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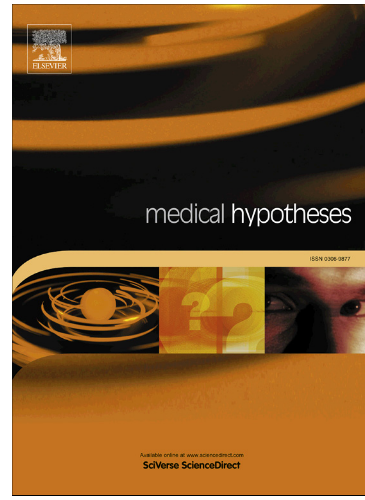

Personality Changes Following Heart Transplantation: The Role of Cellular Memory

Mitchell B. Liester

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Personality Changes Following Heart Transplantation: The Role of Cellular Memory

Mitchell B Liester, MD

Department of Psychiatry

University of Colorado School of Medicine

PO Box 302

Monument, CO 80132

Corresponding author:

Mitchell B Liester, MD

PO Box 302

Monument, CO 80132

(719) 488-0024 (office)

(719) 488-6672 (fax)

mitchell.liester@ucdenver.edu

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ABSTRACT

Personality changes following heart transplantation have been reported for decades and include accounts of recipients acquiring the personality characteristics of their donor. Four categories of personality changes are discussed: (1) changes in preferences, (2) alterations in emotions/temperament, (3) modifications of identity, and (4) memories from the donor's life. The acquisition of donor personality characteristics by recipients following heart transplantation is hypothesized to occur via the transfer of cellular memory and four types of cellular memory are presented: (1) epigenetic memory, (2) DNA memory, (3) RNA memory, and (4) protein memory. Other possibilities, such as the transfer of memory via intracardiac neurological memory and energetic memory, are discussed as well. Implications for the future of heart transplantation are explored including the importance of reexamining our current definition of death, studying how the transfer of memories might affect the integration of a donated heart, determining whether memories can be transferred via the transplantation of other organs, and investigating which types of information can be transferred via heart transplantation. Further research is recommended.

INTRODUCTION

The transfer of personality characteristics from one person to another following heart transplantation has been reported for nearly half a century [1]. However, this phenomenon has not been well researched and is not well understood. Possible explanations for this paucity of investigation include the absence of a mechanism to explain such personality changes and skepticism regarding whether such changes are possible. But, neither the lack of an adequate explanatory model nor doubts regarding the existence of such changes disprove the occurrence of this experience.

The first human to human heart transplant, performed by South African surgeon Christiaan Barnard on December 3, 1967, created a worldwide swell of excitement [2]. However, early enthusiasm dissipated in the 1970's when many centers stopped transplanting hearts due to disappointingly poor survival rates [3,4]. Subsequently, improvement in early diagnosis, the emergence of immunosuppressant medications, and enhanced patient selection criteria revitalized the field of cardiac transplantation [5], with one-year survival rates increasing from 20% in the 1960s, to 80-85% in the 1980s [6,7].

Once the problem of rejection was solved, survival rates lengthened and the focus of research shifted from quantity to quality of life [7-9]. Investigators found heart transplant recipients experienced positive post-surgical changes such as feelings of euphoria [10], improved cognitive functioning [11], and improved social and sexual adjustment [12]. Some even described having religious experiences [13].

However, not all changes were positive. Distressing sequelae were also discovered, with as many as 30 percent of recipients experiencing post-transplant issues [14] including psychosocial problems [5] and emotional distress [15-18]. Descriptions of psychiatric problems included reports of delirium [12], depression, anxiety [3,7,19], psychosis [1,13], and personality changes [7,20].

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Prior to undergoing surgery, some transplant candidates expressed fear they would acquire the personality characteristics or behaviors of their donor [21,22]. Although such concerns were labeled “irrational” [22], numerous transplant recipients described experiencing such changes following surgery [10,13,20,23-25]. These changes occurred despite strong prohibitions against sharing information with recipients about their donors.

Accounts of recipients’ acquiring personality traits of their donor following heart transplantation challenge the notion that the heart is “just a pump,” and highlight a major gap in our understanding of such experiences. In order for personality changes to occur, some form of memory transfer must transpire between the donor and recipient. But, the traditional neuroscientific view is that memory is a function of the brain, not the heart, rendering such a transfer of memory unlikely at best or, even more credibly, impossible.

Early psychological interpretations of reports describing the transmission of personality characteristics following heart transplantation were based upon psychoanalytical concepts. When the first heart transplants occurred in the 1960s, psychoanalysis was a major theoretical framework in psychiatry and therefore early theories about personality changes following heart transplantation were based upon psychoanalytic concepts and the view that the heart is “just a pump.” Examples of psychoanalytic explanations for such personality changes included “incorporation fantasies” [5,10,20] and “magical thinking” [23]. However, contemporary research into cellular memory suggests our historical views may be outdated and in need of revision.

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THE HYPOTHESIS

This article hypothesizes that cellular memory contributes to personality changes following heart transplantation surgery in which the recipient assumes personality traits of the donor. Memories from the donor's life are hypothesized to be stored in the cells of the donated heart and are then "remembered" by the recipient following transplant surgery. Possible mechanisms by which memories may be stored are discussed including epigenetic memory, DNA memory, RNA memory, protein memory, intracardiac neurological memory, and energetic memory.

EVALUATION OF THE HYPOTHESIS

Personality changes following heart transplantation

A literature review was performed to explore accounts of personality changes following heart transplantation and four categories of changes were identified: (1) changes in preferences, (2) alterations in emotions/temperament, (3) modifications of personal identity, and (4) memories from the donor's life. Examples from each category are listed below.

Changes in preferences

Food preference

Changes in food preferences are reported by numerous individuals and include differences in both the types of food preferred as well as the amount of food eaten. For

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example, a 29-year-old woman who received the heart of a 19-year-old donor who was a vegetarian related: “I hate meat now. I can’t stand it. I was McDonald’s biggest money maker, and now meat makes me throw up. Actually, when I even smell it, my heart starts to race” [24, p. 69].

