REVIEW ARTICLE

Brain Death – a review

Edward Oluwole **KOMOLAFE**, Fred Sunday **IGE-ORHIONKPAIBIMA**, Oluwafemi Funso **OWAGBEMI**, Ibironke Oluwakemi **OGUNBAMERU**

AFFILIATION
Neurosurgery Unit
Department of Surgery
Obafemi Awolowo University Teaching Hospitals Complex
Ile-Ife, Osun State, NIGERIA

CORRESPONDING AUTHOR
Edward O **KOMOLAFE**
P. O. Box 1836 Lagere Post Office, Ile-Ife, Osun State NIGERIA

E-mail: eokomolafe@hotmail.com
Phone: +234 803 344 7326

DISCLOSURES: NONE

ABSTRACT

Background: Brain death has been used synonymously with brainstem failure, irreversible coma, cerebral death, and cortical death. It became popular and of great interest with improvement in trauma care and the recent advances in resuscitative and life support technology.

Objective: To review the traditional concepts and criteria used to determine death.

Methodology: The literature was searched using the Pubmed, Medline and other search engines. Relevant literatures were reviewed and presented.

Result: These criteria are found to be constantly reviewed and sometimes revised with further technological advancements taking note of cultural, philosophical and religious aspects, as well as, autonomous principles of the local community.

Conclusion: Every physician, particularly those in the neurosciences, should be able to recognise, and confirm brain death as well as take decisions on what to do next. This is important because patients who are dead should not be treated as though they are alive, thereby, wasting the limited but expensive medical resources and facilities. Brain death is a clinical diagnosis without the need for costly and sophisticated equipment. However, in some situations, ancillary confirmatory tests such as the EEG and blood flow studies may be indicated.

Keywords: *Brain stem function, cardiopulmonary resuscitation, comatose, confirmatory testing, reflexes*

Received: 1st February, 2015 *Accepted: 13th February, 2015*

INTRODUCTION

There has always been some degree of uncertainty as to what constitutes death. Gaius Plinius Secondus (a Roman author popularly referred to as *Pliny the Elder*) who lived between 23AD and 76AD alluded to this fact by saying "so uncertain is men's judgement that they cannot determine even death itself".[1]

Death has been traditionally defined as the irreversible failure of the cardiopulmonary system that transports chemical nutrients and oxygen needed for continued life.[2] With the advent of cardiopulmonary resuscitation techniques, the cardiopulmonary definition of death lost its significance in favour of brain death.[3]

Brain death is defined as irreversible loss of the entire cerebral or brainstem function resulting in coma, absence of spontaneous respiration and loss of brainstem reflexes.[4] While in the United States of America whole brain death is recognized as being equivalent to death, brainstem death is equivalent to death in United Kingdom. This is based on the fact that the diagnosis of brainstem death is inevitably followed by asystole, and cognitive processing is incompatible with death of the midbrain.[3]

HISTORICAL PERSPECTIVE

Despite difficulties and controversies as to when a man dies, some religions have maintained that it is within the competence of medical profession to declare death. In 1957, Pope Pius XII affirmed that "it remains for the doctor to give a clear and precise definition of death and the moment of death of a patient who passes away".[5]

Wertheimer and colleagues first described the death of the nervous system in comatose patients with respiratory arrest being treated by ventilator.[6] It was, however, not until 1959 that two French neurologists, Mollaret and Goulon, in their landmark article described a state they termed *coma de' passe* which means "a state beyond coma", in a group of patients who had primary, irremediable structural brain lesions.[7]

The Harvard Medical School *Ad Hoc* Committee published the first criteria for the diagnosis of brain death in 1968 in a paper titled "A definition of irreversible coma" and advocated the withdrawal of life support for patients with coma, brainstem areflexia and apnoea after 3 minutes off ventilation with no evidence of electrical activity in the brain on electroencephalogram over a 24-hour period.[8]

In 1971, Mohandas and Chau introduced the concept of the existence of irreparable intracranial lesions with irreversible damage to brainstem as a pre-condition for the diagnosis.[9] By 1976, the Royal Medical Colleges conference had further modified the criteria for diagnosis of brainstem death to include the exclusion of conditions that may cause or contribute to coma.[10]

Other important historical aspects of brain death include the 1981 Uniform Determination of Death Act by the President's Commission for the Study of Ethical Problems in Medicine, as well as the 1994 American Academy of Neurology Guidelines for the determination of Brain Death, revised in 2010.[11,12,13] The latter emphasises the fact that the diagnosis is purely clinical. Ancillary tests can be performed if confounding factors are present, and in younger children.

