CLINICAL RESEARCH IN CONTEXT: THE ETHICS AND EPISTEMOLOGY OF CLINICAL SCIENCE

by

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For my mother

Diana Pearson Anderson

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Abstract

In this essay I argue that the usual understanding of the field of research ethics is too narrowly focused on the protection of research participants. While protection of research participants is undoubtedly a desideratum, it is not the only matter of concern. Research ethics must also concern itself with the protection of patients, since the whole point of clinical research is to derive knowledge that will improve patient care. This second area of concern requires us to attend also to the research agenda itself.

There is, however, a conspicuous lack of serious critical work concerning the research agenda in the research ethics literature. No doubt there are historical and practical reasons for this state of affairs, but I believe the problem is primarily conceptual, and can be traced back to one of the foundational conceptual distinctions in research ethics: the distinction between research and practice.

At least since the seminal work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in the 1970's, a fundamental distinction between clinical research and clinical practice has underwritten both conceptual work in research ethics and regulations governing research involving human subjects. I believe that much contemporary interpretation of the distinction between research and practice as drawn by the National Commission in *The Belmont Report* is off the mark. It seems to me, however, that the distinction as found in *The Belmont Report* lends itself to such misinterpretation. If the distinction is to play the fundamental role in research ethics that is it supposed to, I believe it needs to be reworked in such a way that it wears its epistemological and metaphysical presuppositions on its shoulder, so to speak. That is my goal in this essay.

The central results of this work are twofold: (1) an enriched understanding of the epistemology of clinical research, a result of interest in its own right; and (2) insight into how to improve research ethics, facilitating both superior protections for research participants and the improvement of clinical practice.

List of Abbreviations Used

AES – Absolute evidentiary standard

CIHR – Canadian Institutes of Health Research

CIOMS – Council for International Organizations of Medical Sciences

EBM – Evidence-based medicine

DHEW – (U.S.) Department of Health, Education, and Welfare

ICH – International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)

MRI – Magnetic resonance imaging

NIH – (U.S.) National Institutes of Health

NSERC – The Natural Sciences and Engineering Research Council of Canada

POR – Patient-oriented research (as in Applied POR or Basic POR)

REB – Research ethics board

RCT – Randomized controlled trial

SSHRC – The Social Sciences and Humanities Research Council of Canada

SSRI – Selective serotonin re-uptake inhibitor

TCPS – (Canadian) Tri-Council Policy Statement

TO – (Principle of) Therapeutic Obligation

Glossary

The phases of pharmaceutical research:

Phase I:

> Phase I clinical trials conventionally examine the acute, dose-related pharmacological toxicities of new pharmaceutical drugs; they are often conducted in healthy subjects, but may involve patients in studies with interventions that are known to be toxic (TCPS, 1998, 7.1).

Phase II:

> Phase II clinical trials primarily examine the short-term pharmacological toxicities of and, to a lesser extent, the efficacy of new drugs; they are conducted in populations with specific diseases (TCPS, 1998, 7.1).

Phase III:

> Phase III clinical trials primarily examine the pharmacological efficacy and, to a lesser extent, the short-term toxicities of new drugs. Phase III and IV clinical trials are designed to increase the survival or the quality of life of subjects suffering from a specific disease or condition (TCPS, 1998, 7.2).

Phase IV:

> Phase IV clinical trials, also known as post-marketing surveillance studies, primarily examine the long-term efficacy and toxicity of already marketed drugs (TCPS, 1998, 7.2).

Clinical equipoise:

> "honest, professional disagreement among expert clinicians about the preferred treatment" (Freedman, 1987, 144).

The principle of clinical equipoise:

> "[The principle of clinical equipoise says that] at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed" (Freedman, 1987, 144).

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I would be remiss if I didn't also thank the rest of the faculty, the students, and staff of the Department of Philosophy at Dalhousie University. The Department has provided me with a supportive and stimulating home for the last five years or so, and I will miss it greatly.

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James A. Anderson

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Chapter One: Introduction

Privileging brevity over accuracy, the title of this essay misleadingly suggests that it is concerned with the ethics and epistemology of *clinical research*. In fact, this essay is concerned with the ethics and epistemology of *applied patient-oriented research* (Applied POR), a branch of clinical research involving direct contact with patients or healthy volunteers that studies the management of disease.[1] I feel compelled to clarify this point because I insist upon such clarity in the following. Indeed, one of the central theses of this essay is that we cannot make sense of the ethics of research involving human subjects unless we avoid unqualified talk of 'research,' or even 'clinical research,' and get clearer concerning the specific form of inquiry in question. Another crucial thesis is that we can't accomplish this task without paying close attention to the context within which that form of inquiry takes place. Having said that, for the sake of brevity I will persist in using the familiar phrase 'research ethics' to refer to that field of inquiry concerned with the study of the ethics of research involving human subjects despite the fact that this phrase is ambiguous; there are, after all, many different forms of research involving human subjects, conducted for different reasons, using different methods, that are (or should be) governed by correspondingly different ethical and epistemological norms, or so I will argue.

In this essay I offer a critique of the widespread assumption that there is a meaningful (substantive) distinction between research and practice in clinical contexts.

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[1] As I emphasize later on, Applied POR is not restricted to studying the management of *disease*. For the purposes of this essay, studies of the management of *disease* are treated as paradigmatic of Applied POR, but Applied POR also concerns itself with studying interventions designed to enhance well-being more generally, as well as interventions designed to ameliorate injury or manage disability, neither of which are properly construed as diseases.

My primary thesis is that clinical research and clinical practice are, and should be, mutually interdependent, both conceptually and practically. The central intuition guiding my work is that the epistemology and ethics of the two activities are, and should be, intimately connected; failure to acknowledge this fact does damage to clinical research, clinical practice, and research ethics as well.

I believe that the usual understanding of the field of research ethics is too narrowly focused on the protection of research participants. While protection of research participants is undoubtedly a desideratum, it is not the only matter of concern. Research ethics must also concern itself with the protection of patients, since the whole point of clinical research is to derive knowledge that will improve patient care. This second area of concern requires us to attend also to the research agenda itself. As every major set of guidelines since the Nuremberg Code has affirmed, human subjects research is justified only if it promises to yield valuable results. Put another way, valueless research is inherently unjustified because it puts participants at risk for nothing. This point is uncontroversial, though it is far from clear that all or even most clinical research undertaken in recent years satisfies this requirement. Lip service is paid to this requirement, but research that is clearly of dubious value continues apace with the approval of research ethics boards (REBs) charged with enforcing ethical guidelines that include this requirement.

Preoccupation with the protection of the human subjects of research is, no doubt, tied to the history of the field's development: new developments in research ethics have typically followed major scandals in the research community, scandals involving the harmful abuse or neglect of human participants in research. *The Nuremberg Code* (1949)

was developed in response to the war crimes committed by Nazi medical researchers during World War II. The *Declaration of Helsinki*, originally published by the World Medical Association in 1964, was written as a guide to "every doctor in biomedical research involving human subjects" following the belated recognition that unethical research was not a phenomenon isolated to Nazi Germany but could and did happen all over the world. (The *Declaration* has since undergone eight revisions, most recently in 2000.) Additional international guidelines have since been published by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (originally published in 1982, most recently revised in 2002), and by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. (Established in 1990, the ICH's most recent guidelines were published in 2000.)

Similarly, the promulgation of national guidelines typically followed local scandals. In the United States, for example, serious work in research ethics began following a series of now infamous scandals. One of the first major scandals involved Thalidomide, an inadequately tested drug prescribed to pregnant women to combat morning sickness. Between 1950 and 1962, approximately 10,000 children were born with severe birth defects. When this tragedy came to light in 1962, the U.S. government enacted legislation requiring that pharmaceuticals be proven safe as a condition of approval for sale (Katz, 1972).

Four years later, Henry Beecher published his landmark paper "Ethics and Clinical Research" (1966) in the *NEJM*. In this article Beecher described twenty-two medical experiments that clearly endangered the participants either without their

knowledge or under coercive circumstances. One of these cases was the hepatitis experiment at the Willowbrook State Hospital in which severely retarded children were injected with hepatitis virus. Though their parents consented to these injections, since consent was a condition of admission to the hospital, their consent was clearly coerced (Katz, 1972). Another now 'classic' case discussed by Beecher was the cancer experiment at the Jewish Chronic Disease Hospital in 1963. In this experiment, researchers injected live human cancer cells into 22 chronically ill, debilitated non-cancer patients in order to discover whether cancer cells would live longer in debilitated non-cancer patients or debilitated cancer patients. The injections were given without the patients' consent (Katz, 1972).

However, it was the horrors of the Tuskegee syphilis study, revealed to the world in 1972, that finally spurred the U.S. government to enact comprehensive legislation governing research involving human subjects. In this experiment, which was conducted from 1932-1972, the U.S. Public Health Service conducted an experiment on 399 black men in the late stages of syphilis. These men, mostly illiterate farm workers from one of the poorest counties in Alabama, were never told that they were suffering from syphilis. Furthermore, even though effective treatment for syphilis (penicillin) became widely available in the 1940s, researchers intentionally denied the enrolled men treatment. By the end of the experiment 28 of the men had died directly from syphilis, 100 had died of related complications, 40 of their wives had become infected, and 19 of their children had been born with congenital syphilis (Katz, 1972).

Shortly after the Tuskegee scandal broke, the U.S. government created the National Commission for the Protection of Human Subjects of Biomedical and

Behavioral Research in 1974 which, in turn, led to the publication of ten reports (including *The Belmont Report*) and legislation governing publicly funded research involving human subjects. As of 2007, most nations (certainly the so-called developed nations) have guidelines for human subjects research. Canada's *Tri-Council Policy Statement* (TCPS) was published in 1998.

Given the history of the field, it is unsurprising that research ethics is narrowly focused on the protection of the human subjects of research. It is likely, furthermore, that the practical realities of the regulatory system have exacerbated this tendency. Most nations have developed a system of independent prospective review designed to enforce guidelines/legislation governing research involving human subjects. In Canada, for example, research ethics boards (REBs) are charged with monitoring the ethical acceptability of research involving human subjects (as well as research involving human remains, tissues, embryos, or foetuses) as a condition of funding from one of the three national granting councils (i.e., the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC)). In Canada this means ensuring that research occurring in their local jurisdiction (e.g., at the hospital within which the REB is located) is conducted in accordance with the TCPS. The TCPS requires that research involving human subjects be conducted in a manner consistent with eight ethical principles: respect for human dignity; respect for free and informed consent; respect for vulnerable persons; respect for privacy and confidentiality; respect for justice and inclusiveness; balancing harms and benefits; minimizing harm; and maximizing benefits (TCPS, i.5-i.6). The last principle requires that research involving human

subjects yield results that are scientifically and/or socially valuable. But REBs are notoriously overworked and under-supported; perhaps REBs are simply not in a position to make determinations of scientific or social value.

Some or all of these factors are undoubtedly at work here. But all of these features of the real world of REB review do not speak to the dearth of serious critical work concerning the requirement for scientific or social value, or regarding the research agenda more generally, in the research ethics literature. Here, I think, the problem is primarily conceptual, and can be traced back to one of the foundational conceptual distinctions in research ethics: the distinction between research and practice.

At least since the seminal work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the 1970s, a fundamental distinction between research and practice has underwritten both conceptual work in research ethics and regulations governing research involving human subjects. Abbreviated, the distinction runs as follows:

> The term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success... By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizeable knowledge... (*The Belmont Report*, 1978, 3)

This distinction is supposed to capture the disparate methods, goals, and risks associated with these two activities. The distinction, thus, reflects what are taken to be major differences between research and practice: whereas research proceeds according to the dictates of formal protocols, practice proceeds according to the judgment of the attending physician (in consultation with the patient involved); whereas research aims to produce generalizeable knowledge, practice aims to provide optimal care to patients; whereas

research is an activity concerned with groups of patients, practice is concerned with individuals; and whereas research aims to benefit future patients, practice aims to benefit individual patients in the here and now. Finally, all of these differences are taken to add up to a further, perhaps fundamental, difference between research and practice. In clinical practice the interests of physician and patient may converge: both desire the health of the patient. In research, however, the interests of investigator and subject are in principle divergent: whereas the investigator is interested in developing generalizeable knowledge, the patient is interested in therapeutic benefit. We draw a fundamental distinction between research and practice, in other words, because there is supposed to be an inherent potential for exploitation in the context of research that is absent in the context of practice.

There is something undeniably right about the distinction between research and practice; the two activities are, in an obvious way, distinguishable. Furthermore, for certain purposes, notably the purpose for which the distinction was developed – isolating those practices for which review is required – the distinction has been, and continues to be, for the most part, serviceable.[2] The latter comment, however, highlights an important point that I will develop in what follows: the distinction was originally drawn in order to clarify when review was required.[3] It was developed, in other words, for pragmatic reasons. Nonetheless, in recent scholarship, the distinction is increasingly reified,

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[2] That being said, it has become increasingly obvious in recent years that the current distinction does not fit well with fields not originally considered when the distinction was drafted, e.g., public health, quality improvement, etc.

[3] "It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, *in order to know what activities ought to undergo review for the protection of human subjects of research*" (*Belmont Report*, 1978 – emphasis mine).

research and practice treated as essentially different and incompatible activities, invariably by appeal to the National Commission's work.

I believe that much contemporary interpretation of the distinction between research and practice as drawn by the National Commission in *The Belmont Report* is off the mark. However, it seems to me that the distinction as found in *The Belmont Report* lends itself to such misinterpretation. If the distinction is to play the fundamental role in research ethics that is it supposed to, I believe it needs to be reworked in such a way that it wears its epistemological and metaphysical presuppositions on its shoulder, so to speak. That is my goal in this essay.

The essay begins with a quotation of the relevant text from *The Belmont Report* and a brief review of the National Commission's conceptual development. I then argue that the National Commission's distinction between research and practice effectively poses the question as to their relation, a question that has a long and complex history concerning which the National Commission said very little. I illustrate the importance of this question by providing a brief overview of the history of medical epistemology in the 19th century, followed by a summary of some of the contemporary controversy concerning the proper scope of evidence based medicine. Both of these overviews show that, far from being obviously unproblematic, the relationship between research (defined in terms of generality) and practice (defined in terms of particularity) has long been, and continues to be, problematic.

To date, our best solution to this problem are those methods now referred to under the rubric of "clinical research". Curiously, 'clinical research' is never mentioned in *The Belmont Report*. Instead, we have talk of research *simpliciter* defined in terms of

generalizeable knowledge. In Chapters Three and Four I redress this problem, criticizing the National Commission's definitions of research and practice respectively, and offering novel definitions of both. In Chapters Five and Six I apply the results of the previous chapters to a number of central problems in research ethics.

In Chapter Five, I reexamine the randomized controlled trial dilemma (RCT dilemma) and the so-called 'historical question' that issues from it. I argue that the dilemma is false because it is generated by the same conceptual errors that inform the mistaken picture of 'research' and 'practice' I criticize in Chapters Three and Four. I also reframe the so-called historical question in epistemological terms and situate the principle of clinical equipoise as a methodological constraint on the conduct of Applied POR.

In Chapter Six I reexamine the role of the principle of clinical equipoise in the regulation of clinical research in light of my analysis. On my view, the principle is broader in scope than previously believed, and its role in the regulation of clinical research different than previously understood. I then offer a reassessment of the concepts of "therapeutic research" and "non-therapeutic research". Finally, I tackle the so-called therapeutic misconception. On my view, the therapeutic misconception is primarily a problem with the research agenda. If we are asking the right questions, the "therapeutic misconception" largely disappears.

In the concluding chapter, I advocate a reorientation of research ethics away from an exclusive focus on the protection of the human subjects of research. Research ethics must also concern itself with the protection of patients and, thus, with the research agenda itself. The supposition on the part of the National Commission (and their contemporary commentators) that research and practice are sharply distinct has obscured this problem

from view by encouraging a radically decontextualized view of clinical science. We can't (and shouldn't) draw a sharp distinction between clinical research (Applied POR) and clinical practice because determinations of scientific value, or clinical relevance, are themselves morally laden. These determinations shape the content and, therefore, the ethics of clinical practice. Thus, these determinations should be shaped by the norms we deem appropriate in the context of practice: the norms of therapeutic beneficence and non-maleficence.

In sum, I believe that the supposition on the part of the National Commission (and many of its contemporary commentators) that research and practice are sharply distinct activities has encouraged an uncritical stance toward the research agenda by reinforcing problematic assumptions about the epistemology of clinical science. This supposition has forestalled rather than facilitated criticism of the research agenda from within the research ethics literature. It is my hope that this essay will take us some way toward addressing this problem. I hasten to re-emphasize, however, that there are many different forms of research involving human subjects, conducted for different reasons, using different methods, that are (or should be) governed by correspondingly different ethical and epistemological norms. It is not my intention to suggest that clinical research or Applied POR should be prioritized over other forms of health research such as research into public health and prevention. Arguably, these forms of research deserve a much larger share of the available resources. That being said, I do maintain that in the case of Applied POR, the crucial question is whether or not the research agenda is responsive to the realities of clinical practice.

Chapter Two: The Central Problem

Introduction

I begin by quoting the entirety of section A of *The Belmont Report* (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978):

> It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.
>
> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.[1] By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizeable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol and sets forth an objective and a set of procedures designed to reach that objective.
>
> When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is

[1] In the original text there is a lengthy and important footnote at this point which I will also quote in full here: "Although practice usually involves interventions designed solely to enhance the well being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research" (The National Commission, *The Belmont Report*, 1978, 3).

> the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.
>
> Research and practice may be carried on together when research is designed to evaluate a therapy. This need not cause any confusion regarding whether or not an activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects (The National Commission, *The Belmont Report*, 1978, 3).

Prima facie, the distinction between research and practice as found in *The Belmont Report* is rather obvious, even trivial. Abbreviated, the distinction runs as follows:

> The term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success... By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizeable knowledge...

No doubt, the apparent triviality of the distinction is one of its strengths. Furthermore, for the purpose it was ostensibly developed – identifying those practices for which review is required – the distinction has been and continues to be for the most part serviceable. There is, however, a growing tendency to attribute substantive metaphysical, epistemological and, ultimately, moral significance to the distinction. Increasingly, in other words, the distinction is interpreted as a definitive description of the nature and goals of research and practice, rather than a conceptual tool designed to facilitate the implementation of a system of review. This development is reflected in the now widespread acceptance of a sharp distinction between the ethical norms appropriate to the contexts of research and practice respectively, a position that reaches its apogee in a series of papers by Franklin Miller and Howard Brody (See Miller 2002, Miller & Brody,

2003; Miller & Rosenstein, 2003; Miller, 2006; Miller & Brody, 2007), but is reflected in a host of other publications[2].

Significantly, this view of research and practice as essentially (i.e., metaphysically, epistemologically, and therefore ethically) distinct activities is invariably justified by appeal to the National Commission's work. The problem is that the National Commission said rather little about the metaphysical and/or epistemological characteristics of research and practice, and even less about the relationship of research and practice to each other. Furthermore, what they did say – confined almost entirely to the brief discussion in *The Belmont Report* on the "Boundaries Between Practice and Research" quoted above – is ambiguous and misleading. As a result, interpretation of the National Commission's distinction between research and practice has proceeded on the basis of largely unexamined assumptions concerning the epistemic and metaphysical character of these activities.

The aims of this chapter are threefold. First, I provide some background information concerning the National Commission itself, elucidating relevant aspects of their conceptual work, and relating this work to their mandate. My aim is to clarify how the views of the National Commission changed over time, and to show how these changes, and the familiar distinction that issued from them, were pragmatically useful vis-à-vis the National Commission's mandate.

---

[2] See, e.g, Veatch, 2007; Gifford, 2007; London, 2007; Appelbaum et al, 2006; Wasserman et al, 2006. I believe much of the large literature on the so-called therapeutic misconception implicitly makes the same assumption, i.e., that there is a sharp distinction between the ethical norms appropriate to the contexts of research and practice respectively. See, for example, Horng & Grady, 2003; Miller & Brody, 2003; Dresser, 2002.

Second, I examine the distinction from both an epistemological and metaphysical perspective. The prima facie pragmatic utility of the distinction must be balanced against its metaphysical and epistemological shortcomings; once a sharp distinction between research and practice is drawn a further question presents itself: *how are the two activities related*? Unfortunately, the National Commission said very little by way of response to this question. They seem to simply assume that the relationship between research and practice is unproblematic. By insisting upon the generality of research and the specificity of practice, however, the National Commission effectively poses the question as to their relation. To then assume that research can and does lead to improved practice, as the National Commission clearly did, without offering some account of their relation is simply to beg the question as to how the general relates to the specific.

To make matters worse, this question has a long and complex history. The proper epistemic relation between the general (e.g., theoretical knowledge, and/or facts about the 'average patient') and the specific (e.g., concrete knowledge and/or facts about an individual patient) has been controversial at least since the 19th century, and continues to be controversial today. Indeed, David Thomasma and Edmund Pellegrino, following Marx Wartofsky, argue that this question – how theoretical knowledge can be applied to concrete, individual persons with therapeutic results – is THE central epistemological problem of medicine (Thomasma & Pellegrino, 1981; 84). In the second third of this chapter I illustrate the continuity of this problem by providing a brief overview of the history of medical epistemology in the 19th century, followed by a summary of contemporary controversy concerning the proper scope of evidence based medicine. Both

of these overviews show that, far from being obviously unproblematic, the relationship between research and practice has long been, and continues to be, problematic.

In the final section of this chapter, I argue that the National Commission's definitions of research and practice effectively eliminate the conceptual space for the sort of research – bona fide clinical research – required to solve this problem. In other words, the National Commission's definitions of research and practice are problematic because they both raise the specter of the central problem – how can theoretical knowledge be applied to concrete, individual persons with therapeutic results – and effectively eliminate the conceptual space required for its solution: a bona fide clinical research.

The National Commission: The Distinction is Born

The 'locus classicus' for the concepts of research and practice, and the distinction between them, as currently employed in contemporary Anglo-American research ethics is undoubtedly *The Belmont Report*, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in 1978. The National Commission was established by (Title II of) the National Research Act (1974) to study the ethical principles underlying biomedical and behavioral research on human subjects and to make recommendations to the Secretary of the US Department of Health, Education, and Welfare (DHEW), and to Congress, for the protection of human subjects (*Research on the Fetus*, 1975; preface). The Commissioners included three MDs (Kenneth Ryan – Chair, Robert Cooke, and Donald Seldin), two scientific researchers (Joseph Brady and Eliot Stellar), two bioethicists (Albert Jonsen and Karen Lebacqz), two Professors of Law (Patricia King and David Louisell), an

attorney (Robert Turtle), and the President of the National Council for Negro Women, Inc. (Dorothy Height). The Commission also employed a large staff for Professional consultation and administrative support. Among the former was Robert Levine, MD, the principal author of the distinction between research and practice.

The National Commission published ten reports between 1975 and 1978: *Research on the Fetus* (1975); *Research Involving Prisoners* (1976); *Research Involving Children* (1977); *Psychosurgery* (1977); *Disclosure of Research Information Under the Freedom of Information Act* (1977); *Research Involving Those Institutionalized as Mentally Infirm* (1978); *Institutional Review Boards* (1978); *The Belmont Report* (1978); *Ethical Guidelines for the Delivery of Health Services by DHEW* (1978); and *The Special Study (Implications of Advances in Biomedical and Behavioral Research)* (1978).

One of the specific charges to the National Commission was to identify the basic ethical principles that ought to underlie the conduct of human subjects research (*The Belmont Report*, 1978, 2). To carry out the above, the National Commission was further directed to consider, among other things, "...the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine" (*The Belmont Report*, 1978, 2). The National Commission met this charge explicitly in *The Belmont Report*, published near the end of the National Commission's tenure (1978). *The Belmont Report*, then, can be viewed as an articulation of the conclusions of deliberations by the National Commission that began with *Research on the Fetus* almost four years earlier.

In 2004, a series of interviews of key participants in the National Commission were conducted in honour of the 25th anniversary of *The Belmont Report*. In the course of the interview with Robert Levine (the consultant to the National Commission who was

responsible for crafting the definitions of 'research' and 'practice'), Levine observes that clarity concerning the distinction between research and practice was fundamental to the National Commission's contribution to the field of research ethics:

> ...I think the full expression of the Commission's contribution to the field of research ethics is best realized in that report *Research Involving Children* (1977) *because there they had fully come to terms with the meaning of their new definitions of research and practice...* (*Belmont Oral History Project*, 2004 – emphasis mine)

Once, again, the distinction as stated in *The Belmont Report* runs as follows:

> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. (*The Belmont Report*, 4, 1978)

First of all, notice that practice is defined as an activity concerned with a particular individual patient or client, whereas research, presumably, is an activity concerned with groups or populations. Here the National Commission draws a contrast between the universalist character of research and the particularist character of practice. Second, practice is characterized as a pragmatic activity: "the purpose of ...practice is to provide diagnosis, preventive treatment or therapy to particular individuals". Research, on the other hand, is characterized as an epistemic activity: "the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to contribute to generalizeable knowledge (expressed for example in theories, principles, and statements of relationships)". Both of these contrasts are particularly salient with respect to the historical discussion to come.

