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# Acute Stroke Decision-Making in Historical and Philosophical Context, 1960-2014

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UNIVERSITY OF CALGARY

Acute Stroke Decision-Making

in Historical and Philosophical Context, 1960-2014

by

Michel Christopher Frank Shamy

A THESIS

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## Abstract

This thesis applies approaches from the history and philosophy of science to explore the decision-making of contemporary physicians in a common clinical scenario: the treatment of patients with acute stroke. *Acute stroke decision-making* during the period 1960 to 2014 therefore serves as a case study to address broader questions about how doctors make decisions. I argue that acute stroke decision-making is dependent upon a historically-determined concept of the acute stroke, in that the contemporary meaning of the disease “acute stroke” was established in response to the efficacy of the drug tissue plasminogen activator (tPA) as its treatment. Moreover, I propose that treatment decisions about the use of tPA for acute stroke involve simultaneous and inter-related processes of epistemic and ethical evaluation. Acute stroke decision-making can therefore be conceived as a medical, epistemic and ethical process, occurring within a historical context. This interpretation of acute stroke decision-making argues for the necessary role of the humanities — and especially of the history and philosophy of science — in the study of modern medical practice.

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For my parents, with love

## Table of Contents

Abstract	ii
Acknowledgements	iii
Dedication	v
Table of Contents	vi
List of Figures & Illustrations	viii
Glossary	ix
Epigraph	xv
Introduction	1
<i>How Do Doctors Make Decisions?</i>	1
<i>Perspectives on Medical Decision-Making</i>	5
<i>Rationalistic Approaches to Decision-Making</i>	12
<i>Heuristic Approaches to Decision-Making</i>	16
<i>Social Psychological Approaches to Decision-Making</i>	21
<i>Approaches to Decision-Making from the History &amp; Philosophy of Science</i>	26
<i>The Case of Acute Stroke Decision-Making</i>	30
<i>Outline</i>	37
Chapter 1: The Meaning of “Acute Stroke”	40
<i>Introduction</i>	40
<i>History, Epistemology &amp; Ontology</i>	41
<i>A Brief Historiography of Stroke</i>	51
<i>Treatability &amp; Time</i>	56
<i>Acuity &amp; the Acute Stroke</i>	60
<i>Acute Stroke &amp; the NINDS Trial</i>	63
<i>Preconditions of the Acute Stroke</i>	72
<i>Vascular Anatomy</i>	74
<i>Localizability of Pathology</i>	77
<i>Ischemia and Hemorrhage</i>	78
<i>CT Scans</i>	81
<i>Thrombolysis</i>	85
<i>Penumbra</i>	88
<i>Conclusions</i>	92
Chapter 2: Epistemic Evaluation in Acute Stroke Decision-Making	96
<i>Introduction</i>	96
<i>Propositions, Beliefs &amp; Knowledge</i>	98
<i>Epistemic Evaluation &amp; Evidence-Based Medicine</i>	104
<i>Acute Stroke &amp; its Clinical Propositions</i>	112
<i>Epistemology, History &amp; Treatability</i>	118
<i>Conclusions</i>	129

Chapter 3: Ethical Evaluation in Acute Stroke Decision-Making	133
<i>Introduction</i>	133
<i>Principlist Ethics &amp; Everyday Medical Decisions</i>	134
<i>Causes, Consequences &amp; Values in Acute Stroke Decision-Making</i>	142
<i>Evaluating Post-Stroke Outcomes</i>	152
<i>Evaluating Pre-Stroke States</i>	158
<i>Conclusions</i>	164
Conclusions	169
<i>Acute Stroke Decision-Making</i>	169
<i>Implications for Physician Decision-Making</i>	175
Bibliography	181
<i>Primary Sources</i>	181
<i>Secondary Sources</i>	193

## List of Figures & Illustrations

Figure 1. CT Scan of the Brain depicting ischemic stroke	34
Figure 2. Digital Subtraction Angiogram of the Brain	35
Figure 3. “Acute Stroke” in MEDLINE	66
Figure 4. “Acute Stroke” in MEDLINE	67
Figure 5. CT Scan of the Brain depicting intracerebral hemorrhage	84

## Glossary

**American Heart Association:** American charitable organization that funds research into diseases of the heart and vascular system and that establishes national guidelines for the care of patients with these diseases; founded in 1924.

**Angiogram:** An image that depicts blood vessels and the flow of blood through them. In relation to the brain, several techniques may be used. In digital subtraction angiography, catheters are advanced into the chest, neck or head, and radio-opaque dye is injected to depict the flow of blood through vessels in real-time. In CT angiography, radio-opaque dye is injected into the vein and the patient undergoes a CT scan, with an image produced depicting the presence of radio-opaque dye in the arteries or veins at a particular point in time.

**Aphasia:** The inability to produce or comprehend language. A common symptom of stroke, most commonly associated with occlusions of the left middle cerebral artery.

**Apoplexy:** A historical term derived from the Greek for being “struck down.” Over time, it has been used to refer to: any sudden loss of consciousness; the sudden onset of neurological symptoms; intracerebral hemorrhage.

**Artery:** A vessel that carries blood away from the heart and towards the body’s tissues.

**Cerebral Venous Sinus Thrombosis:** A condition in which the veins of the brain or head may become blocked, potentially producing a back up of blood being drained from the head. May lead to hemorrhage into the brain.

**Central Nervous System (CNS):** The brain and spinal cord. In contrast to the peripheral nervous system (PNS), which includes the nerves that run from the spinal cord to the muscles and skin.

**Computerized Tomography (CT):** A technique to visualize the brain or other internal organs using x-ray based technology that resolves organs and tissues of shades of black or white.

**Epidural Hematoma:** Bleeding into the space between the skull and the lining of the brain, most commonly produced by injury to the middle meningeal artery that runs through the skull just above the ear. May present as the sudden onset of neurological symptoms or loss of consciousness. Often fatal if not treated immediately.

**Heart and Stroke Foundation:** Canadian charitable organization that funds research into heart and brain disorders, and advocates for patients at various levels of government.

**Hemiplegia:** The inability to move one side of the body, such as the face, arm and leg. A common symptom of ischemic stroke or intracerebral hemorrhage.

**Hemorrhage:** The release of blood into an organ or tissue, usually resulting from the rupture of an artery.

**Hypoxic-Ischemic Encephalopathy:** A condition in which the whole brain is temporarily deprived of blood flow and oxygen delivery. Occurs in the setting of low blood flow due to blood loss, impaired heart function, or low blood pressure. Most often presents as loss of consciousness.

**Infarction:** A general term that refers to the death of tissue from ischemia (impaired blood flow).

**Intracerebral:** Within the brain.

**Intracerebral Hemorrhage:** Bleeding into the substance of the brain, most commonly due to a small artery. Presents as the sudden onset of neurological symptoms, often accompanied by headache or loss of consciousness. The most common cause is high blood pressure.

**Intracranial:** Within the skull.

**Ischemia:** Dysfunction of a tissue due to impaired blood flow. May apply to any organ, though most commonly used in reference to the brain, heart or skeletal muscle.

**Ischemic stroke:** Dysfunction of the brain due to the deprivation of blood flow from occlusion of an artery in the neck or head. Usually presents with the sudden onset of neurological symptoms such as hemiplegia or aphasia. Common risk factors include high blood pressure, high cholesterol, diabetes and smoking.

**MEDLINE:** Online database of the National Library of Medicine in the United States. Began as a computerized archival system in 1964. Established online in 1996. As of April 2014, its online archives extend to 1946. Contains 19 million citations from 5600 journals.

**Middle Cerebral Artery (MCA):** One of a pair of symmetrical arteries that supplies the majority of blood to each of the brain's hemispheres. Occlusion of the left middle cerebral artery results in a characteristic syndrome of right hemiplegia, aphasia, and right-sided sensory loss. Occlusion of the right middle cerebral artery results in a characteristic syndrome of left hemiplegia, sensory loss, and neglect.

**Myocardial Infarction:** The death of heart muscle due to impaired blood flow through the coronary arteries. Colloquially known as a "heart attack."

**National Institutes of Health (NIH):** Publicly-funded American medical organization that conducts research and provides health care services. Includes 28 different institutes, including the National Institute of Neurological Disease and Stroke (NINDS), and the National Institute for Mental Health (NIMH). Originated as the Marine Hospital Service in 1798. Established in its current form in 1949.

**National Institutes of Health Stroke Scale (NIHSS):** A widely-used grading scale for the severity of stroke. Developed for the 1995 NINDS trial. Used in clinical research and clinical practice throughout North America. Score goes from 0 to 42, where 0 is normal and 42 shows absence of all brain functions tested. A mild stroke is considered to score under 6, a moderate stroke from 7 to 14, and a severe stroke above 15.

**National Institutes of Neurological Disease and Stroke (NINDS):** Publicly-funded American medical organization that conducts research and provides health care in neurological diseases. A part of the National Institutes of Health. Founded in 1950. Sponsored the NINDS Clinical Trial of Tissue Plasminogen Activator in stroke, the results of which were published in the *New England Journal of Medicine* in 1995.

**Occlusion:** Blockage in the flow of blood through an artery or vein.

**Recanalization:** Restoration of blood flow through an artery or vein. The resolution of an occlusion.

**Penumbra:** A physiological concept that refers to the persistence of a region of live brain despite the deprivation of blood flow to that region in the course of an ischemic stroke. By definition, the penumbra is electrically silent, in that it has ceased to perform its functions. However, it has the ability to return to normal functioning with the restoration of blood flow. Defined in opposition to the core, which refers to a region of brain that has died quickly after the deprivation of blood flow and whose function is permanently lost.

**Subarachnoid Hemorrhage:** Bleeding into the lining of the brain, most commonly due to rupture of a brain aneurysm. Commonly presents as sudden onset headache and loss of consciousness. Often fatal if not treated quickly.

**Subdural Hematoma:** Bleeding into the lining of brain, most commonly due to rupture of a vein draining blood from the brain. May present as the sudden onset of headache and neurological symptoms.

**Thrombolysis:** The intentional dissolution of blood clotting using a pharmacological agent or mechanical techniques. “Thrombo-” refers to blood clotting, and “-lysis” to its dissolution. Drugs that perform thrombolysis may be called thrombolytics. Tissue plasminogen activator is a thrombolytic drug. Alternate terminologies include fibrinolysis, in that a significant portion of blood clots consists of the protein fibrin.

**Tissue Plasminogen Activator (tPA):** A thrombolytic enzyme that acts as part of the normal blood clotting cascade in the human body. Enzyme originally called fibrinokinase. May also be referred to as “alteplase,” “tissue-type plasminogen activator” or “recombinant tissue plasminogen activator.” First isolated from ovarian tissue in 1947, later synthesized from melanoma cells in 1980. Modern synthetic production techniques developed by Désiré Collen and Henri Roger Lijnen of the University of Leuven in the early 1980s. Commercially produced by Genentech in the United States. Marketed under the brand name “Activase.” Approved for use in the treatment of clots occurring in arteries in the brain, heart, chest, and legs, and in veins of the lungs and chest.

**Veins:** Vessels that carry blood from the organs back towards the heart.

Time is brain.

Magdy Selim, "Ischemic Stroke in the first 24 hours," eds. Michel T. Torbey, Magdy H. Selim, *The Stroke Book* (Cambridge: Cambridge University Press, 2007), 157.

## Introduction

C'est le plus souvent dans l'urgence que le médecin doit décider.

— Georges Canguilhem, *Études d'histoire et de philosophie des sciences* (1968)

### *How Do Doctors Make Decisions?*

The decisions made by doctors matter. They matter to individual patients, whose present and future health may be largely determined by those decisions. They matter to the friends and family members of those patients, whose happiness can be so intimately tied to their loved ones' fates.<sup>1</sup> They matter to the administrators of health care systems, who must address the economic ramifications of the ways doctors distribute resources.<sup>2</sup> They matter to the politicians and ethicists who must contend with the moral and legal implications of those decisions.<sup>3</sup> And finally, they matter to the doctors themselves, who often feel deeply responsible for their patients' outcomes, or who may worry about lawsuits and professional reprimands.<sup>4</sup>

The decisions made by doctors are complex. In the course of a single interaction, doctors may need to decide upon a diagnosis, a prognosis and a plan of treatment.<sup>5</sup> Depending on the circumstances, doctors may need to make these decisions in a matter of minutes, if not seconds. They may have been awake and deciding for twelve, twenty-four, or even thirty-six straight hours. The variability produced by patients, their symptoms, and their circumstances renders each decision unique.<sup>6</sup> In order to make these decisions, doctors may need to incorporate information from a variety of sources: from patients, from their families,

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<sup>1</sup> J. David Velleman, "A Right to Self-Termination?" *Ethics* 109 (1999): 606-628.

<sup>2</sup> Health Council of Canada, *Decisions, Decisions: Family Doctors as Gatekeepers to Prescription Drugs and Diagnostic Imaging in Canada* (Toronto: Health Council of Canada, 2010), 2.

<sup>3</sup> Albert Jonsen, *A Short History of Bioethics* (Oxford: Oxford University Press, 2000), 100.

<sup>4</sup> Jerome Groopman, *How Doctors Think* (New York: Houghton Mifflin, 2007), 53.

<sup>5</sup> Georges Canguilhem, *Études d'histoire et de philosophie des sciences* (Paris: J. Vrin, 1968), 389.

<sup>6</sup> Kathryn Montgomery, *How Doctors Think: Clinical Judgment and the Practice of Medicine* (Oxford: Oxford University Press, 2005), 3.

from the physical examination, and from a variety of tests. Often, the information available to doctors is incomplete or uncertain.<sup>7</sup>

Doctors' decisions — both their content and their process — are therefore surely a suitable subject for academic study. The more challenging question is: how should we study the decision-making of doctors? In recent years, sociologists,<sup>8</sup> anthropologists,<sup>9</sup> literary scholars<sup>10</sup> and physicians themselves<sup>11,12,13</sup> have made important contributions to the study of doctors' decision-making in matters of diagnosis, prognosis and treatment. Perspectives from psychology<sup>14</sup> and economics<sup>15</sup> have also informed our understanding of how doctors make decisions.

However, little work has sought to contextualize doctors' decision-making in relation to the history and philosophy of science. While historians and philosophers of science have explored issues of evidence and ethics in medicine,<sup>16,17</sup> few have directly addressed the decision-making process of individual physicians.<sup>18</sup> And yet, the process of decision-making in medicine appears to be influenced by many of the issues of interest to historians and philosophers of science. For example, how do doctors define and use common terminologies like *stroke* and *benefit*?<sup>19</sup> In what ways do doctors' decisions relate to foundations in

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<sup>7</sup> Montgomery, *How Doctors Think*, 4.

<sup>8</sup> Darren Flynn, Paul van Schaik, Anna van Wersch, Amy Douglass, Paul Cann, *Non-Medical Influences upon Medical Decision-Making and Referral Behavior: An Annotated Bibliography* (London: Praeger, 2003), 237.

<sup>9</sup> Annemarie Mol, *The Body Multiple: Ontology in Medical Practice* (Durham: Duke University Press, 2002), 172.

<sup>10</sup> Montgomery, *How Doctors Think*, 57.

<sup>11</sup> Groopman, *How Doctors Think*, 3.

<sup>12</sup> Michel C.F. Shamy, Cheryl S. Jaigobin, "The Complexities of Acute Stroke Decision-Making: A Survey of Neurologists," *Neurology* 81(2013): 1130-1133.

<sup>13</sup> Amar Dhand, John Engstrom, Gurpreet Dhaliwal, "How Experienced Community Neurologists Make Diagnoses during Clinical Encounters," *Neurology* 81 (2013): 1460-1466.

<sup>14</sup> Rose McDermott, "Medical Decision Making: Lessons from Psychology," *Urologic Oncology* 26 (2008): 665-668.

<sup>15</sup> Benjamin D. Sommers, Richard Zeckhauser, "Probabilities and Preferences: What Economics Can Teach Doctors and Patients about Difficult Treatment Decisions," *Urologic Oncology* 26 (2008): 669-673.

<sup>16</sup> Maya Goldenberg, "How can Feminist Theories of Evidence Assist Clinical Reasoning and Decision-Making?" *Social Epistemology* 2013, published online July 12, 2013.

<sup>17</sup> Cécile Bensimon, Ross E. G. Upshur, "Evidence and Effectiveness in Decisionmaking for Quarantine," *American Journal of Public Health* 97 (2007): S44-S48.

<sup>18</sup> Michel Shamy, Ross E.G. Upshur, "How Doctors Think," *Perspectives in Biology and Medicine* 51 (2008): 158-161.

<sup>19</sup> Ludwik Fleck, *Genesis and Development of a Scientific Fact*, ed. Thaddeus J. Trenn, Robert K. Merton, trans. Fred Bradley and Thaddeus J. Trenn (Chicago: University of Chicago Press, 1979), 1.

history and theory?<sup>20</sup> How do doctors evaluate the accuracy of their diagnoses, and the efficacy of their treatments?<sup>21</sup>

In this master's thesis, I propose to explore the decision-making of contemporary doctors using approaches from the history and philosophy of science. Specifically, I will apply a perspective informed by history, epistemology and ethics, to elucidate the process and content of doctors' decisions in the treatment of patients with a specific condition, "the acute stroke." *Acute stroke decision-making* will therefore serve as a case study to inform broader conclusions about how doctors make decisions in the contemporary context. Acute stroke decision-making will be characterized as a process that is dependent upon a historically-determined concept of the acute stroke, and that involves simultaneous and inter-related processes of epistemic and ethical evaluation. I will propose that the modern meaning of the term acute stroke has been constructed in relation to the claim that a drug called tissue plasminogen activator (tPA) can effectively treat stroke under certain conditions. Next, I will argue that the process of acute stroke decision-making involves the epistemic evaluation of the proposition that stroke is treatable, and of several related propositions. I will propose that physicians engage in a process of ethical evaluation in which they consider notions of the good — in relation to their patients' pre-stroke states and expected post-stroke outcomes — as part of acute stroke decision-making. Acute stroke decision-making can therefore be conceived as a medical, epistemic and ethical process, occurring within a historical context. From this standpoint, doctors' decision-making generally can also be viewed as a historical, epistemic, and ethical phenomenon.

I have chosen to focus on the case of acute stroke decision-making for several reasons. Stroke is a common disease, affecting more than 50,000 Canadians per year.<sup>22</sup> It is also a serious disease, in that it is the

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<sup>20</sup> Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 50<sup>th</sup> anniversary edition (Chicago: University of Chicago Press, 2012), 144.

<sup>21</sup> Jack D. Pressman, *Last Resort: Psychosurgery and the Limits of Medicine* (Cambridge: Cambridge University Press, 1998), 391.

<sup>22</sup> Antoine M. Hakim, Frank Silver, Corinne Hodgson, "Organized Stroke Care: A New Era in Stroke Prevention and Treatment," *Canadian Medical Association Journal* 159 (1998): S1.

third most common cause of death, and the leading cause of adult disability, in Canada.<sup>23</sup> Therefore, how doctors make decisions in the treatment of stroke is important to large numbers of people every year. Despite its importance, the study of acute stroke decision-making remains preliminary.<sup>24</sup> The treatment of acute stroke is a medical emergency, in that decisions must be made quickly, and patients are often unable to participate in the decision-making process. As a consequence, acute stroke decision-making provides a relatively pure example of how doctors (rather than patients, or doctors in combination with patients) make decisions. Moreover, the care of patients with stroke is generally directed by a specialized subset of physicians: mainly neurologists and emergency physicians, though internists or geriatricians may also participate. Therefore, decision-making processes are likely to be relatively consistent across this specialized group. However, the results of these decisions appear to vary significantly, in that treatment patterns differ between physicians, hospitals and regions.<sup>25</sup> Finally, as a neurologist with specialty training in the management of patients with stroke, I am particularly interested in developing a better understanding of the decisions I face on a daily basis. While I am cognizant of the fact that my membership in the community of physicians I am studying represents a potential source of bias in this analysis, it also affords me a significant advantage in that I have directly observed (and participated in) the practices I seek to study.

This thesis is intended to be descriptive rather than normative in focus. The distinction between descriptive and normative approaches is common in the history and philosophy of science, and therefore I will only briefly comment on it here.<sup>26</sup> Descriptive claims are those that describe the nature of a situation or a state of affairs, such as behaviours and patterns of reasoning. Ideally, such descriptions do not imply and are not derived from any norms. Norms, by contrast, are claims about ideals and values. In short, I intend

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<sup>23</sup> Statistics Canada, *Leading Causes of Death*, published online at <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/hlth36a-eng.htm>, (accessed March 28, 2014).

<sup>24</sup> Shamy, "Complexities," 1130.

<sup>25</sup> Royal College of Physicians Intercollegiate Stroke Working Party. *National Sentinel Stroke Clinical Audit 2010, Round 7*. Public Report for England, Wales and Northern Ireland, 2011.

<sup>26</sup> Peter Godfrey-Smith, *Theory and Reality: An Introduction to the Philosophy of Science* (Chicago: University of Chicago Press, 2003), 6.

to arrive at a description of how doctors *do* make decisions in acute stroke treatment, rather than how doctors *should* make those decisions. While I will necessarily touch upon the implications of the description I develop, it goes beyond the scope of this study to provide a normative theory of physician decision-making.

The historical and geographical scope of this thesis are, by necessity, relatively limited. As argued in Chapter 1, the term “acute stroke” was not used before 1960, and did not come into common usage until the 1990s. The concepts with which the term is aligned, similarly, only began to appear in the medical literature in the late 1950s. Consequently, not much can be said about acute stroke decision-making prior to the mid-20<sup>th</sup> century. Moreover, the options for treatment of the acute stroke were quite limited until 1995. Therefore, my exploration of decision-making in the treatment of acute stroke will focus on the years since 1995, during which time neurologists and emergency doctors have had access to a drug called tissue plasminogen activator, or tPA, as a treatment for acute stroke. Finally, the treatment of patients with tPA requires a relatively elaborate medical infrastructure — paramedics and ambulances, emergency rooms, Computerized Tomography (CT) scanners, trained physicians and nurses — that is only available in relatively wealthy, developed nations.<sup>27</sup> I have therefore concentrated my consideration of acute stroke decision-making on practices in North America and Europe.

### *Perspectives on Medical Decision-Making*

In order to begin to discuss physician decision-making, we must first define our terms. *Decision-making* is a non-specific term that may be applied to any process whereby a choice is made about a particular

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<sup>27</sup> Patrice Lindsay, Gordon Gubitz, Mark Bayley, Michael Hill, Corrine Davies-Schinkel, Sunny Singh, and Stephen Phillips, *Canadian Best Practice Recommendations for Stroke Care* (Update 2010). On behalf of the Canadian Stroke Strategy Best Practices and Standards Writing Group, Canadian Stroke Network. Published online at [strokebestpractices.ca](http://strokebestpractices.ca), (accessed April 12, 2014).

course of action in a given setting.<sup>28</sup> Decision-making can therefore be understood as a mental process that occurs over a period of time, in response to a particular situation. Any more specific conceptualization of decision-making seems to require the particular vocabulary of one of the various theoretical approaches that will be discussed below. The term *medical decision-making* may be used to refer exclusively to the decisions of physicians, or more broadly to include any decision made by an individual engaged in a health-related activity, including (but not limited to) nurses, physiotherapists, and patients.<sup>29</sup> In order to avoid this confusion, I will use the term *physician decision-making* in this thesis. Physician decision-making is meant to refer to the decision-making process conducted by physicians in relation to patients' diagnosis, prognosis, and management plan.

In recent decades, scholarship in medical decision-making has focused on normative questions surrounding the distribution of decision-making authority, often explicitly advocating for the increased involvement of patients in making treatment decisions.<sup>30,31,32,33,34</sup> Anthropologist Annemarie Mol of the University of Amsterdam has termed this focus “the politics of who.”<sup>35</sup> The literature on medical decision-making contrasts three different models of decision-making: the paternalistic model, in which physicians make decisions on the basis of what they think is best for patients; the informed consent model, in which patients have final say about matters of their own health, in accordance with a respect for self-

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<sup>28</sup> Megan Smith, Joy Higgs, Elizabeth Ellis, “Factors Influencing Clinical Decision Making,” eds. Joy Higgs, Mark A Jones, Stephen Loftus & Nicole Christensen, *Clinical Reasoning in the Health Professions*, 3<sup>rd</sup> edition. (Amsterdam: Elsevier, 2008), 89.

<sup>29</sup> Thomas Vandiver Cunningham, “Socializing Medical Practice: A Normative Model for Medical Decision-Making,” (Ph.D diss., University of Pittsburgh, United States of America, 2013), 9.

<sup>30</sup> Benjamin Moulton, Jaime S. King, “Aligning Ethics with Medical Decision-Making: The Quest for Informed Patient Choice,” *Journal of Law, Medicine & Ethics* 38 (2010): 2-14.

<sup>31</sup> Kristy S. Deep, Charles H. Griffith, and John F. Wilson, “Communication and Decision Making About Life-Sustaining Treatment: Examining the Experiences of Resident Physicians and Seriously-Ill Hospitalized Patients,” *Journal of General Internal Medicine* 23 (2008): 1877-1882.

<sup>32</sup> Christopher B. Forrest, Paul A. Nutting, Sarah von Schrader, Charles Rohde, Barbara Starfield, “Primary Care Physician Specialty Referral Decision Making: Patient, Physician, and Health Care System Determinants,” *Medical Decision Making* 26 (2006): 76–85.

<sup>33</sup> Madeleine J. Murtagh, Duika L. Burges Watson, K. Neil Jenkins, Mabel L.S. Lie, Joan E. Mackintosh, Gary A. Ford, Richard G. Thomson, “Situationally-sensitive Knowledge Translation and Relational Decision Making in Hyperacute Stroke: a Qualitative Study,” *PLoS ONE* 7 (2012): e37066.

<sup>34</sup> Elizabeth Murray, Lance Pollack, Martha White, Bernard Lo, “Clinical Decision-making: Physicians' Preferences and Experiences,” *BMC Family Practice* 8 (2007): 10.

<sup>35</sup> Mol, *The Body Multiple*, 172.

determination; and models of shared decision-making, in which doctors, patients and potentially larger communities of stakeholders participate in making individual medical decisions.<sup>36</sup> In emergency situations like acute stroke treatment, paternalistic forms of decision-making occur, and this scenario is generally considered acceptable even by advocates of “patient-centred” decision-making, at least until such time as patients recover the ability to participate in their own care.<sup>37</sup>

In the case of acute stroke, “the politics of who” are largely decided by the nature of a disease that renders patients unconscious, unable to speak, or unaware of their symptoms. Patient involvement in acute stroke decision-making is necessarily limited. Therefore, this thesis will focus on what Mol calls “the politics of what,” meaning the content and process of physicians’ decisions.<sup>38</sup> Even though most contemporary decisions now involve some degree of patient participation, understanding the physician’s decision-making process remains highly relevant. In their role as “medical experts,”<sup>39</sup> physicians frame the options available to patients, and in so doing they can influence patients’ understanding of their illnesses, and their subsequent decisions.<sup>40</sup> Moreover, patients often defer to their physicians, explicitly asking them to make decisions on their behalf.<sup>41</sup> A study of physician decision-making remains compatible with patient-centered models of decision-making.

The way *doctors* make decisions can be understood as a subset of the way *people* make decisions. Therefore, a discussion of the general literature on decision-making, with special attention to doctors, will be presented here. The literature on how people make decisions presents three distinct models, each of which has been applied to the case of doctors. I term these models the *rationalistic*, *heuristic*, and *social*

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<sup>36</sup> Cunningham, “Socializing Medical Practice,” 5.

<sup>37</sup> *Ibid.*, 21.

<sup>38</sup> Mol, *Body Multiple*, 172.

<sup>39</sup> Royal College of Physicians and Surgeons of Canada. “The CanMeds Framework: Medical Expert.” Published online at <http://www.royalcollege.ca/portal/page/portal/rc/canmeds/framework> (accessed April 12, 2014).

<sup>40</sup> J.S. Swindell, Amy L. McGuire, and Scott D. Halpern, “Beneficent Persuasion: Techniques and Ethical Guidelines to Improve Patients’ Decisions,” *American Family Medicine* 8 (2010): 260-264.

<sup>41</sup> Geneviève Demarquay, Laurent Derex, Norbert Nighossian, Patrice Adeleine, Frédéric Philippeau, Jérôme Honnorat, Paul Trouillas, “Ethical Issues of Informed Consent in Acute Stroke,” *Cerebrovascular Diseases* 19 (2005): 65-68.

*psychological* models. I will argue that while each model can contribute to our understanding of the decision-making process of physicians, none can provide a complete description of physician decision-making, largely due to the fact that none relates doctors' decisions to their historical and philosophical contexts.

It is a particular goal of this thesis to develop a sense of how modern doctors' decisions about the treatment of patients with acute stroke are contingent upon the knowledge, beliefs about knowledge, and values, of the communities in which they practice. Only a perspective grounded in the humanities, and in the history and philosophy of science specifically, can thoroughly investigate these historical and philosophical aspects of physician decision-making. Therefore, I will introduce the conceptual advantages of a historical approach here, before providing a more detailed critique of the rationalistic, heuristic and social psychological models of decision-making, as specifically applied to medicine, in the following pages. After critiquing these commonly used models of decision-making, I will then elaborate on the relevant literature within the history and philosophy of science that will inform the analysis to come in this thesis.

Much of the historical scholarship that touches upon questions of decision-making focuses on questions that Mol would categorize under "the politics of who," meaning issues of how decision-making authority is distributed within a political system or a military organization.<sup>42,43</sup> However, several themes from military and political history can still be applied to doctors' decision-making. First, a historical approach recognizes the ways in which decision-making is contingent on one's place in history. For example, the various courses of action that are available for selection as part of a decision-making process will be constrained by the scientific, political and cultural realities of the place and time. Just as it is meaningless to ask why Napoleon Bonaparte (1769-1821), then Emperor of France, did not use an air assault during his 1812 invasion of Russia, it is meaningless to ask why neurologists in the 1940s did not use tPA to treat patients with stroke. Specifically, neither of those options were technologically available under

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<sup>42</sup> Paul Valliere, *Conciliarism: A History of Decision-Making in the Church* (Cambridge: Cambridge University Press, 2012), 3.

<sup>43</sup> George Tsebelis, "Decision Making in Political Systems: Veto Players in Presidentialism, Parliamentarism, Multicamerism and Multipartyism," *British Journal of Political Science* 25 (1995): 289-325.

those historical circumstances. In matters of medicine, decision-making is contingent upon the available technology and infrastructure.<sup>44</sup> When a physician is choosing among treatments for a patient, it is obvious but implicit that those treatment choices are historically-determined: treatment options in 2014 may be very different from treatment options in 1944 or 2044.

Treatment decisions are not only determined by technological realities, but are contingent upon political and administrative systems, as well as cultural norms. A historical approach to decision-making supports the importance of understanding an individual's decisions in relation to the institutions and standards of his or her time and place. For example, a historical study of the decision-making of Pericles of Athens (495-429 BC) by Yale University professor Donald Kagan frames Pericles' decisions in relation to the conceptions of democratic statesmanship that existed in Athens in the fifth century B.C.<sup>45</sup> Pericles could not but make decisions in the world in which he lived. Moreover, had that world been different, Kagan suggests that Pericles might have made different decisions. Kagan writes that, "what happened was the result of decisions made by human beings acting in a world they do not fully control. It suggests that both the decisions and their outcomes could well have been different."<sup>46</sup> The world in which Pericles lived was not of his choosing. To some degree, his decisions were dictated by his context, and as a consequence, so too were the outcomes of those decisions.

Historical perspectives on decision-making also emphasize the importance of biography, personality and relationships in understanding the decisions made by individual people at specific times. For example, historian Joanne Freeman catalogues the ways that the personalities and quarrels of the statesmen of the early American republic influenced their political decisions in her monograph *Affairs of Honor* (2001).<sup>47</sup> Freeman's work also emphasizes how the accounts provided by individuals about their own decisions may

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<sup>44</sup> Stanley Joel Reiser, *Medicine and the Reign of Technology* (Cambridge: Cambridge University Press, 1978), 1.

<sup>45</sup> Donald Kagan, *Pericles of Athens and the Birth of Democracy* (New York: The Free Press, 1991), 3.

<sup>46</sup> Kagan, *Pericles*, xiv.

<sup>47</sup> Joanne Freeman, *Affairs of Honor: National Politics and the New Republic* (New Haven: Yale University Press, 2001), 11.

not necessarily be honest or accurate. Because our concepts of those colourful political personalities are dependent upon the writings they left behind, a historical approach forces us to recognize that we do not have unbiased access inside the minds of decision-makers.<sup>48,49</sup> When dependent upon others' accounts, it is necessary to remember those individuals' perspectives and potential motivations. This consideration is highly relevant given that this thesis is written by a neurologist, about other neurologists, and incorporates commentaries and anecdotes encountered in daily practice.

Finally, the development of social historical approaches emphasizes how our concept of what counts as a historically-important decision should not be limited to the actions of "great men." For example, historian Linda Colley's *Britons: Forging the Nation 1707-1837* (1992) provides an account of the development of the notion of "Britishness" in relation to the actions and beliefs of artists, writers, and ordinary men and women — not just political and military leaders.<sup>50</sup> A historical perspective on doctors' decision-making similarly should not be limited to the decisions of prominent physicians in controversial cases, but should extend to the everyday decisions of unsung doctors. Treatment decisions in acute stroke occur in hospitals around the world many times per day, and therefore may appear routine or mundane. For example, everyday decisions like those surrounding acute stroke are largely ignored by the bioethics literature.<sup>51</sup> And yet, stroke-related decisions matter greatly to the patients and families involved.

Precedent for a historically-based approach to doctors' decision-making exists in the form of the recent monograph, *Broken Hearts: The Tangled History of Cardiac Care*, by psychiatrist and historian David S. Jones of Harvard University. In *Broken Hearts*, Jones offers a "historical perspective on the complexity of medical decision making" by studying the history of two forms of treatment used in the management of

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<sup>48</sup> Freeman, *Affairs of Honor*, 11.

<sup>49</sup> Robert Jervis, "Political Decision Making: Recent Contributions," *Political Psychology* 2 (1980): 86-101.

<sup>50</sup> Linda Colley, *Britons: Forging the Nation 1707-1837* (New Haven: Yale University Press, 1992), 8.

<sup>51</sup> James Bernat, *Ethical Issues in Neurology, 3rd Edition* (Philadelphia: Lippincott, Williams & Wilkins, 2008), 134.

heart disease.<sup>52</sup> Jones' focus on "the decision dilemmas created by the emergence of" these treatments — coronary artery bypass surgery and coronary angioplasty — parallels the focus of this thesis, in that he seeks to understand the complexities of decision-making in relation to historically novel treatments. Jones uses the history of these treatments "to expose vexing ambiguities that persist at the core of the medical enterprise, in particular the challenge of producing definitive knowledge about the efficacy and safety of medical treatment."<sup>53</sup> He is therefore attuned to the epistemic issues I will be exploring in Chapter 2, specifically how physicians conceive of, and apply, medical knowledge. Jones argues that decision-making will never be "just a question of medical knowledge and practice. Instead, medical decisions always involve priorities, values, and preferences."<sup>54</sup> This perspective is consistent with the argument of Chapter 3, namely that doctors' decision-making necessitates some form of normative judgment.

However, Jones' approach differs from that of this thesis in important ways. He never attempts to define decision-making, and he does not engage with the literature on medical decision-making. Jones remains troubled by the fact that the treatments he studies "have been beset with controversy," suggesting that there should be clear and universal answers about their clinical efficacy, costs, and application. This position on medical knowledge, consistent with predominant approaches in contemporary medical epistemology, will be directly challenged in Chapter 2. Jones observes that medical knowledge's dependence on theory renders it "vulnerable to a wide range of influences."<sup>55</sup> His comment suggests that medical knowledge can and should be independent of theory, a view I contest in Chapter 2. While Jones argues for the role of values and preferences in decision-making, he does not suggest *how* they might be involved. In Chapter 3, I will put forward a description of how ethical evaluation figures in physician decision-making. Despite a conclusion that defines "disease and therapeutics" as "social processes that reflect

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<sup>52</sup> David S. Jones, *Broken Hearts: The Tangled History of Cardiac Care* (Baltimore: Johns Hopkins University Press, 2013), x.

<sup>53</sup> Jones, *Broken Hearts*, x.

<sup>54</sup> *Ibid.*, x.

<sup>55</sup> *Ibid.*, 19.

the structures and values of our society,” Jones laments the “impact of non-medical considerations.”<sup>56</sup> His distinction between “medical” and “non-medical considerations” foreshadows the language of rationalistic decision-making, the dominant model of physician decision-making, which I will be introducing and critiquing next.

### *Rationalistic Approaches to Decision-Making*

Rationalistic decision-making refers to the theory of human decision-making that starts from the belief that human beings demonstrate instrumental rationality, meaning that they act in such a way that is consistent with their ends.<sup>57</sup> This notion is commonly traced to the writings of Scottish philosopher David Hume (1711-1776), who proposed that “reason is, and ought only to be the slave of the passions.”<sup>58</sup> Instrumental rationality contains a central normative claim: because humans have it, they should always take those steps that achieve their ends. The process of rational decision-making can therefore be broken down into several steps: it requires that people have the ability to determine their ends, that they are aware of those ends, that they can distinguish which among many courses of action is most consistent with those ends, and that they can select the appropriate course of action. The process of identifying one’s ends depends upon an *a priori* concept of the good, and therefore also necessitates some degree of normative reasoning.

*Rational choice theory*, a commonly-referenced concept from psychology and economics, reflects the application of instrumental rationality to decision-making. Under rational choice theory, people are understood to desire “more, rather than less, of a good,”<sup>59</sup> and to make decisions that maximize these goods. Rational choice theory does not specifically address *why* certain things should be counted as goods. It

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<sup>56</sup> Jones, *Broken Hearts*, 218.

<sup>57</sup> R. Jay Wallace, “Practical Reason,” *The Stanford Encyclopedia of Philosophy* (Summer 2014 Edition), ed. Edward N. Zalta, URL = <http://plato.stanford.edu/archives/sum2014/entries/practical-reason/> (accessed March 30, 2014).

<sup>58</sup> David Hume, *A Treatise of Human Nature, Second edition*, ed. L.A. Selby-Bigge and P. H. Niditch (Oxford: Clarendon Press, 1978), 415.

<sup>59</sup> Daniel Kahnemann, *Thinking Fast and Slow* (Penguin: London, 2011), 270.

allows for differential evaluations of the good, reflected in the term “utility,” which is used to mean the relative value of an end to a particular person.<sup>60</sup> The utility of a given end may vary between people, but is generally considered to be consistent from the point of view of any particular person. Rational choice theory makes both descriptive and normative claims, in that it assumes that people do and should follow its principles. In other words, rational choice theory both intends to describe how rational people make decisions, and expects that rational people should make decisions using its approach.

As applied in economics, decision-making under rational choice theory requires calculating the utility of an end and its probability of occurrence. There are, therefore, two general forms of this theory: Expected Utility Theory, under which the probabilities of outcomes are known, and Subjective Expected Utility Theory, under which those probabilities are unknown. Under Expected Utility Theory, decision-makers are conceived to arrive at weighted utility calculations produced by multiplying the utility values of outcomes by their respective probabilities.<sup>61</sup> A significant body of literature has studied medical decision-making from the perspective of Expected Utility Theory, in which clinicians’ decisions are assumed to be based on the thorough calculation of outcomes and their probabilities.<sup>62, 63, 64</sup> Explicit references to the “expected utility” of various therapeutic strategies are widely found with the medical literature on decision-making.<sup>65</sup> When the probabilities of outcomes cannot be objectively determined, “subjective probabilities” can be inferred in relation to qualities of the decision-maker, such as financial assets, physiological and psychological conditions, social relationships and feelings.<sup>66</sup> This approach is termed Subjective Expected

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<sup>60</sup> Kahnemann, *Thinking*, 270.

<sup>61</sup> Philippe Mongin, “Expected Utility Theory,” eds. J. Davis, W. Hands, U. Maki, *Handbook of Economic Methodology* (Edward Elgar: London, 1997), 342-350.

<sup>62</sup> Howard Bauchner, Lisa Simpson, John Chessare, “Changing Physician Behaviour,” *Archives of Disorders of Children* 84 (2001): 459-462.

<sup>63</sup> Michael V. Boland, Harold P. Lehmann, “A New Method for Determining Physician Decision Thresholds Using Empiric, Uncertain Recommendations,” *BMC Medical Informatics and Decision Making* 10 (2010): 20.

<sup>64</sup> Barry L. Carter, C. David Butler, John C. Rogers, Richard L. Holloway, “Evaluation of Physician Decision Making With the Use of Prior Probabilities and a Decision-Analysis Model,” *Archives of Family Medicine*, 2 (1993): 529-534.

<sup>65</sup> P. Denig, F.M. Haaijer-Ruskamp, “Therapeutic Decision Making of Physicians,” *Pharmaceutisch Weekblad Scientific Edition* 14 (1992): 9-15.

<sup>66</sup> Flynn, *Non-Medical Influences*, 237.

Utility Theory. Under Subjective Expected Utility, decision calculations are allowed to change in relation to variable conditions or novel information, though basic formulation through which utility is calculated remains unchanged.<sup>67</sup>

Consistent with the rationalistic approach to medical decision-making are efforts to model and enhance physician decisions with computerized tools and algorithms.<sup>68, 69</sup> *Decision-modeling* refers to the application of a systematic approach to decision-making under uncertainty. Decision-modeling requires the identification and quantification of the relevant variables involved in a particular decision, so as to arrive at a determination of the optimal decision to be taken given the available knowledge. Attempts to model medical decisions reflect the two central assumptions of rationalistic decision analysis: first, that medical decisions can be modeled, in that they are assumed to follow standardized procedures that could be input into computer systems.<sup>70, 71, 72, 73, 74</sup> Second, decision modeling assumes that decisions can be evaluated normatively. Certain decisions will be designated as “good” or “correct,” while others will be designated “wrong” or “undesirable.”<sup>75</sup> Modeling requires that these normative determinations be stable in relation to certain clinical elements of a case (for example, the diagnosis), and will be independent of other elements that are considered external to the function of the algorithm. For example, elements that might be

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<sup>67</sup> Subjective Expected Utility Theory is often associated with Bayes’ theorem, a mathematical formulation developed by English mathematician and theologian Thomas Bayes (1701-1761) that provides a way of performing statistical adjustments in relation to changing information.

<sup>68</sup> Michael J. Hine, Ken J. Farion, Wojtek Michalowski, Szymon Wilk, “Decision Making By Emergency Room Physicians And Residents: Implications for the Design of Clinical Decision Support Systems,” *International Journal of Healthcare Information Systems and Informatics* 4 (2009): 17-35.

<sup>69</sup> Stuart B. Mushlin, Harry Lemoin Greene, eds., *Decision-Making in Medicine: An Algorithmic Approach*, 3<sup>rd</sup> edition (Philadelphia: Mosby, 2010), 414-418.

<sup>70</sup> Denig, “Therapeutic Decision Making,” 9-15.

<sup>71</sup> Niknam, “How Do Physicians Make A Decision?” 696–699.

<sup>72</sup> John B McKinlay, Deborah A. Potter, Henry A. Feldman, “Non-medical Influences on Medical Decision-making,” *Social Science & Medicine* 42(1996):769-776.

<sup>73</sup> Bas Groot Koerkamp, Milton C. Weinstein, Theo Stijnen, M. H. Heijenbrok-Kal, M. G. Myriam Hunink, “Uncertainty and Patient Heterogeneity in Medical Decision Models,” *Medical Decision Making* 30 (2010): 194–205.

<sup>74</sup> Boland, “A New Method,” 10:20.

<sup>75</sup> Denig, “Therapeutic Decision Making,” 9-15.

particular to the physician, the patient, or to the historical-cultural context are generally excluded from decision models.<sup>76</sup>

In medicine, decision-modeling is then used to develop what are called “decision rules” or “clinical prediction rules.”<sup>77, 78</sup> Use of the word “rule” in this context reinforces the normative, positivistic and universalist nature of the rationalistic approach to decision-making. By normative, I refer to the fact that rules establish standards of practice. A decision rule means that it should be followed, because it is right. By positivistic, I refer to the assumption that decision rules — reflecting that which should be done — can be determined with certainty. This approach assumes that there is, for every clinical scenario, one certain, best decision to be made, and that it can be determined by decision-modeling. By universalist, I refer to the idea that the normative claims of decision rules are expected to be stable across time and space; for example, that administering tPA to a given patient is the right thing to do, without qualification.

Despite its widespread influence, the rationalistic approach to decision-making in medicine is problematic and therefore does not serve as the analytic foundation for this thesis. As elaborated by heuristic approaches to decision-making — which will be presented next — humans (and doctors) do not follow the claims of rationality in all circumstances, and therefore rationalistic approaches do not accurately reflect a large proportion of decisions made.<sup>79</sup> Moreover, rationalistic decision modeling can incorporate only a limited set of variables into its calculations. However, as suggested by Jones and others, medical decision-making is highly complex, and the number of variables inherent in any given decision would render mathematical formulation difficult, if not impossible.<sup>80</sup> Finally, rationalistic decision-making requires the normative evaluation of decisions; it states that certain decisions are right, and others wrong. However,

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<sup>76</sup> Forrest, “Primary Care Physician Specialty Referral,” 76–85.

<sup>77</sup> P. Denig, F.M. Haaijer-Ruskamp, H. Wesseling and A. Versluis, “Towards Understanding Treatment Preferences,” *Social Science & Medicine* 36 (1993): 915-924.

<sup>78</sup> Robert G. Holloway, Curtis G. Benesch, W. Scott Burgin, Justine B. Zentner, “Prognosis and Decision Making in Severe Stroke,” *Journal of the American Medical Association* 294 (2005):725-733.

<sup>79</sup> Kahnemann, *Thinking*, 128.

<sup>80</sup> Michel C. F. Shamy, Mark Fedyk, “What Statistics Cannot Tell Us About the Neurological Examination,” *Annals of Neurology* 71 (2012): 434-435.

it is rare in medicine to determine that one treatment strategy is clearly right or clearly wrong in all cases, let alone in reference to any individual patient. A historically-informed position recognizes that normative judgments about decisions, and the decisions themselves, will be dictated by the cultural values, theories, and technologies of a given place and time. None of these factors is reflected in standard rationalistic approaches to decision-making.

### *Heuristic Approaches to Decision-Making*

Over the course of the last forty years, non-rationalistic perspectives on decision-making have emerged in psychology and economics.<sup>81</sup> One of the most influential approaches is presented here as *heuristic decision-making*, in that it reflects the central role of heuristics in human decision-making. As proposed by American-Israeli psychologists Daniel Kahnemann and Amos Tversky (1937-1996), *heuristics* are mental shortcuts that aid in making rapid decisions.<sup>82</sup> In studying the actual decision-making of individuals when faced with real-world problems (albeit under experimental conditions), Kahnemann and Tversky identified what they call biases, or systematic tendencies that violate the norms of rationalistic decision-making.<sup>83</sup> In short, people do not always make decisions that maximize their ends. Kahnemann and Tversky codified their work under the title *Prospect Theory*, which is a descriptive theory that aims to document and explain systemic violations of the axioms of rationality in decision-making.<sup>84</sup> Prospect Theory proposes that the types of utility calculations conceived under rationalistic theories are rarely performed by human beings in the course of everyday activities. Rather, most decisions are made on the basis of intuitive processes that do not involve the conscious experience of calculation. These intuitive processes are called

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<sup>81</sup> Richard Samuels, Stephen Stich, Michael Bishop, "Ending the Rationality Wars: How To Make Disputes About Human Rationality Disappear," in Renee Elio, ed. *Common Sense, Reasoning and Rationality* (New York: Oxford University Press, 2002), 236-268.

<sup>82</sup> Kahnemann, *Thinking*, 89.

<sup>83</sup> Amos Tversky, Daniel Kahnemann, "Judgment Under Uncertainty: Heuristics and Biases," *Science* 185 (1974): 1124-1131.

<sup>84</sup> Daniel Kahnemann and Amos Tversky, "Prospect Theory: An Analysis of Decision Under Risk," *Econometrica* 47 (1979): 263-291.

heuristics. Moreover, heuristics can also influence decision-making even in circumstances in which individuals do perform rationalistic calculations.

Whether heuristics reflect helpful mechanisms to be celebrated or sources of error to be removed remains contested within the psychological literature, and it goes beyond the scope of this thesis to address the argumentation put forward in this debate in any detail.<sup>85</sup> Briefly put, the work of Kahnemann, Tversky and their collaborators has generally sought to demonstrate the limitations of heuristic mechanisms. In contrast, a Berlin-based group featuring influential psychologist Gerd Gigerenzer has argued for the utility of heuristic mechanisms in rendering decision-making “fast and frugal.”<sup>86</sup> Gigerenzer and colleagues have popularized phrases such as “less is more,” and “take the best,” to describe the advantages afforded by heuristic-based decision-making.<sup>87</sup> They have promoted analyzing “ecological rationality,” by which they mean studying the efficiency of heuristics in relation to a particular task and environment, such as acute stroke decision-making in the emergency department.<sup>88</sup>

Kahnemann and Tversky have documented a number of different heuristic mechanisms. One prominent heuristic is that of “framing,” which suggests that decision-making is heavily influenced by the frame within which information is presented.<sup>89</sup> For example, a patient who is told that surgery carries a 5% chance of death will be less likely to go under the knife than a patient who is told that surgery carries a 95% chance of survival. Another heuristic mechanism is “priming,” in which decision-making is influenced by prior exposure to stimuli.<sup>90</sup> For example, showing a patient a picture of a surgery gone wrong will make

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<sup>85</sup> Samuels, “Ending the Rationality Wars,” 236.

<sup>86</sup> Daniel G. Goldstein and Gerd Gigerenzer, “Models of Ecological Rationality: The Recognition Heuristic,” *Psychological Review* 109 (2002): 75-90.

<sup>87</sup> Gerd Gigerenzer and Henry Brighton, “Homo Heuristicus: Why Biased Minds Make Better Inferences,” *Cognitive Science* 1 (2009): 107-143.

<sup>88</sup> Gigerenzer, “Homo Heuristicus,” 107.

<sup>89</sup> Kahnemann, *Thinking*, 52.

<sup>90</sup> *Ibid.*, 128.

that individual less likely to agree to surgery. Framing and priming have both been documented to occur in medical decision-making.<sup>91</sup>

Another heuristic mechanism is “substitution,” in which a simple question is answered in place of a more complex one.<sup>92</sup> For example, one such substitution involves answering an affective question (“How do I feel about x?”) in place of a cognitive one (“What should I do about x?”). This type of substitution is particularly likely to occur when the original question is difficult, and when there is little time to deliberate on the answer. These circumstances may arise, for example, in the treatment of acute stroke. Because the question of how to manage a particular stroke patient is hard, a physician may instead consider how she feels about stroke patients, or how she feels about post-stroke disability. Or, the question of how to manage stroke in a 95 year old patient may be replaced by the question of how the physician feels about 95 year old patients. As a consequence, a physician’s attitudes and values (be they consciously recognized or not) may impact management in the case of acute stroke treatment decisions.

Recognition of the role of heuristics in decision-making does not eliminate the possibility of rationalistic decision-making, but highlights its limitations. From the perspective of Prospect Theory, two forms of decision-making can therefore be differentiated: first, the intuitive, automatic, biased processes often called Type 1 decision-making; and second, the rational, calculated procedures often called Type 2 decision-making.<sup>93</sup> Type 1 decision-making is considered to occur much more frequently than Type 2 decision-making. When an event is detected that violates the model of the world supported by Type 1 decision-making, then Type 2 mechanisms can take over. Given that the activation of Type 2 decision-making will be dependent upon the function of Type 1 processes, this set up demonstrates how Type 1 decision-making can heavily influence the use of Type 2 decision-making. Moreover, Type 1 decision-

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<sup>91</sup> Vilma L. Patel, David R. Kaufman, Jose F. Arochab, “Methodological Review: Emerging Paradigms of Cognition in Medical Decision-Making,” *Journal of Biomedical Informatics* 35 (2002) 52–75.

<sup>92</sup> Kahnemann, *Thinking*, 97.

<sup>93</sup> *Ibid.*, 24.

making can influence Type 2 decision-making through the production of impressions, intuitions, intentions and feelings that are subsequently confirmed by apparently rationalistic calculations.<sup>94</sup>

While Type 1 decision-making is quick and relatively effortless, Type 2 decision-making requires the expenditure of significant cognitive effort, often over prolonged periods of time. Type 2 decision-making can therefore be thought of as a limited resource: it can only be applied to a small number of problems simultaneously, and it is easily depleted.<sup>95</sup> For example, a study of Israeli appellate court justices found that they were much more likely to rely upon Type 1 decision-making (thereby denying parole to prisoners) when they were tired and hungry than when they had recently eaten or taken a break.<sup>96</sup> Type 1 decision-making is much more likely to be engaged in circumstances where the decision-maker is tired, hungry, required to make multiple decisions, or faced with time pressures and limited information.<sup>97</sup> These are the circumstances of acute stroke decision-making.

While recognition of heuristic approaches to decision-making has influenced recent studies on doctors' decisions, the normative content of the rationalistic approach persists, in that physicians generally expect that their decision-making should be consistent with the norms of rationalistic decision-making despite the frequent use of heuristics. They therefore view the use of heuristics as detrimental, and ideally avoidable. For example, physicians explicitly seek strategies that will minimize what they call "cognitive errors" and reduce "value-induced biases."<sup>98</sup> Pat Crosskerry, an influential Canadian emergency physician, has sought to catalogue "failed biases and heuristics" without consideration of the potential uses of such mechanisms.<sup>99</sup> He thereby reinforces the rationalistic bias towards valuing calculated decisions at the expense of heuristically-mediated decisions. Studies have sought to identify physicians who are so-called

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<sup>94</sup> Kahnemann, *Thinking*, 24.

<sup>95</sup> *Ibid.*, 42.

<sup>96</sup> *Ibid.*, 44.

<sup>97</sup> *Ibid.*, 44.

<sup>98</sup> Pat Crosskerry, "Achieving Quality in Clinical Decision Making: Cognitive Strategies and Detection of Bias," *Academic Emergency Medicine* 9(2002): 1184–1204.

<sup>99</sup> Crosskerry, "Achieving Quality," 1190.

“high quality” decision-makers, in that their decisions are deemed more rationalistic and less influenced by heuristics.<sup>100</sup> For example, physicians are encouraged to abandon “unreasoned rules of thumb” in favour of “rationalizing the choices made.”<sup>101</sup>

In 2007, Harvard physician and *New Yorker* columnist Jerome Groopman authored a widely-cited book entitled *How Doctors Think*, in which he explores “what goes on in a doctor’s mind as he or she treats patients.”<sup>102</sup> Groopman’s central argument is that physicians routinely make errors in their decision-making, and he attributes many of these errors to the influences of heuristic mechanisms. He appropriates the language of Tversky and Kahnemann to describe the “cognitive traps” that might befall physicians: errors of affect, availability, representativeness, and attribution. Like Crosskerry, Groopman spends little time considering how such mechanisms may be helpful. Moreover, Groopman does not explore the way physicians’ values and experiences may influence their decision-making. He argues that the way to mitigate the effects of “cognitive traps” on the part of physicians is to involve patients more actively in medical decision-making, as a check on physician imperfections.<sup>103</sup>

However, heuristic approaches to decision-making can offer a significant advantage over rationalistic approaches. In that the theories of heuristic decision-making were based on empirical studies, they likely represent a more accurate depiction of how physicians make decisions than do rationalistic conceptions. Heuristic approaches incorporate rationalistic models, under those circumstances in which they are appropriate. Moreover, as a descriptive theory of decision-making, a heuristic approach avoids much of the normative judgment that is associated with rationalistic approaches. However, in that they are focused on the cognitive processes of individuals, heuristic approaches can tell us little about the ways that social forces may influence decision-making. Additionally, heuristic approaches have not been and cannot be

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<sup>100</sup> Crosskerry, “Achieving Quality,” 1184.

<sup>101</sup> Denig, “Therapeutic Decision Making,” 9-15.

<sup>102</sup> Groopman, *How Doctors Think*, 3.

<sup>103</sup> *Ibid.*, 10.

historicized, in that the type of experimental interrogations used to identify their presence cannot be performed retrospectively on people of past eras. Therefore, the applicability of heuristics to the understanding the decision-making of physicians outside the present context is limited.

### *Social Psychological Approaches to Decision-Making*

Some of the limitations of heuristic approaches to medical decision-making have been addressed using approaches from sociology and social psychology. For example, recent research has sought to explore how an individual's decisions will be influenced by membership in a larger social context.<sup>104</sup> A prominent approach in social psychology, largely developed by Harvard psychologist Mahzarin Banaji, applies a methodology called the "implicit association test" to demonstrate how implicit racial preferences — reflective of one's social environment — impact the judgments that people make about each other. The implicit association test uses a variety of rapid association scenarios to demonstrate the influence of implicit or unconscious biases (for example, the presence of social stereotypes) on decision-making, even among individuals who disavow such prejudices or are members of the group subject to stereotyping. Banaji has also characterized the ways in which the language of everyday conversation can promote implicit preferences.<sup>105</sup> In 2007, Banaji collaborated with a group of medical researchers at Harvard University to study physicians' decision-making, and used the "implicit association test" methodology to demonstrate the presence of implicit racial preferences in diagnostic and treatment decisions.<sup>106</sup>

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<sup>104</sup> Anthony G. Greenwald, Mahzarin R. Banaji, "Implicit Social Cognition: Attitudes, Self-Esteem and Stereotypes," *Psychological Review* 102 (1995): 4-27.

<sup>105</sup> Oludamini Ogunnaike, Yarrow Dunham, Mahzarin R. Banaji, "The Language of Implicit Preferences," *Journal of Experimental Social Psychology* 46 (2010): 999-1003.

<sup>106</sup> Alexander R. Green, Dana R. Carney, Daniel J. Pallin, Long H. Ngo, Kristal L. Raymond, Lisa I. Iezzoni, Mahzarin R. Banaji, "Implicit Bias among Physicians and its Prediction of Thrombolysis Decisions for Black and White Patients," *Journal of General Internal Medicine* 22 (2007): 1231-1238.

Sociologist John McKinlay has also been influential in advancing our understanding of how doctors' decisions are influenced by characteristics related to the doctor, the patient, and the practice setting.<sup>107</sup> However, McKinlay seems to have appropriated the language of rationalistic methodologies, in that he refers to these elements as “non-medical influences,” thereby creating a distinction between them and so-called “medical influences.” This distinction suggests a normative judgment against “non-medical influences,” in that it implies that they are external or extraneous to medical decision-making. McKinlay has argued that, while important, these “non-medical influences” can and should be excised from medical decision-making, which is a claim I will contest later in this thesis.<sup>108, 109</sup>

McKinlay treats as straightforward the differentiation of medical and non-medical influences, though I will argue that this distinction is often difficult to draw. For example, is patient age a medical or a non-medical factor? While many ethicists might argue that physicians should not make judgments based on patient age, age reflects a physiological process. For example, there are certain diseases that are largely if not entirely age-determined, such as pyloric stenosis in infancy, Type 1 diabetes in childhood, and Alzheimer's Disease in older adulthood. Additionally, when resources are scarce, a defensible argument can be made that the most expensive treatments should be reserved for patients who are most likely to obtain the most benefit, such as younger healthier patients. Therefore, the differentiation of “medical” and “non-medical factors” represents a problematic approach to physician decision-making. I will return to this theme in Chapter 3.

