A Tribute to Dr Robert J. White

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Received, June 3, 2017.
Accepted, June 18, 2018.

Robert J. White is probably best known as the first neurosurgeon to perform successful "cephalic exchange" on monkeys in 1971. However, he was also a pioneer in the field of neurosurgery and contributed tremendously to the field of neuroanesthesia and bioethics. White received medical training at the University of Minnesota, Harvard University, Peter Bent Brigham Hospital, and Mayo Clinic before becoming the first Chief of Neurosurgery at Metrohealth Hospital in Cleveland, Ohio. He made significant strides in the field of spinal cord cooling and hypothermia. White and his team was also the first to successfully isolate the monkey brain with retention of biological activity. In 2004 and 2006, White and colleagues were nominated for the Nobel Prize in Physiology and Medicine, with Harvey Cushing and Wilder Penfield being the only other 2 neurosurgeons ever to be nominated for the award. Aside from his career as a neurosurgeon, he was also an advisor to 2 popes and an advocate for animal research. By the end of his career, White performed over 10 000 brain operations and published over 1000 articles, which has pushed the frontiers of neurosurgical research.

KEY WORDS: Head transplant, History, Metrohealth Hospital, Robert White

Neurosurgery 0:1–8, 2018 DOI:10.1093/neuros/nyy321 www.neurosurgery-online.com

"Humble Bob" was the nickname of Dr Robert J. White, a man who contributed much to his community and to science (Figure 1). Although White was best known for his monkey "head transplant", or more accurately cephalic exchange surgeries, he was also an advocate for accessible healthcare, a giant in the field of bioethics, and a pioneer in the field of neuroscience.

EARLY YEARS

Born on January 21, 1925, White grew up in Duluth, Minnesota in a working-class family (Figure 2). White discovered his interest in the human brain while attending DeLaSalle High School in Minneapolis. After finishing high school at the age of 18, White entered the military and became a laboratory technician during the tail of World War II in 1944.[1] He was discharged as a staff sergeant at the age of 19 (Figure 3). Following his military service, White attended the University of St Thomas (1946-1949), but he stopped before his fourth year after a professor suggested that he should head straight for medical school without completing his Bachelor's degree. White promptly enrolled in the University of Minnesota Medical School for one year before transferring to Harvard Medical School in 1951 on full scholarship. There, he earned his medical degree cum laude in 1953.

PETER BENT BRIGHAM YEARS

White undertook his general surgery and neurosurgical training at Peter Bent Brigham Hospital and Children's Hospital in Boston. It was an exciting time, as the first successful kidney transplant had been performed at Peter Bent Brigham Hospital in 1954, which may have inspired White's ambitious cephalic exchange procedures in the future. While performing an appendectomy in his junior general surgery year, White met his future wife, Patricia Murray, a nurse assisting with the case. They later went on to have 10 children: 4 daughters and 6 sons.

At Brigham, White met Dr Donald Matson who later became the Chief of Neurosurgery. Matson saw White's aptitude for neurosurgery and encouraged him to pursue a career in the field.[2]

MAYO CLINIC YEARS

Following Dr Matson's advice, White pursued a neurosurgical fellowship at Mayo Clinic