Notably absent in *The Belmont Report* is any talk of "therapeutic and nontherapeutic research". As the above quotation from Levine implies, and anyone familiar with the work of the National Commission knows, the Commission's own basic concepts changed over time. In its first two reports (*Research on the Fetus* and *Research Involving Prisoners*) the National Commission employed the concepts of therapeutic and nontherapeutic research. In *Research on the Fetus*, for example, we find the National Commission offering the following definitions:

- 'Research' refers to the systematic collection of data or observations in accordance with a designed protocol.
- 'Therapeutic research' refers to research designed to improve the health condition of the research subject by prophylactic, diagnostic or treatment methods that depart from standard medical practice but hold out a reasonable expectation of success.
- 'Nontherapeutic research' refers to research not designed to improve the health condition of the research subject by prophylactic, diagnostic or treatment methods (*Research on the Fetus*, 1975, 6).

The terms 'therapeutic,' and 'nontherapeutic research' were, it seems, originally introduced to capture the intuition that there was a morally salient difference between research that aimed to provide direct medical benefit to participants and research that did not.

Though these terms were later rejected by the Commission (they no longer appear in *Research Involving Children*)[3] – I will review their arguments for this rejection in a moment – the inclusion in the early reports of these terms speaks to the National Commission's recognition of the complex relationship between research and practice. Indeed, as the following excerpts from the *Research on the Fetus* show, the complexities

[3] In the same interview quoted above, Levine describes the distinction between therapeutic and nontherapeutic research as 'grotesque': "...in the *Research on the Fetus*, they still were using that grotesque dichotomy between therapeutic and non-therapeutic research. I say "grotesque" because it inevitably generates regulations that make no sense" (Belmont Oral History Project, 2004).

of the relationship between research and practice were still very much at the surface of the Commission's early deliberations:

- ...The preponderance of all research involved experimental procedures designed to benefit directly a fetus threatened by premature delivery, disease or death, or to elucidate normal processes of development. Some research constituted an element in the health care of pregnant women... (*Research on the Fetus*, 1975, 62).
- In therapeutic research directed toward the fetus, the fetal subject is selected on the basis of its health condition, benefits and risks accrue to that fetus, and proxy consent is directed toward that subject's own welfare...(*Research on the Fetus*, 1975, 65)..
- Therapeutic research directed toward the pregnant woman may expose the fetus to risk for the benefit of another subject and this is at first glance more problematic. Recognizing the woman's priority regarding her own health care, however, the Commission concludes that such research is ethically acceptable provided that... (*Research on the Fetus*, 1975, 65).
- Therapeutic research directed toward the fetus may be conducted or supported... provided such research (a) conforms to appropriate medical standards... (*Research on the Fetus*, 1975, 73).

In each of these excerpts from the *Research on the Fetus*, there is explicit mention of direct benefits to participants, in this case either the pregnant woman or the fetus. 'Therapeutic research' is, at least partly, *directed toward* the medical benefit of the participants. In the first excerpt, research and therapy are explicitly combined: "...research involved experimental procedures designed to benefit...". Furthermore, the same excerpt states that in some cases research was a *constituent* of medical therapy: "...[s]ome research constituted an element in the health care of pregnant women...". Finally, in the last excerpt, 'therapeutic research' is implicitly analogized with standard, or validated, therapy insofar as the permissibility of therapeutic research is deemed contingent upon its conformity with "appropriate medical standards". Far from suggesting that research and practice are distinct and separable activities, the early work of the National Commission presents a picture wherein research and practice (therapy) are intimately intertwined.

Again, by the time of *Research Involving Children*, the National Commission had rejected the concepts of therapeutic and nontherapeutic research, preferring only 'research' *simpliciter*.[4] Their explicit argument for this change of terminology is given in Chapter 8 of *Research Involving Children*:

> Research, by definition, is intended to develop general knowledge. Therapy, by definition, is for the benefit of an individual and therefore does not inherently involve any generalizeable component. The term 'therapeutic research' thus mixes together two quite different ingredients, and it remains unclear what 'therapeutic research' could mean. (*Research Involving Children*, 1977, 97)

Notice, again, how research and practice are contrasted: first a contrast is drawn between the individualized or particularist character of practice (therapy) and the generalized or universalist character of research; second a contrast is drawn between the pragmatic character of practice and the epistemic character of research. The strict dichotomization of research and practice suggested here is, however, belied in other parts of *Research Involving Children*, particularly in sections concerned with the assessment of harms and benefits. Despite rejecting the notion of therapeutic research, *Research Involving Children* explicitly discusses the relevance of direct benefits to individual participants in a research study for the assessment of ethical permissibility. Thus, in Recommendation 4, the National Commission permits research involving children involving more than minimal risk if, and they are explicit about this, the intervention under study "holds out the prospect of direct benefit for the individual subjects" (*Research Involving Children*, 1977, 5). Furthermore, the same recommendation indexes the acceptable risk/benefit ratio to "available alternative approaches". Though the recommendation itself is ambiguous

[4] In *Research Involving Children*, 'research' is defined as: "a formal investigation designed to develop or contribute to generalizable knowledge".

concerning just what these "alternative approaches" are (i.e., whether they experimental or validated practices), the ensuing commentary is more specific:

> Such risk is acceptable, for example, when all available treatments for a serious illness or disability have been tried without success... It is also appropriate to involve children in research when *accepted therapeutic, diagnostic or preventive methods* involve risk or are not entirely successful, and new biomedical or behavioral procedures under investigation present at least as favorable risk-benefit ratio (sic). (*Research Involving Children*, 1977, 6-7 – emphasis mine)

The relevant 'alternative approaches,' in other words, are those, if any, available outside of the research context in standard medical practice. These aspects of *Research Involving Children* clearly indicate that the National Commission viewed research itself as a sometime vehicle for therapy, and the relevant index for a tolerable risk/benefit ratio in research, the risk/benefit ratio presented by standard medical practice. Again, despite rejecting the notion of therapeutic research, even at the time of *Research Involving Children* the close and complex interrelationship between research and practice (therapy) is still very much at the surface of the National Commission's work.

By the time of *The Belmont Report*, however, the concepts of therapeutic and nontherapeutic research are long gone. Instead we have the distinction between research (*simpliciter*) and practice as seen above. Even in *The Belmont Report*, however, there remains clear acknowledgment of the fact that the distinction between research and practice often *seems* blurred because:

> ...both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called 'experimental' when the terms 'experimental' and 'research' are not carefully defined. (*The Belmont Report*, 1978, 3)

Furthermore, the section on the assessment of risks and benefits is similar to that found in *Research Involving Children*. Thus, the term 'benefit' is defined in *The Belmont Report*

as "something of positive value related to health or welfare". The potential for direct benefits to participants is explicitly mentioned: "[r]isks and benefits of research may affect the individual subjects…". And, concerning the justifiability of research, it is required that "[w]hen research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk, looking usually to the likelihood of benefit to the subject…" (*The Belmont Report*, 1978, 7).

On the other hand, there are important differences between *The Belmont Report* and *Research Involving Children,* not to mention *Research on the Fetus*. There is a shift in emphasis across these three reports (as well as those intervening) away from a picture in which research is intricately intertwined with practice, to a picture wherein research and practice are presented as distinct and different activities. This shift is evidenced in subtle textual differences. For example, in both *Research on the Fetus* and *Research Involving Children*, as noted above, there is much talk of research that "holds out the prospect of direct benefit for the individual subjects". Furthermore, these potential benefits are not presented as accidental features of the research study; rather, they are characterized as features of the study *by design*. The study is partly *directed toward* the medical benefit of the participants.

In *The Belmont Report*, however, the language is weaker, the picture different. Potential benefits to research participants are presented in language that makes their occurrence seem fortuitous. This shift in emphasis is seen most clearly in the discussion of the distinction between research and practice as found in *The Belmont Report*. Consider the following passage, partly quoted above: "[t]he distinction between research and practice is blurred partly because both often *occur* together…" (*The Belmont Report*,

1978, 3 – emphasis mine). Notice how the coincidence of research and practice is treated passively, as an *occurrence*, as something that just happens. In this picture, prophylactic, diagnostic, and/or therapeutic benefits are presented as a side-effect of research, an accidental feature of research not to be confused with its essential nature. Later, I will argue that this picture of research is implausible: therapeutic benefits are an essential feature of research designed to evaluate therapeutic interventions, or so I will contend. For now, however, it suffices to point out that this picture, wherein therapeutic benefits are portrayed as accidental (in both the Aristotelian sense of something inessential, and in the modern sense of something that happens by chance), is significantly different from the picture presented even in *Research Involving Children*.[5] Even if research and practice often occur together, states *The Belmont Report*, research is not directed toward, let alone (even partly) constituted by, therapeutic practice(s).

At this point it is useful to recall that the distinction between research and practice was developed in order to identify those activities (research) for which ethical review was required. As previously mentioned, this was one of the tasks assigned to the National Commission by the National Research Act. Furthermore, acknowledgement of this goal is peppered throughout *The Belmont Report* itself. For example, Section A, "Boundaries Between Practice and Research," begins with the following:

> It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, *in order to know what activities ought to undergo review for the protection of human subjects of research* (*The Belmont Report*, 1978, 3 – emphasis mine).

[5] This picture is also incompatible with the requirements of prospective review as detailed in *The Belmont Report* itself. Prospective review requires us to predict with reasonably high probability the potential benefits of a therapeutic intervention in order to assess the risk/benefit ratio of a proposed study. In this minimal sense, then, *The Belmont Report* is inconsistent.

Later in the text, a long footnote carefully delineates why interventions not designed solely to enhance the well-being of an individual patient, e.g., blood donation, skin grafts, organ transplants, vaccinations, are still classified as practice and, thus, do not require review. The passage is revelatory not only of the purpose for which the distinction was drawn, but also of problems associated with distinguishing research and practice on the basis of their focus on groups vs. individuals respectively (I return to these problems later):

> Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; *thus, it is a practice and need not be reviewed as research* (*The Belmont Report*, 1978, 3 – emphasis mine).

Finally, at the end of Section A, the following statement captures the pragmatic spirit of the distinction very clearly:

> Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review*; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects* (*The Belmont Report*, 1978,3 – emphasis mine).

Even if things get blurry, says the National Commission, there's no cause for concern because we can still identify whether the activity in question requires review by appeal to the general rule adduced above.

Judging from passages like these, it seems clear that the National Commission was not particularly concerned with providing an accurate picture of the metaphysical and/or epistemological characteristics of research and practice, or the relationship between them. Again, given their pragmatic aims, this makes some sense. It is worth noting, however, that there is reason to believe that (at least some of) the members of the

National Commission believed the distinction between research and practice to be so obvious as to not require elucidation. The following statement made by Levine in the same 2004 interview mentioned above is revelatory in this regard:

> What the Commission was asked to do by the Congress was to consider the boundaries between research…on the one hand, and the other hand, routine and accepted practice of medicine or behavioral therapy. I think the Commission responded to that charge very well. It said, "There is no boundary." You know? It's like being asked to consider the boundary between North Dakota and Nebraska – you see (Belmont Oral History Project, 2004, 8).

In case you, like me, are geographically challenged, South Dakota separates North Dakota and Nebraska. Levine appears to be saying that 'research' and 'practice' are so far apart – so distinct – that there is no need to clarify their boundary. Perhaps the dearth of metaphysical and epistemological clarity in the National Commission's reports is a function this assumption: to the members of the National Commission, it seems, the distinction was (is) simply obvious.

The Relationship Between Research and Practice

Given the pragmatic aims of the National Commission, even if a sharp distinction between research and practice is metaphysically and/or epistemically problematic, from the perspective of this goal (i.e., the isolation of activities that require review) the distinction still seems useful. The problem is that once a sharp distinction between research and practice is drawn a further question presents itself: *how are the two activities related.* This question is particularly pressing in this context because the ostensible goal and moral justification for clinical research involving human subjects is the improvement of clinical practice. As every set of guidelines for human subjects research since the Nuremberg Code has affirmed, human subjects research is morally justified only if it

promises to yield valuable results.[6] A necessary condition of value in this context is that the results of a study are, at least potentially, clinically relevant; that is, the results of research must hold out real promise for the improvement of clinical practice. In order for this promise to be fulfilled, however, these two purportedly distinct and different activities (i.e., research and practice) must somehow come into contact with one another.

Unfortunately, the National Commission had very little to say about how research and practice are related. The National Commission's silence on this issue is striking given its obvious ethical import. Having drawn a sharp distinction between research and practice, the National Commission seems to simply assume that the relationship between research and practice is unproblematic. But this assumption is patently false, even by the National Commission's own lights.

By defining research in terms of generalizeable knowledge and practice in terms of the diagnosis, prophylaxis and/or treatment of an individual, the National Commission effectively poses the question as to the relationship between the general (e.g., theoretical knowledge and/or facts about the 'average patient') and the specific (e.g., concrete knowledge and/or facts about an individual patient). To then assume that the relationship between research and practice is unproblematic without offering some account of their relation, is simply to beg the question as to how general relates to the specific.

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[6] See, for example: *The Nuremberg Code* (1949): "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature"; *The Declaration of Helsinki* (1996): "Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objectives is in proportion to the inherent risk to the subject"; *The Belmont Report* (1978): "...In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation"; *The Tri-Council Policy Statement* (1998): "The principle of beneficence imposes a duty to benefit others and, in research ethics, a duty to maximize net benefits... human research is intended to produce benefits for subjects themselves, for other individuals or society as a whole, or for the advancement of knowledge. In most research, the primary benefits produced are for society and for the advancement of knowledge".

To make matters worse, this question has a long and complex history. The proper epistemic relation between the universal and the particular, theory and practice, or the general and the specific has been a controversial question in medical epistemology since Ancient times, and continues to be controversial today. In their book *A Philosophical Basis of Medical Practice* (1981), David Thomasma and Edmund Pellegrino argue that "medicine itself represents a tension between therapeutic aims and explanatory theory" (Thomasma & Pellegrino, 1981, 10). Indeed, following Marx Wartofsky, Thomasma and Pellegrino argue that this question – how theoretical knowledge can be applied to concrete, individual persons with therapeutic results – is THE central epistemological problem of medicine. In Wartofsky's words:

> The interplay between medical practice and medical theory is not simply one topic in the epistemology of medicine; it is the fundamental or categorical framework for the construction of such an epistemology (Wartofsky quoted in Thomasma & Pellegrino, 1981, 83-4).

Underlying both the "central problem" (and the National Commission's distinction between research and practice) is recognition of the specificity of the individual patient. Whereas research is concerned with the abstract and the general (e.g., theories and/or facts about the 'average patient'), practice is concerned with concrete, particular patients, each of whom is more or less idiosyncratic. Furthermore, given the specificity of the individual patient, practice is inherently local because every patient is different. Hence the central problem: how can theoretical knowledge be applied to concrete, individual persons with therapeutic results?

In the following, I illustrate the historical and continuing significance of this problem by providing a brief overview of the history of medical epistemology in the formative years of the 19th century, followed by a summary of contemporary controversy

concerning the proper scope of evidence based medicine (EBM). Both of these overviews show that, far from being obviously unproblematic, the relationship between the general and the specific has long been, and continues to be, problematic. Indeed, our brief look at the history of 19th-century medical epistemology suggests that the problem became even more pressing following the emergence of experimental therapeutics in the final third of the 19th century. Precisely because experimental therapeutics aspired (and continues to aspire) to the universalism of the basic sciences, 'patient-specificity' of the 19th-century variety could not (cannot) survive in the laboratory.[7] EBM arose, in part, as a response to the universalist and reductionist tendencies of this now dominant epistemological paradigm.

In the final section of the chapter, I argue that the National Commission's use of the notion of specificity in *The Belmont Report* differs from the manner in which this notion was employed both by the therapeutic empiricists, and by some contemporary critics of EBM. Whereas the National Commission uses the notion of specificity in order to distinguish research and practice, 19th-century physicians and contemporary critics of

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[7] In the following section, unless I explicitly indicate to the contrary, I mean 'patient-specificity' as opposed to 'disease specificity' when I employ the term 'specificity'. It is important to distinguish the first connotation of the term 'specificity' from the latter because modern usage leans decidedly towards the latter. 'Patient-specificity' refers to the more or less radical idiosyncrasy of an individual's natural state of health and their illnesses. The notion has a long history. Lilian Furst, for example, traces its origins back to Galen's theory of humors. Since every individual had a different temperament or 'humor,' both disease and treatment were necessarily patient-specific:

> From the days of Galen, who was born in A.D. 130, the ubiquitous theory was that of the four 'humors' which corresponded to the four elements: earth, air, water and fire. In the human being, these became manifest as cold, dry, moist, or hot temperaments. Good health resulted from an equal balance of the four; illness, on the other hand, arose when one or the other got an upper hand. The therapeutic corrective was to apply the opposite: hot to cold, dry to moist, and so forth. In practice the most crucial facet of this system was its total reliance on an approach that was at once holistic and fundamentally individual. Since every patient had his or her particular temperament, the physician's primary task was to identify the prevalent humor in order to select the appropriate counteragent to the illness. External factors such as season, climate and age also played an important role in both diagnosis and remedy (Furst, 2007).

'Disease specificity' refers to the specificity of diseases rather than patients. By the end of the 19th century, the modern view that diseases are discrete entities with independent ontological statuses of their own began to take hold.

EBM marshal the notion in order to distinguish between types of knowledge. The therapeutic empiricists distinguished between basic and therapeutic knowledge. Contemporary critics of EBM distinguish between the explicit 'knowledge-that' offered by clinical research and the tacit 'knowledge-how' obtained via clinical experience. Understanding both the notion of specificity and how the National Commission's use of the notion differs from its use both in the past and by contemporary critics of EBM is crucial to understanding why the distinction between research and practice as found in *The Belmont Report* is problematic.

Specificity in 19th-century Medical Epistemology[8]

In order to fully understand the notion of specificity as it was developed and deployed in the first two thirds of the 19th century, it is necessary to put the concept into historical context by reviewing some of the key events of 19th-century medical epistemology. To do so, I rely heavily on the work of John Harley Warner, one of the few historians of medicine who has focused on developments in the epistemology of therapeutics during this period. In particular, I have relied on his account of the history of therapeutics in 19th-century America in *The Therapeutic Perspective: medical practice, knowledge, and identity in America, 1820-1885* (1997).

Warner argues that the notion of specificity rose to the fore in 19th-century medical epistemology as part of an empiricist backlash against medical rationalism. In

[8] The 19th century is a crucial period in the history of medical epistemology because it is during this century both that a peculiarly modern (empirical) version of patient-specificity was built, and the transition from 'patient-specificity' to 'disease-specificity' occurred. This transition is undoubtedly one of the most fundamental revolutions in the history of medicine (see, for example, Furst, 2007).

order to understand the notion of specificity, then, it is necessary to begin with the medical epistemology it replaced: medical rationalism.

Early 19th-century medicine in the West was dominated by the rationalist systems of Scots William Cullen (1710-1790) and John Brown (1735-1788), Americans Benjamin Rush (1745-1813) and John Cooke (1783-1853), and Frenchman F.J.V. Broussais (1772-1838). The work of all of these men reflected the Enlightenment dream that a unifying principle for medicine, mirroring the law of gravitation in the physical sciences, would be found. Since these systems typically reduced all disease to a single pathogenic process, they also reduced treatment to a simple set of operations designed to rectify the underlying pathology. Treatment informed by these systems, therefore, involved the literally systematic application of routine techniques.

Take, for example, John Cooke's system. In his massive *Treatise on Pathology and Therapeutics* (1828), Cooke laid out in great detail what, in essence, amounted to a simple system. For Cooke, 'miasmata' (infectious or noxious vapors) were the cause of virtually all diseases. Miasmata, held Cooke, weakened the action of the heart, which in turn led to cardiac dysfunction, a weakened pulse, slowed capillary circulation, and the accumulation of blood in the vena cava. He claimed that congestion of the vena cava constituted the essence of disease, and led to the various associated derangements of function, in particular the suppression of bile secretion. Reflecting this unitary account of pathology, Cooke's therapeutic regimen involved a unitary therapeutics comprised of stimulating bile secretion in order to arouse weakened organs, thereby relieving congestion and restoring health. Bile secretion was stimulated by calomel (a compound

of rhubarb and aloes), conveniently available in the form of Cooke's Pills (Warner, 1997, 47; see also Cooke, 1828).

One of the last rationalist systems to gain prominence in Europe and the New World was that of Broussais. Broussais' system, like Cooke's, is unitary. But Broussais' system inverts Cooke's. Whereas in Cooke's system pathology is caused by weakened organs (under-stimulation), for Broussais pathology is caused by over-stimulation. For Broussais, the essential feature of disease was a pathological physiological process whereby over-stimulated body functions led to anatomical lesions, typically of the gastrointestinal tract. Since disease was caused by over-stimulation, Broussais advocated treatment that would physiologically lower or deplete the patient, treatments such as the administration of a low, debilitating diet, and local depletion using leeches (Warner, 1997, 49; see also, Broussais, 1831).

Both of these systems are manifestly 'rationalist'; that is, they purport to identify universal principles of pathology and to deduce from them rules of practice. Ironically, both Cooke and Broussais claimed that their systems, as opposed to previous systems advocated by the likes of Cullen and Brown, were based purely on observation (Cooke, 1882, iii-iv; Broussais, 1831, xx and 10). Their critics saw things otherwise. By the 1840s, Cooke and Broussais had been lumped in with the earlier rationalists and they were both criticized accordingly. In his empiricist manifesto of 1844, *An Essay on the Philosophy of Medical Science*, Elisha Bartlett denounced Cullenism, Brownism, Rushism, Cooke-ism, and Broussaisism, "and all the host of other so called rational isms". Pathological systems, wrote Bartlett, "were a priori abstractions, under the misnomer of laws, or principles" (Bartlett in Warner, 1997, 50). Bartlett argued that it

was both deluded and dangerous to deduce therapeutics from such 'a priori abstractions,' and blamed the medical rationalists as the cause of "the abominable atrocities of wholesale and indiscriminate drugging" (Bartlett in Warner, 1997, 50; see also Bartlett, 1844, 201 and 290).

By the 1850s, the very word 'system' had become a term of derision in medical rhetoric, implying dogmatic acceptance of a priori theoretical commitments that led to uncritical treatment by rote. Therapeutic excesses were attributed to the followers of various exclusive systems. Thus, it was alleged by critics that blind adherence to theory led to the dangerously aggressive use of venesection by Rushites, mercury by Cookeites, and leeches by Broussaisists (Warner, 1997). Rationalism was also criticized because it was seen to cause rigidity of mind in its adherents; this rigidity, it was alleged, hindered the progress of therapeutics. Thus, one Washington physician asserted: "[t]his formalism, this routinism, is the bane of improvement in our science" (Henderson in Warner, 1997, 53). Some critics explicitly noted the way dogmatic theoretical commitments could colour observation and foreclose recognition of real anomaly:

> When once a particular set of doctrines have been imbibed, they exert a secret but powerful influence over all our habits of thought and principles of reasoning; and, unknown to ourselves, perhaps, give their peculiar hue to every subject of investigation and reflection... The mind rejects as improbable, unsatisfactory or anomalous, all those facts and principles opposed to, and 'grapples with hooks of steel' such as seem to chime in with preconceived opinions and impressions (Lyle in Warner, 1997, 53).

Medical rationalism, in other words, was criticized precisely because its various exclusive systems were decidedly universalist. Dogmatic commitment to universal principles, it was alleged, coloured observation and slowed theoretical progress by blinding the mind to real differences in pathology. Likewise, in therapeutics, rationalism

encouraged practitioners to see all cases as fundamentally alike, to ignore real differences between patients, and to offer treatment by rote in the form of indiscriminate blood-letting, drugging, and leeching.

The cure sought for these problems was epistemological reform. In the stead of rationalism, critics proposed a new medical epistemology: therapeutic empiricism. "Therapeutic empiricism" referred to a new attitude to medical knowledge, originated by the so-called Paris School, which was characterized by its opposition to "the spirit of system" (Louis, 1840 – see Warner, 1985, 226). Concordantly, the program of therapeutic empiricism was predominantly negative, involving a self-consciously critical attitude toward existing therapeutic knowledge that had not been rigorously clinically validated. Thus, proponents encouraged a critical and undoctrinaire attitude, urging students to test the validity of previous opinion and practice by close observation at the bedside.

Close observation at the bedside was a crucial aspect of the empiricist program because the empiricists were committed to what Warner calls *the principle of specificity*. The principle of specificity states that "an individualized match between medical therapy and the specific characteristics of a particular patient and of the social and physical environments" is an essential component of proper therapeutics (Warner, 1997, 58). For proponents of therapeutic empiricism, it was the rationalists' failure to abide by the principle of specificity that had led to the uncritical embrace of system and mechanical treatment by rote. By contrast with the universalist tendencies of the rationalists, therapeutic empiricists held that treatment must be:

> ...sensitively gauged not to a disease entity but to such distinctive features of the patient as age, gender, ethnicity, socioeconomic position, and moral status, and to

> attributes of place like climate, topography, and population density. (Warner, 1997, 58)

Treatment, in other words, must be indexed to patients in all their individuality. In stark contrast with the universalist character of medical rationalism, therapeutic empiricism was radically particularist. Here, then, we have the origins of the notion of specificity (i.e., patient-specificity) as it is (implicitly) deployed by the National Commission.