Another example comes from a 47-year-old male recipient who experienced a change in his reaction to food following transplantation. The donor was a 14-year-old gymnast who often skipped meals and would sometimes purge. The recipient explained: “. . . there’s something about food. I don’t know what it is. I get hungry, but after I eat, I often feel nauseated and that it would help if I could throw up” [24, p. 69].

A third example was offered by a 48-year-old female recipient who developed a sudden taste for green peppers and chicken nuggets after her transplant, foods she never liked previously. In fact, as soon as she was allowed to drive after surgery, the recipient drove to Kentucky Fried Chicken and ordered chicken nuggets. Later, when she met her donor’s family, she asked if he liked green peppers. The response was, “Are you kidding? He loved them. . . But what he really loved was chicken nuggets” [25, p. 184]. The recipient later learned that when her donor was killed in a motorcycle accident, a container of chicken nuggets was removed from beneath his jacket [25].

Musical preference

A different change in preference involves an altered inclination for music. In a study by Bunzel and colleagues, a 45-year-old recipient who received the heart of a 17-year-old boy reported: “I love to put on earphones and play loud music, something I never did before. . .” [20, p. 254].

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Another example comes from an 18-year-old girl who received the heart of an 18-year-old boy killed in a motor vehicle accident. She described, “I could never play before, but after my transplant, I began to love music. I felt it in my heart. My heart had to play” [24, p. 66]. The donor was a musician who played the guitar.

A third example comes from a 47-year-old white male foundry worker who received the heart of a 17-year-old African American male killed in a drive-by shooting. The recipient described, “I used to hate classical music, but now I love it. So I know it’s not my new heart, because a black guy from the hood wouldn’t be into that. Now it calms my heart. I play it all the time. I more than like it” [24, p. 68].

The recipient’s wife elaborated: “. . . he’s driving me nuts with the classical music. He doesn’t know the name of one song and never, never listened to it before. Now, he sits for hours and listens to it. He even whistles classical music songs that he could never know” [24, p. 68]. The donor’s mother reported, “Our son was walking to violin class when he was hit. Nobody knows where the bullet came from, but it just hit him and he fell. He died right there on the street hugging his violin case. He loved music and his teachers said he had a real thing for it. He would listen to music and play along with it” [24, p. 68].

Sexual preference

Several recipients describe changes in sexual preference after obtaining a new heart. A 25-year-old male who received the heart of a 24-year-old female lesbian artist reported: “Since my surgery, I’ve been hornier than ever and women just seem to look even more erotic and sensual. . . I’m different. I know I’m different. I make love like I

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know exactly how a woman's body feels and responds - almost as if it is my body. I have the same body, but I still think I've got a woman's way of thinking about sex now" [24, p. 67-68].

A 29-year-old lesbian woman who received the heart of a 19-year-old heterosexual woman described experiencing a change in her sexual preference following her transplant: ". . . I'm engaged to be married now. He's a great guy and we love each other. The sex is terrific. The problem is, I'm gay. At least, I thought I was. After my transplant, I'm not . . . I don't think anyway . . . I'm sort of semi- or confused gay. Women still seem attractive to me, but my boyfriend turns me on. Women don't. I have absolutely no desire to be with a woman. I think I got a gender transplant" [24, p. 69].

Other preferences and aversions

Changes in preference for art and colors, as well as certain aversions are described following heart transplantation also. For example, a 25-year-old male graduate student who received the heart of a 24-year-old female landscape artist developed an interest in art following transplantation surgery. The recipient's girlfriend described: ". . . he loves to go to museums. He would never, absolutely never do that. Now he would go every week. Sometimes he stands for minutes and looks at a painting without talking. He loves landscapes and just stares. Sometimes I just leave him there and come back later" [24, p. 68].

A 48-year-old female dancer who received the heart of an 18-year-old male killed in a motorcycle accident found her preference for colors changed following her

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transplant: “I used to be drawn toward hot colors - red, pink, and gold. I had never liked blue or green and had rarely worn them, but ever since the transplant I’ve been attracted to these cooler colors, especially deep forest green. . . most men stay away from hot colors, as I now do” [25, p. 194-195].

Some recipients develop aversions after obtaining a new heart. For example, a 5-year-old boy received the heart of a 3-year-old boy but was not told the age or cause of his donor’s death. Still, he offered the following description of his donor following surgery: “He’s just a little kid. He’s a little brother like about half my age. He got hurt bad when he fell down. He likes Power Rangers a lot I think, just like I used to. I don’t like them anymore though” [24, p. 70]. The donor died after falling from an apartment window while trying to reach a Power Ranger toy that had fallen on the ledge of the window. After receiving his new heart, the recipient would not touch Power Rangers [24].

Another example comes from a 9-year-old boy who received the heart of a 3-year-old girl who drowned in the family pool. Although the recipient had no knowledge of his donor or how she died, he developed an aversion to water following his transplant. His mother explained, “Jimmy is now deathly afraid of the water. He loved it before. We live on a lake and he won’t go out in the backyard. He keeps closing and locking the back door walls. He says he’s afraid of the water and doesn’t know why” [24, p. 69].

Changes in emotions and temperament

Two types of emotional changes are reported following heart transplantation. First, some recipients experience specific emotions that they identify as originating from the donor. Second, recipients' temperament, or emotional reactivity to stimuli, is sometimes altered.

Changes in emotions

A 9-year-old boy who received the heart of a 3-year-old girl described experiencing emotions that he attributed to his donor: "She seems very sad. She is very afraid. I tell her it's okay, but she is very afraid. She says she wishes that parents wouldn't throw away their children. I don't know why she would say that" (24, p. 69).

The recipient's mother explained: "He (the recipient) doesn't know who his donor was or how she died. We do. She drowned at her mother's boyfriend's house. Her mother and her boyfriend left her with a teenage babysitter who was on the phone when it happened. I never met her father, but the mother said they had a very ugly divorce and that the father never saw his daughter. She said she had worked a lot of hours and said she wished she had spent more time with her [24, p. 69].