Despite these limitations, the sociological literature on medical decision-making has introduced several important empirical techniques to the study of physician decisions. Later in this thesis, I will cite the results of studies targeting acute stroke decision-making that apply techniques developed by McKinlay and

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<sup>107</sup> McKinlay, “Non-medical Influences on Medical Decision-making,” 769-776.

<sup>108</sup> Flynn, *Non-Medical Influences*, 1.

<sup>109</sup> Jack A. Clark, Deborah A. Potter, John B. McKinlay, “Bringing Social Structure Back into Clinical Decision Making,” *Social Science & Medicine* 32 (1991): 853-866.

colleagues. One of these techniques is “factorial” experimental design, in which physicians’ decisions are tested in response to versions of a clinical scenario where the “medical” factors are held constant but the “non-medical” factors are randomized. For example, physicians may be exposed to different versions of a case of acute stroke, in which the patient’s age, race, or sex vary but the stroke-specific details remain unchanged. Factorial design was first applied by McKinlay et al. in 1996.<sup>110</sup> The intention of this design is to eliminate confounding variables so as to isolate the impact of a single “non-medical” element, such as patient race or insurance status. The technique was first used to study chest pain and shortness of breath,<sup>111</sup> and has since been applied in breast cancer,<sup>112, 113</sup> polymyalgia rheumatica and depression.<sup>114</sup> While factorial study design necessarily introduces an element of artificiality, it has become increasingly sophisticated, often involving the use of video vignettes featuring professional patient-actors in a standardized environment, thereby limiting the impact of the investigative technique itself.<sup>115</sup> Arguably, the most influential study to apply the factorial design was published in the *New England Journal of Medicine* in 1999. Using a factorial design, Schulman et al. suggested that primary care physicians demonstrate a systematic tendency against referring women and African Americans for investigations of chest pain.<sup>116</sup> Factorial design has since been

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<sup>110</sup> McKinlay, “Non-medical influences,” 770.

<sup>111</sup> *Ibid.*, 769.

<sup>112</sup> Risa B. Burns, Karen M. Freund, Mark A. Moskowitz, Linda Kasten, Henry Feldman, John B. McKinlay, “Physician Characteristics: Do They Influence the Evaluation and Treatment of Breast Cancer in Older Women?” *American Journal of Medicine* 103 (1997): 263-269.

<sup>113</sup> John B McKinlay, R. B. Burns, Howard A. Feldman, Karen M. Freund, J T Irish, L E Kasten, M A Moskowitz, Deborah A. Potter, K Woodman, “Physician Variability and Uncertainty in the Management of Breast Cancer: Results from a Factorial Experiment,” *Medical Care* 36 (1998): 385-396.

<sup>114</sup> John B. McKinlay, T. Lin, Karen Freund, M. Moskowitz, “The Unexpected Influence of Physician Attributes on Clinical Decisions: Results of an Experiment,” *Journal of Health & Social Behavior* 43(2002): 92-106.

<sup>115</sup> Scott K. Aberegg, Peter B. Terry, “Medical decision-making and healthcare disparities: The physician’s role,” *Journal of Laboratory and Clinical Medicine* 144 (2004): 11-17.

<sup>116</sup> Kevin A. Schulman, Jesse A. Berlin, William Harless, Jon F. Kerner, Shyryl Sistrunk, Bernard J. Gersh, Ross Dubé, Christopher K. Taleghani, Jennifer E. Burke, Sankey Williams, John M. Eisenberg, José J. Escarce, “The Effect of Race and Sex on Physician Recommendations for Cardiac Catheterization,” *New England Journal of Medicine* 340 (1999): 618-626.

applied to acute stroke decision-making,<sup>117</sup> and forms the basis of some of the empiric investigation reported later in this thesis.

These sociological and social psychological techniques suggest the value of “context” in studying physician decision-making. The term “context” has been used to refer to a broad number of factors that may influence a particular physician’s decision-making. For example, the notion of “context” has been applied to encompass the institutional, professional, and societal environments within which decisions are made;<sup>118</sup> to physician-specific factors such as biases, opinions, experience, and knowledge; and to patient-specific factors such as patient preferences and behaviours, as well as sex, race or ethnicity.<sup>119</sup> In this way, the concept of “context” has broadly overlapped with the “non-medical factors” outlined by McKinlay, in that they have included elements related to the practice environment, the physician, and the patient. In that contextual approaches begin from the position that decisions cannot be analyzed independently of the circumstances in which they occur, contextual approaches to decision-making are descriptive more than normative in focus, and can be used to support the analysis undertaken in this thesis.

However, I propose that the notion of context can be expanded to reflect factors that are of interest to historians and philosophers. Context can refer to the historical context in which a physician is practicing, as well as to the epistemic and ethical norms of that time and place. In relation to acute stroke decision-making, anthropologist Corinne Hodgson has argued that “clinical decision-making and practice behaviours do not exist in a vacuum but in the context of underlying personal and professional knowledge, attitudes

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<sup>117</sup> Michel Shamy, Karl Meisel, Anthony Kim, Rosendo Rodriguez, Frank Stahnisch, Eric Smith, “Acute Stroke Decision-Making,” unpublished data. Funded by Alberta Innovates Health Solutions, this project is an ongoing, international survey of neurologists’ decision-making in acute stroke. It includes an element of factorial design, in that respondents view 1 of 8 different video vignettes of a patient with the same clinical syndrome but of variable age, race and sex. Power calculations suggest that many of these differences will only be appreciable with 600 responses. Analysis of the first 79 responses will be discussed in subsequent chapters of this thesis.

<sup>118</sup> Larry D. Gruppen, Frederick M. Wolf, Jeffrey K. Stross, “Practice Characteristics of a Context for Primary Care Treatment Decisions: A Preliminary Study,” *Academic Medicine* 65 (1990): S9-S10.

<sup>119</sup> Joshua H. Tamayo-Sarver, Neal V. Dawson, Susan W. Hinze, Rita K. Cydulka, Robert S. Wigton, David W. Baker, “Rapid Clinical Decisions in Context: A Theoretical Model of Physicians’ Decision-Making with an Application to Racial/Ethnic Treatment Disparities,” *Research in the Sociology of Health Care* 23 (2005): 183-213.

and assumptions.”<sup>120</sup> A similar argument is developed in the writings of pediatricians Bauchner et al., who have argued for the importance of the “epistemic domain” of decision-making, by which they mean the contemporary state of medical knowledge.<sup>121</sup> Bauchner and colleagues have also suggested that “societal norms” have a pervasive influence on physician decision-making, though this influence is unlikely to be recognized by physicians making individual decisions. For example, understanding why a physician has administered tPA to a patient with an “acute stroke” will be influenced by the concept of what an “acute stroke” is, in that physician’s time and place. That is exactly the issue I will address in Chapter 1. In Chapter 2, I will explore the “epistemic domain” of acute stroke decision-making, and the notion of norms affecting acute stroke decision-making will be explored in Chapter 3.

The context of a physician’s treatment decisions may therefore be seen to incorporate the contemporary state of medical knowledge, as well as the contemporary state of moral values and beliefs. Moreover, this knowledge and these values will have a history of their own, and will arise in relation to a broader intellectual and scientific history.<sup>122</sup> Therefore, the application of techniques from the history and philosophy of science is likely to be a valuable exercise in the study of acute stroke decision-making, and is central to my methodology in this thesis. However, the notion of historical context is rarely mentioned in studies of physician decision-making, or is mentioned in only a cursory fashion.<sup>123</sup> For example, in an article for the *American Medical Association Journal of Ethics*, bioethicist Abraham Schwab briefly states that decisions about genetic testing would have had little meaning prior to the description of DNA in 1953, though he fails to explore how contemporary practice relates to past events.<sup>124</sup> To my knowledge, no encompassing discussion of the historically-determined nature of stroke treatment has appeared in the literature. I have

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<sup>120</sup> Corrine Hodgson and Kathleen Whelan, “Are Physicians Ready for Thrombolysis for Acute Stroke? A qualitative study,” *Canadian Medical Association Journal* 159 (1998): S19-S24.

<sup>121</sup> Bauchner, “Changing physician behaviour,” 460.

<sup>122</sup> Fleck, *Genesis*, 23.

<sup>123</sup> Joy Higgs, Mark A. Jones, “Clinical Decision-making and Multiple Problem Spaces,” in Joy Higgs, Mark A Jones, Stephen Loftus & Nicole Christensen, eds., *Clinical Reasoning in the Health Professions*, 3<sup>rd</sup> edition. (Amsterdam: Elsevier, 2008), 3-18.

<sup>124</sup> Abraham P. Schwab, “Improving Clinical Decision Making by Excising the Physician’s Judgment,” *Virtual Mentor: American Medical Association Journal of Ethics* 8 (2006): 469-472.

therefore sought to apply concepts from the broader literature in the history and philosophy of science to the questions at the core of this thesis. These sources are presented next.

*Approaches to Decision-Making from the History & Philosophy of Science*

One of the most influential descriptions of scientific knowledge and practice to appear in the last hundred years is Thomas Kuhn (1922-1996)'s *The Structure of Scientific Revolutions* (1962). In his landmark book, physicist and historian of science Thomas Kuhn presents a theory of scientific knowledge that can be applied to my study of medical decision-making. Kuhn famously challenges the traditional narrative of scientific progress as an additive process in which successive discoveries lead to the accumulation of knowledge.<sup>125</sup> Rather, Kuhn proposes that scientists necessarily interpret the world around them from within a paradigm, which he refers to as a “disciplinary matrix” of shared beliefs, values, instruments and techniques.<sup>126</sup> For Kuhn, paradigms are by definition incompatible, and therefore science advances when one paradigm overthrows another. This process of overthrow, which he terms “scientific revolution,” interrupts periods of “normal science” in which one paradigm is dominant and unquestioned within a given field of inquiry.<sup>127</sup> The interpretation of a given phenomenon by any individual scientist will therefore be determined by the paradigm within which she operates. Understanding why and how a scientist approaches a problem in a particular way will be dependent upon understanding her paradigm.

Although Kuhn primarily used examples from the history of physics to support his argument, the notion of scientific paradigms has been broadly applied to medicine, particularly in the study of previous historical eras.<sup>128,129,130</sup> Like scientists, physicians can be understood to interpret the world around them

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<sup>125</sup> Kuhn, *Structure*, 6.

<sup>126</sup> Alexander Bird, “Thomas Kuhn,” *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/thomas-kuhn/>, (accessed April 13, 2014).

<sup>127</sup> Kuhn, *Structure*, 94.

<sup>128</sup> C. E. Quin, “The Ideas of Thomas Kuhn in Relation to Medical Advances in the Sixteenth and Seventeenth Centuries,” *Journal of the Royal Society of Medicine* 90 (1997): 225-228.

<sup>129</sup> J.S. Couto, “Evidence-based Medicine: a Kuhnian Perspective of a Transvestite Non-Theory,” *Journal of Evaluation in Clinical*

(encountered through patient histories, physical examinations, laboratory tests, etc.) through paradigms. Their paradigms would include such content as beliefs about disease (what causes it, how to measure it), and its treatment (what is likely to be effective, how to decide, which ethical principles should guide practice). Furthermore, these paradigms will be historically determined. While the practices of 18<sup>th</sup> century physicians may appear to modern eyes to be superstitious and erroneous (for example, treating pneumonia with bloodletting), they must be understood to be no less scientific from within their paradigm than are contemporary approaches within our paradigm (treating stroke with tPA). Understanding how physicians make decisions in the treatment of stroke in 2014 will therefore depend upon their paradigm. We can therefore ask, what are the foundational beliefs of that paradigm, when did they emerge, and to what degree are they contested? These questions are central to the argumentation of Chapters 1 and 2.

However, there are important ways in which a Kuhnian approach to understanding physician decision-making is insufficient. Perhaps most significant to the central questions of this thesis is that disagreements exist within medicine about basic content that Kuhn would consider central to a paradigm.<sup>131</sup> Members of different disciplines (such as neurologists in contrast to neurosurgeons) whose areas of expertise overlap may acquire different ways of approaching patients and of defining problems. Therefore, it can be hard to argue that all physicians share a single paradigm. Even within one discipline, physicians may disagree about core concepts, such as what is the cause of a particular disease. As a consequence, they may approach clinical situations quite differently. For example, in *Broken Hearts*, Jones chronicles how cardiologists debated for decades whether atherosclerotic plaques in the coronary arteries were the cause or the consequence of myocardial infarction (heart attack).<sup>132</sup>

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*Practice 4* (1998): 267-75.

<sup>130</sup> Evelyn Fox Keller, "Genes, Genomes and Genomics," *Biological Theory* 6 (2012): 132-140.

<sup>131</sup> Marcus Jacobson, *Foundations of Neuroscience* (New York: Plenum Press, 1993), 34.

<sup>132</sup> Jones, *Broken Hearts*, 48.

It likely that the way physicians conceive of diseases and their causes will have an impact on their treatment decisions. To understand how physicians make decisions about stroke, we must understand how they conceive of stroke in the first place. As historian of medicine Charles Rosenberg has famously argued, diseases can be thought of as *social constructs* rather than as *natural kinds*.<sup>133</sup> This distinction will be explored in detail in Chapter 1, but simply put, a natural kind is a thing whose existence or character is determined by nature, while a social construct is a thing that is brought into existence or shaped by social events, forces, and history.<sup>134</sup> While diseases are related to biological events, how they are understood by physicians and patients is socially constructed in a given time and place. In his influential essay “Framing Disease” (1992), Rosenberg argues that a disease does not exist until “we have agreed that it does, by perceiving, naming, and responding to it.”<sup>135</sup> He refers to this process as “framing,” recalling terminology from Tversky and Kahnemann. For example, “stroke” in 2014 is framed differently than it was in 1994 or 1794.

Understanding stroke in 2014 requires understanding what it means to the doctors, nurses, patients and families who engage with it, think about it, and live with it in 2014. Approaching acute stroke as a social construct will inform the arguments at the heart of Chapter 1, and will be explored in greater detail there.

How physicians make decisions about the treatment of certain diseases, and ultimately how those diseases are “framed,” will in large part depend upon the technology of the day. In *Medicine and the Reign of Technology* (1981), historian of medicine Stanley Joel Reiser traces four centuries of technological developments and describes how they have altered medical decision-making. He highlights certain major technological innovations that changed the “visualization” of the inner workings of the body: the stethoscope made the detection of pathology in the heart and lungs appreciable in novel ways; the ophthalmoscope allowed physicians to look into the patient’s eye; the microscope allowed them to explore the “cellular

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<sup>133</sup> Charles E. Rosenberg, “The Therapeutic Revolution: Medicine, Meaning and Social Change in Nineteenth Century America,” in Morris J. Vogel, Charles E. Rosenberg, *The Therapeutic Revolution: Essays in the Social History of American Medicine* (Philadelphia: University of Pennsylvania Press, 1979), 4.

<sup>134</sup> Ian Hacking, *The Social Construction of WHAT?* (Cambridge: Harvard University Press, 1999), 7.

<sup>135</sup> Charles E. Rosenberg, “Framing Disease: Illness, Society and History”, eds. Charles E. Rosenberg & Janet Golden, *Framing Disease: Studies in Cultural History* (New Brunswick, NJ: Rutgers University Press, 1992), xiii.

universe.”<sup>136</sup> He warns that medicine in the mid-20<sup>th</sup> century has become overly dependent upon technologies that it celebrates as certain and objective, though they remain subjective and uncertain.<sup>137</sup> Reiser’s argumentation is relevant to the claims of this thesis on several fronts. First, the importance of technology in defining treatment decisions will be addressed in Chapter 1. The case of the CT scanner, developed in the 1970s, will be shown to have been a seminal event in the development of the contemporary notion of the acute stroke. Second, the idea of modern medical science as certain and objective will be explored, and challenged, in Chapters 2 and 3.

Whether a physician decides to provide tPA to a patient with stroke may depend upon the paradigm within which she is operating, the framing of diseases in her society, or the technological capital of the day. Moreover, a broad body of literature suggests how a physician’s values can influence her decision-making.<sup>138, 139, 140</sup> In Chapter 3, I will explore the ways that physicians’ decisions necessarily require value judgments, and the incorporation of physicians’ own values. Writing in *Virtual Mentor*, the online ethics journal of the American Medical Association, Jack Drescher contends that “No physician can claim to practice value-free medicine. Undoubtedly, physicians are raised with values, religious or otherwise, that shape their decisions to become professional caretakers. Their training is further influenced by professional values.”<sup>141</sup> The ways in which physicians’ value judgments — of ideas, people, and states of disability — impact their decision-making will be addressed in Chapters 2 and 3. Specifically, I will propose that physicians’ decisions about whether to use tPA to treat patients with stroke involves dual processes of epistemic and ethical evaluation.

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<sup>136</sup> Reiser, *Reign of Technology*, 69.

<sup>137</sup> *Ibid.*, 162.

<sup>138</sup> Jones, *Broken Hearts*, 17.

<sup>139</sup> Nicholas A. Christakis, David A. Asch, “Physician Characteristics Associated with Decisions to Withdraw Life Support,” *American Journal of Public Health* 85 (1995): 367-371.

<sup>140</sup> Mark D. Siegel, “End-of-Life Decision Making in the ICU,” *Clinics in Chest Medicine* 30 (2009): 181-184.

<sup>141</sup> Jack Drescher, “Physician Values and Clinical Decision Making” *Virtual Mentor: Ethics Journal of the American Medical Association* 8(2006): 303-308.

Further precedent for my approach to physician decision-making — as a historical, epistemic and ethical process — can be found in the writings of California stroke physician Dr. M. Elizabeth Sandel.

Sandel describes how:

“We bring our life experiences, education and training, personal characteristics, and the biases, values and ideas we learned from our family of origin and culture when we make decisions and when we take action. . . . Following a stroke, the patient confronts the situation with his or her own background and pre-event experiences, and these elements contribute to his or her reactions, responses, and decisions. Opinions and perspectives of the circle of family and friends are also determining factors. For a physician or other health care provider, similar elements are present in encounters with the patient. Of course, in addition to these factors, medical knowledge and previous experiences with other patients with a history of stroke are powerful determinants.”<sup>142</sup>

Sandel identifies the presence of uncertainty, value judgments, conscious bias, and unconscious bias within this broad conception of the factors relevant to physician decision-making. She relates how the attitudes of neurologists regarding stroke has evolved over the course of the last 30 years, abandoning therapeutic nihilism for the belief that recovery is possible. Sandel describes how these multiple influences on decision-making are historically- and epistemically-determined. While her discussion focuses on the study of measures used to enhance recovery post-stroke rather than the use of IV tPA to reverse deficits in a shorter time frame, Sandel’s conceptualization appears highly applicable to contextualizing acute stroke decision-making in relation to the history and philosophy of science.

### *The Case of Acute Stroke Decision-Making*

Medical decision-making, I have argued, is a valid topic of study from the perspective of the history and philosophy of science. Specifically, notions of paradigms, of diseases as social constructs, and of doctors as people with values, may reveal the complexities of the decision-making process. I have chosen the case of acute stroke decision-making to be the subject of this thesis, and it is now time to explain the terms and

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<sup>142</sup> M. Elizabeth Sandel, “Stroke, Disability, and Unconscious Bias: Interrelationships and Overdetermination in Medical Decisions,” *Topics in Stroke Rehabilitation* 18 (2011): 70-73.

basic concepts of the case in question. The term “stroke” appears to have been first used in 1599, though modern conceptions about its clinical features and pathological qualities can be traced to the accomplishments of 19<sup>th</sup> century French and German physicians and pathologists, such as Jean-Martin Charcot (1825-1893), Henri Duret (1849-1921), Otto Heubner (1843-1926) and Rudolf Virchow (1821-1902). Significantly more has come to be known about stroke subtypes and their respective “risk factors” from the work of 20<sup>th</sup> century Canadian and American neurologists such as C. Miller Fisher (1913-2012), Louis R. Caplan, J.P. Mohr, and Henry Barnett.<sup>143</sup>

Stroke is a common and serious disease. It is frequently cited as the leading cause of disability, and the third leading cause of death, in Canada. It is one of the most common neurological diseases, affecting more than 50,000 Canadians per year.<sup>144</sup> In contemporary medicine, the term stroke may be applied non-specifically, referring to any of five discrete pathological processes: ischemic stroke, intracerebral hemorrhage, hypoxic-ischemic encephalopathy, subarachnoid hemorrhage, and cerebral venous sinus thrombosis.<sup>145</sup> The commonality between these processes is that they can share a clinical phenotype, meaning that their symptoms may be similar. Specifically, they may each present as the *sudden onset* (arising and peaking quickly, over a period of seconds or minutes) of *focal neurological symptoms* (the loss of functions of the nervous system, such as the ability to move one side of the body or to produce speech).<sup>146</sup>

In this thesis, I will limit my discussion to ischemic stroke, for several reasons. First, ischemic stroke accounts for upwards of 70% of all events that may be called “strokes,” and is therefore the most common of the five processes introduced above. Second, ischemic stroke is a serious illness: of 100 patients who suffer an ischemic stroke, 20 will die, 20 will return to normal, and 60 will be left with some degree

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<sup>143</sup> Maurizio Paciaroni, Julien Bogousslavsky, “How Did Stroke Become of Interest to Neurologists? A Slow 19<sup>th</sup> Century Saga,” *Neurology* 73 (2009): 724-728.

<sup>144</sup> Lindsay, “Canadian Best Practice Recommendations.”

<sup>145</sup> Catherine Haberland, *Clinical Neuropathology* (New York: Demos, 2007), 43. Ischemic stroke and intracerebral hemorrhage will be discussed in detail in this thesis. For more information on the pathological entities, please see the glossary.

<sup>146</sup> Wade S. Smith, S. Claiborne Johnston, J. Donald Easton. “Cerebrovascular Diseases” in Steven L. Hauser, ed. *Neurology in Clinical Medicine*, (New York: McGraw Hill, 2006), 233-271.

of deficit or disability.<sup>147</sup> Third, and most importantly, ischemic stroke is the only one of the five types of “stroke” whose symptoms can be reversed by a specific intervention, be it medical or surgical. Therefore, the type of decision-making under investigation in this thesis — namely, how doctors decide to administer a particular treatment — is only applicable to ischemic stroke. Henceforth, “stroke” and “acute stroke” will be used to refer exclusively to *ischemic stroke* or *acute ischemic stroke*, respectively. Some consideration of the contemporary understanding of the pathological process of ischemia is now appropriate.

Ischemia refers to an abnormal state in which an organ (in this case the brain) is deprived of adequate blood flow.<sup>148</sup> In ischemic stroke, an interruption in the flow of blood to a particular region of the brain arises due to the blockage of an artery within the head or neck. Arteries are the pipes that deliver blood, oxygen, glucose and important nutrients from the heart to the body’s organs, including the brain.<sup>149</sup> When blood flow in an artery is impaired, a group of brain cells will become starved, and will stop functioning. As a consequence, the patient experiences the sudden loss of the functions previously performed by that part of the brain. For example, he or she may experience the loss of the ability to generate or understand speech, to move one side of the body, to feel touch on one limb, or to see one half of the world. If blood flow remains sufficiently impaired for sufficiently long, then that brain region will die, and those functions will be irreversibly lost.<sup>150</sup>

The number of arteries carrying blood to and within the brain is limited, and their anatomical organization is relatively consistent across the human species.<sup>151</sup> Moreover, the distribution of brain functions (such as speaking or sensation) is relatively consistent as well.<sup>152</sup> When a particular brain artery is blocked, blood flow is lost only to the region served by that artery. This leads to the loss of the functions of that and only that region, in discrete and reproducible ways. Because of the consistency of the association

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<sup>147</sup> Smith, “Cerebrovascular Diseases,” 233-271.

<sup>148</sup> Haberland, *Clinical Neuropathology*, 33.

<sup>149</sup> *Ibid.*, 44.

<sup>150</sup> Smith, “Cerebrovascular Diseases,” 233.

<sup>151</sup> Hal Blumenfeld, *Neuroanatomy Through Clinical Cases, 1<sup>st</sup> edition* (Sunderland, MA: Sinauer, 2002), 367.

<sup>152</sup> Blumenfeld, *Neuroanatomy*, 31.

between functions, brain regions, and arterial supply, neurologists can derive from the clinical symptoms manifested by a patient both the region of the brain affected and the blocked artery.<sup>153</sup> This clinical-anatomical reasoning is central to acute stroke decision-making, and will feature in Chapters 1 and 2. Because of neurologists' familiarity with the structural and functional anatomy of the brain, they are able to determine whether the symptoms demonstrated by a given patient are consistent with the common patterns encountered in ischemic stroke.

When a patient in Canada in 2014 experiences a stroke, she (or someone close by) is liable to call 9-1-1, and the patient is immediately transported to a hospital emergency department. There, the patient may be assessed by an emergency physician, by a neurologist, or by both types of doctors. An account of what transpired — what physicians call the *history* — is obtained as quickly as possible, and then the patient undergoes a *physical examination*, which serves to identify the pattern of symptoms being experienced by the patient. After the physical examination, the patient proceeds to the computerized tomography (CT) scanner, where an x-ray based image of the brain is obtained.<sup>154</sup> The purpose of the CT scan is primarily to exclude intracerebral hemorrhage — bleeding into the substance of the brain — which can have identical clinical symptoms to an ischemic stroke. Intracerebral hemorrhage is managed differently than ischemic stroke, most prominently in that the clot-busting drug tissue plasminogen activator is not used in the treatment of hemorrhage. On the basis of the history, physical examination, CT scan results, and some additional parameters, the clinicians involved will decide whether the patient is a candidate for treatment with the drug called tissue plasminogen activator (tPA).<sup>155</sup>

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<sup>153</sup> Blumenfeld, *Neuroanatomy*, 368.

<sup>154</sup> J.H. Warwick Pexman, Philip A. Barber, Michael D. Hill, Robert J. Sevick, Andrew M. Demchuk, Mark E. Hudon, William Y. Hu, Alastair M. Buchan, "Use of the Alberta Stroke Program Early CT Score (ASPECTS) for Assessing CT Scans in Patients with Acute Stroke," *American Journal of Neuroradiology* 22 (2001):1534-1542.

<sup>155</sup> H. Bart van der Worp, Jan van Gijn, "Acute Ischemic Stroke," *New England Journal of Medicine* 357 (2007): 572-579.

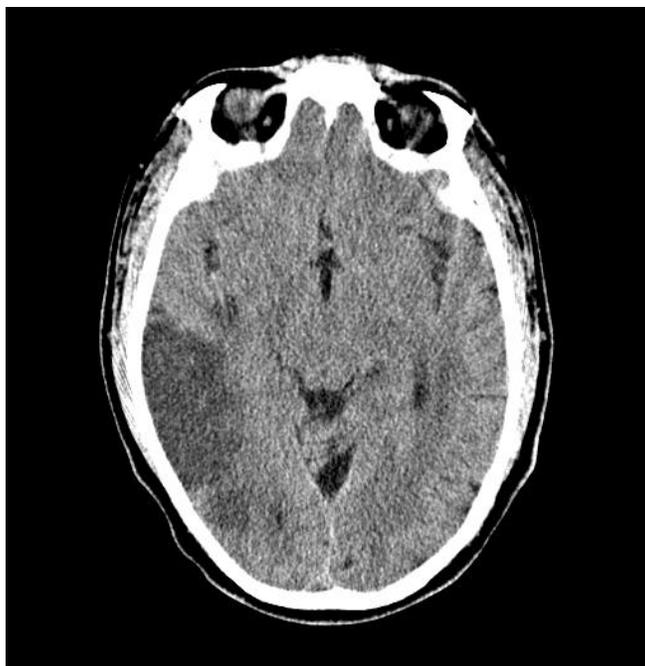


Figure 1. CT scan of the brain, anonymized patient, Toronto, 2010. On a CT scan, air is black, bone is white, and brain is grey. The head is oriented such that the eyes are at the top and the back of the head is at the bottom of the image. An area to the back left that is darker grey represents an ischemic stroke affecting the right middle cerebral artery territory. The fact that the brain in this section is darker than the rest suggests that it is irreversibly damaged.

The use of tPA is based on its presumed ability to re-open blocked arteries, an effect first suggested in a landmark 1995 clinical trial published in the *New England Journal of Medicine*. That trial, now known as the NINDS trial after the governmental agency that funded it,<sup>156</sup> suggested for the first time that a medicine could be used to reverse the signs and symptoms of stroke, leading to better long-term outcomes for patients.<sup>157</sup> Tissue plasminogen activator is a powerful thrombolytic, or clot-buster, that is administered through the vein (IV) to reopen blockages in arteries that can impair blood flow to the brain, as well as in the heart, lungs, or other major arteries.<sup>158</sup> tPA does not work in all cases. Specifically, it is only beneficial in stroke if administered within approximately 3 hours of the onset of a patient's symptoms. Longer than

<sup>156</sup> For more on the National Institute of Neurological Disease and Stroke, please see the Glossary.

<sup>157</sup> The National Institute of Neurological Disorders and Stroke (NINDS) r-tPA Study Group, "Tissue Plasminogen Activator for Acute Ischemic Stroke," *The New England Journal of Medicine* 333 (1995):1581-1587.

<sup>158</sup> Désiré Collen, Henri Roger Lijnen, "Tissue-type Plasminogen Activator: a Historical Perspective and Personal Account," *Journal of Thrombosis and Haemostasis* 2 (2004): 541-546.

that, and tPA brings a greater chance of harm than benefit. The mechanism of that harm is bleeding: as a clot-buster, it can induce potentially fatal hemorrhage, be it in the brain or elsewhere in the body.<sup>159</sup>

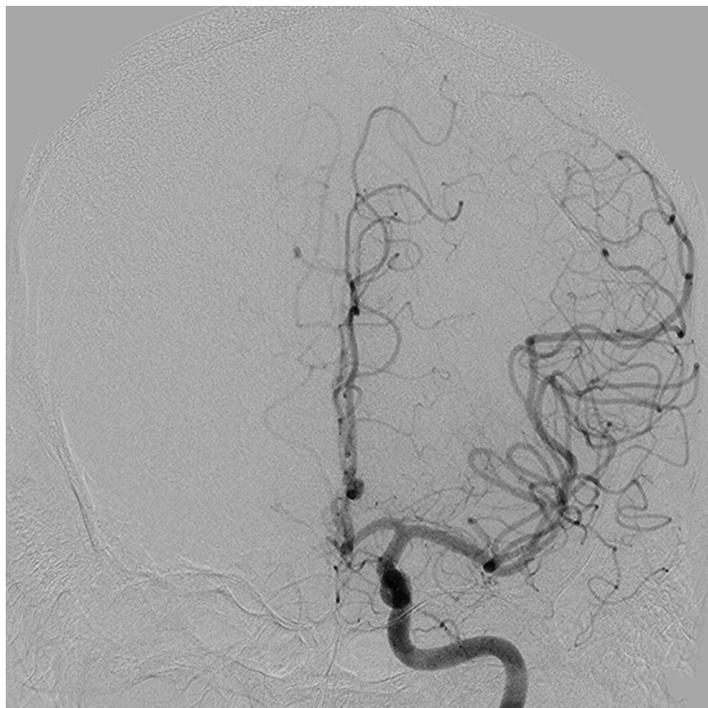


Figure 2. Digital Subtraction Angiogram from an anonymized patient, Toronto, 2010. This image depicts normal blood flow through the left internal carotid artery, which enters the brain and divides into the anterior cerebral artery (midline) and middle cerebral artery (right). This pattern of blood flow is duplicated, with a twin supply arising from the other side of the neck (not shown). This pattern is relatively preserved across the human species.

The decision faced by clinicians in the setting of an acute stroke is whether or not to use tPA.

National guidelines recommend its use, and the developed nations of the world have invested large sums of money to put in place an infrastructure that allows patients to be treated with tPA as quickly as possible.<sup>160</sup>

However, this simple, everyday decision — *yes or no to tPA?* — appears to be quite complex. Many estimates suggest that fewer than 5% of stroke patients receive treatment with IV tPA, largely owing to the fact that many patients do not arrive in hospital quickly enough to be assessed for treatment within 3 hours.

<sup>159</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1581.

<sup>160</sup> Editorial, “Why we should invest in a stroke unit,” *The Guardian*, published February 1, 2008, accessed online at <http://www.theguardian.pe.ca/Opinion/Editorials/2008-02-01/article-1376895/Why-we-should-invest-in-a-stroke-unit/1>, (June 24, 2014).

However, even among eligible candidates for tPA, fewer than 50% of patients receive treatment with tPA.<sup>161</sup> If tPA gives stroke patients their best chance of recovery, shouldn't it be a straightforward matter of administering it to all eligible patients?<sup>162</sup>

The way that cases of acute stroke are reported in the medical literature would certainly suggest so.

A characteristic example appears in a review article in the *New England Journal of Medicine* in 2007:

A 62-year-old man has sudden weakness of the left arm and leg and slurred speech. Except for untreated hypertension, his medical history is unremarkable. He is a current smoker with a smoking history of 45 pack-years. On arrival at the emergency department 1 hour 15 minutes after the onset of symptoms, he reports no headache or vomiting. His blood pressure is 180/100 mm Hg, and his pulse is 76 beats per minute and is regular. Neurologic examination shows dysarthria, a left homonymous hemianopia, severe left-sided weakness, and a failure to register light touch on the left side of the body when both sides are touched simultaneously (left tactile extinction). How should this patient be evaluated and treated in the short term?<sup>163</sup>

This 62 year old man arrives in the emergency department with disabling deficits, referable to a blockage of the right Middle Cerebral Artery, the main artery carrying blood to the right side of the brain. He is within the time window for treatment with IV tPA. The authors conclude their vignette with a question (“How should this patient be evaluated and treated?”), but they do not expect debate: standard management includes a CT scan to exclude intracerebral hemorrhage, and they expect that the patient should receive IV tPA.

In this case, as in much of the stroke literature, the decision-making process is taken to be self-evident: the patient has been diagnosed with a stroke and is in the time window, and therefore should (and will) be treated with tPA. However, any number of relevant assumptions — that there is a disease called an acute ischemic stroke, that the diagnosis of acute ischemic stroke is clear in this patient, that tPA is an effective treatment for acute ischemic stroke, that the physician believes that tPA is the best option for this

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<sup>161</sup> Irene L. Katzan, Maxim D. Hammer, Eric D. Hixson, Anthony J. Furlan, Alex Abou-Chebl, Deborah M. Nadzam, “Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke,” *Archives of Neurology* 61 (2004):346-350.

<sup>162</sup> Nancy K. Hills, S. Claiborne Johnston, “Why are Eligible Thrombolysis Candidates Left Untreated?” *American Journal of Preventive Medicine* 31(2001): S210-S216.

<sup>163</sup> van der Worp, “Acute Ischemic Stroke,” 572.

patient, that the physician will do what is best for this patient — go unmentioned. And yet, these assumptions and values, developed within a particular historical, epistemic, and ethical context, appear highly relevant to acute stroke decision-making. They are the subject of this thesis: how do physicians make treatment decisions surrounding the use of tPA in the management of acute ischemic stroke?

### *Outline*

To begin, what is an “acute stroke” to neurologists in 2014? In Chapter 1, I will argue that the disease called the “acute stroke” is understood as a stroke that potentially treatable through properly administered tPA. This argument takes as its starting point the notion that diseases are social constructs and not natural kinds, and therefore I will introduce the relevant conceptual basis for this position. Given that the efficacy of tPA for acute stroke was first demonstrated in the NINDS trial in 1995, I will explore usages of the term “acute,” “stroke,” and “acute stroke” in the years prior to 1995, as a means of tracing the relevant notions that have since come together in the contemporary concept of the “acute stroke.” Specifically, I will argue that “acute stroke,” as understood today, is conceived in relation to the efficacy of tPA because of the interweaving of several earlier concepts. These earlier concepts, which I label *preconditions*, incorporate key concepts from the history of neurology and medicine dating to the 17<sup>th</sup> century. For example, the contemporary notion of the “acute stroke” depends upon the idea that diseases are localizable within the body (and the brain), meaning that they can be related to dysfunction of specific organs, rather than to dysfunction of the body as a whole. A second precondition is the development of the notion of the clinico-anatomical method, meaning that physicians can identify consistent relations between a disease’s location and a patient’s symptoms. Moreover, the existence of the “acute stroke” depends upon the differentiation of ischemia from hemorrhage, both as pathological entities identified at autopsy, and as clinical entities using the CT scan. Finally, the notion of the “acute stroke” is dependent upon a physiological theory called the penumbra, in which it is posited that brain tissue remains alive in the setting of stroke

despite the interruption of blood flow. These preconditions come together, I argue, in light of the results of the NINDS trial, which was published in 1995. By defining “acute stroke” in relation to a set of preconditions, I argue that contemporary notions of disease — and the decisions that are based upon them — are historically-determined rather than timeless, and contingent rather than inevitable. This historical analysis of the “acute stroke” exemplifies the importance of understanding the genesis and development of ideas in modern medicine.

In Chapter 2, I engage in an exploration of the role of epistemic reasoning in acute stroke decision-making. I propose that acute stroke decision-making involves a process in which clinical propositions (eg. that the acute stroke is treatable with tPA, or that the diagnosis of acute stroke can be made) are subject to epistemic evaluation, and that the results of these epistemic evaluations impact treatment decisions. My conceptualization of this process of epistemic evaluation builds from the scholarship of the Polish biologist and philosopher Ludwik Fleck (1896-1961). Particularly, I argue that physicians evaluate contemporary knowledge (such as the results of the NINDS trial) in relation to what Fleck terms a *thought style*, or a historical body of knowledge and practices.<sup>164</sup> Therefore, differences in the epistemic evaluation of a set of clinical propositions relevant to acute stroke decision-making reflect differences in physicians’ thought styles. Historical knowledge — specifically, knowledge of the preconditions that established the modern meaning of the acute stroke — plays a central part in the epistemic evaluation of the clinical propositions relevant to acute stroke decision-making. My characterization of epistemic evaluation in acute stroke decision-making differs significantly from that offered by evidence-based medicine, which is the dominant theory of medical epistemology in the 21<sup>st</sup> century. As a consequence, I provide a critique of evidence-based medicine, focusing on its depiction of medical knowledge and its role in physician decision-making.

In Chapter 3, I propose that acute stroke decision-making also involves a process of ethical evaluation, in which patients, diseases and outcomes are evaluated by physicians as part of the decision to

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<sup>164</sup> Fleck, *Genesis*, 39.

administer tPA. I provide a justification for exploring the ethical aspects of everyday medical decisions, like those surrounding tPA use, that breaks with the principlist approach to medical ethics that has characterized most bioethics scholarship over the last four decades. I argue that physician decision-making is consequentialist in its orientation, and therefore, medical outcomes are also ethical outcomes, and medical decision-making is also ethical decision-making. I then explore the content of those ethical decisions, namely how clinicians evaluate patients' post-stroke outcomes and pre-stroke states. I conclude that ethical evaluation is an important influence on acute stroke decision-making. I challenge the contemporary notion that medical decisions can be objective, independent of theory and values. I propose that acute stroke decision-making is necessarily subjective and variable.

In my conclusion, I summarize the central argument of this thesis, namely that acute stroke decision-making includes processes of epistemic and ethical evaluation based on historically-determined notions of disease and treatment. I argue that we can generalize from the example of acute stroke decision-making to conceive of physician decision-making as a simultaneously historical, epistemic and ethical process. Moreover, I elaborate the ways that physician decision-making is psychological, social and scientific. If physician decision-making is indeed historical, philosophical and scientific, then analysis based in the disciplines of the humanities — and especially in the history and philosophy of science — is not just helpful but necessary to understand the complexities of contemporary medical practice.

## Chapter 1: The Meaning of “Acute Stroke”

The concept of syphilis must be investigated like any other case in the history of ideas, as being the result of the development and confluence of several lines of collective thought.  
– Ludwik Fleck, *Genesis and Development of a Scientific Fact* (orig. 1935)

### *Introduction*

The intention of this thesis is to analyze how doctors make decisions in the treatment of patients with acute stroke, as a means of better understanding the decision-making processes of doctors in general. Specifically, an approach based in the history and philosophy of science has been applied to the case of acute stroke decision-making in the latter half of the 20<sup>th</sup> century and the beginning of the 21<sup>st</sup> century. An important step in understanding how doctors treat patients with acute stroke is to understand how doctors during this period have come to understand the meaning of the term “acute stroke.” For example, if “acute stroke” is understood as a disease that is irreversibly debilitating and unresponsive to any treatment, then doctors would be unlikely to administer treatment for a condition that they know to be incurable.<sup>165</sup> A philosophical approach to the “acute stroke” will help to identify what is meant by the term, while a historical approach to will help to identify its temporal origins and development.

In this chapter, I will argue that “acute stroke” is understood by contemporary physicians as a stroke that is potentially reversible through the proper administration of the thrombolytic (clot-busting) drug called tPA. I propose that this meaning has arisen in light of the results of the NINDS clinical trial, which in 1995 became the first trial to demonstrate the efficacy of tPA as a treatment for stroke.<sup>166</sup> Moreover, I intend to trace the origins of this modern meaning of the “acute stroke” to a set of preconditions, by which I mean a series of concepts and systems that allowed for the development of acute stroke’s modern meaning.

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<sup>165</sup> William Osler, *The Principles and Practice of Medicine*, 7<sup>th</sup> Edition (New York: D. Appleton and Company, 1911), 981.

<sup>166</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1581.

I will argue that the definition of “acute stroke” in relation to tPA is dependent upon six preconditions: an elaboration of the vascular anatomy of the brain, the conceptualization of pathology as localizable within the body, the pathological distinction of ischemia from hemorrhage, the application of computerized tomography (CT) scanning, the development of thrombolytic therapies, and the conceptualization of the ischemic penumbra.<sup>167</sup>

My analysis of the meaning of the “acute stroke” is based upon a particular characterization of disease: namely, of diseases as social constructs, conceived in relation to a historical era and its scientific, epistemic and ethical content.<sup>168</sup> This view differs from the traditional medical approach to disease. Therefore, I will begin this chapter by addressing the question of how diseases can and should be analyzed. Terminologies and concepts from history, epistemology and ontology will be introduced to serve as the foundation upon which the argument of this chapter will follow, and from which relevant generalizations about doctors’ decision-making will be drawn.

### *History, Epistemology & Ontology*

How are we to answer a question like: “What is the meaning of acute stroke?” On the most basic level, that depends on what kind of thing we think an acute stroke is.<sup>169</sup> If an acute stroke is considered along the lines of gold or oxygen — an entity that exists in nature and bears qualities that are consistent at all times and in all places — then defining its nature is simply a question of identifying those qualities. Its history, then, would be a relatively straightforward narrative of how it was discovered, and how its properties were characterized.<sup>170</sup> If, however, an acute stroke is an idea — like hope or wealth — then defining its nature means understanding what that idea means to the people who share it. Its history

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<sup>167</sup> The neurophysiological concept of the penumbra will be explored in detail later in this chapter. However, I expect that it unfamiliar to most audiences and have provided a brief discussion in the Glossary.

<sup>168</sup> Ian Hacking, *The Social Construction of WHAT?* (Cambridge: Harvard University Press, 1999), 100.

<sup>169</sup> Jeremy R. Simon, “Constructive Realism and Medicine: An Approach to Medical Ontology,” *Perspectives in Biology and Medicine* 51 (2008): 353-366.

<sup>170</sup> Kuhn, *Structure*, 2.

becomes a story of how people in past eras have understood the term, how that meaning existed in relation to other concepts, and how our current understanding developed.<sup>171</sup>

This comparison — of gold on the one hand, and wealth on the other — apposes the notions of *natural kinds* and *social constructs*. A natural kind, as suggested above, is an entity that exists and would exist regardless of human understanding. Traditionally speaking, members of a natural kind are felt to share a common essence.<sup>172</sup> For example, the essence of gold is its atomic structure. From the perspective of *kind essentialism*, this structure “occurs in all and only pieces of gold, and it is a property that all gold must have.”<sup>173</sup> In recent decades, the notion of what identifies a natural kind, particularly in biology, has been hotly contested.<sup>174</sup> The specifics of this debate go beyond the scope of my thesis. However, the notion that there exist in nature certain kinds whose properties are consistent and (relatively) indivisible reflects one way of conceiving of diseases like the acute stroke.

In contrast, the notion of disease as a social construct implies that diseases are conceived and understood through a human lens, in relation to time, place, and person.<sup>175</sup> Columbia University physician and philosopher Jeremy Simon summarizes the social constructivist position when he writes that “patients are arranged in diagnostic categories that are constructed by humans based on criteria that may be related to our methods for gaining knowledge about our patients’ conditions, our means for treating them, or other factors that humans use to categorize each other.”<sup>176</sup> In important ways, even gold and oxygen can be seen as ideas, whose qualities are interpreted by people on the basis of their points of view.<sup>177</sup> In clinical medicine, and much of medical historiography, diseases like the acute stroke are thought to reflect natural

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<sup>171</sup> Kuhn, *Structure*, 10.

<sup>172</sup> Marc Ereshefsky, “Species, Taxonomy and Systematics,” eds. Alex Rosenberg, Robert Arp, *Philosophy of Biology: An Anthology* (Chichester: Wiley-Blackwell, 2010), 255-271.

<sup>173</sup> Marc Ereshefsky, “Natural Kinds in Biology,” *Routledge Encyclopedia of Philosophy*. Published online at [http://people.ucalgary.ca/~ereshefs/#Articles\\_Chapters\\_and\\_Entries](http://people.ucalgary.ca/~ereshefs/#Articles_Chapters_and_Entries), (Accessed April 3, 2014).

<sup>174</sup> Ereshefsky, “Species, Taxonomy and Systematics,” 256.

<sup>175</sup> Hacking, *Social Construction*, 134.

<sup>176</sup> Simon, “Constructive Realism,” 355.

<sup>177</sup> Kuhn, *Structure*, 120.

kinds. However, in this chapter, and in this thesis, I will argue that diseases are best understood as social constructs.

A consequence of approaching diseases as social constructs rather than as natural kinds is that the question of what the “acute stroke” is becomes as much an epistemological question as an ontological question. *Epistemology* is the branch of philosophy concerned with the nature of knowledge, its justification, and its relation to belief.<sup>178</sup> Medical epistemology, therefore, is the study of knowledge and belief in medicine, with attention to questions of what physicians believe to be true, and why they believe it.<sup>179</sup> How physicians conceive of a disease, if there is some conception involved, represents an epistemic question. Issues of epistemology will feature in each chapter of this thesis. *Ontology*, grossly speaking, is the study of determining what exists, and defining the properties of the things that exist.<sup>180</sup> Medical ontology is concerned with the existence, features, and relations of a set of things relevant to medicine, including but not limited to medicine itself, health, disease, and individual diseases like acute stroke.<sup>181</sup> Whether “acute stroke” is a natural kind or a social construct is an ontological question.

In the clinical literature, the “acute stroke,” and diseases in general, are referred to as if they were natural kinds.<sup>182</sup> By this I mean that when they are provided with a meaning, it is in the form of a definition that specifies a fixed set of properties. Moreover, these definitions use the present tense of the verb to be: they occur in the form, “stroke *is*.” For example, in the widely read textbook *Localization in Clinical Neurology* (2007) by neurologist Paul Brazis of the Mayo Clinic, stroke is defined in relation to its clinical

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<sup>178</sup> Matthias Steup, “Epistemology,” *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), forthcoming URL = <http://plato.stanford.edu/archives/spr2014/entries/epistemology/>, (accessed April 3, 2014).

<sup>179</sup> Erwin B. Montgomery, Jr., “Epistemology of medical decision-making and the need for reason-based medicine,” *Neurodegenerative Disease Management* 2 (2012): 95-97.

<sup>180</sup> Thomas Hofweber, “Logic and Ontology,” *The Stanford Encyclopedia of Philosophy* (Spring 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2013/entries/logic-ontology/>, (accessed April 3, 2014).

<sup>181</sup> Alan Jovic, Marin Prcela, Dragan Gamberger, “Ontologies in Medical Knowledge Representation,” Proceedings of the *ITI 2007 29th Int. Conf. on Information Technology Interfaces*, June 25-28, 2007, Cavtat, Croatia, published online at <http://ppr.cs.dal.ca/sraza/files/Ontologies%20in%20Med%20Know%20rep.pdf>, (accessed April 3, 2014).

<sup>182</sup> Marc Ereshefsky, “Defining Health and Disease,” *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (2009) 221-227.

features and underlying pathophysiology as: “the relatively abrupt (seconds to hours) onset of a focal neurological deficit resulting from disease (occlusion or rupture) of the arteries or veins that serve the [central nervous system].”<sup>183</sup>

However, very often, a disease like stroke is not provided with a definition at all. Authors simply assume that the use of the term stroke carries a specific and known meaning that does not require elaboration. In *Neurology in Clinical Practice* (2008), an influential textbook edited by Walter Bradley of the University of Miami, the chapter on stroke begins with the statement that “There are approximately 750,000 new or recurrent strokes annually in the United States,” though no meaning of the term stroke is offered.<sup>184</sup> Similarly, the discussion of “acute stroke” in Bradley’s textbook includes no specific meaning for that term either.<sup>185</sup> The American Heart Association’s 2011 guidelines on stroke prevention<sup>186</sup> begin with the statement that “Stroke is a major source of morbidity and mortality in the United States,” but does not tell the reader what a stroke might be.<sup>187</sup> This phenomenon of not providing a meaning for a disease like stroke is consistent with the notion of diseases as natural kinds, in that it is assumed that the term stroke refers to a category that exists in nature, has specific properties, and that these properties are relatively obvious.

The consideration of diseases as natural kinds is reflected in the practice of retrospective diagnosis, in which physicians or historians of one era attempt to arrive at diagnoses from the historical record of past

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<sup>183</sup> Paul W. Brazis, José C. Masdeu, José Biller, *Localization in Clinical Neurology* (Philadelphia: Lippincott Williams & Wilkins, 2007), 523.

<sup>184</sup> José Biller, Betsy B. Love, Michael J. Schneck, “Ischemic Cerebrovascular Disease,” in Walter G. Bradley, Robert B. Daroff, Gerard M. Fenichel, Joseph Jankovic, eds., *Neurology in Clinical Practice*, 5<sup>th</sup> Edition (Philadelphia: Butterworth Heinemann, 2008), 1165.

<sup>185</sup> Biller, “Ischemic Cerebrovascular Disease,” 1206.

<sup>186</sup> For more information on the American Heart Association, please see the Glossary.

<sup>187</sup> Karen L. Furie, Scott E. Kasner, Robert J. Adams, Gregory W. Albers, Ruth L. Bush, Susan C. Fagan, Jonathan L. Halperin, S. Claiborne Johnston, Irene Katzan, Walter N. Kernan, Pamela H. Mitchell, Bruce Ovbiagele, Yuko Y. Palesch, Ralph L. Sacco, Lee H. Schwamm, Sylvia Wassertheil-Smoller, Tanya N. Turan, Deidre Wentworth, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research, “Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association,” *Stroke* 42 (2011): 227-276.

eras.<sup>188</sup> In his recent monograph *Multiple Sclerosis: The History of a Disease*, Dalhousie University neurologist and historian T. Jock Murray states that “MS is a recurrent demyelinating disease of the white matter in the [Central Nervous System], which usually becomes progressive.”<sup>189</sup> The association of the term “multiple sclerosis” with its meaning occurs through the present tense form of the verb *to be*, rather than through an association bounded by temporal or spatial restrictions. Murray writes that Multiple Sclerosis “was probably always there,” implying that it should be understood as a natural kind, just waiting to be “discovered” by scientists.<sup>190</sup> He begins his history of Multiple Sclerosis with an account of a 14<sup>th</sup> century Dutch girl who he considers to be the disease’s earliest known patient. However, neither the term “multiple sclerosis,” nor its associated content — concepts like demyelination, white matter, and the central nervous system — would have had any meaning to this girl or to her contemporaries. Applying 21<sup>st</sup> century concepts to the suffering of a 14<sup>th</sup> century girl does not help us to understand her experience or our own.<sup>191</sup>

Even in the present, the idea that diseases should be understood as natural kinds appears problematic. For example, physicians in most fields are engaged in endless debates about the particular qualities of the diseases they diagnose. Nowhere is this phenomenon better recognized than in psychiatry. When new editions of the *Diagnostic and Statistical Manual*, the psychiatrist’s encyclopedia, suddenly add or remove new diseases to the list, it is difficult to maintain a belief that these diseases have somehow only recently been “discovered” within nature.<sup>192</sup> The neurological community is also affected by persistent controversy surrounding the definitions of various diseases.<sup>193</sup> For example, the recent American Heart

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<sup>188</sup> Roy Porter, “Chorea and Huntington’s disease – social section,” in German E. Berrios, Roy Porter, eds., *A History of Clinical Psychiatry. The Origin and History of Psychiatric Disorders* (London, Athlone, 1995), 138–46.

<sup>189</sup> T. Jock Murray, *Multiple Sclerosis: The History of a Disease* (Demos: New York, 2005), 3.

<sup>190</sup> Murray, *Multiple Sclerosis*, 2-4.

<sup>191</sup> Axel Karenberg and Ferdinand Peter Moog, “Next Emperor, Please! No End to Retrospective Diagnostics,” *Journal of the History of the Neurosciences* 13 (2004): 143-149.

<sup>192</sup> Allen Frances, “Whither DSM-V?” *British Journal of Psychiatry* 195 (2009): 391-392.

<sup>193</sup> Melissa J. Armstrong, Irene Litvan, Anthony E. Lang, Thomas H. Bak, Kailash P. Bhatia, Barbara Borroni, Adam L. Boxer, Dennis W. Dickson, Murray Grossman, Mark Hallett, Keith A. Josephs, Andrew Kertesz, Suzee E. Lee, Bruce L. Miller, Stephen G. Reich, David E. Riley, Eduardo Tolosa, Alexander I. Tröster, Marie Vidailhet, William J. Weiner, “Criteria for the diagnosis of corticobasal degeneration,” *Neurology* 80 (2013): 496-503.

Association guidelines on stroke prevention address controversy surrounding the definition of a “transient ischemic attack,” (TIA) a diagnosis related to the ischemic stroke in symptomatology and pathology. The guidelines state:

“By conventional clinical definitions, the presence of focal neurological symptoms or signs lasting less than 24 hours has been defined as a TIA. With more widespread use of modern imaging techniques for the brain, up to one third of patients with symptoms lasting less than 24 hours have been found to have an infarction. This has led to a new tissue-based definition of TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.”<sup>194</sup>

The authors of this guideline imply that this “new tissue-based definition of TIA” is superior to the “conventional clinical definition”: it arises from novel information (“modern imaging techniques”) to arrive closer to the essential properties of a TIA. Controversies surrounding disease definitions, and efforts to arrive at consensus, are generally understood by physicians as reflective of an epistemic gap rather than an ontologic gap, meaning that any imperfections in definitions are understood to reflect the limitations of prior knowledge, not fundamental questions about the nature of disease itself.

However, many historians have argued convincingly for the idea that diseases are constructed within a social and historical context. Perhaps the first account of diseases as historically-determined concepts comes from Ludwik Fleck (1896-1961), the Polish microbiologist and early philosopher of medicine who authored *Genesis and Development of a Scientific Fact* in 1935 (translated into English in 1979). Fleck argues that the biological elements of a disease are insufficient to explain it,<sup>195</sup> and explores syphilis as a “case in the history of ideas.”<sup>196</sup> He argues that the idea of syphilis arose, changed and arose again. He identifies the 20<sup>th</sup> century conception of syphilis — defined in relation to an immunological test called the Wassermann reaction — as reflecting the intertwining of four earlier lines of thought, each of which had its

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<sup>194</sup> Furie, “Guidelines,” 228.

<sup>195</sup> Fleck, *Genesis*, 18.

<sup>196</sup> *Ibid.*, 23.

own history.<sup>197</sup> Fleck writes that “the Wassermann reaction in its relation to syphilis constitutes the modern, scientific expression of an earlier pre-idea which contributed to the concept of syphilis.”<sup>198</sup> In this way, Fleck writes that “concepts are not spontaneously created but are determined by their ancestors.”<sup>199</sup> Fleck conceives of diseases, like syphilis or acute stroke, as ideas, arising in relation to earlier ideas. From Fleck, this chapter argues that the contemporary notion of the acute stroke is the product of a set of preconditions. More strongly put, Fleck’s claim that concepts are determined by their ancestors supports my argument that the idea of a disease (in a particular place and at a particular time) cannot be extricated from the intellectual history from which it arises.

The notion of disease as social construct is echoed in the writings of Mirko Grmek (1924-2000), the Croatian-French historian of medicine. In his influential text *Diseases in the Ancient World* (1989), Grmek urges his readers to rid themselves “as completely as possible of the ontologic notion of disease embedded in our everyday language.”<sup>200</sup> By this he means to reject the notion of diseases as natural kinds — as the “constitutive elements” of reality — and to replace it with the notion of diseases as “explanatory models of reality.”<sup>201</sup> He argues that diseases “presuppose a certain medical philosophical or pathological system of reference,” meaning that they reflect a certain set of background assumptions or theories.<sup>202</sup> Grmek elaborates that

The history of Western medicine, as well as the comparative study of medicine in diverse societies, shows clearly that diseases are not inevitably conceptualized as they are nowadays. How they are conceptualized depends as much on the scientific sophistication of a society as on the pathological realities of a given historical moment in a specific geographical area.<sup>203</sup>

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<sup>197</sup> Fleck, *Genesis*, 18.

<sup>198</sup> *Ibid.*, 23.

<sup>199</sup> *Ibid.*, 20.

<sup>200</sup> Mirko D. Grmek, *Diseases in the Ancient World*, Trans. Mireille Muellner & Leonard Muellner (Baltimore: Johns Hopkins University Press, 1989), 1.

<sup>201</sup> Grmek, *Diseases*, 1.

<sup>202</sup> *Ibid.*, 1.

<sup>203</sup> *Ibid.*, 1.

In this passage, Grmek makes explicit that the way a disease is conceived in a particular place and at a particular time is not inevitable. For Grmek, the meaning of a particular term is contingent on the technological state of the society using that term. Moreover, Grmek warns his audience against assuming that the meaning of a word — syphilis, or stroke, for example — remains consistent across time and geography. “Most dangerous are the shifts in meaning — the word remains, the concept changes,” he writes.<sup>204</sup> Grmek’s notions of contingency, of the importance of technology, and of shifting usages of words become central themes in the history of acute stroke to follow.

Perhaps the historian most closely associated with the notion of diseases as social constructs is the Canadian-American historian of medicine Charles Rosenberg of Harvard University. In *Framing Disease* (1992), Charles Rosenberg proposes that a disease be understood as

“at once a biological event, a generation-specific repertoire of verbal constructs reflecting medicine’s intellectual and institutional history, an occasion of and potential legitimation for public policy, an aspect of social role and individual — intrapsychic — identity, a sanction for cultural values, and a structuring element in doctor and patient interactions.”<sup>205</sup>

The way that a disease is understood therefore has wide-ranging implications for patients, physicians, the health care system, and society as a whole. Specific to the central question of this thesis, Rosenberg elaborates on how the framing of diseases impacts the daily practices of physicians. Like Grmek before him,<sup>206</sup> Rosenberg recognizes how physician practices “have always been dependent on time-bound intellectual tools,”<sup>207</sup> in that it is impossible to practice external to one’s social and historical context.

Moreover, Rosenberg develops the notion that the framing of diseases — their identification and attribution of meaning — can occur in response to a number of factors, of which two of the most prominent are technologies and treatments. In *Medicine and the Reign of Technology* (1978), American historian of medicine Stanley Joel Reiser argues that technological advances from the seventeenth to

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<sup>204</sup> Grmek, *Diseases*, 6.

<sup>205</sup> Rosenberg, *Framing*, xiii.

<sup>206</sup> Grmek, *Diseases*, 2.