Crucially, the empiricists recognized that their commitment to the principle of specificity had profound *epistemological* significance. In contrast with the basic medical sciences, such as anatomy, physiology, and chemistry, which they took to be universal, the empiricists held that therapeutics were specific to patient and place. A commitment to the principle of specificity, thus, gave *therapeutic knowledge a fundamentally distinct epistemological status*. From this perspective, the very idea of general rules of therapeutic practice was seen as misguided:

> Constructing universally applicable rules of practice was a wrong-headed endeavor, for the validity of therapeutic knowledge was restricted to a type of patient and environment that closely approximated those from which it had been drawn in the first place… By stressing the specificity, not universalism, of therapeutic (and to some extent diagnostic and prognostic) knowledge, physicians expressed their conviction that knowledge pertinent for certain places or individuals could be inappropriate for others… (Warner, 1997, 59)

For the empiricists, then, medical knowledge was divided into two broad types: basic and therapeutic. Furthermore, whereas the basic medical sciences (e.g., anatomy, physiology, and chemistry) were universal in their application, therapeutics were specific to patient and place. Sometimes this distinction was put in terms of the principles of medicine, which were taken to be universal, and the practice of medicine, which was taken to be indexed to the particularities of person and location. This distinction also

affected how the two forms of knowledge were learned. The former could be learned in the classroom, the lab, or at the dissection table; the latter, however, could only be learned by close observation at the bedside. In this way, therapeutic empiricists stressed the importance of empirical observation of the patient and her circumstances as both a protective against the evils of systematic treatment and a tool for therapeutic improvement. Close observation of the patient was how one acquired specifically therapeutic knowledge.

Of course, it must be stressed that therapeutic empiricism rose to ascendancy largely before the concept of disease-specificity, and the related concept of disease specific treatment, were seen as legitimate. 'Specificity,' as the term was employed by the therapeutic empiricists, connoted 'patient-specificity' not 'disease-specificity'. 'Patient-specificity' refers to the more or less radical idiosyncrasy of an individual's natural state of health and their illnesses. 'Disease-specificity' refers to the specificity of diseases rather than patients. The two connotations must not be confused.[9] Though physicians had begun to acknowledge the existence of specific diseases, via distinctive clusters of symptoms, in the early 1800s, they nonetheless believed that environmental influences could change one disease into another, and that a particular disease could manifest in a variety of forms. Disease entities, in other words, were seen as fluid not fixed, and treatment was viewed similarly (Warner, 1997, 62). 'Specifics' – disease specific treatments – were associated with rationalism and, thus, quackery; specifics were seen as both epistemologically and ethically suspect.

[9] As noted in an earlier footnote, in this section unless otherwise indicated I too mean 'patient-specificity' as opposed to 'disease specificity' when I employ the term 'specificity.'

Broadly, then, therapeutic empiricists argued that the appropriate therapeutic course was determined by the disease concerned (where, for the most part, 'disease' was viewed as non-specific or lacking independent ontological status) in combination with a range of factors specific to the patient and her location. Factors specific to the patient included: age, gender, ethnicity, occupation, socioeconomic position, moral status, hygiene, diet, habits, and their previous response to treatment. Relevant factors of place included whether the patient lived in a rural or urban area, and the particularities of the temperature, rainfall, topography, and vegetation of the geographic region in which they lived.

The implications of this view were many. For one, therapeutic empiricists were skeptical about importing (or exporting) knowledge, particularly when there were salient differences of either person or place across the relevant contexts. For example, dissimilarities of both environment and patient-body suggested to many physicians working in private practice in rural settings that knowledge obtained in large, urban, public hospitals was fundamentally useless to them. This became increasingly problematic as the hospital emerged as the centre of both research and teaching. In response, many physicians advocated for regional medical research and education:

> It is precisely because diseases are not all entities, and do not preserve the same features, wherever met with; and that remedies are not all specifics, or uniform and invariable in their effects, that it becomes necessary to study them where they prevail. (in Warner, 1997, 76)

Advocates of regional medical education stressed the contrast between universal medical principles, and the specificity of regional practice. Education in the basic medical sciences, coupled with clinical training in those branches of medicine that were region specific (diagnosis, prognosis, and treatment) – involving observation at the bedside of

the types of diseases and patients students would face in their practice – became the hallmark of regional training. Again, advocacy for regional training was premised on the notion that it was necessary to study disease, and the effects of treatments, locally, a notion that follows form the principle of specificity.

It is important to understand that, for the empiricists, the principle of specificity went all the way down. At bottom, the principle reflects metaphysical commitments concerning disease, patient, environment, and the relationship between them, commitments that necessarily shaped the nature of therapeutic knowledge. From the perspective of therapeutic empiricism, in order to obtain therapeutic knowledge it was absolutely necessary to study disease and treatments within a local context. For the therapeutic empiricists, in other words, therapeutic knowledge was *in essence* local knowledge. Specificity, not universalism, was essential to the empiricist view of therapeutic knowledge (Warner, 1997, 72).

Physiological Therapeutics: From Patient-Specificity to Disease-Specificity

Much has changed since the heyday of therapeutic empiricism. By the 1860s, the reign of the principle of specificity began to weaken. By the third quarter of the 19th century, the variability of therapeutic knowledge across place and patient began to seem problematic. Furthermore, with the publication of Claude Bernard's *Introduction to the Study of Experimental Medicine* in 1865 a new 'rationalist' foundation for therapeutics presented itself. Instead of close observation at the bedside, Bernard advocated experimentation in the laboratory. Physiological experiment, argued Bernard, would allow us to understand the physiological mechanisms of health and disease, as well as the

actions of remedies. According to Bernard, in other words, knowledge produced in the physiology laboratory could both explain and direct therapeutic behaviour (see Warner, 1980; and Bernard, 1927).

Furthermore, and most significantly for our purposes, experimental or physiological therapeutics promised universal knowledge. Unlike the observational knowledge produced by therapeutic empiricism which, due to the principle of specificity, was necessarily limited in its scope, physiological therapeutics offered the prospect of universal therapeutic laws. Whereas clinical observation was uncertain and local, experimental medicine would reveal the laws of scientific determinism thereby providing certain and universal guidance to therapeutics. As Bernard put it:

> ...only by basing itself [i.e., medicine] on experimental determinism can it become a true science, i.e., a sure science. I think of this idea as the pivot of experimental medicine, and in this respect experimental physicians take a wholly different point of view from so-called observing physicians. (Bernard, 1927, 139)

The advent of physiological therapeutics, thus, represented a fundamental shift in clinical cognition. As Warner notes, "physiological therapeutics sought to elevate therapeutic knowledge to a fundamentally new epistemological category" (Warner, 1997, 93), dissolving the distinction between basic and therapeutic knowledge. Physiological therapeutics, thus, was a new form of rationalism, and its ascendancy marked the return of all those attributes of therapeutic knowledge that the therapeutic empiricists had worked so hard to banish: universalism, fixed laws, systems, and certainty (Warner, 1997, 93).

The rise of physiological medicine, thus, also resulted in a shift move away from the principle of (patient) specificity and the non-specific, relational view of disease with which that principle was associated, towards an increasingly ontological view of disease

wherein diseases were seen as ontologically distinct and independent entities. Commensurately, physicians began to talk in terms of 'normal' as opposed to 'natural' (Warner, 1985, 94; Canguilhem, 1989). Whereas 'natural,' at least as that term was interpreted by the therapeutic empiricists, was unavoidably subjective and patient-specific, 'normal' was quantifiable, objective, and in principle universal. Physicians began to evaluate a patient's well-being not by comparison with that particular individual's natural state of health (which, again, was unavoidably subjective and patient-specific), but by considering discrete physiological indicators of that patient's health against criteria of health expressed as (universal) norms for a population, norms that were defined in the laboratory.

In this way, patient-specificity was replaced by disease-specificity, and local therapeutic knowledge with (the prospect of) a universal therapeutics. Indeed, precisely because the laboratory promised universal knowledge, patient-specificity of the 19th-century variety could not survive in the laboratory.[10] Seen from this perspective, the central problem became all the more pressing following the emergence of experimental therapeutics in the final third of the 19th century because experimental therapeutics aspired (and continues to aspire) to the universalism of the basic sciences.

[10] Of course, the notion that laboratory science is "universalist" in this sense will itself require a certain revolution in epistemology, a revolution that claims: (1) laboratory experiment DOES reveal universal truths, and the related claim that (2) one experimental locality is the same as any other. The *Flexner Report* (1910) was instrumental in effectuating this epistemological revolution in medicine. For discussion of the epistemological status of laboratory results in general see: Cartwright, 1999; Latour, 1988; 1987. For discussion of these issues in the context of medical research see: Porter, 1998, 527; and Bynum, 1994. For discussion of Flexner in this context see: Newton, 2001, 302-3; Porter, 1998, 530-2; and Weatherall, 1995, 56-7).

The New Therapeutic Empiricism: Evidence Based Medicine (EBM)

Due to its enormous success, the new paradigm of physiological therapeutics dominated medical epistemology well into the 20th century, and continues to be a dominant force today. However, by the end of the first third of the 20th century, a new form of therapeutic empiricism (clinical epidemiology) arrived on the scene, no doubt as part of a reaction by clinicians against the dominance of experimental laboratory medicine (Newton, 2001;Vandenbroucke, 1998). Clinical epidemiology, and its later offshoot, evidence based medicine (EBM), emphasize the importance of controlled observation of patient experience in the clinic over the deductive approach characteristic of, e.g., physiological research in the laboratory (EBM Working Group, 1992, 2420). In this sense, clinical epidemiology and EBM are the heirs to therapeutic empiricism, sharing its emphasis on systematic patient observation (though "systematic" now has very different connotations), its distrust of mere authority, and its advocacy of a critical epistemic attitude toward existing therapeutic knowledge.

These features of EBM are clearly reflected in the description of EBM offered by the EBM Working Group in their now seminal 1992 paper:

> [e]vidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and *pathophysiologic rationale* as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. *Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.* (EBM Working Group, 1992, 2420 – emphasis mine)

Much as 19th-century proponents of therapeutic empiricism encouraged "a critical and undoctrinaire attitude, urging students to test the validity of previous opinion and practice by close observation at the bedside," proponents of EBM: (1) urge physicians to "gain the skills to make independent assessments of evidence and … evaluate the credibility of

opinions being offered by experts;" and (2) emphasize the importance of "systematic attempts to record observations in a reproducible and unbiased fashion" (EBM Working Group, 1992, 2421). Indeed, Sackett et al, authors of a now classic introduction to EBM, explicitly connect EBM with the work of Pierre Louis, father of Paris School therapeutic empiricism:

> These ideas [i.e., the ideas constitutive of EBM] have been around for a long time. The authors of this book identify with their expression in post-revolutionary Paris when clinicians like Pierre Louis rejected the pronouncements of authorities and sought the truth in systematic observation of patients... (Sackett et al, 2000, 1-2)

On the other hand, despite EBM's historical roots in therapeutic empiricism, contemporary criticism of EBM shares many of the same concerns 19th-century empiricists had about rationalism. Much as the 19th-century empiricists criticized rationalists for uncritical treatment by rote, many contemporary critics of EBM charge that EBM leads to 'cookbook medicine' (i.e., rote treatment according to an explicit recipe) because of EBM's emphasis on systematic clinical research. (Dopson et al, 2003, 312). Unlike therapeutic empiricism, in which individual clinical observation was the final arbiter of clinical judgment, the final arbiter in EBM is the results of good clinical research.

In part, worries about 'cookbook medicine' are rooted in the use of clinical practice guidelines, which have become closely associated with EBM in practice, but are not necessarily a part of EBM itself. Clinical practice guidelines are supposed to provide both an up-to-date summary of the evidence relevant to a particular diagnosis, e.g., acute myocardial infarction, followed by detailed instructions for applying that evidence to a patient (Sackett et al, 2000, 170). Clinical guidelines are, quite literally, instructions about how best to proceed when faced with a patient suffering from, e.g., acute

myocardial infarction. Given their intended role in guiding practice, it is not difficult to understand why some practitioners criticize the use of practice guidelines as a form of 'cookbook medicine'.

But clinical practice guidelines were developed in the late 20th century in large part to address the fact that clinicians were not taking up the results of research into clinical practice. By the final third of the 20th century, it had become glaringly obvious that many clinicians were employing methods of treatment long shown to be sub-optimal. The continued employment of mastectomy for the treatment of breast cancer long after it had been shown that this was in many cases not superior (in terms of survival) to local excision of the tumor and radiotherapy is an oft-quoted example (Hopkins, 1995, 70). Lack of uptake was also evidenced by widespread and clinically unjustified variation in practice for the management of common conditions. Enormous and clinically unjustified geographical variation in the employment of caesarean is the example most frequently cited here, but there are myriad others (Hopkins, 1995, 70). Clinical practice guidelines have been developed as a way to help clinicians to keep on top of the latest evidence while also helping to limit, through clinical audits, unjustified variation from standard practice as articulated in clinical guidelines (Hopkins, 1995, 70). Thus, clinical practice guidelines can be seen as one way in which governments, medical societies, and hospitals have attempted to implement EBM. Criticism of the use of clinical practice guidelines, thus, is not necessarily central to EBM itself.

More central to EBM is the basic idea of strengthening the scientific basis of clinical practice. EBM, and clinical epidemiology more generally, aims to be a "science of the art of medicine". As Sackett describes in the Preface of *Clinical Epidemiology*:

> [I]t dawned on him [Sackett] that the application of ...epidemiologic principles (plus a few more from biostatistics) to the beliefs, judgments, and intuitions that comprise the art of medicine might substantially improve the accuracy and efficiency of diagnosis and prognosis, the effectiveness of management, the efficiency of trying to keep up to date, and, of special importance, the ability to teach others how to do these things. The opportunity to explore this "science of the art of medicine" burgeoned with the creation of a new medical school at McMaster University... (Sackett et al, 1985, ix)

It is, I think, the notion of a "science of the art of medicine" that most troubles the critics of EBM. Their worries echo those of the 19th-century empiricists. Thus, contemporary critics allege that: EBM involves "the ill-advised and unethical abandonment of the 'human' element in medicine" (Cronje et al, 2003, 354; see also Hellman et al, 1991); the practice of EBM amounts to treating patients as "mass-produced objects on a factory production line" (Evans, 1995, 462); and EBM ignores the specificity of the individual patient in that: "[t]he doctor does not deal with illnesses alone but with people who are ill, and for each individual the illness is unique in terms of his or her experience of it and in its presentation to the doctor" (Sullivan et al, 1996, 941).

Much as the 19th-century empiricists criticized medical rationalism because it ignored the specificity of the patient and misguidedly attempted to construct universally applicable rules of practice, contemporary critics of EBM charge that EBM "ignore[s] the complex variation and individuality inherent in medical work" (Pope, 2003, 273). Precisely because of its generality, scientific evidence is not necessarily applicable to individual patients, and it is up to the clinician to decide whether or not the evidence is relevant to a particular patient.

Furthermore, critics frequently argue that clinical decisions involve a unique form of practical knowledge, a form of knowledge not offered by EBM. Thus, contemporary critics of EBM are not only concerned that EBM ignores the specificity of the patient;

critics also charge that EBM misconstrues the character of therapeutic knowledge. Pope sums up this specifically epistemic concern on the part of critics of EBM in the following passage:

> The critics argued that, in order to make sense of the unique circumstances of the individual case, doctors used a form of practical knowledge or judgment quite different to the knowledge offered by EBM. The evidence base of EBM was technical: it was capable of formulation, and might be written in journals or specified as rules or guidelines. By contrast, the opponents of EBM claimed that medicine drew on a more nebulous type of knowledge… (Pope, 2003, 273)

Like their 19th-century counterparts, contemporary critics of EBM argue that (at least part of) therapeutic knowledge has a fundamentally distinct epistemological status. Distinctly therapeutic knowledge, as opposed to the explicit 'knowledge-that' offered by EBM, is tacit 'knowledge-how' obtained via clinical experience (Pope, 2003; for detailed discussion of the notion of tacit knowledge and knowledge-how see, for example, Polanyi, 1967; Ryle, 1949). Furthermore, much as the therapeutic empiricists criticized the medical rationalists because they failed to recognize the specificity of therapeutic knowledge, contemporary critics of EBM argue that EBM erroneously treats all medical knowledge on the model of the basic sciences: as quantifiable, explicit, and universally applicable. Contemporary critics of EBM hold that EBM fails to identify a distinctly therapeutic knowledge.

Both our brief overview of the history of medical epistemology in the formative years of the 19th century, and contemporary controversy concerning the proper scope of evidence based medicine (EBM) show that, far from being obviously unproblematic, the relationship between the general and the specific has long been, and continues to be, problematic. The central problem – how theoretical knowledge can be applied to concrete, individual persons with therapeutic results – is alive and well. Indeed, given the

virtually unmitigated hegemony of experimental laboratory medicine in the contemporary context, this problem is all the more pressing today than it was in the 19th century. 19th-century experimental therapeutics aspired to the universalism of the basic sciences, but 21st-century experimental medicine has been more successful in this regard than Bernard could possibly have imagined. Physicians are now able to explain (some) disease at the molecular level. 'Patient-specificity' of the 19th-century variety could not, and cannot, survive in this reductionist milieu.

'Research' and 'Practice': A Problematic Transposition

As I have already said above, by defining research in terms of generalizeable knowledge and practice in terms of the diagnosis, prophylaxis and/or treatment of an individual, the National Commission effectively poses the question as to the relationship between the general and the specific, coming face to face with the central problem. Having done so, however, the National Commission seems to simply assume that the relationship between research and practice is unproblematic. I hope the two historical vignettes canvassed above have convinced the reader of the falsity of this assumption. Far from being unproblematic, the question as to the proper relation between the universal and the particular, theory and practice, and/or the general and the specific remains the central problem of medical epistemology. Indeed, it is fair to say that the history of modern medical epistemology may be characterized in terms of the ongoing dialectic between these dualities.

Ironically, given the National Commission's failure to recognize the central problem, the distinction between research and practice as found in *The Belmont Report*

testifies to the persistence of this dialectic, emphasizing as it does the contrast between the generalizeability of research, and the specificity of practice. Notice, however, that the National Commission's distinction distorts this dialectic. Both the therapeutic empiricists and contemporary critics of EBM marshal the notion of specificity in order to distinguish between types of knowledge. The therapeutic empiricists distinguished between basic and therapeutic knowledge. Contemporary critics of EBM draw a distinction between the explicit knowledge-that offered by clinical research, and the tacit knowledge-how obtained via clinical experience. But the National Commission's distinction between research and practice transposes these two kinds of knowledge onto research and practice respectively. However, because practice is conceived by the National Commission as a purely pragmatic endeavour, this transposition effectively strips the specific of epistemic significance.

I believe this transposition is deeply problematic because, once accomplished, 'therapeutic knowledge' simply disappears as a category of medical knowledge. Even if we now reject much of what they believed, the therapeutic empiricists must be praised for recognizing the necessity of achieving a modicum of congruence between method and objective. For them, the exigencies of clinical practice demanded a particular kind of knowledge (therapeutic knowledge) which, in turn, required particular methods (close observation of the patient at the bedside and of the specific character of their physical and social environment). Similarly, even if we do not believe, as some critics of EBM do, that a "science of the art of medicine" is inherently problematic, we can agree that, insofar as EBM fails to acknowledge the distinct epistemological status of therapeutic knowledge, EBM misconstrues the nature of medical knowledge. By defining research in terms of

generalizeable knowledge and practice in terms of the diagnosis, prophylaxis and/or treatment of an individual, definitions which contrast research and practice in terms of the generality and epistemic nature of the former and the specificity and pragmatic nature of the latter, the National Commission effectively eliminates the conceptual space for the sort of research required for the production of specifically therapeutic knowledge. When 'research' and 'practice' are so defined the conceptual space for research that is appropriately sensitive to the specificity of practice is eliminated because, as I argue in Chapter Three, research of this kind necessarily involves practice. Precisely because it aims to generate therapeutic knowledge, intervening (i.e., the diagnosis, prophylaxis and/or treatment of an individual) is an essential feature of this kind of research. If this is right, the National Commission's definitions must be wrong.

Conclusion

In sum, if we take the distinction between research and practice at face value it is far from obvious that the relationship between research and practice is unproblematic, as the National Commission seems to have assumed. To the contrary, by defining research in terms of generalizeable knowledge and practice in terms of the diagnosis, prophylaxis and/or treatment of an individual, the National Commission effectively poses the question at the core of the central problem: how can theoretical knowledge be applied to concrete, individual persons with therapeutic results? Furthermore, by defining research and practice in this way, the National Commission effectively eliminates the conceptual space for the sort of research required for the production of specifically therapeutic knowledge. The latter implication is particularly problematic in this context because, as I have

already pointed out above, research involving humans is morally justified only if it promises to yield valuable results. A necessary condition of value in this context is that the results of a study are, at least potentially, clinically relevant; that is, the results of research must hold out real promise for the improvement of clinical practice. In order for this promise to be fulfilled, however, these two activities must somehow come into contact with one another in order to produce genuine therapeutic knowledge.

To date, our best solution to the problem of developing research methods that are sensitive to the specificity of clinical practice and are, thus, capable of developing genuine therapeutic knowledge, have been those methods now referred to under the rubric of "clinical research". Modern clinical research, in other words, is our best solution to date to the central problem of medical epistemology. Early progenitors of clinical research, like William Osler (1849-1919), recognized the importance of clinical research:

> The organized medical clinic is a clearing house for the scientific traders who are doing business in all parts of the body corporate, and the application of new facts to medicine must come through it, or through that small but happily increasing group of men who find time amid the daily care of practice... to combine experimental work with practice... (Osler, 1907; quoted in Harvey, 1981, xv)

For Osler, clinical research was the best means for the transfer of knowledge from the laboratory to the clinical ward. Similarly, EBM, a movement that stresses the import of evidence from *clinical research*, is explicitly touted as a means by which the results of laboratory research may be transferred, or in current parlance translated, to the bedside.

Clinical research is ideally suited to this task because it is, and ought to be, closely aligned with the realities of clinical practice. Indeed, in the next chapter I will argue that one branch of clinical research, Applied Patient Oriented Research (Applied

POR) is by definition sensitive to the context of practice, including the specificity of actual patients, in a way that laboratory research is not.

Of course contemporary critics of EBM are right to insist that clinical research, even Applied POR, is not sufficient for competent clinical practice. Clinical expertise remains a necessary component of competent clinical practice. Insofar as EBM fails to recognize the importance of clinical expertise, EBM is flawed. However, in actuality many contemporary proponents of EBM recognize the importance of clinical expertise. For example, Sackett et al argue that external clinical evidence from systematic research should support clinical judgment, rather than replace it (Sackett et al, 1996, 71):

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice… (Sackett et al, 1996, 71)

Nonetheless, the proponents of EBM are also right to insist that systematic clinical research, both basic and applied, is a necessary, if not sufficient, condition for competent clinical practice. Furthermore, it would be a mistake to view clinical research and clinical expertise as being at odds with one another. On the contrary, clinical research in general and Applied POR in particular serve their purpose best when they are in close contact with patients and the problems posed by patient care. Indeed, clinical research is our best solution to the central problem of medical epistemology precisely because it is (and ought to be) closely aligned with the realities of clinical practice.

Curiously, 'clinical research' is never mentioned in *The Belmont Report*. Instead, we have talk of research *simpliciter* defined in terms of generalizeable knowledge. As I

have attempted to show in this chapter, this definition of research, combined with a definition of practice in terms of specificity, is problematic because it both raises the specter of the central problem and eliminates the conceptual space required for its solution: a bona fide clinical research. Since clinical research is our best solution to date to the central problem, this is a serious fault indeed. The National Commission's definition of research is problematic for other reasons as well. For one, talk of research simpliciter is problematic because it obscures important differences between forms of research appreciation of which is crucial for their ethical analysis. A more sophisticated analysis of 'research' is required, an analysis that carefully distinguishes clinical research from other kinds of research (e.g., basic or pre-clinical research), and sorts out the different categories of clinical research as well. To this task I turn in the following chapter.

Chapter Three: Clinical Research in Context

Introduction

The distinction between research and practice has undoubtedly been useful for the purposes of demarcating activities that require ethical review from those that do not. Furthermore, the distinction as found in *The Belmont Report* does reflect salient differences between the two classes of activities, differences I have alluded to above. However, I believe that the distinction has also led to a great deal of confusion, not least because it so readily lends itself to misinterpretation.

The purpose of this chapter is both to criticize the National Commission's definition of research *simpliciter* in terms of generalizeable knowledge, and to offer another more qualified definition in its stead. Both the definiens and the definiendum of the National Commission's definition are problematic. I begin with the definiens: 'generalizeable knowledge.'

'Generalizeable knowledge' is problematic because it is suggestive of a decontextualized picture of knowledge and knowledge-seeking, a picture that is reinforced by insistence upon a sharp distinction between research and practice. It makes sense to sharply distinguish the development of generalizeable knowledge from the provision of diagnosis, prophylaxis, and treatment only if the development of generalizeable knowledge can proceed independently of the context of its development and application. But it is now widely acknowledged by philosophers of science and epistemologists that we cannot make sense of inquiry without paying attention to the context within which it takes place. Justification does not proceed independently of the

context of discovery (the distinction between the contexts of discovery and justification is explained in more detail in the section to follow). Rather, inquiry is inherently context-bound because justification is inherently context-bound. 'Generalizeable knowledge' is problematic, then, because it misrepresents inquiry.