Changes in temperament

Some recipients describe changes in temperament after receiving a new heart. For example, one recipient stated, "The new heart has changed me. . . the person whose heart I got was a calm person, not hectic, and his feelings have been passed on to me now" [20, p. 254].

Changes in identity

Changes in personal identity are perhaps the most studied type of personality change following heart transplantation. Examples include a 19-year-old woman who

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received the heart of another woman. The recipient described her donor as follows: "I think of her as my sister. I think we must have been sisters in a former life. I only know my donor was a girl my age, but it's more than that. I talk to her at night or when I'm sad. I feel her answering me. I can feel it in my chest. I put my left hand there and press it with my right. It's like I can connect with her" [24, p. 70].

A 5-year-old boy, who was never told the age or name of his donor, related: "I gave the boy a name. He's younger than me and I call him Timmy. He's just a little kid. He's a little brother like about half my age. He got hurt bad when he fell down [24, p. 70]. The donor was a 3-year-old boy who died after falling from a window. His name was Thomas, but his family called him Timmy [24, p. 70].

Some individuals have dreams or memories of their donor's identity. For example, a 48-year-old female recipient wrote about a dream she had 5 months after her transplant: "It's a warm summer day. I'm standing in an open, outside place, a grassy field. With me is a young man who is tall, thin and wiry, with sandy colored hair. His name is Tim, and I think his last name may be Leighton, but I'm not sure. I think of him as Tim L." [25, p. 5].

Later, she learned her donor was an 18-year-old man named Tim Lamirande. This same woman later started a support group for heart transplant recipients and every member of the group described experiencing a shift in personal identity following transplantation surgery: ". . . all of us had some sense after the transplant that we were not alone. And each of us had at some point spontaneously experienced our new heart as an "other" with whom some form of communication was taking place. . . To a greater or lesser extent, each of us saw the new heart within us as representing a separate being" [25, p. 136].

Changes in memories

Some recipients describe "memories" that do not coincide with events from their own lives. These memories, which may occur during waking consciousness or sleep, include sensory experiences related to their donor. One individual related: "It's really strange, but when I'm cleaning house or just sitting around reading, all of a sudden this unusual taste comes to my mouth. It's very hard to describe, but it's very distinctive. I can taste something and all of a sudden I start thinking about my donor, who he or she is, and how they lived. After a while, the taste goes away and so do the thoughts, but the taste always seems to come first" [26, p. 113].

Tactile memories are described also. For example, a 29-year-old female recipient described feeling the impact of the car accident that killed her 19-year-old female donor. After the accident, but before she died, the donor wrote notes to her mother, who later revealed the contents of these notes, ". . . she kept saying how she could feel the impact of the car hitting them. She said she could feel it going through her body" [24, p. 69].

The recipient described her memories as follows: "When I got my new heart. . . almost every night and still sometimes now, I actually feel the accident my donor had. I can feel the impact in my chest. It slams into me, but my doctor said everything looks fine" [24, p. 69].

Some memories include visual information. A 56-year-old college professor received the heart of a 34-year-old police officer who was killed after being shot in the

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face while attempting to arrest a drug dealer. The recipient described: “A few weeks after I got my heart, I began to have dreams. I would see a flash of light right in my face and my face gets real, real hot. It actually burns” [24, p. 71].

Another recipient described a mixture of visual and tactile sensations following transplantation: “I’m driving fast, speeding around a series of hairpin turns and loving it. Suddenly I can’t make one of the turns, and I fly across the highway, over the divide and into the oncoming traffic. It’s a freeing, wild feeling, like flying in the air, a little like the end of Thelma and Louise as the car drives off the cliff. I’m no longer confined by the road, and I feel boundless” [25, p. 113]. The recipient’s donor was an 18-year-old man who died in a motorcycle accident.

TRANSFER OF MEMORIES

The aforementioned examples offer evidence suggesting personality changes may occur following heart transplants in which the recipient acquires some personality characteristics of their donor. Such accounts raise the question, “What causes these changes?” In addition to the psychoanalytic interpretations previously discussed, several additional explanations have been offered. These include the effects of immunosuppressant drugs [26], preexisting psychopathology [19], and surreptitious acquisition of information about donors from press stories [1]. Dossey proposed the consciousness of the donor and recipient are connected via nonlocal mind [27] whereas Pearsall and colleagues [24] suggested cellular memory might play a role.

One of the most important issues that must be addressed when attempting to understand how personality traits might be acquired following heart transplantation is explaining how memories can be transferred from donor to recipient. In order for a

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transplant recipient to acquire the personality traits of their donor, information about the donor must be stored and then transferred to the recipient with the heart. This transfer of memory is hypothesized to occur via cellular memory.

Cellular memory

Memory is defined as “the capacity of an individual to acquire, store, and retrieve information” [28] and three stages of memory are typically described: (1) acquisition/encoding, (2) consolidation, and (3) retrieval [29]. Memory is typically ascribed to the brain and an abundance of research demonstrates a robust relationship between memory and the addition, elimination, and remodeling of synapses in the brain [30].

Although memory is customarily attributed to changes in the nervous system, other types of memory exist as well. For example, immunological memory involves the immune system’s ability to remember pathogens, tumor cells, and to distinguish self from non-self tissues [31]. Immunological memory is not stored in synapses or neurons, but instead resides in the cells of the immune system.

Cellular memory has previously been suggested to explain the transfer of personal memories from donor to recipient following heart transplantation [24]. Although the existence of cellular memory has been controversial in the past, research in the fields of genetics and epigenetics provides ample evidence supporting the existence of cellular memory. Furthermore, contemporary research has discovered the existence of numerous types of cellular memory [32].

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Epigenetic memory

Epigenetics is the study of factors that influence transcription of the genome without altering the DNA sequence. The human genome consists of 23 pairs of chromosomes and each chromosome is constructed of a complex of DNA and histone proteins known as *chromatin*. This DNA/histone complex is called a *nucleosome*, and nucleosomes are connected by short strands of amino acids and accompanying DNA, creating the appearance of beads on a string [33].