<sup>207</sup> Rosenberg, *Framing*, xvii.

twentieth centuries shaped the ways in which doctors diagnosed illness. Reiser's interest in diagnosis is tightly bound with the entities being diagnosed, namely diseases. He describes how the means of interaction between doctor and patient — the various elements of the assessment including history-taking, physical examination, laboratory tests and imaging — determine the physician's perspective on the nature of illness and disease.<sup>208</sup> For example, prior to the 19<sup>th</sup> century, physicians performed very limited physical examinations, and based their assessments on patients' self-reports of illness. As a consequence, symptoms (the subjective experience of illness reported by the patient) and diseases were considered one and the same. "Fever" was a disease; so too was "cough."<sup>209</sup> However, with the development of examination techniques like percussion (tapping on the chest) and auscultation (listening to internal sounds through the use of the stethoscope), diseases could now be perceived independently of the patient's reports, in relation to elements appreciated empirically by the physician.<sup>210</sup> Cough ceased being a disease, and pneumonia arose as a clinical entity. In the late 19<sup>th</sup> and early 20<sup>th</sup> centuries, the development of bacteriology led to the differentiation of pneumonia into subtypes based on the infectious agent.<sup>211</sup> Subsequent to the development of antibiotics in the mid-20th century, pneumonias could then be differentiated by their response to particular drugs at particular doses.

Treatments, as Rosenberg argues, lie at the heart of any medical system, and as a consequence play a central role in defining disease. In a seminal article from 1979, Rosenberg characterizes how treatment was understood within the context of late 18<sup>th</sup> and early 19<sup>th</sup> century America. Rosenberg writes how the doctor-patient interaction was built upon a certain conceptualization — built upon a common set of epistemic and ethical assumptions shared by doctor and patient— of the body as a system of dynamic

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<sup>208</sup> Reiser, *Reign of Technology*, x.

<sup>209</sup> Paul Starr, *The Social Transformation of American Medicine* (New York: Basic Books, 1982), 136.

<sup>210</sup> Reiser, *Reign of Technology*, 29.

<sup>211</sup> Starr, *Social Transformation*, 137.

interactions with the environment.<sup>212</sup> Diseases did not exist within specific organs, but reflected a disequilibrium within the body.<sup>213</sup> Treatments were understood to “work” in that they produced visible and predictable physiological effects; for example, a diuretic worked because it made the patient urinate, and an emetic worked because it made the patient vomit.<sup>214</sup> The efficacy of the treatment confirmed the physician’s diagnosis. If a treatment did not work, then the physician would be forced to reconsider his diagnosis.

The interaction between diagnosis and treatment has been further explored in more recent scholarship. In *Last Resort* (1998), University of California historian of medicine Jack Pressman (1957-1987) provides an elegant study of the history of psychosurgery in America. The relationship between treatment and disease in the middle decades of the 20<sup>th</sup> century emerges as a central theme of Pressman’s elegant study.<sup>215</sup> The psychiatric diseases treated with psychosurgery had been, up until that point, deemed incurable. But the proliferation of psychosurgery, and its conceptualization as a treatment that “worked” by producing visible and predictable effects in patients, had the impact of redefining psychiatric diseases as treatable, if only for a short period of time and in response to this very specific intervention.<sup>216</sup> Due to their new eligibility for “active treatment,” the psychiatric diseases in question — depression, schizophrenia — changed.<sup>217</sup> Despair was replaced by promise.<sup>218</sup> In the case of acute stroke, a similar transition occurred with the publication of the NINDS trial. Until 1995, the disease called stroke (or its historical pre-idea, apoplexy) had been associated with unbridled therapeutic nihilism. The existence of a successful therapy served as the basis for the development of a new disease, with a new meaning.

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<sup>212</sup> Rosenberg, “Therapeutic Revolution,” 4.

<sup>213</sup> *Ibid.*, 5.

<sup>214</sup> Rosenberg, “Therapeutic Revolution,” 8.

<sup>215</sup> Jack D. Pressman, *Last Resort: Psychosurgery and the Limits of Medicine* (Cambridge: Cambridge University Press, 1998), 15.

<sup>216</sup> Pressman, *Last Resort*, 160.

<sup>217</sup> *Ibid.*, 147.

<sup>218</sup> *Ibid.*, 186.

*A Brief Historiography of Stroke*

Historical scholarship on the topic of stroke and its treatment has so far failed to explore the notions proposed in this thesis, namely that a new concept of “acute stroke” arose in response to the perceived efficacy of the drug tPA. This likely reflects our relative proximity to the events studied in this thesis. However, an additional and fundamental challenge to exploring a conceptual history of stroke is produced by the historical intertwining of the words *stroke* and *apoplexy*. As historian of medicine Roger French (1938-2002) writes, “It is very difficult to trace back through time the identity of modern disease. The name changes. The description is elusive; either everyone at the time knew what it was (plague, pox) and there was no need for description, or the description was one of appearances that were significant in an etiology entirely different from our own”<sup>219,220</sup>

The term apoplexy is found in the Hippocratic corpus, and suggests the act of being struck down. In classical Greek, *apo-* denotes down or away and *-plexein* refers to striking.<sup>221</sup> The word “apoplexy” remained in common usage into the 20<sup>th</sup> century, though its meaning changed. In 1685, British physician and anatomist Thomas Willis (1621-1675) wrote that apoplexy “denotes a striking, and by reason of the stupendous nature of the affect, as tho’ it contain’d somewhat divine, it is called a sideration; for those that are seized with it are planet-struck.”<sup>222</sup> In 1820, British physician John Cooke (1756-1838) used the term apoplexy to denote “a disease in which the patient falls to the ground, often suddenly, and lies without sense or voluntary motion.”<sup>223</sup> By the end of the 19<sup>th</sup> century, apoplexy was no longer used to refer to a specific

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<sup>219</sup> Roger French, *Medicine Before Science: The Rational and Learned Doctor from the Middle Ages to the Enlightenment* (Cambridge: Cambridge University Press, 2003), 232.

<sup>220</sup> Henry S. Schutta, Herbert M. Howe, “Seventeenth Century Concepts of Apoplexy as Reflected in Bonet’s *Sepulchretum*,” *Journal of the History of the Neurosciences: Basic and Clinical Perspectives* 15 (2006): 250-268.

<sup>221</sup> Paul J. Camarata, Roberto C. Heros, Richard E. Latchaw, “Brain Attack: The Rationale for Treating Stroke as a Medical Emergency,” *Neurosurgery* 34 (1994): 144-158.

<sup>222</sup> Thomas Willis, *The London Practice of Physick* (1685) (New York: Classics of Neurology & Neurosurgery Library, 1991), 421.

<sup>223</sup> Cooke, *A Treatise on Nervous Diseases, Volume 1: On Apoplexy* (London: Longman, Hurst, Rees, Orme & Brown, 1820), 159.

disease, but to invoke a collection of symptoms — especially the sudden loss of consciousness — that could arise from any number of pathological processes.<sup>224</sup>

In contrast, the first known use of the term stroke in the medical context was in 1599, with reference to “the stroke of Gods hande.”<sup>225</sup> Though it would appear that the terms stroke and apoplexy co-existed for several centuries, apoplexy remained the dominant term until the mid-19<sup>th</sup> century. For example, Willis spoke exclusively of apoplexy and made no reference to stroke in his medical handbook *The London Practice of Physick* (1685).<sup>226</sup> Similarly, Italian anatomist Giovanni Battista Morgagni (1682-1771) presented the autopsy findings of cases of apoplexy in his seminal text *De Sedibus et Causis Morborum* (1761) without use of the term stroke.<sup>227</sup> Nineteenth century usages of the term stroke retained imagery familiar from apoplexy, in that they included references to the “considerable stroke of a palsy,”<sup>228</sup> “as if struck by lightning,”<sup>229</sup> and “a stroke of paralysis.”<sup>230</sup> An English translation of the lectures of French physician Armand Trousseau (1801-1867), published in 1868, references the entity of “paralytic stroke,” thereby combining the concept of stroke with a symptom (paralysis) that remains its most common feature in modern understanding.<sup>231</sup>

Many historical works on stroke, especially those written by and for clinicians, implicitly accept the notion of diseases as natural kinds, and use the terms stroke and apoplexy interchangeably, making no attempts to define them individually or relationally. For example, Columbia neurosurgeon Donald Quest begins his history of stroke with the statement that “The object of this paper is to trace the development of

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<sup>224</sup> Katherine Daneski, Paul Higgs, “How Far Can Foucault Take Us? An Analysis of the Changing Discourses and Limitations of the Medical Treatment of Apoplexy and Stroke,” *Health* 15 (2010): 369-384.

<sup>225</sup> Pandora Pound, Michael Bury, Shah Ebrahim, “From Apoplexy to Stroke,” *Age and Ageing* 26 (1997): 331-337.

<sup>226</sup> Willis, *London Practice*, 420-424.

<sup>227</sup> Henry S. Schutta, “Morgagni on Apoplexy in De Sedibus,” *Journal of the History of the Neurosciences* 18 (2009): 1-24.

<sup>228</sup> William Heberden, *Commentaries on The History and Cure of Diseases* (London: T. Payne, 1802), 339.

<sup>229</sup> Cooke, *Treatise on Nervous Diseases*, 159.

<sup>230</sup> Robert T. Edes, “Intracranial Hemorrhage and Occlusion of the Cerebral Vessels, Apoplexy, Softening of the Brain, Cerebral Paralysis,” in William Pepper, ed. *A System of Practical Medicine by American Authors, Volume V* (Philadelphia: Lea Brothers, 1886), 945.

<sup>231</sup> Armand Trousseau, *Lectures on Clinical Medicine, Delivered at the Hôtel-Dieu, Paris*, ed. and trans P. Victor Bazire (London: The New Sydenham Society, 1868), 4.

understanding of the pathogenesis of stroke as it has evolved through the course of history,” but he begins his article with a definition of apoplexy and makes no attempt to explicitly relate apoplexy to stroke.<sup>232</sup> In *A History of Stroke: Its Recognition and Treatment*, neurologists William S. Fields and Noreen A. Lemark discuss a set of related concepts (apoplexy, hemiplegia, hemorrhage), though they offer no specific meaning for stroke in relation to these terminologies, at any particular point in history.<sup>233</sup> In a more recent article on the history of stroke, American neurologist Michael Kelly states that “Prevention and treatment of stroke has changed substantially since the time of Franklin Delano Roosevelt, who died of an intracerebral hemorrhage in 1945.”<sup>234</sup> However, Kelly fails to define stroke or intracerebral hemorrhage; nor does he attempt to draw any conclusions about the impact of treatment on the understanding of disease.

Within the historiography of stroke, a handful of articles stand out for their rigorous and nuanced approach to questions of its epistemology and ontology, including the relationship between apoplexy and stroke. In “From Apoplexy to Stroke,” sociologists Pandora Pound and Michael Bury and neurologist Shah Ebrahim consider how the disease entities “apoplexy,” “cerebrovascular disease” and “stroke” have represented different ways of conceptualizing patterns of illness over the course of the last three centuries.<sup>235</sup> They relate the changes in terminologies and conceptualizations to broader changes in medical theory. For example, they describe how a shift away from the symptomatic notion of apoplexy towards the pathologically-based “cerebrovascular disease” occurred as a consequence of the decline of the humoral approach to disease, in which diseases were understood to exist within the body as whole, and the rise of the clinico-anatomical method in the late 18<sup>th</sup> and early 19<sup>th</sup> centuries.<sup>236</sup> The development and dissemination of clinical examination techniques in this period led to the reclassification of diseases “according to changes inside the body that seemed to deviate from normal,” rather than on the basis of

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<sup>232</sup> Donald O. Quest, “Stroke: A Selective History,” *Neurosurgery* 27 (1990): 440-445.

<sup>233</sup> William S. Fields, Noreen A. Lemark, *A History of Stroke: Its Recognition and Treatment* (Oxford: Oxford University Press, 1989), 18.

<sup>234</sup> Michael Kelly, “Stroke: A Modern History,” *American Journal of Therapeutics* 18 (2011): 51-56.

<sup>235</sup> Pound, “From Apoplexy,” 334.

<sup>236</sup> *Ibid.*, 334.

patients' reported symptoms.<sup>237</sup> Pound, Bury and Ebrahim then argue that the adoption of the colloquial term “stroke” by the medical profession in the middle decades of the 20<sup>th</sup> century reflected a renewed concept of the disease that placed the patient — for whom a word like stroke had much more significance than “cerebrovascular disease” — at its centre.<sup>238</sup> The authors make no reference to the term “acute stroke” which is not surprising given that they were writing in 1997, shortly after the publication of the first tPA trials in stroke. They do, however, engage with the notion of treatment influencing the conceptualization of disease, through the vehicle of rehabilitation. They conclude that “the more treatment becomes available, the more uncertainty this appears to give rise to,” in that the previous nihilism associated with stroke might be rejected in light of new therapies.<sup>239</sup>

British sociologists Katharine Daneski and Paul Higgs apply a Foucauldian approach to “the changing discourses and limitations of the medical treatment of apoplexy and stroke,” in their article “How Far Can Foucault Take Us? An Analysis of the Changing Discourses and Limitations of the Medical Treatment of Apoplexy and Stroke.” French academic Michel Foucault (1926-1984) famously argued for “epistemes,” or particular “epistemological fields” that defined the possibility for knowledge in a time and place.<sup>240</sup> In their article on “Apoplexy and Stroke,” Daneski and Higgs reject the notion of discrete epistemes in the history of stroke as they conclude that early modern concepts of apoplexy were not distinctly replaced by newer concepts as Foucault would expect, but that they persisted and overlapped with more technologically advanced concepts like stroke.<sup>241</sup>

In the course of their analysis, Daneski and Higgs explicitly refer to stroke as “a condition which is untreatable even to this present day.”<sup>242</sup> This analysis is interesting for several reasons. First, Daneski and

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<sup>237</sup> Pound, “From Apoplexy,” 334.

<sup>238</sup> *Ibid.*, 336.

<sup>239</sup> *Ibid.*, 336.

<sup>240</sup> Gary Gutting, “Michel Foucault,” *The Stanford Encyclopedia of Philosophy* (Summer 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/sum2013/entries/foucault/>, (accessed April 16, 2014).

<sup>241</sup> Daneski, “How Far,” 381.

<sup>242</sup> *Ibid.*, 370.

Higgs support the theoretical approach of this chapter by emphasizing the important relationship between a disease and its treatment. However, their article includes no reference to the use of tPA in the treatment of stroke. This is surprising, considering that their article was published in 2010, and that tPA was approved for the treatment of stroke in the United States in 1996, in Canada in 1999 and in Britain in 2007.<sup>243</sup> Rather, they argue that it was the publication of guidelines for post-stroke care by the Royal College of Physicians in Britain 2002 that marked an “epistemological shift” in the treatment of stroke. They propose that the recognition of the efficacy and need for rehabilitation changed stroke “from a disease with gloomy prognosis to a condition for which greater expectations of stroke medicine are expressed.”<sup>244</sup> Daneski and Higgs explicitly state that “This optimism does not, however, spring from a dramatic new cure or treatment for the disease, but from meta-analyses of research suggesting that outcomes for stroke patients will be improved through better organization of services.”<sup>245</sup> It is unclear why they would have ignored the rise of thrombolysis in stroke.

Finally, an encompassing body of literature on the history of stroke has been published in a series of articles in the *Journal of the History of the Neurosciences* by German historian Axel Karenberg. Karenberg’s publications do not extend as much into the late 20<sup>th</sup> century to cover the period I am most concerned with in this thesis. However, he identifies and analyses a series of controversies surrounding usages of the term “apoplexy,” dating from antiquity.<sup>246,247</sup> Recalling the writings of Daneski and Higgs, Karenberg traces a central dilemma in the clinical literature on stroke: namely what should a physician do for “hopeless cases,”

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<sup>243</sup> NICE Alteplase for the treatment of acute ischaemic stroke. *NICE technology appraisal guidance 122*. June 2007. Available at <http://www.nice.org.uk/TA122>, (accessed April 3, 2014)

<sup>244</sup> Daneski, “How Far,” 370.

<sup>245</sup> *Ibid.*, 370.

<sup>246</sup> Axel Karenberg, Irmgard Hort, “Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part I: The Struggle for Terms and Theories — Late Antiquity and Early Middle Ages (300-800),” *Journal of the History of the Neurosciences* 7 (1998): 162-173.

<sup>247</sup> Axel Karenberg, Irmgard Hort, “Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part II: Between Galenism and Aristotelism — Islamic Theories of Apoplexy (800-1200),” *Journal of the History of the Neurosciences* 7 (1998): 174-185.

meaning cases for which no treatment is available.<sup>248</sup> He reminds us that in the medieval period, “the treatment of incurably ill individuals, it may be recalled, was not regarded as a doctor’s job.”<sup>249</sup> As will be argued in this chapter, the notion that stroke should have been considered incurable, from antiquity until the very recent past, demonstrates the significance of the “epistemological shift” brought about by tPA in the late 20<sup>th</sup> century. Karenberg concludes his survey of the history of stroke by arguing that medieval and contemporary physicians “face the same conundrums: What, essentially, are the causes of stroke? Which criteria enable the physician to know the disease’s course? What kind of treatment is best for an individual patient?”<sup>250</sup> These questions point to the inter-relatedness of the ontological, epistemic, ethical, and clinical, echoing the interdisciplinary approach of this thesis.

### *Treatability & Time*

What, therefore, is the meaning of “acute stroke” in the contemporary historical context? The contemporary meaning of acute stroke appears to be strongly linked with the perceived efficacy of IV tPA as its treatment. This efficacy was first suggested in the NINDS trial that was published in 1995, and has been supported by subsequent investigations. As a consequence, I propose that acute stroke is generally understood in the contemporary context as a stroke that is treatable with properly administered IV tPA. That I am proposing a generally accepted meaning of acute stroke in the contemporary context does not exclude the presence of controversy or debate about its particulars. Indeed, such debate will be the focus of Chapter 2.

What does it mean to say that the acute stroke is a stroke that is treatable through the proper administration of tPA? First, an acute stroke is understood as a form of stroke, in that stroke refers to the

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<sup>248</sup> Axel Karenberg, Irmgard Hort, “Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part III: Multiplying Speculations — The High and Late Middle Ages (1000-1450),” *Journal of the History of the Neurosciences* 7 (1998): 186-200.

<sup>249</sup> Karenberg, “Multiplying Speculations,” 196.

<sup>250</sup> *Ibid.*, 199.

sudden onset of neurological symptoms.<sup>251</sup> Second, an acute stroke is treatable, meaning that its symptoms are potentially reversible. However, the potential for treatment does not require that symptoms are successfully reversed in all circumstances. Finally, that acute stroke is treatable through the proper administration of tPA necessitates an understanding of the way that tPA is administered. Specifically, this clause references what physicians call the inclusion and exclusion criteria, meaning the restraints placed upon the use of a drug. Inclusion and exclusion criteria are usually developed in the context of a clinical trial, so as to identify those patients most likely to benefit from the therapy under investigation.<sup>252</sup> Indeed, in the case of tPA, the widely-recognized inclusion and exclusion criteria date from the NINDS trial. Among these criteria, the most important elements are the timing of the intervention (tPA must be used within 3 hours of the onset of symptoms to be effective), and the performance of a CT scan to exclude intracerebral hemorrhage prior to the drug's administration.<sup>253</sup>

The proposition that stroke may be reversed through the use of tPA stands in stark contrast to millennia of therapeutic nihilism surrounding the treatment of stroke and apoplexy. By nihilism, I refer to the belief that no treatment would be effective to reverse the signs and symptoms of stroke.<sup>254</sup> As reviewed by Karenberg, stroke had been generally understood since antiquity as an untreatable condition.<sup>255</sup> In the 17<sup>th</sup> century, British anatomist and physician Thomas Willis (1621-1675) had stated that apoplexy was associated with a prognosis that was “fatal and dubious.”<sup>256</sup> In 1817, Scottish physician Marshall Hall (1790-1857) had described how “an attack of apoplexy often proves speedily fatal; frequently life is continued, and

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<sup>251</sup> Brazis, *Localization*, 523.

<sup>252</sup> Stephen R. Levine, Pooja Khatri, Joseph P. Broderick, James C. Grotta, Scott E. Kasner, D. Kim, B.C. Meyer, P. Panagos, J. Romano, P. Scott, for the NINDS rtPA Study Group, “Review, Historical Context, and Clarifications of the NINDS rtPA Stroke Trials Exclusion Criteria. Part 1: Rapidly Improving Symptoms.” *Stroke* 44 (2013): 2500-2505.

<sup>253</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1582.

<sup>254</sup> Jason Szabo, *Incurable and Intolerable: Chronic Disease and Slow Death in Nineteenth Century France* (New Brunswick: Rutgers University Press, 2009), 10.

<sup>255</sup> Karenberg, “Multiplying Speculations,” 195.

<sup>256</sup> Willis, *London Practie*, 422.

the patient remains ever after paralytic.”<sup>257</sup> British physician John Cooke quoted the Hippocratic corpus when in 1820 he declared “that it is impossible to cure the strong apoplexy,” and urged doctors to avoid “unsuccessful attempts” for they “might bring disgrace on themselves and on the profession.”<sup>258</sup>

Medical texts of the late 19<sup>th</sup> and early 20<sup>th</sup> century reiterate a similar message. Harvard University professor Robert Thaxter Edes (1838-1923) declared in 1886 that “When the apopleptic attack has actually occurred, treatment, though apparently urgently demanded, is really of little avail. If a patient is about to die in an hour or two from rapidly increasing pressure, nothing within the reach of medical science can stop him.”<sup>259</sup> He specified that “there is no sufficient reason to suppose that any drug is of any value in the restoration of the nervous system.”<sup>260</sup> Canadian-born physician Sir William Osler (1849-1919), later of Johns Hopkins and Oxford Universities, echoed his forebears in the seventh edition of his influential textbook: “The treatment of softening from thrombosis or embolism is very unsatisfactory... Very little can be done for the hemiplegia which remains. The damage is too often irreplaceable and permanent.”<sup>261</sup> Osler made it clear that it is the duty of the physician “to explain to the patient, or to his friends, that the condition is past relief, that medicines and electricity will do no good, and that there is no possible hope of cure.”<sup>262</sup>

Writing in 1944, American-Israeli neurologist Dr. Israel Wechsler (1886-1962) provided a more developed, albeit equally pessimistic, approach to treatment:

The treatment of cerebral vascular accidents may be divided into prophylaxis, the management of the acute insult, and the subsequent attempt to hasten recovery from the hemiplegia. It is doubtful whether in the present state of our knowledge we can really prevent hemorrhage or thrombosis. The cause of cerebral arteriosclerosis is unknown, syphilitic thrombosis often occurs despite vigorous treatment, essential hypertension is still an obscure problem, infectious thrombosis is beyond our power to prevent, and embolism

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<sup>257</sup> Marshall Hall, *On Diagnosis in Four Parts* (London: Longman, Hurst, Rees, Orme and Brown, 1817), 126.

<sup>258</sup> Cooke, *Treatise on Nervous Diseases*, 289.

<sup>259</sup> Edes, “Intracranial Hemorrhage,” 975.

<sup>260</sup> *Ibid.*, 978.

<sup>261</sup> Osler, *Principles*, 981.

<sup>262</sup> *Ibid.*, 982.

in vegetative endocarditis is not easily stopped. Much is said in favor of the iodides in the treatment of arteriosclerosis, but I doubt if they have any value at all.<sup>263</sup>

Wechsler does not use the term stroke, but rather references the notion of “cerebral vascular accident,” a term still in use in the 21<sup>st</sup> century. The idea of “accident” captures the way that stroke seemingly occurs without warning, while “cerebral vascular” references its locus of causation, meaning the blood vessels of the brain. Wechsler divides the pathology of cerebral vascular accidents into hemorrhage and thrombosis, which were clinically indistinguishable until the advent of the CT scanner in the 1970s. Wechsler suggests that while the treatment of stroke may theoretically include three distinct stages — prophylaxis (prevention), acute management, and recovery (rehabilitation) — he is equally nihilistic about all three.

Against this tradition of nihilism, American neurosurgeons Bernard Sussman and Thomas Fitch were the first to elaborate and test a concept of treatability for stroke in their 1958 article “Thrombolysis with Fibrinolysin in Cerebral Arterial Occlusion.”<sup>264</sup> Sussman and Fitch report the results of their first attempts to use fibrinolysin, a clot-dissolving drug, to treat three patients with profound weakness presumed to be due to ischemic stroke. They describe how, in one patient, an occlusion of the middle cerebral artery seen on angiography disappeared after the intravenous administration of fibrinolysin. They consider this finding suggestive of fibrinolysin’s “specific usefulness in treatment” for stroke.<sup>265</sup> Sussman and Fitch postulate that the success of any treatment in stroke will depend upon a “critical period” just after the onset of symptoms, during which time the stroke may be reversible.<sup>266</sup> In their study, patients had received treatment with fibrinolysin between 6 hours to 6 days after the onset of their symptoms. None of the patients experienced significant improvement. However, Sussman and Fitch’s work introduced the concept that would come to define the acute stroke, namely that of treatability in relation to time.

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<sup>263</sup> Israel Wechsler, *A Textbook of Clinical Neurology, Fifth edition* (Philadelphia: W. B. Saunders & Co., 1944), 362.

<sup>264</sup> Bernard J. Sussman, Thomas S. P. Fitch, “Thrombolysis with Fibrinolysin in Cerebral Arterial Occlusion,” *Journal of the American Medical Association* 167 (1958): 1705-1709.

<sup>265</sup> Sussman, “Thrombolysis” (1958), 1709.

<sup>266</sup> *Ibid.*, 1706.

*Acuity & the Acute Stroke*

The complex history of the term stroke has already been presented. But when and how was the term “acute” first used in relation to stroke, and what did it mean? A survey of seminal texts in the history of neurology suggests that the term “acute” has had a temporal implication since it first appeared in relation to stroke in 1893. Initially, “acute” was used as a synonym for sudden, referring to the manner in which the symptoms of stroke or apoplexy began. However, by the mid-20<sup>th</sup> century, usages of the term “acute” appear to be synonymous with “recent,” rather than with “sudden,” emphasizing the duration of symptoms rather than the manner of their presentation. I will argue then, that the combination of the term “acute” with “stroke” in 1960 established the notion of acuity as a marker of duration of symptoms, and as an indication of treatability.

The earliest identified use of “acute” in reference to stroke comes in the 1893 textbook of neurology by British neurologist William Gowers (1845-1915). Gowers describes “acute softening” of the brain, softening being the pathological term that was applied to cerebral infarction in his era. The word “acute” appears only once in Gowers’ text, and receives no specific definition.<sup>267</sup> In a 1925 textbook, American neurologist Charles Dana (1852-1935) also uses the term “acute softening,” apparently in reference to suddenness of the onset of clinical symptoms: “Acute softening is a condition caused by plugging of a blood vessel with an embolus or thrombus, and is characterized by a comparatively sudden (embolism) or gradual (thrombus) apoplectic seizure, the symptoms eventually running a course much like that of cerebral hemorrhage.”<sup>268</sup> That the adjective “acute” is used to denote a “sudden” pathophysiological process is supported by Dana’s later phrasing in discussing the symptoms of intracerebral hemorrhage: “A preceding period of feeling unusually well precedes some acute and fatal hemorrhage.”<sup>269</sup> In 1944, Wechsler speaks of an “*acute apoplectic stroke* or ictus” to refer to a sudden attack that makes the patient “rapidly

<sup>267</sup> W.R. Gowers, *A Manual of Diseases of the Nervous System*, Second Edition, Volume II (London: J & A Churchill, 1893), 421.

<sup>268</sup> Charles L. Dana, *Textbook of Nervous Diseases, Tenth Edition* (New York: William Wood & Co., 1925), 460.

<sup>269</sup> Dana, *Textbook*, 463.

comatose or even dropping to the ground as if struck on the head.”<sup>270</sup> Within the stroke literature of the mid to late 20<sup>th</sup> century “acute” is occasionally used to refer to the suddenness of onset of symptoms,<sup>271,272</sup> though is more commonly used in opposition to “chronic”<sup>273</sup> as a reflection of the duration of symptoms.

According to MEDLINE, the online database of the National Library of Medicine,<sup>274</sup> the first use of the combined term “acute stroke” was in a short article entitled “Cerebral Angiography in the Diagnosis of the Acute Stroke” by British neurologists J.W.D. Bull, John Marshall and D.A. Shaw that appeared in *The Lancet* in March, 1960.<sup>275</sup> The article reports the results of a trial of cerebral angiography (imaging the brain’s arteries using dye injected through wires inserted into the chest, neck and brain) as a diagnostic aid in the management of patients “within seventy-two hours of the onset of an acute stroke.” The novelty of the term “acute stroke” is suggested by the authors’ perceived need to define it, particularly in relation to time. For Bull and colleagues, the “acute stroke” referred to the first 72 hours after the onset of symptoms. It was on this basis that “specific methods of treating patients with acute strokes” might be developed.<sup>276</sup>

Usage of the term “acute stroke” to refer to the duration of symptoms became more common in the 1960s and 1970s.<sup>277</sup> In 1969 an American group led by Dr. John Gilroy (1925-2008) of Wayne State University published the first clinical trial for “acute stroke,” using the sugar-like molecule Dextran.<sup>278</sup> In another clinical trial, conducted and reported by British geriatrician A.K. Admani in 1978, “acute” is used

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<sup>270</sup> Wechsler, *Textbook*, 349. Italics are author’s.

<sup>271</sup> Robert L. Clarke, Eugene E. Clifton, “The Treatment of Cerebrovascular Thromboses and Embolism with Fibrinolytic Agents,” *American Journal of Cardiology* 6 (1960): 546-551.

<sup>272</sup> Fletcher H. McDowell, “Cerebrovascular Diseases,” in Paul B. Beeson, Walsh McDermott, eds. *Cecil-Loeb Textbook of Medicine*, 13<sup>th</sup> edition (Philadelphia: W.B. Saunders, 1971), 190.

<sup>273</sup> “Acute,” *Taber’s Cyclopedic Medical Dictionary*, 14<sup>th</sup> Edition (Philadelphia: F.A. Davis, 1981), 31.

<sup>274</sup> MEDLINE searches are a commonly used methodology in medical historical research. For more information on MEDLINE, please see the Glossary.

<sup>275</sup> J.W.D. Bull, John Marshall, D.A. Shaw, “Cerebral Angiography in the Diagnosis of the Acute Stroke,” *The Lancet* 275 (1960): 562-564.

<sup>276</sup> Bull, “Cerebral Angiography,” 564.

<sup>277</sup> McDowell, “Cerebrovascular Diseases,” 206.

<sup>278</sup> John Gilroy, Marion I. Barnhart, John S. Meyer, “Treatment of Acute Stroke with Dextran 40,” *Journal of the American Medical Association* 210 (1969): 293-298.

interchangeably with “recent” rather than with “sudden.”<sup>279</sup> For example, Admani speaks of acute stroke but entitles his article “New Approach to Treatment of Recent Stroke.”<sup>280</sup> In other articles of this period, “acute” is contrasted with the “chronic” or “convalescent” phases of disease, rather with the “gradual” or “progressive” onset of symptoms.<sup>281,282</sup>

Despite growing research interest in the fundamental mechanisms of stroke and in potential treatments, no therapeutic successes had occurred by the late 1980s. While the concepts of treatability and time were intertwined, the specifics of both elements had yet to be established. In 1987, neurologist Michael Sloan (1954-2011), then of the University of Maryland, echoed the comments of Sussman and Fitch from 1958 in calling for a trial of a thrombolytic drug administered quickly after stroke. Sloan wrote, “the time is, therefore, ripe for a trial of thrombolytic therapy with tissue-type plasminogen activator administered intra-arterially or intravenously in cases of early ischemic cerebral infarction.”<sup>283</sup> For Sloan, the way forward would be to administer a thrombolytic, or clot-busting agent, like tissue plasminogen activator. Moreover, this agent would have to be administered early enough in the wake of the stroke to be effective. In 1992, American neurologists Tom Brott and Steven Levine differentiated between the notion of “acute stroke” and “truly acute (“hyperacute”) treatment,”<sup>284</sup> suggesting that while “acute” was often used to refer to the first 12-24 hours after a stroke,<sup>285</sup> the “critical period” for treatment would likely be significantly shorter. Brott and Levine call for a “sense of temporal urgency” in order to achieve success in treatment.<sup>286</sup> Referring to the traditional nihilism surrounding stroke treatment, American neurologist

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<sup>279</sup> A. K. Admani, “New Approaches to Treatment of Recent Stroke,” *British Medical Journal* 2 (1978): 1678-1679.

<sup>280</sup> Admani, “New Approaches,” 1678.

<sup>281</sup> M. Martin, H. Auel, “Thrombolytic Therapy in Arterial Thromboembolism,” *Progress in Cardiovascular Disease* 10 (1979): 351-374.

<sup>282</sup> Herbert I. Goldberg, “CT Scan and Angiography in the Diagnosis of Cerebrovascular Disorders,” in John Stirling Meyer & Terry Shaw, editors, *Diagnosis and Management of Stroke and TIAs*. (Menlo Park: Addison-Wesley Publishing Co., 1982), 90.

<sup>283</sup> Sloan, “Thrombolysis,” 764.

<sup>284</sup> Steven R. Levine, Thomas G. Brott, “Thrombolytic Therapy in Cerebrovascular Disorders,” *Progress in Cardiovascular Disease* 24 (1992): 235-262.

<sup>285</sup> Joseph M. Zabramski, John A. Anson, “Diagnostic Evaluation of Ischemic Cerebrovascular Disease,” in Issam A. Awad, editor, *Cerebrovascular Occlusive Disease and Brain Ischemia* (Park Ridge, IL: American Association of Neurological Surgeons, 1992), 75.

<sup>286</sup> Levine, “Thrombolytic Therapy,” 235.

Bruce Mackay further elaborated on the relationship between treatability and time in a 1992 article: “This sense of futility will clearly be perpetuated if treatment continues to be given at times in which there is very little potential for clinical benefit.”<sup>287</sup> For Mackay, therefore, an end to the “therapeutic nihilism”<sup>288</sup> that had surrounded stroke for millennia would come from identifying the time frame during which treatment could be administered effectively.

#### *Acute Stroke & the NINDS Trial*

In the section above, I have proposed that experiments in the 1950s and 1960s suggested that the success of treatment for stroke would depend upon the rapidity of its initiation. Moreover, I have argued that the term “acute stroke” came to refer to a stroke very early on in its course, when the potential for treatment might exist. I will now argue that the “acute stroke” came to mean a stroke that could be successfully treated through the proper use of the drug tPA, whose efficacy was first suggested in the 1995 NINDS trial. In 1988, researchers in California had begun experimenting with the thrombolytic drug tissue plasminogen activator, and their “preliminary experience with 19 patients” informed the design of a “two-stage prospective study” that became known as the NINDS trial.<sup>289</sup> In the NINDS trial, the concepts of treatability and time were strongly related, for it was the first trial to suggest that “acute stroke” was indeed treatable, but only within 3 hours of the onset of symptoms. Several other trials, which had attempted treatment at 4.5, 6 and 8 hours after the onset of symptoms, had failed to show a beneficial effect to patients.<sup>290</sup>

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<sup>287</sup> Bruce Mackay, “Endovascular Thrombolysis and Angioplasty,” in Issam A. Awad, ed. *Cerebrovascular Occlusive Disease and Brain Ischemia* (Park Ridge, IL: American Association of Neurological Surgeons, 1992), 234.

<sup>288</sup> Paul J. Camarata, Roberto C. Heros, Richard E. Latchaw, “Brain Attack: The Rationale for Treating Stroke as a Medical Emergency,” *Neurosurgery* 34 (1994): 144-158.

<sup>289</sup> Gregory J Del Zoppo, “Investigational Use of tPA in Acute Stroke,” *Annals of Emergency Medicine* 17 (1988): 1196-1201.

<sup>290</sup> Levine, “Thrombolytic Therapy,” 248.

In December 1995, the NINDS trial was published in the *New England Journal of Medicine* under the title “Tissue Plasminogen Activator for Acute Ischemic Stroke.”<sup>291</sup> The article, authored by a multinational collaboration of physicians, begins by quoting statistics regarding the incidence of stroke and its impact on population health. However, no specific definition of stroke or “acute stroke” is offered. Then, in a few sentences set out in the article’s introductory paragraph, the theory and methodology of the trial are explained.

Cerebral angiography conducted soon after the onset of stroke demonstrates arterial occlusions in 80 percent of acute infarctions. Thrombolytic canalization of occluded arteries may reduce the degree of injury to the brain if it is done before the process of infarction has been completed. Since intracerebral hemorrhage was a frequent major complication reported in early trials of thrombolytic therapy, the use of recombinant human tissue plasminogen activator (t-PA) for cerebral arterial thrombolysis requires a careful evaluation of both the risks and the potential benefits. The safety of intravenous t-PA for the treatment of acute cerebral ischemia was previously tested in two open-label, dose-escalation studies, which emphasized very early treatment — within 90 and 180 minutes of the onset of the stroke — to reduce the risk of hemorrhage and to maximize the potential for recovery. These studies suggested that doses of less than 0.95 mg of t-PA per kilogram of body weight were relatively safe and resulted in early neurologic improvement in a substantial proportion of patients. These results were enough to justify further investigation in the form of a larger, randomized, placebo-controlled trial.<sup>292</sup>

The argument offered by the NINDS Study Group can be reconstructed as follows: an occlusion in a major artery in the brain can be identified in most patients with stroke; opening these occlusions may reduce the degree of injury sustained by the brain; the use of a thrombolytic may achieve this goal, albeit with a risk of hemorrhage; the risk of hemorrhage decreases, and the chance of recanalization increases, the earlier the drug is administered; preliminary evidence from smaller studies provided the rationale for a large, randomized, clinical trial. In these few sentences, the authors of the article enumerate key concepts in the idea of the acute stroke: the notion of ischemic vascular disease arising from arterial occlusion, the importance of time in determining the success of potential reperfusion, the development of tPA as a specific agent potentially able to reopen occluded vessels leading to beneficial reperfusion, and the issue of balancing

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<sup>291</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1581.

<sup>292</sup> *Ibid.*, 1581.

the risk of hemorrhage in the face of thrombolytic activity. These are the foundations of the modern meaning of the “acute stroke.”

The authors then describe the structure of their trial, in which patients were randomized to receive either tPA or placebo within 3 hours of the onset of their symptoms.<sup>293</sup> Every patient had to have a CT scan of the brain to exclude intracerebral hemorrhage as a cause of their symptoms. When followed out to 90 days (3 months), the authors found “a benefit of intravenous tPA therapy for patients with ischemic stroke when treatment was initiated within three hours of the onset of symptoms. As compared with patients given placebo, patients treated with IV tPA were at least 30 percent more likely to have minimal or no disability at three months.”<sup>294</sup> The authors conclude, in the final sentence of their article, that “an improvement in clinical outcome at three months was found in patients treated with intravenous tPA within three hours of the onset of acute ischemic stroke.”<sup>295</sup> For the first time in the history of stroke, a treatment could be said to be effective in reversing its signs and symptoms, albeit if administered under particular conditions. Specifically, the authors were clear that tPA is effective “within three hours of the onset of *acute ischemic stroke*.” With this concluding phrase, the contemporary meaning of the “acute stroke” was introduced.

The NINDS trial became representative of the new concept of the acute stroke, a stroke that could be effectively treated within 3 hours of onset with the drug tPA. For example, in the September 1996 edition of *Academic Emergency Medicine*, experts from the neurological and emergency medicine communities wrote how “until recently, no clinically effective treatment for acute ischemic stroke has been available,” implying very clearly that this scenario had changed. The authors declare that “intravenous tPA improves 3-

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<sup>293</sup> Randomization refers to the process, common in modern clinical trials, whereby patients are randomly assigned to receive one of the treatments under investigation. In the case of the NINDS trial, the two treatments with tPA and placebo (an inactive comparator). Often, patients and their physicians are both kept unaware of patients’ assignments.

<sup>294</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1586.

<sup>295</sup> *Ibid.*, 1586.

month neurologic outcome in patient with acute ischemic stroke.”<sup>296</sup> The first line of a 2007 text entitled *The Stroke Book* states unequivocally that “acute stroke management begins the moment the emergency response system is activated.”<sup>297</sup> The importance of time and treatment are thereby preserved, and reinforced with the popular phrase: “Time is brain. Every minute matters in patients with acute stroke.”<sup>298</sup> In a 2012 review of the literature, neurologists Roger Kelley and Sheryl Martin-Schild declare that “It is now increasingly recognized that acute ischemic stroke is an emergent issue that is potentially amenable to interventions that may have a significant effect on outcome.”<sup>299</sup>

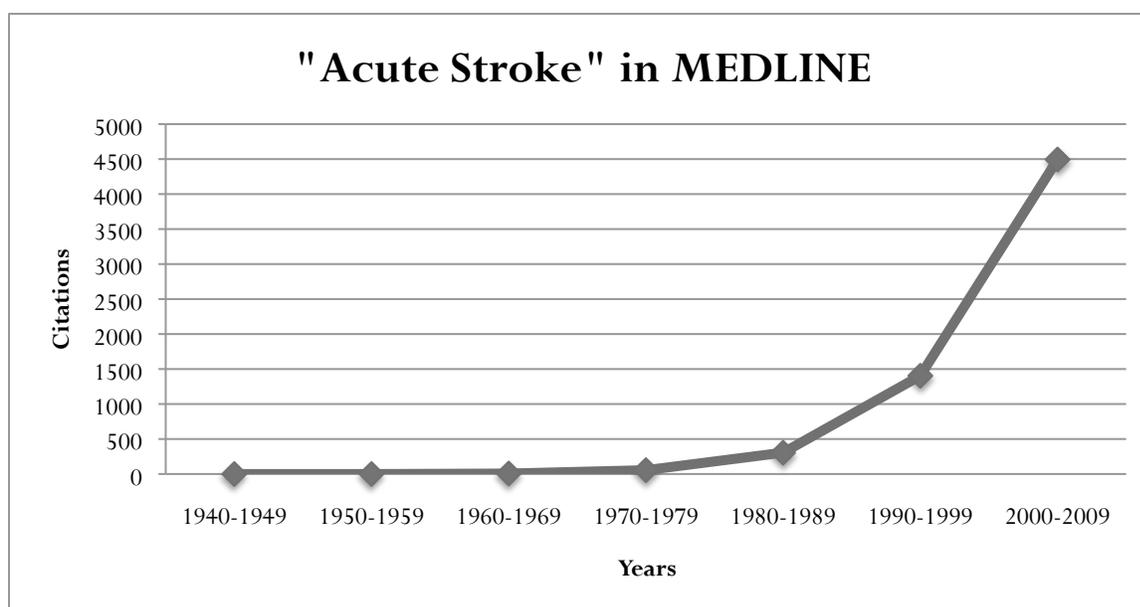


Figure 3. Uses of the term “acute stroke” in the MEDLINE Database, by decade.

The argument for the importance of the NINDS trial to the modern conception of the acute stroke is supported by a brief bibliometric analysis of the uses of the term “acute stroke” in the biomedical

<sup>296</sup> Rashmi Kothari, Aruthur Pancioli, Thomas Brott, Joseph Broderick, “Thrombolytic Therapy for Cerebral Infarction,” *Academic Emergency Medicine* 3 (1996): 881-892.

<sup>297</sup> Denis Lemke, Michel T. Torbey, “Emergency Medical Services: First line of defense against stroke,” eds. Michel T. Torbey, Magdy H. Selim, *The Stroke Book* (Cambridge: Cambridge University Press, 2007), 1.

<sup>298</sup> Magdy Selim, “Ischemic Stroke in the first 24 hours,” eds. Michel T. Torbey, Magdy H. Selim, *The Stroke Book* (Cambridge: Cambridge University Press, 2007), 157.

<sup>299</sup> Roger E. Kelley, Sheryl Martin-Schild, “Ischemic Stroke: Emergencies and Management,” *Neurological Clinics* 30 (2012): 187-210.

literature between 1940 and 2013. According to a search of MEDLINE, the online catalogue of the National Library of Medicine, the term “acute stroke” has been used 9237 times in the medical literature. As described, the earliest known reference came in J.W.D. Bull’s 1960 article. “Acute stroke” was then used 7 times of the course of the next decade. Fifty-five instances arose in the 1970s, 305 in the 1980s, and 1404 in the 1990s. In the first decade of the 21<sup>st</sup> century, the term was used 4494 times. While this rapid increase may in some part reflect the proliferation of medical research and archived publications, the suggestion of a particular causal relation in its usage persists. Within the decade 1990-1999, there were 376 usages prior to 1995 (the year the NINDS study was published), and 1028 afterwards. Looking back to the start of MEDLINE with 1995 as the inflection point, there were 743 usages of “acute stroke” prior to 1995, and there have been 8494 usages since. This clear distinction suggests the importance of the year 1995, and the NINDS trial, to usage of the term “acute stroke.” Moreover, I suggest that it reflects the establishment of the meaning of “acute stroke,” in reference to the results of the NINDS trial.

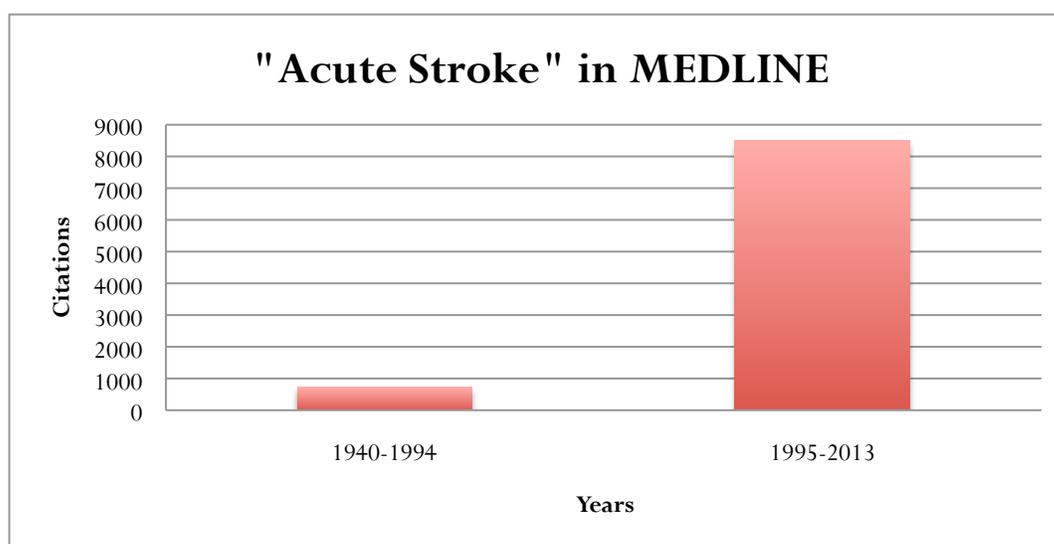


Figure 4. Uses of the term “acute stroke” in the MEDLINE database, pre- and post-1995.

In light of the results of the NINDS trial, “acute stroke” was carved off from stroke, and arguably became a disease of its own. Given that diseases reflect ways of understanding patterns of illness manifested

by patients, diseases can be redefined in relation to each other. In her 2005 book *Lovers and Livers*, Queen's University historian of medicine Dr. Jacalyn Duffin explores the example of hepatitis to illustrate how diseases may be defined by novel clinical features, novel treatments, or a novel prognosis.<sup>300</sup> In the case of acute stroke, all three apply. An acute stroke is diagnosed if the symptoms are those of stroke, if the patient arrives in hospital within 3 hours of the onset of symptoms, and if the CT scan excludes hemorrhage. The treatment, if all conditions are met, is tPA. And as a consequence of tPA, the prognosis for a patient has the potential to be much brighter than it might have been otherwise.

With this conceptualization of the acute stroke came a new linguistic style with which to describe it. In the 1994 edition of *House Officer Series: Neurology*, a handbook for neurological trainees by American neurologists Howard Weiner and Lawrence Levitt, discussion of the treatment of stroke is limited to issues of prevention, without mention of the possibility of reversing symptoms.<sup>301</sup> By the next edition, published in 1999, the tone had changed dramatically. Whereas in 1994 the chapter on stroke begins with the assertion "Stroke is one of the most common neurologic problems,"<sup>302</sup> the chapter in 1999 begins with the statement that "Therapy of stroke is evolving with the introduction of newer medications and interventions" and the authors emphasize the need for "urgent assessment."<sup>303</sup> In fact, the authors provide an introductory clinical case, written in a particularly staccato style that has become characteristic of the stroke literature since 1995.

A 67-year old diabetic man with longstanding hypertension and a pack/day smoking habit presents to the emergency room 45 minutes after suddenly dropping his fork from his right hand at lunch. His wife noticed he was using the wrong words and had trouble understanding her, and he had to be assisted to the ambulance because of right leg weakness. In the emergency room, he shows signs of a global aphasia, right hemiparesis affecting the arm and face more than the leg, and moderate hypertension. A computed tomography (CT) scan

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<sup>300</sup> Jacalyn Duffin, *Lovers and Livers: Disease Concepts in History* (Toronto: University of Toronto Press, 2005), 92.

<sup>301</sup> Harold L. Weiner, Lawrence P. Levitt, *House Officer Series: Neurology*, 5<sup>th</sup> edition (Baltimore: Williams & Wilkins, 1994), 16.

<sup>302</sup> Weiner, *House Officer Series: Neurology*, 5<sup>th</sup> edition, 16.

<sup>303</sup> Harold L. Weiner, Lawrence P. Levitt, Alexander Rae-Grant, *House Officer Series: Neurology*, 6<sup>th</sup> edition (Philadelphia: Williams & Wilkins, 1999), 90.

shows no evidence of hemorrhage or cerebral edema. He is considered for thrombolytic therapy.<sup>304</sup>

This narrative structure is reproduced in many other acute stroke case reports, most prominently in the “Clinico-pathological Conferences of the Massachusetts General Hospital,” which are regularly featured in the *New England Journal of Medicine*. In 2004, the case of a 57 year old man is reported in a similarly staccato form, with each event precisely timed: “He was last seen well by his mother-in-law at 2 pm; at 2:15 pm, she noted that he was drooling, had slurred speech, and could not swallow pills. . . He was brought to the hospital by ambulance at 4:30 pm.”<sup>305</sup> In the discussion of the case, neurologist Lee Schwamm of Harvard University comments that “A patient, such as this one, with suspected acute ischemic stroke, must be evaluated immediately in order to assess his or her eligibility for thrombolytic therapy.”<sup>306</sup> Statements like this suggest how the diagnosis of acute ischemic stroke is dependent upon his potential eligibility for treatment with tPA.

Interestingly, similar narrative structures appeared in the cardiac literature approximately 10 years earlier, following the clinical trials that showed that tPA could be effective in the treatment of myocardial infarction (heart attack). In the modern conceptualization of the myocardial infarction, an artery carrying blood to the heart muscle becomes blocked, and can be reopened through the use of a thrombolytic agent like tPA, if administered quickly enough.<sup>307</sup> For example, a 1987 review of the development of tPA for heart disease describes a typical case reminiscent of the stroke narratives:

“A 58 year old man developed substernal chest pain, nausea, diaphoresis and shortness of breath at 11:00 am on April 9, 1986. At 11:40 am, he was admitted to the hospital, where he continued to have chest pain. An ECG revealed 1.5 mm ST segment elevation in V1 and V2. The diagnosis of an

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<sup>304</sup> Weiner, *House Officer Series, Neurology*, 6<sup>th</sup> edition, 90.

<sup>305</sup> Bob S. Carter, James D. Rabinov, Rolf Pfannl, Lee H. Schwamm, “Case 5-2004: A 57-Year-Old Man with Slurred Speech and Left Hemiparesis,” *New England Journal of Medicine* 350 (2004): 707-716. An ECG is an electrocardiogram, a test of the heart’s electrical activity which can identify abnormalities in the course of a myocardial infarction. The ST segment is a portion of the heart’s contractile rhythm which commonly demonstrates changes during myocardial infarction. References to V1 and V2 invoke the particular leads, or electrodes, where such changes are demonstrated, correlating to a particular anatomical region of the heart.

<sup>306</sup> Carter, “Case 5-2004,” 709.

<sup>307</sup> Jones, *Broken Hearts*, 71.

acute anterior myocardial infarction was made, and intravenous tissue plasminogen activator (tPA) was administered 30 minutes later.”<sup>308</sup>

As in stroke, time serves as an important determinant of efficacy in the treatment of myocardial infarction.

This is reflected in the familiar use of quick, short sentences, relating events in a tight chronology.

Moreover, the use of the word “acute,” in combination with “anterior myocardial infarction,” suggests that a similar process of conceptualization may have occurred in the cardiac community with regards to Acute Myocardial Infarction (AMI). Up until the 1990s, a “chicken and egg” debate existed within cardiology: was the dead heart muscle that was found in myocardial infarction was the cause or the consequence of blocked coronary arteries? In his history of cardiac therapeutics, David Jones relates how the successful use of thrombolytics in the 1980s was an important factor in convincing the cardiac community that the primary problem was indeed the arterial blockage, and that muscle death was a consequence of the blockage.<sup>309</sup>

While Jones argues that thrombolysis contributed to the conceptualization of a known disease (myocardial infarction), he does not suggest that *acute myocardial infarction* became a distinct disease, and it goes beyond the scope of this thesis for me to propose such a conclusion.

However, the role of therapy in understanding, and even potentially defining, disease, can be further explored in relation to myocardial infarction. The case report cited above is followed by a historically-minded commentary that touches upon the way treatment changes over time:

“Ten years ago, the therapeutic approach to this patient would have been bed rest and IV morphine as required for chest pain. The availability of recombinant tPA has allowed a more aggressive approach to the treatment of myocardial infarction. Instead of merely treating the symptoms of myocardial ischemia, therapy has now been designed to interrupt the pathologic process directly, causing acute coronary insufficiency by lysing the coronary arterial thrombus.”<sup>310</sup>

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<sup>308</sup> Kenneth R. Chien, Robert Meidell, Robert Gerard, “Tissue Plasminogen Activator: From Molecular Biology to Myocardial Infarction,” *American Journal of Medical Science* 293 (1987): 201-207.

<sup>309</sup> Jones, *Broken Hearts*, 64.

<sup>310</sup> Chien, “Tissue Plasminogen Activator,” 201.

As in stroke, the availability of tPA for the treatment of myocardial infarction allowed for a shift in focus towards intervening in the putative disease process. This drastically changed the management of myocardial infarction, and led to the development of “acute myocardial infarction” response teams in hospitals around the world.<sup>311</sup> On the basis of the availability of acute intervention for myocardial infarction, the notion of a “heart attack” was popularized. The concept of “heart attack” was later appropriated by the stroke community in advertising stroke as a “brain attack” requiring immediate evaluation and treatment.<sup>312</sup> The imagery of the “brain attack” recalls the etymological origins of apoplexy: being struck down suddenly. However, the sense of urgency that the stroke community sought to communicate to the general public was not predicated on the severity of stroke, but on the potential treatment that could now be offered.

Though multiple avenues of investigation support the association between acute stroke and its treatability, I have not found any definitional statement to that effect in the medical literature. Perhaps the absence of essentialist statements reflects a recognition of the fact that acute stroke is a disease that was born and popularized within the clinical lifetimes of most practicing physicians. They may have come to think of it as an epistemic concept rather than as a natural kind. Alternatively, they may continue to see acute stroke as a disease that was simply “discovered” in light of scientific advancements. Regardless, recognition that acute stroke did not pop into existence one day appears to be reflected in the medical literature. For example, neurologists Kelley and Martin-Schild explain how “demonstration of efficacy in thrombolytic therapy was not an overnight event,” recalling the experimental process that led to the NINDS trial, and the persistent controversies that surround it. This comment recalls the work of Ludwik Fleck, who argued that the modern concept of syphilis did not arise overnight, but reflected the intertwining of several lines of

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<sup>311</sup> Jones, *Broken Hearts*, 65.

<sup>312</sup> Camarata, “Brain Attack,” 144.

thought over many years.<sup>313</sup> I will now seek to untangle those intertwining lines of thought in relation to the meaning of the acute stroke.

### *Preconditions of the Acute Stroke*

I have argued that, in the contemporary context, the term “acute stroke” is understood as a disease that is potentially treatable through the administration of intravenous tPA. While “acute stroke” appropriated its meaning in relation to the success of the NINDS trial in 1995, this association reflects the confluence of a set of earlier concepts and conditions which made the NINDS result (and its general interpretation) possible. I now propose that the conceptualization of “acute stroke” in reference to tPA was possible due to a set of six interwoven preconditions: the elaboration of the vascular supply of the brain; the localization of pathology to specific organs within the body; the pathological differentiation of ischemia from hemorrhage; the dissemination of CT scanners; the development of thrombolytic agents; and the elaboration of the concept of the penumbra in cerebral ischemia. Each of these preconditions will be considered, roughly in chronological order.

These preconditions should not be considered independent phenomena, in that they interact and overlap with each other; hence my appropriation of the imagery of “interweaving” or “intertwining” from Fleck.<sup>314</sup> In *Genesis and Development of a Scientific Fact*, Fleck writes of “the four lines of thought intertwining to form the modern aspect of syphilis.”<sup>315</sup> As Fleck elaborates so eloquently in the case of syphilis, an idea exists only in relation to a long and complicated history of ideas that came before. For Fleck, “concepts are not spontaneously created but are determined by their “ancestors.”<sup>316</sup> He relates the modern conception of syphilis to a particular chemical test called the Wassermann reaction, but he argues that the idea of syphilis

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<sup>313</sup> Fleck, *Genesis*, 17.

<sup>314</sup> *Ibid.*, 9.

<sup>315</sup> *Ibid.*, 17.

<sup>316</sup> *Ibid.*, 20.

“cannot be proved with an isolated experiment.” Rather, it arises out of past experience, successful and unsuccessful experiments, “and — epistemologically most important — from *several adaptations and transformations of concepts*.”<sup>317</sup> The historical elaboration of a set of stroke-specific adapted and transformed concepts is the subject of this section.

Sociologist of medicine and practicing anesthesiologist Michael Nurok of Harvard University offers a complementary view of the way medical concepts acquire their meaning. In his article “Elements of the Medical Emergency’s Epistemological Alignment: 18<sup>th</sup>-20<sup>th</sup> century perspectives,” Nurok explores how the modern conception of the “medical emergency” arose in light of medical developments and historical events.<sup>318</sup> Specifically, he argues that the concept of the “medical emergency” as understood in the 20<sup>th</sup> century could not have developed “until a series of related concepts had been elucidated, and its epistemology became aligned.”<sup>319</sup> By “epistemological alignment,” he means that semantic networks (ie. meanings) become linked to particular terminologies (ie. words) only when historical conditions render this association possible.<sup>320</sup> In essence, Nurok argues that the acquisition of meaning by a particular term — such as “acute stroke” — is a historically-determined and historically-contingent epistemological process.<sup>321</sup> Nurok begins from a Kuhnian perspective to argue that epistemological alignment led to the development of the contemporary meanings of terms such as accident, sudden death, and resuscitation.<sup>322</sup> The ways in which the modern concept of acute stroke arose from a similar process will now be explored.

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<sup>317</sup> Fleck, *Genesis*, 98.

<sup>318</sup> Michael Nurok, “Elements of the Medical Emergency’s Epistemological Alignment: 18<sup>th</sup>-20<sup>th</sup> century perspectives,” *Social Studies of Science* 33 (2003): 563-579.

<sup>319</sup> Nurok, “Epistemological Alignment,” 563.

<sup>320</sup> *Ibid.*, 563.

<sup>321</sup> *Ibid.*, 563.

<sup>322</sup> *Ibid.*, 564.