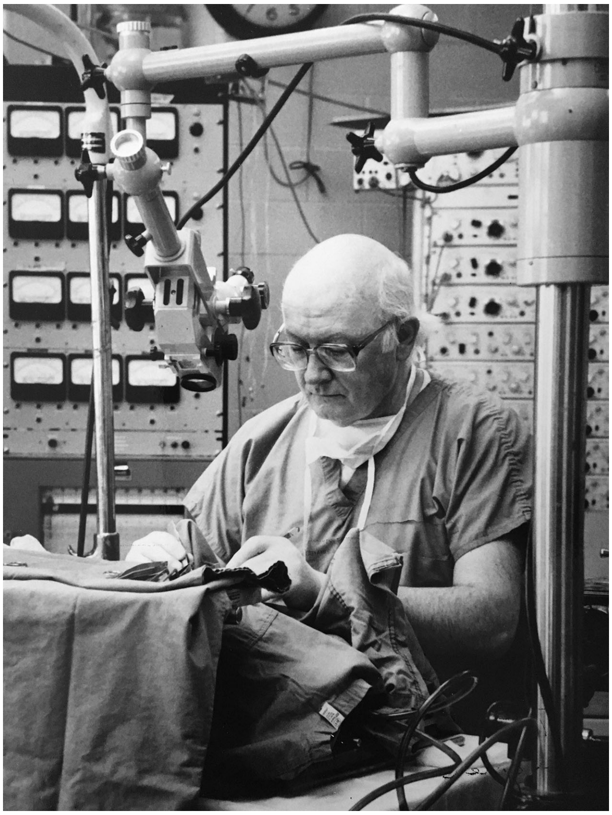

FIGURE 1. *Photograph of Dr Robert J. White performing a brain operation. Photo courtesy of Ruth White.*

(1955-1959) and was appointed Assistant to the Staff and Research Associate. Soon after starting his fellowship, White was disappointed by the poor outcomes of spinal cord trauma surgery and became interested in developing methods to improve these outcomes through both basic science and clinical research. The use of hypothermia in cardiac surgery had been under clinical investigation since the 1950s.[3,4] However, the belief that damage to the spinal cord was not amenable to treatment, even after hypothermic cooling, limited its utility in neurosurgery. White had a different opinion: "I recall vividly seeing the exposed spinal cord after a laminectomy a few hours after injury in patients who were totally quadri- or paraplegic.... Yet, I was amazed that the spinal cord, aside from localized swelling and a small amount of subarachnoid and subpial bleeding, so frequently demonstrated anatomic integrity".[5,6]

White teamed up with Dr David Donald to develop a technique where they could selectively cool the brain by pumping blood from the femoral artery through a Brown-Harrison heat exchange unit to the common carotid artery through a T cannula. Cerebral ischemia was induced by dividing the first 4 or 5 intercostal arteries and bilateral mammary arteries between ligature and clamping the brachiocephalic and left subclavian arteries at their aortic origins. Lowering the temperature of the brain to below 15°C protected the tissue against an otherwise fatal ischemia. However, the technique required continuous anticoagulation due to increases in apparent viscosity of the blood at lower temperatures.[6] The duo deemed this inappropriate for acute trauma patients who often had other injuries and were at risk for hemorrhage.

In White's point of view, the main obstacle to applying hypothermia following spinal cord trauma was the difficulty in selectively cooling the spinal cord and the preservation of neural integrity without inducing further injury. White worked with William Hitselberger on a model for subarachnoid cooling. They inserted a silastic catheter beneath the dura, secured it with sutures at the fourth to fifth lumbar segment, and cooled the spinal cord with 0.85% sodium chloride solution at 5°C. This model selectively cooled the spinal cord without significantly affecting core body temperature. However, Hitselberger's departure left the project on hold for several months until White was introduced to Maurice S. Albin, a neuroanesthesiologist.[5] Undeterred by his previous experimental failures, White went on to conduct some of the most ambitious neurosurgical research with Albin.

Albin described White as a "deceptive individual in the sense that underneath his truly cheerful, kind, and jovial visage lay an extraordinary erudite person graced with consummate surgical skill, a near eidetic memory, a great sense of humor, and innate kindness."[6] Together, White and Albin developed an anterior-inferior neck approach for safely exposing the basilar artery and measuring the physiological response after ligation of the basilar artery in rhesus monkeys.[7] They used a wire-spiral endotracheal tube in their technique to ensure airway patency when displacing midline structures to increase the field of view. They demonstrated for the first time that animals closely akin to humans could survive ligation of the basilar artery with minimal postoperative deficits.

In the 1960s, the scientific community knew that freezing temperatures induced neural fiber degeneration in vitro; however, little was known about the direct effects of hypothermia on the nervous tissue in vivo due to limitations of whole-body cooling techniques. White and Albin thus carried out experiments to study the effects of cold temperature on the canine spinal cord using the selective cooling model devised earlier. Their 1963 publication demonstrated that cooling the spinal cord to a temperature of 5.86°C–6.33°C for 4 h was not associated with neurological sequelae nor evidence of histopathologic damage to the cord.[8]

White was not only productive in the clinical arena during his 6 year at Mayo, he also received his PhD from the University of Minnesota. His thesis involved experimental total hemispherectomy in monkeys, demonstrating the viability of the procedure as a potential treatment for large tumors or intractable epilepsy.[9] His mentors, Collin S. MacCarty, chairman of neurosurgery at Mayo, and John H. Grindlay, a professor in the division