Part of the problem, however, is the National Commission's starting point, the definiendum: 'research.' By the time of *The Belmont Report*, as we saw in Chapter One, the National Commission had eliminated the more qualified concepts of therapeutic and non-therapeutic research in favour of research *simpliciter*. But talk of research *simpliciter* is just as problematic as talk of generalizeable knowledge *simpliciter* because it obscures important differences between forms of research. Indeed, it is striking that the National Commission never provided a definition of clinical research, even though their work is, in the main, clearly concerned with clinical research not research in general. After all, the National Commission was charged with studying the ethical principles underlying *biomedical and behavioral research on human subjects*, not those underlying research in general. A more sophisticated analysis of 'research' is required. Fortunately, Edward Ahrens has already carried out such an analysis in his 1992 book *The Crisis in Clinical Research.*

A crucial premise of Ahrens' analysis is that we cannot adequately distinguish various forms of inquiry on the basis of the material they study. On Ahrens' view, an adequate analysis turns on the "nature of the questions asked and the manner in which an answer is sought" (Ahrens, 1992, 36). An analysis on these grounds, notice, is both incompatible with a non-trivial characterization of research in general and consistent with a contextualist understanding of knowledge and justification. The fundamental idea of

contextualism is that "standards for correctly attributing or claiming knowledge are not fixed but subject to circumstantial variation" (Williams, 2001, 159). Local circumstances are determined largely by the interests at stake. By defining clinical research in terms of "the questions asked and the manner in which an answer is sought," Ahrens implicitly acknowledges the interest-relative nature of knowledge and inquiry; it is the questions we are interested in that both demarcate clinical research from other forms of research and allow us to determine the standards of justification (i.e., the manner in which an answer is sought) appropriate for clinical research.

Having summarized Ahrens' findings, I then proceed to make explicit the contextual constraints implicit in Ahrens' characterization of applied patient-oriented-research (Applied POR - one of seven sub-categories of clinical research). This contextualist analysis shows that forms of inquiry, in this case Applied POR, are constituted by very specific contextual commitments that only come into view when we are attentive to the particular interests at stake in this form of inquiry. These commitments are obscured if we insist upon talking in terms of research in general, which is problematic because in the absence of a detailed understanding of the contextual constraints constitutive of Applied POR we cannot even pose the relevant questions, let alone determine the justificatory status of a proposed response.

The implications of this chapter are threefold. First of all, insofar as "an ethical framework that provides normative guidance about a practice should accurately characterize the practice" (Miller & Brody, 2003, 20), the development of an adequate ethics for human subjects research is obstructed rather than facilitated by talk of research in general. We must replace the National Commission's definition of research with

definitions of the specific forms of inquiry in question; here I have focused on Applied POR because, historically, research ethics has been primarily concerned with research of this kind. Second, our contextualist analysis shows that insistence upon a sharp distinction between research and practice is problematic because we cannot even make sense of Applied POR independently of the context of practice. Third, because the context of practice is and ought to be partly shaped by the moral norms characteristic of practice, Applied POR is and ought to be shaped by these moral norms as well; Applied POR cannot and should not be carried out independently of the moral norms embedded in the context of practice.

Generalizeable Knowledge

Given both the epistemological importance of clinical research – its role as a bridge between bench and bedside – it is striking that the term "clinical research" never appears in *The Belmont Report*. This absence is all the more striking since the work of the National Commission is clearly concerned with clinical research, not research in general. Instead we are offered a definition of 'research' *simpliciter*, in terms of the development of 'generalizeable knowledge'. Both the definiens and the definiendum are problematic. I begin with the definiens: 'generalizeable knowledge'.

The National Commission offers a loose definition of 'generalizeable knowledge' as knowledge that can be "expressed, for example, in theories, principles and statements of relationships" (*The Belmont Report*, 1979, 3). For the National Commission, it seems, 'generalizeable knowledge' is synonymous with 'scientific knowledge'. (In the following, I will assume the synonymy of these two terms, i.e., 'generalizeable

knowledge' and 'scientific knowledge,' and use them interchangeably.) The problem with 'generalizeable knowledge' so defined is that it is suggestive of a decontextualized picture of scientific knowledge and inquiry, a picture made even more implausible by the National Commission's insistence upon a sharp distinction between research and practice. Without more elaboration, in part because it is natural to suppose that the context of practice is a crucial context of discovery for clinical research, one might interpret the distinction as insisting upon the context-independence of research.

As I have already pointed out, this is exactly what seems to have happened in much of the research ethics literature. There is a growing tendency to attribute substantive metaphysical, epistemological and, ultimately, moral significance to the distinction. Increasingly, the distinction is interpreted as a definitive description of the nature and goals of research and practice, rather than a conceptual tool designed to facilitate the implementation of a system of review. And commentators have been all too ready to derive normative conclusions concerning the ethics of research directly from the distinction so interpreted. For example, it is now widely accepted that there should be a sharp distinction between the ethical norms appropriate to the contexts of research and practice respectively, a position that is invariably justified by appeal to the work of the National Commission.[1]

However, assuming that the context of practice is in fact a crucial context of discovery for clinical research, it makes sense to insist upon a sharp distinction between

[1] Again, see Miller & Brody, 2007; Veatch, 2007; Gifford, 2007; London, 2007; Appelbaum et al, 2006; Wasserman et al, 2006; Miller & Brody, 2003; Miller & Rosenstein, 2003; Miller, 2002. I believe much of the large literature on the so-called therapeutic misconception implicitly makes the same assumption, i.e., that there is a sharp distinction between the ethical norms appropriate to the contexts of research and practice respectively. See, for example, Horng & Grady, 2003; Miller & Brody, 2003; Dresser, 2002.

the norms appropriate to the contexts of research and practice, ethical and otherwise, only if the development of generalizeable knowledge can proceed independently of the context of practice. It makes sense, in other words, only if the contexts of discovery and justification are independent. But this supposition is deeply problematic. Many philosophers of science and epistemologists now believe that we cannot make sense of inquiry without paying close attention to the context within which it takes place. I am one of them. And it is for this reason that I believe that the distinction between research and practice, particularly as it is currently interpreted by some commentators, is deeply problematic: so interpreted, the distinction recapitulates the distinction between the contexts of discovery and justification.

Decontextualized Knowledge

The distinction between the contexts of discovery and justification was first introduced by Hans Reichenbach in his book *Experience and Prediction* (1938) in order to distinguish factors that lead to the discovery (or invention) of a hypothesis or theory from factors that would justify it. Reichenbach recognized that decisions concerning the research agenda are clearly value laden in the sense that they are subject to extra-scientific moral and political norms circulating in society. Obviously, these norms can affect whether or not a theory is 'discovered' in the first place. However, Reichenbach was also concerned with maintaining the objectivity of science. In an effort to do so, Reichenbach argued that these extra-scientific norms are confined to the context of discovery. The context of discovery, no doubt, is subject to political, moral and other social norms. But the context of discovery, insisted Reichenbach, is distinct from the

'context of justification'. In the latter context we find the empirical norms characteristic of the scientific method that specify when a theoretical hypothesis is justified on the basis of evidence (e.g., norms of predictive success, observation independence, explanatory power, and the like). These norms, at least when science is conducted properly, are not subject to the influence of social norms external to the scientific enterprise. Testing of a hypothesis, even if its investigation was politically motivated, is not a political matter, but a matter of logic. And the logic of justification, unlike politics, is disinterested and objective. Thus, the contexts of justification and discovery are independent.

The distinction between the contexts of discovery and justification has had a long and successful career. Indeed, the distinction undoubtedly expresses both the pre-theoretical intuitions of many non-philosophers (including scientists) concerning science and, even today, the avowed position of some philosophers of science. That being said, other philosophers have argued that the distinction is misplaced. Specifically, they have argued that the contexts of discovery and justification are not independent. There are at least two broad types of argument to this effect. The first type involves arguing that the norms of science cannot be applied independently of the context of discovery. I will briefly review two tokens of this type of argument in the following. The second type of argument takes issue with the very idea of "the norms of science," in part because the idea of "scientific knowledge" as a genuine theoretical kind is rejected; at best, we can speak of knowledge about this or that subject. Sciences, and the knowledge(s) they produce, are as various as the interests that drive them. Since some of these interests are almost invariably non-epistemic in nature, they would traditionally be located in the

context of discovery. The upshot is that the norms of a particular science cannot even be fully identified, let alone applied, independently of that context.

Before turning to these arguments, however, I should make a few things clear. First of all, I should point out that the following review is not meant to be exhaustive. Many other philosophers have made arguments similar to those canvassed here. Broadly, my aim is to show how, from a variety of theoretical perspectives, we can see that a sharp boundary between the contexts of justification and discovery is unjustifiable. Second, I should make it clear that I will not offer a full defence of the positions canvassed here, despite the fact that, for the purposes of this essay, I rely heavily on Williams' contextualist epistemology (the token of the second type of argument canvassed here) (Williams, 1996). It would take me too far afield to defend Williams' position against rival epistemologies, or to fully explain why I favour Williams' approach over Longino's (1990), Campbell's (1998), or other similar positions in the literature. For present purposes, suffice it to say that I do so because I believe that the relationship between context and justification is systematic in a way that is not captured by the former type of argument. Contextual factors do not merely affect the application of a set of justificatory standards already given; rather, they play an essential role in constituting and identifying the justificatory standards appropriate to a particular form of inquiry. I believe Williams approach provides a perspicuous framework for identifying and analysing these contextual factors, not least because his approach is truer to the way inquiry actually proceeds.

Type One: Longino

Helen Longino's argument against the context-independence of justification involves an appeal to underdetermination. It is a commonplace in the philosophy of science that, given the evidence E, there will always be some rival hypothesis consistent with E. If and when, in light of the evidence E, we normatively assess a hypothesis H_1 against the standards of predictive success, observation independence, explanatory power (i.e., the norms found in the context of justification), our judgment that H_1 is justified is in fact underdetermined by the evidence. On their own, these norms do not justify the judgement that H_1 is justified because, again, there will always be some rival hypothesis H_2 that would be equally justified if, in light of the evidence available, they were assessed against these same standards. Ultimately, given underdetermination, factors external to the context of justification are necessarily involved when a hypothesis is judged to be justified. These factors, which may be pragmatic, moral and/or political in nature, are located in the context of discovery. Justification, therefore, is not context-independent (Longino, 1990).

Longino notes that science is commonly thought to provide us with a view of the world that is objective in two quite different, but related, senses of the term:

> In one sense objectivity is bound up with questions about the truth and referential character of scientific theories, that is, with issues of scientific realism. In this sense to attribute objectivity to science is to claim that the view provided by science is an accurate description of the facts of the natural world as they are... In the second sense objectivity has to do with modes of inquiry. In this sense to attribute objectivity to science is to claim that the view provided by science is one achieved by reliance upon nonarbitrary and nonsubjective criteria for developing, accepting, and rejecting hypotheses and theories that make up the view. The reliance upon and use of such criteria as well as the criteria themselves are what is called scientific method. Common wisdom has it that if science is objective in the first sense it is because it is objective in the second. (Longino, 1990, 62-63)

Clearly, contextual values (of the wrong sort) are a threat to objectivity in the second sense. In light of the unavoidable context-dependence of justification, Longino argues that a method of inquiry is objective to the degree that it permits 'transformative criticism,' which on Longino's view is an explicitly and irreducibly social process. In Longino's words:

> Scientific communities will be objective to the degree that they satisfy four criteria necessary for achieving the transformative dimension of critical discourse: (1) there must be recognized avenues for the criticism of evidence, of methods, and of assumptions and reasoning; (2) there must exist shared standards that critics can invoke; (3) the community as a whole must be responsive to such criticism; (4) intellectual authority must be shared equally among qualified practitioners. (Longino, 1990, 76)

For Longino each of these criteria is essentially social in nature. This is obvious enough in the case of criteria (3) and (4), but equally true of criteria (1) and (2): avenues of criticism must be recognized by a *community*; and critical standards must be *public and shared by the relevant (sub-)community*. The crucial point is that, for Longino, objectivity in the second sense (i.e., objectivity of method) is ultimately a function of the social structure of the context within which inquiry occurs.

Type One: Campbell

On Longino's view, objectivity of method is ultimately a function of social structure. However, given that objectivity is also bound up with questions about truth (objectivity in the first sense), Longino's view entails that truth, too, is a function of social structure. For Longino, again, inquiry is objective to the degree that it satisfies the four criteria necessary for transformative criticism. If inquiry satisfies these criteria to the appropriate degree, then, inquiry *is* objective in both of the senses Longino identifies; that

is, the view such inquiry provides is "achieved by reliance upon nonarbitrary and nonsubjective criteria," and "is an accurate description of the facts of the natural world as they are" (Longino, 1990, 62). If inquiry satisfies these criteria, in other words, inquiry provides an accurate (i.e., true) description of the facts of the natural worlds as they are. But this view entails a form of anti-realism because on Longino's view, if the criteria for transformative inquiry are met, we cannot be wrong about a particular question or object of inquiry. If nothing else, realism implies that, no matter how we proceed, we may be wrong precisely because realism implies a world that exists independently of how we think about it (even if 'thinking' is a social process).

Richmond Campbell provides an argument against the context-independence of justification that is consistent with realism. Unlike Longino, Campbell does not appeal to underdetermination. Rather, Campbell's argument focuses on the constitutive norms of science themselves. Campbell shows that we cannot apply the standards of predictive success, observation independence, and explanatory power without relying on factors located in the context of discovery. His discussion of the standard of explanatory power is, perhaps, the most dramatic (Campbell, 1998).

The norm of explanatory power requires that, apart from the hypothesis in question, there must be no plausible alternative explanation of the predicted outcome, should it be observed (Campbell, 1998; Giere, 1997). The norm of explanatory power is, in other words, comparative in nature. However, whether or not alternative explanations of the predicted outcome have been identified, let alone investigated, will depend upon the contextual values located in the context of discovery. If plausible alternative explanations have not been deemed worthy of exploration, due to, e.g., a lack of financial

incentive, the hypothesis in question, whatever it may be, will not satisfy the norm of explanatory power since there will be a plausible alternative explanation of the predicted outcome, should it be observed. In this way, concludes Campbell, the context of justification depends upon the context of discovery (Campbell, 1994; 1998). The context of justification, therefore, is not independent of the context of discovery.

Type Two: Williams

Both tokens of the first type of argument involve arguing that the norms of science cannot be applied independently of the context of discovery. Both Longino and Campbell argue, albeit in different ways, that the context of discovery forms an intrinsic part of the context of justification because we cannot apply the norms of science, or determine that they are satisfied, without appealing to factors located in the context of discovery. The second type of argument involves a different strategy. This type of argument takes issue with the idea that 'scientific knowledge' is a genuine totality or theoretical kind and, thus, with the notion that there is any such thing as 'the norms of science'. On this view, the norms that govern particular sciences and the knowledge(s) they produce cannot even be identified, let alone applied, independently of the context of the inquiry in question.

Michael Williams is, perhaps, the most articulate proponent of this view. For Williams, the supposition that 'scientific knowledge' is a genuine theoretical kind amounts to the supposition that there are fundamental epistemological relations that cut across ordinary disciplinary boundaries. Underlying the variable standards of scientific

practice, in other words, we are to suppose that there is an invariant justificatory structure on the basis of which, ultimately, all our scientific beliefs are justified.[2]

Williams illustrates this idea by drawing an analogy with our treatment of theoretical terms like 'heat'. In ordinary usage, we use the term 'heat,' and its derivatives, in many different ways: 'the water was heating on the stove,' 'he heated his feet by the fire,' 'the curry is hot,' or 'the argument was heated'. To a contemporary reader, it is obvious that some of these uses are literal, some not. But, to a reader in the 17th century this may not have been as obvious. For example, in his natural history of heat, notes Williams, Bacon provides a list of examples of heating including heating by radiation, friction, exothermic reactions, and by 'hot' spices that 'burn' the tongue. What we have here, says Williams, is a clear case of a nominal kind comprised of the things commonly called hot. Hot spices are only metaphorically, not literally, hot.

But heat is also a natural kind, some examples of which turn up in Bacon's list.[3] We sort the "genuine from spurious examples," notes Williams, by relying "on a physical theory which identifies some underlying property, or structure of more elementary components, common to hot things, [e.g., the motion of particles]" (Williams, 1996, 108). Explaining theoretically significant, or natural, kinds in this way, Williams correctly points out, is typical of scientific realism: "For the scientific realist, deep structural

[2] In fact, Williams is concerned with knowledge more generally; that is, he is concerned with showing that knowledge is not a genuine theoretical kind, not just science. However, it is safe to say that Williams would extend the same argument to science itself. After all, he argues that the supposition that there are invariant epistemological constraints on justification misrepresents the way that justification and inquiry proceed both in common life and in *science*. For a similar discussion which is explicitly concerned with science see, Richard Rorty, "Is Natural Science a Natural Kind?" in *Construction and Constraint*, Notre Dame Indiana: University of Notre Dame Press, 1988.

[3] I should point out that Bacon himself distinguishes between the genuine examples of heat in his list , i.e., those that are tokens of the natural kind 'heat,' and those that are purely nominal.

features of the elementary components of things determine the boundaries of natural, as opposed to merely nominal or conventional, kinds" (Williams, 1996, 108).

Williams' insight is to observe that attempts to explicate the theoretical unity of epistemic kinds, e.g., scientific knowledge, proceed in an analogous fashion.[4] Much as the scientific realist appeals to deep structural features of things (e.g., heat) in order to demarcate natural from nominal kinds, here the idea is that, if scientific knowledge is a genuine theoretical kind, there must be a deep epistemological structure underlying all instances of genuine scientific knowledge: hence we get the supposition that there are invariant epistemological constraints underlying the shifting standards of everyday justification. This approach to demonstrating the theoretical unity of epistemic kinds presupposes what Williams calls (by analogy) epistemological realism: realism about the objects of epistemological inquiry (in our case, science).

I should clarify that Williams is concerned with epistemological realism because he believes it is the fundamental basis of scepticism. He urges a repudiation of epistemological realism in favour of a contextualist approach to justification (i.e., an approach to justification in which "standards for correctly attributing or claiming knowledge are not fixed but subject to circumstantial variation" (Williams, 2001, 159)) mainly to show that scepticism is not an unavoidable problem, but, rather, a product of our own problematic theoretical presuppositions. Williams' primary concern, in other words, is not our own.

That being said, a more local form of scepticism does, I think, haunt the work of the National Commission. As we saw in the previous chapter, once we have drawn a sharp distinction between research and practice, the question as to their epistemic

[4] Of course, science is not a purely epistemic endeavour, but that is part of the point.

relationship becomes problematic. Significantly, Williams notes that it is characteristic of sceptical problems that they depend on invidious distinctions between what, prima facie, 'we are allowed to know,' and what 'we hope to know'; between privileged and problematic classes of knowledge:

> ...sceptical problems about particular 'kinds' of knowledge seem to depend on making... cuts between what we are allowed to know, at least for the sake of argument, and what we hope (or like to think) we know... Sceptical arguments begin by partitioning propositions into privileged and problematic classes. Propositions in the (at least) relatively privileged class are taken to provide the (ultimate) evidence for those in the problematic class and skeptical arguments challenge us to explain how they manage to do this. This challenge is not easy to meet, which is why propositions in the problematic class are problematic. (Williams, 1996, 52)

The distinction between research and practice makes just such a cut between what 'we are allowed to know,' e.g., the effects of treatment X in a population, and what 'we hope to know,' e.g., the effect of treatment X in an individual patient. Furthermore, 'propositions in the...privileged class,' i.e., the class of propositions or hypotheses vetted by good research, 'are taken to provide the (ultimate) evidence for those in the problematic class.' However, as we have already seen, given the distinction between research and practice as found in *The Belmont Report*, it is far from clear how propositions produced by research manage to provide the relevant evidence. To this extent, Williams' concern is not so different from our own.

Furthermore, concerns with scepticism aside, Williams work is directly relevant to our own in another way: he believes that epistemological realism misrepresents the way that justification and inquiry proceed in science and, for that matter, in common life. Williams observes that it is far from clear that there are any invariant constraints on justification underlying the shifting standards of justification in particular contexts:

"...justification, like explanation, seems interest-relative, hence context sensitive..." (Williams, 1996, 113). Later he adds, "[i]n both science and everyday life, constraints on justification are many and various" (Williams, 1996, 117). Indeed, Williams goes so far as to offer a five-fold classification of the contextual factors that influence the epistemic status of claims, which I summarize here (since these factors are supposed to apply to all forms of knowledge, scientific and otherwise, I will drop the modifier "scientific" in the following summary of Williams' classification of contextual constraints).

Intelligibility or Semantic Constraints[5]

Williams begins by noting that justification is subject to intelligibility or semantic constraints. Intelligibility/semantic constraints place general constraints on what it makes sense to doubt in *any* context. The idea is that in order to raise meaningful questions at all, certain types of doubt must be excluded such as, for example, doubts about the meaning of my words. "If you are not certain of any fact," notes Wittgenstein, "you cannot be certain of the meaning of your words either" (Wittgenstein, 1969, para 114). And later: "If, therefore, I doubt or am uncertain about this being my hand (in whatever sense), why not in that case about the meaning of these words as well" (Wittgenstein, 1969, para 456).

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[5] In keeping with Williams' terminology, I refer to 'constraints' on justification throughout my discussion. I hasten to point out that all this talk of constraints on justification is not intended to imply the possibility of unconstrained inquiry or that, ideally, inquiry would be unconstrained. On Williams' view, all inquiry is constrained in various ways because justification is essentially contextual. On Williams' view, inquiry minus the constraints imposed by context is impossible because, absent the constraints imposed by context, inquiry ceases to be intelligible. Absent the constraints imposed b y context, in other words, "[t]here is no fact of the matter as to what kind of justification [a proposition] either admits of or requires" (Williams, 1996, 119).

Wittgenstein illustrates this point with the following example: "[s]uppose a man could not remember whether he had always had five fingers or two hands? Should we understand him? Could we be certain of understanding him?" (Wittgenstein, 1969). The answer is no, we could not be certain. "At some point," notes Williams, "'mistakes' shade off into unintelligibility. Someone who cannot do the simplest calculations, or perform the simplest counting operations, is not making arithmetical mistakes: he does not understand numbers" (Williams, 2001, 160).

Similarly, Wittgenstein suggests, if someone persistently doubted everything, we could not understand him:

> There are cases such that, if someone gives signs of doubt where we do not doubt, we cannot confidently understand his signs as signs of doubt. I.e.: if we are to understand his signs of doubt as such, he may give them only in particular cases and may not give them in others. (Wittgenstein, 1969, para 154)

In other words, doubt presupposes certainty. Raising doubts about everything is impossible precisely because, in order to question everything you must be certain about something, minimally, the meaning of your words. As Williams puts it: "[H]olding many true beliefs, or not being subject to certain kinds of error," says Williams, "is a [*necessary*] condition of making sense, thus of being in a position to raise questions at all" (Williams, 2001, 159). Questioning needs a lot of stage-setting.

Disciplinary or Methodological Constraints

The second class of constraints Williams identifies is disciplinary or methodological constraints. Methodological constraints are propositions that must be excluded from doubt in order to raise questions of a particular kind. Methodological

constraints, thus, are intelligibility constraints specific to a particular form of investigation, commitments that must be accepted because they are constitutive of a particular form of inquiry. They determine the direction of inquiry characteristic of that form of inquiry and, thus, necessarily lie outside of the 'route traveled' by that form of inquiry.

Williams' favourite example involves the study of history: "...introducing sceptical doubts about whether the Earth really existed a hundred years (or five minutes) ago does not lead to a more careful way of doing history: it changes the subject, from history to epistemology" (Williams, 1996, 122). In order to conduct historical inquiry, we must accept the proposition that the Earth existed in the past; it is a methodological necessity, not a matter of laziness or credulity.

Of course, if we were no longer interested in doing history, commitment to the proposition that the Earth existed in the past would no longer be necessary (at least not for the sake of doing history!). In this sense, methodological constraints are determined, at least partly, by our interests. As Williams puts it, "some doubts are logically excluded by forms of investigation that I find significant, important, or perhaps just interesting" (Williams, 1996, 122). Notice, furthermore, that these constraints are not merely formal; rather, they involve substantial factual commitments. Williams illustrates this crucial point using, again, the example of historical inquiry:

> For a subject like history, there is more to method than abstract procedural rules. This is because the exclusion of certain questions (about the existence of the Earth, the complete and total unreliability of documentary evidence, etc.) amounts to the acceptance of substantial factual commitments. These commitments, which must be accepted, if what we understand by historical inquiry is to be conducted at all, have the status, relative to that form of inquiry, of methodological necessities. (Williams, 1996, 123)

Dialectical Constraints

The third class of constraints Williams identifies is dialectical constraints. Dialectical constraints reflect the current state of a particular argument or inquiry. Constraints on justification vary according to the specific objections or challenges that have been raised against a particular claim or hypothesis. A claim that was, heretofore justified may be undermined by a new objection or problem. As Williams puts it:

> Given a certain direction of inquiry, various possible defeaters may or may not be in play. Sometimes, claims may face standing objections, in which case they will not enjoy default status. But default status can be lost as new problems arise, just as hitherto accepted justifications can be undermined by new evidence. (Williams, 2001, 161)

Justification, thus, is question-relative or sensitive to the dialectical context.

Economic Constraints

Constraints in a fourth class are economic constraints. Economic constraints determine what counts as a reasonable objection, and this will vary with the context. "A defeater does not come into play simply by virtue of being mentioned," notes Williams, "there has to be some reason to think that it might obtain. How much reason [sic] we require fixes the severity of our epistemic standards..." (Williams, 2001, 161). Economic constraints, in other words, reflect the level of epistemic severity deemed contextually reasonable. If we insist that even remote error possibilities be ruled out we are setting the level of epistemic severity very high. If, on the other hand, we are very much interested in resolving some question, and the costs associated with error are relatively low, relaxed standards of justification may be appropriate. Calculations of cost and benefit determine

the appropriate level of epistemic severity. Furthermore, the relevant costs and benefits will not, typically, be purely epistemic in nature. Nor will the relevant costs be purely monetary. Williams calls these factors 'economic' in order to stress that "there is typically no purely epistemological answer to the question of what level of epistemic severity is contextually reasonable" (Williams, 1996, 161).