### *Vascular Anatomy*

The first precondition of the acute stroke is the conceptualization of the brain's vascular anatomy, meaning the idea and mechanism by which blood arrives at the brain. The earliest known studies of the brain's vascular anatomy were performed by Erasistratus of Cos (330-255 BC) and Herophilus of Chalcedon (330-260 BC), who were the first to recognize that arteries and veins were associated with each of the body's organs.<sup>323</sup> Physician and scholar Galen of Pergamon (129-216 AD) was the dominant influence on medicine's understanding of the brain's vascular anatomy until the early modern period. In Galen's physiological system, veins supplied the brain with blood and nutrients, while the arteries yielded blood and the vital spirit.<sup>324</sup> According to Galen, the passage of blood through the *rete mirabile*, a network of arteries located at the base of the skull, converted the vital spirit into animal spirit, which was essential to the transmission of movement and sensation throughout the body. Galen's concept of the *rete* was questioned by Italian physician Giacomo Berengario da Carpi (1460-1530), and was famously challenged by Belgian anatomist Andreas Vesalius (1514-1564) in his influential atlas *De Humanis Corporis Fabrica* of 1543.<sup>325</sup> The *rete* did not exist in humans, but could be found in other mammals, from whom Galen's anatomical conclusions had been drawn. Galen's vascular physiology was further challenged by the English anatomist William Harvey (1578-1657), who demonstrated that blood flowed from the heart through arteries and to the heart through veins.<sup>326</sup> However, Harvey did not reject all Galenic conceptions, for in his famous anatomical lectures of 1616, Harvey cited Galen in declaring that the brain "is cold, for it is bloodless."<sup>327</sup>

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<sup>323</sup> Heinrich von Staden, "Body, Soul, and Nerves: Epicurus, Herophilus, Erasistratus, the Stoics, and Galen," eds. John P. Wright, Paul Potter, *Psyche and Soma: Physicians and Metaphysicians on the Mind-Body Problem from Antiquity to Enlightenment* (Oxford: Clarendon Press, 2000), 92.

<sup>324</sup> Axel Karenberg, "Reconstructing a doctrine: Galen on apoplexy," *Journal of the History of the Neurosciences* 3 (1994): 85-101.

<sup>325</sup> Andrew Wear, "Early Modern Europe, 1500-1700," in Lawrence I Conrad, Michael Neve, Vivian Nutton, Roy Porter, Andrew Wear, *The Western Medical Tradition 800 BC to 1800 AD* (Cambridge: Cambridge University Press, 1995), 279.

<sup>326</sup> Wear, "Early Modern Europe," 333.

<sup>327</sup> Gweneth Whitteridge, *The Anatomical Lectures of William Harvey: Praelectiones Anatomie Universalis de Musculis (1616)* (Edinburgh: E. & S. Livingstone Ltd, 1964), 317.

The significance of this conclusion should not be lost: no vascular anatomy can be described when the brain is felt to be without blood.

English anatomist and physician Thomas Willis built upon earlier work by Gabriel Fallopius (1523-1562), Giulio Casserius (1545-1605), Johann Vesling (1595-1649) and Johannes Jakob Wepfer (1620-1695), to famously describe the brain's basic blood supply: the two carotid arteries in the front of the neck and the two vertebral arteries in the back.<sup>328</sup> Moreover, he described the ways in which these four arteries shared supply to the brain through a circle at its base, which is now referred to as the "Circle of Willis."<sup>329</sup> Willis documented the extensive intercommunications (what we term collateralization) between the brain's arteries. He found that dye injected into one artery would spread "into every corner and secret place of the brain and cerebel."<sup>330</sup> Willis drew clinical significance from this collateralization when he dissected the brain of a patient who was found to have had an asymptomatic occlusion of the internal carotid artery.<sup>331</sup> To Willis, collateralization allowed the brain to retain its blood supply despite the loss of flow in any one artery. He suggested that this collateralization protected against the clinical entity of apoplexy. He did not elaborate further on this association, but we can interpret that to Willis there existed a causal link between arterial obstruction and the development of the symptoms of apoplexy.<sup>332</sup>

The importance of vascular anatomy to neurological disease was a topic of extensive research in the 19<sup>th</sup> century. The influential French neurologist and pathologist Jean-Martin Charcot (1825-1893) remarked that "the vascular system (arteries, veins, capillaries) governs the situation," by which he meant

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<sup>328</sup> Andrew N. Williams, "Thomas Willis' Understanding of Cerebrovascular Disorders," *Journal of Stroke and Cerebrovascular Diseases* 12 (2003): 280-284.

<sup>329</sup> Thomas Willis, *Five Treatises* (London: T. Dring, C. Harper, J. Leigh, S. Martin, 1681), 84.

<sup>330</sup> Mark D. Wilson, "The Life and Times of Thomas Willis and his Impact on Contemporary Medicine," *Journal of the History of the Neurosciences* 21 (2012): 127-131.

<sup>331</sup> M. J. Eadie, "A Pathology of the Animal Spirits — the Clinical Neurology of Thomas Willis, Part 1 – Background, and Disorders of Intrinsically Normal Animal Spirits," *Journal of Clinical Neuroscience* 10 (2003): 14-29.

<sup>332</sup> Schutta, "Seventeenth Century," 254.

that vascular supply was central to understanding many diseases of the brain.<sup>333</sup> In his lectures, Charcot provided detailed accounts of the divisions and connections of the intracranial arteries.<sup>334</sup> He appropriated concepts that had been elaborated by contemporaries including Henri Duret (1849-1921) and Otto Heubner (1843-1926). Writing at the turn of the century, Sir William Osler recognized the importance of the cerebral circulation to neurological disease when he wrote that “There is much that is still indefinite in the physiology of the circulation of the brain, but that which is known is of the greatest practical moment to the physicians.”<sup>335</sup> He suggested that the specific “intercommunication” between branches of the arteries was subject to considerable variation “which may be of extreme importance in pathological conditions.”<sup>336</sup>

The commentaries of Charcot and Osler suggest that the vascular supply of the brain was understood to be important, but that the fullest extent of that relevance had not yet been elaborated in their times. The concept that blood flowed to the brain — in consistent and reproducible ways — would prove central to the ability of physicians to interpret clinical and radiographic features of patients with acute stroke. Additionally, the notion that arterial supplies overlap to produce protective redundancies would prove central to the later concept of the penumbra. The description of thrombi — blood clots — within the arteries of the brain, and the subsequent development of “softenings” or infarction allowed for the association of clinical syndromes with regions of damage, and in turn with the obstruction of specific vessels. This clinico-anatomico-pathological correlation remains at the core of the neurologist’s process of decision-making in acute stroke management. In this way, notions of the brain’s vascular anatomy, the localizability of pathology, and the theory of the penumbra are interwoven in the development of the concept of the acute stroke.

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<sup>333</sup> Jean-Martin Charcot, *Lectures on the Localisation of Cerebral and Spinal Diseases, Delivered at the Faculty of Medicine of Paris*, trans. Walter Baugh Hadden (London: The New Sydenham Society, 1883), 40.

<sup>334</sup> Charcot, *Lectures*, 42.

<sup>335</sup> Osler, *Principles*, 961.

<sup>336</sup> *Ibid.*, 961.

### *Localizability of Pathology*

The dominant concept of disease from Hellenic to early modern times was the humoral theory that viewed disease as a product of an imbalance in the four humors of the body: blood, phlegm, yellow bile and black bile.<sup>337</sup> The humoral approach understood disease as a process affecting the whole body and not specific organs. Beginning in the 17<sup>th</sup> century, and not fully actualized until the 19<sup>th</sup> century, a rival conceptualization placed individual diseases within the confines of specific organs, and further specifically within tissue types within organs. This “anatomical concept” is frequently associated with the work of Italian pathologist Giovanni Battista Morgagni (1682-1771), whose seminal work *De Sedibus et causis morborum per anatomem indagatis* was published in 1761 and first translated into English in 1779.<sup>338</sup> In *De Sedibus*, Morgagni paired case histories with autopsy reports, establishing a narrative and causal link between a patient’s symptoms in life and post-mortem pathological findings. French historian of medicine Georges Canguilhem (1904-1995) wrote that Morgagni’s “creation of a system of pathological anatomy made it possible to link the lesions of certain organs to groups of stable symptoms, such that nosographical classification found a substratum in anatomical analysis.”<sup>339</sup>

The notion that pathology could be localized within the body, particularly at autopsy, can itself be understood as reflecting the interweaving of a set of ideas. Specifically, the clinico-anatomical concept as exemplified by the work of Morgagni reflects the confluence of three notions that were largely novel in the 18<sup>th</sup> century: that diseases would have visible correlates within the body, that exploring the body would speak towards the causation of symptoms and death, and that it was only upon opening of the body that these processes would be appreciable.<sup>340</sup> For example, and importantly for this thesis, opening the body

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<sup>337</sup> Vivian Nutton, “Medicine in the Greek World, 800-50 BC,” eds. Lawrence I Conrad, Michael Neve, Vivian Nutton, Roy Porter, Andrew Wear, *The Western Medical Tradition 800 BC to 1800 AD* (Cambridge: Cambridge University Press, 1995), 24.

<sup>338</sup> Roy Porter, “The Eighteenth Century,” eds. Lawrence I. Conrad, Michael Neve, Vivian Nutton, Roy Porter, Andrew Wear, *The Western Medical Tradition 800 BC to 1800 AD* (Cambridge: Cambridge University Press, 1995), 410.

<sup>339</sup> Georges Canguilhem, *On the Normal and the Pathological*, trans. Carolyn R. Fawcett (Dordrecht: D. Reidel Publishing Company, 1966), 13.

<sup>340</sup> Porter, “Eighteenth Century,” 410.

allowed for the recognition that what was called apoplexy in life might be associated with a variety of pathological findings. Most prominently among these were brain ischemia and brain hemorrhage.<sup>341</sup> The differentiation of these entities would prove essential in the development of the concept of the acute stroke.

### *Ischemia and Hemorrhage*

What caused apoplexy? Writing in 1820, British physician John Cooke listed “blood, serum, pus, hydatids, tumours of different kinds, organic lesions, polypous concretions, ossification, and exostoses” as the chief “morbid appearances” of apoplexy, referring to the various pathologies that might be identified at autopsy in a patient who had died of apoplexy.<sup>342</sup> Cooke’s statement expands upon a notion, famously proposed by Johannes Jakob Wepfer in his treatise on apoplexy of 1658, that distinct pathological entities described after death (especially brain hemorrhage and occlusive disease of the vessels), could result in the same clinical presentation during life (specifically, apoplexy).<sup>343</sup> Wepfer had argued that multiple disease processes might cause the symptoms of apoplexy: clot obstructing the carotid or vertebral arteries; compression of these arteries in the neck due to enlarged glands or some other local swelling; intracerebral bleeding from a ruptured blood vessel; obstruction of the origins of the nerves where they arose due to exudate or compression from excessive blood; or an abnormal deposition of blood.<sup>344</sup>

Wepfer’s work implies three important conclusions: that clinical entities and pathological entities could be understood as distinct processes; that the pathological entity was the cause of the clinical entity; and that, at least in the case of apoplexy, it might not be possible to differentiate among the causative pathological entities on clinical grounds alone. For this final reason, French physician and encyclopedist Gabriel Andral (1797-1876) abandoned the term apoplexy in his influential 1838 textbook, replacing it

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<sup>341</sup> Eadie, “A Pathology,” 24.

<sup>342</sup> Cooke, *A Treatise on Nervous Diseases*, 178.

<sup>343</sup> Axel Karenberg, “Johann Jakob Wepfers Buch über die Apoplexie (1658): Kritische Anmerkungen zu einem Klassiker der Neurologie,” *Nervenarzt* 69 (1998): 93-98.

<sup>344</sup> Eadie, “A Pathology,” 24.

with discussions of “hemorrhage of the cerebral hemispheres” and “softenings of the cerebral hemispheres.” He wrote of paralysis as “the most characteristic symptom of cerebral hemorrhage,”<sup>345</sup> and shared how the differentiation of hemorrhage from softening on purely clinical grounds was “often impossible.”<sup>346</sup> In 1868, French neurologist Armand Trousseau (1801-1867) explained to his students that hemorrhage and apoplexy should not be considered synonymous: “apoplexy is a generic term which must be specified, because apoplectiform phenomena are often connected with pathological conditions very different from hemorrhage... on the other hand, cerebral hemorrhage is not necessarily accompanied by symptoms of apoplexy.”<sup>347</sup>

The recognition that apoplexy might be associated with either hemorrhagic or ischemic pathology in the brain set the stage for the pathological description of these two entities. As early as the 16<sup>th</sup> century, it had been known that blood was commonly found in the brains of patients with apoplexy.<sup>348</sup> However, the pathological description of ischemia and hemorrhage became increasingly sophisticated from the 18<sup>th</sup> to the early 20<sup>th</sup> centuries. The notion that bleeding in the brain was produced by rupture of blood vessels was discussed by Wepfer and Morgagni and was widely accepted by the mid-19<sup>th</sup> century.<sup>349</sup> The specific regions of the brain most likely to experience hemorrhage — for example the thalamus and basal ganglia — were largely identified through case studies by Andral and his contemporary Maxime Durand-Fardel (1815-1899).<sup>350</sup>

Pathological understanding of ischemia also progressed from the 17<sup>th</sup> to the 19<sup>th</sup> centuries. The notion that the obstruction of cerebral vessels could lead to clinical disease was perhaps first suggested in the writings of the French physician François Bayle (1622-1709) who in 1677 associated the development of

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<sup>345</sup> Gabriel Andral, *Medical Clinic: or, Reports of Medical Cases*, ed. and trans D. Spillan (Philadelphia: Haswell, Barrington, and Haswell, 1838), 151.

<sup>346</sup> Andral, *Medical Clinic*, 190.

<sup>347</sup> Armand Trousseau, *Lectures on Clinical Medicine, Delivered at the Hôtel-Dieu, Paris*, ed. and trans. P. Victor Bazire (London: The New Sydenham Society, London, 1868), 4.

<sup>348</sup> Schutta, “Seventeenth Century,” 250.

<sup>349</sup> Charcot, *Lectures*, 41.

<sup>350</sup> *Ibid.*, 66.

arteriosclerosis (hardening of the arteries) with the clinical syndrome of apoplexy.<sup>351</sup> In *De Cerebri Anatome* of 1664, Willis had expressed surprise that a patient with an internal carotid artery occlusion had not developed symptoms from it, suggesting that the association between arterial occlusion and clinical symptoms was relatively well-established at this time.<sup>352</sup> In *De Sedibus*, Morgagni described how obstructed cerebral arteries caused areas of “softening.”<sup>353</sup> In the mid-19<sup>th</sup> century, French pathologist Léon Rostan (1790-1866) popularized the notion of “spontaneous cerebral softening” as a specific pathological entity arising from arterial occlusion.<sup>354</sup>

Working in Charcot’s laboratory at *La Salpêtrière*, Henri Duret elaborated a classification system differentiating softening from hemorrhage, and mapped the areas of softening attributable to occlusions of the brain’s major arteries.<sup>355</sup> Working at the same time, the German Otto Heubner arrived at very similar results, allowing for the eventual differentiation of finer and finer vascular-anatomical regions.<sup>356</sup> However, the notion that vessel occlusion could lead to focal softening remained controversial until the influential German pathologist Rudolf Virchow (1821-1902) described the process of thromboembolism in 1856.<sup>357</sup> Virchow originated the term “ischemia” to describe the ill effects of “arteriosclerosis” on the brain. By the 1860s, occlusion was understood to cause softening, and occlusion could be due to thrombosis (a local process) or embolism (occlusion due to a travelling clot originating elsewhere in the body).<sup>358</sup> In 1893, American physician William Pepper (1843-1898) declared that “the region involved in softening depends upon the artery which is plugged and the location of the obstructing body.”<sup>359</sup> The pathological study of ischemia became sufficiently reliable that symptoms in life could be correlated with regions of infarction,

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<sup>351</sup> Schutta, “Seventeenth Century,” 256.

<sup>352</sup> Wilson, “Life and Times,” 130.

<sup>353</sup> Daneski, “How Far,” 376.

<sup>354</sup> Paciaroni, “How Did Stroke,” 724.

<sup>355</sup> Lawrence B. McHenry, *Garrison’s History of Neurology: Revised and Enlarged with a Bibliography of Classical, Original and Standard Works in Neurology* (Springfield, IL: Charles Thomas, 1969), 383.

<sup>356</sup> Charcot, *Lectures*, 48.

<sup>357</sup> Paciaroni, “How Did Stroke,” 726.

<sup>358</sup> Andral, *Medical Clinic*, 240.

<sup>359</sup> Edes, “Intracerebral Hemorrhage,” 949.

and hence with the locations of arterial occlusions. Hence the differentiation of ischemia from hemorrhage interweaves with the clinico-anatomical method as preconditions to the contemporary notion of the acute stroke. However, the ability to differentiate hemorrhage from ischemia in the midst of the clinical assessment remained impossible until the dissemination of the CT scan in the late 20<sup>th</sup> century.

### *CT Scans*

Efforts to use thrombolytics to reverse the symptoms of stroke in the 1950s and 1960s were severely hampered by clinicians' inability to differentiate between hemorrhagic and ischemic processes on clinical grounds. For example, early experiments with angiography and thrombolytics in acute stroke — such as those reported by Sussman and Fitch, and Bull and colleagues — likely included patients with intracerebral hemorrhage, for whom the administration of a thrombolytic would have been quickly fatal.<sup>360</sup> The standard of care in that era was to use a combination of factors — blood pressure, lumbar puncture, and x-ray images of the skull — as a means of excluding intracerebral hemorrhage, though this protocol was insufficiently accurate to rule out many cases of hemorrhage, and was recognized to be problematic.<sup>361</sup> Bull's 1960 study, in which the term “acute stroke,” first appeared, intended to investigate the value of angiography as a potential means of differentiating ischemia from hemorrhage *in medias res*.<sup>362</sup> With the dissemination of the CT scan in the 1970s and 1980s, physicians gained a new means of quickly distinguishing ischemia from hemorrhage, which allowed for the selection of stroke patients for enrollment into the clinical trials of the late 1980s and 1990s.

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<sup>360</sup> Bull, “Cerebral Angiography,” 562.

<sup>361</sup> Myoung C. Lee, Lois M. Heaney, Ronald L. Jacobson, Arthur C. Klassen, “Cerebrospinal Fluid in Cerebral Hemorrhage and Infarction,” *Stroke* 6 (1975): 638-641.

<sup>362</sup> Bull, “Cerebral Angiography,” 561.

The first commercially-viable CT scanner was developed at EMI Central Research Laboratories in Great Britain by Geoffrey Hounsfield in the early 1970s.<sup>363</sup> The prototype was tested at the Atkinson Morley Hospital in London in 1971. Britain's National Health Service ordered the first CT scanners for hospitals in London, Manchester and Glasgow. The first CT scanners to be installed in the United States were at the Mayo Clinic in Rochester, Minnesota, and the Massachusetts General Hospital in Boston, both in 1973.<sup>364</sup> By 1976, 17 different companies were producing CT scanners for sale. In May 1977, there were 401 operational scanners in the United States and 21 in Great Britain. The rate of adoption of these machines rose exponentially from 1973 to 1977. Approximately 80% of CT scans performed in those years were of the head.<sup>365</sup>

The earliest CT scans were only able to identify large abnormalities such as large tumours and hemorrhages, but the technology advanced rapidly.<sup>366</sup> Within a few years, scanners could identify "cerebral lesions as small as 1 cm<sup>3</sup>."<sup>367</sup> By the early 1980s, CT scanners were able to demonstrate changes in the appearance of the brain in patients with stroke "between 24 and 48 hours" after the onset of symptoms, sometimes even "within 8 hours."<sup>368</sup> CT scanners identified hemorrhage in approximately 25% of patients deemed to have had ischemic stroke on clinical grounds.<sup>369</sup> CT scans could also identify non-ischemic processes with high accuracy, such as "subdural hematoma and metastatic and primary brain tumor or abscess, which may at times present as a typical acute stroke syndrome. Cerebral angiography is no longer required to exclude these possible surgical lesions in those patients in whom the diagnosis of stroke is in

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<sup>363</sup> E. C. Beckmann, "CT Scanning the Early Days," *British Journal of Radiology* 79 (2006): 5-8.

<sup>364</sup> Beckmann, "CT Scanning," 5.

<sup>365</sup> H. David Banta, Barbara J. McNeil, "Evaluation of the CAT Scanner and Other Diagnostic Technologies," *Health Care Management Review* 3 (1978): 7-19.

<sup>366</sup> Kelly, "Stroke," 54.

<sup>367</sup> Jankovic, "Differential Diagnosis," 82.

<sup>368</sup> Goldberg, "CT Scan," 90.

<sup>369</sup> Jankovic, "Differential Diagnosis," 82.

doubt.”<sup>370</sup> Early estimates suggested that CT scan results changed treatment plans in approximately 15% of patients.<sup>371</sup>

Prior to the availability of CT scanners, the clinician’s ability to differentiate ischemia from hemorrhage had not significantly evolved since the mid-19<sup>th</sup> century. For example, in 1912, Manchester-based neurologist Judson Bury (1852-1944) had declared that “the cerebral symptoms caused by arterial obstruction closely resemble those of hemorrhage and without an appeal to other circumstances it is generally impossible to determine the nature of the lesion.”<sup>372</sup> The CT scanner was immediately considered to have “revolutionized the diagnosis of stroke.”<sup>373</sup> The use of CT scans to permit the diagnosis of stroke *in vivo* has been termed a novel “clinical gaze,” a reference to Foucault’s work in *Birth of the Clinic*.<sup>374</sup> For the first time, physicians could see into the substance of the brain without having to cut through the skull. Like the development of the stethoscope by René Laennec (1781-1826) in the early 19<sup>th</sup> century, the CT scanner allowed physicians of the mid 20<sup>th</sup> century to “see with a better eye.”<sup>375</sup> The use of the CT scanner therefore redefined diseases such as stroke and hemorrhage, paving the way for the definition of “acute stroke” in the 1990s.

Prior to the CT scan, patients were diagnosed with ischemic stroke (in contrast to hemorrhage or other possible diseases) on the basis of the physician’s interpretation of a set of clinical variables, of which the patient’s history and physical examination findings were most important. A physician’s clinical diagnosis was considered accurate, as no alternative was available short of autopsy. However, with the advent of the CT scanner, the definition of ischemic stroke changed: it became defined in reference to its radiological features. If the attending neurologist diagnosed a certain patient with ischemic stroke rather than

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<sup>370</sup> Goldberg, “CT Scan,” 90.

<sup>371</sup> Banta, “Evaluation,” 7.

<sup>372</sup> Judson S. Bury, *Diseases of the Nervous System* (Manchester: Manchester University Press, 1912), 619.

<sup>373</sup> John Stirling Meyer, Terry Shaw, eds., *Diagnosis and Management of Stroke and TIAs* (Menlo Park, CA: Addison-Wesley Publishing Co., 1982), vii.

<sup>374</sup> Daneski, “How Far,” 370.

<sup>375</sup> Jacalyn Duffin, *To See With A Better Eye: A Life of R.T.H. Laennec* (Princeton: Princeton University Press, 1988), 1.

hemorrhage, but the CT scan showed hemorrhage, it was the CT scan's result that was privileged. The scanner over-ruled the clinician. The CT scan was felt to have more direct access to pathological truth than the clinician. Stroke and hemorrhage therefore ceased to be diseases that could be diagnosed with certainty on the basis of clinical assessment alone; radiographic assessment was considered definitive.

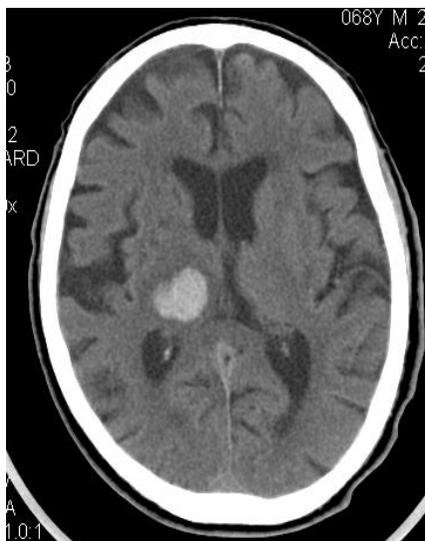


Figure 5. CT Scan of the brain, anonymized patient, Toronto 2010. This image demonstrates a right thalamic intracerebral hemorrhage. The hemorrhage is the rounded white area just to the left of midline.

Reflecting this redefinition of stroke in radiological terms, Levine and Brott criticized stroke trials from the pre-CT era as not having investigated “true” stroke.<sup>376</sup> To them, “true stroke” could only be determined on the basis of the CT scan. Successful treatment with thrombolytics would depend upon the ability to identify “true stroke.” The idea that the treatment of stroke would depend upon the ability to differentiate ischemia from hemorrhage in the live patient had been considered as early as 1912, when Judson Bury had recommended that “where it is impossible to determine whether thrombosis or hemorrhage is present it is well to avoid active medication.”<sup>377</sup> In the CT era, active medication no longer

<sup>376</sup> Levine, “Thrombolytic Therapy,” 236.

<sup>377</sup> Bury, *Textbook*, 630.

needed to be avoided, as the differentiation of ischemia from hemorrhage became a part of everyday clinical practice.

### *Thrombolysis*

In this chapter, the contemporary meaning of the acute stroke has been related to its treatment with tPA. However, this association is predicated on the existence of the thrombolytic drug tissue plasminogen activator. The development of the process of acute stroke thrombolysis, I propose, consisted of three parts: the development of the idea of thrombolysis, the synthesis of a suitable compound, and the testing of this compound in preliminary clinical trials. Efforts to produce and test agents that might dissolve arterial clots eventually led to the development of tissue plasminogen activator, which was found to be successful in the treatment of patients with stroke in the NINDS trial. I will now expand on this history, as it serves as an important precondition of the contemporary meaning of the acute stroke.

The idea of chemical thrombolysis — of dissolving blood clots through the administration of a drug — arose in light of several developments in the 1940s and 1950s: the increased use of angiography, and particularly cerebral angiography, to visualize vessels and their occlusions; and increasingly sophisticated understandings of the basic mechanisms by which thrombosis (blood clotting) occurs.<sup>378</sup> Tissue plasminogen activator, or tPA, was first identified in 1947 when a naturally-occurring compound was isolated that showed a particular ability to convert plasminogen to plasmin, activating the body's clot-busting cascade.<sup>379</sup> Initially called fibrinokinase, it was renamed tissue plasminogen activator, reflecting its mechanism of action. The enzyme tPA was found to have minimal activity in the absence of fibrin, a blood enzyme that is only generated when active clotting is occurring. It therefore had an advantage over other pharmaceutically available thrombolytics like streptokinase and urokinase, in that it would have more specific activity at the

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<sup>378</sup> Jacalyn Duffin, *History of Medicine: A Scandalously Short Introduction* (Toronto: University of Toronto Press, 1999), 187.

<sup>379</sup> Désiré Collen, Henri Roger Lijnen, "Tissue-type plasminogen activator: a historical perspective and personal account," *Journal of Thrombosis and Haemostasis* 2 (2004): 541-546.

site of the troublesome clot, and fewer blood thinning effects throughout the body.<sup>380</sup> In 1979, tPA was purified from human uterine tissue, and from melanoma cells in 1980.<sup>381</sup> Based on these discoveries, its gene was cloned to allow for mass production.<sup>382</sup>

Starting in the 1950s, several different thrombolytic agents were developed and trialed, including trypsin, fibrinolysin (aka. plasmin), thrombolyisin, streptokinase, urokinase and tissue plasminogen activator.<sup>383</sup> The first report on the clinical efficacy of fibrinolysin appeared in 1957, when it was tested in 27 patients with venous and arterial thrombi in various locations. In their 1958 trial, Sussman and Fitch had also tested fibrinolysin for cerebral arterial occlusion.<sup>384</sup> Streptokinase and urokinase were investigated in many cardiac trials in the 1960s and 1970s, as well as in stroke trials.<sup>385</sup> In the 1980s, trials of streptokinase in myocardial infarction, administered very soon after the onset of symptoms, resulted in the first signs of efficacy. In stroke trials, urokinase and streptokinase were associated with significant rates of fatal hemorrhage.<sup>386</sup>

The ability of tPA to dissolve arterial occlusions in animals was first demonstrated in 1980.<sup>387</sup> Two patients with renal vein thrombosis after kidney transplantation received tPA in the Netherlands in 1981, with observed dissolution of the occlusions. The first study in which tPA was administered to patients with acute myocardial infarction was initiated in 1983. The drug was shown to have opened occluded vessels in 6 of 7 patients within 60 minutes of administration.<sup>388</sup> A randomized, blinded, multicentre clinical trial was initiated in 1984, with 50 patients enrolled in the United States. Recanalization of the previously occluded

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<sup>380</sup> Kim Hoang, Peter Rosen, "The Efficacy and Safety of Tissue Plasminogen Activator in Acute Ischemic Stroke," *The Journal of Emergency Medicine* 10 (1992): 345-352.

<sup>381</sup> Collen, "Tissue-type plasminogen activator," (2004), 541.

<sup>382</sup> Désiré Collen, Henri Roger Lijnen, "The Tissue-Type Plasminogen Activator Story," *Arteriosclerosis, Thrombosis and Vascular Biology* 29 (2009): 1151-1155.

<sup>383</sup> Camarata, "Brain Attack," 148.

<sup>384</sup> Sussman, "Thrombolysis" (1958), 1705.

<sup>385</sup> Levine, "Thrombolytic Therapy," 237.

<sup>386</sup> *Ibid.*, 237.

<sup>387</sup> Collen, "Tissue-type plasminogen activator," (2004), 543.

<sup>388</sup> *Ibid.*, 544.

artery was demonstrated in 75% of these patients.<sup>389</sup> International clinical trials in the treatment of myocardial infarction established the efficacy of tPA in the treatment of coronary artery occlusion in the late 1980s and early 1990s.<sup>390</sup>

Experimentation with tPA in acute stroke began in 1990. The first trial, conducted in Japan, found no overall difference between those patients who received tPA and those who received urokinase.<sup>391</sup> However, non-controlled studies (meaning studies in which tPA was administered without a comparator arm) reported that as many as 50% of patients improved within 2 hours of its use.<sup>392</sup> Under the guidance of neurosurgeon Dr. Michael Walker, the stroke section of the National Institutes of Neurological Disease and Stroke (NINDS) began funding research into agents that might reverse the signs and symptoms of stroke.<sup>393</sup> The NINDS, known as the National Institutes of Neurological Disease and Blindness until 1968, not only conducted and funded large scale research, but established many of the conventions of clinical trial research in stroke and other disciplines.<sup>394</sup> The NINDS rtPA Study Group performed two dose-escalation trials of tPA in the late 1980s and early 1990s, the first including patients up to 8 hours after symptom onset, the second within only 3 hours.<sup>395</sup> A Japanese trial testing different doses of the drug administered up to 6 hours after symptom onset found that as many as 50% of patients experienced recanalization, and those patients who had received tPA did far better than those who had not.<sup>396</sup> On the basis of these experiments, the NINDS rtPA Study Group designed of the NINDS trial with a dose of 0.9 mg/kg of tPA to be administered to patients under 3 hours of symptom onset.

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<sup>389</sup> Collen, "Tissue-type Plasminogen Activator" (2004), 544.

<sup>390</sup> Levine, "Thrombolytic Therapy," 249.

<sup>391</sup> *Ibid.*, 239.

<sup>392</sup> *Ibid.*, 239.

<sup>393</sup> Lewis P. Rowland, *The NINDS at 50: An Incomplete History Celebrating the Fiftieth Anniversary of the National Institute of Neurological Disorders and Stroke* (New York: Demos, 2003), 113.

<sup>394</sup> Rowland, *NINDS*, 113.

<sup>395</sup> Levine, "Thrombolytic Therapy," 241.

<sup>396</sup> *Ibid.*, 243.

### *Penumbra*

The final precondition to the contemporary meaning of the acute stroke this set is the physiological concept of the penumbra. The *penumbra* refers to the concept that, even after arterial occlusion, some brain tissue that stops functioning remains capable of returning to normal with the restoration of blood flow. The idea of the penumbra requires conceiving that the effects of ischemic stroke are not immediately permanent. According to the theory of the penumbra, dead (irreversibly damaged) brain can be differentiated from potentially dead (reversibly damaged) brain. To borrow a phrase from Michael Nurok, the theory of the penumbra states that the brain can be resuscitated.<sup>397</sup> Writing in 1992, Scottish neurologist Donald Grosset argued that “Two basic principles dominate recent work in the field of drug treatment for acute ischaemic stroke: the concept of the ischaemic penumbra, and the recognition that early treatment is essential for maximal benefit.”<sup>398</sup> It will be shown how these two concepts — the penumbra and early treatment — are not distinct entities but represent two sides of the same coin. The theory of the penumbra explains why the efficacy of treatment with tPA should be time-dependent, and why the acute stroke must therefore be defined in relation to time from the onset of symptoms.

As early as 1958, Sussman and Fitch had advocated for the rapid treatment of ischemic stroke;<sup>399</sup> in 1961, they proposed that the viability of ischemic brain be considered a function of time.<sup>400</sup> In the setting of decreased blood flow due to an occluded artery, a region of the brain might become electrically silent (ie. stop functioning, thereby producing clinical deficits) while remaining structurally intact (and therefore capable of being restored to function). This concept became known as the penumbra. The penumbra was defined in contrast to *the core*, a region of irreversibly damaged tissue that grows the longer an artery

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<sup>397</sup> Nurok, “Epistemological Alignment,” 566.

<sup>398</sup> Donald G. Grosset, “What have drugs to offer the patient with acute stroke?” *British Journal of Clinical Pharmacology* 33 (1992): 467-472.

<sup>399</sup> Sussman, “Thrombolysis” (1958), 1709.

<sup>400</sup> Sussman, “Thrombolysis” (1961), 171.

remains occluded.<sup>401</sup> The term penumbra is appropriated from the Latin, in which it refers to the area adjacent to a shadow. The penumbra, similarly, is imagined as an area of the brain that remains alive in the setting of arterial occlusion, but is adjacent to an area that has already died. These dead areas are referred to as the core of an infarction.

For centuries, it had been assumed that the brain could only tolerate being deprived of blood flow for a few minutes.<sup>402</sup> The physiologic suggestion that the brain might demonstrate a certain degree of resistance — that brain deprived of blood may be restored to function with the reinstatement of flow — came from animal experiments conducted in the 1970s and 1980s.<sup>403</sup> Experiments on monkeys, baboons, and rats suggested that neuronal tissue might demonstrate two thresholds with regards to dysfunction in the face of impaired blood flow: a higher threshold across which neuronal activity ceased, and a lower threshold across which the cell's metabolism failed, leading to death.<sup>404</sup> Tissue experiencing blood flow between these two thresholds was considered to be part of the penumbra.<sup>405</sup> The area of penumbral brain was initially imagined as a ring around an irreversibly-damaged core, though later experiments suggested that this approximation might be overly simple and that the distinction between penumbra and core might reflect more a patchwork pattern.<sup>406</sup>

As the theory goes, regions of brain that could be qualified as penumbra become core the longer the occlusion persists. The penumbra is therefore not a static region of brain tissue: it is dynamic, with penumbra converting to core as time passes.<sup>407</sup> Experiments in monkeys in the 1950s had suggested that an arterial occlusion could be maintained up to 50 minutes with minimal consequence, but any occlusion

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<sup>401</sup> Patrick D. Lyden, "The Ischemic Penumbra and Neuronal Salvage," in Patrick D. Lyden, editor, *Thrombolytic Therapy for Stroke* (Totowa, NJ: Humana, 2001), 43.

<sup>402</sup> Lyden, "Ischemic Penumbra," 43.

<sup>403</sup> J. Astrup, B. K. Siesjö, L. Symon, "Thresholds in Cerebral Ischemia — the Cerebral Penumbra," *Stroke* 12 (1981): 723-725.

<sup>404</sup> Astrup, "Thresholds," 724.

<sup>405</sup> *Ibid.*, 723.

<sup>406</sup> Lyden, "Ischemic Penumbra," 43.

<sup>407</sup> Grosset, "What Have Drugs," 467.

longer than 60 minutes led to the same catastrophic result in terms of irreversible brain cell death.<sup>408</sup> In dogs and cats, occlusion of the middle cerebral artery for up to 2-3 hours would not necessarily result in significant infarction or neurologic deficits. Later experiments suggested a similar effect, on a similar timescale, in larger primates.<sup>409</sup> These experiments led to the conclusion that a penumbral region of salvageable brain tissue may persist up to three hours after arterial occlusion.<sup>410</sup>

The physiologic substrate for the existence of the penumbra is understood to be the presence of collateralization within the brain. In 1664, Thomas Willis had concluded that one brain region may receive blood from multiple potential pathways, and that this arrangement might be a protective factor against vascular occlusion.<sup>411</sup> For example, he commented that dye injected from one location flowed “into every corner and secret place of the brain and cerebel.”<sup>412</sup> The detailed elaboration of the brain’s arterial tree, achieved by researchers in the 19<sup>th</sup> century, further supported the concept that the brain’s vasculature was collateralized, in that neighbouring vessels could provide blood flow to overlapping regions, providing a certain degree of redundancy. The fact that a region of the brain might receive some — if not its usual amount — of blood flow through collateral channels was thought to support its potential for survival. Accordingly, Sussman and Fitch proposed that “collateral circulation can compensate to some degree” for arterial occlusion.<sup>413</sup> In cases of ischemic stroke, they suggested that it might be failure of this collateral supply, rather than the arterial occlusion itself, that accounted for irreversible brain damage.<sup>414</sup>

However, the existence of the penumbra could not be directly verified in humans. To do so would have required inducing arterial occlusion in a controlled setting, and restoring flow at various points in time

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<sup>408</sup> Levine, “Thrombolytic Therapy,” 235.

<sup>409</sup> *Ibid.*, 255.

<sup>410</sup> Stephen Davis, “Medical Management of Acute Brain Ischemia,” in Issam A. Awad, ed., *Cerebrovascular Occlusive Disease and Brain Ischemia* (Park Ridge, IL: American Association of Neurological Surgeons, 1992), 150.

<sup>411</sup> William Feindel, “The Beginnings of Neurology: Thomas Willis and his Circle of Friends,” in F. Clifford Rose, ed., *A Short History of Neurology: The British Contribution* (Oxford: Butterworth Heinemann, 1999), 1.

<sup>412</sup> Wilson, “Life and Times,” 131.

<sup>413</sup> Sussman, “Thrombolysis” (1961), 171.

<sup>414</sup> *Ibid.*, 171.

thereafter. However, evidence that arterial occlusion might not produce irreversible cerebral dysfunction was suggested by clinical experiences. In 1973, experiments on patients undergoing carotid endarterectomy (surgery to reopen narrowed or blocked arteries in the neck) demonstrated sudden and reversible changes in electrical activity after test occlusion of the artery.<sup>415</sup> As part of the same experiment, it was shown that these changes in electrical activity only occurred when blood flow fell below a certain threshold (23 mL/100g/min), and that these changes were more pronounced when blood flow fell even lower. Restoration of blood flow was associated with the return of normal electrical activity in these patients. However, occlusion of the carotid artery occurred for no longer than 2 minutes in these experiments, providing no proof of a durable penumbra.

The importance of the theory of the penumbra to the modern meaning of the acute stroke cannot be understated. The existence of a brief “therapeutic window” after arterial occlusion, suggested by the concept of the penumbra, was used as justification for the selection of the 3 hour limit in the NINDS trial.<sup>416</sup> And it was that 3 hour window which, arguably, served as the basis for the success of tPA in that trial. Stroke neurologist Patrick Lyden, now of the University of California Los Angeles, has argued that a clinician who contemplates the use of thrombolysis in acute stroke is “acknowledging *de facto* the existence of a penumbra that cannot be measured or documented.”<sup>417</sup> He contends that “successful thrombolytic trials support the notion that some portion of ischemic brain remains salvageable for hours after symptom onset.”<sup>418</sup> In essence, the clinical efficacy of thrombolysis is taken as proof of the existence of the penumbra, while the penumbra is justification for the use of thrombolysis. The interweaving of these two lines of thought led to the modern meaning of the acute stroke.

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<sup>415</sup> W. Trojaborg, G. Boysen, “Relation between EEG, Regional Cerebral Blood Flow and Internal Carotid Artery Pressure During Carotid Endarterectomy,” *Electroencephalography and Clinical Neurophysiology* 34 (1973): 61-69.

<sup>416</sup> Davis, “Medical Management,” 150.

<sup>417</sup> Lyden, “Penumbra,” 44.

<sup>418</sup> *Ibid.*, 44.

### *Conclusions*

If the decision-making process of physicians in the treatment of patients with acute stroke is to be understood, then some attempt at specifying the meaning of the term “acute stroke” appears highly relevant. In this chapter, I have sought to uncover the contemporary meaning of the “acute stroke” by approaching it from a historical perspective. Specifically, I have built my argument upon a foundation of scholarship derived from Fleck, Kuhn and Rosenberg to argue that diseases should be studied as ideas, constructed in relation to a historical, social and epistemic context.<sup>419,420,421</sup> Therefore, I have sought to elaborate the historical origins and contemporary meaning of the acute stroke in relation to a broader intellectual history in medicine, with a focus on developments in the latter half of the 20<sup>th</sup> century.

I have proposed that the acute stroke is understood, in the contemporary context, as a stroke that is treatable through the use of the thrombolytic drug tPA. The notion that a form of stroke, in this case the acute stroke, is potentially reversible through the administration of a specific pharmacologic agent represents a significant departure from thousands of years of medical dogma, in which the predominant attitude had been one of nihilism towards stroke and its historically-related concept of apoplexy.<sup>422</sup> The earliest known usages of the term “acute stroke” around the year 1960 suggested that treatment might be possible if an appropriate agent could be found, and if it could be administered quickly enough.<sup>423,424</sup> These conditions were met for the first time in the NINDS trial, published in 1995, which established that the administration of tPA to patients with acute stroke under 3 hours from the onset of their symptoms could result in improved outcomes.<sup>425</sup>

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<sup>419</sup> Fleck, *Genesis*, 23.

<sup>420</sup> Kuhn, *Structure*, 2.

<sup>421</sup> Rosenberg, *Framing*, xiii.

<sup>422</sup> Daneski, “How Far,” 370.

<sup>423</sup> Bull, “Cerebral Angiography,” 562.

<sup>424</sup> Sussman, “Thrombolysis” (1961), 170.

<sup>425</sup> NINDS rtPA Study Group, “Tissue plasminogen activator,” 1587.

However, this result did not arise in isolation. Rather, it reflects a process in which “several lines of collective thought” converged in the NINDS trial.<sup>426,427</sup> Specifically, I have argued that six preconditions, interwoven over the course of four centuries, allowed for the term “acute stroke” to acquire its current meaning. As such, the modern meaning of the acute stroke can be understood only in relation to its place in the history of these ideas. In his study of syphilis, Ludwik Fleck provides a similar argument that the definition of syphilis in relation to the Wassermann immunological reaction occurred during a unique historical process. Fleck’s characterization of the relation between the Wassermann reaction and syphilis can be understood as reflective of my conception of the relationship of acute stroke to its treatability with tPA. Fleck writes,

*From this point of view the relation between the Wassermann reaction and syphilis — an undoubted fact — becomes an event in the history of thought. This fact cannot be proved with an isolated experiment but only with broadly based experience; that is, by a special thought style built up from earlier knowledge, from many successful and unsuccessful experiments, from much practice and training, and — epistemically most important — from several adaptations and transformation of concepts.*<sup>428</sup>

After Fleck, the significance of the NINDS trial is not sufficient to establish the meaning of the acute stroke, but rather it is in light of a history of experiments and experience that the epistemic existence of the acute stroke is established. I have argued that this history reflects a set of six preconditions: the description of the brain’s vascular anatomy, the development of the notion of the localizability of pathology within the body and within the brain, the differentiation of ischemia from hemorrhage, the dissemination of the CT scanner, the development of thrombolytic drugs like tPA, and the physiological theory of the penumbra. I will return to Fleck’s passage in the next chapter, when the epistemic evaluation and justification of acute stroke’s treatability will be explored as part of the decision-making process.

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<sup>426</sup> Nurok, “Epistemological Alignment,” 563.

<sup>427</sup> Fleck, *Genesis*, 23.

<sup>428</sup> *Ibid.*, 98. Italics are the author’s.

Three immediate implications arise from the conception of the acute stroke as an idea, constructed in a particular place and time, and in light of a history of thought. First, it suggests that other diseases might similarly be considered to be constructs, contingent on a historical and social context. Fleck's example of syphilis is now well known, but less well known is the history of coronary artery disease explored by David Jones in his recent monograph *Broken Hearts*. Jones characterizes how, for several decades in the mid 20<sup>th</sup> century, two rival conceptions of the phenomenon of myocardial infarction existed.<sup>429</sup> Recognition of the social construction of diseases increases the importance of historical and social analysis in understanding physician decision-making.

Second, if diseases are social constructs, then those constructions are contingent, and not inevitable.<sup>430</sup> The way that contemporary medicine conceives of diseases is not the only way that they have been conceived or could be conceived. As Fleck writes, medical science is "open-ended."<sup>431</sup> Therefore, modern medicine too has the potential ability to change its constructions of diseases. Arguably, a moral imperative exists to reframe our concepts of diseases in light of new knowledge and experiences. How and when should this happen? Following Kuhn, an alternative construction for a given disease may be preferred if it allows for better predictions, better problem-solving, and better outcomes for patients.<sup>432</sup>

Third, it is important to recognize that, because diseases are constructed in relation to a particular history of thought, not every physician practicing in the same historical moment may understand a disease in the same way. Fleck proposes the notion of a *thought collective* — a group of individuals sharing a particular set of historical ideas and practices, which he terms the *thought style*.<sup>433</sup> A thought style arises from a particular intellectual history. Individuals who do not appreciate that history — who are unaware of it or

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<sup>429</sup> Jones, *Broken Hearts*, 30.

<sup>430</sup> Hacking, *Social Construction*, 19.

<sup>431</sup> Fleck, *Genesis*, 95.

<sup>432</sup> Kuhn, *Structure*, 97.

<sup>433</sup> Fleck, *Genesis*, 39.

who contest it — cannot participate in that thought style.<sup>434</sup> Those physicians who, in 2014, conceive of acute stroke as a stroke that is treatable with tPA, are members of a thought collective sharing a thought style. However, not all members of the medical community may necessarily be members of that thought collective. Variations in thought style may exist. Similarly, variations in how a disease is understood may exist, and with these variations different decisions about treatment may follow. For example, if a physician were to contest the notion that an acute stroke is a stroke that is treatable with tPA, then he or she would be unlikely to use tPA as a treatment for stroke. This scenario — conceived as a question of epistemic evaluation and justification — will be explored in Chapter 2.

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<sup>434</sup> Fleck, *Genesis*, 39.

## Chapter 2: Epistemic Evaluation in Acute Stroke Decision-Making

Concepts are not spontaneously created but are determined by their “ancestors.” That which has occurred in the past is a greater cause of insecurity — rather, it only becomes a cause of insecurity —when our ties with it remain unconscious and unknown.

– Ludwik Fleck, *Genesis and Development of a Scientific Fact* (orig. 1935)

### *Introduction*

This thesis is an enquiry into the decision-making process of physicians, with a focus on the decisions that surround treating patients with acute stroke. In this chapter, I will begin to address the question of how physicians make treatment decisions about the use of tPA for acute stroke, approaching the question from an epistemic perspective. Most generally, in what way does epistemic reasoning feature in acute stroke decision-making? In this chapter, I propose that a process of epistemic evaluation features prominently in acute stroke decision-making. Whereas the predominant modern theory of medical epistemology — what is called *evidence-based medicine* — holds that decision-making simply requires physicians to apply medical knowledge, I contend that physician decision-making requires evaluating and interpreting that knowledge in relation to individual cases. Specifically, I point to the presence of significant debate about the treatment of patients with acute stroke as a demonstration of the process of epistemic evaluation. Finally, I contend that variations in physicians’ epistemic evaluations reflect the influence of a body of historical knowledge. In the case of acute stroke, the preconditions outlined in Chapter 1 — those interwoven lines of thought that allowed for the modern conception of the acute stroke to be established — represent a core component of that body of knowledge, and hence play a significant role in physicians’ epistemic evaluation in acute stroke decision-making.

This characterization of epistemic reasoning in acute stroke decision-making challenges the dominant theory of contemporary medical epistemology, which is called evidence-based medicine.<sup>435</sup> Evidence-based medicine (EBM) is defined by its founder, Canadian physician David Sackett, as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”<sup>436</sup> Sackett’s definition of EBM suggests a normative claim: that physicians should use “best evidence” in their treatment decisions. This claim is based upon the assumption that there can be such a thing as “best evidence.” Given that EBM provides specific criteria for what “best evidence” should mean, determining that which is “best evidence” should therefore be relatively straightforward.<sup>437</sup> If this were indeed the case, then there should be relative agreement about whether tPA use in acute stroke is epistemically justified on the basis of “best evidence.” We would expect the use of tPA to be relatively standardized. However, significant controversy persists about the epistemic justification of tPA use.<sup>438,439</sup> Moreover, significant variabilities exist with regards to physicians’ real-world usage of tPA, as measured from doctor to doctor, hospital to hospital, and country to country.<sup>440</sup>

I contend that the normative and descriptive claims of evidence-based medicine are insufficient to capture the epistemic component of acute stroke decision-making. First, the epistemic content of acute stroke decision-making will be unpacked to develop a set of five clinical propositions, by which I mean statements about the nature of the acute stroke that directly impact upon treatment decisions. These five propositions suggest the complexity of the knowledge necessary to inform acute stroke decision-making. Second, these propositions will be shown to be subject to epistemic evaluation — to evaluations about their

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<sup>435</sup> Jeremy Howick, *The Philosophy of Evidence-Based Medicine* (Chichester: Wiley-Blackwell, 2011), 3.

<sup>436</sup> David L. Sackett, William C. Rosenberg, J.A. Muir Gray, R. Brian Haynes, W. Scott Richardson, “Evidence-Based Medicine: What It Is and What It Isn’t,” *British Medical Journal* 312 (1996): 71-72.

<sup>437</sup> Howick, *Philosophy*, 5.

<sup>438</sup> David J. Robinson, “Should Physicians Dive tPA to Patients with Acute Ischemic Stroke? For: Thrombolytics in Stroke: Whose Risk is it Anyway?” *Western Journal of Medicine* 173 (2000): 148-149.

<sup>439</sup> Jerome Hoffmann, “Should Physicians give tPA to Patients with Acute Ischemic Stroke? Against: And Just What is the Emperor Wearing?” *Western Journal of Medicine* 173 (2000): 149-150.

<sup>440</sup> Shamy, “Complexities,” 1130.

epistemic validity — that occur in light of historical knowledge. In this way, physicians' epistemic evaluations in the setting of acute stroke decision-making reflect the historical preconditions of the concept of the acute stroke. Third, this process of epistemic evaluation will be shown to result in variable results, meaning that not all physicians agree about the validity of these clinical propositions. I will support these arguments by analyzing recent debates within the stroke literature, as well as by presenting data from surveys of physicians involved in stroke care.<sup>441,442</sup> In order to inform this discussion of epistemic evaluation in acute stroke decision-making, I will first review some working definitions of the relevant epistemic terms, namely propositions, beliefs and knowledge.

### *Propositions, Beliefs & Knowledge*

In this chapter, I will argue that the contemporary meaning of acute stroke that was developed in Chapter 1 can lead to the elaboration of a set of propositions whose evaluation impacts treatment decisions about the use of tPA. I have chosen to use the term *propositions* (rather than claims, beliefs, assumptions or facts) to refer in a non-judgmental way to a set of concepts that appear to be relevant to acute stroke decision-making. As discussed in the philosophical literature, propositions are shareable objects of belief or doubt.<sup>443</sup> Propositions are shareable because they can be expressed in a manner that is communicable from the person who possesses them, to another person who does not. Propositions are bearers of truth or falsity in that they express meaning, but they are not guaranteed or required to be true in and of themselves. Propositions are distinct from concrete events or facts, which presumably cannot be false. Propositions,

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<sup>441</sup> Shamy, "Complexities," 1130.

<sup>442</sup> One of those surveys is our ongoing project that seeks to develop a deeper understanding of diagnostic and treatment decisions in an international sample of neurologists who care for stroke patients. Data from the first 79 (of 600) respondents will be referenced in the footnotes. Data presented in this thesis is unpublished and preliminary.

<sup>443</sup> McGrath, Matthew, "Propositions," *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), forthcoming URL = <http://plato.stanford.edu/archives/spr2014/entries/propositions/>, (accessed February 14, 2014).

therefore, can be believed and shared, but are not necessarily believed by all, nor are they necessarily true.<sup>444</sup>

In contrast, a *belief* is generally understood as an attitude that we have whenever we take something to be true.<sup>445</sup> Specifically, belief is often referred to as a “propositional attitude,” in that it is the mental state about a particular proposition in which that proposition is felt to be true. As philosopher Eric Schwitzgebel writes, “Forming beliefs is thus one of the most basic and important features of the mind, and the concept of belief plays a crucial role in both philosophy of mind and epistemology.”<sup>446</sup> However, the fact that something is believed does not guarantee that it is true. Moreover, that something is believed does not require that it is being or has been actively reflected upon; most of what is believed is not subject to routine scrutiny.<sup>447</sup> The justification for any given belief may reflect any number of its qualities: for example, its source (ie. a figure of authority), the methodology of its derivation (ie. randomized controlled trials), or its agreement with previously accepted knowledge.<sup>448</sup> An *assumption* is a proposition that has been taken for granted to be true, often on the basis of having been handed down or built into a belief system.

Within contemporary philosophy, *knowledge* is commonly defined as justified true belief.<sup>449</sup> For a proposition to be considered knowledge, it must be true, someone must believe that it is true, and that belief must be justified. Each of these clauses is subject to some degree of controversy, and a thorough analysis of the nature of knowledge extends beyond the scope of this thesis. Directly relevant to my argumentation is the work of philosophers, sociologists and anthropologists who have elaborated how different societies may designate different propositions to be true, and how different methods may be

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<sup>444</sup> McGrath, “Propositions.”

<sup>445</sup> Eric Schwitzgebel, “Belief,” *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), forthcoming URL = <http://plato.stanford.edu/archives/spr2014/entries/belief/> (accessed March 30, 2014).

<sup>446</sup> Schwitzgebel, “Belief.”

<sup>447</sup> Ibid.

<sup>448</sup> Howick, *Philosophy*, 4.

<sup>449</sup> Jonathan Jenkins Ichikawa, Matthias Steup, “The Analysis of Knowledge,” *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/knowledge-analysis/>, (accessed March 30, 2014).

employed to determine which propositions are considered knowledge.<sup>450</sup> A proposition may qualify as knowledge in one community or historical context, whereas it may not do so in another. Similarly, one individual within a community may consider a proposition to be knowledge, whereas another may not.

Scientific knowledge, or knowledge acquired by doing science, is a type of knowledge. Modern scholarship has elaborated the ways in which scientific knowledge has four qualities relevant to the argument of this chapter: scientific knowledge is dependent upon theory, it is historical, it is uncertain, and it is social.<sup>451</sup> For example, Fleck points to the theory-dependence of scientific knowledge when he calls the prospect of scientific observation without underlying theory “non-sense.”<sup>452</sup> Thomas Kuhn’s influential concept of the paradigm represents a particular way that scientific knowledge is acquired on the basis of a set of shared theories, methodologies, and interests.<sup>453</sup> Sociologist of science Barry Barnes has argued that scientific knowledge is necessarily theoretical knowledge, in that “there is no independent language of observation and no set of theory-independent observational statements.”<sup>454</sup>

Moreover, scientific knowledge has a historical dimension. Fleck proposes that a scientific fact cannot be separated from its history, which includes earlier knowledge and experiences.<sup>455</sup> For Barnes, a body of knowledge exists as a tradition, with new propositions interpreted in light of past knowledge.<sup>456</sup> The importance of past knowledge in the interpretation of new hypotheses was developed by American philosopher Nelson Goodman (1906-1998) in his seminal book *Fact, Fiction and Forecast*, first published in 1954.<sup>457</sup> For Goodman, questions of confirmation or projectibility require using “the record of past

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<sup>450</sup> Barry Barnes, “Sociological Theories of Scientific Knowledge,” eds R.C. Olby, G.N. Canthor, J.R.R. Christie, and M.J.S. Hodge, *Companion to the History of Modern Science* (Abingdon: Routledge, 1990), 60.

<sup>451</sup> Godfrey-Smith, *Theory and Reality*, 163.

<sup>452</sup> Fleck, *Genesis*, 92.

<sup>453</sup> Kuhn, *Structure*, 37.

<sup>454</sup> Barnes, “Sociological Theories,” 63.

<sup>455</sup> Fleck, *Genesis*, 98.

<sup>456</sup> Barnes, “Sociological Theories,” 67.

<sup>457</sup> Nelson Goodman, *Fact, Fiction, and Forecast*, 4<sup>th</sup> Edition (Cambridge, MA: Harvard University Press, 1983), 84.

predictions actually made and their outcomes.”<sup>458</sup> We approach problems — like the evaluation of new hypotheses — “not empty-headed but with some stock of knowledge, or of accepted statements, that may fairly be used in reaching a solution.”<sup>459</sup> Because different scientists may bring different “stocks of knowledge” to the evaluation of a given hypothesis, different assessments of the validity of that hypothesis may result.<sup>460</sup>

A historical perspective on scientific knowledge suggests how many beliefs that were considered justified in the past — for example, that the sun revolves around the earth, or that pneumonia should be treated with bloodletting — were subsequently modified or rejected. Similarly, many contemporary beliefs, despite being considered justified in the here and now, may subsequently be modified or rejected in the future. This realization is consistent with the widely held contemporary notion of the fallibility of scientific knowledge: that any of our beliefs about the external world may turn out to be false.<sup>461</sup> For Fleck, the scientific process “is continuous. It has no demonstrable beginning and is open-ended. Knowledge exists in the collective and is continually being revised.”<sup>462</sup> The notion of fallibilism is strongly associated with the writings of C.S. Peirce (1839-1914) and Karl Popper (1902-1994), though it is often traced to the writings of English philosopher John Stuart Mill (1806-1873). In *On Liberty* (1859), Mill argues that “there is no such thing as absolute certainty,” and he proposed that “the steady habit of correcting and completing [one’s] own opinion by collating it with those of others... is the only stable foundation for a just reliance on it.”<sup>463</sup> Peirce considered truth out of the reach of any individual, but imagined that the opinions of the “community

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<sup>458</sup> Goodman, *Fact, Fiction and Forecast*, 85.

<sup>459</sup> *Ibid.*, 86.

<sup>460</sup> Mark Fedyk, Michel Shamy, “Projectibility, Disagreement and Consensus: A Challenge to Clinical Equipose,” *Theoretical & Applied Ethics*, forthcoming.

<sup>461</sup> Ross Upshur, “Seven characteristics of medical evidence,” *Journal of Evaluation in Clinical Practice* 6 (2000): 93-97.

<sup>462</sup> Fleck, *Genesis*, 95.