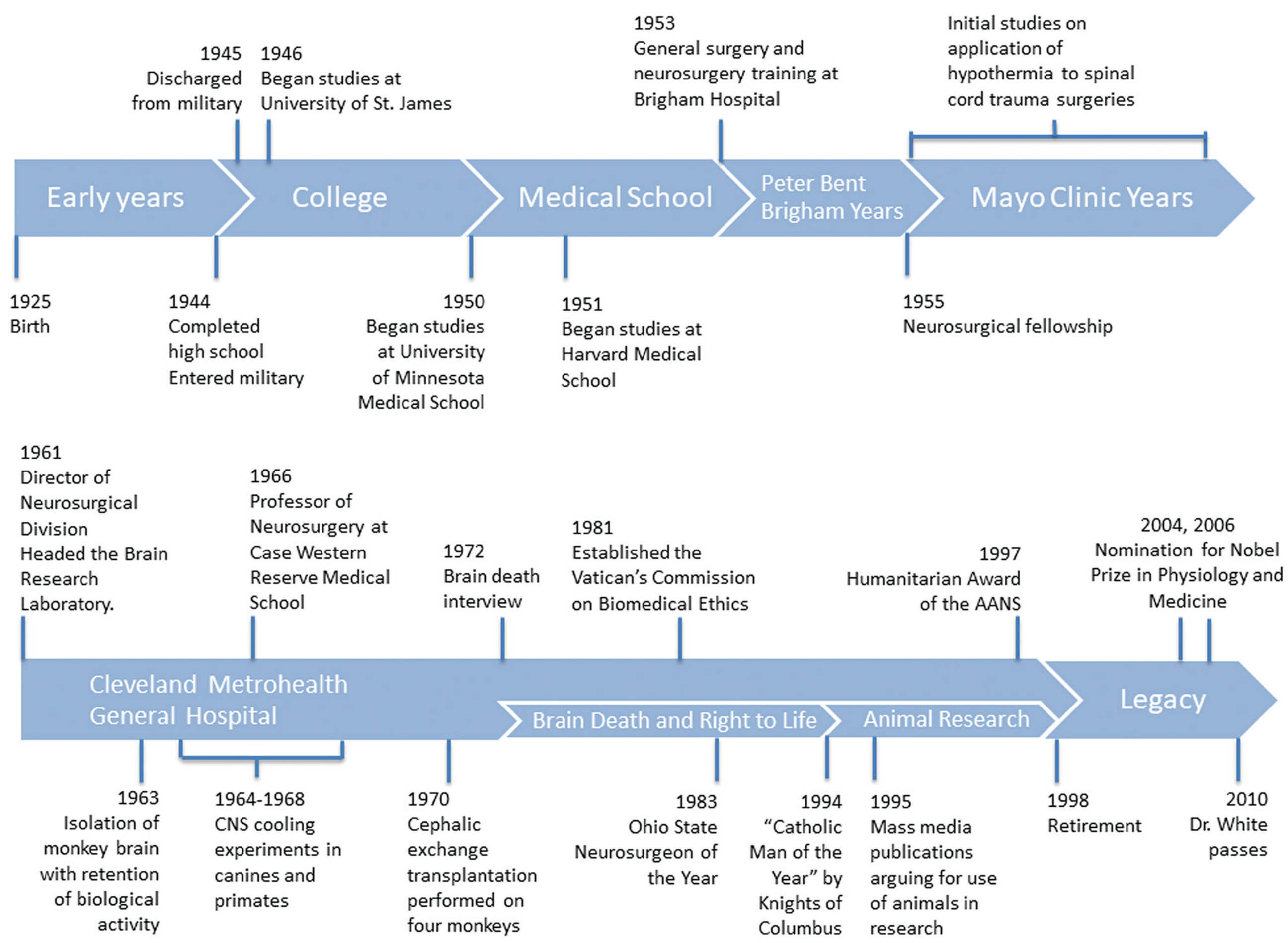

FIGURE 2. *Timeline of Dr White's personal and professional life.*

of experimental medicine at Mayo, helped guide his research during this time. In 1962, White formally received his PhD degree in neuroscience from the University of Minnesota and he continued to apply animal research into his future investigative endeavors.