The New York State Health Department Guideline first published in 2005, and revised in 2011, recommended notification of relatives

when the process of brain death diagnosis is to be instituted.[4]

EPIDEMIOLOGY

The exact incidence of brain death remains to be accurately documented.[1] Reports in the 80s put the incidence at 1% of all deaths in Japan and annual incidence of 4000 cases in UK.[14,15] In a recent review, diagnosis of brain death was made in 162 patients over a 5-year period in a tertiary hospital in Saudi Arabia. The mean age was 28+/-17 years with male predominance (92%).[16]

The diagnosis was made in 1251 patients between June 2007 and December 2009 in 100 New York hospitals.[17] Brain death is accepted in 80 countries, with 70 countries having practice guidelines, and 55 countries have a legal standard document on the practice.[18] There is no local study report from Nigeria.

AETIOPATHOGENESIS OF BRAIN DEATH

The human brain consists of the cerebral cortex which controls cognition, voluntary motor and sensory functions, and the brainstem consisting of the midbrain, pons and medulla oblongata. The brainstem, amongst other nuclei, contains the nuclei of cranial nerves III (pupillary reflex), IV and VI (conjugate eye reflex), V and VII (corneal reflex, sensation and facial grimace) and IX and X (gag and cough reflexes).

The reticular formation (RF) /activating system (RAS) is situated in the brainstem and mediates wakeful consciousness, control of heartbeat, breathing and circulation as well as coordination of acoustic, vestibular, respiratory and cardiovascular processes. The midbrain RF contains centres for visuospatial orientation and eating behaviour.

The average human brain (weighing about 1400g) constitutes only about 2% of the total body weight of a 70kg man, consumes about 3.5ml of oxygen per 100g/min. This is equivalent to about 49ml of oxygen/min and accounts for 20% of whole body oxygen consumption of 250mls/minute. This makes it one of the most metabolically active organs in the body.[19] This amount of oxygen consumption is needed for metabolism of glucose to maintain its electrical activities, i.e. the chemically driven excitation and conduction.

In order to maintain the cerebral appetite for oxygen, uninterrupted blood flow is required. Complete or partial interruption of cerebral blood flow will result in hypoxia or anoxia which can result in widespread death of neural tissues and even the whole of the brain in 8minutes.[1,19] Widespread ischaemic changes are common in brain death but there is no neuropathological finding that is diagnostic of brain death.[20] Severe head injury from road traffic accident accounts for over 50% of all Brain Deaths. It accounts for up to 82% in children.[21] Haemorrhagic shock topped the list of causes of brain death in a 2004 review in Argentina.[22]

Other causes of brain death include subarachnoid haemorrhage from aneurysmal rupture, massive intracerebral haemorrhage, prolonged cardiac arrest and fulminant hepatitis. Irrespective of the aetiology, diffuse brain oedema and increased intracranial pressure is the end result.[1] A rise in intracranial pressure results in reduced cerebral blood flow. This leads ultimately to neuronal death and cessation of cerebral and brainstem function when the intracranial pressure exceeds the mean arterial pressure.[23] Since the brain controls the cardiopulmonary

system, the death of the brain will, ultimately, lead to cardiopulmonary death.[24]

ASSESSMENT OF PATIENTS WITH SUSPECTED BRAIN DEATH

Death has been described as a process with a timeline that cannot be viewed as a one-time event with two dichotomous states.[24] As a result, there is need for physicians to determine the time a person enters a point of no-return from a rapid irreversible cause of death.[5,24] With advancing knowledge and better technology, this point of no-return can be pronounced earlier than before.