Epigenetic changes occur when enzymes attach or remove specific molecules to or from chromatin, or when RNAs are produced, resulting in a modification of gene expression. Examples include DNA methylation, histone modification, and the production of miRNAs. This entire process can either enhance or suppress the production of a gene's product [34]. Persisting epigenetic changes create an *epigenetic code* that determines whether a specific gene is transcribed [35] and encode information that can be stored and retrieved over time. The entirety of an individual's epigenetic changes at any given point in time is known as the *epigenome* [36].

Information saved in the epigenome provides a historical record of interactions between an individual and the environment. Stored via chemical and structural alterations of chromatin or short strands of RNA, this information persists as a type of cellular memory known as *epigenetic memory*. In some cases, *epigenetic memory* can be passed down to an individual's progeny through a process known as *transgenerational epigenetic inheritance* or *epigenetic inheritance* [37-39].

The epigenome provides a mechanism for encoding, storing, and retrieving interactions between the environment and an individual's genome, similar to the way the

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genome provides a historical record of the interactions between a species and its environment.

The existence of epigenetic memory in no way negates the existence of neuronal memory. Rather, epigenetic memory and neuronal memory serve as unique pathways, demonstrating that multiple mechanism can be utilized to encode, store, and retrieve information.

DNA memory

Another type of memory involves the storage of information in DNA. DNA is capable of storing large amounts of information, as researchers from the European Bioinformatics Institute demonstrated when they created a strand of synthetic DNA in which they encoded all 154 of Shakespeare's sonnets, a copy of Watson and Crick's 1953 paper describing the molecular structure of DNA, a color photograph of the European Bioinformatics Institute, a 26 second excerpt from Martin Luther King's 1963 "I Have A Dream" speech, along with the code used to convert bytes to base-3 digits. They stored this information in 4 different formats (ASCII text, PDF, JPEG, and MP3), then shipped the synthetic DNA at ambient temperature from the United States to Germany using no special packaging. The DNA sequences were then decoded and the original digital files were reconstructed with 100 percent accuracy [40].

Cardiocytes, as well as most other cells throughout the body, secrete extracellular, membrane-enclosed microvesicles known as *exosomes* [41,42]. Exosomes are small (i.e. 30-150 nm) packages of proteins, nucleotides, and receptors that travel throughout the body delivering their contents to other cells, thus providing a means of intercellular and multiorgan communication [41-45].

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Exosomes are known to contain double-stranded genomic DNA that spans all chromosomes [45,46]. This DNA can be transferred to recipient cells, resulting in the *horizontal* or *lateral transfer of DNA* [47]. Once the DNA is released into the cytosol of recipient cells, it localizes to the nucleus and is transcribed [47].

Could DNA be transferred from a donor's heart to a recipient's body? No research could be found investigating this possibility, yet it appears plausible that horizontal gene transfer via exosomes could provide a mechanism for the transfer of information/memories from donor to recipient.

RNA memory

Another form of cellular memory that could mediate the transposition of memories from donor to recipient involves the transfer of RNA. Ribonucleic acid (RNA) is structurally similar to DNA with the exception of three differences: (1) RNA is a single strand whereas DNA is double stranded, (2) the sugar that forms the backbone of RNA is ribose whereas the sugar in DNA's backbone is deoxyribose (deoxyribose contains one less oxygen atom than ribose), and (3) the DNA nucleotide thymine is replaced with the nucleotide uracil in RNA.

RNA is produced when a single strand of DNA is copied through the process of *transcription*. RNA may then be converted into a protein via *translation*. However, less than 2% of the human genome codes for proteins [48]. The remaining 98%, which for decades was considered "junk" DNA, is transcribed into *non-coding RNAs* (*ncRNAs*), which performs a variety of functions [49]. ncRNAs are subdivided into *long non-coding RNAs* (*lncRNA*) (>200 nucleotides in length) and *small non-coding RNAs* (*sncRNA*) (<200 nucleotides in length).

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Exosomes contain a wide variety of RNA species including miRNA, transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), and piwi-interacting RNA (piRNA) [50,51]. Once secreted by donor cells, RNAs can be taken up by recipient cells where they influence the function of those cells [52].

A recent study demonstrated the ability of RNA to transfer information between individuals. Using the sea mollusk *Aplysia*, Bedecarrats and colleagues demonstrated that memories can be transferred from one individual to another [53]. First, they trained animals to respond to an electrical shock to their tails. They did this repeatedly to establish *long-term memory* (*LTM*). Then, they removed RNA from the trained animals and injected it into naïve animals. The naïve animals responded as if they had been trained to respond to the electrical shock, thus demonstrating that long-term memory can be transferred via RNA.

The demonstration that LTM can be stored in cells and then transferred between individuals via RNA suggests heart transplant recipients might be capable of receiving LTM from their donors via the transfer of RNA in exosomes produced by the donors cardiac cells.

What types of memories could be transferred? In the case of Aplysia, sensory neuron hyperexcitability was transferred. Such heightened responsiveness to sensory input could be expected to underlie changes in preferences for food, music, art, sex, etc. which have been described in heart transplant recipients. Furthermore, sensory memories (e.g. visual memories such as flashes of light, and images of faces and tactile memories such as feeling a car wreck) might also be stored in RNA.

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Protein memory

Proteins are another possible vehicle for the transfer of memories from donor to recipient. De Ortiz and Arshavsky hypothesized long-term memories could be stored in nerve cells in the form of novel proteins that have been produced from recombinant DNA [54]. Although their hypothesis focused on the presence of proteins in cerebral neurons, it is possible that other neurons, such as cardiac neurons, might also contain novel proteins that store memories. Also, other types of cells, such as cardiocytes, might be capable of producing proteins that encode memories.

One specific type of protein involved in memory is *prions*. Prions are small, folded proteins that impose their three-dimensional shape on other proteins with similar amino acid sequences. These proteins were initially discovered as infectious agents (thus the name “prion” from “proteinaceous infectious particles”) responsible for neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) [55], but were later found to be involved in essential physiological roles, including synaptic plasticity and long-term memory [56].