METROHEALTH GENERAL HOSPITAL YEARS

In 1961, White assumed the position of director for the Neurosurgical Division of Cleveland Metrohealth General Hospital and headed the Brain Research Laboratory. In 1966, he was appointed professor of Neurosurgery at Case Western Reserve University School of Medicine, a position that he held for 40 year, and in 1970, he became the co-chairman of Neurosurgery. During this time, White revolutionized the field of neurosurgery through his work on cerebral hypothermia, isolation of the mammalian brain, and cephalic exchange.

Shortly after White started at Metrohealth General Hospital, Albin joined him as a member of the Anesthesiology Department. In their 1966 publication, they selectively cooled canine brains using a femoral to carotid arterial perfusion circuit without an oxygenator. The hypothermia protected the brain against cerebral ischemia and reduced the time for anticoagulation therapy.[10] Two years later, they demonstrated that spinal cord cooling in monkeys following a 4-h delay after a T-10 spinal cord injury reduced swelling of the cord; 50% of the monkeys were able to climb and run within 3 d after the operation.[11] These astounding results merited a trial in humans. White and Albin tested the effect of spinal cord cooling in seriously injured patients. Although spinal cord cooling could not be initiated prior to 6 h post-injury in any of the patients, the neurological outcomes often exceeded their

FIGURE 3. *Photograph of a young Robert J. White standing beside his mother after returning home from World War II as Staff Sergeant (circa 1945). Photo courtesy of Ruth White.*

expectations.[12] Unfortunately, the trial occurred during an era of malpractice controversy. With these severely injured patients often being high risk and in critical conditions, they were forced to terminate the study.[5]

One of White's other interests had always been the isolation and preservation of the brain to better study the organ. In 1963, White, Albin, and Verdura published the first successful total isolation of the monkey brain with retention of biological activity.[13] They eliminated all extracranial vasculature except for the internal carotid arteries and jugular veins (Figure 4). The carotid arteries were then cannulated to permit extracorporeal perfusion of freshly drawn, oxygenated, heparinized monkey blood from 5 matched donor rhesus monkeys. In a follow-up *Nature* study in 1964, the group reported the viability of the isolated monkey brain (Figure 5).[14] They demonstrated that the brain swelled 3 h after the initiation of extracorporeal circulation, and there was an associated decrease in electrocortical activity and increase in cerebrovascular resistance. Furthermore, an accumulation of cerebral metabolism breakdown products (high levels of lactate and pyruvate) was noted, along with gradually developing acidosis after 2 to 3 h. This was the first time researchers documented the viability of a primate brain as a completely isolated organ supported by mechanical circulation. In 1965, the team similarly isolated 6 canine brains and grafted them into the neck of recipient canines (Figure 6).[15] The authors noted difficulty in establishing cervical vascular connections between the carotid arteries of the isolated brain with the donor's proximal internal carotid via a siliconized stainless steel fork cannula. The transplanted brains remained viable for 6 to 48 h as indicated by electroencephalography activity and A-VO_2 as well as A-VCO_2 differences. Failures of the grafts were attributed to low arterial perfusion pressure by the recipient or to compromised venous outflow. No signs of tissue rejection were observed.[15] Finally, a year later, White and his team demonstrated that rewarming brains (stored for 2-4 h at $2 \pm 1°C$ without circulation) restored electroencephalographic and metabolic activities. However, rewarming perfusion for greater than 6 h resulted in irreversible cerebral edema.[16] As a result of these landmark studies on the isolation of the mammalian brain, Robert J. White, Maurice Albin, and Javier Verdura were nominated for the Nobel Prize in Physiology and Medicine in 2004 and 2006. The only other 2 neurosurgeons ever to be nominated for a Nobel Prize are Harvey Cushing and Wilder Penfield.[17] To this day, however, no neurosurgeon has received the award.

After successfully isolating the brain of canines and monkeys, White and his team announced that they would attempt to perform the first cephalic exchange involving rhesus monkeys (Figure 7). The surgery gained wide media attention and was referred to as the first ever "head transplant". Controversy shrouded the operation and divided the scientific community. The People for the Ethical Treatment of Animals even began to call Dr White, "Dr Butcher".[18] But the experiments carried on.