Situational Constraints

A fifth, and final, class of constraints identified by Williams is situational constraints. Unlike the previous four classes of constraints, which are indexed to the particular form of inquiry in question, situational constraints reflect facts about the world that are independent of the inquiry in question. Though certain propositions must 'stand fast' in particular contexts of inquiry, inquiries informed by these propositions will yield knowledge only if these propositions are true, which they may not be. Acknowledgment of situational constraints, thus, reflects a commitment to the *objective* adequacy of our beliefs (Williams, 2001, 162).

Claims to knowledge commit us to both epistemically responsible behaviour and objective adequacy.[6] Justified belief is what we get by living up to appropriate standards of epistemic justification, i.e., by behaving in an epistemically responsible fashion. However, a belief can be said to be *objectively* well justified, and thus a bona fide

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[6] Post Gettier, the standard tri-partite analysis of 'knowledge,' is often supplemented with a fourth condition. Williams endorses the following *extended* analysis: S knows that p (where 'S' stands for an arbitrary epistemic agent and 'p' for an arbitrary proposition) if and only if:

1. S believes that p.
2. p is true.
3. S is (personally) justified in believing that p.
4. S believes that p on the basis of adequate grounds.

The fourth condition rules out the accidental coincidence of the justification for one's belief and the truth of that belief. Given the fourth condition, one's grounds must *in fact* be reliable (Williams, 2001, 23).

knowledge claim, only when my epistemic behaviour in the context in question was *in fact* reliable. Williams makes this point as follows:

> [a] belief of mine can be said to be objectively well justified when my epistemic procedure, in the circumstances in which it was executed, was *in fact* reliable: for example, when my grounds for holding a given proposition true really do establish its truth. (Williams, 1996, 22)

Ultimately, it is the world or, more specifically, one's external situation or circumstances, that determines whether or not one's grounds are objectively adequate. Situational constraints, thus, reflect the fact that epistemic responsibility is not sufficient for knowledge. Even if we have behaved in a scrupulously responsible fashion, it might turn out that our justificatory grounds were not objectively adequate; that is, it might turn out that our grounds were not in fact reliable. In this way, our 'situation' constrains (the objectivity of) justification.

If Williams is right that justificatory standards vary according to these five classes of constraints, and I think he is, the mischief caused by the supposition that 'scientific knowledge' constitutes a genuine theoretical kind should be plain. This supposition is problematic because, insofar as it presupposes invariant epistemological constraints on justification, it gravely misrepresents the way that justification and inquiry proceed. For one, particular forms of inquiry are constituted by the constraints on justification characteristic of them. Thus, we cannot even identify (define) a particular form of inquiry independently of contextual factors, including non-epistemic factors traditionally located in the context of discovery. Second, we cannot determine when, if ever, belief in a hypothesis/proposition tested in a particular scientific discipline is justified independently of those same contextual factors because, in the absence of such contextual factors, there is simply no way of determining what justification amounts to. We cannot even identify

the justificatory norms that govern particular sciences, let alone apply them, independently of the context of the inquiry in question. Williams sums up this point as follows:

> ...the antidote to ... epistemological realism ..., is a contextualist view of justification. To adopt contextualism, however, is not just to hold that the epistemic status of a given proposition is liable to shift with situational, disciplinary and other contextually variable factors: it is to hold that, independently of all such influences, a proposition has no epistemic status whatsoever. There is *no fact of the matter* as to what kind of justification it either admits of or requires. (Williams, 1996, 119)

In sum, from the point of view of Williams' work, the supposition that the contexts of discovery and justification are independent is false because "[q]uestions about justification are essentially context-bound" (Williams, 1996, 118). For Williams, the supposed context-independence of justification is problematic, not merely because we cannot apply the norms of science independently of contextual factors, but because, independently of all such factors, we can't even identify the relevant norms let alone apply them. Independently of contextual factors "[t]here is no fact of the matter as to what kind of justification it either admits of or requires" (Williams, 1996, 119).

I hope it is now clear why defining 'research' in terms of 'generalizeable knowledge' is problematic. Combined with National Commission's insistence upon a sharp distinction between research and practice, this definition suggests a decontextualized picture of knowledge and inquiry, a picture in which the distinction between research and practice simply recapitulates the distinction between the contexts of discovery and justification. But the latter distinction is deeply problematic, not least because it presupposes notions of scientific knowledge and justification that are wildly at odds with both scientific practice and the logic of justification.

An Analysis of 'Research'

Part of the problem, however, is the starting point (the definiendum): 'research'. By the time of *The Belmont Report*, as we saw in Chapter One, the National Commission had eliminated the more qualified, if somewhat misleading, concepts of therapeutic and non-therapeutic research, in favour of research simpliciter. But talk of research simpliciter is just as problematic as talk of generalizeable knowledge simpliciter, because it obscures important differences between forms of research, appreciation of which is crucial for their ethical analysis, or so I will argue.[7] Viewed from this perspective, it is striking that the National Commission never provided a definition of clinical research, even though their work is, in the main, clearly concerned with clinical research, not research in general. The implication is that the National Commission did not recognize that there were any salient (e.g., epistemologically or ethically relevant) differences in kind between research generally construed, and research of this or that type (e.g., biomedical research in general, or clinical research in particular, not to mention sub-types of clinical research). But this is clearly a mistake. After all, the National Commission was charged with studying the ethical principles underlying *biomedical and behavioral research on human subjects*, not those underlying research in general. A more sophisticated analysis of "research" is required, an analysis that carefully distinguishes clinical research from other kinds of research (e.g., basic or pre-clinical biomedical

[7] In this I disagree with both the National Commission and others (including the authors of Canada's Tri-Council Policy Statement) who ignore distinctions between different forms of research involving humans and/or human tissue (including distinctions between medical/biological research and social science and humanities research, between so-called basic research and clinical research, and between different forms of clinical research), presumably because they did not believe that these distinctions were relevant to their ethical analysis. There have been many vocal opponents to this strategy, particularly within the social sciences.

research), and sorts out the different categories of clinical research as well. Fortunately, Edward Ahrens has already carried out such an analysis in his 1992 book *The Crisis in Clinical Research.* In the following, I summarize Ahrens' findings.

Basic vs. Applied Research

Ahrens begins by providing a thoughtful discussion of the oft-used but very misleading distinction between basic and applied research. Frequently, this distinction is drawn in terms of motives: basic research is characterized by the pursuit of knowledge for its own sake, with no practical goal in mind, whereas applied research is characterized by its utilitarian bent (Ahrens, 1992). A similar strategy distinguishes basic and applied research in terms of the freedom of the investigator to pursue whatever he or she desires to investigate. On this version of the distinction, basic research is investigator-centered, whereas applied research is subject centered (i.e., targeted) (Kidd, 1959, quoted in Ahrens, 1992, 35). Another closely related form of this distinction focuses on the product of research. On this version of the distinction, basic research is characterized as "purposeless, almost random activity in which the search for [sic] useful or usable information is obtained," whereas applied research is "seen as exclusively concerned with products ready for marketing" (President's Biomedical Research Panel, 1976, quoted in Ahrens, 1992, 35). Finally, though Ahrens doesn't mention it, there is a version of this distinction that draws the distinction in terms of the object studied. On this view, the distinction between basic and applied research essentially recapitulates reductionism: whereas basic research involves the study of the most basic (i.e., smallest) constituents of a given phenomenon in terms of which we seek to explain that phenomenon, applied

research studies phenomena at higher levels. On the most extreme version of this view, only particle physics counts as basic research. In the context of the life-sciences, however, the distinction is typically drawn with molecular biology, chemistry, and the like on one side (the basic side), and studies involving (whole) human beings and their diseases on the other (the applied side).[8] Tied up with all versions of this distinction is the familiar evaluative stance wherein basic research is valorized and applied research looked down upon as pedestrian and derivative. Alvan Feinstein captures this aspect of the basic/applied distinction with typical acuity in the following passage:

> The new idea of basic science reinforced the traditional alignment of intellectual prestige in the academic totem pole of scholarship, where pure or basic entities have much higher rank then those regarded as applied. Just as the philosopher looks down on the pure mathematician, who looks down on the statistician, who looks down on the biostatistician, a pure basic biologist is more intellectually respectable than someone who studies the applied biology of disease... Being inversely proportional to the structural size of the object under investigation, prestige increased as the investigated material became smaller... .(Feinstein, 1999, 462)

Ahrens rejects all of these versions of the basic/applied distinction, along with the differential prestige this distinction so often connotes. Instead, he prefers the following two versions of the distinction, both of which appeared in 1976. The first, offered by Comroe and Dripps, describes research as basic when:

> ...the investigator, in addition to observing, describing and measuring, attempts to determine mechanisms responsible for the observed effects; with our definition, basic research can be on healthy or sick people, on animals, tissues, cells or subcellular components. (Comroe & Dripps, 1976)

On Comroe and Dripps' view, then, basic research involves the investigation of mechanisms whereas applied research involves observing, describing and measuring the observed effects of those mechanisms. The second of the two versions of the distinction

[8] This distinction is so widely accepted it represents the way many North American medical schools (implicitly if not explicitly) organize their departments: basic (non-clinical) vs. applied (clinical).

preferred by Ahrens, offered by the President's Biomedical Research Panel, draws the distinction in terms of certainty and uncertainty:

> We suggest that basic and applied science differ in their relative degrees of certainty and uncertainty...It is characteristic of basic research as a primarily exploring activity that it must be done in an atmosphere of some uncertainty. [A competent investigator] can proceed with confidence that he will get answers, but since he is working in unknown territory he cannot have certainty as to the nature of those answers...[A]pplied science is done quite differently, under the influence of a necessarily high degree of certainty, [which ensures that] the outcome can be predicted. (President's Biomedical Research Panel, 1976)

The Panel goes on to note that the methods employed in order to conduct the two kinds of research are radically different. Basic research is imaginative and requires the investigator to "change his mind and his approach, when new developments occur," but "[a]pplied science requires that the work be laid out sequentially on carefully arranged schedules – [and] the protocol for the experiment, once launched cannot be changed on individual whim" (President's Biomedical Research Panel, 1976).

For Ahrens, these two versions of the definition of basic research and, thus, the distinction between basic and applied research, boil down to the same thing:

> [I]t is the nature of the question asked and the manner in which an answer is sought that characterize basic [and applied] research. It is not the doctoral degree of the researcher, or the name of the department in which that person performs the research, or the object under study, be it a marine animal, a leafy tree, or a human. (Ahrens, 1992, 36)

On Ahrens' view, then, it is not necessarily the (size of the) object studied, the product of the research, the freedom of the investigator, or the motives that drive his work that distinguishes basic from applied research, though basic and applied research may often be distinguishable along these lines. Rather, for Ahrens, it is the nature of the questions asked and the manner in which an answer is sought that distinguishes basic from applied research.

I should point out that Ahrens' analysis of the distinction between basic and applied research also runs contrary to prominent contemporary formulations. Consider, for example, the three part definition of clinical research offered by the NIH Director's Panel on Clinical Research in their 1997 report. Prima facie, their definition is similar to Ahrens'. However, the Panel defines clinical research in terms of interaction with patients, and persists in contrasting clinical research with basic research in these terms.[9] According to the Panel, clinical research involves direct interaction with patients/human subjects (at the very least, clinical research is "research in which it is necessary to know the identity of the patients from whom the cells or tissues under study are derived"), whereas basic research does not.[10]

However, as we shall see below, Ahrens argues that we cannot adequately distinguish various forms of inquiry on the basis of the material they study. Ahrens argues that such a categorization is not descriptively adequate. For Ahrens, both basic and clinical research may be (and in fact are) performed entirely on animals, tissues, cells, or subcellular components. Basic and clinical research, thus, are not adequately distinguished in terms of the object studied. Rather, for Ahrens, an adequate analysis turns on the "nature of the questions asked and the manner in which an answer is sought" (Ahrens, 1992, 36).

Of course, descriptive adequacy is not the only reason I favour Ahrens' approach, though it is undoubtedly important. I also favour Ahrens' analysis because an analysis on

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[9] In this the Panel is not alone. Many commentators define clinical research, and contrast it with basic research, in this way. See, for example, Goldstein & Brown, 1997; Schechter, 1998; Rees, 2004. Goldstein and Brown's so called "handshake test" seems to be particularly popular: "[a]s a rule of thumb, if the investigator shakes hands with the patient in the course of the research, that scientist is performing POR [i.e., clinical research]" (Goldstein & Brown, 1997; 2806).

[10] See the Executive summary of the NIH Director's Panel on Clinical Research Report, 1997, 1.

these grounds is both incompatible with a non-trivial characterization of research in general, and consistent with a contextualist approach to (scientific) knowledge and justification.

Clinical Research

Ahrens distinguishes clinical from non-clinical research in the same way: in terms of the nature of the questions asked and the manner in which an answer is sought. Research is clinical on Ahrens' view if it is driven, at least in part, by an interest in the diagnosis, treatment, of prophylaxis of a clinical disorder, or by an interest in explaining the underlying mechanisms of disease. Again, Ahrens prefers a definition (of clinical research) offered by Comroe and Dripps:

> We define research as clinically oriented, even if it is performed entirely on animals, tissues, cells, or sub-cellular particles, if the author mentions even briefly an interest in the diagnosis, treatment, or prevention of a clinical disorder, or in explaining the [underlying] mechanisms of a sign or symptom of the disease itself. (Comroe & Dripps, 1976)

According to Ahrens, then, research is clinical if it is at all concerned with questions related to the explanation of the mechanisms of human disease, or the diagnosis, treatment, or prevention of a clinical disorder. For Ahrens, then, clinical research is characterized by its questions, questions that "originate in stated or implied questions dealing with human health or disease" (Ahrens, 1992, 42). And these questions may be answered at the molecular level, at the cellular level, or at the level of whole-organisms (e.g., non-human animals, humans).

Before moving on to the subcategories of clinical research identified by Ahrens, notice that when 'basic,' 'applied,' 'clinical,' and 'non-clinical' are defined in this way

(i.e., in terms of the questions they address), current usage of these terms is deeply misleading. For example, it is misleading to call the non-clinical departments of a medical school faculty the basic departments, as many medical schools do, because to do so implies that they never engage in clinically relevant research and also that the clinical departments are only capable of carrying out targeted or utilitarian research. But investigations of the mechanisms of human disease (i.e., basic research on Comroe and Dripps' definition) may be, and in fact often are, carried out in clinical departments.[11] Similarly, applied research as defined here may be, and often is, undertaken in non-clinical departments. Given these definitions, in other words, it is simply misleading to correlate clinical with applied research and non-clinical with basic research; clinical research is constituted by the particular angle of its inquiry, not the level, a point I will return to shortly.

Categories of Clinical Research

Ahrens further dissects clinical research into seven categories. This categorization is useful for a number of reasons. First of all, much as it is potentially misleading to speak of research in generic, decontextualized terms, it is also problematic to speak of clinical research in this way. Clinical research, particularly when defined in the inclusive manner Ahrens favours, is a highly differentiated activity. Each category of

[11] Indeed, there is every reason to believe that investigations of human disease necessitate the input of people who have traditionally worked in clinical departments. Consider the following passage from Feinstein: "The material studied for these basic challenges [i.e., the challenges constitutive of explanation and intervention] can have at least three different levels of functional structure: intact organisms (such as persons); organs and organ-systems; and cells and molecules. All three levels require different approaches and methods of research, and different research hypotheses and subsequent analyses. Because each level will need its own distinct scientific procedures, a singly, monolithic basic science cannot possibly supply all the different approaches and ingenuity" (Feinstein, 1999, 465).

clinical research, on Ahrens' view, involves different objectives, skills, facilities, and funding. Ahrens' categorization is doubly useful, thus, because it both emphasizes the diversity of clinical research and brings coherence to these diverse activities by identifying the questions, skills, and facilities shared by each category of clinical research. The latter exercise is particularly useful because it clarifies the questions and 'strategies of attack' constitutive of each category. In the following, I reproduce Ahrens' seven categories of clinical research, along with his examples, verbatim:

1. Studies of Mechanisms in Human Disease
   This consists of studies in which the investigator seeks to refine current characterization of disease processes (or health) and to explore unresolved questions in human biology by controlled observation or manipulations (or both) of patients or volunteers and their environments (such extrinsic factors as diet, exercise, sleep, study setting, stress, drugs, etc.). Pharmacokinetic studies belong in this category. These various kinds of mechanistic studies require the special facilities of a clinical research center with dedicated in-patient or out-patient areas (or both) and trained support staffing. The responsible investigator may or may not have performed the required laboratory work personally, but he does have control over both the benchwork and the clinical aspects of such studies.

   Example: metabolic studies of volunteers on diets rich in palmitic vs. stearic acid in relation to changes in plasma lipids and lipoproteins; pharmacologic studies on the mode of action of a plasma-lipid-lowering drug in patients with hypercholesterolemia.

2. Studies of Management of Disease[12]
   This consists of studies in which the investigator, working directly with patients or volunteers, prospectively conducts controlled observations on an incompletely tested new diagnostic or therapeutic technique or device, often in comparison with an accepted one. This category also encompasses tests of preventive measures, all drug studies aimed at establishing safety and efficacy, and studies of patient-compliance, since all are directly relevant to management of disease.

   Example: a large-scale, controlled clinical trial of a drug in relation to the incidence of new events of coronary heart disease.

[12] Of course, strictly speaking this category of clinical research is not restricted to studying the management of *disease*. Studies of management of disease are paradigmatic of this form of clinical research, but this category of research also concerns itself with managing well-being, conceived more broadly than disease, and with managing injury, disability, and the like, none of which can or should be categorized as diseases.

3. In Vitro Studies on Materials of Human Origin
   These studies are conducted in relation to a stated or strongly implied clinical issue in which the patients or volunteers providing such materials as blood, tissues, or excreta are not directly managed or experimentally manipulated by the laboratory investigator who works on those materials. Human genome studies fall into this category, as do the research results of autopsy and surgical pathology studies.

   Example: definition of receptor defects in fibroblasts derived from skin biopsy specimens of patients with familial hypercholesterolemia, and their genetic determinants.

4. Animal Models of Human Health or Disease
   Here the investigator explores some aspect of human physiology or clinical disease through studies performed in animals (sometimes in mathematical or computer models) by means of experimental manipulations, usually prospectively.

   Example: studies in non-human primates of the regression of arteriosclerotic lesions produced by dietary manipulations.

5. Field Surveys
   Here the investigator or teams of investigators search for risk factors for human disease in open population groups, either descriptively or through active manipulations (epidemiologic studies). The kindred studies of geneticists fall into this category, as do psychological surveys aimed at refinements in understanding of clinical issues or human behavior.

   Example: the search in open populations for risk factors for coronary heart disease.

6. Development of New Technologies
   The invention, development and quality-control testing of new diagnostic and therapeutic methods (bioassays, scanning techniques, biostatistical methods, vaccines, etc.) in this category are clearly distinct from their application in management of disease (Category 2).

   Example: studies attempting to define the optimal technical conditions under which arteriography can be used to measure changes in the size of arteriosclerotic lesions in major blood vessels.

7. Assessment of Health Care Delivery
   In these studies, investigators examine the societal and economic consequences of health management practices, both old and new, or study the infrastructure of delivery systems (medical or allied health professional education, hospital or clinical administration, medico-legal studies, health insurance studies, geographic

> distribution of professional skills, health manpower needs, resource allocations). This field has come to be called 'health sciences research.'
>
> Example: comparative evaluations of the efficacy of coronary bypass surgery in terms of costs and side effects in different treatment centers. (Ahrens, 1992, 40-2)

For Ahrens, then, each category of research is constituted by its questions, by its 'strategies of attack,' i.e., "the methods of thinking employed by their investigators – how to frame the question and how to tackle it" (Ahrens, 1992, 43), and by the facilities, training, and funding each requires. Before examining the import of Ahrens' analysis, I must introduce a little more terminology. At this point in his discussion, Ahrens introduces the term 'patient-oriented-research' (POR), as well as two subcategories of POR: 'Basic POR,' and 'Applied POR'. For Ahrens, POR is research that requires human beings as subjects of study and experimentation (Ahrens, 1992).[13] 'Basic POR' denotes studies that fall into Category 1 (i.e., mechanistic studies of patients or volunteers). 'Applied POR' denotes studies that fall into Category 2 (i.e., studies on the management of disease). Ahrens defends this usage by appeal to his favored definitions of 'basic' and 'applied' research as follows:

> Category 1 POR is better called "Basic" POR because it describes the kind of research that is undertaken in an atmosphere of uncertainty (the President's Biomedical Research Panel Report's definition of 'basic' in 1976) and that focuses on testing hypotheses about some aspect of human biology that we do not yet fully understand (Comroe and Dripps' definition of 'basic'). Category 2 POR is better called "Applied" POR because it is performed in the certainty that a clear-cut 'yes' or 'no' outcome will be revealed: for instance, a new diagnostic or therapeutic procedure will be found to be better or worse than one relied on before, or a new drug will prove to be more or less effective and safe than others in generally accepted use. (Ahrens, 1992, 45)

[13] Though Ahrens' definition of clinical research is arguably more expansive than that of the NIH Director's Panel on Clinical Research, his definition of POR is narrower: whereas the Panel's definition of POR includes both Ahrens' categories 3 and 6, Ahrens restricts POR to categories 1 and 2. See the Executive summary of the NIH Director's Panel on Clinical Research Report, 1997, 1.

From now on I will use these terms (i.e., 'Basic POR' and 'Applied POR') to refer to Category 1 and 2 studies respectively.

Contextualism and Clinical Research

Ahrens' analysis of clinical research is decidedly contextualist in spirit, even if he does not explicitly tie his account to a contextualist epistemology. He explicitly distinguishes different forms of research by appeal to 'the nature of the question asked and the manner in which an answer is sought.' Forms of inquiry, thus, are distinguished, at least in part, by the interests that drive them. Thus, according to Ahrens, research is clinical if it is driven even partly by an interest in the diagnosis, treatment, or prophylaxis of a clinical disorder, or by an interest in explaining the underlying mechanisms of disease, a decidedly contextualist approach to distinguishing disciplines. Furthermore, given Ahrens' definitions of basic and applied research, these questions may be answered at the molecular level, at the cellular level, or at the level of whole-organisms (e.g., non-human animals, humans). Thus, for Ahrens, forms of inquiry are constituted by the particular angle of inquiry, not the level.[14] Again, this strategy is decidedly contextualist.

According to contextualism, recall, justificatory standards are subject to circumstantial variation. There is no fundamental, invariant justificatory structure on the basis of which all scientific beliefs are justified. Rather, justificatory standards vary across contexts, contexts that are defined, in large part, by our interests and the direction of inquiry those interests dictate. But the direction of inquiry has to do with what Williams' calls "the angle of inquiry," not the level. We accept the methodological

[14] I am paraphrasing Williams: "The direction of inquiry has to do, not with the level, but with the angle of scrutiny. There is no simple relation between level and angle" (Williams, 2001, 160).

propositions constitutive of a form of inquiry, not because we have lowered the level of scrutiny to which claims are subjected, but because we cannot doubt these propositions and at the same time inquire in this direction. As Williams puts it:

> The need to recognize methodological limitations on doubt is not, as the sceptic has it, a reflection of our practical limitations but a fundamental fact about the logic of inquiry. Nor is it a matter of our applying more relaxed standards, lowering what Robert Fogelin calls the 'level of scrutiny' to which claims are subjected. The direction of inquiry has to do, not with the level, but with the angle of scrutiny. (Williams, 2001, 160)

Analogously, on Ahrens' view, basic research is not distinguished from applied research on the basis of the purportedly fundamental character of the phenomena studied in basic research (e.g., molecules, genes). Basic and applied research are not distinguished by the level of inquiry undertaken in these two domains;[15] rather, they are distinguished in terms of the questions asked, the interests at stake, or the angle of inquiry. Finally, these interests and the questions to which they give rise, determine the appropriate methods to be used, and thus the skills, facilities, and funding required.

In this section, I want to explore in more detail the contextual constraints implicit in Ahrens' analysis of clinical research. I focus primarily on Category 2 – Applied POR. I restrict myself primarily to this category because the literature on the ethics of research on human subjects is, for the most part, concerned with research of this kind. Furthermore, it is in Applied POR that the distinction between research and practice is most strained.

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[15] Much as Williams denies that there is a deep epistemological structure underlying all instances of genuine knowledge, there are those who deny that there is a deep structure underlying everything in human life. See, for example, Feinstein: "If something is to be called basic only if it is fundamental to everything else in human life, then nothing can be basic. No entity or collection of entities can encompass the rich complexity of human existence, ranging from the glorious art and compassionate love that emerge from mind and heart, to the cerebral mitochondria and cardiac myocytes of medical biology. The complexity of human systems can extend from social groups to intact persons, and from endocrine glands to DNA. The form and function of each of these systems has its own material, its own basic challenges, and its own methods of fundamental scientific research" (Feinstein, 1999, 465).