Cytoplasmic polyadenylation element-binding protein 3 (CPEB3) is a protein with prion-like features that functions as an RNA-binding protein required for memory storage. Physiological signals trigger a change in the structure of this protein, triggering a change in protein synthesis. This modulation of protein synthesis occurs because in its basal state, CPEB3 binds to and represses translation of its target mRNAs in the brain [57]. However, when the structure of CPEB3 changes to an aggregated form, this protein becomes an activator of translation. Thus, a physiologically triggered conformational change in CPEB3 from its basal state to its aggregated form produces a

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change in this protein's function from a repressor to an activator of translation, thereby increasing protein synthesis, which produces structural synaptic changes that stabilize long-term memory [56,58-60].

Prions have been found to be highly expressed in exosomes, suggesting one possible mechanism by which these proteins may spread from cell to cell [61]. Exosomes facilitate the movement of proteins and other molecules between cells [62], thus facilitating intercellular communication [63]. Further studies are needed to investigate the role played by prions and other proteins with prion-like domains in the formation and storage of long-term memory, as well as the possible transfer of such memories via exosome encapsulated proteins between donor and recipient following heart transplantation.

Other types of memory

In addition to the various types of cellular memory discussed above, additional types of memory could contribute to the transfer of memories from donor to recipient. These include cardiac neurological memory and energetic memory.

Cardiac neurological memory

The heart has two distinct networks of nerves, one consisting of nerve cells within the heart and the other made up of nerves originating outside the heart. Both networks have the potential to encode, store, and retrieve memories. However, only the nerves within the human heart are transplanted with the heart. These nerves are known as the "*intracardiac nervous system*."

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The human *intracardiac nervous system* (ICNS) is made up of 700 - 1500 *intracardiac ganglia* (ICG), each composed of 200 - 1000 neurons. Groups of ICG combine with interconnecting nerves to form *ganglionated plexi* (GP), which are located in specific regions of the heart. Each group of ICG contains sensory, efferent, and interconnecting neurons that control multiple cardiac functions [64]. Based upon similarities with the cerebral brain, this complex system of neurons has been termed the “heart brain” [65].

Neurons in the heart communicate with one another via the release of neurotransmitters, many of which are also found in the brain. These include norepinephrine (NE), serotonin (5-HT), histamine (H), L-DOPA, dopamine (DA), acetylcholine (Ach), vasoactive intestinal peptide (VIP) and nitric oxide (NO) [64,66].

The intracardiac nervous system has been found to remodel itself after cardiac transplantation, a process known as *neuroplasticity* [67]. Neuroplasticity is one of the fundamental characteristics of the cerebral brain that is believed to be involved in the formation, storage, and retrieval of memories. Thus, it is possible that memories are stored within the intracardiac nervous system and are transferred to the recipient at the time of transplantation.

Energetic memory

Pearsall suggested personality changes following heart transplantation may result from changes in the energy of the heart. Pearsall equates energy with information, explaining: “energy and information are the same thing. Everything that exists has energy, energy is full of information, and stored info-energy is what makes up cellular memories” [26, p. 13].

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One type of energy is electromagnetic energy and one source of electromagnetic energy is the heart. The heart generates its own electromagnetic field, which is the largest such field in the body, producing an amplitude 60 times greater than the amplitude of the brain's electromagnetic field [68].

Is it possible that the body contains mechanisms for reading this electromagnetic field, similar to how "readers" analyze epigenetic changes and then modify gene expression? If so, what types of information might be obtained?

Descriptions from different cultures describe two types of information or knowledge, one located in the brain and the second centered in the heart. The ancient Greeks described these two types of knowledge as *diakresis* (i.e. rational or deductive knowledge) and *gnosis* (i.e. intuitive or spiritual knowledge). The source of the latter was attributed to the *nous*, an organ located in the region of the heart, which was also referred to as the "eye of the heart" [69, p. 360]. Ken Wilber described these two types of knowledge as *dualistic* and *non-dualistic* knowledge [70, p. 31], whereas William James referred to them as *conceptual* and *intuitive* knowledge [71, p. 154].

Intuitive knowledge transcends rational knowledge [72], allowing access to information from a source other than the brain. Although this type of knowledge is often ignored by contemporary Western science, it has been valued and relied upon by other cultures for thousands of years.

What types of information can be stored in electromagnetic energy? To answer this question, we need only turn on the radio, TV, or computer to find examples of information that is encoded, transmitted, and decoded as electromagnetic energy.

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Replacing one person's heart with the heart of another changes the recipient's electromagnetic field. If information is stored in the donor's electromagnetic field, as suggested by Pearsall [26], transferring information via heart transplantation could alter the recipient's personality via changes in preferences, emotions, temperament, memory, and identity.

CONSEQUENCES OF THE HYPOTHESIS

The improved success rate of heart transplantation following the introduction of cyclosporine in 1981 created an unintended problem - a growing list of people applied for organ transplantation, thus creating a relative shortage of organs for transplantation. An additional unexpected complication was the difficulty determining how to define death [73].

In the 19th century, death was declared when the heart and lungs stopped functioning [73], but in the 20th century this changed. Death came to be equated with "irreversible coma," as it was defined by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death [74, p. 361]. The concept of irreversible loss of brain function, known as "brain death" [74], was supported by physicians such as neurosurgeon Hannibal Hamlin who stated, "The human spirit is the product of a man's brain, not his heart" [75, p. 84]. However, some believe the identification of brain death was designed primarily to help transplant surgeons avoid legal complications, after more than one surgeon faced prosecution for wrongful death because he removed the organs from an individual for transplantation [74].

Yet, numerous reports exist of people recovering from apparent brain death. For example, orthopedic surgeon Mary Neal returned to life after drowning while kayaking

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[76]. American surgeon and assistant professor at Yale, Richard Selzer spontaneously returned to life 10 minutes after being declared dead while hospitalized for Legionnaires disease [77]. George Ritchie returned to life more than 10 minutes after being pronounced dead twice after succumbing to pneumonia [78]. Don Piper was pronounced dead twice, 90 minutes apart, before returning to life [79].

But, these and numerous other accounts of recovery from apparent death were not supported by objective measurements indicating cessation of electrical activity in the brain, leading some to question whether these individuals were truly dead. There is one report, however, that did include such measurements.