Better understanding of brainstem death clearly increases the number of patients in whom mechanical ventilation can electively be stopped following early diagnosis using brain death criteria. This will prevent wastage of resources on patients, in whom there will be no hope of recovery, avoiding an excessively long and tragic waiting period for the family as well as encouraging early consent for organ donation or harvesting of organs for research purposes where it is legally permissible.[23,25]

Most guidelines on brain death emphasise that clinical diagnosis is accurate, reliable and reproducible hence, confirmatory testing is not mandatory except in doubtful cases or when confounding factors hinder full bedside clinical evaluation. Confirmatory testing is obligatory in children especially those younger than 2years.[13,26,27] None of the physicians making the diagnosis of brain death must, however, be a party of interest in organ donation or transplantation.[28,29]

The practical aspects of declaring brain death – the specialty and training of the physician, number of observers, timing of first clinical examination and requirement for repeat examination – vary across the world.[30] The clinical evaluation can be done by any physician trained in the art in some countries. However, others limit this role to specialists such as neurosurgeons, neurologists and intensive care physicians.[1,13,27] Repeat evaluation which was once the norm, is now an exception.[4,18,24,31]

Many studies have demonstrated that waiting for a second examination is of no benefit particularly where organ donation is envisaged.[17,31]

There are three steps in making a clinical diagnosis of brain death.[1,32] These are:

a. Establishing the presence of an aetiology which is usually a catastrophic insult to the brain
b. Exclusion of reversible conditions that may produce signs similar to brain death, and
c. Demonstration of the clinical signs of brain death i.e. coma, brainstem areflexia and apnoea.

EXCLUSION OF CONDITIONS

Following establishment of clinical or radiological evidence of catastrophic brain damage, the following should be excluded before clinical signs of brain death are evaluated:

a. Presence of central nervous system depressants such as barbiturates, alcohol and anaesthetic agents; when present, clearance time of up to 5times the half-life of the agent, should be allowed; serum drug levels can also be measured to ensure that acceptable values are within non-harmful ranges; in case of alcohol intoxication, safe driving level of 0.08% or less, is accepted.
b. Hypothermia: this is particularly so in patients in whom hypothermia might have been induced for therapeutic purposes; such patients should be

warmed up to core body temperature of >36^{o}C.

c. No evidence of residual paralytics – electrical stimulation demonstrating train of four should be done if paralytics used.
d. Absence of severe acid-base, electrolyte, endocrine abnormality.
e. Hypotension: systolic blood pressure should be maintained at 100mmHg or higher.[1,13]

DEMONSTRATION OF CLINICAL SIGNS OF BRAIN DEATH

For a patient to be certified brain dead, the clinician should elicit the following signs:

a. Presence of coma: patient must demonstrate lack of motor response to noxious stimuli such as pressure on the supraorbital ridge, nail bed or trapezius; non-brain dead patients in coma will show some grimace or purposeful motor response in the absence of neuromuscular blockade; examination with a bedside peripheral nerve stimulator is needed if neuromuscular blockade is suspected; a train-of-four stimulus should result in four thumb twitches.
b. Absence of brainstem reflexes: a brain dead patient will have absence of the following craniofacial reflexes;
   Pupillary reflexes: normal pupils constrict in response to bright light pointing at it or the contralateral pupil. A brain dead patient will usually have midsize pupils with no response to light;
   Oculocephalic reflex (Doll's head-eye movements): This is demonstrated by turning the head from a neutral position to the side. A normal response is the eyeballs moves to the opposite side but that of brain death patients does not show any movement;
   Corneal reflexes: with patient's eyes open, the cornea on the lateral aspect of the eyeball is touched with a light wet cotton swab introduced from outside the visual field. The normal reflex blinking is absent in brain death;
   Absence of motor response in any cranial nerve distribution i.e. any response to stimulation of face, limb or trunk;
   Oculovestibular reflex (cold caloric test): this is performed with the patient positioned about 30° head up; irrigate the tympanic membrane with cold water and observe patient for 1minute after irrigating the ear, with a 5-minute interval between testing of each ear; the normal response is for both eyes to move towards the opposite side of the stimulus; in patients with brain death, there will be no response;
   Gag reflex & cough reflex: these are mediated by cranial nerve IX and X and can be demonstrated by tugging on the endotracheal tube and deep suctioning of the carina through the endotracheal tube respectively; a normal response is grimace or coughing which is absent in brain death.
c. Presence of apnoea (Apnoeic test): This test is necessary though not innocuous and should only be embarked on if brainstem areflexia is confirmed;[1,22,33] the examiner should ensure that there is no cervical spine injury, patient is euvolaemic with core temperature of > 36^{o}C and a blood pressure 100mmHg or more as well as having baseline eucapnia – pC02 40mmHg or more; while techniques vary, the following are major steps in apnoeic test:
   i. Pre-oxygenate with 100% oxygen for about 10 to 15minutes
   ii. Allow baseline P_aCO_2 to be at least 40 mmHg