<sup>463</sup> John Stuart Mill, *The Basic Writings of John Stuart Mill: On Liberty, The Subjection of Women, and Utilitarianism* (New York: Modern Library, 2002), 22.

of philosophers” might arrive at truth.<sup>464</sup> Popper famously proposed that a hypothesis cannot be proven but only falsified, and imagined efforts at falsification occurring within a community of scientists.<sup>465</sup>

The notion that scientific knowledge has a social dimension is also suggested in the philosophical writings of Mill, Peirce, and Popper, and elaborated in the historical scholarship of Kuhn and Fleck. Mill argued for the importance of collating one’s opinions with those of others, as a means of ensuring the validity of one’s ideas. For Peirce and Popper, it was within a “community” that intellectual progress might occur.<sup>466</sup> For Kuhn, intellectual “schools” arise through the sharing of some “implicit body of intertwined theoretical and methodological belief.”<sup>467</sup> Most generally, it can be concluded that knowledge has a relevant social dimension, as supported by a wide range of scholarship.

Fleck uses the example of syphilis to explore the way that facts arise as the product of a thought style (*Denkstille*) shared by a thought collective (*Denkkollektiv*). For Fleck, a thought collective is a “community of persons mutually exchanging ideas or maintaining intellectual interaction.”<sup>468</sup> A thought collective serves as a carrier for a thought style. A thought style, simply put, is a particular way of looking at the world. Fleck defines a thought style as “the special carrier for the historical development of any field of thought, as well as for the given stock of knowledge and level of culture.”<sup>469</sup> As explained by Thaddeus Trenn (1937-2013), Fleck’s thought style “functions by constraining, inhibiting, and determining the way of thinking.”<sup>470</sup> Initiation into a thought collective means taking on its thought style, which would allow a novice “to see what has hitherto been invisible to him.”<sup>471</sup> For Fleck, thought styles are mutually

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<sup>464</sup> Helen Longino, “The Social Dimensions of Scientific Knowledge,” *The Stanford Encyclopedia of Philosophy* (Spring 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2013/entries/scientific-knowledge-social/>, (accessed April 16, 2014).

<sup>465</sup> Longino, “Social Dimensions.”

<sup>466</sup> *Ibid.*

<sup>467</sup> Kuhn, *Structure*, 17.

<sup>468</sup> Fleck, *Genesis*, 39.

<sup>469</sup> *Ibid.*, 39.

<sup>470</sup> Thaddeus J. Trenn, Robert K. Merton, “Descriptive Analysis,” in Ludwik Fleck, *Genesis and Development of a Scientific Fact*, ed. by Thaddeus J. Trenn and Robert K Merton, trans by Fred Bradley and Thaddeus J. Trenn (Chicago: University of Chicago Press, 1979), 159.

<sup>471</sup> Fleck, *Genesis*, 104.

incompatible, as are Kuhn's paradigms. Indeed, Kuhn was aware of Fleck's work and cited it in *The Structure of Scientific Revolutions*.<sup>472</sup>

In that medical knowledge is a form of scientific knowledge, it should share these features: it is likely to be theory-dependent, historically-determined, uncertain, and social. Certainly, a long tradition of scholarship has demonstrated the ways in which medical knowledge is constructed in relation to theory and history.<sup>473,474</sup> For example, the famous essay *On the Falling Sickness* by historian of medicine Owsei Temkin elaborated on the variable perceptions of epilepsy in light of religious, political and moral theories.<sup>475</sup> Moreover, the centrality of uncertainty in medicine has developed as a recurring theme in recent decades, with important contributions from historians, philosophers, anthropologists and sociologists.<sup>476,477,478</sup> For example, Dutch anthropologist Annemarie Mol argues that the most pressing challenge for modern medical practice is to address "how to live with doubt."<sup>479</sup> University of Toronto physician and philosopher Ross Upshur has advocated for fallibilism as an overarching theory of medical knowledge.<sup>480</sup> He has argued that medical knowledge is necessarily provisional, defeasible, and incomplete. The ethical implications of fallibilism have been elaborated in an attempt to inform recent debates over clinical trial enrollment.<sup>481</sup>

The challenge of managing uncertainty in medical practice is a central theme of Kathryn Montgomery's *How Doctors Think: Clinical Judgment and the Practice of Medicine* (2006).<sup>482</sup> Montgomery, emeritus professor of medical humanities at Northwestern University, makes a central ontological claim

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<sup>472</sup> Kuhn, *Structure*, xli.

<sup>473</sup> Fleck, *Genesis*, 20.

<sup>474</sup> Rosenberg, *Framing*, xiii.

<sup>475</sup> Owsei Temkin, *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginning of Modern Neurology* (Baltimore: Johns Hopkins University Press, 1945), 1.

<sup>476</sup> Montgomery, *How Doctors Think*, 3.

<sup>477</sup> Mol, *The Body Multiple*, 126.

<sup>478</sup> Lynn Valerie Knight, Karen Mattick, " 'When I first came here, I thought medicine was black and white': Making sense of medical students' ways of knowing," *Social Science & Medicine* 63 (2006): 1084-1096.

<sup>479</sup> Mol, *The Body Multiple*, 165.

<sup>480</sup> Upshur, "Seven characteristics," 93.

<sup>481</sup> Mayank Goyal, Michel Shamy, Bijoy K. Menon, Jeffrey L. Saver, Hans-Christoph Diener, J Mocco, Vitor Mendes Pereira, Tudor G. Jovin, Osama Zaidat, Elad I. Levy, Antoni Davalos, Andrew Demchuk, Michael D. Hill, "Endovascular Stroke Trials: Why We Must Enroll All Eligible Patients," *Stroke* 44 (2013): 3591-3595.

<sup>482</sup> Montgomery, *How Doctors Think*, 4.

about medicine: that it is a practice, rather than a science. The central skill of medical doctors, she argues, is clinical judgment, an interpretive capacity required to apply general rules to individual cases, in light of pervasive uncertainty and contingency.<sup>483</sup> Montgomery's description of clinical judgment informs this thesis' study of decision-making, though her discussion of how doctors specifically evaluate their knowledge is limited. She points out that physicians tend to think of medicine as a science in the positivistic sense, "science as the explanation of how things work, how they really are."<sup>484</sup> From this ontologic belief flows medicine's general view of its own knowledge: as definitively true, in all places and all times.<sup>485</sup> I will now elaborate on medicine's view of its own epistemology, with special attention to the modern theory of evidence-based medicine.

#### *Epistemic Evaluation & Evidence-Based Medicine*

Over the last twenty years, medical epistemology has become dominated by a theory known as evidence-based medicine (EBM).<sup>486</sup> The concept of evidence-based medicine was first proposed by the Canadian physician and epidemiologist David Sackett in 1991.<sup>487</sup> Sackett has repeatedly defined EBM in relation to the use of "best evidence" in decision-making.<sup>488</sup> Evidence-based medicine makes specific claims about what should be considered "best evidence," and provides an epistemic hierarchy that privileges knowledge produced by randomized clinical trials. Specifically, evidence-based medicine holds that knowledge acquired from randomized controlled trials is to be privileged over all other forms of

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<sup>483</sup> Montgomery, *How Doctors Think*, 5.

<sup>484</sup> *Ibid.*, 9.

<sup>485</sup> Ross E. G. Upshur, "Priors and Prejudice," *Theoretical Medicine and Bioethics* 20 (1999):v319-327.

<sup>486</sup> Peter C. Wyer, Suzana A. Silva. "Where is the wisdom? I – A conceptual history of evidence-based medicine," *Journal of Evaluation in Clinical Practice* 15 (2009): 891–898.

<sup>487</sup> David L. Sackett, Peter Tugwell, Gordon H. Guyatt, *Clinical epidemiology: a basic science for clinical medicine* (Boston: Little, Brown, 1991).

<sup>488</sup> David L. Sackett, "Evidence-Based Medicine," *Seminars in Perinatology* 21 (1997): 3-5.

knowledge, including knowledge derived from laboratory experiments, individual experience, case studies, and medical history.<sup>489</sup>

Sackett has related the origins of EBM to his experiences as a medical trainee, when early studies in clinical epidemiology inspired him to question medical dogma and openly challenge the “pontification” of authority figures.<sup>490</sup> He has frequently traced the historical roots of evidence-based medicine “to mid-19<sup>th</sup> century Paris and earlier,” referencing the numerical approaches to health and illness that were introduced in Parisian hospitals at that time. Historians of EBM consistently cite key figures from the turn of the 19<sup>th</sup> century as the intellectual forebears of their movement.<sup>491,492,493</sup> However, the historical account provided by EBM misses much of the subtlety and controversy that accompanied the development of the quantitative methods it values. For example, French physician and statistician Pierre Charles Louis (1787-1872) is celebrated as a hero of evidence-based medicine for having conducted chart reviews that challenged the practice of bloodletting as a treatment for pneumonia.<sup>494</sup> However, advocates of EBM would disapprove of his methodology were it to be used today, and they would reject many of his conclusions, for example that purging (meaning forced vomiting and diarrhea) is an effective treatment for typhoid fever.<sup>495</sup>

These historical inconsistencies reflect the complicated relationship that evidence-based medicine has with medical knowledge. Arguably, EBM continues to struggle with a set of tensions surrounding the acquisition and use of medical knowledge that have been present since well before “mid-19<sup>th</sup> century

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<sup>489</sup> Howick, *Philosophy*, 5.

<sup>490</sup> David L. Sackett, “A 1955 Clinical Trial Report that Changed my Career,” *Journal of the Royal Society of Medicine* 103 (2010): 254-255.

<sup>491</sup> Kenneth W. Goodman, *Ethics and Evidence-Based Medicine: Fallibility and Responsibility in Clinical Science* (Cambridge: CUP, 2002), 6.

<sup>492</sup> Gerry Greenstone, “The Roots of Evidence-Based Medicine,” *BC Medical Journal* 51(2009): 342-344.

<sup>493</sup> James Harrison, Kunal Kulkarni, Mohamed Baguneid, Bernard Prendergast, *Oxford Handbook of Key Clinical Evidence* (Oxford: Oxford University Press, 2009), 2.

<sup>494</sup> Reiser, *Reign of Technology*, 32.

<sup>495</sup> Terence D. Murphy, “Medical Knowledge and Statistical Methods in Early Nineteenth Century France,” *Medical History* 25 (1981): 301-319.

Paris.”<sup>496</sup> For example, in the Hellenistic period (third to first centuries BC), the practice of medicine was explicitly defined by debate over the appropriate definition of medical knowledge.<sup>497</sup> Three prominent sects, each with its own epistemic position, dominated literate medicine in the Mediterranean world in this period. The Rationalist sect sought to understand human life and disease in terms of physiological mechanisms.<sup>498</sup> They were interested in the experimental demonstration of anatomical evidence, and in the development of theories to explain their findings. In contrast, the Empiric sect approached medical practice based solely on perception; they held that experience took precedence over reasoning or experimentation. They were interested only in the ability to cure disease and not in determining its cause.<sup>499</sup> A third group, the Methodist sect, applied a consistent method in all medical scenarios. In essence, the Methodists held that the search for medical knowledge was closed: all diseases could be treated by either the constriction or relaxation of pores, and hence all that needed to be known was known.<sup>500</sup>

In the era of EBM, these tensions — between empiricism, rationalism, and authority — persist. EBM’s privileging of randomized controlled trials is often framed as a rigorous form of empiricism, in that knowledge should come exclusively or primarily from direct sensory experience. For example, prominent EBM advocate Gordon Guyatt of McMaster University has defined evidence as “any empirical observation about the apparent relation between events.”<sup>501</sup> However, the methodology of randomized clinical trials — which requires enrolling large number of patients and following their aggregate outcomes — means that no physician actually has direct sensory experience of the results.<sup>502</sup> In various eras, empiricism has been

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<sup>496</sup> Michael Loughlin, “The Basis of Medical Knowledge: Judgment, Objectivity and the History of Ideas,” *Journal of Evaluation in Clinical Practice* 15 (2009): 935-940.

<sup>497</sup> Vivian Nutton, “Medicine in the Greek world, 800-50 BC,” in L.I. Conrad, ed., *The Western Medical Tradition 800 BC to 1800*, (Cambridge: Cambridge University Press, 1995), 35.

<sup>498</sup> C.E. Cosans, “Galen’s Critique of Rationalist and Empiricist Anatomy,” *Journal of the History of Biology* 30 (1997): 35-54.

<sup>499</sup> Nutton, “Medicine in the Greek World,” 36.

<sup>500</sup> *Ibid.*, 41.

<sup>501</sup> Gordon Guyatt, Drummond Rennie, eds. *Users’ Guide to the Medical Literature* (Chicago: American Medical Association Press, 2002), 6.

<sup>502</sup> Howick, *Philosophy*, 16.

celebrated in opposition to knowledge from authority, and EBM still makes that claim.<sup>503</sup> Yet in the 21<sup>st</sup> century clinical trial methodology has become a source of unquestionable authority in its own right, limiting and biasing the kinds of experiments that are funded and published.<sup>504,505,506</sup> For example, Harvard University neurologist Louis Caplan has sarcastically called evidence-based medicine “a shibboleth, a sacrosanct icon almost like motherhood.”<sup>507</sup>

Under EBM, physicians rarely speak of knowledge, or of argumentation, but rather of “the evidence.” When a clinical question arises, physicians frequently ask: “What is *the evidence*?”<sup>508,509,510</sup> They expect that asking such a question will lead to the production of a conclusive answer. When physicians write that there is “evidence of” a particular claim, or “evidence for” a particular intervention, they mean that these propositions are true because they are supported by evidence that is certain and accurate. In this sense, “the evidence” is conceived as a singular entity, a complete and definitive body of knowledge that justifies a particular course of action. In a recent review article, neurologist Alastair Buchan, Dean of the Medical School at Oxford University, discusses the “*exact science* of stroke thrombolysis,” taking for granted that such a thing exists.<sup>511</sup>

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<sup>503</sup> Guyatt, *Users' Guide*, 8.

<sup>504</sup> David M. Eddy, “Evidence-Based Medicine: A Unified Approach,” *Health Affairs* 24 (2005):9-17.

<sup>505</sup> Ignaas Devisch, Stephen J Murray, “We hold these truths to be self-evident: deconstructing ‘evidence-based’ medical practice,” *Journal of Evaluation in Clinical Practice* 15 (2009): 950-954.

<sup>506</sup> John Worrall, “What Evidence in Evidence-Based Medicine?” *Philosophy of Science* 69 (2002): S316-S330.

<sup>507</sup> Louis R. Caplan, “Evidence-Based Medicine: Concerns of a Clinical Neurologist,” *Journal of Neurology Neurosurgery and Psychiatry* 71 (2001): 569-574.

<sup>508</sup> Stella Karantzoulis, Christopher Randolph, “Modern Chronic Traumatic Encephalopathy in Retired Athletes: What is the Evidence?” *Neuropsychological Reviews* 4 (2013): 350-360.

<sup>509</sup> Janne Marieke Veerbeek, Erwin van Wegen, Roland van Peppen, Philip Jan van der Wees, Erik Hendriks, Marc Rietberg, Gert Kwakkel, “What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis,” *PLOS One* 9 (2014): 1-33.

<sup>510</sup> David C Wraith, Michel Goldman, Paul-Henri Lambert, “Vaccination and Autoimmune Disease: What is the Evidence?” *The Lancet* 362(2003): 1659-1666.

<sup>511</sup> Joyce S. Balami, Gina Hadley, Brad A. Sutherland, Hasneen Karbalai, Alastair M. Buchan, “The Exact Science of Stroke Thrombolysis and the Quiet Art of Patient Selection,” *Brain* 136 (2013): 3528-3553.

Under EBM, physicians value objectivity as an epistemic virtue,<sup>512</sup> and they consider that their scientific methods are objective due to an independence from the bias of subjective interpretation.<sup>513</sup> The source of this objectivity is felt to arise from modern research methodologies, namely the double blind, randomized controlled trial.<sup>514</sup> It is these trials that are felt to produce the “best evidence” invoked by EBM. At the most basic level, a clinical trial involves selecting a group of patients to receive one or several interventions, and then following their outcomes over time. Randomization is a research methodology in which the assignment of a given patient to a particular treatment is randomly selected by a computer program, in that neither the physician nor the patient’s preference impacts on the selection of the treatment for that patient.<sup>515</sup> Randomization is intended to protect against physicians’ conscious or unconscious opinions about treatments and patients, both of which might impact how patients are assigned. Randomization is also intended to balance (and thereby eliminate the influence of) confounding variables, which are qualities of the patient or of the disease that may impact outcomes independent of the intervention being tested. Blinding is an additional methodology that prevents patients from knowing the particular intervention to which they are assigned. In double blinding, both the patient and the physician are unaware of the treatment assignment.<sup>516</sup>

The advantages of randomization and blinding are felt to justify the privileging of the results of randomized controlled trials over knowledge acquired from all other forms of experimentation.<sup>517</sup> Randomized trials are explicitly termed the “gold standard,” which in medicine means that they are felt to reflect the best source of knowledge.<sup>518</sup> Specifically, randomized trials are preferred over laboratory

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<sup>512</sup> Lorraine Daston, Peter Galison, *Objectivity* (New York: Zone Books, 2010), 4.

<sup>513</sup> Cheryl Misak, “Experience, Narrative and Ethical Deliberation,” *Ethics* 118 (2008): 614-632.

<sup>514</sup> John Worrall, “Evidence and Ethics in Medicine,” *Perspectives in Biology and Medicine* 51 (2008): 418-431.

<sup>515</sup> Howick, *Philosophy*, 43.

<sup>516</sup> *Ibid.*, 44.

<sup>517</sup> Benjamin Djulbegovic, Gordon Guyatt, Richard Ashcroft, “Epistemological Inquiries in Evidence-Based Medicine,” *Cancer Control: Journal of the Moffitt Cancer Center* 16 (2009): 158-168.

<sup>518</sup> Gunver S Kienle, Helmut Kiene, “Clinical Judgment and the Medical Profession,” *Journal of Evaluation in Clinical Practice* 17 (2011): 621-627.

studies, in that conclusions from physiological or pharmacological experimentation may not translate to living patients outside of a controlled environment.<sup>519</sup> Additionally, clinical trials are preferred over the results of individual experiences with a particular intervention in a particular patient. Knowledge derived from personal experiences is termed “anecdotal,” and is felt to be unreliable as an indicator of efficacy, due to the potential influence of a physician’s bias in interpreting findings, or due to the potential impact of confounders.<sup>520</sup> Detailed case studies were the predominant means of deriving and communicating medical knowledge until the mid-20<sup>th</sup> century, though they are now unpublishable in most prominent journals. Observational studies, in which large groups of patients may be followed with regards to a particular outcome (e.g. death) in relation to a particular exposure (e.g. graduate school), are also felt to be of lesser value than randomized controlled trials because of the potential influence of biases such as patient selection and recall, or again due to the role of confounders.<sup>521</sup>

The acquisition and evaluation of medical knowledge under EBM is felt to be theory-free, in that theory reflects a set of beliefs or practices that bias one’s approach to “the evidence.”<sup>522</sup> This is reflected in EBM’s claims about its empirical nature. Physicians frequently conclude that “the evidence speaks for itself,” and they do not mean this figuratively.<sup>523,524,525</sup> Contemporary physicians generally believe that evidence can and does exist independently of a theoretical framework, and that it is convincing due to this independence from theory. In a search of MEDLINE, the online database of the National Library of Medicine, references to “theory” in the last decade are outnumbered by references to “evidence” at a rate of 5:1. Among those

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<sup>519</sup> Howick, *Philosophy*, 136.

<sup>520</sup> Kienle, “Clinical Judgment,” 621.

<sup>521</sup> Howick, *Philosophy*, 4.

<sup>522</sup> Michael Loughlin, Ross E. G. Upshur, Maya J. Goldenberg, Robyn Bluhm and Kirstin Borgerson, “Philosophy, Ethics, Medicine and Health Care: the Urgent Need for Critical Practice,” *Journal of Evaluation in Clinical Practice* 16 (2010): 249–259.

<sup>523</sup> D. Morgan, “Arthrotec: the evidence speaks for itself,” *Scandinavian Journal of Rheumatology* Supplement 109 (1999): 13-18.

<sup>524</sup> C.M. Cobb, “Evidence Speaks for Itself,” *Journal of the Western Society of Periodontology / Periodontal abstracts* 50 (2002): 36.

<sup>525</sup> C. Neville, “The Evidence Speaks for Itself,” *Nursing Older People* 25 (2013): 12.

references to “theory,” the vast majority occur in the context of sociological or psychological theories of medical phenomena, rather than in the context of physicians considering their own knowledge.<sup>526,527</sup>

And yet Evidence-Based Medicine is itself a theory of epistemic justification, and has occasionally been referenced as a “paradigm.”<sup>528</sup> EBM is a theory that informs how physicians should interpret and evaluate evidence, and how they should make clinical decisions.<sup>529</sup> Specifically, EBM claims that “the hierarchy implies a clear course of action for physicians addressing patient problems: they should look for the highest available evidence from the hierarchy.”<sup>530</sup> For example, a physician may reject the claim that endovascular therapy (a form of treating stroke that involves advancing wires up into the brain) is an effective treatment, because there is “no evidence.”<sup>531</sup> However, she may not recognize that such a rejection is based upon a process of epistemic evaluation dependent upon a theory of evidence that privileges randomized controlled trial data. There may indeed be evidence for the proposition that endovascular therapy is effective, but if it does not come from a randomized controlled trial, it will be devalued or ignored under modern EBM.

Because “the evidence” is felt to be straightforward, physicians fail to differentiate between propositions that they believe to be true, and justified knowledge. They fail to recognize that propositions may be subject to epistemic evaluation on the basis of a particular theoretical approach. As a consequence, differences of opinion about a particular proposition (for example, that tPA is an effective therapy for stroke) are considered to arise from differences in the quality of the knowledge possessed by different

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<sup>526</sup> J. Bos, “The Rise and Decline of Character: Humoral Psychology in Ancient and Early Modern Medical Theory,” *History of the Human Sciences* 22 (2009): 29-50.

<sup>527</sup> Frank Töpfer, Urban Wiesing, “The Medical Theory of Richard Koch: Theory of Science and Ethics,” *Medicine and Health Care Philosophy* 8 (2005): 207-19.

<sup>528</sup> Evidence-Based Medicine Working Group, “Evidence-Based Medicine: A New Approach to the Teaching of Medicine,” *Journal of the American Medical Association*. 268(1992): 2420-2425.

<sup>529</sup> Suzana A. Silva, Peter C. Wyer, “Where is the Wisdom? II – Evidence-Based Medicine and the Epistemological Crisis in Clinical Medicine,” *Cancer Control* 16 (2009): 158–168.

<sup>530</sup> Guyatt, *Users’ Guide*, 8.

<sup>531</sup> Marc I. Chimowitz, “Endovascular Treatment for Acute Ischemic Stroke — Still Unproven,” *New England Journal of Medicine* 368 (2013): 952-955.

individuals, rather than from theoretical, historical, or social differences that might affect how they interpret that knowledge. For example, in discussing a case where physicians' opinions diverge, Guyatt relates these differences to "piecemeal reporting of research," suggesting that the source of disagreement is the incompleteness of some of the physicians' awareness of "the evidence."<sup>532</sup> He encourages the use of "systematic reviews" — meaning thorough surveys of the literature — as "a solution to the variable reporting of research results."<sup>533</sup> In fact, clinicians are urged to "guard against any use of judgement" in reference to data from clinical trials.<sup>534</sup> Differences in practice — what are termed "gaps from knowledge to practice" — are therefore conceived as issues of the quantity of knowledge possessed by physicians. Either sufficient evidence does not exist and more clinical trials are needed, or the evidence does exist but clinicians are unaware of it.<sup>535</sup>

These are the fundamental epistemic assumptions of "knowledge translation," a new field of medical research that seeks to address the fact that "health systems fail to use evidence optimally" by developing ways of "putting knowledge into action."<sup>536</sup> The Canadian Institutes of Health Research (CIHR) define knowledge translation as the "synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the health care system."<sup>537</sup> From this definition, we can see how knowledge is understood to be implicitly straightforward. What counts as knowledge, how that assessment is performed, and why there might be variations in this process are questions with no bearing on "knowledge translation" as commonly conceived.

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<sup>532</sup> Guyatt, *Users' Guide*, 213.

<sup>533</sup> *Ibid.*, 213.

<sup>534</sup> Kienle, "Clinical Judgment," 621.

<sup>535</sup> William Whiteley, Peter Sandercock, Joanna Wardlaw and Richard Lindley, "Uncertainties About Thrombolysis for Stroke Should Be Addressed With Large-Scale Randomized Trials," *Stroke* 37 (2006): 2662.

<sup>536</sup> Sharon E. Straus, Jacqueline Tetroe, Ian Graham, "Defining Knowledge Translation," *Canadian Medical Association Journal* 181 (2009): 165-168.

<sup>537</sup> Canadian Institutes of Health Research, "About Knowledge Translation and Commercialization," published online at <http://www.cihr-irsc.gc.ca/e/29418.html>, accessed March 14, 2014.

The characterization of evidence-based medicine that I have presented here may appear to be a straw man, an oversimplification of an otherwise robust and defensible approach to medical epistemology.<sup>538</sup> Certainly, the tenets of EBM have been advocated in different ways since their introduction in 1991, with varying degrees of subtlety and sophistication.<sup>539</sup> However, EBM's central claims — that there is such a thing as “best evidence,” that EBM knows what that “best evidence” consists of, and that this “best evidence” should be followed above all other forms of evidence — have remained consistent over the last 20 years.<sup>540</sup> For example, in an editorial that appeared in the *Annals of Neurology* in 2012, prominent neurologists Clay Johnston and Stephen Hauser criticize the neurological examination — those physical manoeuvres performed at the bedside, such as checking reflexes and sensation — because “little evidence actually supports its value.”<sup>541</sup> Because randomized controlled trials have not been performed to study the physical examination, Johnston and Hauser assert that “it has little evidence to support it.”<sup>542</sup> They take for granted that clinical trial evidence alone counts as “high quality research,” and that such evidence will directly inform everyday decision-making. I will now explore how neurologists use, and evaluate, evidence in the process of acute stroke decision-making.

### *Acute Stroke & Its Clinical Propositions*

In Chapter 1, I argued that contemporary physicians understand the “acute stroke” to be a stroke that is treatable through the use of tPA. However, characterizing the meaning of the acute stroke is insufficient to explain how doctors make decisions when faced with patients. For example, the meaning of acute stroke does not describe how doctors decide whether a particular patient is suffering from a stroke, or how they decide whether that stroke would be considered “acute.” Most importantly, the meaning of the

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<sup>538</sup> Montgomery, *How Doctors Think*, 9.

<sup>539</sup> *Ibid.*, 39.

<sup>540</sup> Guyatt, *Users' Guide*, 8.

<sup>541</sup> S. Claiborne Johnston, S.L. Hauser, “The Beautiful and Ethereal Neurological Exam: An Appeal for Research,” *Annals of Neurology* 70 (2011): A9-A10.

<sup>542</sup> Johnston, “Neurological Exam,” A9.

acute stroke cannot speak to the ways in which that meaning is itself justified, or to the degree to which it is accepted, within the community of physicians who treat patients with stroke.

Therefore, a set of clinical propositions about stroke and its treatment must be developed from the meaning in order to produce a theory of acute stroke decision-making. I propose that, in the case of acute stroke decision-making, five clinical propositions can be elaborated: that a clinical entity called the acute stroke exists; that the acute stroke can be effectively treated with IV tPA; that the acute stroke can be diagnosed *in medias res*; that physicians can identify those patients who are candidates for treatment with tPA in the acute stroke setting; and that physicians can establish prognoses for their acute stroke patients. As shall be argued in the next section of this chapter, these propositions become the subject of epistemic evaluation in the context of acute stroke decision-making.

The first proposition is primarily ontologic: that there is something (in this case, a historically-constructed clinical entity) that is referenced by the term “acute stroke.” As we have seen, the term “acute stroke” does not appear to have been used prior to 1960, and its current meaning was established in 1995. The central feature of the modern “acute stroke” is its potential for reversibility through treatment, which has been operationalized through the protocols of the NINDS trial. It is not difficult to imagine that a physician who does not possess this concept of “acute stroke” would treat patients differently than one who does. If a physician has no concept of acute stroke at all, then she will have no ability to look for it, yet alone diagnose it or initiate treatment for it. Personally, I was once instructed by a clinical mentor that in order to diagnose a condition, you must first think of it; in order to think of it, you must have heard of it.<sup>543</sup> Note that the issue being addressed here — whether a physician possesses a concept of “acute stroke” — does not depend upon whether physicians consider diseases to be natural kinds or social constructs, a distinction addressed in the previous chapter. Rather, the question is whether the physician can draw upon some reference to the clinical entity of the acute stroke.

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<sup>543</sup> Personal communication with a senior neurologist, Mount Sinai Hospital, Toronto, Ontario, January 2006.

The second proposition of acute stroke decision-making is that the “acute stroke” is treatable by using tPA. At first, this proposition may seem redundant, in that we have defined the acute stroke as a stroke that is potentially reversible through the use of tPA. However, I would contend that a physician may recognize “acute stroke” as a disease that is potentially treatable — that it is possible for stroke symptoms to be reversed — while lacking a concept of how to achieve this end, or disputing the results of the NINDS trial. It is relatively intuitive that a physician who denies that tPA is an effective treatment for acute stroke would be much less likely to use it. Indeed, emergency physician Jerome Hoffman of UCLA has become a prominent advocate of the view that tPA is not an effective treatment for acute stroke, and should not be used for this purpose.<sup>544</sup>

The third proposition is that “acute stroke” can be accurately diagnosed in time to initiate therapy; in other words, that the diagnosis of “acute stroke” can be made *in medias res*, or in the middle of things. As argued in Chapter 1, the efficacy of tPA as a treatment for acute stroke is understood to depend upon its initiation within a narrow window of time after the start of symptoms. Therefore, the diagnosis must also be determinable during that time frame. A thorough analysis of the psychological and epistemological dimensions of diagnosis goes beyond the scope of this thesis. Briefly put, the diagnosis of acute stroke resembles that of myocardial infarction<sup>545</sup> in that it depends upon a combination of clinical (the patient’s history and examination) and paraclinical features (radiologic or chemical tests), rather than on the basis of one feature alone, such as the characteristic appearance of the rash of chickenpox.<sup>546</sup> In the case of “acute stroke,” the diagnosis is achieved through a combination of clinical features along with the results of the CT scan. The inability to interpret the history and physical examination findings of patients with acute stroke — to quickly localize those findings in relation to the known vascular anatomy of the brain — would be

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<sup>544</sup> Hoffman, “Should Physicians Give tPA,” 149.

<sup>545</sup> Guy S. Reeder, Harold L. Kennedy, “Criteria for the Diagnosis of Acute Myocardial Infarction,” <http://www.uptodate.com/contents/criteria-for-the-diagnosis-of-acute-myocardial-infarction>, (accessed March 14, 2014).

<sup>546</sup> Mary A. Albrecht, “Diagnosis of Varicella Zoster Infection,” <http://www.uptodate.com/contents/diagnosis-of-varicella-zoster-virus-infection>, (accessed March 14, 2014).

expected to impact physicians' treatment decisions in stroke. Physicians unable to interpret those clinical features might not initiate therapy for stroke at all, or might use it more or less indiscriminately.

Prior to the dissemination of CT scanners in the 1970s and 1980s, it was impossible for clinicians to differentiate ischemic stroke from hemorrhage on the basis of clinical features alone; the diagnosis of ischemic stroke could only be made with certainty at autopsy, after the patient's death. At that point, treatment would be futile. Over the course of the last three decades, increasing sophistication in the description of acute stroke through CT images has led to the ability not only to exclude hemorrhage, but also to identify features specific to stroke within a few hours of the onset of symptoms.<sup>547</sup> A physician who did not have access to a CT scanner, or who did not possess sufficient knowledge to interpret its findings (either to rule out hemorrhage or to identify the features of acute stroke), would be unlikely to initiate therapy with tPA due to the risk of hemorrhage from the inappropriate use of a thrombolytic drug like tPA.

The fourth proposition relevant to acute stroke decision-making is that physicians can determine, among patients diagnosed with acute stroke, those who are to be considered candidates for therapy with tPA. In many respects, this ability reflects knowledge of the NINDS protocol, which established inclusion and exclusion criteria for enrollment in the trial.<sup>548</sup> Many physicians will follow a trial's inclusion and exclusion criteria even after its conclusion, inferring that a particular treatment can only be justified in the exact population of patients who had been enrolled in a given trial. Other physicians interpret such criteria more loosely, and extend the treatment protocols derived from a trial to populations of patients who may not have been included in the original study.

In the case of the NINDS trial, inclusion criteria were intended to select patients most likely to experience benefit from tPA, and exclusion criteria were intended to identify those patients most likely to

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<sup>547</sup> Philip A. Barber, Andrew M. Demchuk, J Zhang, Alastair M. Buchan, "Validity and Reliability of a Quantitative Computed Tomography Score in Predicting Outcome of Hyperacute Stroke before Thrombolytic Therapy," *Lancet* 355 (2000): 1670-1674.

<sup>548</sup> NINDS rtPA Study Group, "Tissue plasminogen activator," 1581.

experience hemorrhage, the most concerning complication of tPA use.<sup>549</sup> Core elements of these criteria include: the 3 hour window; the absence of hemorrhage on the CT scan; the absence of obvious signs of irreversible infarction on the CT scan; and any feature that would predispose the patient to bleeding, such as abnormalities of clotting, or the concomitant use of other blood thinning medications.<sup>550</sup> Clinicians who lack knowledge of these criteria may be inclined to administer tPA to patients who have a much greater chance of developing post-tPA hemorrhage. By extension, such experiences may lead physicians to conclude that tPA is an ineffective, and even dangerous, therapy.

The fifth proposition relevant to acute stroke decision-making is the ability to prognosticate, by which I mean the ability to develop a concept of the patient's likely outcome, both in the short-term and in the long-term. Prognostication in the matter of stroke generally refers to the estimation of the patient's likelihood of returning to previous levels of functioning (or very close) in contrast to the likelihood of death or significant disability. Prognostication has been a central element of medical decision-making for millennia,<sup>551</sup> and physicians have long debated whether it is ethically- and medically-sound to intervene in cases that are thought to be hopeless.<sup>552</sup> A physician who expects a patient's prognosis to be dismal, whether therapy is provided or not, will be less likely to intervene, with its expectant costs and risks. However, prognostication in stroke is notoriously difficult. Despite the development of various prognostic scores to aid in stroke decision-making, they show only moderate agreement, and their accuracy remains contested.<sup>553</sup> Persistent interest in developing prognostic scores indicates the importance of prognostication in acute stroke decision-making, and reflects the belief that accurate prognostication would improve

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<sup>549</sup> Balami, "Exact science," 3530.

<sup>550</sup> NINDS rtPA Study Group, "Tissue plasminogen activator," 1582.

<sup>551</sup> Thomas M. Gill, "The Central Role of Prognostication in Clinical Decision-Making," *Journal of the American Medical Association* 307 (2012): 199-200.

<sup>552</sup> Cooke, *Treatise on Nervous Diseases*, 289.

<sup>553</sup> Adam G. Kelly, Bogachan Sahin, and Robert G. Holloway, "Ethical Considerations in Stroke Patients," *Current Opinion in Neurology* 27 (2014): 61-65.

decision-making. Imaging technologies have also been proposed to aid in acute stroke prognostication, though they remain controversial and have been inconsistently adopted.<sup>554</sup>

Considerations of prognostication lead to questions of accuracy and of confidence, which would be expected to impact acute stroke decision-making. For example, physicians who arrive at overly pessimistic prognoses will likely be reluctant to use tPA, potentially leading to a “self-fulfilling prophecy.”<sup>555</sup> Physicians who recognize the limitations of their prognostic accuracy may be reluctant to use tPA in acute stroke due to concerns of worsening outcome or accruing costs. In contrast, a physician who is able to derive a prognosis with confidence (either of good or bad outcome) will likely be more confident in her use of tPA and may use it more frequently.

While these five propositions can be individuated from the contemporary understanding of the acute stroke, they also overlap and interact in meaningful ways. The existence of the acute stroke appears intimately tied to its treatability, and that treatability is dependent upon the efficacy of tPA. The use of tPA is dependent upon fulfilling the diagnostic and methodological criteria developed through the NINDS trial, which identify the features of patients who should be considered eligible for therapy. Therefore questions of the existence of an “acute stroke” and its treatability overlap, as do questions of diagnosis and patient selection. The diagnosis of acute stroke depends upon the specification of its features, and on the ability of physicians to accurately identify those features (through history-taking, examination, and CT scanning) in a timely manner (under 3 hours). The assessment of patients with regards to their eligibility for tPA is therefore a reflection of their current status and of some consideration of their future outcome; in this way, questions of candidacy and prognostication also overlap.

The goal of this chapter is to describe the role of epistemic reasoning in acute stroke decision-making. I have proposed that, contrary to the dominant theory of modern medical epistemology, physicians

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<sup>554</sup> Mark W. Parsons, “Perfusion CT: Is It Clinically Useful?” *International Journal of Stroke* 3 (2008): 41-50.

<sup>555</sup> J. Claude Hemphill III, Douglas B. White, “Clinical Nihilism in Neuroemergencies,” *Emergency Medicine Clinics North America* 27 (2009) 27-37.

do not simply follow the results of randomized controlled trials in acute stroke decision-making. Rather, I have sought to elaborate a set of clinical propositions that, I believe, are subject to epistemic evaluation and around which variations in clinical practice may develop. It is now possible to consider how these propositions are evaluated, what justification is offered for their evaluation, and how they contribute to decision-making. The key proposition — that acute stroke is treatable with tPA — will be the starting point from which the nature of epistemic evaluation in acute stroke decision-making is developed.

*Epistemology, History & Treatability*

The results of the NINDS trial were published in the *New England Journal of Medicine* in December 1995, and in some circles they were quickly hailed as “revolutionary.”<sup>556,557</sup> However, a sense existed within the medical community that these results might be deemed controversial. In 1996, the Heart and Stroke Foundation of Ontario, a charitable organization that funds medical research, hired medical anthropologist Corrine Hodgson and nurse Kathleen Whelan to investigate this phenomenon. In 1998, Hodgson and Whelan published an article in the *Canadian Medical Association Journal* entitled “Are physicians ready for thrombolysis for acute stroke?”<sup>558</sup> Hodgson and Whelan argued that physicians’ willingness to use tPA in acute stroke would be strongly influenced by their acceptance of stroke’s “treatability.” After surveying neurologists and emergency physicians across Canada, they concluded that “Unless stroke is seen as treatable, clinicians will not make the effort necessary to integrate new behaviours into their practice.”<sup>559</sup> Their conclusion is relevant to the argument of this chapter in two ways: first, that the proposition of stroke’s treatability is central to acute stroke decision-making; second, that this proposition was not intuitively obvious or universally accepted in 1998.

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<sup>556</sup> NINDS rt-PA Stroke Study Group, “Tissue plasminogen activator,” 1581.

<sup>557</sup> Kothari, “Thrombolytic Therapy,” 881.

<sup>558</sup> Hodgson, “Are Physicians Ready,” S23.

<sup>559</sup> Hodgson, “Are Physicians Ready,” S23.

Efforts to capture the opinions of physicians with regards to tPA's efficacy suggest that a proportion of physicians have doubted the efficacy of tPA since the publication of the NINDS trial. A survey of neurologists conducted in 1997 and 1998 found that the majority of respondents (67%) considered the results of the NINDS trial "somewhat convincing" of the efficacy of tPA, with only 30% considering the results "very convincing" and 3% "not convincing."<sup>560</sup> In a survey of 47 Ontario neurologists conducted between 2009 and 2010, 4% of respondents did not believe in the efficacy of tPA for stroke.<sup>561</sup> Given that this opinion contradicts the prevailing epistemic position within the neurological community, it is possible that 4% is an underestimation, and that a larger number of physicians are skeptical about the treatability of acute stroke. A 2013 poll of physicians on the BMJ website found that a minority (46%) felt the benefits outweighed the risks of tPA use in acute stroke.<sup>562,563</sup>

Among emergency physicians specifically, multiple surveys have documented how the treatability of stroke has been, and remains, contested. In most hospitals, emergency physicians are the first responders to evaluate patients with suspected stroke, and often collaborate with neurologists in acute stroke decision-making. In some hospitals, neurologists are not available at all hours of day and night, and therefore emergency physicians may make decisions about the use of tPA independently. A 2005 survey of 1105 American emergency physicians found that 40% of respondents would be unlikely to use tPA for stroke

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<sup>560</sup> Irene L. Katzan, Cathy A. Sila, Anthony J. Furlan and David C. Howse, "Community Use of Intravenous Tissue Plasminogen Activator for Acute Stroke: Results of the Brain Matters Stroke Management Survey," *Stroke* 32 (2001): 861-865.

<sup>561</sup> Shamy, "Complexities," 1131.

<sup>562</sup> British Medical Journal, "Do Risks Outweigh Benefits in Thrombolysis for Stroke?" published online at <http://www.bmj.com/about-bmj/poll-archive>, (accessed March 13, 2014).

<sup>563</sup> Preliminary data from our 2014 survey of neurologists in Canada and the United States has found that 1 out of 79 (1%) respondents feel that tPA is not an effective treatment for stroke. Respondents cite the medical literature (57%), their clinical experience with stroke patients (33%), peer opinions at their institutions (5%), personal experience with stroke patients (3%), and institutional practice guidelines (2%) as the basis for their positions on stroke's treatability. When asked about the factors that might influence their use of IV tPA, 32% of respondents agree that their beliefs about the efficacy of IV tPA could influence their treatment decisions. This number seems oddly low: shouldn't it be apparent to every physician that their beliefs about the efficacy of a given treatment would impact their use of it? While several interpretations may be drawn from this preliminary finding, I propose that these physicians who do not feel their belief in the efficacy of tPA affects their treatment responded in this way because they do not consider that they hold beliefs about the efficacy of treatments. Rather, they consider their decisions to be based on "the evidence," which exists as an independent, unbiased, theory-free source of knowledge. From this perspective, the concept of "belief" would have little relevance.

even “under ideal conditions,” suggesting questions about its efficacy.<sup>564</sup> (The nature of “ideal conditions” was not specified in the publication.) A separate 2005 survey of emergency physicians in New York found that only 66% of respondents considered tPA to be an “appropriate agent for the treatment of acute ischemic stroke.”<sup>565</sup> In 2010, a survey of “attitudes and beliefs of Michigan Emergency Physicians toward Tissue Plasminogen Activator Use in Stroke” found that only 49% felt that the scientific evidence regarding the use of tPA was convincing, while 30% remained neutral and 21% declared the evidence unconvincing. When asked about the use of tPA in acute stroke, 57% of respondents from the Michigan study considered it “ideal,” 42% considered it “acceptable,” and 1% declared it “unacceptable patient care.”<sup>566</sup> These terms were not explicitly defined, though it can be inferred that they refer to the perceived strength of the ethical and epistemic justification for the use of tPA. More than 80% of respondents indicated that they were likely or very likely to use tPA, which suggests that the proportion of physicians who were likely to use tPA exceeded the proportion of physicians who felt its use was justified by the available evidence. Were the epistemic reasoning suggested by evidence-based medicine to be applicable in this scenario—namely, following the conclusions of randomized trials—we would not expect to encounter such a paradox. Additionally, 65% of the respondent emergency physicians were uncomfortable administering tPA without the assistance of a neurologist.<sup>567</sup>

These studies suggest two general conclusions: first, that physicians did not, and have not, been universally convinced about the efficacy of tPA on the basis of the results of the NINDS trial and its related

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<sup>564</sup> Devin L. Brown, William G. Barsan, Lynda D. Lisabeth, Michael E. Gallery, Lewis B. Morgenstern, “Survey of Emergency Physicians About Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke,” *Annals of Emergency Medicine* 46 (2005): 56-60.

<sup>565</sup> Yu-Feng Chan, Thomas G. Kwiatkowski, Joseph G. Rella, William P. Rennie, Robert K. Kwon, Robert A. Silverman, “Tissue Plasminogen Activator for Acute Ischemic Stroke: A New York City Emergency Medicine Perspective,” *The Journal of Emergency Medicine* 29 (2005): 405-408.

<sup>566</sup> Phillip A. Scott, Zhenzhen Xu, William J. Meurer, Shirley M. Frederiksen, Mary N. Haan, Michael W. Westfall, Sandip U. Kothari, Lewis B. Morgenstern, John D. Kalbfleisch, “Attitudes and Beliefs of Michigan Emergency Physicians Toward Tissue Plasminogen Activator Use in Stroke: Baseline Survey Results From the INcreasing Stroke Treatment through INteractive behavioral Change Tactic (INSTINCT) Trial Hospitals,” *Stroke* 41 (2010): 2026-2032.

<sup>567</sup> Scott, “Attitudes and Beliefs,” 2028.

trials. Second, it would appear that emergency physicians demonstrate significantly more skepticism about the proposition that acute stroke is treatable with tPA than do neurologists. From an evidence-based medicine perspective, neither of these findings would be expected. According to EBM, the results of clinical trials offer the “best evidence” with which to guide treatment, and should therefore be followed.<sup>568</sup> However, an alternative interpretation, informed by the historical-epistemic approach of Ludwik Fleck, can make sense of these findings. According to Fleck, no experiment exists in isolation, but arises as the product of interwoven lines of thought, and is interpreted in relation to its historical context.<sup>569</sup> Fleck specifies that those propositions considered to be “facts” — those that are generally accepted as true, such as the efficacy of tPA for acute stroke — “cannot be proved with an isolated experiment, but only with broadly based experience; that is, by a special thought style built up from earlier knowledge, from many successful and unsuccessful experiments.”<sup>570</sup> From a Fleckian perspective, it would be unreasonable to expect that one experiment, regardless of how well it was conducted, would be sufficient to change medical practice. Rather, the epistemic evaluation of any experiment will vary depending upon the thought style through which it is contextualized.

Therefore, a Fleckian analysis suggests that different epistemic evaluations of an experiment or a proposition are indicative of the presence of multiple, distinct thought styles. For, when two scientists with different thought styles evaluate the same experiment, they will do so differently, in line with their different background knowledge. For Fleck, a thought style is necessarily shared by a thought collective.<sup>571</sup> He defines a thought collective as “a community of persons mutually exchanging ideas or maintaining intellectual interaction... it also provides the special “carrier” for the historical development of any field of thought, as

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<sup>568</sup> Guyatt, *Users' Guide*, 8.

<sup>569</sup> Fleck, *Genesis*, 98.

<sup>570</sup> *Ibid.*, 98.

<sup>571</sup> *Ibid.*, 39.

well as for the given stock of knowledge and level of culture.”<sup>572</sup> Fleck’s thought collective is a community, engaging in intellectual activities, that shares a body of knowledge and a particular culture. In light of these features, and in light of the striking difference between neurologists and emergency doctors’ interpretations of the efficacy of tPA for acute stroke, it would not seem unreasonable to suggest that the two communities of specialists represent different thought collectives, with different thought styles.

The idea of a medical specialty as an epistemic-historical community is supported by recent scholarship on the history of medical specialization. In his monograph *Divide and Conquer* (2006), McGill University historian George Weisz argues that medical specialization became a “mode of practice” in the 20<sup>th</sup> century, by which he means that specialization came to determine the way physicians approach problems, and the way they identify the types of problems in which they are interested.<sup>573</sup> Weisz’s depiction of specialization resembles the description offered by Kuhn of a scientific community that shares a paradigm: in order to “practice its trade,” a scientific community must share received beliefs, methodologies, and interest in particular problems.<sup>574</sup> Kuhn argues that students join a community by studying its paradigm and by accepting its “fundamentals.”<sup>575</sup> The training of physicians in a particular specialty recalls this notion, in that students acquire a particular approach to a specific set of problems. For example, neurologists often speak of the “neurological formulation” as an organized, thorough and universal means of structuring neurological problems.<sup>576</sup> Different communities will share different sets of practices and different sets of background knowledge.

Another way to explore the situation of neurologists’ and emergency physicians’ differential epistemic evaluation of the claim that acute stroke is treatable is to invoke Nelson Goodman’s concept of

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<sup>572</sup> Fleck, *Genesis*, 39.

<sup>573</sup> George Weisz, *Divide and Conquer: A Comparative History of Medical Specialization* (Oxford: Oxford University Press, 2006), xv-xvi.

<sup>574</sup> Kuhn, *Structure*, 4.

<sup>575</sup> *Ibid.*, 11.

<sup>576</sup> Rahman Pourmand, *Practicing Neurology: What You Need to Know, What You Need to Do*, 2<sup>nd</sup> Edition (Totowa, NJ: Humana Press, 2008), 4.

projectibility judgments. As a consequence of different background knowledge, physicians from different communities will be positioned to make different projectibility judgments about a wide range of hypotheses, including the likelihood of a given treatment's efficacy. The notion that a particular treatment is "effective," that it "works," has been shown to be a product of one's background knowledge and expectations, which exist within a historical context.<sup>577</sup> For example, 19<sup>th</sup> century physicians believed their therapies "worked" because they induced the expected physiological changes — diuretics made patients urinate, emetics made patients vomit.<sup>578</sup> In *Last Resort*, Jack Pressman argues that psychosurgery was felt to "work" as a treatment for severe depression in the mid 20<sup>th</sup> century because it relieved many of the challenging behavioural problems associated with mental illness.<sup>579</sup>

If, indeed, it is a question of different thought style, or different background knowledge, that accounts for neurologists and emergency doctors' differential epistemic evaluation of the treatability of acute stroke, can we establish what intellectual content accounts for these differential evaluations? In other words, can it be established that it is the presence or absence of concept X or experience Y that accounts for the different communities' approaches to the treatability of acute stroke? I propose that by analyzing the most commonly cited arguments in the medical literature surrounding the efficacy of tPA, it might be possible to isolate the key components of neurologists' and emergency doctors' thought styles. Specifically, I contend that it is the presence of the preconditions of the acute stroke — concepts like vascular anatomy, localization, and the penumbra — in the background knowledge of neurologists and not in the background knowledge of emergency physicians that serves as the basis for their differential epistemic evaluations.

The most commonly cited argument questioning the proposition that stroke is treatable addresses the validity of the results of the NINDS trial, in relation to other clinical trials. Critics argue that the 624

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<sup>577</sup> Rosenberg, "Therapeutic Revolution," 8.

<sup>578</sup> *Ibid.*, 8.

<sup>579</sup> Pressman, *Last Resort*, 6.

patients enrolled in the NINDS trial represent an insufficient number to establish efficacy,<sup>580</sup> particularly when relating the NINDS trial to earlier and contemporaneous stroke trials.<sup>581</sup> These other trials — ECASS I, ECASS II, ATLANTIS A and ATLANTIS B — enrolled 1847 patients up to 6 hours after symptom onset, and failed to show benefit for tPA. In fact, they demonstrated very high rates of post-tPA intracerebral hemorrhage, which led to high rates of mortality.<sup>582</sup>

At first glance, this criticism would appear to arise from routine statistical argumentation about the importance of sample size: when an effect is found in a trial of 624 patients, but not found in trials of 1847 patients, the trial with the larger population is more likely to be valid.<sup>583</sup> However, a significant difference exists between the NINDS trial and all other stroke trials, which reveals the subtext of this criticism, and with it the importance of the theory of the penumbra. Only the NINDS trial enrolled all of its patients under 3 hours from the onset of symptoms. The selection of the 3-hour window was based upon animal experimentation that suggested the existence of a penumbra: a region of brain tissue that could survive despite being deprived of blood flow, if only for a few hours.<sup>584</sup> Interestingly, the concept of the penumbra is cited commonly in articles arguing for the treatability of stroke,<sup>585,586,587</sup> and is not mentioned in any articles that would challenge it.<sup>588,589,590</sup>

Without the concept of the penumbra, and its operational correlate of the 3 hour window, there would indeed be no basis to differentiate between the NINDS trial and its related trials. The justification for

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<sup>580</sup> Jeffrey Mann, “Emergency Physician Survey: Recombinant Tissue Plasminogen Activator for Stroke,” *Annals of Emergency Medicine* 48 (2006): 476.

<sup>581</sup> Radecki, “My ACEP tPA Policy Critique,” published online at [www.emlitofnote.com/2014/02/my-acep-tpa-policy-critique.html](http://www.emlitofnote.com/2014/02/my-acep-tpa-policy-critique.html), (accessed April 15, 2014).

<sup>582</sup> ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators, “Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials,” *Lancet* 363 (2004): 768-774.

<sup>583</sup> Gordon Guyatt, *Users’ Guide*, 224.

<sup>584</sup> Lyden, “Ischemic Penumbra,” 43.

<sup>585</sup> Kothari, “Thrombolytic Therapy,” 881.

<sup>586</sup> Stephen H. Thomas, Lee H. Schwamm, Michael Lev, “Case 16-2006: A 72-Year-Old Woman Admitted to the Emergency Department for Change in Mental Status,” *New England Journal of Medicine* 354 (2006): 2263-2271.

<sup>587</sup> Khaja, “Acute Ischemic Stroke,” 943.

<sup>588</sup> Mann, “Emergency Physician Survey,” 476.

<sup>589</sup> Brown, “Survey of Emergency Physicians,” 59.

<sup>590</sup> Radecki, “My ACEP Critique.”

analyzing the NINDS trial separately from those trials that enrolled patients up to 6 hours after stroke onset would fade away, and indeed the benefit appreciated in the NINDS trial would be submerged in the results of the other trials. From this perspective, it would be reasonable to conclude that tPA is not effective, and that acute stroke is not treatable. And yet, emergency physicians Robert Silbergleit and Philip A. Scott of the University of Michigan have argued strongly that such a perspective is flawed:

“It would be incorrect, then, to consider the series of clinical trials of thrombolysis in stroke, using different agents and different treatment protocols, as a cumulative attempt to prove the concept of thrombolytic therapy in stroke. Rather, the trials represent competing attempts to identify the details of implementation: the clinical parameters in which this concept might translate into patient benefit. In this context, it is expected that some trials would be negative and others positive. Hence, the conflicting data from these trials are not surprising and do not suggest ambiguity in the soundness of the underlying concept of thrombolytic use in stroke.”<sup>591</sup>

Indeed, it is interesting that Silbergleit and Scott’s article on tPA is the only one written by emergency physicians that references the penumbra as the physiological rationale for thrombolysis under 3 hours.<sup>592</sup>

Therefore, epistemic evaluation of the acute stroke trials through a thought style that reflects the concept of the penumbra leads to a different conclusion than does evaluation through a thought style that excludes the penumbra.

A separate challenge to the efficacy of IV tPA focuses on the risk of intracerebral hemorrhage, that most dangerous potential side effect of tPA use. According to the NINDS trial, approximately 6% of patients who receive tPA experienced an intracerebral hemorrhage, in contrast to 0.6% in those who did not.<sup>593</sup> Debates within the medical community about the risk of intracerebral hemorrhage after tPA have not centred on the validity of the 6% statistic, but on its interpretation. Emergency physicians have expressed a concern that a 6% risk of hemorrhage is simply “unacceptable.”<sup>594</sup> Though no specific

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<sup>591</sup> Robert Silbergleit, Philip A. Scott, “Thrombolysis for Acute Stroke: The Incontrovertible, The Controvertible, and the Uncertain,” *Academic Emergency Medicine* 12 (2005): 348-351.

<sup>592</sup> Silbergleit, “Thrombolysis,” 350.

<sup>593</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1581.

<sup>594</sup> Brown, “Survey of Emergency Physicians,” 58.

justification was offered, a group of emergency physicians who were surveyed in 2005 settled on 3.4% as the upper limit of tolerable risk in the face of post-tPA hemorrhage.<sup>595</sup> For them, a 6% chance of hemorrhage outweighed the 35% chance of benefit derived from tPA use, but a 3.4% risk did not. In this instance, critics of tPA are not arguing that the NINDS results are inaccurate; they are arguing about their meaning, in relation to a thought style.

Once again, this criticism is found mostly among the emergency medicine community, rather than among neurologists. I contend that the main difference between neurologists and emergency physicians, which accounts for this ethical-epistemic challenge to the use of tPA in acute stroke, reflects differential understanding of the process by which acute stroke is diagnosed. Difficulty in diagnosing patients with acute stroke may lead to concerns about the efficacy of tPA and hence the willingness to use it. The diagnosis of acute stroke depends upon physicians' ability to localize patients' symptoms in relation to an understanding of the brain's vascular and functional anatomies. This ability is central to the practice of the neurologist, but is often lacking from the experience of emergency physicians, whose knowledge is necessarily broader and shallower in scope. Silbergleit and Scott have also suggested that the concern over hemorrhage may be related to clinician experience, in that "the infrequency of treatment, both in the community setting and within emergency medicine training programs" contributes to the fear of post-tPA hemorrhage.<sup>596</sup>

The consistent suggestion that emergency physicians are uncomfortable administering tPA to patients with acute stroke without the aid of neurologist may also be interpreted as support for their diagnostic uncertainty. Additional support comes from a recent debate that occurred among members of the American Academy of Neurology stroke listserv. Dr. Scott Segan, a neurologist based at St. Barnabas Hospital in New York, suggested that "the dirty little secret" of the debate around tPA administration is that emergency physicians "feel inadequate to diagnose stroke. I don't think they mind as much if a neurologist

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<sup>595</sup> Brown, "Survey of Emergency Physicians," 58.

<sup>596</sup> Silbergleit, "Thrombolysis," 350.

comes down and gives tPA, and if they had a blood test like troponin they'd be giving it every time the lab told them it was positive."<sup>597</sup> In this instance, Segan is alluding to the diagnostic process for myocardial infarction (heart attack), in which a blood test for the enzyme troponin features prominently. In patients with chest pain and a troponin result above a certain threshold, the diagnosis of myocardial infarction is made. Diagnosing acute stroke is distinctly more challenging. In a recent debate about stroke treatment, emergency physician Dr. Anand Swaminathan of New York University similarly expressed concerns about the fact that "we don't know who to give the drug to."<sup>598</sup>

The question of whether a drug is effective as a treatment for a particular condition will depend upon the selection of appropriate patients. For example, an intervention designed to reduce the risk of stroke will appear to have a different efficacy if it is applied to patients who are at increased risk of stroke, in contrast to a population in which the background risk of stroke is already very low.<sup>599</sup> The use of thrombolytic agents like tPA to treat acute stroke was difficult prior to the availability of CT scanners, because clinicians could not differentiate patients with ischemic stroke from those with intracerebral hemorrhage.<sup>600</sup> Therefore, questions of tPA's efficacy must be explored in relation to the ability of physicians to identify those patients most likely to benefit. Asking "Is tPA an effective treatment?" needs to be qualified: "Is tPA an effective treatment *in whom?*" In light of these issues, there is a very real way in which the efficacy of a treatment for acute stroke is dependent upon the ability to diagnose acute stroke.

The association between treatment and diagnostic certainty has been reflected in the writings of tPA sceptic Dr. Ryan Radecki, an emergency physician at the University of Texas. Radecki identifies

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<sup>597</sup> Dr. Scott Segan, posted to the AAN Stroke Section listserv on February 9, 2014 at 20:42 EST, AAN\_Stroke\_Section@googlegroups.com.

<sup>598</sup> Podcast 116 — the tPA for Ischemic Stroke Debate," EMCrit Blog [emcrit.org/podcasts/tPA-for-ischemic-stroke-debate](http://emcrit.org/podcasts/tPA-for-ischemic-stroke-debate), accessed on March 14, 2014.

<sup>599</sup> Jeffrey J. Perry, Mukul Sharma, Marco L.A. Sivilotti, Jane Sutherland, Andrew Worster, MD, Marcel Emond, Grant Stotts, Albert Y. Jin, Wieslaw J. Oczkowski, Demetrios J. Sahlas, Heather E. Murray, Ariane MacKey, Steve Verreault, George A. Wells, Ian G. Stiell, "A Prospective Cohort Study of Patients With Transient Ischemic Attack to Identify High-Risk Clinical Characteristics," *Stroke* 45 (2014): 92-100.