Cardiologist Michael Sabom described a 35-year-old woman who underwent surgery to repair a large basilar artery aneurysm. In order to successfully complete the surgery, the patient underwent a procedure known as “hypothermic cardiac arrest” in which she was connected to a cardiopulmonary bypass machine and then her blood was chilled before it was pumped back into her body, causing her body temperature to drop to 60 degrees. Her heartbeat was then stopped by an intravenous infusion of potassium chloride. Once her EEG showed no signs of electrical activity and auditory evoked potentials registered no brainstem activity, the cardiopulmonary bypass machine was shut off, the head of the operating table was raised, and the blood was drained from her body. After the neurosurgeon repaired the aneurysm, the cardiopulmonary bypass machine was restarted and warmed blood was infused back into the patient’s body. Shortly thereafter, the auditory evoked potentials began to register activity in the brainstem and the EEG showed activity in her cerebral hemispheres. When the electrocardiogram showed the patient was in ventricular fibrillation, the cardiac surgeon applied defibrillator panels to her chest. After shocking her heart with 50 joules, then 100 joules of electricity, her heart resumed normal sinus rhythm. The patient subsequently made a full recovery [80].

Despite the fact that discussions of cases such as these seem to inevitably become mired in debates about their possible physiological underpinnings (e.g. see 81,82), these and numerous other accounts seem to indicate that "death," whether it be attributed to cessation of the heart and lungs, or termination of brain activity, may be "reversible" in some cases.

According to the World Health Organization, 5,400 heart transplants were performed worldwide in 2008 [83]. In the U.S. alone, 3,408 heart transplants were performed in 2018 [84] and 73,510 people received heart transplants in the U.S. in the last 3 decades [85]. These numbers indicate that a large number of individuals have the potential to experience personality changes following heart transplantation surgery.

Although such personality changes have been reported for decades, this topic remains largely uninvestigated and many questions remain to be answered. How common are personality changes following heart transplantation? Are these changes temporary or permanent? Can changes occur despite recipients knowing nothing about their donor? What are the ramifications of transplanting a living heart from one individual into the body of another person? Is the donor "dead" if their brain has stopped functioning but their heart is still beating? Current medical and legal definitions unequivocally state the donor is dead once their brain ceases to function. But what if the donor's heart possesses personality traits such as preferences, emotions, and

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memories? Is the donor dead if their heart continues to sense and respond to the environment?

Does the recipient's experience of their donor's personality traits influence the likelihood of rejection? For example, if a recipient dislikes or feels uncomfortable with characteristics or personality traits of his/her donor are they more likely to reject the heart? On the other hand, if the recipient admires or has positive feelings about the traits of their donor, does this improve their ability to accept and integrate their new heart? Are heart transplant recipients more likely to experience personality changes than individuals who undergo transplantation of other organs, such as kidney or liver? If so, might this suggest that the high number of neurons found in the heart contribute to the personality changes?

Many questions regarding cellular memory remain to be answered as well. For example, what types of information can be stored in the epigenome, DNA, RNA, and proteins, and how resilient is this storage? What about identity? Can an individual's name be stored in their cells such that a heart transplant recipient could identify the name of their donor merely by decoding stored information in their heart? Further research is needed to answer these questions and others.

These questions and others are beyond the scope of this article but highlight important topics for future research. Our willingness to consider possibilities beyond the current widely accepted view that memory and personal identity are brain dependent will likely determine how quickly our knowledge in this area will advance. Further research has the potential to not only expand our knowledge about personality changes following heart transplantation, but also increase our understanding of the cellular basis

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of memory and biological contributions to personal identity. Such advances can help providers offer additional assistance to individuals undergoing heart transplantation, thereby facilitating the acceptance and integration of their new heart.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

[1] Lunde DT. Psychiatric complications of heart transplants. Am J Psychiatry 1969;126(3):117-21.

[2] Silbergleit A. Norman E. Shumway and the early heart transplants. Tex Heart Inst J 2006;33(2):274-5.

[3] Freeman AM, Watts D, Karp R. Evaluation of cardiac transplant candidates: preliminary observations. Psychosomatics 1984;25(3):197-9,202-3,207.

[4] Tilney NL. *Transplant: from myth to reality*. New Haven: Yale University Press; 2003.

[5] Bunzel B, Wollenek G, Grundbock A. Living with a donor heart: Feeling and attitudes of patients toward the donor and the donor organ. J Heart Lung Transplant 1992;11(6);1151-5.

Journal Pre-proofs

[6] Harvison, A., Jones BM, McBride M, Taylor F, Wright O, Chang VP. Rehabilitation after heart transplantation: the Australian experience. J Heart Transplant 1988;7(5):337-41.

[7] Jones BM, Chang VP, Esmore D, et al. Psychological adjustment after cardiac transplantation. Med J Aust 1988;149(3):118-22.

[8] Lough ME, Lindsey EM, Shinn JA, Stotts NA. Life satisfaction following heart transplantation. J Heart Transplant 1985;4(4):446-9.

[9] O'Brien BJ, Buxton MJ, Ferguson BA. Measuring the effectiveness of heart transplant programmes: quality of life data and their relationship to survival analysis. J Chronic Dis 1987;40(Suppl 1):137S-158S.

[10] Castelnuovo-Tedesco P. Organ transplant, body image, psychosis. Psychoanal Q 1973;42:349-63.

[11] Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. Acta Neurol Scand 1995;91(4):260-5.

[12] Mai FM. Psychiatric aspects of heart transplantation. Br J Psychiatry 1993;163:285-92.

[13] Kraft AI. Psychiatric complications of heart transplantation. Semin Psychiatry 1971;3(1):58-69.

[14] Mauthner OE, De Luca E, Poole JM, et al. Heart transplants: identity disruption, bodily integrity and interconnectedness. Health (London) 2015;19(6),578-94.

Journal Pre-proofs

[15] Burker EJ, Evon DM, Losielle M, Finkel JB, Mill MR. Coping predicts depression and disability in heart transplant candidates. J Psychosom Research 2005;59(4):215-22.