On March 14, 1970, White, along with his team of approximately 30 doctors, nurses, and technicians, performed cephalic exchange on 4 monkeys. They isolated the head from the donor monkey by severing the spinal cord and ligating all the vasculature except for the carotid arteries and jugular veins, which were directly sutured to the carotid and jugular veins of the recipient monkey heads. Continuous heparin infusion was required due to the possibility of clot formation from the direct vascular anastomoses. Three to four hours postoperatively, the recipients' heads demonstrated the ability to chew, swallow, track movement with eyes, and bite. The heads also performed learned responses from prior to the procedure, suggesting intact higher cortical function. Recording electroencephalograms showed awake activity patterns. The monkeys, however, were unable to move the transplanted body, as the spinal cords were not connected. With subsequent blood loss and the need for continuous mechanical respiratory support due to severing of the spinal cord, the monkeys survived for 6 to 36 h.[19] White and his team received a great amount of press and coverage. The idea of keeping the brain alive as an isolated organ and performing cephalic exchange in humans

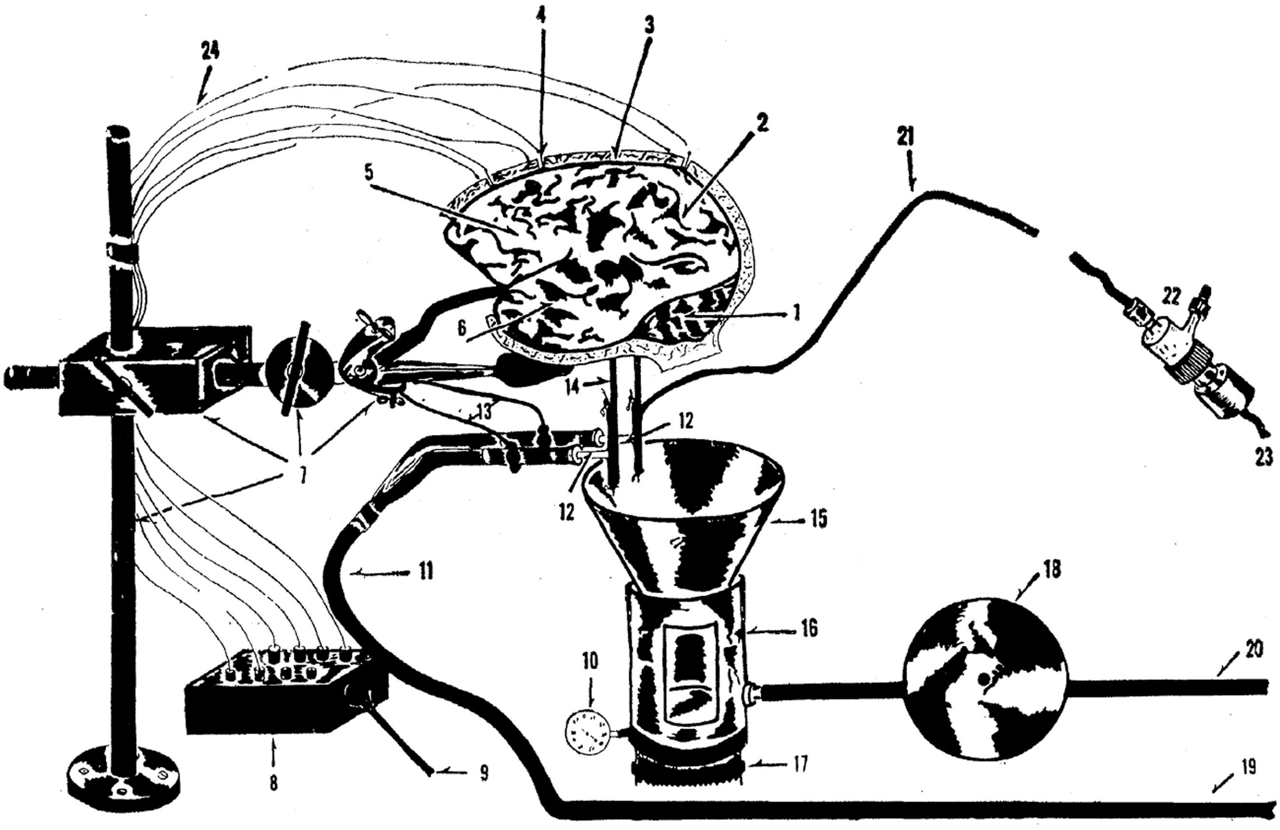

FIGURE 4. *Illustration of extracorporeal circulation preserving an isolated monkey brain. Labels: 1 - cerebellum, 2 – occipital lobe, 3 – skull with electrode, 4 – cortical electrodes, 5 – frontal lobe, 6 – temporal lobe, 7 – fixation unit, 8 – EEG plug-in-box, 9 – electrode cable connected EEG preamplifiers, 10 – venous reservoir thermistor, 11 – arterial line, 12 – carotid T cannulae, 13 – stirrup wire supporting arterial cannulae, 14 – internal carotid arteries, 15 – funnel for venous reservoir, 16 – venous reservoir, 17 – heater for venous reservoir, 18 – occlusive venous pump, 19 – arterial line from femoral artery of donor monkey, 20 – venous line to femoral vein of donor monkey, 21 – arterial pressure line, 22 – pressure transducer, 23 – cable connected to oscillographic recorder, and 24 – EEG leads. From White RJ, Albin MS, Verdura J. Isolation of the Monkey Brain: In Vitro Preparation and Maintenance. Science. 1963;141(3585):1060-1061.*[13] *Reprinted with permission from AAAS.*