<sup>600</sup> Sussman, "Thrombolysis" (1958), 1705.

“diagnostic certainty” as a central element that would render tPA use “more appropriate.”<sup>601</sup> Oxford university neurologist Alastair Buchan and colleagues similarly identify “rapid diagnosis” as a central element of treatment decision-making in acute stroke.<sup>602</sup> In a survey of Ontario neurologists conducted by researchers from the University of Toronto, 100% of respondents identified diagnostic uncertainty as factor that would impact their management of patients with suspected stroke, though the vast majority felt they encountered it only “rarely.”<sup>603,604</sup> Moreover, epidemiological studies suggest that approximately 20% of patients with suspected acute stroke are found to have a different final diagnosis.<sup>605</sup> In some series, 3% of patients who receive tPA for acute stroke may be felt to have a different final diagnosis.<sup>606</sup>

The presence of diagnostic uncertainty in acute stroke can be reframed as support for the notion that there is variability in the epistemic evaluation of the proposition that “acute stroke can be diagnosed *in medias res*.” Uncertainty is a challenge to the process of diagnosing stroke. What is the basis for this uncertainty? A certain amount of uncertainty is expected (and arguably necessary) surrounding any diagnostic process. Buchan and colleagues have argued that the “sudden onset of focal neurological deficits” is the characteristic element of the acute stroke, and should be the focus of the history and physical examination.<sup>607</sup> Buchan’s conceptualization is consistent with what I have earlier proposed, namely that the diagnosis of stroke is dependent upon a conception of the brain’s vascular and functional anatomy, in order to identify the “focal neurological deficits” that would point to the occlusion of a particular artery.

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<sup>601</sup> Radecki, “My ACEP Critique.”

<sup>602</sup> Balami, “Exact Science,” 3529.

<sup>603</sup> Shamy, “Complexities,” 1133.

<sup>604</sup> In our ongoing survey of neurologists in Canada and the United States, 56% of respondents endorse “uncertainty surrounding the diagnosis of acute ischemic stroke” as a factor that might influence their use of IV tPA.

<sup>605</sup> W. Oliver Tobin, Joseph G. Hentz, Bentley J. Bobrow, and Bart M. Demaerschalk, “Identification of Stroke Mimics in the Emergency Department Setting,” *Journal of Brain Disease* 1(2009): 19-22.

<sup>606</sup> Edward C. Jauch, Jeffrey L. Saver, Harold P. Adams, Jr, Askiel Bruno, J.J. (Buddy) Connors, Bart M. Demaerschalk, Pooja Khatri, Paul W. McMullan, Jr, Adnan I. Qureshi, Kenneth Rosenfield, Phillip A. Scott, Debbie R. Summers, David Z. Wang, Max Wintermark, Howard Yonas, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology, “Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association,” *Stroke* 44 (2013): 870-947.

<sup>607</sup> Balami, “Exact science,” 3529.

Knowledge of these anatomical patterns is differentially expressed among neurologists, and even more so between neurologists and emergency physicians. While the development of a working ability to localize “focal neurological deficits” is a key element of the neurological paradigm, and is a particular quality of the neurological community, emergency physicians are not trained in the same ways and do not share the same knowledge. As a consequence, the diagnostic process is more challenging for them, and they are in turn reliant upon assistance from neurologists when making acute stroke diagnoses.<sup>608</sup> Differential epistemic evaluation of the proposition that the acute stroke is diagnosable *in medias res* can therefore be related to differential appreciation of the set of historical preconditions that allowed for the development of the modern meaning of the “acute stroke.”

### *Conclusions*

The goal of this thesis is to arrive at a naturalistic description of the decision-making process of physicians, with a focus on decision-making in the use of the drug tPA to treat patients with acute stroke. In some way, acute stroke decision-making must involve the application of knowledge. However, the questions to be explored in this chapter were: what knowledge is applied in acute stroke decision-making, and in what way? Standard accounts of medical knowledge — those derived from the theory of evidence-based medicine — suggest that knowledge from randomized controlled trials is to be the primary, if not the exclusive, basis for physician decision-making.<sup>609</sup> Evidence-based medicine is clear that there is such a thing as “best evidence,” that “best evidence” is determined by the EBM hierarchy that privileges knowledge from randomized trials, and that when making decisions, physicians should “look for the highest available evidence from the hierarchy.”<sup>610</sup>

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<sup>608</sup> Radecki, “My ACEP Critique.”

<sup>609</sup> Montgomery, *How Doctors Think*, 40.

<sup>610</sup> Guyatt, *Users' Guide*, 8.

However, the existence of persistent debate surrounding the results of randomized controlled trials in the field of acute stroke treatment<sup>611</sup> — and, as a consequence, debate about a set of core clinical propositions relevant to acute stroke decision-making<sup>612</sup> — suggest that EBM’s depiction of the epistemic reasoning involved in acute stroke decision-making is incomplete. Applying an approach grounded in the work of historians and philosophers of science — most prominently Ludwik Fleck’s *Genesis and Development of a Scientific Fact* — I have proposed a more nuanced description of the role of knowledge in acute stroke decision-making. Specifically, I have argued that the results of clinical trials are insufficient to explain treatment decisions, in that the knowledge derived from clinical trials is evaluated by physicians in relation to a body of historical knowledge. A single clinical trial result, or even a collection of trial results, has little meaning or force to compel practice, except when contextualized in relation to what Fleck has called “a special thought style built up from earlier knowledge, from many successful and unsuccessful experiments, from much practice and training, and — epistemologically most important — from *several adaptations and transformations of concepts*.”<sup>613</sup> In the case of acute stroke, the presence or absence of the interwoven preconditions outlined in Chapter 1 — which form the foundations of the modern meaning of the “acute stroke” — determine the epistemic evaluation of clinical trial results like those of the NINDS trial.

This line of argumentation has several important implications for understanding acute stroke decision-making, and with it physician decision-making in general. Different attitudes towards the use of a particular treatment — and with it, differences in the use of that treatment — can be referable to the process by which physicians epistemically evaluate the knowledge and propositions relevant to that treatment. Moreover, this process of epistemic evaluation reflects the contextualization of novel knowledge in relation to a historical body of knowledge. Therefore, the process of epistemic evaluation is historical in

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<sup>611</sup> Hoffman, “Should physicians give,” 149.

<sup>612</sup> Podcast 116 — the tPA for Ischemic Stroke Debate,” EMCrit Blog [emcrit.org/podcasts/tPA-for-ischemic-stroke-debate](http://emcrit.org/podcasts/tPA-for-ischemic-stroke-debate), (accessed on March 14, 2014).

<sup>613</sup> Fleck, *Genesis*, 98.

two important senses. First, it is historical in that the epistemic context through which treatments and trials are evaluated develops over time through the “confluence of several lines of collective thought.”<sup>614</sup> Second, it is historical in that the temporal position of any given physician, relative to that historical body of knowledge, will influence how she evaluates novel claims. A neurologist in 2014, looking at a clinical trial from 1995, will evaluate that trial in relation to a body of knowledge that extends from the murky past up to 2014. In contrast, a neurologist in 1995, looking at the data from that same trial, would evaluate it in relation to a body of knowledge that ends in 1995. Two physicians from different points in time will evaluate the same knowledge differently. The way that physicians evaluate knowledge is historically-determined and contextualized.

In essence, the physician from 1995 and the physician from 2014 interpret that same knowledge differently because they come to it with different bodies of knowledge, or what Fleck calls thought styles. A thought style encompasses the historical development of a field of thought, a particular stock of knowledge, and a culture.<sup>615</sup> A thought style is shared by a thought collective, a group of people with a mutually exchanging and maintaining intellectual interaction.<sup>616</sup> I have suggested that neurologists and emergency doctors, with their different evaluations of the clinical trials that inform acute stroke treatment, reflect different thought collectives, with different thought styles. The description of medical specialties as thought collectives echoes Kuhn’s reference to specialty groups as scientific communities, sharing a “disciplinary matrix.”<sup>617</sup> Conceiving of medical specialties in this fashion suggests that the way to bridge the epistemic gaps between them — to whatever extent this can be done — is not to collect more clinical trial results, or to increase the availability of those results.<sup>618</sup> Rather, what is needed is to develop an historical understanding of the differences between extant thought styles, in order to understand how they have

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<sup>614</sup> Fleck, *Genesis*, 23.

<sup>615</sup> *Ibid.*, 39.

<sup>616</sup> *Ibid.*, 39.

<sup>617</sup> Kuhn, *Structure*, 181.

<sup>618</sup> Straus, “Defining Knowledge Translation,” 165.

arisen. It would not be inappropriate to call such a process “knowledge translation,” in that what I am describing involves translating the meaning of a particular trial result between thought styles.

Finally, recognition of the central role of thought style in the evaluation and contextualization of medical knowledge demonstrates how the perspective on knowledge advocated by evidence-based medicine — that of knowledge as certain and objective — becomes untenable.<sup>619</sup> Because physicians will necessarily evaluate knowledge in relation to a thought style, and because there will be multiple thought styles within a medical community at any point in time, there can be no, one, “underlying truth.”<sup>620</sup> The way physicians evaluate knowledge is subjective, relative to their thought style. As a consequence, the way they make, and justify, their clinical decisions, will be subjective, and relative to their thought style. The notions of “best practices” and “best evidence,” as championed by evidence-based medicine, have little meaning when the subjectivity and uncertainty of medical decision-making are revealed.

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<sup>619</sup> Guyatt, *Users' Guide*, 225.

<sup>620</sup> *Ibid.*, 225.

## Chapter 3: Ethical Evaluation in Acute Stroke Decision-Making

How do we decide what is valuable? The problem seems to me to be existential, moral, epistemological, and metaphysical.

– Dr. Sam Smith, *General Practitioner, Warrington, Cheshire, UK* <sup>621</sup>

### *Introduction*

How do doctors make decisions in the treatment of acute stroke? In the first chapter of this thesis, I sought to understand how contemporary physicians conceptualize an “acute stroke,” so that we might be better positioned to understand doctors’ decision-making in a more general way. In the second chapter, I proposed that physicians demonstrate significant differences in their epistemic evaluation of the proposition that tPA can be an effective treatment for acute stroke. By this I mean that not all physicians agree that tPA is beneficial when administered to patients with acute stroke. However, there is another dimension to the question of whether tPA provides patients with benefit that requires unpacking: namely, what is meant by *benefit*? Even among physicians who agree that a given therapy can be beneficial to at least some patients, what counts as a *good outcome*, in contrast to a *bad outcome* for those patients? In this third chapter, I seek to show that a process of ethical evaluation — in which questions of evaluating benefit and outcome feature prominently — occurs as part of acute stroke decision-making.

Insofar as treatment decisions depend upon a conceptualization of benefit for patients, they require the consideration of medical, epistemic and ethical factors, as constructed within a particular historical and social context. I propose that acute stroke decision-making requires physicians to make value judgments about patients’ quality of life pre-stroke, and expected quality of life post-stroke, as part of their consideration of benefit. Moreover, these evaluations will necessarily be influenced by physicians’ own

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<sup>621</sup> Sam Smith, “Postmodernity and a Hypertensive Patient: Rescuing Value from Nihilism,” *Journal of Medical Ethics* 24 (1998): 25-31.

values, and therefore represent a potential source of variation in decision-making. Ultimately, the consequences of acute stroke treatment decisions will be both medically and ethically relevant. Despite recent attention to the role of social and ethical values in scientific reasoning,<sup>622</sup> analysis of medical decision-making from this perspective remains underexplored in the recent literature.<sup>623,624,625</sup>

My argument in this chapter will consist of several parts. First, I will propose that the dominant view in contemporary bioethics, that of principlism, ignores the ethical reasoning involved in everyday medical decisions such as those surrounding tPA use in acute stroke. Then, I will argue that acute stroke decision-making involves ethical reasoning because it involves the consideration of benefits, values and outcomes, which are necessarily ethically significant. Finally, I will seek to characterize the ethical evaluation that occurs as part of acute stroke decision-making as a process that involves the evaluation of patients' pre-stroke and post-stroke states. This argumentation will be supported by a close reading of the medical literature, and by results from recently completed and ongoing surveys of neurologists' decision-making in acute stroke therapy.

### *Principlist Ethics & Everyday Medical Decisions*

In Chapter 2, I proposed that acute stroke decision-making involves a process of epistemic evaluation, in which physicians are required to evaluate available medical knowledge in order to inform their treatment decisions. The argument that medical decision-making should have some relation to medical

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<sup>622</sup> Heather E. Douglas, *Science, Policy, and the Value-Free Ideal* (Pittsburgh: University of Pittsburgh Press, 2009), 1. A prominent contributor to the recent literature on science and values is professor Heather Douglas of the University of Waterloo, whose work has explored the role of values in science and in expert reasoning, the nature of objectivity, and the origins of the idealization of science as something free of values. While much of her work focuses on the policy-implications of values in science and is therefore not directly applicable to the subject of this thesis, Douglas' conceptualization of scientists as experts embedded within a broader society shares many features with the description of physicians I have sought to develop in this thesis.

<sup>623</sup> Shamy, "Complexities," 1133.

<sup>624</sup> Anthony J. Furlan, George Kanoti, "When is Thrombolysis Justified in Patients with Acute Ischemic Stroke? A Bioethical Perspective," *Stroke* 28 (1997): 214-218.

<sup>625</sup> Sophie Crozier, "Enjeux éthiques des limitations et arrêts de traitements à la phase aiguë des accidents vasculaires cérébraux graves," *Presse Médicale* 41 (2012): 525-531.

knowledge appears relatively intuitive; similarly, it may appear relatively intuitive that medical decision-making should involve some form of ethical reasoning. The existence of bioethics as a discipline suggests that at least some medical decisions are the subject of ethical analysis.<sup>626</sup> However, matters of stroke appear relatively infrequently as topics of ethical analysis.<sup>627,628,629,630,631,632,633</sup> For example, in the widely read monograph *Ethical Issues in Neurology* by Dartmouth neurologist James Bernat, “stroke,” “acute stroke” and “tPA” do not appear at all.<sup>634</sup> Modern bioethics appears uninterested in the ethical aspects of everyday decisions like the administration of tPA, though these kinds of decisions remain ethically significant and involve ethical reasoning.

In recent decades, scholarship in medical ethics has been dominated by a particular theoretical approach, which has come to be known as bioethical principlism. Introduced by American philosophers Thomas Beauchamp and James Childress in the 1970s, principlism is an approach to bioethics that advocates for the use of a set of four principles to navigate ethical challenges. These principles are autonomy, non-maleficence, beneficence, and justice.<sup>635</sup> In its selection of principles, principlism seeks to combine elements of the consequentialist and deontological traditions in ethics. The principle of autonomy refers to the norm of respecting the decision-making capacities of autonomous persons, and is generally considered the central tenet of principlist ethics. Nonmaleficence refers to the norm of avoiding the causation of harm to patients.

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<sup>626</sup> Thomas F. Beauchamp, James L. Childress, *Principles of Biomedical Ethics, 5th Edition* (Oxford: Oxford University Press, 2001), 1.

<sup>627</sup> Kjell Asplund, “Ethics of Life Support in Patients With Severe Stroke,” *Stroke* 20 (1989): 1107-1112.

<sup>628</sup> Furlan, “When is Thrombolysis Justified,” 214.

<sup>629</sup> Leonard M. Fleck, Oliver W. Hayes, “Ethics and Consent to Treat Issues in Acute Stroke Therapy,” *Emergency Medicine Clinics of North America* 20 (2002): 703-715.

<sup>630</sup> Stephen J. Louw, Jeffrey A Keeble, “Stroke Medicine: Ethical and Legal Considerations,” *Age and Ageing* 31 (2002): 31-35.

<sup>631</sup> Geneviève Demarquay, Laurent Derex, Norbert Nighoghossian, Patrice Adeleine, Frédéric Philippeau, Jérôme Honnorat, Paul Trouillas, “Ethical Issues of Informed Consent in Acute Stroke: Analysis of the Modalities of Consent in 56 Patients Enrolled in Urgent Therapeutic Trials,” *Cerebrovascular Diseases* 19 (2005): 65-68.

<sup>632</sup> M. Mangset, R. Førde, J. Nessa, E. Berge, T. Bruun Wyller, “‘I don’t like that, it’s tricking people too much...’: acute informed consent to participation in a trial of thrombolysis for stroke,” *Journal of Medical Ethics* 34 (2008): 751-756

<sup>633</sup> Adam G. Kelly, Bogachan Sahin, Robert G. Holloway, “Ethical considerations in stroke patients,” *Current Opinions in Neurology* 27 (2014): 61-65.

<sup>634</sup> James Bernat, *Ethical Issues in Neurology, 3rd Edition* (Philadelphia: Lippincott, Williams & Wilkins, 2008), 511.

<sup>635</sup> Beauchamp, *Principles*, 12.

Beneficence refers to the norm of providing benefits and balancing benefits against risks and costs, and justice to the norm of fairly distributing benefits, risks and costs.<sup>636</sup>

It goes beyond the scope of this thesis to present a detailed critique of principlist ethics, though such critiques exist.<sup>637</sup> However, one aspect of the principlist approach is directly relevant to the topic of this chapter. That is: under principlism, *when* is ethical reasoning thought to occur in medicine? Specifically, does principlist ethics provide a framework to analyze the ethical aspects of everyday medical decision-making, such as those decisions involved in treating acute stroke? I will argue that principlist ethicists say little about the ethics of everyday decisions, as they focus on “moral dilemmas” and a standard set of controversies such as abortion and euthanasia.

Beauchamp and Childress are explicitly interested in aiding health professionals to reason through what they term “moral dilemmas.”<sup>638</sup> In their influential textbook *Principles of Biomedical Ethics*, Beauchamp and Childress define moral dilemmas as “circumstances in which moral obligations demand or appear to demand that a person adopt each of two (or more) alternative actions, yet the person cannot perform all the required alternatives.”<sup>639</sup> In that Beauchamp and Childress define moral dilemmas in reference to a person’s obligation to adopt one of several courses of action, they frame moral dilemmas as occasions for decision-making. For Beauchamp and Childress, a moral dilemma forces clinicians to choose between conflicting moral obligations that require alternate and exclusive courses of action, such as providing a blood transfusion to the child of Jehovah’s witnesses, or respecting her parents’ religious beliefs.<sup>640</sup>

Does the principlist conception of “moral dilemma” include everyday medical decisions, such as those surrounding the use of tPA? Despite the broad way in which they define the “moral dilemma,” several counterarguments suggest that Beauchamp and Childress are not interested in everyday decisions. First of

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<sup>636</sup> Beauchamp, *Principles*, 12.

<sup>637</sup> John Harris, “In Praise of Unprincipled Ethics,” *Journal of Medical Ethics* 29 (2003): 303-306.

<sup>638</sup> Beauchamp, *Principles*, 10.

<sup>639</sup> *Ibid.*, 10.

<sup>640</sup> Raanan Gillon, “Four Scenarios,” *Journal of Medical Ethics* 29 (2003): 267-268.

all, they do not speak to the role of ethical reasoning in medical decision-making generally. For example, references to “decision-making” in *Principles of Bioethics* focus nearly exclusively on issues surrounding patient decision-making, rather than on the decision-making of physicians.<sup>641</sup> Secondly, by advancing a particular definition of the “moral dilemma,” namely as a scenario in which clinicians perceive that their moral obligations require them to choose between mutually exclusive actions, Beauchamp and Childress are implicitly suggesting that only some medical decisions will count as moral dilemmas.

Thirdly, and perhaps most convincingly, a review of the topics considered in principlist discourses reveals a restricted and consistent set of clinical scenarios that principlists consider to be “moral dilemmas.” In the first edition of their textbook *Contemporary Issues in Bioethics* (1978), Thomas Beauchamp and colleague LeRoy Walters identify a set of four themes which have reappeared in principlist scholarship ever since. In *Contemporary Issues*, Beauchamp and Walters organize their discussion under four headings: “Life and Death,” which includes cases of abortion and euthanasia; “Allocation,” referring to the allocation of scarce medical resources; “Human Experimentation,” exploring cases of informed consent and research design; and “Biomedical and Behavioral Technologies,” discussing cutting-edge genetic and reproductive technologies.<sup>642</sup> Recent principlist scholarship reflects similar types of cases, to the exclusion of everyday medical decisions. Principlist bioethicist Albert Jonsen, then of the University of California, produced a retrospective analysis of “ethical events” of the 20<sup>th</sup> century as part of his monograph, *A Short History of Bioethics* (2000). The identification of certain events as “ethical” implies that most other events in medicine are *not* “ethical,” reinforcing the principlist perspective that only certain decisions require ethical deliberation. Of the 13 “ethical events” Jonsen chooses to highlight, all but one could be classified under the four headings developed by Beauchamp and Walters in the 1978 edition of *Contemporary Issues*.<sup>643</sup> In 2003, the *Journal of Medical Ethics* published a special issue that featured essays on four “standard” bioethics cases: the Jehovah’s

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<sup>641</sup> Beauchamp, *Principles*, 2.

<sup>642</sup> Tom L. Beauchamp, LeRoy Walters, *Contemporary Issues in Bioethics* (Encino: Dickenson Publishing Company, 1978), vi-ix.

<sup>643</sup> Jonsen, *A Short History*, 99-114.

witness case, the child of a Jehovah's witness case, the selling of kidneys for transplantation, and genetic manipulation for the purposes of germline enhancement.<sup>644</sup> That there should be such “standard” cases in a field as expansive as medical ethics further emphasizes the relatively restrictive focus of principlist ethics. Moreover, the fact that “the Jehovah's witness case” is all that needs to be said to identify the dilemma in question — that of providing a blood transfusion against a patient's religious beliefs — speaks to the familiarity the bioethical audience has with these cases.

Despite the fact that principlists seem uninterested in everyday medical decisions like prescribing antibiotics or administering tPA, it is necessary to ask whether these decisions should still be considered “moral dilemmas” in the principlist sense. Under principlism, a decision would become a moral dilemma if three circumstances are met: if the clinician is aware of the fact that he or she has moral obligations, if these obligations demand different courses of action, and if these courses of action are mutually exclusive.<sup>645</sup> I would argue that many physicians are unaware of the ways in which their everyday decisions have ethical dimensions, and therefore they do not appreciate the tensions produced by conflicting moral obligations. References to the ethical nature of everyday decisions are rare within the medical literature, and even rarer in everyday discussions. For example, the reports of complex stroke cases that have appeared in the *New England Journal of Medicine* since 1995 make no reference to ethics at all.<sup>646,647</sup> Moreover, a recent study that sought to characterize the subjects of ethics consultations that were obtained in an American stroke centre found that all the circumstances in which the ethics service became involved would have been considered “moral dilemmas” from a principlist perspective, such as the withdrawal of ventilatory support in severely brain-injured patients.<sup>648</sup>

In his monograph *Ethical Issues in Neurology*, neurologist James Bernat of Dartmouth University

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<sup>644</sup> Gillon, “Four Scenarios,” 267-268.

<sup>645</sup> Beauchamp, *Principles*, 10.

<sup>646</sup> Carter, “Case 5-2004,” 707-716.

<sup>647</sup> Thomas, “Case 16-2006,” 2263-2271.

<sup>648</sup> Adrienne R. Boissy, Paul J. Ford, Randall C. Edgell, Anthony J. Furlan, “Ethics Consultations in Stroke and Neurological Disease: A 7-Year Retrospective Review,” *Neurocritical Care* 9 (2008): 394-399.

proposes to distinguish between “ethical dilemmas” and “ethical problems,” in that “ethical problems” represent a weaker standard than “ethical dilemmas.”<sup>649</sup> Bernat states that “not all ethical problems encountered in clinical practice rise to the level of dilemmas,” suggesting that the category of “dilemma” should be reserved for particularly controversial circumstances.<sup>650</sup> He defines ethical dilemmas as “clinical problems in which all feasible solutions require breaking a moral rule.”<sup>651</sup> Bernat’s “ethical dilemma” therefore resembles Beauchamp and Childress’ construction of a “moral dilemma,” in that ignoring a moral obligation can be seen as similar to breaking a moral rule. Bernat provides examples of “ethical dilemmas” which are consistent with principlist themes: issues of informed consent in research, the allocation of scarce resources, and the provision of end of life care to patients with dementia.<sup>652</sup>

Bernat then defines an “ethical problem” as any situation that results in “discomfort” around “trying to decide if a situation is morally (as opposed to medically) right or wrong.”<sup>653</sup> According to this definition, the “ethical problem” still fails to serve as a framework for analyzing the ethics of everyday decisions, for two reasons. First, Bernat’s “ethical problem” is dependent upon the clinician’s perception of “discomfort,” which may not be present in everyday medical decisions. However, the absence of “discomfort” on the part of the clinician does not serve as an absolute standard of ethics because a decision may still be ethically significant regardless of the physician’s experience of it.<sup>654</sup>

Second, Bernat’s construction of an “ethical problem” contrasts the process of determining whether a situation is *morally right* from the process determining whether it is *medically right*. This distinction suggests that ethical decision-making is somehow separate and separable from medical decision-making, at least when it comes to decision-making around “ethical problems.” If, as Bernat suggests, moral reasoning is separable from medical reasoning, then moral reasoning can be understood as an added layer of complexity

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<sup>649</sup> Bernat, *Ethical Issues*, 134.

<sup>650</sup> *Ibid.*, 135.

<sup>651</sup> *Ibid.*, 135.

<sup>652</sup> *Ibid.*, 135.

<sup>653</sup> *Ibid.*, 135.

<sup>654</sup> Jussi Niemelä, “What Puts the ‘Yuck’ in the Yuck Factor?” *Bioethics* 25 (2011): 267-279.

that only exists in certain medical scenarios. Routine or everyday decisions, such as those surrounding tPA use in acute stroke, would likely not fall into this category. Therefore, Bernat's conception of "ethical problems" and "ethical dilemmas" would not provide a framework for exploring the ethical reasoning involved in everyday decisions like acute stroke decision-making.

Principlist ethics fails to address the role of ethical reasoning in everyday medical decisions. However, a theoretical basis for studying the ethics of everyday decisions like those surrounding tPA can be found in more traditional approaches to ethics, as well as in recent work in social psychology. For example, German philosopher Immanuel Kant's (1724-1804) categorical imperative, introduced in the *Groundwork of the Metaphysics of Morals*, explicitly considers the ethical implications of everyday decisions.<sup>655</sup> The imperative to "act only according to that maxim through which you can at the same time will that it become a universal law" is intended to be applicable to all individual actions.<sup>656</sup> Moreover, English philosopher Jeremy Bentham (1748-1832)'s *The Principles of Morals and Legislation* (1781) begins with descriptive claims about the nature of decision-making: that humans are "under the governance of two sovereign masters, pain and pleasure," and that any action can be ethically evaluated "according to the tendency which it appears to have to augment or diminish the happiness of the part whose interest is in question."<sup>657</sup> Bentham makes explicit that his framework should apply "to every action whatsoever," and therefore could be used to guide ethical reasoning in everyday medical decisions.<sup>658</sup>

Within the recent literature, critics of principlist ethics have tended to argue from a perspective based in virtue ethics.<sup>659,660</sup> Virtue ethics, a school of ethical thought that can be traced to the writings of Aristotle (384-322 BCE), emphasizes the importance of the virtue, or moral character, with which

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<sup>655</sup> Immanuel Kant, *Groundwork of the Metaphysics of Morals*, ed. and trans. Mary Gregor and Jens Timmermann (Cambridge: Cambridge University Press, 2012), 34.

<sup>656</sup> Kant, *Groundwork*, 34.

<sup>657</sup> Jeremy Bentham, *The Principles of Morals and Legislation* (New York: Prometheus Books, 1988), 2.

<sup>658</sup> Bentham, *Principles*, 2.

<sup>659</sup> Christopher Cowley, "The Dangers of Medical Ethics," *Journal of Medical Ethics* 31 (2005): 739-742.

<sup>660</sup> Patrick Gardiner, "A Virtue Ethics Approach to Moral Dilemmas in Medicine," *Journal of Medical Ethics* 29 (2003): 297-302.

individuals lead their daily lives.<sup>661</sup> As Aristotle writes in the *Nicomachean Ethics*, “moral virtue comes about as a result of habit, whence also its name *ethike* is one that is formed by a slight variation from the word *ethos* (habit).”<sup>662</sup> Because it is one’s daily habits that make one ethically virtuous, a virtue ethics approach recognizes the importance of everyday decisions in the determination of one’s goodness. More specifically, Aristotle says that people become virtuous by behaving in a virtuous fashion: “we become just by doing just acts, temperate by doing temperate acts, brave by doing brave acts.”<sup>663</sup> In fact, he argues that it is our daily habits that determine whether we are virtuous, for “states of character arise out of like activities.”<sup>664</sup> The point is made even more clearly: “It makes no small difference, then, whether we form habits of one kind or of another from our very youth; it makes a very great difference, or rather *all* the difference.”<sup>665</sup>

From a virtue ethics perspective, all medical decisions would be considered “ethical events,” in that every act may be carried out in a virtuous or a non-virtuous manner. Advocating for virtue-based bioethics, Irish philosopher Christopher Cowley has argued that “ethics is a unique subject matter precisely because of its widespread familiarity in all areas of life.”<sup>666</sup> Writing in the *Journal of Medical Ethics*, British general practitioner Patrick Gardiner has similarly described the way that ethics is a ubiquitous presence in his medical practice: “I am, rather, a general practitioner (GP), who deals with moral issues and dilemmas every day of my working life. These range from the daily awareness of distributive justice as I sign every prescription, to discussing and balancing the complex issues involved in choices made by patients with terminal disease. I find many of these situations challenging and some quite perplexing.”<sup>667</sup> From a virtue ethics perspective, everyday medical decisions can be considered ethically-significant decisions, and therefore suitable for ethical analysis.

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<sup>661</sup> Rosalind Hursthouse, “Virtue Ethics,” The Stanford Encyclopedia of Philosophy (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/ethics-virtue/> (accessed March 30, 2014).

<sup>662</sup> Aristotle, *The Basic Works of Aristotle*, ed. Richard McKeon (New York: The Modern Library, 1941), 952.

<sup>663</sup> Aristotle, *Basic Works*, 952.

<sup>664</sup> *Ibid.*, 953.

<sup>665</sup> *Ibid.*, 953.

<sup>666</sup> Cowley, “Dangers,” 739-742.

<sup>667</sup> Gardiner, “Virtue Ethics,” 297-302.

Furthermore, recent research in social psychology and ethics also recognizes the ethical significance of everyday decisions. In a special issue of the journal *Social Justice Research*, Harvard University professors Mahzarin Banaji (a social psychologist) and Max H. Bazerman (a business ethicist) argue for the importance of “ordinary” behaviours in applied ethics.<sup>668</sup> They argue that the ethical components of everyday decisions are often missed, specifically because they are ordinary. Bazerman and Banaji argue that unethical behaviours do not simply occur when people choose “self-rewarding behavior over what is right,” such as when they cheat or steal.<sup>669</sup> Rather, Bazerman and Banaji propose that decision-making is ethical in more complex and subtle ways. For example, it is in the context of everyday interactions between people that implicit or unconscious mechanisms may be particularly influential, leading us to make decisions influenced by stereotyping and prejudices.<sup>670</sup> This conclusion is particularly relevant to the argument of this chapter, in that I will suggest that physicians bring to acute stroke decision-making a set of values — explicit and implicit — which influence the ways they make treatment decisions. A core component of ethical education, argue Bazerman and Banaji, must be to learn to recognize the ethical implications of one’s actions, including those actions that are routine and “ordinary.”<sup>671</sup> It is the central goal of this chapter to develop a nuanced and accurate account of the ethical implications of acute stroke decision-making.

#### *Causes, Consequences & Values in Acute Stroke Decision-Making*

In this section, I will outline the ways in which everyday decisions, and especially those surrounding the treatment of acute stroke, involve ethical reasoning. To begin, I will provide a brief account of how physicians generally understand causation in decision-making, in order to establish that physicians generally judge their actions from a consequentialist perspective. I will then argue that medical decisions such as those

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<sup>668</sup> Max H. Bazerman, Mahzarin Banaji, “The Social Psychology of Ordinary Ethical Failures,” *Social Justice Research* 17 (2004): 111-115.

<sup>669</sup> Bazerman, “Social Psychology,” 112.

<sup>670</sup> *Ibid.*, 112.

<sup>671</sup> *Ibid.*, 114

surrounding the use of tPA in acute stroke treatment should be recognized as ethical decisions at the same time. In that acute stroke decision-making requires normative judgments to be made, it is subject to the influence of physicians' values, which may influence decisions in explicit or implicit ways.

Within medicine, treatment decisions — like administering IV tPA to patients with acute stroke — are felt to be causally associated with treatment outcomes.<sup>672</sup> The nature of that causal relationship is complex and variable, and a full elaboration of the metaphysics of medical treatment is beyond the scope of this thesis.<sup>673</sup> While physicians recognize that an outcome that follows an intervention will not always be causally tied to the intervention, they do believe that their interventions *can* have clear and discernible effects in a specific patient's case.<sup>674</sup> In their article on "Clinical Judgement," German physicians Gunver Kienle and Helmut Kiele argue that valid causal assessments in medicine result from "gestalt cognition," in which physicians assess "the wholeness of a pattern that is irreducible to its parts and conceivable independent from its particulars."<sup>675</sup> By this Kienle and Kiele mean that analyses of causal relations are based upon a whole pattern of events, which may reflect one of several "correspondence relations" between causes and effects. For example, they discuss the notion of a "time correspondence," such as when uncontrollable bleeding suddenly stops after the administration of a pro-clotting drug or a "morphological correspondence," such as when the pattern of anesthesia manifested by a patient reflects the known pattern supplied by a given nerve.<sup>676</sup>

Physicians believe that their interventions can have causal associations with patient outcomes, and indeed they judge their interventions on the basis of those outcomes.<sup>677</sup> Therefore, physicians demonstrate a consequentialist approach to the ethics of everyday decisions. Consequentialism refers to the view that

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<sup>672</sup> Kienle, "Clinical Judgment," 621.

<sup>673</sup> Simon, "Constructive Realism," 353.

<sup>674</sup> Kienle, "Clinical Judgment," 622.

<sup>675</sup> *Ibid.*, 622.

<sup>676</sup> *Ibid.*, 623.

<sup>677</sup> Montgomery, *How Doctors Think*, 60.

actions should be judged on the basis of their consequences.<sup>678</sup> In short, physicians generally consider the rightness or wrongness of their decisions in light of the outcomes of those decisions. Therefore, when making a decision, physicians consider the expected outcome of that decision. This emphasis on consequence can be traced to early versions of the Hippocratic Oath, which exhort the physician “to help and not to harm.”<sup>679</sup> The consequentialist tradition is further reflected in modern principlist ethics by recognition of the value of beneficence and non-maleficence, meaning the imperative to do good and avoid harm.<sup>680</sup> What renders a given decision “good” or “bad” is the outcome of that decision. Traditional deontological theories, which evaluate decision-making in light of the decision-maker’s intentions, do not appear as relevant to physicians’ ethical reasoning, perhaps because physicians are generally acting (or thought to be acting) with the intention of producing “good” outcomes for their patients.<sup>681</sup>

Physicians are most often act consequentialists, in that they tend to evaluate individual actions on the basis of their consequences.<sup>682</sup> For example, a “good” decision will be one that leads to a “good” outcome for the patient. If a patient is administered IV tPA and experiences the resolution of her stroke symptoms, then this will be considered to have been a “good” decision. Under certain circumstances, physicians may use a rule consequentialist approach, in which a general policy rather than a specific act is judged on its consequences. For example, if a patient is administered tPA and develops an unexpected allergic reaction, the decision to have given tPA may still be deemed a “good” one because the adverse outcome was unpredictable and the use of tPA would generally have been considered the “best” decision in similar circumstances.

The consequentialist nature of acute stroke decision-making was suggested as early as 1997, in an

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<sup>678</sup> Walter Sinnott-Armstrong, “Consequentialism,” *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2014/entries/consequentialism/>, (accessed April 8, 2014).

<sup>679</sup> Jonsen, *Short History*, 2

<sup>680</sup> Beauchamp, *Principles*, 12.

<sup>681</sup> Michelle van Ryn, Somnath Saha, “Exploring Unconscious Bias in Disparities Research and Medical Education,” *Journal of the American Medical Association* 306 (2011): 995-996.

<sup>682</sup> Sinnott-Armstrong, “Consequentialism.”

article by neurologist Anthony Furlan and ethicist George Kanoti of Case Western Reserve University.<sup>683</sup> In their article “When is Thrombolysis Justified in Patients with Acute Ischemic Stroke? A Bioethical Perspective,” Furlan and Kanoti seek to justify the use of tPA on the basis of its expected consequences.<sup>684</sup> Moreover, Furlan and Kanoti develop a multidimensional approach to consequences, in that they consider medical-ethical outcomes such as safety and efficacy, and economic-ethical outcomes such as cost-effectiveness. For Furlan and Kanoti, the decision to administer tPA to a patient with stroke therefore reflects a complex, integrative process that depends upon “scientific, ethical and economic standards.”<sup>685</sup>

The fact that physicians demonstrate a consequentialist approach in acute stroke decision-making has three important implications for the argument of this chapter. First, it suggests that medical outcomes are also ethical outcomes. Second, it suggests that medical decisions are also ethical decisions. Third, it requires that physicians engaged in acute stroke decision-making are concerned with evaluating the good, a necessarily ethical process. Each of these suggestions will be developed shortly. Broadly speaking, this line of argumentation supports the conclusions of Dutch anthropologist Annemarie Mol, who in her publications has emphasized that “medicine is entwined with the good.”<sup>686</sup> By this she means that medical decision-making necessarily involves and impacts considerations of the good. For Mol, questions of “what to do” — decisions about treatment, like the use of tPA — have, and are recognized to have, “a normative dimension.”<sup>687</sup> In this chapter, I am seeking to describe the normative dimension of acute stroke decision-making, and explore how it impacts the decisions that are made in the use of tPA.

It is relatively intuitive that medical decisions will have medical outcomes, but I propose that these medical outcomes also register from an ethical perspective. Whether a patient lives or dies, improves or worsens, is significant from a medical and from an ethical point of view. Administering tPA to a patient

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<sup>683</sup> Anthony J. Furlan, George Kanoti, “When is Thrombolysis Justified in Patients with Acute Ischemic Stroke? A Bioethical Perspective,” *Stroke* 28 (1997): 214-218.

<sup>684</sup> Furlan, “When is Thrombolysis Justified,” 214.

<sup>685</sup> *Ibid.*, 215.

<sup>686</sup> Mol, *The Body Multiple*, 166.

<sup>687</sup> *Ibid.*, 172.

with an acute stroke would not be considered an ethical dilemma by principlists, but even such a routine decision will have ethically-relevant outcomes. If the patient is able to return to her previous state of health, then that outcome will be considered medically and ethically good, and therefore the decision that led to it will be considered a medical and ethical success. However, if the patient suffers an intracerebral hemorrhage and dies as a consequence of tPA, then that outcome will be considered bad, and the decision will be a medical and ethical failure. Moreover, when physicians practice in a health care system with limited resources, every decision — to prescribe tPA, to schedule a follow up appointment, to order an MRI scan — has broader economic ramifications.<sup>688</sup> Because of resource limitations, every decision made by a physician impacts the availability of resources for other decisions, and therefore the ethical implications of even a simple decision like the administration of tPA may be widespread.<sup>689</sup>

If medical decisions can have ethical outcomes, then medical decisions can also be considered ethical decisions. Though physicians may not recognize that their medical decision-making is concomitantly ethical decision-making, I contend that clinicians making everyday decisions like those surrounding tPA are considering the ethical implications of their decisions when they consider the medical outcomes. When a physician chooses the intervention that is most likely to lead to the best medical outcome for her patient, she is also choosing the intervention that, in her opinion, will lead to the best ethical outcome. Furthermore, I contend that many physicians are aware of the broader implications of their individual decisions, and act in a manner that is cognizant of the system-wide consequences of their decisions. For example, a physician may choose not to prescribe tPA for a given patient because of concerns about the magnitude of benefit for that patient, while at the same time recognizing that other patients may be more

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<sup>688</sup> Gordon H. Guyatt, R. Brian Haynes, Roman Z. Jaeschke, Deborah J. Cook, Lee Green, C. David Naylor, Mark C. Wilson, W. Scott Richardson, for the Evidence-Based Medicine Working Group, "Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care," *Journal of the American Medical Association* 284 (2000): 1290-1296.

<sup>689</sup> Tony Hope, *Medical Ethics: A Very Short Introduction* (Oxford: Oxford University Press, 2004), 39.

likely to benefit from that drug or from those resources.<sup>690</sup>

I have proposed that physicians make medical decisions based on what they think is the medically best outcome, and that medical outcomes should also be thought of as ethical outcomes. But how do physicians determine what counts as a *best outcome*, or a *good outcome*? What does it mean to a physician when she says that a particular patient is likely to *benefit* from an intervention like tPA? In medical parlance the notion of benefit is associated with increasing or promoting the good.<sup>691</sup> But what is *the good*? The determination of *the good* is a fundamental problem in ethics, and many approaches have been proposed to define and measure it since antiquity.<sup>692,693</sup> In that there is no universal definition of the good, the nature of the good remains contested from a philosophical perspective. As Mol has argued, there is no universally acknowledged definition of the good in medicine either. She writes that, “The end points, the very goals of medical interventions, are essentially contested.”<sup>694</sup> By this, she means that doctors will disagree about how to define the good, and hence about how to achieve it.

Moreover, Mol elaborates how considerations of the good are necessarily personal — they reflect the values of the individuals (physicians and patients) involved. Considerations of the good, she writes, “are intertwined with different, dissonant, ways of life.”<sup>695</sup> In relation to the case of decision-making in cardiac care, David Jones writes how doctors and patients “bring their own interests and values to the table.”<sup>696</sup> For Furlan and Kanoti, deciding whether tPA use in acute stroke is justified “depends not only on how one looks at the question but also through whose eyes.”<sup>697</sup> In writing about the decisions made in the wake of stroke, Dr. Claire Creutzfeld of the University of Washington and Dr. Robert Holloway of the University of

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<sup>690</sup> Siegel, “End-of-Life Decision Making,” 181-194.

<sup>691</sup> Tom Beauchamp, “The Principle of Beneficence in Applied Ethics,” *The Stanford Encyclopedia of Philosophy* (Winter 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/win2013/entries/principle-beneficence/>, accessed March 20, 2014).

<sup>692</sup> Bentham, *Principles*, 2.

<sup>693</sup> Mark Timmons, ed. *Disputed Moral Issues: A Reader, 2<sup>nd</sup> Edition* (Oxford: Oxford University Press, 2010), 13.

<sup>694</sup> Mol, *Body Multiple*, 175.

<sup>695</sup> *Ibid.*, 175.

<sup>696</sup> Jones, *Broken Hearts*, 17.

<sup>697</sup> Furlan, “When is Thrombolysis Justified,” 217.

Rochester argue that “physicians’ decisions are also influenced by their own personal values and professional characteristics.”<sup>698</sup> As Thomas Cunningham writes in his recent dissertation on medical decision-making, “the idea of valuing implies *agents who value*.”<sup>699</sup> From this elegant phrase we are reminded that physicians’ decisions require a process of evaluation, which will reflect the values that they hold.

In a recent article entitled “Principles for Applying the Users’ Guide to Patient Care,” McMaster University epidemiologist and physician Gordon Guyatt and colleagues suggest that clinical decision-making requires “a judgment about the trade offs between risks and benefits, and because values or preferences differ, the best course of action will vary between patients and clinicians.”<sup>700</sup> They argue that value judgments are a part of every decisions, though these judgments may be “unapparent” in routine cases.<sup>701</sup> Guyatt et al. highlight how “judgments often reflect clinician or societal values concerning whether intervention benefits are worth the cost,” and they illustrate this point by providing an example from stroke medicine. When choosing between two drugs that can be used to prevent stroke, the more effective drug also being more expensive,

“Many authoritative bodies recommend first-line treatment with the less effective drug, presumably because they believe society’s resources would be better used in other ways. Implicitly, they are making a value or preference judgment about the trade-offs between deaths and strokes prevented, and resources spent. By values and preferences, we mean the underlying processes we bring to bear in weighing what our patients and our society will gain or lose when we make a management decision.”<sup>702</sup>

The description provided by Guyatt et al. mirrors the argument I have been laying out in this chapter: namely, that considerations of risk and benefit such as those that go into choosing a drug to prevent stroke, implicitly reflect value judgments (what I have termed ethical evaluation) about the potential outcomes of those decisions. In this way, Guyatt et al. acknowledge “that values play a role in every important patient

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<sup>698</sup> Claire J. Creutzfeld, Robert G. Holloway, “Treatment Decisions after Severe Stroke: Uncertainty and Biases,” *Stroke* 42 (2012): 3405-3408.

<sup>699</sup> Cunningham, *Socializing Medicine*, 15. Italics are the author’s.

<sup>700</sup> Guyatt, “Principles,” 1291.

<sup>701</sup> *Ibid.*, 1291.

<sup>702</sup> *Ibid.*, 1291.

care decision,<sup>703</sup> and I contend that this is phenomenon is reflected in acute stroke treatment decisions as well.

However, physicians may not be aware of the values they bring to bear on the process of acute stroke decision-making. As Daniel Kahnemann and Amos Tversky have demonstrated in empirical experiments, most of the decisions we make are determined by unconscious processes, and those that are associated with a sense of conscious effort will still be influenced by our unconscious tendencies.<sup>704</sup> These unconscious tendencies may include sociocultural biases and prejudices. As defined by Kahnemann, biases are systematic tendencies towards particular patterns of behaviour, in contradiction to the expectations of purely rationalistic decision-making.<sup>705</sup> While biases are not necessarily normatively adverse, they can reflect prejudicial attitudes, for example towards members of certain demographic groups. Arguably, prejudice can be understood as an *a priori* process of ethical evaluation in which members of a certain group — determined by socioeconomic status, race, sex or age — are deemed less valuable, less valued, and less good.

Indeed, recent scholarship in social psychology has demonstrated the ways that individual decisions — including those of physicians — may reflect prejudices, even when such tendencies are consciously disavowed.<sup>706</sup> A widely cited paper by Schulman et al., published in the *New England Journal of Medicine* in 1999, used a factorial study design to demonstrate the presence of biases in the ways physicians treat patients with suspected myocardial infarction.<sup>707</sup> In the factorial design, eight actors of varying age, race and sex depict a standardized clinical scenario. Each participating physician is asked to provide a diagnosis and treatment plan after having observed one version of the scenario. In Schulman's experiment, physicians were less likely to refer patients for assessment of their chest pain, and less likely to engage in treatment, if

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<sup>703</sup> Guyatt, "Principles," 1292.

<sup>704</sup> Kahnemann, *Thinking*, 24.

<sup>705</sup> *Ibid.*, 3.

<sup>706</sup> Green, "Implicit Bias," 1231-1238.

<sup>707</sup> Schulman, "Effect of Race," 618.

the patient was black rather than white, and female rather than male.<sup>708</sup> In 2007, a group of medical researchers at Harvard University applied the influential and widely-used “implicit association test” methodology, developed by psychologist Mahzarin Banaji, to suggest that physicians demonstrate implicit racial preferences when they make diagnostic and treatment decisions.<sup>709</sup> The implicit association test uses various interactive tools to demonstrate the association of demographic states (age, race, sex) with value judgments in participants’ responses. It seeks to address the existence of prejudices of which the respondents themselves may even be unaware.<sup>710</sup> In this study, respondents’ implicit preferences (but not their explicit preferences) predicted their likelihood of offering thrombolysis to patients with acute myocardial infarction, meaning that those physicians who demonstrated the greatest implicit prejudice towards African Americans were least likely to offer them treatment.<sup>711</sup>

Experiments like these demonstrate that physicians’ decisions may be subject to unrecognized influences. While such influences may reflect biases within North American culture and language,<sup>712</sup> they may also originate within medicine itself. One such source of bias is the “hidden curriculum,” a phenomenon first suggested by Frederick Hafferty and Ronald Franks of the University of Minnesota in 1994. The “hidden curriculum” refers to the way that medical trainees tacitly acquire a set of values by observing daily clinical practice, which are distinct from the values they are explicitly taught in the classroom.<sup>713</sup> On wards and in clinics, trainees learn to judge their patients and the diseases from which they suffer. For example, physicians may demonstrate negative attitudes towards patients who they feel are unlikely to improve, such as those with mental disorders, critical illnesses or terminal diagnoses.<sup>714</sup>

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<sup>708</sup> Shulman, “Effect of Race,” 618.

<sup>709</sup> Green, “Implicit Bias,” 1231

<sup>710</sup> Greenwald, “Implicit Social Cognition,” 4-27.

<sup>711</sup> Green, “Implicit Bias,” 1231.

<sup>712</sup> Ogunnaiké, “Language of Implicit Preferences,” 999-1003.

<sup>713</sup> Frederick W. Hafferty, Ronald Franks, “The Hidden Curriculum, Ethics Teaching, and the Structure of Medical Education,” *Academic Medicine* 69 (1994): 861-871.

<sup>714</sup> Frederick W. Hafferty, “Beyond Curriculum Reform: Confronting Medicine’s Hidden Curriculum,” *Academic Medicine* 73 (1998): 403-407.

Clinicians' attitudes about patients and their diseases have been suggested to be powerful determinants of their decision-making.<sup>715,716</sup> Kathryn Montgomery alludes to the hidden curriculum when she writes that “medical education is a moral as well as an intellectual education: experiential, behavioral, and in important ways covert.”<sup>717</sup> The hidden curriculum therefore represents another potential source of value judgments that may impact the way physicians evaluate patients and their outcomes as part of acute stroke decision-making, or decision-making generally. In short, physicians may bring significant biases — derived from their general culture, or from the culture of medicine itself — to the process of performing the ethical evaluations involved in making treatment decisions.

Parisian neurologist Dr. Sophie Crozier has begun to explore the impact of biases in acute stroke decision-making. In her recent article entitled “*Enjeux éthiques des limitations et arrêts de traitements à la phase aiguë des accidents vasculaires cérébraux graves*,” Crozier proposes a view of acute stroke decision-making that includes considerations of tPA use, but also includes decisions about the withdrawal or withholding of life support measures such as intubation and cardiopulmonary resuscitation.<sup>718</sup> For Crozier, these types of decisions require physicians to envision what would count as an “unacceptable” degree of disability, and to judge the value of a given individual’s life in those circumstances.<sup>719</sup> Crozier argues that physicians’ decisions in acute stroke require some attempt at measurement of “the good,” and that in doing so they are subject to their own beliefs and attitudes, organizational constraints, hospital policies, and personal experiences.<sup>720</sup>

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<sup>715</sup> Christakis, “Physician Characteristics,” 367-372.

<sup>716</sup> Seiji Bito, Atsushi Asai, “Attitudes and Behaviors of Japanese Physicians Concerning Withholding and Withdrawal of Life-Sustaining Treatment for End-of-Life Patients: Results from an Internet Survey,” *BMC Medical Ethics* 8 (2007): 7.

<sup>717</sup> Montgomery, *How Doctors Think*, 4.

<sup>718</sup> Crozier, “Enjeux éthiques,” 525. Title translated by the author as “Withdrawing and Withholding Treatment in Acute Severe Stroke Patients: Clinical and Ethical Issues.”

<sup>719</sup> *Ibid.*, 526.

<sup>720</sup> *Ibid.*, 529.

*Evaluating Post-Stroke Outcomes*

So far, I have proposed that acute stroke decision-making involves a process of consequentialist reasoning that recognizes medical outcomes as ethical outcomes, and medical decision-making as ethical decision-making. I have proposed that this process of ethical reasoning involves explicit evaluations of benefit, and it may also reflect the influence of unconscious or implicit biases, such as those derived from cultural prejudices or medicine's hidden curriculum. However, I have yet to describe exactly what is being evaluated in the course of acute stroke decision-making. Therefore, I will now describe the core content of physicians' ethical evaluation in acute stroke decision-making: namely, post-stroke outcomes and pre-stroke quality of life.

The ethical evaluation of post-stroke outcomes involves recognition of two important themes: first, that ethical evaluation in acute stroke decision-making is interwoven with epistemic reasoning. Considerations of outcomes are dependent upon physicians' abilities to predict possible outcomes and to assess their probabilities of occurring.<sup>721</sup> Recent scholarship in the history and philosophy of science and medicine has pointed to the ways that many questions of ethics (e.g. "What should we do?") are related to questions of epistemology (e.g. "What do we know?").<sup>722,723,724</sup> In the case of acute stroke decision-making, evaluations of benefit as outlined by Furlan and Kanoti exist in relation to a belief that benefit is possible and in relation to an expectation of what that benefit may look like, both of which are informed by knowledge of the relevant disease process.<sup>725</sup> For Crozier, acute stroke decisions — including those surrounding tPA use and the withdrawal or withholding of life-sustaining measures — depend upon physicians' prognoses for patients. Specifically, Crozier proposes that physicians' decisions depend upon "the prediction of disability and quality of life," which is to some degree uncertain and may be influenced by beliefs and

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<sup>721</sup> Sommers, "Probabilities and Preferences," 670.

<sup>722</sup> Daston, *Objectivity*, 51.

<sup>723</sup> Howick, *Philosophy*, 24.

<sup>724</sup> Ross E.G. Upshur, "A Call to Integrate Ethics and Evidence-Based Medicine," *Virtual Mentor: American Medical Association Journal of Ethics* 15 (2013): 86-89.

<sup>725</sup> Beauchamp, "Beneficence."

expectations.<sup>726</sup>

Second, the evaluation of post-stroke outcomes reflects an ontologic approach to disease more closely allied with normativistic rather than naturalistic theories.<sup>727</sup> Here, I am referring to the longstanding controversy surrounding how “health” and “disease” should be defined.<sup>728</sup> Specifically, are health and disease scientific concepts reflecting biological properties, or are they normative concepts reflecting value judgments? University of Calgary philosopher of science Marc Ereshefsky has proposed that, for any given state of health or disease, we can distinguish between state descriptions, by which he means “descriptions of physiological or psychological states,” and normative claims, by which he means “claims about what states we value or disvalue.”<sup>729</sup> Ereshefsky’s approach implicitly accepts that there can be a normative dimension to any state of health or disease. Therefore, the vast majority of perspectives on this debate — other than very restrictive naturalistic approaches — recognize that states of health and disease are commonly associated with normative claims, in that states of disease are generally valued and desired less than states of health, whatever they may mean.<sup>730</sup> This is the fundamental starting point for our consideration of how physicians evaluate post-stroke outcomes: states of disease are generally valued less than states of health.

In the setting of acute stroke decision-making, how do physicians evaluate potential outcomes?<sup>731</sup> I propose that the judgment of whether a patient will benefit from tPA requires evaluation of that patient’s quality of life before the stroke, of the patient’s expected quality of life as a consequence of the stroke, and the patient’s possible quality of life through the administration of tPA. A medical (and ethical) imperative to intervene exists when there is a significant difference between the patient’s quality of life prior to the stroke, and the patient’s expected quality of life post-stroke. Each of the potential outcomes — disability

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<sup>726</sup> Crozier, “Enjeux éthiques,” 526.

<sup>727</sup> Marc Ereshefsky, “Defining Health and Disease,” *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (2009): 221-227.

<sup>728</sup> Ereshefsky, “Health and Disease,” 221.

<sup>729</sup> *Ibid.*, 221.

<sup>730</sup> *Ibid.*, 225.

<sup>731</sup> Crozier, “Enjeux éthiques,” 528.

from stroke, return to normal, or death — is evaluated by the physician in terms of its relative value, and its likelihood of occurrence. The wide array of outcome measures used in clinical stroke care and stroke trials — from clinical indices such as the National Institutes of Health Stroke Scale Score and the modified Rankin Score, to economic measures such as Quality-Adjusted Life Years — suggest both the importance of evaluation in stroke decision-making, and the lack of a universal standard of evaluation.<sup>732</sup> Clinically, the most widely used measure is the National Institutes of Health Stroke Scale Score, which is reported in nearly every case report of acute stroke treatment in the contemporary context.<sup>733</sup>

For example, a patient who was fully independent before the onset of a left middle cerebral artery territory stroke now faces the potential of a lifetime of hemiplegia (inability to move the right side) and aphasia (inability to produce or understand language). There is an evident difference between the patient's pre-stroke state and her post-stroke state. Specifically, the post-stroke state is liable to be valued less (by the physician and patient both) than the patient's pre-stroke state. However, in a circumstance like this, where the patient is unable to communicate, the physician's evaluation will be the basis for a decision about treatment. Because the use of tPA may improve the patient's post-stroke state — from a medical and ethical perspective — it is likely to be favoured by the physician. The possibility that tPA might mitigate this difference, and return the patient to her previous state of health (or close to it), creates an opportunity for benefit. This, I propose, is the general structure of ethical evaluation in acute stroke decision-making.

However, the physician's impetus to administer tPA may be moderated based on the patient's pre- or post-stroke states. In a recent review article entitled "Evaluation and Management of Acute Ischemic Stroke," Dr. Pooja Khatri of the University of Cincinnati urges her readers that "all neurologic deficits present at the time of the treatment decision should be considered in the context of individual risk and

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<sup>732</sup> Piet N. Post, Anne M. Stigelbout, Peter P. Wakker, "The Utility of Health States After Stroke: A Systematic Review of the Literature," *Stroke* 32 (2001): 1425-1429.

<sup>733</sup> Adam G. Kelly, "Patient Management Problem," *Continuum: Lifelong Learning in Neurology* 20 (2014): 476-481.

benefit, as well as the patient's baseline functional status."<sup>734</sup> What does she mean by this? In a situation in which the stroke is relatively mild and the patient's quality of life is unlikely to be affected, the use tPA is less likely to provide significant benefit, meaning that the patient's post-stroke states with and without tPA are unlikely to be significantly different.<sup>735</sup> Or, if a patient is already severely disabled prior to the stroke, the opportunity for producing benefit with tPA will also shrink. Similarly, in a case where the stroke is felt to be so advanced that treatment is expected to provide minimal benefit, it is unlikely to be offered.<sup>736</sup> The centrality of this process of evaluation is reflected in the fact that many tPA guidelines, and especially those used in the conduct of clinical trials, establish a minimal functional status (for example, being able to walk without assistance) as a necessary prerequisite to receive treatment with tPA.<sup>737</sup>

An additional example may be particularly revelatory here from a more personal perspective. During my clinical training in neurology, I heard from several different preceptors about the case of a concert violinist who had suffered a stroke affecting his bow hand.<sup>738</sup> This patient, who I never encountered, is reputed to have suffered a very mild stroke causing only weakness of the one hand. He would have been judged to have a very low score on the National Institutes of Health Stroke Scale (NIHSS) score, and would likely not have been offered tPA on the basis of that score.<sup>739</sup> However, because of the severity of the injury *to him* — because his post-stroke quality of life would have been so significantly affected by weakness of the hand — treatment with tPA was felt to be potentially beneficial. The patient, reportedly, regained full function of the affected hand and returned to his work as a concert violinist. This case demonstrates the kind of ethical evaluation that I propose to be a core component of acute stroke decision-making, namely that patients' post-stroke outcomes are evaluated in light of their pre-stroke states.

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<sup>734</sup> Pooja Khatri, "Evaluation and Management of Acute Ischemic Stroke," *Continuum: Lifelong Learning in Neurology* 20 (2014): 283-295.

<sup>735</sup> Khatri, "Evaluation and Management," 289.

<sup>736</sup> James F. Burke, "Cost and Utility in the Diagnostic Evaluation of Stroke," *Continuum: Lifelong Learning in Neurology* 20 (2014): 436-440.

<sup>737</sup> Khatri, "Evaluation and Management," 289.