My strategy is to make explicit the various constraints on justification implicit in Ahrens' analysis of Applied POR. Before turning to Applied POR proper, however, I must elucidate a key constraint on justification constitutive of clinical research as a whole. Recall, again, that for Ahrens research is clinical if (and only if) it is driven at least partly by an interest in the diagnosis, treatment, or prophylaxis of a clinical disorder, or by an interest in explaining the underlying mechanisms of human disease. I can think of at least one broad constraint on justification proper to clinical research that follows from 'clinical research' so conceived. Since clinical research is concerned either with understanding the mechanisms or the management of human disease or disorder, in order to pursue this form of inquiry we must accept the proposition that human disease and disorder are real or, more specifically, that the particular human disease or disorder under study is 'real'. Though this proposition may seem trivial, in some areas of clinical research it is very controversial. For example, many people are sceptical of the 'reality' of a host of new psychiatric diagnoses, e.g., social anxiety disorder. Furthermore, their scepticism may turn out to be well founded. Nonetheless, in order to carry out clinical research on social anxiety disorder, if that is what you are interested in doing, commitment to the proposition that social anxiety disorder is a 'real' disease (or disorder) is a methodological necessity.[16]

Of course, 'real' is highly ambiguous in this context and by these remarks I do not intend to be taking a stand on the ontological status of disease(s). One might be a eliminativist or dissolutionist with respect to (a) disease yet still be interested in pursuing

[16] Given Ahrens' analysis of basic and applied research, investigations concerning whether or not X is a real disease are strictly speaking pre-clinical or basic insofar as we are not necessarily investigating the mechanisms or management of human disease. Put another way, insofar as investigations of this kind are not driven by an interest in the diagnosis, treatment, or prophylaxis of a human disease, they are not clinical.

clinical research about a particular knot of symptoms which we may refer to as disease X. The methodological commitment is simply pressed down a level. So conceived, clinical inquiry requires a commitment to the proposition that the symptoms in question are real, which in some cases may mean nothing more than this: persons in fact suffer from these symptoms. Oddly, it seems persons may suffer from a disease even when it is not 'real' in the ontological sense, precisely because, in the course of studying, treating and suffering from it, doctors and patients believe it to be. [17]

Now that we are clear about at least one of the key constraints on justification proper to clinical research as a whole, we are in a position to turn to Applied POR itself. Recall Ahrens' characterization of Category 2 clinical research (Applied POR):

> 2. Studies of Management of Disease
> This consists of studies in which the investigator, working directly with patients or volunteers, prospectively conducts controlled observations on an incompletely tested new diagnostic or therapeutic technique or device, often in comparison with an accepted one. This category also encompasses tests of preventive measures, all drug studies aimed at establishing safety and efficacy, and studies of patient-compliance, since all are directly relevant to management of disease.

In the following, I will identify and explain justificatory constraints implicit in Ahrens' analysis of Applied POR from four of the five categories of constraints identified by Williams. I do not discuss intelligibility/semantic constraints here because to do so would be an exercise in triviality. Intelligibility/semantic constraints, recall, place general constraints on what it makes sense to doubt in *any* context, thus their elucidation here would be both impractical and uninteresting, or so I assume.

[17] Hacking's discussion of multiple personality disorder, fugue, and the 'looping effect of human kinds' is particularly illuminating with respect to these issues. See Hacking, 1995; 1998.

Methodological Constraints

Insofar as Applied POR is defined in terms of the improvement of the management of disease, questions proper to this form of research are questions concerning the preferred modality of disease management.[18] Hypotheses proper to Applied POR, then, are hypotheses about whether or not an experimental intervention (for the purposes of the following, an "intervention" is defined as "a modality for the management of disease in humans") is preferable to an accepted intervention, or if there is not an accepted intervention for the disease or disorder in question, hypotheses about whether or not an experimental intervention is preferable to doing nothing. Insofar as Applied POR is concerned with the improvement of the management of disease, in other words, Applied POR is by definition concerned with evaluating (experimental) prophylactic, diagnostic, and/or therapeutic *interventions*.

Consider, for example, a Phase II clinical trial of an experimental drug X for the treatment of disorder Y. Let's suppose that there is already a first generation treatment for Y, Z, against which X will be compared. In a conventional superiority study, the two treatments are compared to test if one of them is significantly superior. Thus, the null hypothesis (H_0) is that treatments X and Z do not differ by more than a defined amount D, and the alternative hypothesis (H_a) is that treatments X and Z do differ by more than D. Notice, however, that even if we fail to reject the null hypothesis, even if the

[18] Some might wonder where 'improvement' came from here; others may take it to be obvious that Applied POR is concerned with the improvement of the management of disease. In the interests of clarity, I will be explicit: I am reading improvement into the connotation of 'new' as that term is used in Ahrens' definition of Applied POR. It seems to me that, insofar as we are concerned with the management of disease, we are necessarily concerned with hypotheses about interventions that promise to improve the management of disease, rather than hypotheses about interventions that are merely novel. Analogously, as we saw in Chapter One, it is widely recognized that human subjects research is morally justified only if it promises to yield valuable results, i.e. results that hold out real promise for the improvement of clinical practice. From this perspective as well, newness is not sufficient for moral justification, unless 'new' implies improved; as in "new and improved!"

conclusion of this study is that the experimental drug X is not the preferred treatment modality for disorder Y, the study was nonetheless designed to evaluate the relative efficacy of two *treatments*, albeit one that is experimental and one that is not.

In order for this study to take the particular direction it does, therefore, various commitments must be made. First of all, since this study is designed to compare the efficacy of an experimental treatment against an accepted one, it must be conceded that there is such a thing as an experimental treatment; otherwise, questions of this kind could not be posed.[19] Again, this concession may seem trivial, but it is not. Bona fide hypotheses about the efficacy of experimental treatments have a particular character. Since Applied POR is defined in terms of the improvement of the management of disease, and an efficacy study is a token of this type, a bona fide hypothesis about the efficacy of an experimental treatment is necessarily a hypothesis about the efficacy of a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease, where 'legitimate' means 'epistemically justified by evidence from other studies in Applied POR, Basic POR, Animal modeling, or Pre-clinical research'. This gives us a definition of 'experimental treatment': *an experimental treatment, qua object of study in Applied POR, is a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of a disease.*[20] A significant feature of this definition is that it makes clear that despite being incompletely tested, an experimental treatment is, nonetheless, a treatment; indeed, it is an experimental treatment![21] With this definition in hand, we can now be

[19] I am assuming it will be readily conceded that there is such a thing as an accepted treatment.
[20] I am not merely stipulating this definition; the idea is that the logic of inquiry characteristic of Applied POR demands an object of study so defined.
[21] I think a great deal of confusion has entered the literature on the back of an illicit inference from the epistemic character of an experimental treatment, i.e. its status as incompletely tested, to its metaphysical character, i.e., its status as a treatment. I will return to this point later, but I hope that I have already shown that the invalidity of such an inference must be conceded if anything like Applied POR is to be conducted.

explicit: since this study is designed to compare the efficacy of an experimental treatment against an accepted one, it must be conceded that there is such a thing as 'a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease.' Otherwise, questions of this kind could not be posed.

Of course, the concession that there is such a thing as an experimental treatment in general is not sufficient for *this* study to take the particular direction it does; rather, in order for this study to take the particular direction it does, the proposition that *drug X* itself is an experimental treatment, or more explicitly, that 'treatment X is a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease Y,' must be accepted. Furthermore, if this is right, the conduct of this study presupposes a standard or norm, the application of which allows for the identification of a treatment that is a legitimate rival candidate for the optimal treatment of disorder Y. A plausible candidate for this norm might look something like this:

> A treatment X is a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be.

As will be apparent to anyone familiar with the research ethics literature, I have paraphrased this proposition from Benjamin Freedman or, more precisely, from the work of his commentators who have endeavored to specify just how much disagreement is necessary among the community of expert practitioners before a clinical trial may be initiated. Later I will say more about the relationship between this proposition and Freedman's principle of clinical equipoise. However, it should be noted that the obvious congruencies between the two are not accidental, nor do these congruencies merely reflect my attitude to Freedman's principle (though I am sympathetic); rather, the logic of

Applied POR demands something very much like this proposition. Given the logic of Applied POR, in other words, we might disagree about the content of the definiens in the above definition/norm (e.g., we might suppose that a rival is legitimate if and only if, on the basis of good but incomplete evidence, at least one responsible and legitimate physician justifiably believes it to be), but we cannot do without a proposition of this form because of the role this proposition plays in this context. Since the role of this proposition in this context is to facilitate the identification of an experimental intervention, as defined above, this proposition must provide an operational definition of "a legitimate rival candidate for the optimal management of disease" of some kind or another. And, as we shall see later, it is this reference to 'a legitimate rival' that fundamentally connects this proposition to the principle of clinical equipoise.[22]

Stated generally, then, there are (at least) three overlapping methodological constraints on Applied POR; in order for Applied POR to take the particular direction it does, in other words, we must be committed to accepting the following propositions[23]:

1) There is such a thing as a legitimate, yet incompletely tested, (rival) candidate for the optimal management of a disease (i.e., an experimental intervention);
2) Intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease Y;

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[22] As I will argue later on, commitment to these propositions, i.e., (1) There is such a thing as a legitimate, yet incompletely tested, (rival) candidate for the optimal management of a disease; (2) Intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease Y; and (3) an intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be, amounts to committing oneself to the principle of clinical equipoise, albeit for epistemological as opposed to moral reasons.

[23] It seems likely to me that recognition of the necessity of committing oneself to something like these propositions (in order to conduct Applied POR) lies behind the 'logic' of the double blind. The double blind operationalizes this commitment, ensuring that, even if the investigator conducting the study is not a member of the minority convinced of the effectiveness of the experimental intervention, her lack of commitment will not undermine the experiment. Of course, the double blind is designed to control for expectations of success as well as failure. Notice, however, that this is achieved by ensuring that both the experimental and control interventions look like *legitimate treatments*. We don't go to great lengths to ensure that an experimental treatment looks experimental. But we do go to great lengths to ensure that an experimental treatment looks like an accepted one, or that a placebo control looks legitimate.

And

3) An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be.[24]

Of course, commitment to the second proposition, at least once the variables are bound, implies commitment to the first. Furthermore, commitment to the third, again, once the variables are bound, implies commitment to the second and, thus, to the first. We can summarize things, then, by insisting that commitment to the third proposition, or something very much like it, is necessary in order to undertake inquiry of this form; otherwise, we are not in a position to even pose, let alone answer questions concerning the optimal management of disease.

Of course, at this point it might be objected that committing oneself to the third proposition is question-begging since the aim of Applied POR is precisely to demonstrate whether or not belief in the legitimacy of an experimental rival is justified. There are two related responses to this objection.

First of all, this objection makes the mistake of treating this proposition as an empirical proposition when, in this context, it is playing the role of a norm. It is easy to make this mistake because one and the same proposition may be an empirical proposition in one context and a norm in another. As Wittgenstein notes, "...there is no sharp boundary between methodological propositions and propositions within a method" (Wittgenstein, 1969; 318). In different contexts, the same proposition may be a proposition constitutive of a form of inquiry (i.e., a methodological proposition) or a

[24] Note: 'legitimate' modifies 'rival,' not the beliefs of members of the community of expert practitioners. Furthermore, on my view, whether or not members of the community of expert practitioners are justified in believing that a novel intervention is a legitimate rival turns, in part, on whether or not the grounds for their belief are *in fact* reliable. See Williams, 2001, 23.

proposition to be tested by, or within, that form of inquiry (i.e., a proposition within a method). However, a proposition cannot be both a methodological proposition and a proposition within a method in the *same* context, because, as we have already seen, inquiry of this or that form is constituted by its methodological propositions; inquiry of this or that form cannot proceed, in other words, without presupposing the methodological propositions (constraints) that are constitutive of it.

Consider the following example. Acids were once defined as 'substances that turn blue litmus paper red'. Within the chemical theory of the day this statement was a norm of representation (or a methodological proposition). The proposition 'an acid is a substance that turns blue litmus paper red' was used to test hypotheses concerning whether or not a given chemical was an acid (i.e., propositions within the method). At the time, in other words, this proposition was a methodological proposition; it was partly constitutive of chemistry.

Later, however, chemists realized that many acids were not detected by the litmus test. More general definitions of acids were developed from the late 19th century through to the early 20th. In 1923, for example, the chemists Bronsted and Lowry independently propounded a definition of acids that revolves around an acid's ability to donate protons to another compound, called a base, in a chemical reaction (*Webster's Online Dictionary*; accessed July 20th, 2007). Turning litmus paper red ceased to be a criterion for something's being an acid. Rather, determining which acids turned blue litmus paper red and which did not became a subject of investigation within chemistry. The proposition 'an acid is a substance that turns blue litmus paper red' changed from being a methodological proposition to being a proposition within a method.

In the late twentieth century commitment to the proposition 'an acid is a substance that turns blue litmus paper red' is question-begging because this proposition is a proposition within a method (i.e., chemistry). However, earlier such a commitment was not question-begging because at that time it was a methodological proposition. The objection that commitment to the second proposition above is question-begging is problematic in the same way: the objection illegitimately treats a methodological proposition as a proposition within a method.

Second, there is a sense in which a commitment to the proposition in question is question-begging; the previous, I hope, made this clear. All methodological propositions are, at least in principle, question-begging because, at least in principle, all methodological propositions are empirical propositions in another context of inquiry. To return to Williams' example, if you are interested in whether or not the Earth really existed a hundred years (or five minutes) ago, the proposition that the Earth existed in the past (if asserted without justification…) is question-begging within this context of inquiry. But this does not obviate the necessity of committing oneself to the proposition that the Earth did exist in the past if you are interested in pursuing historical research. In the latter context of inquiry, commitment to the proposition that the Earth existed in the past is a methodological necessity. Similarly, though we must commit ourselves to this proposition (i.e. 'an intervention is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease if a significant minority of the community of expert practitioners justifiably believes it to be') in the context of Applied POR, in a multitude of different contexts, this proposition is undoubtedly question-begging.

For instance, we might be interested in inquiring as to whether this proposition is the appropriate methodological norm for Applied POR. We might disagree about the if-clause in this proposition. We might, for example, argue that the relevant standard by which to identify experimental treatments is the justified belief of a majority, rather than a significant minority, of the community of expert practitioners. In this context of inquiry, this proposition is question begging (if asserted without justification). However, this does not change the fact that, if you are interested in conducting Applied POR, commitment to something like this proposition is a methodological necessity.

In another context, we might be concerned about whether or not the relevant group of believers is in fact justified in believing that a treatment is a legitimate rival. We might, in other words, be concerned about the quality of the evidence upon which their belief is based. Suppose, for example, that a significant minority of the community of expert practitioners believes that a new Selective Serotonin Reuptake Inhibitor (SSRI), 'S', is a legitimate rival for the optimal management of depression. Furthermore, suppose that, accepting the proposition "'S' is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of depression because a significant minority of the community of expert practitioners justifiably believes it to be,' a researcher working in Applied POR is about to initiate a clinical trial of this drug. Now suppose that you are a researcher interested in the causes of depression, and you are sceptical about the quality of the evidence indicating that depression is caused by a dearth of serotonin in the brain. From the perspective of this context of inquiry, the proposition that "'S' is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of depression because a significant minority of the community of expert practitioners *justifiably*

believes it to be,' is question-begging because it presupposes that the relevant experts are in fact justified in believing what they do. In fact, you might be convinced that the evidence for their believing what they do is faulty, or that, in fact, depression is not caused by low serotonin levels. But these are questions characteristic of inquiry into the causes of depression. Even if this proposition is question-begging from the perspective of the latter context, this does not obviate the necessity of committing oneself to this proposition if you are interested in pursuing Applied POR concerning the optimal management of depression.

Dialectical Constraints

Dialectical constraints play a crucial role in Applied POR. Again, recall that Applied POR is defined in terms of the (optimal) management of disease. The epistemic status of hypotheses concerning the (optimal) management of disease changes relative to the dialectical environment. Suppose that, given the available evidence (which, let us assume is credible), it is widely accepted in the relevant expert community that the preferred treatment for Y is Z. The proposition (P) that Z is the preferred treatment for Y, in other words, currently enjoys a kind of default status: until challenged by some plausible evidence to the contrary the epistemic status of P is stable. However, as soon as new evidence emerges that Z may not be the preferred treatment for Y (i.e., evidence emerges that treatment X is a legitimate rival candidate for the optimal treatment of Y), evidence that is convincing to at least a significant minority of the relevant expert community, P no longer enjoys default status. Given such a legitimate challenge, in other words, P is no longer justified unless the challenge can be met, by, for example,

demonstrating that, ceteris paribus, treatment Z differs from (i.e., is superior to) treatment X by more than D in a controlled trial comparing the two treatments. The epistemic status of P changes as the dialectical environment changes.

Economic Constraints

Of course, determinations of the legitimacy of challenges and the sufficiency of responses to them will depend on the severity of the epistemic standards we deem appropriate. For example, as already suggested above, we might demand that new evidence that an intervention is a legitimate rival candidate for the optimal management of disease be convincing to a majority, rather than a significant minority, of the relevant expert community, setting the level of epistemic severity very high. Conversely, we might deem a response to such a challenge sufficient if the equivalence of treatment Z and treatment X, rather than the superiority of Z over X, can be demonstrated, setting the level of epistemic severity somewhat lower; given such a result, both treatments are, ceteris paribus, 'optimal'. Notice, however, that insofar as we are concerned with answering questions concerning the optimal management of disease, we cannot respond to such a challenge without comparing the two treatments head to head. Lacking such a comparison, the challenge remains unmet, and P remains unjustified. The epistemic status of P becomes all the more tenuous if, as is now frequently the case, it is shown that treatment X, like treatment Z (let us assume that Z is a first generation treatment), is significantly superior to a placebo. Such a finding simply deepens the challenge to P, further eroding its epistemic status. However, lacking a head to head comparison of Z and X, the alternative hypothesis – that X is the preferred treatment for Y – also remains

unjustified; the preferred treatment for Y, thus, remains unknown, an untenable circumstance if we are committed to a rational therapeutics (in Chapter Four, I define 'rational therapeutics' as: the provision of therapy the safety and effectiveness of which have been demonstrably justified, or are capable of demonstrable justification).

Situational Constraints

It must be emphasized that methodological necessity does not entail truth. Though we must commit ourselves to various propositions in order to pursue a particular form of inquiry, the methodological necessity that these propositions 'stand fast' does not entail that they are true. Furthermore, inquiries of this or that form will produce knowledge only if, in fact, these propositions are true. Williams sums up this crucial point in the following passage:

> It is also crucial to note that, if epistemic status is determined by the direction of inquiry, the reason why, in a given inquiry, certain propositions have to stand fast, has to be separated from the reason why that inquiry results in knowledge, if it does... In particular contexts of inquiry, certain propositions stand fast as a matter of methodological necessity. But inquiries informed by them will yield knowledge only if those propositions are true, which they need not always be. (Williams, 1996, 124)

Again, unlike the previous four classes of constraints, which are indexed to the particular form of inquiry in question, situational constraints reflect facts about the world that are independent of the inquiry in question.

Broadly, then, Applied POR investigating the efficacy of treatment X will yield knowledge only if, for example, the proposition "intervention X is a legitimate, yet incompletely tested, rival candidate for the optimal treatment of Y" is true. And the truth of this proposition may be influenced by a range of facts about the actual situation in which research is pursued. Facts about the heterogeneity of subgroup response to X, for

example, may affect the truth of this proposition, or facts about the mechanism of disease Y. If, to return to one of our examples above, it turned out to be false that depression is caused by low serotonin levels in the brain, the (known) situational constraints on Applied POR in this context would change. Even if the results of a trial of this SSRI (indeed, any SSRI) were positive, the epistemic status of our beliefs concerning the efficacy of this SSRI (indeed, any SSRI) would change because we would no longer know why the treatment was effective. Our belief in the efficacy of this SSRI would be purely empirical, in the negative sense of that word. It would lack theoretical justification and, to this extent, epistemological justification as well.

The Relationship Between Research and Practice

At this point, having made explicit (some of) the contextual constraints implicit in Ahrens' analysis of clinical research and Applied POR, we are in a position to both appreciate what is wrong with the National Commission's definition of "research" in terms of "generalizeable knowledge," and propose a replacement. First of all, recall the problem elucidated in Chapter Two. In Chapter Two, I argued that, by contrasting research and practice in terms of BOTH the generality of research and the specificity of practice AND the epistemic nature of the former and the pragmatic nature of the latter, the National Commission effectively poses the question at the core of the central problem – how can theoretical knowledge be applied to concrete, individual persons with therapeutic results – and eliminates the conceptual space required for its solution. I spent most of Chapter Two on the former claim. I attempted to show that the National Commission was wrong to assume, as they apparently did, that the relationship between

research (defined in terms of generality), and practice (defined in terms of specificity) is unproblematic; the central problem has long been, and continues to be, problematic. However, with respect to the latter claim – that the National Commission's definitions of research and practice effectively eliminate the conceptual space for the sort of research required for the production of specifically therapeutic knowledge – I said very little, promising an argument in Chapter Three. We now have the conceptual resources required to make this argument in hand. In the final section of this chapter, then, I spell out the argument for this claim and, finally, offer a new, more qualified, definition (of Applied POR) as a replacement for the National Commission's definition of research *simpliciter*.

One of the key insights gained from our contextualist analysis of clinical research is that, insofar as Applied POR is defined in terms of the improvement of the management of disease, Applied POR is concerned with developing knowledge of a very particular sort. Questions proper to Applied POR are questions concerning the preferred modality of disease management, questions about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic *interventions*. Thus, the sort of knowledge developed by Applied POR is knowledge about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic interventions, knowledge that is directly relevant to the management of disease, or, simply, clinically relevant knowledge.

Furthermore, insofar as Applied POR is defined in terms of the *improvement* of the management of disease, notice that we cannot define Applied POR independently of the context of practice. If questions proper to Applied POR are questions about the *comparative* safety and efficacy of (experimental) interventions, which is implied by

'improvement' in this context, these questions must always be posed in relation to current practice; current practice, either implicitly or explicitly, is the standard against which experimental interventions are compared.[25] Indeed, if I am right, 'experimental intervention,' *qua* object of study in Applied POR, is itself defined in relation to the context of practice (an experimental treatment, *qua* object of study in Applied POR, is a legitimate, yet incompletely tested, (*rival*) candidate for the optimal treatment of disease). Furthermore, the standard by which bona fide experimental interventions are identified is also indexed to the context of practice, specifically, to the justified beliefs of (at least a significant minority) of the community of expert practitioners. And this standard, or something like it, is partly constitutive of Applied POR. Applied POR, therefore, cannot be (fully) defined independently of the context of practice.[26]

If the foregoing is right, intervening is an essential, or constitutive, feature of Applied POR. Again, insofar as questions proper to Applied POR are questions concerning the preferred modality of disease management – questions about the (comparative) safety and efficacy of experimental interventions – intervening is an essential feature of Applied POR because these questions can be answered only via the application of these experimental interventions (in the context of a trial or experiment). Applied POR, in other words, necessarily involves practice (properly construed).

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[25] Insofar as Applied POR is defined in terms of the *improvement* of the management of disease, a hypothesis counts as a bona fide hypothesis in Applied POR only if it involves the evaluation of an intervention that promises to improve the management of disease. However, this does not mean that all trials of second-generation interventions must explicitly involve comparison with the accepted first-generation treatment in order to count as Applied POR, though this is ideal; it does mean that all trials of second-generation interventions must involve, at the very least, an implicit comparison with the accepted first-generation treatment. Of course, the validity of implicit comparisons is suspect.

[26] Some might wonder at this argument given that Ahrens seems to have managed to provide a definition of Applied POR, a definition which I have relied on here, without referring to the context of practice. Notice, however, that Ahrens' definition refers to "incompletely tested *new* diagnostic or therapeutic technique[s]..."(emphasis mine). Furthermore, he explicitly states that the latter are often tested by "comparison with an accepted one". To my mind, both 'new' and 'comparison with an accepted one' refer to the context of practice, implicitly in the former instance, explicitly in the latter. See footnote 18 (Ch 3).

This picture of the relationship between research (i.e., Applied POR) and practice contrasts starkly with the picture presented in *The Belmont Report*. Recall that, by the time of *The Belmont Report*, the National Commission offered a picture of the relationship between research and practice wherein their coincidence is presented as merely accidental, as something that just happens; "[t]he distinction between research and practice is blurred," they note, "because both often *occur* together…" (*The Belmont Report*, 1978, 3 – emphasis mine). In this picture, for example, prophylactic, diagnostic and/or therapeutic benefits are presented as a side-effect of research, as an accidental feature of research involving patients, not to be confused with its essential nature. Now we are in a position to see just how wrong they were on this point.

Recall, now, the definition of 'practice' as found in *The Belmont Report*: "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success". Far from an accidental side-effect, 'practice,' so defined is an essential feature of Applied POR. First of all, we have already established that intervening is an essential feature of Applied POR: we must intervene in order to determine the (comparative) safety and efficacy of an experimental intervention. Second, although it is not the case that, in the context of Applied POR, we intervene "*solely* to enhance the well-being of an individual patient (emphasis mine)," all subjects enrolled in Applied POR are 'administered' an intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success" (where the 'reasonability' of this expectation is always relative to the prevailing standard of care).[27] And this is true even in the case of

[27] Furthermore, as I will argue in Chapter Four, we never intervene solely to enhance the well-being of an individual patient, if by 'solely' the National Commission intends to exclude from the doctor-patient

Phase I trials in Applied POR involving healthy subjects. Of course, healthy subjects enrolled in a Phase I trial are not typically in a position to obtain diagnostic, prophylactic, or therapeutic benefits from trial participation. Nonetheless, practice is necessarily involved in a Phase I trial because Phase I trials are designed to determine the toxicity or dynamics of an intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success."