iii. Place patient on oxygen 6L/min
iv. Ensure continuous monitoring of oxygen saturation, blood pressure and electrocardiac activities
v. Disconnect the ventilator
vi. Look closely for respiratory movements
vii. Measure tidal volume with spirometer if in doubt
viii. Measure arterial pO2, pCO2, and pH after 10 to 15 minutes and reconnect the ventilator
ix. Test should be aborted if patient shows signs of respiration or develops hypotension, cardiac arrhythmia, or falling oxygen saturation

If test is aborted for reasons other than spontaneous respiration, arterial blood should be taken for blood gas analysis. A positive apnoeic test is absence of spontaneous respiration after 10 to 15 minutes of no mechanical ventilation or a rise in pCO2 above 60mmHg or >20mmHg above baseline.[2,33] If the test is indeterminate, it can be repeated after variable interval or a confirmatory test for brain death is performed.

PITFALLS IN CLINICAL EVALUATION OF BRAIN DEATH

Conditions that may meet some criteria of brain death but are, however, not brain death include deep coma in non-brain dead patients, locked-in state, akinetic mutism, persistent vegetative state and the minimally conscious state, all of which are in varying states of consciousness. The issue of consciousness itself has raised several debates amongst philosophers and neuroscientists.[34] Table 1 shows the comparison of this clinical scenarios.[35]

Several factors may hinder the proper evaluation of brain dead patients. They include severe facial trauma, pre-existing pupillary abnormalities, toxic levels of any sedative drugs, sleep apnoea or severe pulmonary disease resulting in chronic retention of CO_2.

False signs that might confuse the examiners include sweating, blushing, tachycardia, normal blood pressure without pharmacologic support or sudden increases in blood pressure, and absence of diabetes insipidus.

Table 1. Comparison of brain death and some differentials (modified from S. Laurey, *et al*. Cerebral function in Coma, Vegetative state, Minimally Conscious State, Locked-in Syndrome and Brain Death

Condition	Consciousness	Sleep/ wake	Brainstem reflexes	Motor function	Visual traction	Communication	Respiration
Brain Death	Absent	Absent	Absent	Absent except some spinal reflexes	Absent	Absent	Absent
Coma	Absent	Absent	Present	May be present	Absent	Absent	Depressed
Locked-in syndrome	Preserved	Normal	Present	Absent except eye movement	Absent	Absent verbal	Normal

Akinetic mutism	Preserved	Normal	Present	Absent	Present	Absent verbal	Normal
Persistent vegetative state	Absent	Normal	Present	No purposeful movement		Absent	Normal
Minimally conscious state	Minimally present	Normal	Present	Minimal, reproducible voluntary movement	May be present	May be present	Normal

Deep tendon reflexes, superficial abdominal reflexes, triple and Babinski reflex may still be present and are compatible with diagnosis of brain death but confirmatory test is warranted if clinical evaluation is equivocal.[1, 13] Each brain dead patient is a potential donor of organs, and all neurosurgeons must be well aware of the rules, regulations and the essential criteria required for such a diagnosis.[25]

BRAIN DEATH CONFIRMATORY TESTS

Clinical diagnosis is sufficient for diagnosis of brain death. Confirmatory tests are not 100% specific or sensitive, but can be useful in cases where the cause of coma is not known or when confounding clinical conditions limit the clinical examination. It is particularly important in children less than 2years, although the upper age limit varies. Table 2 show the various tests and common findings in brain death.[2,4]

ETHICAL CONSIDERATIONS

Despite the fact that guidelines and legislations exist in many parts of the world, there are still rancorous religious, political and pseudoscientific bitter arguments kindled by this concept in those countries where it is being initiated or modified.[36]

Table 2: Different confirmatory tests and findings in brain death

Test	Common findings
Electroencephalo-graphy	Loss of bioelectric brain activity for at least 30 minutes of recording using at least 18 leads device
Somatosensory evoked potential	Bilateral absence of N20-P22 response with median nerve stimulation
Transcranial Doppler Ultrasonography	Absence of Doppler signal Small systolic peak in early systole without diastolic flow Reverberating flow
Angiography (conventional CTA or MRA)	No intracerebral filling at the level of the carotid bifurcation or circle of Willis Patent external carotid Delayed superior sagittal sinus filling may be seen
Isotope Scan Technetium-99m hexamethyl propylene amine oxime	Shows "hollow skull phenomenon'' i.e. failure of uptake of isotope by the brain

