of the most urgent medical dilemmas of our generation.

Most organ donors die in car crashes. A third of all people who die from traumatic brain injuries (TBIs) die in car crashes. Therefore, TBI victims supply most organs viable for donation and transplant. Of these organs, the liver has posed a particular problem for the medical community. I am currently working on a project with the University of Arizona's College of Medicine to determine a long-unexplored question: why does liver transplant tend to fail if the donor has had a traumatic brain injury?

Now, this is not a hard-fast rule. Young, healthy organs from motorcyclists who die of TBI are often described as the best candidates for transplant. But since the first successful liver transplant in the 1960s, it has been a mantra in the medical community that if your donor dies from a TBI, you don't take their liver, because it will probably fail. Nobody knows why. This is especially worrisome because brain-dead donors make up most of the population of car-operators, motorcyclists, and pedestrians killed each year (not to mention athlete and veteran populations who often undergo severe, if not fatal, brain injuries). Even worse, liver transplant failure occurs not only after a donor's injury, but also in brain-injured recipients, who are already struggling to stay alive. So, what's going on in the body?



BAM! Your car crashes, and your head whips forward, knocking you unconscious. Your periphery starts shutting down to keep your brain alive. Adrenaline and norepinephrine, examples of hormones called catecholamines, upregulate when you walk onto a stage — or give yourself a head injury. Your heart starts pumping, your hands start sweating, you may even lose control of your bladder; your body starts to shut down to prioritize other systems. In severe head injuries, a "catecholamine storm" may occur, resulting in vasoconstriction, spinal cord paralysis, and lack of oxygen — all in an effort to maintain cerebral perfusion, the amount of blood and oxygen in your brain. Normally, your mere three-pound brain uses 20% of the body's oxygen. Now, your brain is starving, and your body does everything it can, even at the expense of the rest of you, to maintain those oxygen levels. This redirection of oxygen causes organ damage throughout the body, including viable livers.

> In the medical community, if your donor dies from a traumatic brain injury (TBI), you don't take their liver, because it will probably fail. Nobody knows why.

Transplant aggravates the recipient's immune system, which, detecting a foreign body, attacks the new organ. Cytokines, molecules that signal immune cells to respond to a disease or injury, can be pro-inflammatory or anti-inflammatory. Often the cytokines we see with brain injury (such as IL-6, TNFa, or IL1B) are pro-inflammatory. Pro-inflammatory responses increase swelling, giving immune cells more access to the injured area of the brain. However, these cytokines can also affect the donor's immune cells responsible for long-term response, called B cells and T cells. An individual has their own set of B and T cells that remember markers, called antigens, on immune cell surfaces. This is how B and T cells distinguish self from non-self (e.g., a virus or dead cell debris). During preparation for organ transplant, antigens must be washed from the organ's surface so the organ is not recognized as non-self and thereby attacked by the recipient's immune system.

After washing the organ of antigens to get ready for transplant and reduce the risk of non-self recognition and rejection, we still have a problem that is even more prevalent in the case of brain injury. The massive upregulation of cytokines and cellular damage we see after fatal head trauma may have affect peripheral immune cells. Certain cytokines, like TNFa, contribute to direct cell death and necrosis, causing liver damage and dysregulation.

Cytokines are at the heart of the problem in all three of these mechanisms. My hypothesis is that a massive cytokine increase shortly before donor death could result in the liver becoming neuroimmune, leading to recipient graft rejection.

One method to reduce inflammation caused by cytokines involves the administration of prednisone, a steroid that acts on the endocrine system to downregulate NFkB signaling, repressing pro-inflammatory responses. But prednisone treatment has proved to be complex. One study found that after prednisone administration in brain-dead rats, cytokines were favorably regulated in the kidney, but not in the liver. A major inflammatory cytokine, IL-6, was highly upregulated after brain death in the kidney and liver, but reduced after prednisone administration in only the kidney.

Another molecule responsible for programmed cell death is C-3, part of the complement system generated in the liver. The complement system serves to enhance the ability of antibodies to promote inflammation and attack foreign microbes. After prednisone administration, this molecule is downregulated in the kidney but significantly unregulated in the liver. Other studies have shown variable efficacy in prednisone and steroid administration both in the liver and in organs more generally.

Despite these efforts to understand the workings of TBI-related liver rejection, much remains unknown. The body is an incredibly complex machine whose systems interweave beyond imagination. Ethics, public knowledge, and family consent are other roadblocks in procuring lifesaving organs. But we might just discover the cure for this ongoing medical dilemma. So do not give up — donate to science, do research, and consider registering to be an organ donor. ●