Of course, it might be objected that I am equivocating on the meaning of 'practice' here and, prima facie, this objection is a good one. However, I believe that 'practice' is inherently, and necessarily ambiguous in this sense. On the one hand, 'practice' connotes '*actions* that are *intended* to enhance the well-being of an individual patient;' on the other hand, 'practice' connotes 'a particular thing or strategy, e.g., a drug or regimen, that is devised to enhance the well-being of an individual patient'. The former reading is undoubtedly the traditional or standard reading. But the latter reading is also essential. Indeed, insofar as we are committed to what I call a rational therapeutics (see Chapter Four) the former reading presupposes the latter. Furthermore, I doubt we can even make sense of Applied POR as it is conducted today without relying on 'practice' in the latter sense. I pursue these points in detail in Chapter Six.

To return to the main line of argument, although we likely cannot justifiably expect the same level of success in the case of an experimental treatment as we can of an accepted one, we do, indeed we must, have a 'reasonable expectation' of its success in

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relationship commitments other than a commitment to enhancing the well-being of an individual patient. Given a scarcity of resources and a commitment to distributional justice, a physician's commitment to enhancing the well-being of an individual patient is necessarily mitigated by a commitment to ensuring an efficient, effective, and just distribution of the health resources available. And this is true whether or not it is the physician herself or a third party policy maker that is so committed. In either case, someone has "intentionally made a decision that we have good reason to believe will cause certain people to get less than optimal treatment" (Gifford, 1986, 360).

order to initiate a trial. This follows from the third methodological constraint identified above:

3) An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be.

Given this proposition, an intervention is a bona fide experimental intervention, *qua* object of study in Applied POR, only if 'a significant minority of the community of expert practitioners *justifiably* believes it to be'. Granted, an experimental intervention is, by definition, incompletely tested. However, the beliefs of the relevant experts must be justified on the basis of credible evidence from elsewhere (e.g., other studies in Applied POR, Basic POR, Animal modeling, or Pre-clinical research). In other words, the relevant experts must have a reasonable expectation of the success of the experimental intervention, though, again, the level of success that can be justifiably expected of an experimental treatment is likely lower than that of an accepted one. But this is unsurprising: practice in the context of Applied POR is not identical to practice outside of this context, however, it is practice nonetheless.[28]

If this is right, the National Commission is wrong to suppose that practice is merely an accidental feature, a side effect, of research. If the research in question is Applied POR, practice (properly construed) is an essential feature of it. Indeed, I believe it is perfectly accurate to describe Applied POR as "therapeutic research" (I will say more about this in Chapter Six). The National Commission's concerns with the term "therapeutic research" follow from their definitions of research and practice and are revelatory, not of difficulties inherent in the idea of therapeutic research per se, but of

[28] Perhaps I am getting ahead of myself here. Treatment in the context of Applied POR is practice given a slightly revised definition of practice that omits 'solely'. I develop such a definition in Chapter Four.

problems with these definitions. Once these definitions are appropriately revised, the notion of therapeutic research becomes unproblematic, which is right and good because that term accurately describes a great deal of Applied POR.[29]

If this is right, furthermore, it reveals what is wrong about the National Commission's definition of research. Let's quickly summarize the argument thus far. If Applied POR is defined in terms of the improvement of the management of disease, questions proper to Applied POR are questions about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic *interventions*. If questions proper to Applied POR are questions about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic *interventions*, then intervening (i.e., practice) is an essential feature of Applied POR because these questions can be answered only via the application of these experimental interventions (in the context of a trial or experiment). And, finally, if Applied POR necessarily involves practice, i.e., the application of interventions designed to enhance the well-being of an individual patient, the knowledge developed by Applied POR is not only of a very particular sort, but of a very particular scope. Knowledge developed in Applied POR, precisely because that knowledge is obtained via the controlled observation of *the effects of an experimental intervention on individuals*, will only be as generalizeable as individuals (specifically, individual response to interventions) are similar.

[29] Research subjects seem to understand this point far better than the experts. The lion's share of research subjects who agree to enroll in studies of novel therapies do so because they are hoping to benefit from the experimental treatment. Of course, many experts insist that these hopes are based on a "therapeutic misconception". I think this conclusion, like the rejection of the notion of therapeutic research, often reflects a problematic conception of research rather than a problem of informed consent. I develop these thoughts in Chapter Six.

Here, finally, the central problem resurfaces. By insisting upon the specificity of practice, the National Commission effectively rules out (conceptually) the possibility of general knowledge about practice. If individuals are radically idiosyncratic, as the National Commission's definition of practice might be taken to suggest, the project of developing general knowledge about practice makes little sense because, given radical idiosyncrasy, we cannot make valid inferences from an observed feature of an average patient (i.e., the overall effect of treatment X in sample Y) to the efficacy of treatment X in an individual outside that sample. Indeed, given radical idiosyncrasy, the term 'average patient' is problematic, denoting a numerical mean rather than a group of individuals who are in fact relevantly similar.

Furthermore, by insisting upon the generality of research in conjunction with the specificity of practice, the National Commission effectively eliminates the conceptual space for the sort of research that is appropriately sensitive to the specificity of practice. Given the specificity of practice, we need research that produces knowledge that is appropriately local, or, specific. By defining research in terms of generality, at least without elaboration, the National Commission closes off the possibility of specific knowledge.

In fact, the supposition that individuals are radically idiosyncratic appears to be false. The success of Applied POR suggests that we can sometimes make valid inferences from sample to population. The results of good clinical trials have proven useful in the clinic. Sometimes we can, and do, make valid inferences from sample to population.

On the other hand, the limits of Applied POR are also relatively well established. We know that inferences made on the basis of the observed overall effect of intervention

X on an 'average patient' rarely license inferences to all patients. Though we can sometimes make valid inferences from a representative sample to the population that sample is representative of (which implies that at least some individuals are relevantly similar to each other), inferences outside of that population are suspect. Individuals may not be radically idiosyncratic, but they are not homogeneous either.

In actuality, the degree of similarity between individuals seems to lie somewhere between these two extremes. In general, individuals (more precisely, their responses to intervention) are neither radically idiosyncratic nor homogeneous; rather, though response is variable, variations clump together. There are, in other words, subgroups within which response to intervention is more or less homogeneous, but across which response is variable. Inferences from sample to population are valid, therefore, as long as the selection criteria are sensitive to subgroup variation. Such inferences are valid, in other words, as long as the sample, or a part of it, is representative of the pertinent subgroup of the general population.

It is precisely because Applied POR is sensitive to idiosyncrasies like subgroup variation (at least when it is done properly) that Applied POR is ideally suited to the task of producing the sort of knowledge required to close the gap between bench and bedside. Put another way, because Applied POR involves practice, because Applied POR develops knowledge via the controlled observation of the effects of an experimental intervention on actual individuals, Applied POR must be sensitive to idiosyncrasies like sub-group variation if it hopes to produce valid, clinically relevant knowledge.

But this same sensitivity to idiosyncrasy means that the scope of the knowledge developed by Applied POR is rarely universal; rather, the scope of this knowledge is

typically restricted to clinical subgroups of the population within which response to intervention is more or less homogeneous. It is, thus, misleading to contrast research and practice, as the National Commission's distinction does, in terms of generality and specificity. If individual patients were radically idiosyncratic such that practice was specific to each patient, a rational therapeutics along the lines of EBM would be impossible. Clearly, we can and do sometimes make valid inferences from sample to population. Thus, practice is not accurately characterized in terms of specificity (at least not without elaboration).

Similarly, Applied POR is not accurately characterized in terms of generality (without elaboration). Precisely because of the more or less radical specificity of individual patients, clinically relevant knowledge is rarely generalizeable to all patients. Rather, clinically relevant knowledge is typically restricted to clinically relevant subgroups. In this sense, clinically relevant knowledge is, in an important sense, quite specific. Indeed, it is because Applied POR produces this quite specific knowledge that it serves to close the gap between the bench and the bedside. Applied POR, unlike laboratory research, does not (and should not) aspire to universality, and this is why it works. However, precisely because the National Commission defines research in terms of generality and practice in terms of specificity, the National Commission eliminates the conceptual space for Applied POR.

Instead of a definition of research simpliciter, we need discipline-specific definitions that are sensitive to their epistemological, metaphysical, and moral differences. In this essay I have focused on Applied POR because, historically, research

ethics has been primarily concerned with research of this kind. I propose the following definition of Applied POR, paraphrased from Ahrens, as a starting point:

> Applied POR is research involving direct contact with patients or healthy volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.

This definition, of course, has the virtue of specificity: it is a definition of a very specific form of inquiry – Applied POR. This definition also shares many of the virtues of Ahrens' definition of Applied POR, from which it borrows liberally. Thus, it stresses the fact that Applied POR involves the controlled observation of actual patients in order to determine the optimal modality for the management of disease. Applied POR, therefore, is easily differentiated from other forms of clinical research, and pre-clinical research, which have different methods and goals. Finally, this definition has the virtue of making more explicit the contextual constraints on justification implicit in Ahrens' analysis. Specifically, the inclusion of the phrase "a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease" invokes the three constraints on justification elucidated above:

1) There is such a thing as a legitimate, yet incompletely tested, (rival) candidate for the optimal management of a disease (i.e., an experimental intervention);
2) Intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease Y;
   And
3) An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only, on the basis of good but incomplete evidence, if a significant minority of the community of expert practitioners justifiably believes it to be.

As I have already shown above, bona fide Applied POR presupposes all three of these constraints. In order for Applied POR to take the particular direction it does, we

must be committed to accepting (at least) these three propositions. Of course, as I have already noted above, commitment to the third proposition implies commitment to the first and second, so we can summarize things by insisting that commitment to the third proposition, or something very much like it, is necessary in order to undertake inquiry of this form; otherwise, we are not in a position to even pose, let alone answer questions concerning the optimal management of disease. Furthermore, as I hope I have shown in this chapter, commitment to this proposition has very particular epistemic, metaphysical, and ultimately moral implications.

Conclusion

In Chapter Two I argued that the National Commission's definitions of research and practice are problematic because they both raise the specter of the central problem and effectively eliminate the conceptual space required for its solution. In this Chapter, building on Ahrens' analysis, I offered a contextualist analysis of clinical research and Applied POR. This contextualist analysis revealed that Applied POR is constituted by very specific contextual commitments that only come into view when we are attentive to the particular interests at stake in this form of inquiry, commitments that are themselves revelatory of the epistemological, metaphysical, and ultimately moral, character of this form of inquiry.

First of all, our analysis revealed that we cannot even fully define Applied POR independently of (the context of) practice. Insofar as Applied POR is defined in terms of the improvement of the management of disease, insofar as questions proper to Applied POR are questions about the (*comparative*) safety and efficacy of (experimental)

interventions, these questions must always be posed in relation to current practice; current practice, either implicitly or explicitly, is the standard against which experimental interventions are compared. Applied POR, in other words, is partly constituted by the context of practice within which it takes place.

Second, our contextualist analysis of Applied POR made it clear that the epistemological status of claims made on the basis of Applied POR is essentially related to the context within which those claims are made, i.e. the context of practice. The various constraints on justification implicit in Ahrens' analysis of Applied POR delineate the space within which Applied POR takes place, and each of these constraints refers essentially to the context of practice. In this sense, too, the context of practice is constitutive of this form of inquiry. As Williams puts it, "in the absence of a detailed specification of a particular context of inquiry…the question 'What is to be tested by what' has no answer" (Williams 1996, 118); in the absence of these constraints on justification, constraints that essentially refer to the context of practice, we cannot even pose the relevant questions, let alone determine the justificatory status of a proposed response.

These metaphysical and epistemological characteristics of Applied POR, revealed by close attention to the particular contextual interests at stake in Applied POR, are obscured if we insist upon talking in terms of research in general. This is deeply problematic because, insofar as "an ethical framework that provides normative guidance about a practice should accurately characterize the practice" (Miller & Brody, 2003, 20), talk of research simpliciter obstructs rather than facilitates the development of an

adequate ethics for human subjects research. We must replace the National Commission's definition of research with definitions of the specific forms of inquiry in question.

In this chapter I have focused on Applied POR because, historically, research ethics has been primarily concerned with research of this kind. I offered the following definition of Applied POR:

> Applied POR is research involving direct contact with patients or healthy volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.[30]

This definition is important because it makes (more) explicit the epistemological and metaphysical character of Applied POR. It is also important because it paves the way for an adequate ethical analysis of Applied POR. As we will see in Chapter Five, much as the context of practice shapes the epistemological and metaphysical character of Applied POR, it also informs its moral analysis, providing a crucial constraint on the moral justification of human subjects research. Indeed, as I will argue later on, commitment to the methodological propositions delineated above amounts to committing oneself to the principle of clinical equipoise, albeit for epistemological as opposed to moral reasons. Constraints on epistemic and moral justification converge. Before turning to this argument, however, we must first reexamine the National Commission's definition of practice. This is the aim of Chapter Four.

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[30] Again, strictly speaking Applied POR is not restricted to studying the management of *disease*. Studies of management of disease are paradigmatic of this form of clinical research, but this category of research also concerns itself with managing well-being, conceived more broadly than disease, and with managing injury, disability, and the like, none of which can or should be categorized as diseases.

Chapter Four: Rethinking the Duty of Care

Introduction

Much as attention to the context of inquiry shows that we cannot make sense of Applied POR independently of the context of practice, attention to the context of practice shows that we cannot make sense of practice independently of the context of research. Of course, in a sense this point is a truism. Given a commitment to a rational therapeutics e.g., in the form of a commitment to evidence-based-medicine (EBM), clearly we cannot make sense of practice independently of the context of research: given such a commitment, best practice is and ought to be determined by the results of good clinical research.

Despite the truistic character of this point, however, it is worthy of emphasis and elaboration because the National Commission's distinction between research and practice suggests a misleading picture of practice as well as research. The purpose of this chapter, then, is to provide such an elaboration, an elaboration in the course of which I will both criticize the National Commission's definition of practice and offer another definition in its stead.

The problem is that the distinction presents a picture of practice as a purely pragmatic and morally unitary endeavour. Recall the National Commission's definition of practice: "'practice' refers to interventions that are *designed solely to enhance the well-being of an individual patient or client* that have a reasonable expectation of success" (emphasis mine). Whereas the goal of research is epistemic in nature, i.e. the

development of generalizeable knowledge, the goal of practice is *solely* pragmatic in nature, i.e. the enhancement of well-being.

But this contrast is misleading in two ways. First of all, this contrast is misleading because it suggests that the duty of care is a unitary moral duty; that is, it suggests that practice is *solely* concerned with enhancing the well-being of an individual patient. But this is false. Other interests inevitably mitigate the doctor's commitment to her patient. Given a scarcity of resources and a commitment to distributional justice on the part of health policy makers, for example, a physician's commitment to enhancing the well-being of an individual patient will be circumscribed by policies designed to ensure a just distribution of the health resources available. Furthermore, these limits are not merely external. The very knowledge to which physicians must appeal when determining how best to act with unqualified fidelity to their patient's health, is itself qualified in the relevant sense. The content of the duty of care itself is constituted partly in response to factors that are themselves social in nature, factors like cost and availability, typically deemed external by the traditional picture of the doctor-patient relationship. Considerations of efficiency, distributional justice, and myriad other relevant interests are, and ought to be, built into the doctor-patient relationship from the outset. Thus, if 'solely' is meant to exclude from the doctor patient relationship interests and commitments other than a commitment to enhancing the well-being of an individual patient, physicians cannot, and should not, intervene solely to enhance the well-being of an individual patient.

Second, this contrast is misleading because it obscures the fact that, given a commitment to a rational therapeutics, the interventions in question cannot be specified

independently of evidence provided by good clinical research. It is misleading, in other words, because it suggests that the duty of care is a purely moral duty. Given a commitment to a rational therapeutics, however, this suggestion is also false because the relationship between epistemological justification and therapeutic practice is internal: our moral commitment to the provision of good personal care goes hand in hand with a commitment to epistemic justification. Given a commitment to a rational therapeutics, in other words, we cannot determine what counts as an "intervention…that [has] a reasonable expectation of success" without an informed (i.e., critical) understanding of the relevant evidence, evidence provided by good clinical research. Minus such an understanding of the relevant, best evidence, we cannot satisfy the duty of care. Furthermore, since critical appraisal of the relevant best evidence presupposes the existence of such evidence, satisfying the duty of care also depends upon the ongoing conduct of clinical research. The duty of care, therefore, involves both moral duties, i.e., the provision of personal care justified by the evidence, and epistemic duties, i.e., the critical appraisal of evidence for the safety and effectiveness of the care provided via good clinical research, and support for its ongoing conduct. Practice is both a pragmatic and epistemic activity; it is as much about knowing as it is about doing.

We need a new understanding of the duty of care, and a less misleading definition of practice. The chapter closes by offering the following definition in the stead of the National Commission's: "practice" refers to "interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success." By omitting the term 'solely' from the National Commission's definition, the suggestion that practice is morally unitary is removed. By

adding the phrase 'justifiably believe,' furthermore, the fact that practice involves both moral and epistemic duties is made explicit. The Chapter begins with a critique of the moral unitarity suggested by the National Commission's definition of practice.

Practice: A Unitary Moral Duty?

Recall the National Commission's definition of practice:

> "[P]ractice" refers to interventions that are *designed solely to enhance the well-being of an individual patient or client* that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (*The Belmont Report*, 1978, 4. Emphasis mine)

Practice, so defined, is supposed to contrast with research in a number of now familiar ways: whereas research is designed to produce generalizeable knowledge, practice aims to provide optimal care to patients; whereas research proceeds according to the dictates of a formal protocol, practice proceeds in accordance with the judgment of the attending physician (in consultation with the patient involved); whereas research is an activity concerned with groups of patients, practice is concerned with individuals; and whereas research aims to benefit future patients, practice aims to benefit individual patients in the here and now. In the previous chapter, I argued that many of these contrasts are misleading, if not illegitimate, because we cannot make sense of research, specifically Applied POR, without appealing to the context of practice. I tried to show that conceptually, epistemologically, and ultimately morally, research is inherently bound up with the context of practice. I argued for these claims on the basis of a contextualist analysis of research. In this chapter, however, I want to examine the relationship between research and practice from the opposite direction: in terms of an analysis of practice.

In this section, I am specifically concerned with criticizing the notion, implicit in the above list of contrasts, but explicit in the National Commission's definition of practice, that practice is *solely* concerned with enhancing the well-being of an individual patient. As I understand it, 'solely' functions in this definition to exclude other commitments, i.e., commitments other than a commitment to enhancing the well-being of an individual patient, from the doctor patient relationship. According to this definition of practice, unmitigated fidelity to the patient's well-being is the key feature of the doctor-patient relationship. Indeed, traditionally, this is what is meant by the doctor's duty of care: unmitigated fidelity to her patient's well-being. This is in contrast with research, wherein 'other commitments,' specifically a commitment to producing generalizeable knowledge, are an essential feature of the investigator-subject relation: the investigator-subject relation is not exhausted by fidelity to the subject's well-being.

This view of the doctor-patient relationship, as a relation characterized by an unmitigated duty of care to the patient, has a long history. Arguably, this picture of the doctor-patient relationship is that presented in the Oath of Hippocrates: "...I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous..." (Oath of Hippocrates, set out in J. Katz, *Experimentation with Human Beings*, 1972, 311). As Charles Fried has pointed out, however, this formulation is ambiguous in this context because it refers to patients in the plural. An investigator might well believe that, by committing himself to producing generalizeable knowledge of the relevant sort, he is working to benefit his patients as a class (Fried, 1974, 50). However, later statements concerning the doctor-patient relationship are less ambiguous on this score. Consider, for

example, *The Declaration of Geneva of the World Medical Association*: "The health of my patient will be my first consideration" (*The Declaration of Geneva*, set out in J. Katz, *Experimentation with Human Beings*, 1972, 312). *The International Code of Medical Ethics* is even clearer: "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest" (Quoted in the *New England Journal of Medicine*, 1964, 473 (271).

But this view of the doctor-patient relationship is undoubtedly expressed most clearly by several seminal thinkers in bioethics. In his influential book *The Patient as Person* (c2002, 1970), Paul Ramsey characterizes the doctor-patient relationship in terms of a moral covenant between doctor and patient involving complete fidelity: "...the doctor cannot in respect to his ... patient become an agent of another person. His is a covenant with that patient, and faithfulness to him should be controlling" (Ramsey, 2002, 36). Similarly, Edmund Pellegrino and David Thomasma argue that the moral principle of beneficence, i.e., to act in the best interests of the person who is ill, is and must be the sine qua non of the doctor-patient relationship:

> ...in actual practice, one ordering principle provides the moral sine qua non; it is the primacy of the moral obligation of the health care profession to act in the best interests of the person who is ill. This is the moral principle of beneficence contained in traditional codifications of the physician's obligations. This is, has always been, and must remain the telos of the healing relationship, the end built into the nature of medicine and without which it becomes something other than a healing relationship. (Pellegrino and Thomasma, 1987; cited in Pellegrino, 1997, 322)

Finally, it is this understanding of the doctor-patient relationship that, historically, has been taken to generate the so-called randomized-controlled trial (RCT) dilemma (the subject of Chapter Five): a conflict between the doctor's duty of care and his commitment to a program of research. Thus, this picture of the relationship also turns up in the text of

authors concerned with this problem. In *Medical Experimentation*, for example, Fried notes that "[t]he traditional concept of the physician's relation to his patient is one of unqualified fidelity to that patient's health" (Fried, 1974, 50). Similarly, in his 1983 paper "Leaving Therapy to Chance," Don Marquis relies on this picture of the doctor-patient relationship when he characterizes the physician's obligation to patients in terms of the 'therapeutic obligation' (TO): "A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis" (Marquis, 1983, 42).

Despite the pedigree and persistence of this view of the doctor patient relationship, i.e. as a relation characterized by an unmitigated duty of care to the patient, it undoubtedly misrepresents reality both past and present. Doctors have always worked under constraints of one kind or another, constraints that necessarily mitigate their ability to truly make an unqualified commitment to personal care. Consider, for example, justice and scarcity, two relatively uncontroversial constraints on a physician's practice. Given a commitment to distributional justice and a scarcity of health resources, it seems to follow that personal care will necessarily be constrained such that it will sometimes be sub-optimal with respect to the patient's individual interests.

Fried recognizes this problem:

> Doctors have always had to weigh the interest of one patient against those of another, have always had to weigh the interests of a particular patient against the interests of a larger group of patients. It is argued that the paradigm of the physician who bears unreserved loyalty to the interests of his particular patient can never have been anything but a myth. Doctors have always had to decide which cases constituted emergencies, so that the real, but less urgent needs of one patient would be sacrificed to the more urgent needs of another. Insofar as the paradigm ever had much force, it reposed on the foundation of hypocrisy. To the

> extent that the doctor has been able to approach the 'ideal' of giving unstinting loyalty to the needs of his individual patients, this has only been possible because of deliberate choices or the semi-deliberate acquiescence in a system the result of which was to limit drastically the number of persons who stood to the doctor in the privileged relationship of patient. (Fried, 1974, 57)

Having recognized the problem, Fried spends the rest of his book attempting to solve it. Schematically, Fried argues that the doctor-patient relationship is a personal relationship and that personal relationships involve fundamental interests and therefore rights. Personal relationships therefore take precedence over abstract, impersonal relationships precisely because the interests involved in personal relationships are protected by rights, rights that must not be compromised because they are the conditions for the very possibility of personal relations:

> ...the realization of the bond of significant personal relationships takes precedence over the conferring of benefits in abstract, impersonal relations. Benefits conferred in the context of particular, concrete relations are not only weightier goods than impersonal benefits but involve rights. And these rights must not be compromised because candor and faithfulness are the very conditions of any significant relationship at all. (Fried, 1974, 133)

Fried anticipates a number of objections to this argument. First of all, he notes that prioritizing personal relations in this way may lead to sub-optimal outcomes for persons with whom the doctor in question has not yet made personal contact. Because personal care is ultimately indivisible, i.e., personal care requires a minimum of time and effort less than which it does not amount to personal care, all her available time and effort may well, indeed likely will, be taken up by attending to those patients who happen to be at the front of the queue. Those patients at the rear will be shortchanged.

Fried bites this bullet. He concedes that some patients will likely, perhaps inevitably, be shortchanged, but he believes that the doctor's behaviour is justified precisely because the doctor is obligated to provide personal care to those patients with

whom she has already entered into personal relations. It is, Fried says, "of the essence of the doctor-patient relationship that it is the creation of a relationship and the assuming of an obligation" (Fried, 1974, 135). Structuring our social obligations in terms of our personal obligations in this way, notes Fried, inevitably creates a bias toward those who are already in personal relationships. But the price of rectifying this injustice, at least at the personal level, is too high; indeed, efforts to do so are, in the Kantian sense, self-contradictory, rendering impossible the personal caring in the name of which these efforts would be undertaken:

> ...it is inevitable that this structuring of the social situation in terms of relationships and their obligations will allocate a greater proportion of time to those who are in existing situations of obligation, than to those to whom obligations have not yet been assumed. And the only consolation that can be offered to the latter is that the violence that would have to be done in order to serve their interests would be a violence that ultimately would destroy the world for which they wish to survive. (Fried, 1974, 135)

As distasteful as this outcome may be, with respect to the individual doctor, argues Fried, it is justified because "[h]e must fulfill the obligations of the situations in which he finds himself" (Fried, 1974, 135).