As Pope John Paul II expressly put it, ''human experience shows that once death occurs certain biological signs inevitably follow, which medicine has learnt to recognize with increasing precision". In this sense, the criteria for ascertaining death used by medicine today should not be understood as the technical-scientific determination of the exact moment of a person's death, but as a scientifically secure means of identifying the biological signs that a person has indeed died.[37]

The ethical principle is to educate the relatives and carry them along with involvement of the Ethics Committee and the clergy. The right words should be used in passing the news of brain death to the relatives rather than euphemisms.

CONCLUSION

The definition of death has shifted from the traditional cardiopulmonary death to brain death. While brain death has been largely accepted as death throughout the world, few controversies still surround it that are yet to be resolved. The diagnosis of brain death has become a norm in many countries, with standards set for diagnosis and harvesting of organs, where the laws permit.

However, several parallel developments such as advancements in resuscitation and critical care, research into underlying physiology of consciousness, growing technology, medical futility, and the ethics of end of life, are the principal driving forces, and not organ donation. With increasing awareness, there is need for research in the area of brain death in Nigeria. Such research can provide the needed impetus for producing acceptable guidelines that can also serve as a legal frame work with necessary legislative backing in line with international best practices.

REFERENCES

1. VA Thamburaj, Textbook of Contemporary Neurosurgery (Volume 1) First Edition: 2012, Jaypee Brothers Medical Publishers (P) New Delhi, India.
2. Ajay Kumar Goila and Mridula Pawar. The diagnosis of Brain Death. *Indian J Crit Med* 2009 Jan-Mar; 13: 7-11.
3. Anant Dattatray Dhanwate, Brainstem death: A comprehensive review in Indian perspective; *Indian J Crit Care Med 2014* Sept; 18:596-605.
4. New York State Department of Health. Guideline for Determining Brain Death. www.health.ny.gov/professionals/hospital_administration/letters/2011/brain_death_guidelines.html
5. National Catholic Bioethics Center; Jahi Mcmath and catholic Teaching on Determination of Death. Available at www.ncbcenter.org/resources/jahi-mcmath-and-catholic-teaching-on-the-determination-of-death.
6. Wertheimer P, Jouvet M, Descotes J. Diagnosis of death of the nervous system in comas with respiratory arrest treated by artificial respiration. *Presse Med* 1959; 67:87-88.
7. Mollart P, Goulon M. Le coma dépassé. *Rev Neurol* 1959; 101:3-15.
8. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *JAMA* 1968; 205:337-340.
9. Mohandas A, Chou SN. Brain death. A clinical and pathological study. *J Neurosurg* 1971; 35:211-218.
10. Conference of Medical Royal Colleges and their Faculties in the UK. Diagnosis of brain death. *Brit Med J* 1976; 2:1187-1188.
11. Presidential commission on The Study of Ethical Problems in Medicne and Biomedical and Behavioral Research. Defining Death: Medical, Legal and Ethical Issues in The Determination of Death. Washington DC.: Government Printing Office; 1981. Available from:http://www.euthanasia.procon.org/source/PrecommdefiningDeath.
12. Uniform Death determination Act. Available from:http://wwww.lchc.ucsd.edu/cogn_150/Reading/death_act.
13. Wijdicks EF, Varela PN, Gronseth GS, Greer DM. American Academy of Neurologist. Evidence-Based Guidelines Update: Determining Brain death in Adult: Report of The Quality Standard Subcommittee of the American Academy of Neurologist. *Neurology* 2010; 74:1911-1918.
14. Shiogai T, Takeuchi K. Brain death in a neurosurgical unit in Japan. *No To Shinkei* 1984; 36:781-7.
15. Jennett B, Gleave J, Wilson P. Brain Death in Three Neurosurgical Units. *Br Med J* 1981; 282:533-539.