[16] Dew MA, DiMartini AF. Psychological disorders and distress after adult cardiothoracic transplantation. J Cardiovasc Nurs 2005;20(5 Suppl):S51-66.

[17] Dew MA, Myaskovsky L, Switzer GE, DiMartini AF, Schulberg HC, Kormos RL. Profiles and predictors of the course of psychological distress across four years after heart transplantation. Psychol Med 2005;35(8):1215-27.

[18] Ross H, Abbey S, De Luca E. et al. What they say versus what we see: "hidden" distress and impaired quality of life in heart transplant recipients. J Heart Lung Transplant 2010;29(10):1142-9.

[19] Kuhn WF, Myers B, Brennan AF, et al., Psychopathology in heart transplant candidates. J Heart Transplant 1988;7(3):223-6.

[20] Bunzel B, Schmidt-Mohl B, Grundbock A, Wolleneck, G. Does changing the heart mean changing personality? A retrospective inquiry on 47 heart transplant patients. Qual Life Res 1992;1(4):251-6.

[21] Frierson RL, Lippman SB. Heart transplant candidates rejected on psychiatric indications. Psychosomatics 1987;28(7):347-55.

[22] Tabler JB, Frierson RL. Sexual concerns after heart transplantation. J Heart Transplant 1990;9(4):397-403.

[23] Inspector &, Kutz I, David D. Another person's heart: magical and rational thinking in the psychological adaptation to heart transplantation. Isr J Psychiatry Relat Sci 2004;41(3):161-73.

Journal Pre-proofs

[24] Pearsall P, Schwartz GE, Russek LG. Changes in heart transplant recipients that parallel the personalities of their donors. Integr Med 1999;2(2):65-72.

[25] Sylvia C, Novak W. A change of heart: a memoir. New York: Warner Books; 1977.

[26] Pearsall P. The heart's code: Tapping the wisdom and power of our heart energy. New York: Broadway; 1998.

[27] Dossey L. Transplants, cellular memory, and reincarnation. Explore (NY) 2008;4(5):285-93.

[28] Khalaf O, Graff J. Structural, synaptic, and epigenetic dynamics of enduring memories. Neural Plast 2016;2016:3425908.

[29] Poo M, Pignatelli M, Ryan TJ, et al. What is memory? The present state of the engram. BMC Biology 2016;14:40.

[30] Bailey CH, Kandel ER, Harris KM. Structural components of synaptic plasticity and memory consolidation. Cold Spring Harb Perspect Biol 2015;7(7):a021758.

[31] Zanetti M. Immunological memory [Internet]. Wiley Online Library 2001 [updated 2013 February 15; cited 2019 June 28]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470015902.a0000951.pub3

[32] D'Urso A, Brickner JH. Mechanisms of epigenetic memory. Trends Genet 2014;30(6):230-6.

[33] Hudson AJ. Consciousness and cell memory: a dynamic epigenetic interrelationship. Can J Neurol Sci 2011;38(5);681-8.

[34] Yao B, Christian KM, He C, Jin P, Ming GL, Song H. Epigenetic mechanisms in neurogenesis. Nat Rev Neurosci 2016;17(9):537-49.

Journal Pre-proofs

[35] Day JJ, Sweatt JD. Epigenetic mechanisms in cognition. Neuron 2011;70(5):813-29.

[36] National Human Genome Research Institute. Epigenomics fact sheet [Internet]. Bethesda, MD; [updated 2016 April 1; cited 2019 June 23]. Available from: https://www.genome.gov/about-genomics/fact-sheets/Epigenomics-Fact-Sheet

[37] Babenko O, Kovalchuk I, Metz GA. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev 2015;48:70-91.

[38] Bonduriansky R, Day T. Extended heredity: A new understanding of inheritance and evolution. Princeton, NJ: Princeton University Press; 2018.

[39] Greer EL, Beese-Sims SE, Brookes E., et al. A histone methylation network regulates transgenerational epigenetic memory in C. elegans. Cell Rep 2014;7(1):113-26.

[40] Goldman N, Bertone P, Chen S, et al. (2013). Toward practical high-capacity low-maintenance storage of digital information in synthesised DNA. Nature 2013; 494(7435),77-80.

[41] Davidson SM, Takov K, Yellon DM. Exosomes and cardiovascular protection. Cardiovasc Drugs Ther 2017;31(1):77-86.

[42] Poe AJ, Knowlton AA. Exosomes and cardiovascular cell-cell communication. Essays Biochem 2018;62(2):193-204.

[43] Pironti G, Strachan RT, Abraham D, et al. Circulating exosomes induced by cardiac pressure overload contain functional angiotensin II type 1 receptors. Circulation 2015;131(24):2120-30.

Journal Pre-proofs

[44] Waldentrom A, Genneback N, Hellman U, Ronquist G. Cardiomyocyte microvesicles contain DNA/RNA and convey biological messages to target cells. PLoS One 2012;7(4):e34653.

[45] Kalluri R, LeBleu VS. Discovery of double-stranded genomic DNA in circulating exosomes. Cold Spring Harb Symp Quant Biol 2016;81:275-80.

[46] Kahlert C, Melo SA, Protopopov A, et al. Identification of double-stranded genomic DNA spanning all chromosomes with mutated KRAS and p53 DNA in the serum exosomes of patients with pancreatic cancer. J Biol Chem 2104;289(7):3869-75.

[47] Cai J, Han Y, Ren H, et al. Extracellular vesicle-mediated transfer of donor genomic DNA to recipient cells is a novel mechanism for genetic influence between cells. J Mol Cell Biol 2013;5(4):227-38.

[48] Elgar G, Vavouri T. Tuning in to the signals: noncoding sequence conservation in vertebrate genomes. Trends Genet 2008;24(7):344-52.

[49] Gaudi S, Guffanti G, Fallon J, Macciardi F. Epigenetic mechanisms and associated brain circuits in the regulation of positive emotions: A role for transposable elements. J Comp Neurol 2016;524(15):2944-54.