<sup>738</sup> Personal communication with senior neurologists, Sunnybrook Hospital, Toronto, Ontario, 2010.

<sup>739</sup> Khatri, "Evaluation and Management," 288.

In their 1999 monograph entitled *Stroke: Epidemiology, Evidence and Clinical Practice*, British geriatricians Shah Ebrahim and Rowan Harwood urge physicians to ask “Is it a *bad stroke?*” when making treatment decisions.<sup>740</sup> This question supports my description of acute stroke decision-making as a process in which patients’ outcomes are evaluated as part of treatment decisions. Ebrahim and Harwood expand on the subjective and variable nature of their question, recognizing that there is no universal standard by which to evaluate stroke severity. They propose that the outcome of a stroke:

“can be described in many different ways, ranging from the patient’s perception, the amount of physiological disturbance, and the consequent disability and handicap caused, to the burden to society. The severity of a stroke may be assessed in terms of the amount of brain damaged, the extent of any arterial lesion demonstrated on angiography, or the function of the brain.”<sup>741</sup>

Ebrahim and Harwood appose clinical, pathological, radiological and personal interpretations of stroke severity, and do not suggest that one is more right than the other. Rather, their description recalls the language of Furlan and Kanoti, who recognized that the justification of tPA use would vary with one’s perspective. Moreover, it echoes Annemarie Mol, who wrote that ethical evaluation in medicine was “intertwined with different, dissonant, ways of life.”<sup>742</sup>

Ebrahim and Harwood also consider how the use of tPA may lead to better outcomes for many patients but to a higher rate of mortality “among patients who would have survived with moderate to severe disability without treatment.”<sup>743</sup> This statement reflects a particular interpretation of the early tPA data, in that it was thought that some patients who would have survived a stroke with moderate to severe disability might have a higher chance of dying if given tPA. While this interpretation of the clinical trial results is questionable, the relevant point is that Ebrahim and Harwood acknowledge that a scenario in which more patients die may be better than one in which more patients survive with variable degrees of disability. They

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<sup>740</sup> Ebrahim, *Stroke: Epidemiology*, 115. Italics are the authors’.

<sup>741</sup> *Ibid.*, 115.

<sup>742</sup> Mol, *Body Multiple*, 175.

<sup>743</sup> Ebrahim, *Stroke Epidemiology*, 166.

continue that, “if, as some work has suggested... survival in a disabled state is valued very poorly, this is a reasonable trade-off. However, there is considerable variation between people on their valuations of health states.”<sup>744</sup> The comments of Ebrahim and Harwood suggest that post-stroke outcomes are subject to ethical evaluation, that these evaluations may lead to contested results, and that such evaluations may be a source of variation in acute stroke decision-making.

Acute stroke decision-making requires physicians to evaluate states of health and states of disease. Generally, states of disease are valued less than states of health, though death may not be considered the worst outcome of a stroke. In a recently published survey of Ontario neurologists, 70% of respondents agreed with the statement that a stroke affecting the left middle cerebral artery territory — which would leave a patient unable to move the right side, unable to speak, unable to understand language, and potentially unable to swallow or self-toilet — was a “fate worse than death.”<sup>745</sup> Such a conclusion is significant for several reasons. First, it supports the notion that physicians are to some degree familiar and comfortable with the ethical evaluation of patients’ post-stroke outcomes. Second, it suggests that many physicians consider a life of disability to be worse than death, an evaluation that conflicts with traditional Judeo-Christian values, in which life is prized above all else.<sup>746</sup> Third, it points to the fact that a significant difference of opinion exists among the physicians who completed this survey. Opinion was decidedly split on this issue.

When respondents were asked about their acute stroke decision-making in a different manner, 37% of respondents identified a large left middle cerebral artery stroke (a severe neurological injury) as a factor that would make them less likely to offer tPA to a patient.<sup>747</sup> Similarly, 30% agreed that in cases where they expected the patient to have a poor outcome — for example, that the patient would need to reside in an

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<sup>744</sup> Ebrahim, *Stroke Epidemiology*, 166.

<sup>745</sup> Shamy, “Complexities,” 1130.

<sup>746</sup> Timmons, *Disputed Moral Issues*, 13.

<sup>747</sup> Shamy, “Complexities,” 1132.

assisted living facility after the stroke — they would be less likely to offer treatment. These two findings support the notion that some physicians are less likely to offer treatment to patients who they feel are likely to be severely affected by their stroke, and are therefore potentially less likely to experience benefit from tPA. Again, the fact that only one in three neurologists would be less likely to give tPA in these circumstances suggests the existence of variation around these types of evaluations. These results also suggest that physicians' prognostications — their expectations of outcome — influence the ways they make treatment decisions. That this phenomenon of evaluation occurs in stroke is particularly interesting given how uncertain the prognostication process can be, especially within the first few hours.<sup>748,749</sup>

### *Evaluating Pre-Stroke States*

The evaluation of benefit from intervention with tPA takes as its reference point the patient's pre-stroke state. For example, if a patient's pre-stroke state is so poorly valued that it is unlikely to be significantly worsened by the unmitigated effects of the stroke, then tPA will be seen to have limited potential benefit. Pre-stroke states are therefore subject to evaluation, both intrinsically, and in relation to expected outcomes. My discussion will focus on two complex issues — age and dementia — as representative of the ways that medical, ethical and epistemic factors are interwoven in acute stroke decision-making. Moreover, in the process of performing ethical evaluations, clinicians' decisions are liable to be influenced by implicit or unconscious biases, such as those acquired from within medicine's "hidden

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<sup>748</sup> Crozier, "Enjeux éthiques," 526.

<sup>749</sup> In a currently ongoing survey of neurologists in Canada and the United States, we further explored the role of physician values in decision-making. Preliminary analysis of the first 79 responses demonstrates that 55% of neurologists surveyed would consider a left middle cerebral artery stroke to be a "fate worse than death." When asked to provide the basis for their response to this question, our respondents overwhelmingly cited their "clinical experience" (70%) rather than, say, the medical literature. Therefore, there is early evidence to support the argument that a consistent majority of neurologists would evaluate a severe left middle cerebral artery stroke more poorly than death. Moreover, I contend that the fact that this opinion is the product of clinical experience supports the conclusion that ethical evaluation informed by everyday experiences is an important contributor to acute stroke decision-making.

curriculum.”<sup>750</sup>

As in the evaluation of post-stroke states, the process by which clinicians attempt to establish patients’ pre-stroke states is complex and uncertain. Stroke patients arriving in the emergency department are often unable to recount their own histories, and are unable to provide an accurate description of their daily lives. Physicians must become adept at interpreting clues, and extrapolating from these clues to develop a sense of the patient’s pre-stroke state. As a consequence, physicians may (consciously or unconsciously) fill in the gaps in their knowledge based on beliefs associated with patients’ social categories.<sup>751</sup> Uncertainty creates an opportunity for physicians’ own values to impact the ways in which they assess their patients’ states. For example, physicians may favor those patients with whom they feel some form of kinship or association, at the expense of patients who are different.<sup>752</sup>

Moreover, significant uncertainty exists surrounding how physicians should adapt general practices — such as the administration of tPA to patients with stroke — to the treatment of members of particular demographic groups. If the results of clinical trials were to suggest that patients over a certain age would be less likely to experience benefit from tPA, is that a sufficient reason to withhold treatment? To what degree can (and should) statistical averages be applied to direct the treatment of individual patients?<sup>753</sup> While it goes beyond the scope of this thesis to provide a full review of the literature on the treatment of stroke in the elderly, a brief summary suggests that older patients (usually defined as greater than age 75 or 80), appear to have higher rates of disability and mortality after stroke.<sup>754</sup> However, they also appear less likely to receive treatment with tPA.<sup>755,756,757,758,759</sup> In the 2009-2010 survey of Ontario neurologists, 29% of

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<sup>750</sup> Hafferty, “Hidden Curriculum,” 861.

<sup>751</sup> Diana J. Burgess, Steven S. Fu, Michelle van Ryn, “Why Do Providers Contribute to Disparities and What Can be Done About It?” *Journal of General Internal Medicine* 19 (2004): 1154-1159.

<sup>752</sup> Burgess, “Why Do Providers,” 1156.

<sup>753</sup> Caplan, “Evidence-based medicine,” 571.

<sup>754</sup> Gustavo Saposnik, Sandra E. Black, Antoine Hakim, Julie Fang, Jack V. Tu, Moira K. Kapral, “Age Disparities in Stroke Quality of Care and Delivery of Health Services,” *Stroke* 40 (2009): 3328-3335.

<sup>755</sup> Joseph Kwan, Peter Hand, Peter Sandercock, “A Systematic Review of Barriers to Delivery of Thrombolysis for Acute Stroke,” *Age and Ageing* 33 (2004): 116-121.

respondents said that they would be less likely to administer tPA to a patient over the age of 80, simply on the basis of age. In our ongoing international survey, 58% of neurologists endorse patient age as a factor that might influence their use of tPA.<sup>760</sup>

Physicians' acute stroke decisions also seem to be impacted by the presence of concomitant dementia. Dementia refers to a group of conditions common in the elderly in which patients suffer the gradual and inexorable loss of cognitive functions.<sup>761</sup> Alzheimer's Disease is the best-known and most common cause of dementia, though many other forms of dementia exist.<sup>762</sup> Again, questions of uncertainty overlap with ethical evaluation. It is very likely that patients with dementia have higher rates of disability after stroke than patients without dementia,<sup>763</sup> but it is not clear whether tPA is any more or less effective in this group of patients.<sup>764</sup> When Ontario neurologists were asked about factors that might decrease their likelihood of administering tPA to patients with stroke, 79% agreed that dementia would be one such factor. When presented with clinical vignettes depicting a patient with a left middle cerebral artery territory stroke of a standardized severity, 100% of respondents would have administered tPA to a man over age 80, 64% would have administered tPA to a 64-year-old man with mild dementia, and only 37% would have administered tPA to a 77-year-old woman from a nursing home with advanced dementia.<sup>765</sup>

Responses like these suggest that neurologists consider patients with dementia to be less likely to benefit from tPA, although such reasoning is ethically and medically complicated. These patterns of

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<sup>756</sup> Hills, "Eligible Thrombolysis Candidates," S210.

<sup>757</sup> C. Schwark, P.D. Schellinger, "Is Old Age Really a Reason to Withhold Thrombolytic Therapy?" *Journal of Neurology, Neurosurgery and Psychiatry* 77 (2006): 289.

<sup>758</sup> J. Claude Hemphill, Patrick Lyden, "Stroke Thrombolysis in the Elderly: Risk or Benefit?" *Neurology* 65 (2005): 1690-1691.

<sup>759</sup> L.P. Kammersgaard, H.S. Jorgensen, J. Reith, H. Nakayama, P.M. Pedersen, T.S. Olsen, "Short- and Long-Term Prognosis for Very Old Stroke Patients. The Copenhagen Stroke Study," *Age and Ageing* 33 (2004): 149-154.

<sup>760</sup> Shamy, "Acute Stroke Decision-Making," unpublished data.

<sup>761</sup> Thomas D. Bird, Bruce L. Miller, "Alzheimer's Disease and Other Dementias," in Stephen L. Hauser, ed. *Neurology in Clinical Medicine* (New York: McGraw Hill, 2006), 273.

<sup>762</sup> Bird, "Alzheimer's Disease," 275.

<sup>763</sup> D.F. Cechetto, V. Hachinski, S.N. Whitehead, "Vascular Risk Factors and Alzheimer's disease," *Experimental Reviews in Neurotherapeutics* 8 (2008): 743-750.

<sup>764</sup> Gustavo Saposnik, Moira Kapral, Robert Coté, "Is Pre-Existing Dementia an Independent Predictor of Outcome after Stroke? A Propensity Score-Matched Analysis," *Journal of Neurology* 259 (2012): 2366-2375.

<sup>765</sup> Shamy, "Complexities," 1131.

decision-making — tendencies against administering tPA treatment to patients with severe deficits, of advanced age, or with concomitant dementia — may reflect a process of deliberate ethical evaluation involving consideration of patients’ pre- and post-stroke states. Physicians will often be open about the fact that they are unwilling to offer risky and costly interventions to patients with dementia. The fact that neurologists have provided such direct responses to straightforward questions about their likelihood of using tPA in patients with dementia suggests that they are aware of performing these evaluations, and that they consider them sufficiently justified to not feel the need to hide them.

However, physicians’ ethical evaluations of pre-stroke life in patients with dementia, or with other conditions, may also reflect unconscious biases. Within the culture of medicine, the “hidden curriculum” can lead to the dehumanization of patients, especially those who are old and infirm.<sup>766</sup> In the semi-biographical novel *The House of God*, psychiatrist Stephen Joseph Bergman (under the pseudonym Samuel Shem) recounts how medical trainees in the United States in the 1970s were indoctrinated into a culture that spoke of old and demented patients as “GOMERs” — patients who should “Get Out of My Emergency Room.”<sup>767</sup> In the appendix to the novel, Shem offers the definition of a GOMER, as he came to understand it: “a human being who has lost — often through age — what goes into being a human being.”<sup>768</sup> These pejorative views can be interpreted as evidence of physicians’ evaluations of patients’ states acquired within medicine’s culture. The reasons for which clinicians make treatment decisions are liable to be complex, and many reasons may even go unnoticed.

When physicians perform ethical evaluations of their patients’ pre-stroke states, these evaluations are potentially produced by a combination of influences: cultural attitudes, intra-medical attitudes, personal values, medical knowledge, and the evaluation of that knowledge. While performing an interview for a podcast published by the American Academy of Neurology in September 2013, neurologist Brett Kissella of

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<sup>766</sup> Hafferty, “Hidden Curriculum,” 861.

<sup>767</sup> Samuel Shem, *The House of God* (New York: Random House, 1978), 29.

<sup>768</sup> Shem, *House of God*, 385.

the University of Cincinnati alludes to the way these various factors may interact. He asks his audience:

“Have you ever evaluated a stroke patient acutely, to make decisions about whether they would get tPA? I hope so, ‘cause that’s what we neurologists do. It’s part of most neurologists’ daily practice. If yes, have you ever seen such a patient where you thought that they met inclusion criteria and didn’t have any contraindications to tPA, but where you just had that feeling in your gut that it wouldn’t be a good idea to treat them? Maybe you were trying to find a reason to exclude them? If you just said or thought no, I think you’re lying, or you haven’t seen enough stroke patients, or maybe you’ve just had good luck. But I know I’m often having this kind of internal debate in the ER at 2 am.”<sup>769</sup>

Dr. Kissella’s commentary begins with the notion that stroke patients are “evaluated,” echoing the focus of this chapter. He identifies acute stroke decision-making as a central element of the neurologist’s identity: “that’s what we neurologists do.” He suggests that this common process includes “internal debate,” which by definition implies that acute stroke decision-making is complex rather than straightforward. In fact, Kissella suggests that physicians who deny this complexity are lying. It would seem that Kissella’s “debate” centres around a conflict between unconscious influences — what he terms “that feeling in your gut” — and “evidence-based” inclusion criteria and contraindications. His recognition that physicians bring to the acute stroke decision-making process a “feeling” from the gut supports the argument of this chapter, namely that clinicians’ decisions are influenced by processes of ethical evaluation that may reflect unconscious biases. Kissella states that he is often “trying to find a reason” to exclude patients from receiving treatment with tPA. In these circumstances, it would appear that Kissella is aware of wanting to not administer tPA to a patient, though he may be unaware of the reasons for this desire. The suggestion that implicit evaluations may influence physicians’ considerations of exclusion criteria reflects the results of a 2006 study, which suggested that neurologists in California might be more likely to grade strokes as too mild to treat, or too late to treat, when the patients were older or members of visible minorities.<sup>770</sup> The recognized exclusion criteria for tPA, developed as part of the original NINDS trial, therefore become instruments of

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<sup>769</sup> Brett Kissella, “The Complexities of Acute Stroke Decision-Making,” *Neurology Podcast* published online September 24, 2013 at [http://www.aan.com/rss/index.cfm/getfile/AAN\\_2650.mp3](http://www.aan.com/rss/index.cfm/getfile/AAN_2650.mp3), (accessed March 25, 2014).

<sup>770</sup> Hills, “Eligible Thromblysis Candidates,” S215.

unconscious ethical evaluation in acute stroke decision-making.

At Foothills Medical Centre of the University of Calgary, stroke neurologists frequently speak of a 90 year old woman who suffered a stroke and who was treated with tPA because she had been baking bread at the time of her stroke.<sup>771</sup> When the elderly lady arrived in the emergency department, she reportedly demonstrated the signs and symptoms of a left middle cerebral artery territory stroke, in that she could not move the right side of her body and she could not talk. Therefore, the clinicians involved could not establish with certainty when her symptoms had started, and they could not determine her baseline level of functioning. However, because the paramedics had found bread baking in her oven, and because the bread had not yet burned, the treating neurologist decided that her symptoms must not have been greater than three hours' old, and that her pre-stroke state was sufficiently functional to benefit from treatment with tPA. In fact, the example of baking bread has come to be used as a functional standard in tPA administration, at least in Calgary: I have heard several neurologists declare that if they were 90 years old and suffered a stroke, they would want to be left to die *unless they were able to bake bread*. Statements like this one reflect the impact of physicians' ethical evaluations of pre-stroke states in acute stroke decision-making. In the minds of those neurologists, being able to bake bread at age 90 is a marker of a life worth living. As a consequence, a patient who can bake bread is deemed eligible for benefit from tPA use, while a patient who cannot bake bread is better off dead than alive. The ability to bake bread has come to be used as a standard against which future ethical evaluations may be judged. This anecdote supports the notion that ethical evaluation occurs in acute stroke decision-making, and that this process of evaluation is subjective and based on individual clinical experiences.

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<sup>771</sup> Personal communication, Foothills Medical Centre, Calgary, Alberta, 2012.

### Conclusions

The central argument of this chapter — that acute stroke decision-making involves a process of ethical evaluation — may at first appear banal. Is it not obvious that medical decision-making should involve ethical reasoning? Physicians openly speak about making decisions that will benefit their patients.<sup>772</sup> Principlist ethicists highlight “beneficence” and “non-maleficence” as two of the core norms of modern medical practice.<sup>773</sup> And yet, little work has sought to examine how ethical reasoning features in everyday medical decisions, and how physician decision-making may vary in light of such ethical reasoning. I have sought to show that ethical evaluation is a core component of acute stroke decision-making. I have argued that the justification of decisions on the basis of their outcomes means that medical outcomes are also ethical outcomes. In that physicians are required to evaluate the nature of possible outcomes in order to make assessments about the benefits of tPA, they are performing a process of ethical evaluation in acute stroke decision-making. Moreover, I have suggested that the consideration of patients’ pre-stroke and post-stroke states is a subjective process that reflects the influence of uncertainty and biases.

To recall the phrasing offered by Fleck, the process of ethical evaluation in acute stroke decision-making is interwoven with epistemic evaluation.<sup>774</sup> Physicians perform ethical evaluations of their patients’ potential outcomes. But first, these potential outcomes are conceived in relation to a physician’s knowledge of the medical aspects of that scenario. However, that knowledge may be inaccurate, may contain uncertainty, or may underdetermine the relevant scientific technicalities.<sup>775</sup> Therefore, the outcomes being evaluated ethically are the product of an uncertain epistemology. As bioethicist Nancy Rhoden (1952-1989) once wrote, “when medical uncertainty leads to moral uncertainty, it seems preferable, albeit harder, to confront the dual ambiguities than to bury them under either statistical criteria or unrelenting moral

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<sup>772</sup> M. Reiter, Y. Teuschl, L. Seyfang, M. Brainin for the Austrian Stroke Unit Registry Collaborators, “Diabetes and Thrombolysis for Acute Stroke: A Clear Benefit for Diabetics,” *European Journal of Neurology* 21 (2014): 5-10.

<sup>773</sup> Beauchamp, *Principles*, 12.

<sup>774</sup> Fleck, *Genesis*, 29.

<sup>775</sup> Mol, *Body Multiple*, 171.

certitude.”<sup>776</sup> In that this thesis has a primarily descriptive focus, its goal is to reveal the “dual ambiguities” of ethical and epistemic evaluation in acute stroke decision-making.

The process of ethical evaluation in acute stroke decision-making overlaps with questions of economic evaluation. It is now commonplace that novel medical interventions are assessed in terms of their benefit to patients (generally measured on the basis of some quantifiable scale) and on their cost-effectiveness, meaning the incremental cost of that added benefit.<sup>777</sup> Interventions that produce benefit may therefore not be taken up or approved if they are felt to be too costly for the expected benefit. Alternatively, highly valued resources may be rationed, requiring careful deliberation about which patients receive access. A widely-publicised case of resource rationing occurred in the early days of dialysis, when a “Life and Death Committee” was established in Seattle, Washington in the 1960s to evaluate potential candidates for the life-prolonging therapy.<sup>778</sup> The decisions of this committee consistently privileged married, white males, and have been subsequently studied as evidence of the pervasive prejudices that exist in North American culture and health care delivery.

Members of the neurological community have been quick to criticize the presence of ethical evaluation in acute stroke decision-making, though they have not denied it. In an editorial in the journal *Neurology*, neurologist and ethicist Adrienne Boissy of the Cleveland Clinic has argued that “clinicians should recognize when and why they are making value judgments rather than clinical judgments about the role of tPA in a specific stroke patient.”<sup>779</sup> With this statement, Dr. Boissy appears to be accepting that physicians can, and do, make value judgments in their tPA decision-making. However, she distinguishes between “value judgments” and “clinical judgments,” implying that they are separate and separable, recalling the way

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<sup>776</sup> Nancy K. Rhoden, “Treating Baby Doe: The Ethics of Uncertainty,” eds. Thomas L. Beauchamp, Leroy R. Walters *Contemporary Issues in Bioethics, 4th Edition* (Belmont, CA: Wadsworth Publishing Company, 1994), 426.

<sup>777</sup> Sommers, “Probabilities and Preferences,” 671.

<sup>778</sup> Jonsen, *Short History*, 110.

<sup>779</sup> Adrienne R. Boissy, “IV Tissue Plasminogen Activator in Acute Stroke: What are Neurologists Thinking?” *Neurology* 81 (2013): 1110-1111.

James Bernat distinguished between what was “*medically* (as opposed to *morally*) right.”<sup>780</sup> In this chapter, I have sought to argue directly against Boissy’s perspective: namely, that the medical and ethical aspects of a decision are inseparable because medical outcomes are ethically significant, and because they are used to justify decisions from a consequentialist perspective.

Boissy suggests that the use of value judgments in acute stroke decision-making needs to somehow be justified, in that neurologists should know “when and why they are making value judgments.”<sup>781</sup> Her distinction between clinical and value judgments implies that the latter should have no place in tPA decision-making. Dr. Boissy expects that “health care professionals are likely able to determine accurately whether the patient has any contraindications to tPA and fulfills inclusion criteria,” and that these determinations alone should guide tPA use.<sup>782</sup> Neurologists Mohit Sharma and Priyand Khandelwal of the State University of New York outline a similar criticism in a letter to the editor of the journal *Neurology*.<sup>783</sup> Sharma and Khandelwal consider neurologists’ “personal experiences and beliefs” to be “one of the many ethical and legal issues concerning the use of tPA that could eventually be detrimental to the patient’s prognosis.”<sup>784</sup> Like Boissy, Sharma and Khandelwal begin from the position that the incorporation of a physician’s values and beliefs into decision-making can only be a detriment to the care of patients.

What would acute stroke decision-making look like without ethical evaluation? Without ethical evaluation, treatment decisions about tPA use would be expected to follow universal guidelines: the same treatment would be applied to all patients, at all times, in all places. Specially, acute stroke decision-making would follow evidence-based “best practices,” derived from “best evidence.”<sup>785</sup> This prospect recalls rationalistic notions of medical decision-making, which seek to arrive at optimal standardized algorithms for

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<sup>780</sup> Bernat, *Ethical Issues*, 135.

<sup>781</sup> Boissy, “What are Neurologists Thinking?,” 1110.

<sup>782</sup> *Ibid.*, 1111.

<sup>783</sup> Mohit Sharma, Priyank Khandelwal, “The Complexities of Acute Stroke Decision-Making: A Survey of Neurologists,” *Neurology* 82 (2014): 904.

<sup>784</sup> Sharma, “The Complexities,” 904.

<sup>785</sup> Silva, “Where is the Wisdom?” 903.

physicians to follow in the management of all patients.<sup>786</sup> Acute stroke decision-making without ethical evaluation recalls the naturalistic approach to diseases, in which they are defined from a purely scientific perspective that ignores their normative dimensions.<sup>787</sup> It also recalls the notion of acute stroke as a natural kind: an entity whose properties are stable across time and space, and whose management therefore should be equally consistent.<sup>788</sup> Acute stroke decision-making without ethical evaluation would mean that a 90 year old man suffering from severe dementia would receive the same treatment for stroke as a 45 year old woman with no other medical issues. I contend that anything more individual than that — any consideration of what might be *best* for that individual patient — requires ethical evaluation.

And yet, as I have proposed in this chapter, any attempt to determine what is best is dependent upon the application of an ethical framework. Any ethical framework begins with some *a priori* determination of values, and these are necessarily subjective. As Annemarie Mol writes in the conclusion to her book *The Body Multiple*, “medicine is entwined with the good,” but the good has multiple potential definitions.<sup>789</sup> Despite the fact that modern medical epistemology has sought to “objectify the good and turn values into facts,” Mol reminds us that “the end points, the very goals of medical interventions, are essentially contested.”<sup>790</sup> In a recent essay on “Experience, Narrative and Ethical Deliberation” in medicine, philosopher Cheryl Misak of the University of Toronto argues for the irreducibility of subjective experience and judgment in medical decision-making.<sup>791</sup> Misak urges us to “describe those experiences which embody moral responses,” as doing so will allow us to access and understand our “values or norms.”<sup>792</sup> This chapter has explored the role of “values or norms” in decisions about the use of tPA in the treatment of patients with stroke. We are now positioned to draw some general conclusions about how doctors make decisions, based

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<sup>786</sup> Khatri, “Evaluation and Management,” 290.

<sup>787</sup> Ereshefsky, “Health and Disease,” 221.

<sup>788</sup> Ereshefsky, “Natural Kinds.”

<sup>789</sup> Mol, *Body Multiple*, 166.

<sup>790</sup> *Ibid.*, 175.

<sup>791</sup> Cheryl Misak, “Experience, Narrative and Ethical Deliberation,” *Ethics* 118 (2008): 614-632.

<sup>792</sup> Misak, “Experience,” 623.

on a conception of acute stroke decision-making as an historical, epistemic and ethical process.

## Conclusions

The more we adhere to a narrow, laboratory-science image of medicine as the defining basis of the profession, the less will be known about what it actually means to be a physician in the modern world.

— Jack D. Pressman, *Last Resort* (1998)

### *Acute Stroke Decision-Making*

How do doctors make decisions? And more specifically, how do doctors make decisions about the use of the drug tPA in the treatment of patients with acute stroke? In this thesis, I have sought to analyze acute stroke decision-making from the perspective of the history and philosophy of science, with the aim of better understanding the decision-making process of physicians in the late 20<sup>th</sup> and early 21<sup>st</sup> centuries. I chose to focus on the treatment of patients with acute stroke because stroke is a common and serious disease. Moreover, the decisions that must be made in the treatment of acute stroke are complex and time-sensitive. Finally, in my position as a neurologist who treats patients with stroke, I may be particularly well positioned to develop insights into acute stroke decision-making.

In the introduction to this thesis, I proposed that medical decision-making should be studied from a contextual approach that recognizes the role of historical, epistemic and ethical factors in physicians' decisions. This approach to medical decision-making generally, and to acute stroke decision-making specifically, diverges from traditional conceptualizations of physician decision-making as a purely rational and deliberative process.<sup>793,794,795,796</sup> Rather, a contextual approach is grounded in scholarship in the history and philosophy of science — such as that of Thomas Kuhn, Ludwik Fleck, and Charles Rosenberg, among others — which has demonstrated how the decision-making of scientists and physicians reflects the values

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<sup>793</sup> Denig, “Therapeutic Decision Making,” 9.

<sup>794</sup> Niknam, “How Do Physicians Make a Decision?” 696.

<sup>795</sup> Mushlin, *Decision-Making in Medicine*, 414.

<sup>796</sup> Goyal, “Acute Stroke,” 256.

and ideas of their time and place.<sup>797,798</sup> A contextual approach also draws from recent scholarship in psychology, economics and sociology that suggests how the decisions people make are influenced by factors of which they may not be aware, such as unconscious cognitive mechanisms and social biases.<sup>799,800</sup> The notion of context elaborated in the introduction was therefore meant to be sufficiently broad to incorporate these historical, philosophical, social and psychological aspects of decision-making.

In Chapter 1, I sought to analyze how contemporary neurologists conceive of the disease they call “acute stroke.” The term “acute stroke” was introduced in 1960 as a way of referencing the possibility that stroke could be reversed, if treatment could be initiated quickly enough.<sup>801,802</sup> This novel conceptualization marked a shift from earlier historical definitions of stroke that had elaborated a pathological understanding of the disease process but had recognized no possibility for successful treatment.<sup>803</sup> I proposed that a specific meaning to the term “acute stroke” — as a stroke that was treatable through the use of the drug tPA — arose after 1995, in reference to the results of the NINDS clinical trial that established the efficacy of tPA as a treatment for stroke.<sup>804</sup> A bibliometric analysis was used to suggest that the year 1995 marked a significant change in the frequency of use of the term “acute stroke,” and examples from the medical literature were analyzed to demonstrate the development of a new vocabulary surrounding decision-making in “acute stroke.”<sup>805</sup>

I then sought to show how this contemporary meaning of the “acute stroke” arose in light of a set of intertwining preconditions, to borrow the imagery of Ludwik Fleck.<sup>806</sup> In his study of the meaning of syphilis, Fleck had proposed that diseases should be understood as ideas resulting from a particular

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<sup>797</sup> Fleck, *Genesis*, 23.

<sup>798</sup> Kuhn, *Structure*, 10.

<sup>799</sup> Kahnemann, *Thinking*, 20.

<sup>800</sup> Greenwald, “Implicit Social Cognition,” 4.

<sup>801</sup> Sussman, “Thrombolysis” (1958), 1705.

<sup>802</sup> Bull, “Cerebral Angiography,” 564.

<sup>803</sup> Daneski, “How Far,” 370.

<sup>804</sup> NINDS rtPA Study Group, “Tissue Plasminogen Activator,” 1581.

<sup>805</sup> Weiner, *House Officer Series, Neurology*, 6<sup>th</sup> Edition, 90.

<sup>806</sup> Fleck, *Genesis*, 17.

intellectual tradition, what he called “the development and confluence of several lines of collective thought.”<sup>807</sup> From this perspective, I traced the development of the “acute stroke” in relation to six preconditions: the description of the brain’s vascular anatomy, the localizability of pathology, the differentiation of ischemia from hemorrhage, the clinical use of CT scans, the production of chemical thrombolytics, and the development of the physiological concept of the penumbra. The case of the acute stroke supports the view that diseases are best understood as historical and social constructs,<sup>808</sup> rather than as natural kinds, which is the predominant way they are discussed in the medical literature.<sup>809</sup>

On the basis of a deeper understanding of the “acute stroke” in its historical context, analysis of the process of acute stroke decision-making could begin. In Chapter 2, I proposed that deciding about the use of tPA in the treatment of patients with acute stroke involves a process of epistemic evaluation, in that physicians are required to evaluate their knowledge in order to apply it to decision-making in any particular case of stroke. This view was contrasted to the epistemic theory of evidence-based medicine, in which the results of randomized controlled trials are considered “best evidence,” are seated atop a “hierarchy of evidence,” and are considered clear and direct guides for clinical decision-making.<sup>810</sup> In short, I argued that acute stroke decision-making requires a complex process of epistemic reasoning in relation to a thought style, and I termed this process epistemic evaluation.

Specifically, I argued that the contemporary meaning of the acute stroke, developed in Chapter 1, allows for the elaboration of six clinical propositions that are subject to epistemic evaluation in acute stroke decision-making. These propositions are: that the acute stroke exists; that the acute stroke is treatable; that the acute stroke can be diagnosed *in medias res*; that physicians can determine which patients should be treated with tPA; and that physicians can arrive at prognoses in cases of acute stroke. I then proposed that

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<sup>807</sup> Fleck, *Genesis*, 98.

<sup>808</sup> Hacking, *Social Construction*, 21.

<sup>809</sup> Brazis, *Localization*, 523.

<sup>810</sup> Howick, *Philosophy*, 4.

differential evaluation of these propositions — meaning, that not all physicians consider them to be epistemically justified — can be related to differences in what Fleck has called the thought style. A thought style refers to the background knowledge and cultural practices that are shared by a group of scientists in relation to the historical development of their field of thought.<sup>811</sup> A core component of the thought style is a historical body of knowledge, and I argued that variable recognition of acute stroke’s preconditions — of those concepts that serve as the foundation for the modern meaning of the “acute stroke” — in the thought styles of neurologists and emergency physicians accounts for their differential epistemic evaluation of acute stroke’s clinical propositions, namely that tPA is an effective treatment for acute stroke.

The argument of Chapter 2 builds from the scholarship of Polish biologist and philosopher Ludwik Fleck, who has proposed that medical concepts are “determined by their ‘ancestors.’”<sup>812</sup> Fleck suggests that epistemic insecurity arises when scientists are unaware of the historical origins of their ideas, and that this insecurity might be relieved by a deeper historical understanding of contemporary ideas.<sup>813</sup> Schisms within the medical community about acute stroke treatment — specifically, about whether the use of tPA is justified on the basis of medical knowledge — indicate the presence of deep epistemic insecurities, which remain unaddressed by ahistorical analyses of that knowledge.<sup>814,815</sup> Because the proponents of evidence-based medicine argue that the results of clinical trials should be sufficiently certain and universal to directly inform treatment decisions,<sup>816</sup> 21<sup>st</sup> century physicians often fail to recognize how they evaluate their knowledge, and that they to do so in relation to lines of thought that can be traced back centuries. The case of epistemic evaluation in acute stroke supports the importance of history as a key factor in the contextualization and evaluation of modern medical knowledge.

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<sup>811</sup> Fleck, *Genesis*, 39.

<sup>812</sup> *Ibid.*, 98.

<sup>813</sup> *Ibid.*, 98.

<sup>814</sup> Robinson, “Should Physicians Give,” 148.

<sup>815</sup> Hoffman, “Should Physicians Give,” 149.

<sup>816</sup> Montgomery, *How Doctors Think*, 34.

In Chapter 3, I argued that physicians' decision-making about the use of tPA in the treatment of patients with acute stroke also involves a process of ethical evaluation, in which physicians make judgments about the potential risks and benefits of therapy. I proposed that physician decision-making is consequentialist in orientation, in that physicians make acute stroke decisions based on their expected consequences, and then evaluate their decisions on the basis of those consequences. I argued that the considerations of outcome and benefit central to acute stroke decision-making necessitate considerations of the good.<sup>817</sup> As a consequence, when physicians make decisions about acute stroke therapy on the basis of evaluations of benefit, they are producing an ethical evaluation. I sought to identify those factors that are subject to this process of ethical evaluation, namely patients' likely outcomes, and elements of their pre-stroke states such as age and concomitant dementia. These evaluations appear to be influenced by physicians' personal values, as well as by the unconscious biases originating from psychological mechanisms, North American culture, and the "hidden curriculum" within medicine.<sup>818</sup>

Physicians' decision-making in the treatment of acute stroke involves consideration of what is valuable, to doctors, patients and to society. As part of their decisions about tPA use, physicians are engaged with questions like: is it better to live with disability, or to die?<sup>819</sup> Dr. Samuel Smith, a general practitioner from Cheshire in the United Kingdom, has written that deciding about what is valuable in medicine requires consideration of the "existential, moral, epistemological, and metaphysical."<sup>820</sup> He elaborates that "existentially, value contributes meaning to life. Morally, value is judged in the light of what is good or better, and charges that we address the tension between the individual and the social good. Epistemologically, value is related to knowledge and truthfulness, which in turn seems to demand a quest

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<sup>817</sup> Beauchamp, "Beneficence."

<sup>818</sup> Montgomery, *How Doctors Think*, 4.

<sup>819</sup> Ebrahim, *Stroke Epidemiology*, 166.

<sup>820</sup> Smith, "Postmodernity," 27.

for metaphysical foundation.”<sup>821</sup> In that acute stroke decision-making requires consideration of what is valuable — life, death, health, disease, ability, disability — physicians are engaged with ethical, epistemic and ontologic questions. The goal of this thesis has been to begin to describe the complex interactions of the ethical, epistemic, ontologic and historical aspects of acute stroke decision-making.

Specifically, I have sought to characterize acute stroke decision-making using techniques from the history and philosophy of science, with a particular focus on historical, epistemic and ethical analysis. The history and philosophy of science reflects an interdisciplinary approach to understanding how science is conducted today, and how science was conducted in the past. At stake are questions about the existence and features of science, medicine, health and disease:<sup>822</sup> questions about the sources, qualities, and justification of medical knowledge;<sup>823</sup> and questions about the moral, legal, and social implications of discovery and development.<sup>824</sup> I have sought to show how ontologic, epistemic and ethical questions can be asked about acute stroke decision-making, and that their consideration can lead to a better understanding of how doctors make decisions. The argumentation in this thesis has reflected the influences of prominent historians and philosophers of science and medicine— among them Ludwik Fleck, Thomas Kuhn, Nelson Goodman, and Jack Pressman — whose work has allowed me to analyze acute stroke decision-making in relation to its place in “the history of thought.”<sup>825</sup>

While a perspective based in the history and philosophy of science has, I believe, revealed a great deal about acute stroke decision-making, a full elaboration of the context in which these decisions are made would require analysis from anthropological, psychological, sociological, and economic perspectives as well.<sup>826,827,828,829,830</sup> It goes beyond the scope of this thesis to analyze even so small a topic as acute stroke

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<sup>821</sup> Smith, “Postmodernity,” 27.

<sup>822</sup> Ereshefsky, “Health and Disease,” 221.

<sup>823</sup> Upshur, “Seven Characteristics,” 97.

<sup>824</sup> Pressman, *Last Resort*, 17.

<sup>825</sup> Fleck, *Genesis*, 97.

<sup>826</sup> Mol, *Body Multiple*, 171.

<sup>827</sup> Dhand, “How Experienced Community Neurologists,” 1460.

decision-making from these varied points of view, and I do not pretend to be an expert in their methods. However, the opportunities for further study and collaboration are large. For example, an ethnographic study of physician decision-making in the treatment of acute stroke might reveal even more fruitful insights into this process. Modeled after the work of Northwestern University professor Kathryn Montgomery, embedding an external observer in a stroke team might further develop the description of acute stroke decision-making provided here.<sup>831</sup> A psychological study seeking to elaborate the influence of patient race, sex and age on tPA use could further characterize the role of conscious and unconscious biases in acute stroke decision-making. A more detailed analysis of the ways that various imaging modalities are used for diagnosis and prognosis in acute stroke decision-making could further develop our understanding of the epistemic, ethical, technological and cultural dimensions of physician decision-making.

#### *Implications for Physician Decision-Making*

In this thesis, acute stroke decision-making has been used as a case study from which to draw conclusions about the way doctors make decisions. However, it must first be established whether acute stroke decision-making can be considered representative of physician decision-making generally. Stated in another way, is there reason to believe that the processes of acute stroke decision-making are different from the processes involved in other medical scenarios? Because the doctors who treat patients with acute stroke also treat patients with other conditions, it is unlikely that the structure of decision-making — the involvement of epistemic and ethical evaluation, reflecting a historical context — would suddenly change because the disease being diagnosed has changed. In that the doctors who make acute stroke decisions hail from several disciplines — neurology, emergency medicine, internal medicine, geriatrics — they can be

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<sup>828</sup> McKinlay, “Non-Medical Influences,” 769.

<sup>829</sup> McDermott, “Medical Decision Making,” 665.

<sup>830</sup> Sommers, “Probabilities and Preferences,” 669.

<sup>831</sup> Montgomery, *How Doctors Think*, 3.

seen as a diverse sample of physicians with different specialty training. Therefore, the processes of acute stroke decision-making elaborated in this thesis are unlikely to reflect the ways of an isolated specialty group. Because medical training is relatively standardized in its structure and content — at least across North America, in the period covered in this thesis — it can be assumed that students are unlikely to study and practice completely distinct forms of decision-making. Finally, in that physicians spend much of their training rotating across disciplinary boundaries, they necessarily come into contact with doctors from different specialties. This inter-specialty contact would render it unlikely that physicians in one community could develop and maintain a unique approach to decision-making in stroke treatment.

In light of these considerations, I believe that acute stroke decision-making can be considered a representative example of physician decision-making more generally, and that certain conclusions can therefore be drawn as a consequence. What does acute stroke decision-making say about physician decision-making? First and foremost, it suggests that physician decision-making is *historical*. The decisions that physicians face are contingent on their historical context, and the options between which they must choose are also historically determined. The way that decision points are conceived is dependent upon the technological and theoretical realities of one's present day. The phenomenon of acute stroke decision-making as it exists in 2014 did not exist in 1994. Asking a neurologist in 1994 about why she did or did not use tPA would have had little meaning for the physician or the patient.

Moreover, the standards by which treatments are ethically and epistemically evaluated are also historically-determined. Belief in the efficacy of a given therapy depends upon broader concepts of health and disease, good and bad, risk and benefit, which will all be historically variable. As Jack Pressman writes in his history of psychosurgery, “the factors that shape the evaluation of medical therapies are rooted in specific moments and hence are subject to change.”<sup>832</sup> For example, Pressman argues that psychosurgery was felt to be beneficial to patients in the United States in the 1940s and 1950s specifically because of the

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<sup>832</sup> Pressman, *Last Resort*, 8.

state of medical knowledge in that era, because of beliefs about what was best for patients, because of political and social concerns, and because of alternate treatment options (or lack thereof). Medicine speaks of the efficacy of treatments as if they were “immediate and yet transcendent, equally visible across the decades,”<sup>833</sup> though the work of Pressman, Rosenberg and Duffin among others, points out how “clinical assessment is a contingent historical product.”<sup>834</sup>

As per Fleck, the ideas and systems that contextualize physician decisions are themselves historical, in that they develop in relation to past events and concepts. Fleck writes that “theories of the elements and of chemical composition, the law of conservation of matter, the principle of a spherical earth as well as the heliocentric system each underwent a historical development from somewhat hazy proto-ideas.”<sup>835</sup> In short, those principles that we currently take for unshakeable fact have a history of their own: there was a time when the sun revolved around a flat Earth. Moreover, there may be a time in the future when those claims we take to be fact are no longer considered truth. Pressman highlights the “transitory nature of medical convictions,” whose contingencies are laid bare by the “shifting sands of scientific knowledge.”<sup>836</sup> The context within which 21<sup>st</sup> century physicians make treatment decisions is reflective of a mutable, historical moment.

The example of acute stroke decision-making also suggests how physician decision-making is *epistemic*. Physician decision-making requires the application of medical knowledge, but it also requires the selection and evaluation of that knowledge to inform a given decision. In this way, medical decision-making means having epistemic principles, virtues or values upon which to base the evaluation of knowledge; the prioritization of the results of randomized controlled trials in evidence-based medicine is one such epistemic principle in modern medicine. However, there is not a singular way of evaluating medical knowledge, and

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<sup>833</sup> Pressman, *Last Resort*, 5.

<sup>834</sup> *Ibid.*, 8.

<sup>835</sup> Fleck, *Genesis*, 24.

<sup>836</sup> Pressman, *Last Resort*, 5.

tensions may arise as principles conflict.<sup>837</sup> Physicians may be unaware of the fact that they perform epistemic evaluation in their decision-making, let alone of how they do so. If the case of acute stroke decision-making serves as an accurate guide, a key component of epistemic evaluation in physician decision-making is the background knowledge that individual physicians bring to their decisions.

In addition to revealing the epistemic nature of decision-making, acute stroke decision-making suggests that physician decision-making is *ethical* as well. The argument that medical outcomes are ethical outcomes too — it matters whether patients live or die — does not apply exclusively to acute stroke decision-making. Any medical decision has consequences, and those consequences will be ethically relevant. Moreover, even simple decisions such as prescribing antibiotics may have wide-ranging consequences, in that patients, their families, and society as a whole may be impacted by the medical, ethical, and economic implications. In that physicians generally desire to do good and avoid harm — as per their Hippocratic duties — they are required to have some concept of what good is and what harm is, and therefore they must be engaged in ethical reasoning.

However, physician decision-making is *psychologically complex*. Not all of medical decision-making can be attributed to reasoning and deliberation. Kahnemann and Tversky's research points to the importance of heuristic mechanisms in the decision-making of physicians.<sup>838</sup> Moreover, physicians' decisions reflect the biases commonly held within their communities.<sup>839,840</sup> Specifically, as members of medicine's community, physicians will have learned the lessons of a "hidden curriculum" that devalues patients when they are at their most vulnerable.<sup>841</sup> Moreover, the concept of the hidden curriculum provides independent support for the idea that physicians' knowledge of how to do decision-making is tacitly acquired.<sup>842</sup> Tacit knowledge refers to knowledge that is largely transferred through practice, for example learning how to

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<sup>837</sup> Howick, *Philosophy*, 10.

<sup>838</sup> Kahnemann, *Thinking*, 12.

<sup>839</sup> Green, "Implicit Bias," 1231.

<sup>840</sup> Schulman, "Effect of Race," 618.

<sup>841</sup> Hafferty, "Hidden Curriculum," 861.

<sup>842</sup> Kuhn, *Structure*, 190.

play the piano or how to conduct the neurological examination. Because the processes of decision-making reflect tacit knowledge, physicians may be unable, or at least greatly challenged, to explain how it is that they make decisions.

Physician decision-making is also *social*. The medical decision-making process begins with an interaction between two people: a doctor and a patient.<sup>843</sup> The decisions physicians make impact patients, their families, their communities, and an entire health care system. In that physicians and patients are members of racial, ethnic, or cultural groups, they import these identities into the decision-making process.<sup>844</sup> When physicians become members of medical groups through the process of training and specialization, they take on the approach, beliefs and interests of that group.<sup>845</sup> More explicitly, physicians are members of a scientific community, sharing a particular way of looking at the world: whether it is termed a paradigm or a thought style, physicians' decisions will be shaped by the principles and practices of their social groupings.

Finally, acute stroke decision-making suggests the ways that physician decision-making is *scientific*. Characterization of the subjectivity, contingency and uncertainty of medical decision-making means rejecting the view that medicine is an “old-fashioned, positivist, Newtonian” science, but it does not mean rejecting the notion that medical decision-making is itself scientific.<sup>846</sup> Physicians are engaged in solving problems,<sup>847</sup> in reasoning between the general and the particular,<sup>848</sup> and in explaining the narratives of health and disease.<sup>849</sup> They engage with complicated concepts based in biology, chemistry, and physics.<sup>850</sup>

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<sup>843</sup> Groopman, *How Doctors Think*, 3.

<sup>844</sup> Christakis, “Physician Characteristics,” 367.

<sup>845</sup> Kuhn, *Structure*, 37.

<sup>846</sup> Montgomery, *How Doctors Think*, 6.

<sup>847</sup> Kuhn, *Structure*, 24.

<sup>848</sup> Montgomery, *How Doctors Think*, 86.

<sup>849</sup> Carol Cleland, “Prediction and Explanation in Historical Natural Science,” *British Journal of the Philosophy of Science* 62 (2011): 551-582.

<sup>850</sup> Montgomery, *How Doctors Think*, 41.

They develop and test hypotheses.<sup>851</sup> But physicians' decisions do not need to be reducible to algorithms or modelable by computers in order to be scientific.<sup>852,853</sup> Decision-making is scientific in the ways that science is now understood (by historians and philosophers of science) to be “uncertain, paradox-laden, judgment-dependent,” a “creative social enterprise” occurring in a historical context.<sup>854</sup>

If physician decision-making is all of these things — *historical, epistemic, ethical, psychological, social and scientific* — then further attempts to study it will be most successful if they follow conceptual approaches that reflect these qualities. Understanding physician decision-making will require understanding contemporary medical science, as well as understanding the genesis and development of that science.<sup>855</sup> It will require characterizing what physicians consider established facts, and why they do so.<sup>856</sup> It will require exposing the assumptions and values of a particular place and time.<sup>857</sup> It will require confronting the uncertainty and subjectivity of daily medical practice.<sup>858</sup> It will require exploring the relationships that exist between physicians and patients, and between students and teachers.<sup>859</sup> Finally, it will require studying physicians as scientists, philosophers, psychologists, economists — but most importantly, as people. Physician decision-making is a fundamentally human exercise, and serves as an important example of the ways that techniques from the humanities — and especially from the history and philosophy of science — are not just helpful but necessary to understand modern medicine.

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<sup>851</sup> Canguilhem, *Études d'histoire*, 389.

<sup>852</sup> Mushlin, *Decision-Making*, 414.

<sup>853</sup> Koerkamp, “Uncertainty,” 194.

<sup>854</sup> Montgomery, *How Doctors Think*, 4.

<sup>855</sup> Fleck, *Genesis*, 94.

<sup>856</sup> *Ibid.*, xxvii.

<sup>857</sup> Owsei Temkin, *The Double Face of Janus* (Baltimore: Johns Hopkins University Press, 1977), 39.

<sup>858</sup> Daston, *Objectivity*, 198.

<sup>859</sup> Montgomery, *How Doctors Think*, 103.

## Bibliography

### *Primary Sources*

Adams, Raymond D., Maurice Victor and Allan H. Ropper. *Principles of Neurology, 6<sup>th</sup> Edition. Companion Handbook*. New York: McGraw Hill, 1998.

Admani, A.K. "New Approach to Treatment of Recent Stroke." *British Medical Journal* 2 (1978): 1678-1679.

Armstrong, Melissa J., Irene Litvan, Anthony E. Lang, Thomas H. Bak, Kailash P. Bhatia, Barbara Borroni, Adam L. Boxer, Dennis W. Dickson, Murray Grossman, Mark Hallett, Keith A. Josephs, Andrew Kertesz, Suzee E. Lee, Bruce L. Miller, Stephen G. Reich, David E. Riley, Eduardo Tolosa, Alexander I. Tröster, Marie Vidailhet, and William J. Weiner. "Criteria for the diagnosis of corticobasal degeneration." *Neurology* 80 (2013): 496-503.

Astrup, J., B. K. Siesjö, and L. Symon. "Thresholds in cerebral ischemia – the cerebral penumbra." *Stroke* 12 (1981): 723-725.

ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators, "Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials." *Lancet* 363 (2004): 768-774.

Balami, Joyce S., Gina Hadley, Brad A. Sutherland, Hasneen Karbalai, and Alastair M. Buchan. "The exact science of stroke thrombolysis and the quiet art of patient selection." *Brain* 136 (2013): 3528-3553.

Beeson, Paul B. and Walsh McDermott, eds. *Cecil-Loeb Textbook of Medicine. 13th Edition*. Philadelphia: W. B. Saunders Co., 1971.

Bender, Morris B. Editor. *A Mount Sinai Hospital Monograph on The Approach to Diagnosis in Modern Neurology*. New York: Grune and Stratton, 1967.

Bluhmki, Erich et al. "Stroke treatment with alteplase given 3.0–4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial." *Lancet Neurology* 8 (2009): 1095-1102.

Bradley, Walter G., Robert B. Daroff, Gerard M. Fenichel, and Joseph Jankovic, eds. *Neurology in Clinical Practice*, 5<sup>th</sup> edition. Philadelphia: Butterworth Heinemann, 2008.

Brazis, Paul W., José C. Masdeu, and José Biller. *Localization in Clinical Neurology*. Philadelphia: Lippincott Williams & Wilkins, 2007.

Bull, J.W.D., John Marshall, and D.A. Shaw. "Cerebral angiography in the diagnosis of the acute stroke." *The Lancet* 275 (1960): 562-564.

Burke, James F. "Cost and Utility in the Diagnostic Evaluation of Stroke." *Continuum: Lifelong Learning in Neurology* 20 (2014): 436-440.

Burrows, George. *On Disorders of the Cerebral Circulation; and on the Connection between Affections of the Brain and Diseases of the Heart*. London: Longman, Brown, Green & Longmans, 1846.

Bury, Judson S. *Diseases of the Nervous System*. Manchester: Manchester University Press, 1912.

Buzzard, E. Farquhar and J. Godwin Greenfield. *Pathology of the Nervous System*. London: Constable & Co., 1921.

Camarata, Paul J., Roberto C. Heros, and Richard E. Latchaw. "Brain Attack: The Rationale for Treating Stroke as a Medical Emergency." *Neurosurgery* 34 (1994): 144-158.

Carter, Bob S., James D. Rabinov, Rolf Pfannl, and Lee H. Schwamm. "Case 5-2004: A 57-Year-Old Man with Slurred Speech and Left Hemiparesis." *New England Journal of Medicine* 350 (2004): 707-716.

Chaturvedi, Seemant, Bryan Bertasio and Lorraine Femino. "Emergency Physician Attitudes Toward Thrombolytic Therapy in Acute Stroke." *Journal of Stroke and Cerebrovascular Diseases* 7 (1998): 442-445

Clarke, Robert L., and Eugene E. Clifton. "The Treatment of Cerebrovascular Thromboses and Embolism with Fibrinolytic Agents." *American Journal of Cardiology* 6 (1960): 546-551.

Cooke, John. *A Treatise on Nervous Diseases. Volume 1: On Apoplexy* (1820). Birmingham, AB: Gryphon editions, 1984.

Cooke, John. *History and Method of Cure of the various species of Palsy: being the first part of the second volume of A Treatise on Nervous Diseases*. London: Longman, Hurst Rees, Orme & Brown, 1821.

Dana, Charles L. *Textbook of Nervous Diseases. Tenth Edition*. New York: William Wood & Co., 1925.

Del Zoppo, Gregory J. "Investigational Use of tPA in Acute Stroke." *Annals of Emergency Medicine* 17 (1988): 1196-1201.

Del Zoppo, Gregory J. "Acute Stroke — On The Threshold of a Therapy?" *New England Journal of Medicine* 333 (1995): 1632-1633.

Ebrahim, Shah. *Clinical Epidemiology of Stroke*. Oxford: Oxford University Press, 1990.

Ebrahim, Shah and Rowan Harwood. *Stroke: Epidemiology, Evidence and Clinical Practice, 2<sup>nd</sup> Edition*. Oxford: Oxford University Press, 1999.

Furie, Karen L., Scott E. Kasner, Robert J. Adams, Gregory W. Albers, Ruth L. Bush, Susan C. Fagan, Jonathan L. Halperin, S. Claiborne Johnston, Irene Katzan, Walter N. Kernan, Pamela H. Mitchell, Bruce Ovbiagele, Yuko Y. Palesch, Ralph L. Sacco, Lee H. Schwamm, Sylvia Wassertheil-Smoller, Tanya N. Turan, Deidre Wentworth, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. "Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association." *Stroke* 42 (2011): 227-276.

Garber, Judy E. and Esther Oliva. "Case 28-1997 – A 67-Year-Old Women with Increasing Neurologic Deficits and a History of Breast and Ovarian Cancer." *The New England Journal of Medicine* 337 (1997): 770-777.

Gilroy, John, Marion I. Barnhart, and John S. Meyer. "Treatment of Acute Stroke with Dextran 40." *Journal of the American Medical Association* 210 (1969): 293-298.

Greenberg, David, A., Michael J. Aminoff and Roger P. Simon. *Clinical Neurology 5<sup>th</sup> Edition*. New York: Lange, 2002.

Greer, David. Editor. *Acute Ischemic Stroke: An Evidence-Based Approach*. Hoboken, NJ: Wiley, 2007.

Gorelick, Alissa R., Philip B. Gorelick, and Edward P. Sloan. "Emergency Department Evaluation and Management of stroke: Acute assessment, stroke teams and care pathways." *Neurologic Clinics* 26 (2008): 923-942.

Gowers, W.R. *A Manual of Diseases of the Nervous System. Second Edition. Volume II*. London: J&A Churchill, 1893.

Grond, M. "Clinical Thrombolysis in Stroke." *Thrombosis Research* 103 (2001): S135–S142.

Grosset, Donald G. "What have drugs to offer the patient with acute stroke?" *British Journal of Clinical Pharmacology* 33 (1992): 467-472

Guiloff, Roberto J., ed. *Clinical Trials in Neurology*. London: Springer, 2001.

Hacke, Werner, Markku Kaste, Cesare Fieschi, Danilo Toni, Emmanuel Lesaffre, Rudiger von Kummer, Gudrun Boysen, Erich Bluhmki, Godehard Hoxter, Marie-Helene Mahagne, and Michael Hennerici, for the ECASS Study Group. "Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke: The European Cooperative Acute Stroke Study (ECASS)." *Journal of the American Medical Association* 274 (1995): 1017-1025.

Hacke, Werner, Markku Kaste, Cesare Fieschi, Rudiger von Kummer, Antoni Davalos, Dieter Meier, Vincent Larrue, Erich Bluhmki, Stephen Davis, Geoffrey Donnan, Dietmar Schneider, Exuperio Diez Tejedor, and Paul Trouillas, for the Second European-Australasian Acute Stroke Study Investigators. "Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)." *Lancet* 352 (1998): 1245–1251

Hadden, Walter Baugh, ed. *Lectures on the Localisation of Cerebral and Spinal Diseases. Delivered at The Faculty of Medicine of Paris by J. M. Charcot*. London: The New Sydenham Society, 1883.

Hall, Marshall. *On Diagnosis in Four Parts*. London: Longman, Hurst, Rees, Orme and Brown; Baldwin, Craddock, Joy; Pater Noster Row; and W. Blackwood, 1817.

Heberden, William. *Commentaries on The History and Cure of Diseases*. (1802) New York: Hafner Publishing Co., 1962.

Hennerici, Michael G., Michael Daffertshofer, Louis R. Caplan, and Kristina Szabo. *Case Studies in Stroke: Common and Uncommon Presentations*. Cambridge: Cambridge University Press, 2007.

Hoang, Kim and Peter Rosen. "The Efficacy and Safety of Tissue Plasminogen Activator in Acute Ischemic Stroke." *The Journal of Emergency Medicine* 10 (1992): 345-352.

Hoffmann, Jerome. "Should physicians give tPA to patients with acute ischemic stroke? Against: And just what is the emperor wearing?" *Western Journal of Medicine* 173 (2000): 149-150.

Kelley, Roger E. and Sheryl Martin-Schild. "Ischemic Stroke: Emergencies and Management." *Neurology Clinics* 30 (2012): 187-210.

Kelly, Adam G. "Patient Management Problem." *Continuum: Lifelong Learning in Neurology* 20 (2014): 476-481.

Khaja, Aslam M. "Acute Ischemic Stroke Management: administration of thrombolytics." *Neurology Clinics* 26 (2008): 943-961.

Khatri, Pooja. "Evaluation and Management of Acute Ischemic Stroke." *Continuum: Lifelong Learning in Neurology* 20 (2014): 283-295.

Kissella, Brett. "The complexities of acute stroke decision-making." *Neurology Podcast* published online September 24, 2013 at [http://www.aan.com/rss/index.cfm/getfile/AAN\\_2650.mp3](http://www.aan.com/rss/index.cfm/getfile/AAN_2650.mp3), (accessed March 25, 2014).

Kothari, Rashmi, Arthur Pancioli, Thomas Brott and Joseph Broderick. "Thrombolytic Therapy for Cerebral Infarction." *Academic Emergency Medicine* 3 (1996): 881-892.

Lees, Kenedy R. "Therapeutic interventions in acute stroke." *British Journal of Clinical Pharmacology* 34 (1992): 486-493.