seemed within reach. However, reconnecting the spinal cord between the recipient and the donor remains to this day to be achieved.

Despite protests and direct threats to him and his family, White still carried out the experiments. His goal was to push the boundaries of neurosurgery and medicine, so paraplegic patients and those with spinal cord diseases could one day have a better life. His daughter, Ruth, said that her father never let the protestors get to him, played it down in front of his family, and reassured them that everything will be ok.

With nearly 1000 publications, Dr White also performed extensive work in other areas of neurosurgery as well, including cerebrovascular disease, neuroendocrinology, and head injury.[20-26] Still, he considered the monkey cephalic exchange surgeries to be the centerpiece accomplishment of his scientific and medical career, and continued to give interviews to reporters all over the world well into his retirement.

THE PROFESSOR

White was praised as a great mentor at Metrohealth. Dr Likavec, the chair of Neurosurgery after White, said White was "a bundle of fun in the operating room" and he "loved what he did, was good at it, and he had an excitement about it…his excitement was infectious." White was always cheerful and loved making jokes, but was never distracted from patient care. According to White himself, he never had a malpractice suit against him during his entire career.

White's residents affectionately nicknamed him "The Professor". Each Saturday, White would hold meetings with

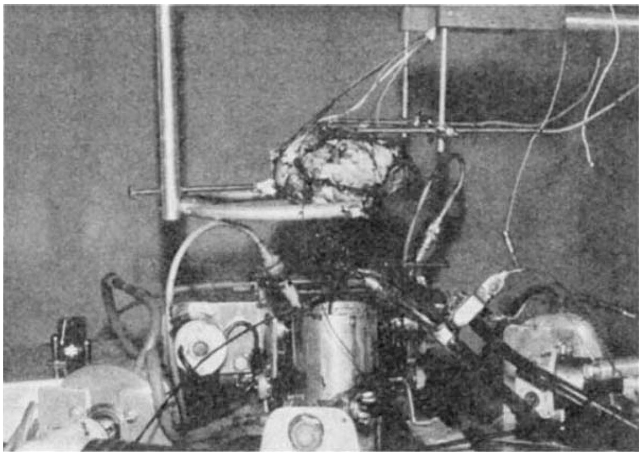

FIGURE 5. *Picture of isolated monkey brain preserved using a mechanical extracorporeal circulation. Reprinted by permission from Springer Nature, Nature, Preservation of Viability in the Isolated Monkey Brain Utilizing a Mechanical Extracorporeal Circulation, White RJ, Albin MS, Verdura J,*[14] *© 1964.*