16. Aldawood A, Al Qahtani S, Dabbagh O, Al Sayyari AA. Organ DonationAfter Brain Death, Experience over 5 years in a Tertiary Hospital. *Saudi J Kidney Dis Transpl* 2007: 18, 2007: 60-64.
17. Lustbader D, O'Jara D. Wijdick EF, et al, Second Brain Death Examination May Negatively Affect Organs Donation. *Neurology* 2011 Jan.11, 16: 119-124.
18. Micheal A De Georgia; History of brain Death as Death: 1968 to the present. *J Critical Care* Aug 2014; 28: 673-678.
19. George J. Siegel, Bernard Agranoff, R. wayne Alber, Stephen K Fisher and Michael D Uhler (*Ed*). Regulation of Cerebral Metabolic rate. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th ed. Philadelphia: Lippincott-Raven; 1999.
20. Wijdicks EF, Pfeifer EA. Neuropathology of Brain Death in The Modern transplant Era. *Neurology* 2008; 70:1234–1237.
21. Tsai WH, Lee WT, Hung KL, authors. Determination of brain death in children: A Medical Centre Experience. *Acta Paediatr Taiwan*. 2005; 46:132–137.
22. Saposnik G, Rizzo G, Sabbatiello R, Deluca JL. Problems Associated with The Apnoeic Test in The Diagnosis of Brain Death. *Neurol India* 2004; 53: 342-345
23. Joel S. Cohen. Brain death: Anatomy and physiology. www.hods.org/English/ppt/DrCohen
24. Omar Hassan Kasule. Brain death, Criteria, Signs, and Tests. *Journal of Taibah University Medical Sciences*, April 2013, Vol 8: 1-6.
25. Tandon PN, Ramamurthi R. Ramamurthi and Tandon's Textbook of Neurosurgery 3ed: 2012
Jaypee Brothers Medical Publishers (P) Ltd New Delhi.
26. Bohatyrewicz R, Bohatyrewicz A. and Zukowski M, *et al*. Reversal to Whole-Brain Death Criteria after 15years: Experience with Brainstem Death in Poland. *Transplant Proc* 2009; 41: 2959-2960.
26. Government of India. Ministry of Law, Justice
and Company Affairs (Legislative Department) New Delhi.
27. The Transplantation of Human Organs (Amendment) Act, 2011. (No. 16 of 2011) Available from: http://www.mohanfoundation.org/THO-amendment-act-2011.
28. Draft Guiding Principles On Human Organ Transplantation – 44th World Health Assembly Geneva, 6-16 May 1991 WHA44/1991/REC/1. Annexes-Annex 6 Human Organ Transplantation 1.
29. WHO, Human Organ and Tissue Transplantation: Report by the Secretariat, 2 May 2003.
30. Busl KM, Greer DM. Pitfalls in the Diagnosis of Brain Death. *Neurocritical Care* 2009; 11: 276-287.
31. Varela PN, Rehman M and Abdelhak T, *et al*. Single Brain Death Examination is Equivalent to Dual Brain Death Examination. *Neurocrit Care* 2011 Dec; 15: 547-553.
32. Haupt WF, Rudolf J. European Brain Death Codes: A Comparison of National Guidelines. *J Neurol* 1999; 246: 432-437.
33. Calixto Machado, Jesus Perez1, Claudio Scherle1, Alejandro Areu1, Alejandro Pando. Brain death diagnosis and apnea test safety. *Ann Indian Acad Neurol*; 12:197-200.
34. Burkeman O. Why can't the world's greatest minds solve the mystery of consciousness? http://www.theguardian.com/science/2015/jan/21/-sp-why-cant-worlds-greatest-minds-solve-mystery-consciousness
35. Laurey S, Berre J, Goldman S. Cerebral function in Coma, Vegetative State, Minimally Conscious State, Locked-in Syndrome and Brain Death. 2001 Yearbook of Intensive Care an Emergency Medicine. Vincent JL (Ed), Springer, Berlin: 386-396.
36. Long T, Sque M, Addington-Hall J. What Does a Diagnosis of Brain Death Mean To The Family Member For Organ Donation? A Review of the Literature. *Progress in Transplantation* June 2008, 18:118-125.
37. Pope John Paul II "Address of the Holy Father John Paul II to the 18th International Congress of the Transplantation Society." August 29th, 2000. Available online at http://www.vatican.va/holy_father/john_pa

ul_ii/speeches/2000/jul_sep/documents/hf_jp-ii_spe_20000829_transplants_en.html