[50] Huang X, Yuan T, Tschannen M, et al. Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC Genomics 2013;14:319.

[51] Li M, Zeringer E, Barta T, Schageman J, Cheng A, Vlassov AV. Analysis of the RNA content of the exosomes derived from blood serum and urine and its potential as biomarkers. Philos Trans R Soc Lond B Biol Sci 2014;369(1652):20130502.

Journal Pre-proofs

[52] Kosaka N, Iguchi H, Yoshioka Y, Takeshita F, Matsuki Y, Ochiya T. Secretory mechanisms and intercellular transfer of microRNAs in living cells. J Biol Chem 2010;285(23):17442-52.

[53] Bedecarrats A, Chen S, Pearce K, Cai D, Glanzman DL. (2018). RNA from trained Aplysia can induce an epigenetic engram for long-term-sensitization in untrained Aplysia. eNeuro 2018;5(3):ENEURO.0038-18.2018.

[54] De Ortiz S, Arshavsky Y. DNA recombination as a possible mechanism in declarative memory: a hypothesis. J Neurosci Res 2001;63(1):72-81.

[55] Prusiner SB, Bolton DC, Groth DF, Bowman KA, Cochran SP, McKinley MP. Further purification and characterization of scrapie prions. Biochemistry 1982;21(26):6942-50.

[56] Si K, Kandel ER. The role of functional prion-like proteins in the persistence of memory. 2016;8(4):a021774.

[57] Pavlopoulos E, Trifilieff P, Chevaleyre V, et al. Neuralized1 activates CPEB3: a function for nonproteolytic ubiquitin in synaptic plasticity and memory storage. Cell 2011;147(6):1369-83.

[58] Papassotiropoulos A, Wollmer MA, Aguzzi A, Hock C, Nitsch RM, de Quervain DJ. The prion gene is associated with human long-term memory. Hum Mol Genet 2005;14(15):2241-6.

[59] Fioriti L, Myers C, Huang YY, et al. The persistence of hippocampal-based memory requires protein synthesis mediated by the prion-like protein CPEB3. Neuron 2015;86(6):1433-48.

Journal Pre-proofs

[60] Rayman JB, Kandel ER. Functional prions in the brain. Cold Spring Harb Perspect Biol. 2017;9(1):a023671.

[61] Cheng L, Zhao W, Hill AF. Exosomes and their role in the intercellular trafficking of normal and disease associated prion proteins. Mol Aspects Med 2018;60:62-68.

[62] Hartmann A, Muth C, Dabrowski O, Krasemann S, Glatzel M. Exosomes and the prion protein: More than one truth. Front Neurosci 2017;11:194.

[63] Kramer-Albers EM, Hill AF. Extracellular vesicles: interneural shuttles of complex messages. Curr Opin Neurobiol. 2016;39:101-7.

[64] Durães Campos I, Pinto V, Sousa N, Pereira VH. A brain within the heart: A review on the intracardiac nervous system. J Mol Cell Cardiol 2018;119:1-9.

[65] Randall DC. Towards an understanding of the function of the intrinsic cardiac ganglia. J Physiol 2000;528(Pt 3):406.

[66] Kukanova B, Mravec B. Complex intracardiac nervous system. Bratisl Lek Listy 2006;107(3):45-51.

[67] Murphy DA, Thompson GW, Ardell, JL, et al., The heart reinnervates after transplantation. Ann Thorac Surg 2000;69:1769-81.

[68] McCraty R. The energetic heart: bioelectromagnetic communication within and between people. In: Rosch PJ, Markov MS, editors. Clinical Applications of Bioelectromagnetic Medicine. New York: Marcel Dekker; 2004. p. 541-62.

[69] Nikodimos, Makarios, editors. The Philokalia, volume 3. Palmer GEH, Sherrard P, Ware K (translators). London: Faber & Faber; 1984.

[70] Wilber K. The spectrum of consciousness. Wheaton, IL: Quest; 1973.

Journal Pre-proofs

[71] James W. The knowing of things together. In: McDermott JJ, editor. The writings of William James. Chicago: The University of Chicago Press; 1977. p.152-168.

[72] Suzuki DT. Studies in zen. Mansfield Centre, CT: Martino; 2013.

[73] Sharp LA. Organ transplantation as a transformative experience: anthropological insights into the restructuring of the self. Med Anthropol Q 1995;9(3):357-89.

[74] Lock M. Human body parts as therapeutic tools: contradictory discourses and transformed subjectivities. Qual Health Res 2002;12(10):1406-18.

[75] What is life? When is death? Time Magazine 1966;87(21):84.

[76] Neal MC. To heaven and back: A doctor's extraordinary account of her death, heaven, angels, and life again: A true story. Colorado Springs, CO: WaterBrook; 2012.

[77] Selzer R. Raising the dead: A doctor's encounter with his own mortality. New York: Penguin Books; 1993.

[78] Ritchie GG. Return from tomorrow. Grand Rapids, MI: Chosen Books; 1978.

[79] Piper D. 90 minutes in heaven: A true story of death and life. Grand Rapids, MI: Revell; 2004.

[80] Sabom M. Light and Death. Grand Rapids, MI: Zondervan; 1998.

[81] Woerlee GM. Could Pam Reynolds hear? A new investigation into the possibility of hearing during this famous near-death experience. JNDS, 2011;30(1):3-25.

[82] Carter C. Response to “Could Pam Reynolds hear?” JNDS 2011;30(1):29-53.

[83] World Health Organization. Transplantation [Internet]. Geneva: World Health Organization; 2019 [cited 2019 June 26]. Available from: https://www.who.int/transplantation/gkt/statistics/en/

Journal Pre-proofs

[84] U.S. Department of Health & Human Services. Organ Donor Statistics [Internet]. Rockville: Health Resources and Services Administration; 2019 January [cited 2019 June 26]. Available from: https://www.organdonor.gov/statistics-stories/statistics.html

[85] United Network for Organ Sharing. Data [Internet]. Richmond: United Network for Organ Sharing; 2019 [cited 2019 June 26]. Available from: https://unos.org/data/transplant-trends/

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CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to report.

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