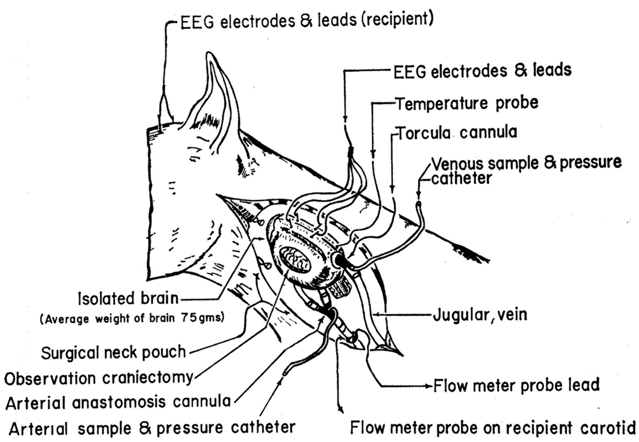

FIGURE 6. *Canine brain transplanted into a donor canine neck. The transplanted brain's perfusion was supplied by the recipient animal's carotid circulation. Venous return from the brain was provided through a torcula cannula that shunted the blood into the jugular vein of the recipient animal. A survey system was implanted to provide continuous measure of electrocortical activity, cerebral blood flow, temperature, A-VO2, V-ACO2, and glucose consumption. From White RK, Albin MS, Locke GE, Davidson E. Brain transplantation: prolonged survival of brain after carotid-jugular interposition. Science. 1965;150(3697):779-781. Reprinted with permission from AAAS.*

all the residents to plan for upcoming surgeries for the next week. Dr Likavec described these meetings as National Football League (NFL) chalkboard sessions. Despite little collaboration between the 3 major hospitals in Cleveland at the time (Cleveland Clinic, University Hospitals, and Metrohealth), White often invited neurosurgeons from these institutions to discuss interesting cases. He especially welcomed discussion of cases with complications.

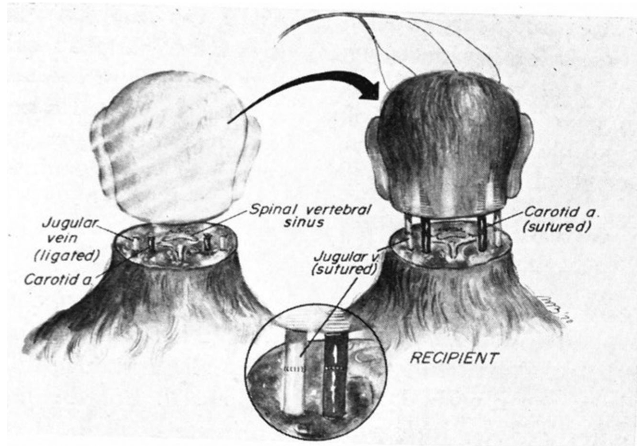

FIGURE 7. *Illustration of cephalic exchange by direct suture of the carotid and jugular vessels between the donor and recipient primate. Reprinted with permission from White et al.*[19] *This article was published in Science, 70(1), White RJ, Wolin LR, Massopust LC Jr, Taslitz N, Verdura J. Cephalic exchange transplantation in the monkey, 135–139, Copyright Elsevier 1971.*

He emphasized that the point of these meetings was never to criticize but to learn from mistakes.

BIOETHICS

The topic of brain death was not systemically studied until the Harvard Medical School Ad Hoc Committee published their report in 1968. Brain death, or irreversible coma, was characterized by[27]:

1. Unreceptivity and unresponsivity
2. No movements or breathing
3. No reflexes

There was controversy regarding withdrawal of care for brain dead patients and retrieving organs for transplantation as improvements in medical technology allowed the sustenance of vital functions despite a cessation in brain activity. Continued care for brain dead patients not only placed further burden on the patient, but also on their family, the hospital, and other patients that were in dire need of a hospital bed. In a radio interview in 1972, White stated, "when the brain is dead, the patient – or person – is dead."[1] White played an active role in supporting the validity of brain death both with the general public and with the Vatican, and called for its adoption during numerous interviews and articles. He was even invited to discuss the topic with Pope Paul VI in the 1970s. The debate within the medical community ultimately resulted in the passage of the Uniform Determination of Death Act in 1981.[28]

A devout Catholic, White also became close to Pope John Paul II (Figure 8), and was invited to join the Pontifical Academy of Science; White once joked that he had a direct line to the