Lees, Kennedy R., Erich Bluhmki, Rudiger von Kummer, Thomas G Brott, Danilo Toni, James C Grotta, Gregory W Albers, Markku Kaste, John R Marler, Scott A Hamilton, Barbara C Tilley, Stephen M Davis, Geoffrey A Donnan, Werner Hacke, for the ECASS, ATLANTIS, NINDS, and EPITHET rt-PA Study Group Investigators. "Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials." *Lancet* 375 (2010): 1695-1703.

Levine, Steven R. and Thomas G. Brott. "Thrombolytic Therapy in Cerebrovascular Disorders." *Progress in Cardiovascular Diseases* 34 (1992): 235-262

Lindsay, Kenneth, W., Ian Bone and Robin Callander. *Neurology and Neurosurgery Illustrated, 2<sup>nd</sup> Edition*. Edinburgh: Churchill Livingstone, 1991.

Lindsay, Kenneth W., and Ian Bone. *Neurology and Neurosurgery Illustrated, 3<sup>rd</sup> Edition*. Edinburgh: Churchill Livingstone, 1997.

Lindsay, Kenneth W., and Ian Bone. *Neurology and Neurosurgery Illustrated, 4<sup>nd</sup> edition*. Edinburgh: Churchill Livingstone, 2004.

Lyden, Patrick, ed. *Thrombolytic Therapy for Stroke*. Totowa, NJ: Humana Press, 2001.

Martin, M. "Thrombolytic Therapy in Arterial Thromboembolism." *Progress in Cardiovascular Diseases* 21 (1979): 351-374

Merritt, H. Houston, Fred A. Mettler and Tracy Jackson Putnam. *Fundamentals of Clinical Neurology*. Philadelphia: The Blakiston Company, 1947.

Meyer, John S., John Gilroy, Marion I. Barnhart and J. Frederic Johnson. "Anticoagulants Plus Streptokinase Therapy in Progressive Stroke." *Journal of the American Medical Association* 189 (1964): 373.

Meyer, John Stirling, and Terry Shaw, eds. *Diagnosis and Management of Stroke and TIAs*. Menlo Park: Addison-Wesley Publishing Co., 1982.

Osler, William. *The Principles and Practice of Medicine. Seventh Edition*. New York and London: D. Appleton and Company, 1911.

Pepper, William, ed. *A System of Practical Medicine by American Authors. Volume V. Diseases of the Nervous System*. Philadelphia: Lea Brothers & Co., 1886.

Perry, Jeffrey J., Mukul Sharma, Marco L.A. Sivilotti, Jane Sutherland, Andrew Worster, MD, Marcel

Emond, Grant Stotts, Albert Y. Jin, Wieslaw J. Oczkowski, Demetrios J. Sahlas, Heather E. Murray, Ariane MacKey, Steve Verreault, George A. Wells, and Ian G. Stiell. "A Prospective Cohort Study of Patients With Transient Ischemic Attack to Identify High-Risk Clinical Characteristics." *Stroke* 45 (2014): 92-100.

Reiter, M., Y. Teuschl, L. Seyfang, and M. Brainin for the Austrian Stroke Unit Registry Collaborators. "Diabetes and Thrombolysis for Acute Stroke: A Clear Benefit for Diabetics." *European Journal of Neurology* 21 (2014): 5-10.

Robinson, David J. "Should physicians give tPA to patients with acute ischemic stroke? For: Thrombolytics in Stroke: whose wisk is it anyway?" *Western Journal of Medicine* 173 (2000): 148-149.

Singer, Charles. *Vesalius on the Human Brain. Introduction, Translation of De Fabrica, first edition (1543)*. London: Oxford University Press, 1952.

Sloan, Michael A. "Thrombolysis and Stroke: Past and Future." *Archives of Neurology* 44 (1987): 748-768

Sobel, Burton, E. "Coronary Thrombolysis: Progress and Promise." *Journal of Cardiovascular Pharmacology* 6 (1984): S910-S913.

Sussman, Bernard J. and Thomas S. P. Fitch. "Thrombolysis with Fibrinolysin in Cerebral Arterial Occlusion." *Journal of the American Medical Association* 167 (1958): 1705-1709.

Sussman, Bernard J. and Thomas S. P. Fitch. "Thrombolysis with Fibrinolysin in Cerebral Arterial Occlusion." *Angiology* 12 (1961): 169-173.

Thomas, Stephen H., Lee H. Schwamm and Michael H. Lev. "Case 16-2006: A 72-Year-Old Woman Admitted to the Emergency Department because of a Sudden Change in Mental Status." *New England Journal of Medicine* 354 (2006): 2263-2271.

Torbey, Michel T. and Magdy H. Selim, eds. *The Stroke Book*. Cambridge: Cambridge University Press, 2007.

Trousseau, Armand. *Lectures on Clinical Medicine, Delivered at the Hôtel-Dieu, Paris*. Ed. and trans P. Victor Bazire. London: The New Sydenham Society, 1868.

Trojaborg, W., and G. Boysen. "Relation between EEG, Regional Cerebral Blood Flow and Internal Carotid Artery Pressure During Carotid Endarterectomy." *Electroencephalography and Clinical Neurophysiology* 34 (1973): 61-69.

Van der Worp, H. Bart and Jan van Gijn. "Acute Ischemic Stroke." *New England Journal of Medicine* 357 (2007): 572-579.

Vasa, Miten et al. "The Eyes Have It." *New England Journal of Medicine* 367 (2012): 938-943.

Wechsler, Israel S. *A Textbook of Clinical Neurology. Fifth edition*. Philadelphia: W.B. Saunders Co, 1944.

Wechsler, Lawrence R. "Intravenous Thrombolytic Therapy for Acute Ischemic Stroke." *New England Journal of Medicine* 36 (2011): 2138-2146.

Weibel, Jorge and William S. Fields. *Atlas of Arteriography in Occlusive Cerebrovascular Disease*. Stuttgart: Georg Thieme Verlag, 1969.

Weiner, Howard L. and Lawrence P. Levitt. *House Officer Series: Neurology, 5<sup>th</sup> Edition*. Baltimore: Williams & Wilkins, 1994.

Weiner, Howard L., Lawrence P. Levitt and Alexander Rae-Grant. *House Officer Series: Neurology, 6<sup>th</sup> Edition*. Philadelphia: Williams & Wilkins, 1999.

Whitteridge, Gweneth. Editor. *The Anatomical Lectures of William Harvey. Prelectiones Anatomie Universalis de Musculis (1616)*. Edinburgh & London: E & S Livingstone Ltd, 1964.

Wilkins, Robert H. and Irwin A Brody. *Neurological Classics*. New York and London: Johnson Reprint Corporation, 1973.

Wilkinson, Iain and Graham Lennox. *Essential Neurology, 4<sup>th</sup> Edition*. Malden MA: Blackwell Publishing, 2005.

Willis, Thomas. *Five Treatises*. London: T. Dring, C. Harper, J. Leigh, S. Martin, 1681.

Willis, Thomas. *The London Practice of Physick* (1685). New York: Classics of Neurology and Neurosurgery Library, 1991.

Yager, Phoebe H., Aneesh B. Singhal, and Raul G. Nogueira. "Case 31-2012: An 18-Year-Old Man with Blurred Vision, Dysarthria, and Ataxia." *New England Journal of Medicine* 367 (2012):1450-1460.

#### *Secondary Sources*

Aberegg, Scott A., and Peter B. Terry. "Medical decision-making and healthcare disparities: The physician's role." *Journal of Laboratory and Clinical Medicine* 144 (2004): 11-17.

Mary A. Albrecht, "Diagnosis of varicella zoster infection," <http://www.uptodate.com/contents/diagnosis-of-varicella-zoster-virus-infection>, (accessed March 14, 2014).

Aristotle. *The Basic Works of Aristotle*, ed. Richard McKeon. New York: The Modern Library, 1941.

Asplund, Kjell. "Ethics of Life Support in Patients With Severe Stroke." *Stroke* 20 (1989): 1107-1112.

Barber, Philip A., Andrew M. Demchuk, J Zhang, and Alastair M. Buchan. "Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy." *Lancet* 355 (2000): 1670-1674.

Barber, Philip A., Michael D. Hill, Andrew M. Demchuk, Alastair M. Buchan. "Doubts, Fears and Misconceptions: What is the Future of Thrombolysis in Acute Stroke?" *Canadian Journal of Neurological Sciences* 27 (2000): 283-287.

Bauchner, Howard, Lisa Simpson, John Chessare. "Changing physician behaviour." *Archives of Disorders of Children* 84 (2001): 459-462.

Bazerman, Max H., and Mahzarin Banaji, "The Social Psychology of Ordinary Ethical Failures." *Social Justice Research* 17 (2004): 111-115.

Beauchamp, Thomas L., and LeRoy Walters. *Contemporary Issues in Bioethics*. Encino: Dickenson Publishing Company, 1978.

Beauchamp, Thomas L. and James L. Childress. *Principles of Biomedical Ethics, 5<sup>th</sup> Edition*. Oxford: Oxford University Press, 2001.

Beauchamp, Thomas. "The Principle of Beneficence in Applied Ethics." *The Stanford Encyclopedia of Philosophy* (Winter 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/win2013/entries/principle-beneficence>, (accessed March 20, 2014).

Bensimon, Cécile, and Ross E. G. Upshur. "Evidence and Effectiveness in Decisionmaking for Quarantine." *American Journal of Public Health* 97 (2007): S44-S48.

Bentham, Jeremy. *The Principles of Morals and Legislation*. New York: Prometheus Books, 1988.

Berrios, German E. and Roy Porter, eds. *A History of Clinical Psychiatry. The Origin and History of Psychiatric Disorders*. London: Athlone, 1995.

Bernat, James. *Ethical Issues in Neurology*, 3rd edition. Philadelphia: Lippincott, Williams & Wilkins, 2008.

Bhatnagar, P., D. Sinha, R.A. Parker, P. Guyler, and A. O'Brien. "Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age." *Journal of Neurology Neurosurgery and Psychiatry* 82 (2011): 712-717.

Bird, Alexander. "Thomas Kuhn." *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/thomas-kuhn/>, (accessed April 13, 2014).

Bito, Seiji and Atsushi Asai. "Attitudes and Behaviors of Japanese physicians concerning withholding and withdrawal of life-sustaining treatment for end-of-life patients: results from an Internet survey." *BMC Medical Ethics* 8(2007): 7.

Blumenfeld, Hal. *Neuroanatomy Through Clinical Cases*, 1<sup>st</sup> edition. Sunderland, MA: Sinauer, 2002.

Boissy, Adrienne R. "IV Tissue Plasminogen Activator in Acute Stroke: What Are Neurologists Thinking?" *Neurology* 81 (2013): 1110-1111.

Boissy, Adrienne R., Paul J. Ford, Randall C. Edgell, Anthony J. Furlan. "Ethics Consultations in Stroke and Neurological Disease: A 7-Year Retrospective Review." *Neurocritical Care* 9 (2008): 394-399.

Boland, Michael V., and Harold P. Lehmann. "A new method for determining physician decision thresholds

using empiric, uncertain recommendations.” *BMC Medical Informatics and Decision Making* 2010, 10:20.

Bos, J. “The rise and decline of character: humoral psychology in ancient and early modern medical theory.” *History of the Human Sciences* 22 (2009): 29-50.

Brown, Devin L., William G. Barsan, Lynda D. Lisabeth, Michael E. Gallery, Lewis B. Morgenstern.  
“Survey of Emergency Physicians About Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke.” *Annals of Emergency Medicine* 46 (2005): 56-60.

Burgess, Diana J., Steven S. Fu, and Michelle van Ryn. “Why do providers contribute to disparities and what can be done about it?” *Journal of General Internal Medicine* 19 (2004): 1154-1159.

Burns, Risa B., Karen M. Freund, Mark A. Moskowitz, Linda Kasten, Henry Feldman, and John B. McKinlay. “Physician Characteristics: Do They Influence the Evaluation and Treatment of Breast Cancer in Older Women?” *American Journal of Medicine* 103 (1997): 263–269.

Canguilhem, Georges. *On the Normal and the Pathological*. Trans. Carolyn R. Fawcett. Dordrecht: D. Reidel Publishing Company, 1966.

Canguilhem, Georges. *Études d’histoire et de philosophie des sciences*. Paris: Librairie Philosophique J. Vrin, 1979.

Canguilhem, Georges. *Ideology and Rationality in the History of the Life Sciences*. Trans. Arthur Goldhammer. Cambridge: MIT Press, 1988.

Caplan, Louis R. "Evidence-Based Medicine: Concerns of a Clinical Neurologist." *Journal of Neurology, Neurosurgery and Psychiatry* 71 (2001): 569-574.

Caplan, Louis R. "Treatment of Acute Stroke: Still Struggling." *Journal of the American Medical Association* 292 (2004): 1883-1885.

Caplan, Louis R. "Stroke Thrombolysis: Slow Progress." *Circulation* 114 (2006): 187-190.

Caplan, Louis R. "The last 50 years of cerebrovascular disease: part 1" *International Journal of Stroke* 1 (2006): 104-108.

Caplan, Louis R. "Caplan's short rendition of Stroke during the 20th century: Part II" *International Journal of Stroke* 1 (2006): 228-234.

Carter, Barry L., C. David Butler, John C. Rogers, Richard L. Holloway. "Evaluation of Physician Decision Making With the Use of Prior Probabilities and a Decision-Analysis Model." *Archives of Family Medicine* 2 (1993): 529-534.

Cechetto, D.F., V. Hachinski, and S.N. Whitehead. "Vascular risk factors and Alzheimer's disease." *Experimental Reviews in Neurotherapeutics* 8 (2008): 743-750.

Chan, Yu-Feng, Thomas G. Kwiatkowski, Joseph G. Rella, William P. Rennie, Robert K. Kwon, Robert A. Silverman. "Tissue Plasminogen Activator for Acute Ischemic Stroke: A New York City Emergency Medicine Perspective." *The Journal of Emergency Medicine* 29 (2005): 405-408.

Chaturvedi, Seemant, Bryan Bertasio, Lorraine Femino. "Emergency Physician Attitudes Toward Thrombolytic Therapy in Acute Stroke." *Journal of Stroke and Cerebrovascular Diseases* 7 (1998): 442-445.

Chien, Kenneth R., Robert Meidell, and Robert Gerard. "Tissue Plasminogen Activator: From Molecular Biology to Myocardial Infarction." *American Journal of Medical Science* 293 (1987): 201-207.

Chimowitz, Marc I. "Endovascular Treatment for Acute Ischemic Stroke — Still Unproven." *New England Journal of Medicine* 368 (2013): 952-955.

Clark, Jack A., Deborah A. Potter, and John B. McKinlay. "Bringing Social Structure Back into Clinical Decision Making." *Social Science & Medicine* 32 (1991): 853-866.

Clarke, Edwin. "Apoplexy in the Hippocratic Writings." *Bulletin of the History of Medicine* 37 (1963): 301-314.

Cobb, C.M. "Evidence speaks for itself." *Journal of the Western Society of Periodontology / Periodontal abstracts* 50 (2002): 36.

Collen, Désiré, and Henri Roger Lijnen. "Tissue-type Plasminogen Activator: A Historical Perspective." *Journal of Thrombosis and Haemostasis* 2 (2004): 541-546.

Collen, Désiré, and Henri Roger Lijnen. "The Tissue-type Plasminogen Activator Story." *Arteriosclerosis, Thrombosis and Vascular Biology* 29 (2009): 1151-1155.

Colley, Linda. *Britons: Forging the Nation 1707-1837*. New Haven: Yale University Press, 1992.

Conrad, Lawrence I., Michael Neve, Vivian Nutton, Roy Porter, and Andrew Wear. *The Western Medical Tradition 800 BC to AD 1800*. Cambridge: Cambridge University Press, 1995.

Cosans, C.E. "Galen's Critique of Rationalist and Empiricist Anatomy." *Journal of the History of Biology* 30 (1997): 35-54.

Couto, J.S. "Evidence-based medicine: a Kuhnian perspective of a transvestite non-theory." *Journal of Evaluation in Clinical Practice* 4 (1998): 267-275.

Cowley, Christopher. "The dangers of medical ethics." *Journal of Medical Ethics* 31 (2005): 739-742.

Creutzfeld, Claire J., and Robert G. Holloway. "Treatment Decisions after Severe Stroke: Uncertainty and Biases." *Stroke* 42 (2012): 3405-3408.

Croskerry, Pat. "Achieving Quality in Clinical Decision Making: Cognitive Strategies and Detection of Bias." *Academic Emergency Medicine* 9 (2002): 1184-1204.

Crozier, Sophie. "Enjeux éthiques des limitations et arrêts de traitements à la phase aiguë des accidents vasculaires cérébraux grave." *Presse Médicale* 41 (2012): 525-531.

Cunningham, Thomas Vandiver. "Socializing Medical Practice: A Normative Model for Medical Decision-Making." Ph.D Thesis, University of Pittsburgh 2013. Published online at <https://d-scholarship.pitt.edu/20142>, (accessed March 29, 2014).

Daneski, Katherine, and Paul Higgs. "How far can Foucault take us? An analysis of the changing discourses and limitations of the medical treatment of apoplexy and stroke." *Health* 15 (2010): 369-384.

Daston, Lorraine and Peter Galison. *Objectivity*. New York: Zone Books, 2010.

De Reuck, J.L. "Historical Anatomical Aspects of Stroke." *Journal of the History of the Neurosciences* 3 (1994): 103-107.

Deep, Kristy S., Charles H. Griffith, and John F. Wilson. "Communication and Decision Making About Life-Sustaining Treatment: Examining the Experiences of Resident Physicians and Seriously-Ill Hospitalized Patients." *Journal of General Internal Medicine* 23 (2008): 1877-1882.

Demarquay, Geneviève, Laurent Derex, Norbert Nighoghossian, Patrice Adeleine, Frédéric Philippeau, Jérôme Honnorat, and Paul Trouillas. "Ethical Issues of Informed Consent in Acute Stroke." *Cerebrovascular Diseases* 19 (2005): 65-68.

DeMers, Gerard, William J. Meurer, Richard Shih, Steve Rosenbaum, Gary M. Vilke. "Tissue Plasminogen Activator and Stroke: Review of the Literature for the Clinician." *The Journal of Emergency Medicine* 43 (2012): 1149-1154.

Denig, P., and F.M. Haaijer-Ruskamp. "Therapeutic Decision making of physicians." *Pharmaceutisch Weekblad Scientific edition* 14 (1992): 9-15.

Denig, P., F.M. Haaijer-Ruskamp, H. Wesseling and A. Versluis. "Towards understanding treatment preferences." *Social Science & Medicine* 36 (1993): 915-924.

Devisch, Ignaas and Stephen J. Murray. "We hold these truths to be self-evident: deconstructing 'evidence-based' medical practice." *Journal of Evaluation in Clinical Practice* 15 (2009): 950-954.

Dhand, Amar, John Engstrom, and Gurpreet Dhaliwal. "How Experienced Community Neurologists Make Diagnoses during Clinical Encounters." *Neurology* 81 (2013): 1460-1466.

Djulgovic, Benjamin, Gordon H. Guyatt, and Richard E. Ashcroft. "Epistemological Inquiries in Evidence-Based Medicine." *Cancer Control* 16 (2009): 158-168.

Drescher, Jack. "Physician Values and Clinical Decision Making." *Virtual Mentor: Ethics Journal of the American Medical Association* 8 (2006): 303-308.

Duffin, Jacalyn. *To See With a Better Eye: A Life of R.T.H Laennec*. Princeton: Princeton University Press, 1998.

Duffin, Jacalyn. *History of Medicine: A Scandalously Short Introduction, 1<sup>st</sup> Edition*. Toronto: University of Toronto Press, 1999.

Duffin, Jacalyn. *Lovers and Livers: Disease Concepts in History*. Toronto: University of Toronto Press, 2005.

Eadie, M.J. "A Pathology of the Animal Spirits — The Clinical Neurology of Thomas Willis (1621-1675). Part I – Background and Disorders of Intrinsically Normal Animal Spirits." *Journal of the History of the Neurosciences* 10 (2003): 14-29.

Eddy, David M. "Evidence-Based Medicine: A Unified Approach." *Health Affairs* 24 (2005): 9-17.

Ereshefsky, Marc. "Natural Kinds in Biology." Routledge Encyclopedia of Philosophy. Published online at [people.ucalgary.ca/~ereshefs/.../Natural%20Kinds%20in%20Biology.doc](http://people.ucalgary.ca/~ereshefs/.../Natural%20Kinds%20in%20Biology.doc), (accessed April 13, 2014).

Ereshefsky, Marc. "Defining Health and Disease." *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (2008): 221-227.

Evidence-Based Medicine Working Group. "Evidence-based medicine: a new approach to the teaching of medicine." *Journal of the American Medical Association* 268(1992): 2420-2425.

Fedyk, Mark and Michel Shamy. "Projectibility, Disagreement and Consensus: A Challenge to Clinical Equipoise." *Theoretical & Applied Ethics*, forthcoming.

Fields, William S. and Noreen A. Lemark. *A History of Stroke: Its Recognition and Treatment*. Oxford: Oxford University Press, 1989.

Fleck, Leonard M., and Oliver W. Hayes. "Ethics and consent to treat issues in acute stroke therapy." *Emergency Medicine Clinics of North America* 20 (2002): 703-715.

Fleck, Ludwik. *Genesis and Development of a Scientific Fact*. Ed. Thaddeus J. Trenn and Robert K. Merton. Trans. Fred Bradley and Thaddeus J. Trenn. Chicago: University of Chicago Press, 1979.

Flynn, Darren, Paul van Schaik, Anna van Wersch, Any Douglass, and Paul Cann. *Non-Medical Influences upon Medical Decision-Making and Referral Behavior: An Annotated Bibliography*. London: Praeger, 2003.

Forrest, Christopher B., Paul A. Nutting, Sarah von Schrader, Charles Rohde, and Barbara Starfield. "Primary Care Physician Specialty Referral Decision Making: Patient, Physician, and Health Care System Determinants." *Medical Decision Making* 26 (2006): 76–85

Foucault, Michel. *The Birth of the Clinic*, trans. A. M. Skenda Smith. New York: Vintage, 1994.

Fox Keller, Evelyn. "Genes, Genomes and Genomics." *Biological Theory* 6 (2012): 132-140.

Frances, Allen. "Whither DSM-V?" *British Journal of Psychiatry* 195 (2009): 391-392.

Freeman, Joanne. *Affairs of Honor: National Politics and the New Republic*. New Haven: Yale University Press, 2001.

Furlan, Anthony J., George Kanoti. "When is Thrombolysis Justified in Patients with Acute Ischemic Stroke? A Bioethical Perspective." *Stroke* 28 (1997): 214-218

Gardiner, Patrick. "A virtue ethics approach to moral dilemmas in medicine." *Journal of Medical Ethics* 29 (2003):297-302.

Gibson, Lorna M., Miriam Brazzelli, Brenda M. Thomas and Peter A.G. Sandercock. "A systematic review of clinical trials of pharmacological interventions for acute ischaemic stroke (1955-2008) that were completed, but not published in full." *Trials* 11 (2010): 43-55.

Gigerenzer, Gerd and Henry Brighton, "Homo Heuristicus: Why Biased Minds Make Better Inferences," *Cognitive Science* 1 (2009): 107-143.

Gill, Thomas M. "The central role of prognostication in clinical decision-making." *Journal of the American Medical Association* 307 (2012): 199–200.

Gillon, Raanan. "Four scenarios." *Journal of Medical Ethics* 29 (2003): 267-268.

Godfrey-Smith, Peter. *Theory and Reality: An Introduction to the Philosophy of Science* Chicago: University of Chicago Press, 2003.

Goldstein, Daniel G., and Gerd Gigerenzer. "Models of Ecological Rationality: The Recognition Heuristic." *Psychological Review* 109 (2002): 75-90.

Goodman, Kenneth W. *Ethics and Evidence-Based Medicine: Fallibility and Responsibility in Clinical Science*. Cambridge: Cambridge University Press, 2002.

Goodman, Nelson. *Fact, Fiction and Forecast, 4<sup>th</sup> Edition*. Cambridge: Harvard University Press, 1979.

Goyal, Mayank, Michel Shamy, Bijoy K. Menon, Jeffrey L. Saver, Hans-Christoph Diener, J Mocco, Vitor Mendes Pereira, Tudor G. Jovin, Osama Zaidat, Elad I. Levy, Antoni Davalos, Andrew Demchuk, and Michael D. Hill. "Endovascular Stroke Trials: Why We Must Enroll All Eligible Patients." *Stroke* 44 (2013): 3591-3595.

Goyal, Mayank, Kyle M. Fargen, and Bijoy K. Menon. "Acute stroke, Bayes' theorem and the art and science of emergency decision-making." *Journal of Neurointerventional Surgery*, published online ahead of print December 13, 2013; <http://jn.is.bmj.com/content/early/2013/12/13/neurintsurg-2013-011056.full?sid=b17aa1a5-de0e-40b8-abeb-628a0c949c2f>, (accessed March 30, 2014).

Green, Alexander R., Dana R. Carney, Daniel J. Pallin, Long H. Ngo, Kristal L. Raymond, Lisa I. Iezzoni, Mahzarin R. Banaji, "Implicit Bias among Physicians and its Prediction of Thrombolysis Decisions for Black and White Patients." *Journal of General Internal Medicine* 22 (2007): 1231-1238.

Greenstone, Gerry. "The roots of evidence-based medicine." *BC Medical Journal* 51(2009): 342-344.

Greenwald, Anthony G., and Mahzarin R. Banaji. "Implicit Social Cognition: Attitudes, Self-Esteem and Stereotypes." *Psychological Review* 102 (1995): 4-27.

Grmek, Mirko D. *Diseases in the Ancient World*. trans. Mireille Muellner and Leonard Muellner. Baltimore: Johns Hopkins University Press, 1989.

Groopman, Jerome. *How Doctors Think*. New York: Houghton Mifflin, 2007.

Gruppen, Larry D., Frederick M. Wolf, and Jeffrey K. Stross. "Practice Characteristics of a Context for Primary Care Treatment Decisions: A Preliminary Study." *Academic Medicine* 65 (1990): S9-S10

Gurdjian, E. Steven and Edwin S. Gurdjian. "History of Occlusive Cerebrovascular Disease I. From Wepfer to Moniz." *Archives of Neurology* 36 (1979): 340-343.

Gurdjian, E. Steven and Edwin S. Gurdjian. "History of Occlusive Cerebrovascular Disease II. After Moniz, With Special Reference to Surgical Treatment." *Archives of Neurology* 36 (1979): 427-432.

Guyatt, R. Gordon H., Brian Haynes, Roman Z. Jaeschke, Deborah J. Cook, Lee Green, C. David Naylor, Mark C. Wilson, and W. Scott Richardson, for the Evidence-Based Medicine Working Group. "Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care." *Journal of the American Medical Association* 284 (2000): 1290-1296.

Guyatt, Gordon, and Drummond Rennie, eds. *Users' Guide to the Medical Literature*. Chicago: American Medical Association Press, 2002.

Haberland, Catherine. *Clinical Neuropathology*. New York: Demos, 2007.

Hacking, Ian. *The Social Construction of WHAT?* Cambridge: Harvard University Press, 1999.

Hafferty, Frederic W. "Beyond Curriculum Reform: Confronting Medicine's Hidden Curriculum."

*Academic Medicine* 73 (1998): 403-407.

Hafferty, Frederic W., and Ronald Franks. "The Hidden Curriculum, Ethics Teaching, and the Structure of Medical Education." *Academic Medicine* 69 (1994): 861-871.

Hakim, Antoine M., Frank Silver and Corinne Hodgson. "Organized stroke care: A new era in stroke prevention and treatment." *Canadian Medical Association Journal* 159 (1998): S1.

Halvorsen, K., A. Slettebo, P. Nortvedt, R. Pedersen, M. Kirkevold, M. Nordhaug, and B.S. Brinchmann. "Priority dilemmas in dialysis: the impact of old age." *Journal of Medical Ethics* 34 (2008): 585-589.

Harris, John. "In praise of unprincipled ethics." *Journal of Medical Ethics* 29 (2003): 303-306.

Harrison, James, Kunal Kulkarni, Mohamed Baguneid, and Bernard Prendergast. *Oxford Handbook of Key Clinical Evidence*. Oxford: Oxford University Press, 2009.

Hauser, Stephen L., ed. *Neurology in Clinical Medicine*. New York: McGraw Hill, 2006.

Health Council of Canada. *Decisions, Decisions: Family Doctors as Gatekeepers to Prescription Drugs and Diagnostic Imaging in Canada*. Toronto: Health Council of Canada, 2010.

Hemphill, J. Claude III and Patrick Lyden. "Stroke thrombolysis in the elderly: Risk or benefit?" *Neurology* 65 (2005): 1690-1691.

Hemphill, J. Claude III, and Douglas B. White. "Clinical Nihilism in Neuroemergencies." *Emergency Medicine Clinics of North America* 27 (2009): 27-37.

Higgs, Joy, Mark A Jones, Stephen Loftus & Nicole Christensen, eds. *Clinical Reasoning in the Health Professions, 3<sup>rd</sup> Edition*. Amsterdam: Elsevier, 2008.

Hills, Nancy K., and S. Claiborne Johnston. "Why are eligible thrombolysis candidates left untreated?" *American Journal of Preventive Medicine* 31 (2001): S210-216.

Hine, Michael J., Ken J. Farion, Wojtek Michalowski, and Szymon Wilk. "Decision Making By Emergency Room Physicians And Residents: Implications for the Design of Clinical Decision Support Systems." *International Journal of Healthcare Information Systems and Informatics* 4 (2009): 17-35

Hofweber, Thomas. "Logic and Ontology." *The Stanford Encyclopedia of Philosophy* (Spring 2013 Edition), Edward N. Zalta (ed.), URL = <<http://plato.stanford.edu/archives/spr2013/entries/logic-ontology/>>, (accessed April 3, 2014).

Hodgson, Corine and Kathleen Whelan. "Are physicians ready for thrombolysis for acute stroke? A qualitative study." *Canadian Medical Association Journal* 159 (1998): S19-S24.

Holloway, Robert G., Curtis G. Benesch, W. Scott Burgin, and Justine B. Zentner. "Prognosis and Decision Making in Severe Stroke." *Journal of the American Medical Association* 294 (2005): 725-733.

Hope, Tony. *Medical Ethics: A Very Short Introduction*. Oxford: Oxford University Press, 2004.

Hopyan, Julia, Anthony Ciarallo, Dar Dowlatshahi, Peter Howard, Verity John, Robert Yeung, Liying Zhang, Jisung Kim, Genevieve MacFarlane, Ting-Yim Lee, Richard I. Aviv. "Certainty of Stroke Diagnosis: Incremental Benefit with CT Perfusion Over Noncontrast CT and CT Angiography." *Radiology* 255 (2010): 142-153.

Howick, Jeremy. *The Philosophy of Evidence-Based Medicine*. Chichester: Blackwell Publishing, 2011.

Hume, David. *A Treatise of Human Nature (1738)*. Eds. L. A. Selby-Bigge and P. H. Niditch. Oxford: Clarendon Press, 1978.

Hursthouse, Rosland. "Virtue Ethics." *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/ethics-virtue/> (accessed March 30, 2014).

Ichikawa, Jonathan Jenkins and Matthias Steup. "The Analysis of Knowledge." *The Stanford Encyclopedia of Philosophy* (Fall 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2013/entries/knowledge-analysis/>, (accessed March 30, 2014).

IST-3 Collaborative group. "The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (IST-3): a randomized controlled trial." *Lancet* 379 (2012): 2352-63.

Jacobson, Marcus. *Foundations of Neuroscience*. New York: Plenum Press, 1993.

Jauch, Edward C., Jeffrey L. Saver, Harold P. Adams Jr., Askiel Bruno, J.J. (Buddy) Connors, Bart M. Demaerschalk, Pooja Khatri, Paul W. McMullan Jr., Adnan I. Qureshi, Kenneth Rosenfield, Phillip A. Scott, Debbie R. Summers, David Z. Wang, Max Wintermark, Howard Yonas, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. "Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association." *Stroke* 44 (2013): 870-947.

Jervis, Robert. "Political Decision Making: Recent Contributions." *Political Psychology* 2 (1980): 86-101.

Johnston, S. Claiborne, and Stephen L. Hauser. "The Beautiful and Ethereal Neurological Exam: An Appeal for Research." *Annals of Neurology* 70 (2011): A9-A10.

Jones, David S. *Broken Hearts: The Tangled History of Cardiac Care*. Baltimore: Johns Hopkins University Press, 2013.

Jonsen, Albert. *A Short History of Bioethics*. Oxford: Oxford University Press, 2000.

Jovic, Alan, Marin Prcela, and Dragan Gamberger. "Ontologies in Medical Knowledge Representation." Proceedings of the *ITI 2007 29th Int. Conf. on Information Technology Interfaces*, June 25-28, 2007, Cavtat, Croatia, published online at <http://ppr.cs.dal.ca/sraza/files/Ontologies%20in%20Med%20Know%20rep.pdf>, accessed April 3, 2014.

Joyce, James. "Bayes' Theorem." *The Stanford Encyclopedia of Philosophy* (Fall 2008 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2008/entries/bayes-theorem/>, (accessed March 30, 2014).

Kagan, Donald. *Pericles of Athens and the Birth of Democracy*. New York: The Free Press, 1991.

Kahnemann, Daniel. *Thinking Fast and Slow*. Penguin: London, 2011.

Kahnemann, Daniel and Amos Tversky. "Prospect Theory: An Analysis of Decision Under Risk." *Econometrica* 47 (1979): 263-291.

Kammersgaard, L.P., H.S. Jorgensen, J. Reith, H. Nakayama, P.M. Pedersen, and T.S. Olsen. "Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study." *Age and Ageing* 33 (2004): 149-154.

Kant, Immanuel. *Groundwork of the Metaphysics of Morals*, ed. and trans. Mary Gregor and Jens Timmermann. Cambridge: Cambridge University Press, 2012.

Karantzoulis, Stella and Christopher Randolph. "Modern chronic traumatic encephalopathy in retired

athletes: what is the evidence?" *Neuropsychological Reviews* 4 (2013): 350-360.

Karenberg, Axel. "Johann Jakob Wepfers Buch über die Apoplexie (1658) Kritische Anmerkungen zu einem Klassiker der Neurologie." *Nervenarzt* 69 (1998): 93-98.

Karenberg, Axel. "Reconstructing a doctrine: Galen on apoplexy." *Journal of the History of Neurosciences* 3 (1994): 85-101.

Karenberg, Axel, and Irmgard Hort. "Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part I: The Struggle for Terms and Theories – Late Antiquity and Early Middle Ages (300–800)." *Journal of the History of the Neurosciences* 7 (1998): 162-173.

Karenberg, Axel, and Irmgard Hort. "Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part II: Between Galenism and Aristotelism — Islamic Theories of Apoplexy (800-1200)." *Journal of the History of the Neurosciences* 7 (1998): 174-185.

Karenberg, Axel, and Irmgard Hort. "Medieval Descriptions and Doctrines of Stroke: Preliminary Analysis of Select Sources. Part III: Multiplying Speculations — The High and Late Middle Ages (1000-1450)." *Journal of the History of the Neurosciences* 7 (1998): 186-200.

Karenberg, Axel and Ferdinand Peter Moog. "Next Emperor, Please! No End to Retrospective Diagnostics." *Journal of the History of the Neurosciences* 13 (2004): 143-149.

Katzan, Irene L., Maxim D. Hammer, Eric D. Hixson, Anthony J. Furlan, Alex Abou-Chebl, and Deborah M. Nadzam. "Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke." *Archives of Neurology* 61 (2004): 346-350.

Kelly, Adam G., Kathryn D. Hoskins, Robert G. Holloway. "Early Stroke Mortality, Patient Preferences, and the Withdrawal of Care Bias." *Neurology* 79 (2012): 941-944.

Kelly, Adam G., Bogachan Sahin, and Robert G. Holloway. "Ethical considerations in stroke patients." *Current Opinion in Neurology* 27 (2014): 61-65.

Kelly, Michael A. "Stroke: A Modern History" *American Journal of Therapeutics* 18 (2011): 51-56.

Kidwell, Chelsea S., David S. Liebeskind, Sidney Starkman, and Jeffrey L. Saver. "Trends in Acute Ischemic Stroke Trials Through the 20th Century." *Stroke* 32 (2001): 1349-1359.

Kienle, Gunver S. and Helmut Kiene. "Clinical Judgment and the Medical Profession." *Journal of Evaluation in Clinical Practice* 17 (2011): 621-627.

Knight, Lynn Valeri and Karen Mattick. "'When I first came here, I thought medicine was black and white:' Making sense of medical students' ways of knowing." *Social Science & Medicine* 63 (2006): 1084-1096.

Koerkamp, Bas Groot, Milton C. Weinstein, Theo Stijnen, M. H. Heijnenbrok-Kal, and M. G. Myriam Hunink. "Uncertainty and Patient Heterogeneity in Medical Decision Models." *Medical Decision Making* 30 (2010): 194-205.

Konstas, A.A., G.V. Goldmakher, T.-Y. Lee, M.H. Lev. "Theoretic Basis and Technical Implementations of CT Perfusion in Acute Ischemic Stroke, Part 1: Theoretic Basis." *American Journal of Neuroradiology* 30 (2009): 662-668.

Konstas, A.A., G.V. Goldmakher, T.-Y. Lee, M.H. Lev. "Theoretic Basis and Technical Implementations of CT Perfusion in Acute Ischemic Stroke, Part 2: Technical Implementations." *American Journal of Neuroradiology* 30 (2009): 885-892.

Kuhn, Thomas S. *The Structure of Scientific Revolutions, 50<sup>th</sup> anniversary edition*. Chicago: University of Chicago Press, 2012.

Kwan, Joseph, Peter Hand, and Peter Sandercock. "A systematic review of barriers to delivery of thrombolysis for acute stroke." *Age and Ageing* 33 (2004): 116-121.

Lenzer, Jeanne. "Alteplase for Stroke: Money and Optimistic Claims Buttress the 'Brain Attack' Campaign." *British Medical Journal* 324 (2002): 723-729.

Lindsay, Patrice, Gordon Gubitz, Mark Bayley, Michael Hill, Corrine Davies-Schinkel, Sunny Singh, and Stephen Phillips. *Canadian Best Practice Recommendations for Stroke Care* (Update 2010). On behalf of the Canadian Stroke Strategy Best Practices and Standards Writing Group, Canadian Stroke Network. Published online at [www.strokebestpractices.ca](http://www.strokebestpractices.ca) (accessed April 12, 2014).

Longino, Helen. "The Social Dimensions of Scientific Knowledge." *The Stanford Encyclopedia of Philosophy* (Spring 2013 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2013/entries/scientific-knowledge-social/> (accessed March 30, 2014).

Loughlin, Michael. The basis of medical knowledge: judgment, objectivity and the history of ideas. *Journal of Evaluation in Clinical Practice* 15 (2009): 935-940.

Loughlin, Michael, Ross E. G. Upshur, Maya J. Goldenberg, Robyn Bluhm and Kirstin Borgerson. "Philosophy, ethics, medicine and health care: the urgent need for critical practice." *Journal of Evaluation in Clinical Practice* 16 (2010): 249–259.

Louw, Stephen J., and Jeffrey A Keeble. "Stroke medicine: ethical and legal considerations." *Age and Ageing* 31 (2002): 31-35.

Luker, J.A., K. Wall, J. Bernhardt, I. Edwards, and K.A. Grimmer-Somers. "Patients' age as a determinant of care received following acute stroke: a systematic review." *BMC Health Services Research* 11 (2011): 161-170.

Mangset, M., R. Førde, J. Nessa, E Berge, and T. Bruun Wyller. "I don't like that, it's tricking people too much...": Acute Informed Consent to Participation in a Trial of Thrombolysis for Stroke." *Journal of Medical Ethics* 34 (2008): 751-756.

Mann, Jeffrey. "Emergency Physician Survey: Recombinant Tissue Plasminogen Activator for Stroke." *Annals of Emergency Medicine* 48 (2006): 476.

Maroo, A., and E.J. Topol. "The Early History and Development of Thrombolysis in Acute Myocardial Infarction." *Journal of Thrombosis and Haemostasis* 2 (2004): 1867-1870.

Marshall, John. "Clinical Developments in Cerebrovascular Disease." *Journal of the History of the Neurosciences* 3 (1994): 115-118.

McDermott, Rose. "Medical Decision Making: Lessons from Psychology." *Urologic Oncology* 26 (2008): 665-668.

McGrath, Matthew, "Propositions," *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), forthcoming URL = <http://plato.stanford.edu/archives/spr2014/entries/propositions/>, (accessed February 14, 2014).

McHenry, Lawrence B. *Garrison's History of Neurology. Revised and Enlarged with a Bibliography of Classical, Original and Standard Works in Neurology*. Springfield, IL: Charles C. Thomas, 1969.

McKinlay, John B., Deborah A. Potter, Henry A. Feldman, "Non-medical influences on medical decision-making," *Social Science & Medicine* 42 (1996): 769-776.

McKinlay, John B., R. B. Burns, Howard A. Feldman, Karen M. Freund, J T Irish, L E Kasten, M A Moskowitz, Deborah A. Potter, and K. Woodman. "Physician variability and uncertainty in the management of breast cancer. Results from a factorial experiment." *Medical Care* 36 (1998): 385-396.

McKinlay, John B., T. Lin, Karen Freund, and M. Moskowitz. "The unexpected influence of physician attributes on clinical decisions: results of an experiment." *Journal of Health & Social Behavior* 43 (2002): 92-106.

Miké, Valerie. "Outcomes Research and the Quality of Health Care: The Beacon of an Ethics of Evidence." *Evaluation and the Health Professions* 22 (1999): 3-32.

Mill, John Stuart. *The Basic Writings of John Stuart Mill: On Liberty, The Subjection of Women, and Utilitarianism*. New York: Modern Library, 2002.

Misak, Cheryl. "Experience, Narrative and Ethical Deliberation." *Ethics* 118 (2008): 614-632.

Mol, Annemarie. *The Body Multiple: Ontology in Medical Practice*. Durham: Duke University Press, 2002.

Mongtomery, Erwin B, Jr. "Epistemology of medical decisions and the need for reason-based medicine." *Neurodegenerative Disease Management* 2 (2012): 95-97.

Montgomery, Kathryn. *How Doctors Think: Clinical Judgment and the Practice of Medicine*. Oxford: Oxford University Press, 2006.

Morgan, D. "Arthrotec: the evidence speaks for itself." *Scandinavian Journal of Rheumatology* Supplement 109 (1999): 13-18.

Moulton, Benjamin, and Jaime S. King. "Aligning Ethics with Medical Decision-Making: The Quest for Informed Patient Choice." *Journal of Law, Medicine & Ethics* 38 (2010): 2-14.

Murphy, Terence D. "Medical Knowledge and Statistical Methods in Early Nineteenth Century France." *Medical History* 25 (1981): 301-319.

Murray, Elizabeth, Lance Pollack, Martha White, Bernard Lo. "Clinical decision-making: physicians' preferences and experiences." *BMC Family Practice* 8 (2007): 10.

Murray, T. Jock. *Multiple Sclerosis: The History of a Disease*. Demos: New York, 2005.

Murtagh, Madeleine J., Duika L. Burges Watson, K. Neil Jenkins, Mabel L.S. Lie, Joan E. Mackintosh, Gary A. Ford, Richard G. Thomson. "Situationally-sensitive knowledge translation and relational decision making in hyperacute stroke: a qualitative study." *PLoS ONE* 7 (2012): e37066.

Mushlin, Stuart B., and Harry Lemoin Greene, eds. *Decision-Making in Medicine: An Algorithmic Approach*, 3<sup>rd</sup> edition. Philadelphia: Mosby, 2010.

Neville, C. "The evidence speaks for itself." *Nursing Older People* 25 (2013): 12.

Niemelä, Jussi. "What puts the 'yuck' in the yuck factor?" *Bioethics* 25 (2011): 267-279.

Niknam, Kaiser, Mahdi Ghorbani Samini, Hedyeh Mahmudi, and Sahar Niknam. "How do physicians make a decision?" in T. Jarm, P. Kramar, A. Županič, eds., *11th Mediterranean Conference on Medical and Biological Engineering and Computing 2007: MEDICON 2007*. Ljubljana, Slovenia: Springer, 2007.

Nurok, Michael. "Elements of the Medical Emergency's Epistemological Alignment: 18<sup>th</sup>-20<sup>th</sup> Century Perspectives." *Social Studies of Science* 33 (2003): 563-579.

Olby, R.C., G.N. Canthor, J.R.R. Christie, and M.J.S. Hodge. *Companion to the History of Modern Science*. Abingdon: Routledge, 1990.

Ogunnaike, Oludamini, Yarrow Dunham, and Mahzarin R. Banaji. "The language of implicit preferences." *Journal of Experimental Social Psychology* 46 (2010): 999-1003.

Paciaronia, Maurizio, and Julien Bougousslavsky. "How Did Stroke Become of Interest to Neurologists? A Slow 19<sup>th</sup> Century Sage." *Neurology* 73 (2009): 724-728.

Parsons, Mark W. "Perfusion CT: Is It Clinically Useful?" *International Journal of Stroke* 3 (2008): 41-50.

Patel, Vilma L., David R. Kaufman, and Jose F. Arochab. "Methodological Review: Emerging paradigms of cognition in medical decision-making." *Journal of Biomedical Informatics* 35 (2002) 52–75

Pellegrino, Edmund D. "The Ethical Use of Evidence in Biomedicine." *Evaluation and the Health Professions* 22 (1999): 33-43.

Post, Piet N., Anne M. Stigelbout, and Peter P. Wakker. "The Utility of Health States After Stroke: A Systematic Review of the Literature." *Stroke* 32 (2001): 1425-1429.

Pound, Pandora, Michael Bury and Shah Ebrahim. "From apoplexy to stroke." *Age and Ageing* 26 (1997): 331-337.

Pourmand, Rahman. *Practicing Neurology: What You Need to Know, What You Need to Do*, 2<sup>nd</sup> Edition. Totowa, NJ: Humana Press, 2008.

Pressman, Jack D. *Last Resort: Psychosurgery and the Limits of Medicine*. Cambridge: Cambridge University Press, 1998.

Quest, Donald O. "Stroke: A Selective History" *Neurosurgery* 27 (1990): 440-445.

Quin, C.E. "The ideas of Thomas Kuhn in relation to medical advances in the sixteenth and seventeenth centuries." *Journal of the Royal Society of Medicine* 90 (1997): 225-228.

Reiser, Stanley Joel. *Medicine and the Reign of Technology*. Cambridge: Cambridge University Press, 1978.

Reeder, Guy S., and Harold L. Kennedy. "Criteria for the diagnosis of acute myocardial infarction," <http://www.uptodate.com/contents/criteria-for-the-diagnosis-of-acute-myocardial-infarction>, (accessed March 14, 2014).

Rose, F. Clifford, ed. *A Short History of Neurology: The British Contribution 1660-1910*. Oxford: Butterworth Heinemann, 1999.

Rosenberg, Alex and Robert Arp, eds. *Philosophy of Biology: An Anthology*. Chichester: Wiley-Blackwell, 2010.

Rosenberg, Charles E., and Janet Golden, eds. *Framing Disease: Studies in Cultural History*. New Brunswick, NJ: Rutgers University Press, 1992.

Royal College of Physicians Intercollegiate Stroke Working Party. National Sentinel Stroke Clinical Audit 2010, Round 7. Public Report for England, Wales and Northern Ireland. 2011.

Sackett, David L. "Evidence-Based Medicine." *Seminars in Perinatology* 21 (1997): 3-5.

Sackett, David L. "A 1955 clinical trial report that changed my career." *Journal of the Royal Society of Medicine* 103 (2010): 254-255.

Sackett, David L., Peter Tugwell, and Gordon H. Guyatt. *Clinical epidemiology: a basic science for clinical medicine*. Boston: Little, Brown, 1991.

Sackett, David L., William C. Rosenberg, J.A. Muir Gray, R. Brian Haynes, W. Scott Richardson, "Evidence-Based Medicine: What It Is and What It Isn't," *British Medical Journal* 312 (1996): 71-72.

Samuels, Richard, Stephen Stich, and Michael Bishop. "Ending the Rationality Wars: How To Make

Disputes About Human Rationality Disappear.” in Renee Elio, ed. *Common Sense, Reasoning and Rationality*. New York: Oxford University Press, 2002.

Sandel, M. Elizabeth. “Stroke, Disability, and Unconscious Bias: Interrelationships and Overdetermination in Medical Decisions.” *Topics in Stroke Rehabilitation* 18 (2011): 70-73.

Saposnik, Gustavo, Sandra E. Black, Antoine Hakim, Julie Fang, Jack V. Tu, and Moira K. Kapral. “Age Disparities in Stroke Quality of Care and Delivery of Health Services.” *Stroke* 40 (2009): 3328-3335.

Saposnik, Gustavo, Moira Kapral, and Robert Coté. “Is pre-existing dementia an independent predictor of outcome after stroke? A propensity score-matched analysis.” *Journal of Neurology* 259 (2012): 2366-2375.

Saver, Jeffrey L, Chelsea S Kidwell, Sidney Starkman. “Thrombolysis in stroke: It Works!” *British Medical Journal* 324 (2002): 727-728.

Schwark, C., and P.D. Schellinger. “Is old age really a reason to withhold thrombolytic therapy?” *Journal of Neurology Neurosurgery and Psychiatry* 77 (2006): 289.

Scott, Philip A., Zhenzhen Xu, William J. Meurer, Shirley M. Frederiksen, Mary N. Haan, Michael W. Westfall, Sandip U. Kothari, Lewis B. Morgenstern, and John D. Kalbfleisch. “Attitudes and Beliefs of Michigan Emergency Physicians Toward Tissue Plasminogen Activator Use in Stroke: Baseline Survey Results From the INcreasing Stroke Treatment through INteractive behavioral Change Tactic (INSTINCT) Trial Hospitals.” *Stroke* 41 (2010): 2026-2032.

Schaffner, Kenneth F. *Discovery and Explanation in Biology and Medicine*. Chicago: University of Chicago Press, 1993.

Schulman, Kevin A., Jesse A. Berlin, William Harless, Jon F. Kerner, Shyryl Sistrunk, Bernard J. Gersh, Ross Dubé, Christopher K. Taleghani, Jennifer E. Burke, Sankey Williams, John M. Eisenberg, and José J. Escarce. "The Effect of Race and Sex on Physician Recommendations for Cardiac Catheterization." *New England Journal of Medicine* 340 (1999): 618-626.

Schutta, Henry S. "Morgagni on Apoplexy in De Sedibus: A Historical Perspective." *Journal of the History of the Neurosciences* 18 (2009): 1-24.

Schutta, Henry S., and Herbert M. Howe. "Seventeenth Century Concepts of "Apoplexy" As Reflected in Bonet's Sepulchretum." *Journal of the History of the Neurosciences* 15 (2006): 250-268.

Schwab, Abraham P. "Improving clinical decision making by excising the physician's judgment." *Virtual Mentor: American Medical Association Journal of Ethics* 8 (2006): 469-472.

Schwitzgebel, Eric. "Belief." *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2014/entries/belief/> (accessed March 30, 2014).

Shamy, Michel and Ross E.G. Upshur, "How doctors think." *Perspectives in Biology and Medicine* 51 (2008): 158-161.

Shamy, Michel and Mark Fedyk. "What Statistics Cannot Tell Us About the Neurological Examination."

*Annals of Neurology* 71 (2012): 434-435.

Shamy, Michel C.F., and Cheryl S. Jaigobin. "The Complexities of Acute Stroke Decision-Making: A

Survey of Neurologists." *Neurology* 81 (2013): 1130-1133.

Sharma, Mohit, and Priyank Khandelwal. "The Complexities of Acute Stroke Decision-Making: A Survey of

Neurologists." *Neurology* 82 (2014): 904.

Shem, Samuel. *The House of God*. New York: Delta, 1978.

Siegel, Mark D. "End-of-Life Decision Making in the ICU." *Clinics in Chest Medicine* 30 (2009): 181-194.

Silbergleit, Robert and Philip A. Scott. "Thrombolysis for Acute Stroke: The Incontrovertible, the

Controvertible, and the Uncertain." *Academic Emergency Medicine* 12 (2005): 348-351.

Silva, Suzana A. and Peter C. Wyer. "Where is the wisdom? II – Evidence-based medicine and the

epistemological crisis in clinical medicine." *Journal of Evaluation in Clinical Practice* 15 (2009): 899-906.

Simon, Jerome. "Constructive Realism and Medicine: An Approach to Medical Ontology." *Perspectives in*

*Biology and Medicine* 51 (2008): 353-366.

Sinnott-Armstrong, Walter. "Consequentialism." *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2014/entries/consequentialism/>, (accessed April 8, 2014).

Smith, Sam. "Postmodernity and a hypertensive patient: rescuing value from nihilism." *Journal of Medical Ethics* 24 (1998): 25-31.

Sommers, Benjamin D., and Richard Zeckhauser. "Probabilities and Preferences: What Economics Can Teach Doctors and Patients about Difficult Treatment Decisions." *Urologic Oncology* 26 (2008): 669-673.

Starr, Paul. *The Social Transformation of American Medicine*. New York: Basic Books, 1982.

Steup, Matthias. "Epistemology." *The Stanford Encyclopedia of Philosophy* (Spring 2014 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/spr2014/entries/epistemology/>. (accessed April 3, 2014).

Straus, Sharon E., Jacqueline Tetroe, and Ian Graham. "Defining Knowledge Translation." *Canadian Medical Association Journal* 181 (2009): 165-168.

Swindell, J.S., Amy L. McGuire, Scott D. Halpern. "Beneficent Persuasion: Techniques and Ethical Guidelines to Improve Patients' Decisions." *Annals of Family Medicine* 3 (2010): 260-264.

Tamayo-Sarver, Joshua H., Neal V. Dawson, Susan W. Hinze, Rita K. Cydulka, Robert S. Wigton, and David W. Baker. "Rapid Clinical Decisions in Context: A Theoretical Model of Physicians' Decision-

Making with an Application to Racial/Ethnic Treatment Disparities.” *Research in the Sociology of Health Care* 23 (2005): 183-213

Temkin, Owsei. *The Falling Sickness: A History of Epilepsy from the Greeks to the Beginning of Modern Neurology*. Baltimore: Johns Hopkins University Press, 1945.

Temkin, Owsei. *The Double Face of Janus and Other Essays in the History of Medicine*. Baltimore: John Hopkins University Press, 1977.

Timmons, Mark, ed. *Disputed Moral Issues: A Reader, 2<sup>nd</sup> edition*. Oxford: Oxford University Press, 2010.

Tobin, Oliver, Joseph G. Hentz, Bentley J. Bobrow, Bart M. Demaerschalk. “Identification of Stroke Mimics in the Emergency Department Setting.” *Journal of Brain Disease* 1(2009): 19-22.

Töpfer, Frank, and Urban Wiesing. “The medical theory of Richard Koch I: theory of science and ethics.” *Medicine and Health Care Philosophy* 8 (2005): 207-219.

Trotter, Griffin. “Why Were the Benefits of tPA Exaggerated? The Role of Interpretation Bias.” *The Western Journal of Medicine* 176 (2002): 194-197.

Tsebelis, George. “Decision Making in Political Systems: Veto Players in Presidentialism, Parliamentarism, Multicamerism and Multipartyism.” *British Journal of Political Science* 25 (1995): 289-325.

Tversky, Amos and Daniel Kahnemann. "Judgment Under Uncertainty: Heuristics and Biases." *Science* 185 (1974): 1124-1131.

Upshur, Ross E.G. "Priors and Prejudice." *Theoretical Medicine and Bioethics* 20 (1999): 319-327.

Upshur, Ross E.G. "Seven characteristics of medical evidence." *Journal of Evaluation in Clinical Practice* 6 (2000): 93-97.

Upshur, Ross E.G. "The Ethics of Alpha: Reflections on Statistics, Evidence and Values in Medicine." *Theoretical Medicine* 22 (2001): 565-576.

Upshur, Ross E.G. "A Call to Integrate Ethics and Evidence-Based Medicine." *Virtual Mentor: American Medical Association Journal of Ethics* 15 (2013): 86-89.

Valliere, Paul. *Conciliarism: A History of Decision-Making in the Church*. Cambridge: Cambridge University Press, 2012.

Van der Worp, H. Bart, Jan van Gijn. "Acute Ischemic Stroke." *New England Journal of Medicine* 357 (2007): 572-579.

Van Ryn, Michelle, and Somnath Saha, "Exploring Unconscious Bias in Disparities Research and Medical Education." *Journal of the American Medical Association* 306 (2011): 995-996.

Velleman, J. David. "A Right to Self-Termination?" *Ethics* 109 (1999): 606-628.

Veerbeek, Janne Marieke, Erwin van Wegen, Roland van Peppen, Philip Jan van der Wees, Erik Hendriks, Marc Rietberg, Gert Kwakkel. "What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis." *PLOS One* 9 (2014): 1-33.

Vogel, Morris J., and Charles E. Rosenberg, eds. *The Therapeutic Revolution: Essays in the Social History of American Medicine*. Philadelphia: University of Pennsylvania Press, 1979.

Wallace, R. Jay. "Practical Reason." *The Stanford Encyclopedia of Philosophy* (Summer 2014 Edition), Edward N. Zalta (ed.), URL = <<http://plato.stanford.edu/archives/sum2014/entries/practical-reason/>>., accessed March 30, 2014.

Warwick Pexman, J.H., Philip A. Barber, Michael D. Hill, Robert J. Sevick, Andrew M. Demchuk, Mark E. Hudon, William Y. Hu, and Alastair M. Buchan. "Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT Scans in Patients with Acute Stroke." *American Journal of Neuroradiology* 22 (2001): 1534-1542.

Waymack, Mark H. "Yearning for Certainty and the Critique of Medicine as 'Science.'" *Theoretical Medicine and Bioethics* 30 (2009): 215-229.

Wechsler, Lawrence R. "Intravenous Thrombolytic Therapy for Acute Ischemic Stroke." *New England Journal of Medicine* 364 (2011): 2138-2146.

Weisz, George. *Divide and Conquer: A Comparative History of Medical Specialization*. Oxford: Oxford University Press, 2006.

Whiteley, William, Peter Sandercock, Joanna Wardlaw. "Uncertainties About Thrombolysis Should Be Addressed with Large-Scale Randomized Trials." *Stroke* 36 (2006): 2662.

Williams, Andrew N. "Thomas Willis' Understanding of Cerebrovascular Disorders." *Journal of Stroke and Cerebrovascular Diseases* 12 (2003): 280-284.

Worrall, John. "What Evidence in Evidence-Based Medicine?" *Philosophy of Science* 69 (2002): S316-S330.

Worrall, John. "Evidence in Medicine and Evidence-Based Medicine." *Philosophical Compass* 2 (2007): 981-1022.

Worrall, John. "Evidence and Ethics in Medicine." *Perspectives in Biology and Medicine* 51 (2008): 418-431.

Worrall, John. "Evidence: Philosophy of Science Meets Medicine." *Journal of Evaluation in Clinical Practice* 16 (2010): 356-362.

Wraith, David C., Michel Goldman, and Paul-Henri Lambert. "Vaccination and autoimmune disease: what is the evidence?" *The Lancet* 362 (2003): 1659-1666.

Wyer, Peter C., and Suzana A. Silva. "Where is the wisdom? I – A conceptual history of evidence-based medicine." *Journal of Evaluation in Clinical Practice* 15 (2009): 891-898.

Young, John. "From Apoplexy to Stroke: Plus Ça Change..." *Age and Ageing* 26 (1997): 329-330.