FIGURE 8. *Photograph of Dr Robert J. White with Pope John Paul II. Reprinted with permission from Malchesky PS,*[29] *© 2011, Copyright the Author [Malchesky]. Artificial Organs © 2011, International Center for Artificial Organs and Transplantation and Wiley Periodicals, Inc.*

Pope. He served as an adviser to the Church and established the Vatican's Commission on Biomedical Ethics in 1981. Through the Commission, White would sway the church's stance on various topics, ranging from brain death and organ transplant to in vitro fertilization.[29] He also received several papal knighthoods. He was proud of these achievements with the Church as they confirmed his belief that science and religion could co-exist peacefully.[29] In 1994, the Knights of Columbus named White "Catholic Man of the Year".[2,29] His son, Robert, described his father as a man who "worked a lot to trying to bridge the gap between doctors and religious people."

White was also a proponent of animal research. To this end, he wrote several pieces in both scientific literature and popular media championing the necessity of animal research.[30] In a New York Times article in 1995, he stated "our understanding of neural tissue injury has been almost exclusively derived from animal studies… the linkage between animal research and clinical investigation has resulted in a drug that can improve neurological function in these patients".[31] However, White often met criticism and backlash for these views. Undiscouraged, White continued to argue for the ability of animal research to help advance medicine and provide not only insight into the physiology of the body, but also improvement to the lives of patients.

WHITE'S LEGACY

White passed away in 2010 in his Geneva Township after battling diabetes and prostate cancer. He was active in both teaching and writing well beyond his retirement in 1998. He would continue teaching at Metrohealth hospital until his retirement in 1998. Not only did White participated in numerous academic societies and received numerous awards for his accomplishments during his career, but he was also a down-to-earth and outspoken man who never shied away from a challenge, whether it be in the operating room, in research, or through debate.[2,32] One of Dr White's children, Michael, said, "my dad treated everyone the same, from the janitor to his colleagues."[33] Ruth, the youngest of his 10 children, said the reason why her father insisted on working at a rough county hospital rather than at a national institution was because "the connection between Metrohealth and Case Western Reserve University allowed him to conduct his research, and that working in a county hospital meant that he could never turn anyone away that was in need."[1]

White's research changed the approach to neurological surgeries and made cephalic exchange a potential reality. But White doesn't deserve to be only remembered as the neurosurgeon that performed the first cephalic exchange in monkeys; he was much more. He was an innovator in the field of neurosurgical research. He was and still is a model for the neurosurgical community, encouraging medical scientists to openly discuss difficult topics such as brain death and animal research. Finally, Dr White demonstrated that medicine can be used to push the boundaries of life and, with effort, knowledge, and a bit of audacity, give hope to those with hopeless diseases.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

We'd like to sincerely thank Ruth White, Robert White, and Christopher White (children of Robert White) for reviewing the article, answering questions regarding Robert White's personal life, and providing us with photographs. We thank Dr Matt Likavec, Emeritus Professor of Neurological Surgery at Case Western Reserve University, for an interview and providing us with information regarding Robert White's time at Metrohealth Hospital.

COMMENT

This biographical review outlines the professional accomplishments and personal attributes that marked a prolific and enthusiastic, if not at times controversial, neurosurgeon, the late Dr Robert J. White. The authors present his legacy not only of advanced neurosurgical technique but also of bioethical engagement and public policy. His projects of exchanging primate heads through anastomosing great neck vessels in a living model demonstrated all of these qualities. For these contributions, Dr White joined Harvey Cushing and Wilder Penfield as 1 of 3 neurosurgeons nominated (unsuccessfully) for the Nobel Prize in physiology and medicine.

A neurosurgeon with a dose of "audacity", Dr White embraced and then advanced the technology available to him, and he engaged publicly with several important debates of his time, including those bioethical conversations surrounding organ transplantation, animal research studies, and brain death diagnosis, all of which regularly affect neurosurgeons today. As such he exercised leadership in our field.

By reading this article, current neurosurgeons may receive all the benefits of historical inquiry: inspiration for their own researches, cautionary warnings regarding the limits of an individual, and the importance of collaboration in scientific advancement. The topic of cephalic exchange appears with increasing frequency in the popular media, even as many in the neurosurgery community know little of its pioneer, and engage infrequently in discussions of its ethical implications. The authors appropriately honor the noble intentions and lifetime dedication of Dr White to our field.

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