But Fried is more than willing to attribute fault for the inequity of the social situation to the policy makers who failed to anticipate demand for health resources in the first place. Doctors are obligated to provide personal care to those patients with whom they have already entered into personal relations, even if this leads to an unjust distribution of health care, but policy makers are entrusted with ensuring distributional justice. If, in fact, there are too few doctors available and it is because adequate plans were not made for physician training, this is the fault of policy makers. But doctors cannot be held accountable for the failures of others:

> ...it is fallacious to argue from the premise that in another, better world where everyone did his duty no none would be without care, to the conclusion that, therefore, I must myself single-handedly try to approximate the conditions of such a world even where others have failed in their obligations. I need not sacrifice myself to right the wrongs of others. All the more so I need not, indeed I must not, violate my obligations to identified others for the same reason. (Fried, 1974, 136)

Fried, thus, attributes moral fault for the inequity of the social situation to decision makers at the meso- and macro- levels, and insists that, so long as the doctor fulfills her obligations at the micro-level, i.e. at the level of patient care, she is blameless.

The problem with Fried's argument is that the micro-level cannot be insulated from the meso- or macro- levels. Indeed, this seems to be Fried's own point in the argument just quoted. It *is* fallacious to argue from the premise that in another, better world where everyone did his or her duty no one would be without care, to the conclusion that, therefore, I must myself single-handedly try to approximate the conditions of such a world even where others have failed in their obligation. Their failure limits the range of possibilities open to me: even if I wanted to correct for their failure, I simply cannot single-handedly compensate for it. Given that 'ought' implies 'can', I am not morally obligated to compensate for their failure because I cannot in fact do so.

But it is similarly problematic to insist that a physician must not violate her obligations to identified patients in similar circumstances, i.e., inequitable social circumstances. Recall Marquis' principle of therapeutic obligation (TO):

> TO: A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis.

It is problematic to insist that a physician must not violate her obligations to identified patients in circumstances of social inequity because, assuming that unqualified fidelity to

a patient's health means something like acting on Marquis' principle TO, she sometimes cannot do so.

Policy makers at the meso- and macro- levels are not merely responsible for ensuring that there is an adequate number of doctors available; rather, they are responsible for the whole gamut of allocation decisions, ranging from macro-level policy decisions about the amount spent on health as a whole, to meso-level decisions concerning the type and quantity of interventions available (e.g. drugs, MRIs). The failure of policy makers to fulfill their duty to anticipate demand for health resources and plan accordingly means not only that some patients will not receive care, but also that some of those who do will receive care that is sub-optimal relative to the state of present medical knowledge.

Indeed, given scarcity and a commitment to distributional justice on the part of policy makers, even when policy makers fulfill their duty, just policy decisions at the meso- and macro- levels will inevitably result in limits on the use of interventions that are currently known to be optimal. This point is made by Fred Gifford in a 1986 article:

> Of course, one tries as hard as possible in such cost containment measures to leave out only that which is not important, but surely there is some limitation in the use of certain treatments which would in fact [given present medical knowledge] provide some significant expected benefit. And the benefit in terms of health care costs that accrues from this is distributed generally, so this is not a case where some single decision-maker prefers to forgo a certain amount of good. (Gifford, 1986, 360)

Given scarcity and a commitment to distributional justice on the part of policy makers, then, a physician's commitment to enhancing the well-being of an individual patient will be circumscribed by the limits imposed by non-epistemic factors, e.g. economic factors, as well as epistemic factors, i.e. the present state of medical knowledge. Even if we

presently *know* that treatment X would be optimal for patient Y, given scarcity and a commitment to distributional justice on the part of policy makers, there will be cases where Y's physician will be unable to give this treatment to patient Y. A physician cannot be morally required to do what she in fact cannot do. Thus, Fried is wrong to insist that a physician must act with unqualified fidelity to each patient's health.[1]

At this point it might be objected that I am being unfair to Fried. Since scarcity *is* a given in any possible world close to our own, it is trivial to assert that a physician's commitment to personal care is necessarily qualified due to scarcity. Furthermore, to suppose that Fried was unaware of the limits imposed by scarcity seems grossly uncharitable. A more charitable reading of Fried would have him insisting that the physician's relation to her patient is, indeed must be, one of unqualified fidelity to that patient's health given the limits imposed by scarcity and policy decisions made to cope with it. Even if we have to give up on the traditional picture of the physician's relation to her patient as one of totally unqualified fidelity to that patient's health, we may yet preserve a relativized version of this traditional picture.

Gifford has explored this possibility in the same article quoted from above:

> It may be claimed that while a general policy decision is made that constrains the decisions of individual physicians in ways that yield sub-optimal treatments for patients, individual physicians still (within that framework) act on the TO to the best of their ability. (Gifford, 1986, 360)

In this picture, there is a division of moral labour and, thus, a division of moral responsibility. Policy makers are morally responsible for policy decisions, and doctors

[1] Indeed, it seems to that even if we restrict ourselves to the micro level, i.e., patient care, the doctor-patient relationship cannot be characterized in terms of unqualified fidelity to an individual patient's health. Assuming that a physician has more than one patient, i.e. at least two, his relationship to his patients cannot be characterized in terms of an unqualified fidelity to their health because his commitment to the health of the first patient is necessarily qualified by his commitment to the health of the second.

are morally responsible for treatment decisions made within the constraints imposed by policy makers.

While this proposal may seem plausible enough, it reveals a fundamental problem with the traditional picture. Let's suppose that the traditional picture of the doctor-patient relationship as endorsed by Fried and others is captured by Marquis' principle TO. Again that principle says:

> TO: A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis.

Marquis' principle has the advantage that, unlike the other articulations of the traditional picture reviewed above, it makes explicit the epistemological aspect of the duty of care. As I will argue in the second half of this chapter, given a commitment to a rational therapeutics, a doctor cannot identify the course of action that is in the best interests of her patient lacking the evidence provided by good clinical research. The duty of care is both moral and epistemic in character. By framing the doctor's obligation to her patient in terms of present medical knowledge, Marquis draws our attention to this feature of (modern) medical practice.

Notice, now, that traditional conceptions of the doctor-patient relationship insist upon a sharp distinction between the doctor-patient relationship and the circumstances within which that relationship takes place. Thus, Fried insists that, despite an inequitable social environment, a doctor need not, indeed must not, violate her obligations to patients with whom she already has a personal relationship. For Fried, it is of the essence of the doctor-patient relationship that it be insulated from the contingencies of context. The division of moral labour argument canvassed above makes this distinction explicit,

offering what looks like a plausible proposal for enacting this traditional picture in practice. Although we are forced to concede that the doctor-patient relationship is not completely insulated from external influences, a relativized version of this traditional picture is preserved wherein, given the limits imposed by scarcity and policy decisions made to cope with it, "individual physicians still (within that framework) act on the TO to the best of their ability" (Gifford, 1986, 360). Within the constraints imposed by this framework, in other words, the doctor's relation to her patient is still one of unqualified fidelity. Call this interpretation of the traditional picture the moderate version and the version I criticized above the extreme version.

The moderate version reveals a fundamental problem with the traditional picture, a problem that is shared by both the moderate and extreme versions. The problem is that the traditional picture of the doctor-patient relationship assumes that the content of the TO (the content of the duty of care) can be identified independently of those forces deemed external by the traditional picture. On the traditional view, the content of the duty of care is internal to the doctor-patient relationship, whereas the social context within which that relationship takes places is external to that relationship. This is why Fried is able to maintain that, despite the inequity of the social situation, a doctor must not violate her obligations to patients: the doctor's obligations to her patient can be identified independently of that social context. But the assumption that the content of the TO can be identified independently of the social context is false.

Part of the problem is a failure to explicitly distinguish "medical knowledge" from "clinically relevant knowledge". As I noted above, Marquis' principle has the virtue of making explicit the epistemic side of the duty of care. Marquis explicitly frames the

duty of care with reference to medical knowledge. But "medical knowledge" is problematically ambiguous. As our earlier discussion reveals, "medical knowledge" may be clinically irrelevant. We may know that when it comes to shrinking tumors, X is optimal. However, due to its side effects, difficulty of administration, or prohibitive cost, X may be judged impractical by policy makers, by physicians themselves, or both, such that it is not incorporated into clinical practice. Given this judgment, however, X is effectively clinically irrelevant. Medical knowledge and clinically relevant knowledge can come apart.

However, in general, it does not make sense to suppose that, though we possess some bit of clinically relevant knowledge, the "external" context is such that we cannot act upon it because clinical relevance is defined, in part, in terms of just the sort of factors deemed external by the traditional picture of the doctor-patient relationship. When members of the community of experts judge the promise of an experimental treatment, their judgment is typically based on a range of factors, including pragmatic factors like cost and ease of administration. Clinical choice, as opposed to what we might call – in keeping with the language of the central problem – theoretical or abstract choice, is complicated by the exigencies of the real world. This is a point emphasized by Benjamin Freedman when he contrasts theoretical and clinical equipoise (a point I will return to in Chapter Five):

> Clinical choice is commonly more complex. The choice of A or B depends on some combination of effectiveness, consistency, minimal or relievable side effects, and other factors. On close examination, for example, it sometimes appears that even trials that purport to test a single hypothesis in fact involve a more complicated, portmanteau measure – e.g., the "therapeutic index" of A versus B. (Freedman, 1987, 143)

Accordingly, an intervention X may justifiably be judged a legitimate rival candidate for the optimal management of disease Y if there is good (albeit incomplete) evidence suggesting that: (1) it is more effective than the alternative Z; (2) it is as effective, but easier to administer; (3) it is as effective, but cheaper; (4) it is less effective, but cheaper and easier to administer; or (5) it is more effective, cheaper, and easier to administer. Indeed, many other factors may come into play; this list is not meant to be exhaustive. The point is that judgments of clinical relevance, like clinical judgments more generally, are multi-factorial, involving consideration of epistemic factors, i.e., the present state of medical knowledge, and non-epistemic factors, e.g. economic factors. Thus, clinically relevant knowledge cannot be defined independently of those factors deemed external by the traditional picture, let alone inform clinical recommendations that are systematically in conflict with those forces.[2]

Once we have explicitly distinguished "clinically relevant knowledge" from "medical knowledge," it is clear that the content of the TO is given by the former, not the latter.[3] However, once this substitution is made, it becomes clear that both the extreme and moderate versions of the traditional picture of the doctor-patient relationship are incoherent. Again, Marquis' principle says:

> TO: A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis.

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[2] Of course, it is possible that we may be mistaken about the clinical relevance of a particular bit of knowledge. We may have misjudged the therapeutic potential of an experimental treatment, or the social circumstances may have changed in such a way such that it is no longer practical to incorporate this bit of knowledge into the clinical arsenal. But it does not make sense to suppose that clinically relevant knowledge could come into systemic, or generalized, conflict with the social context precisely because clinical relevance is partly defined in terms of that context.

[3] Again, I am assuming that, given a commitment to a rational therapeutics, the content of the TO (i.e., the duty of care) is determined, in large part, by the evidence provided by good clinical research. I argue this point in the second half of this chapter.

Once we substitute "clinically relevant knowledge" for "medical knowledge," it must be conceded that determining what counts as "acting on the TO" ultimately depends on just those contextual factors deemed external to the doctor-patient relationship by both the moderate and extreme versions of the traditional picture, because determinations of what counts as clinically relevant knowledge depend on these contextual factors. In short, the content of the TO (i.e., the duty of care) cannot be identified independently of those forces. Thus, it does not make sense to draw a sharp distinction between the limits imposed from without (e.g., the decisions of policy makers) and the limits imposed from within (i.e., the decisions of a responsible physician) as both the moderate and extreme versions of the traditional picture do, since policy makers and the community of expert practitioners who decide what counts as a responsible decision on the part of a physician are, and should be, responding to (many of) the same contextual constraints.

The division of moral labour argument, thus, fails to preserve even a relativized version of the traditional picture because the objection I raised against the extreme version (that the duty of care is necessarily circumscribed by external forces) resurfaces, as it were, on the inside. The very knowledge to which physicians must appeal when determining how best to act with unqualified fidelity to their patient's health, i.e., clinically relevant knowledge, is itself qualified in the relevant sense. Precisely because determinations of clinical relevance depend on the same factors deemed external by the traditional picture, clinically relevant knowledge is itself circumscribed by these forces. Due to the logic of clinical research (specifically Applied POR), clinically relevant knowledge is (and ought to be) attuned to the social environment from the outset. Insofar as clinically relevant knowledge determines the content of the duty of care, that content

too is constituted partly in response to factors that are themselves social in nature. Pragmatic factors like cost, availability, etc., factors typically deemed external by the traditional picture of the doctor-patient relationship are, thus, internal to that relationship from the outset. It makes little sense, therefore, to characterize the doctor-patient relationship in terms of unqualified fidelity to the patient because determinations of what counts as unqualified fidelity – the content of the duty of care – are qualified (i.e., social) from the outset (or should be).

Clinically relevant knowledge, and thus the content of the duty of care, is the product of a complex process of negotiation during which trade-offs are made and compromises accepted such that the knowledge achieved is inherently sub-optimal for most, if not all, patients. All sorts of real world factors work to circumscribe both the availability of treatments presently known to be optimal (my objection to the extreme version) AND the pursuance of hypotheses for which we have good, albeit incomplete, evidence of efficacy, but judge impractical due to cost, side effects, difficulty of administration, or any number of other pragmatic factors (my objection to the moderate version). Of course, sometimes these negotiations are fraught with disagreement. Sometimes there may be good reasons for revising decisions made by the expert community precisely because the prevailing social norms disadvantage some patients unduly. But these negotiations always involve trade-offs that will, ultimately, disadvantage some patients. And, precisely because the relationship between (clinical) science and responsible therapeutic practice is internal, sub-optimality, in the sense explicated here, is also internal to the doctor-patient relationship.

Recall, now, the National Commission's definition of practice: ""practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client that have a reasonable expectation of success". We are now in a position to see clearly one of the ways in which this definition is misleading: practice is not *solely* concerned with enhancing the well-being of an individual patient. Rather, the duty of care is necessarily mitigated by other interests and commitments. In the case of particular interests, for example interests that are deeply at odds with or even antithetical to a relation of fidelity between doctor and patient, it may be appropriate to view particular interests as external to the doctor-patient relationship. However, "other" interests and commitments, i.e., interests other than an interest in enhancing the well-being of an individual patient, are not in any general sense external to this relationship. Indeed, precisely because clinical relevance is defined partly in terms of interests and commitments that are, according to the traditional picture, external to the doctor-patient relationship, some specific interests and commitments ought to shape the content of the duty of care and, thus, the doctor-patient relationship. Efficiency and justice seem like plausible commitments of this kind, but some will undoubtedly disagree about this and some sort of compromise will have to be negotiated. The point, however, is that there is no doctor-patient relationship that somehow exists independently of, or prior to, these negotiations. These negotiations constitute that relationship. In sum, if "solely" is meant to exclude interests and commitments like these from the doctor-patient relationship, physicians cannot and should not intervene *solely* to enhance the well-being of an individual patient.

The alleged contrast between the moral plurality of research and the moral unitarity of practice does not hold. The supposition that the doctor-patient relation is exhausted by fidelity to the (enhancement of the) patient's well-being, whereas the investigator-subject relation is not, is false. Like the investigator-subject relation, the doctor-patient relation is not exhausted by fidelity to the (enhancement of the) patient's health; rather, other interests and commitments do and should mitigate this commitment. To be clear, I am not suggesting that these 'other' commitments necessarily qualify fidelity to the patient's well-being in exactly the same way, or to exactly the same extent. But I am suggesting that, insofar as research and practice are contrasted in terms of the moral unitarity of the latter and the moral plurality of the former, to this extent, the contrast is inaccurate.

The Duty of Care: A Purely Moral Duty?

Now I turn to another misleading notion implicit in the National Commission's characterization of practice. Again, recall their definition: ""practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client that have a reasonable expectation of success". Again, the supposition is that whereas the goal of research is epistemic in nature, i.e. the development of generalizeable knowledge, the goal of practice is *solely* pragmatic in nature, i.e. the enhancement of well-being. I have just shown that this contrast is misleading because it suggests that the duty of care is morally unitary. But this contrast is also misleading because it obscures the fact that, given a commitment to a rational therapeutics, the interventions in question cannot be specified independently of evidence provided by good clinical research. It is

misleading, in other words, because it suggests that the duty of care is a purely moral duty. In fact, the duty of care involves both moral duties and epistemic duties, or so I will argue.

'Modern' medicine is typically distinguished from its pre-modern antecedents on the basis of its relationship to science. Modern medicine, thus, is supposed to be rational in a way that pre-modern science was not: modern medicine is based on scientific reason. Of course, many 'pre-modern' physicians also stressed the importance of science and described their medical theories as rational and scientific. Thus, Cooke insisted that his ideas were grounded in observation alone, derided earlier theories as based on assertion rather than evidence, and prefaced his treatise by stating he was applying the methods of Newton to medicine (Cooke, 1828, iii-iv; quoted in Warner, 1997, 47). Similarly, despite the manifest rationalism of his system, Broussais disparaged earlier systems as the work of "obscure & purely speculative logicians, who follow in the treatment of human infirmities, the chimeras of their imaginations, rather than the real disorders that are presented to their senses" (Broussais, 1831, 10; quoted in Warner, 1997, 49).

However, by the late 19th century, the responsible practice of medicine demanded the possession of scientific knowledge of a very particular sort. It was no longer enough for a physician to act in a certain way (e.g., the provision of mercury if he was a Cookeite, or leeches if he was a Broussaisist), even if those actions were prescribed by a theory that was (more or less) consistent with observation at the bedside. By the late 19th century, physicians began to insist on higher epistemic standards. Driven by the work of the internationally renowned French physiologist Claude Bernard, and reinforced by the achievements of late 19th-century laboratory science, the arbiter of professional

legitimacy increasingly became experimental laboratory science. In the laboratory, the hidden causes of patients' symptoms could be uncovered, and the mechanism and efficacy of drug action could be tested under controlled conditions. By the turn of the century, experimental science was the standard for what counted as rational therapy.

Historian Harry Marks charts the history of therapeutic reform in America from 1900-1990 in his book *The Progress of Experiment* (1997). It is from Marks that I have appropriated the term 'rational therapeutics'. Marks locates the origins of the intellectual program for a rational therapeutics, as I have, in the work of late 19th-century medical school professors inspired by Claude Bernard. These reformers gathered under the banner of 'rational therapeutics,' and insisted upon an experimentally based therapeutics (Marks, 1997, 21). Though the meaning of rational therapy changed a great deal through the 19th century and, indeed, during the 20th, Marks identifies two interrelated goals pursued by therapeutic reformers in the United States at the outset of the 20th century in the name of a rational therapeutics: "On the one hand, they sought to control the introduction and promotion of new drugs. On the other, they attempted to foster a scientific and critical attitude toward therapeutics in the medical profession" (Marks, 1997, 22). Marks explicates the former goal as follows:

> [In this sense] a rational therapeutics referred first to the use of therapeutic agents whose mechanisms of action were scientifically established prior to their introduction into clinical practice. A rational, as opposed to an empirical remedy, was one whose effects were demonstrable in the laboratory and ideally one that acted on the cause, not the symptoms, of disease. Where no specific cure existed, however, symptomatic treatment was accepted as "rational," provided researchers were able to demonstrate and justify symptomatic relief. (Marks, 1997, 21-22)

Marks explicates the latter goal in this way:

> At the same time, rational therapeutics referred to the conduct of clinical practice. In rational practice, the dosage and uses of a drug were in accordance with what

> was known about its pharmacological activity and effects. It made no sense to use even an effective drug at doses that were subtherapeutic in clinical circumstances where it could not possibly benefit the patient. (Marks, 1997, 22)

For our purposes, the crucial point is the extent to which Marks' therapeutic reformers emphasized the importance of demonstrable knowledge. For the therapeutic reformers, "rational" means something like "capable of being demonstrably justified," a "rational therapy" is a therapy the mechanisms of which we understand and the efficacy of which has been demonstrated (experimentally), and "rational practice" is practice that proceeds in accordance with what is known. The common denominator here, again, is the insistence upon demonstrable knowledge and the epistemic standards such knowledge demands. In light of this common denominator, we can offer a broad definition of "rational therapeutics" as the provision of therapy the safety and effectiveness of which have been demonstrably justified, or are capable of demonstrable justification.

Of course, as I have already noted, both the scope and the form of rational therapeutics have evolved since the beginning of the last century. The twentieth century witnessed the integration of science and medicine to an extent probably unimaginable in the 19th century. Furthermore, the last century witnessed the development of a host of medical sciences that did not exist in the 19th century, including the science we are principally concerned with here: Applied POR (see Chapter Three). By the end of the 20th century, evidence-based medicine (EBM) rose to prominence as the dominant strategy for therapeutic reform. Due to both the current prominence of EBM and the unprecedented explicitness with which EBM places epistemic demands on the physician, I will use EBM as the basis for my argument in the remainder of this chapter. However, before turning to that argument I want to make another brief historical observation.

Significantly, both the early therapeutic reformers and their mid-twentieth century counterparts conceived of therapeutic reform as both an epistemic and moral endeavour. As Warner observes, by the late 19th century "experimental science was the arbiter of both therapeutic activity and professional morality. [Increasingly, it was believed that] science would decide the most prudent course" (Warner, 1997, 263). By defining the limits of legitimate practice, experimental science also acted as a kind of moral arbiter, distinguishing legitimate practice from quackery. Those practitioners who practiced in accordance with the dictates of science practiced ethically. Those who persisted in prescribing therapy dictated by sectarian dogma did not. Similarly, mid-20th-century reformers viewed the relationship between practice and epistemic justification in moral terms. Physicians who did not practice in accordance with the evidence produced by clinical research practiced unethically:

> Reformers' remarks about the medical knowledge that underwrote physicians' therapeutic practices were highly ethically charged. The ethics in question was the traditional ethics of therapeutic reformers, who tried to persuade physicians that their beliefs about therapy were unjustified. It was, reformers asserted, the physician's responsibility to be guided by medical knowledge, not by drug company misinformation or the uninformed desires of patients. The physician who did not rely on evidence from controlled clinical trials was behaving unethically… (Marks, 1997, 157)

Here, then, we have historical precedents for the argument I am about to make: given a commitment to a rational therapeutics, the duty of care involves both moral and epistemic duties. In the words of mid-20th-century reformers, it is "the physicians' responsibility to be guided by medical knowledge," i.e. to live up to the appropriate epistemic standards. Furthermore, the physician who fails to live up to these epistemic standards is "behaving unethically".

Evidence Based Medicine (EBM)

I begin be quoting, again, the description of EBM offered by The Evidence-Based Medicine Working Group (McMaster University):

> Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. (EBM Working Group, 1992, 2420)

As noted already in Chapter Two, EBM places clinical research at the very center of clinical practice, and places new epistemic demands on the physician:

> Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature. (EBM Working Group, 1992, 2420)

Again, as noted in Chapter Two, one of the principal innovations of EBM is its de-emphasis of authority as a legitimate source of epistemic justification. In the new paradigm proposed by proponents of EBM, rather than relying on the testimony of experts, physicians are expected to have the skills to critically appraise the evidence and the opinions of experts:

> The new paradigm puts a much lower value on authority. The underlying belief is that physicians can gain the skills to make independent assessments of evidence and thus evaluate the credibility of opinions being offered by experts. (EBM Working Group, 1992, 2421)

EBM, thus, raises the epistemic bar for the average physician.

The crucial point for our purposes is that EBM, a rational approach to therapeutics if there ever was one, explicitly connects the responsible practice of medicine with the satisfaction of specific standards of epistemic justification. Indeed, a fundamental assumption of the EBM movement is that following the strictures of EBM will lead to superior care: "[a] final assumption of the new paradigm is that physicians whose

practice is based on an understanding of the underlying evidence will provide superior patient care" (EBM Working Group, 1992, 2421). Furthermore, the Working Group stresses that critical appraisal of the validity and relevance of the evidence, a fundamentally epistemic activity, is a central and pragmatic aspect of optimal patient care: "...critical appraisal is a pragmatic and central aspect, not an academic or tangential element of optimal patient care" (EBM Working Group, 1992, 2423). From the perspective of EBM, in other words, the satisfaction of the relevant standards of epistemic justification is a necessary condition for the provision of optimal care.

Now, as we saw above, one of the central elements of the doctor-patient relation is the doctor's duty of care to his patient. Other things being equal (i.e. ignoring for the moment the ways in which "other interests" necessarily mitigate the optimality of patient care), it is the physician's duty to recommend optimal care to his patient. Given a commitment to EBM, however, notice that a physician's commitment to satisfying this duty entails a commitment to meeting the demands for epistemic justification imposed by EBM. Furthermore, notice that the latter commitment is not ancillary, or tangential to the former. Rather, as the quotation in the last paragraph confirms, from the perspective of EBM the epistemic demands in question (i.e. a commitment to critically appraise the evidence) are a central and pragmatic element of optimal patient care. Put another way, given a commitment to EBM, meeting these epistemic demands is partly constitutive of one's commitment to optimal patient care.

Alternatively, we might say that, given a commitment to EBM (or a rational therapeutics more generally) the relationship between epistemological justification and therapeutic practice is internal: we cannot determine what counts as optimal treatment

without a critical understanding of the relevant, best evidence. Put in terms of the National Commission's definition of practice, given a commitment to EBM, we cannot determine what counts as an "intervention…that [has] a reasonable expectation of success" without a critical understanding of the relevant, best evidence. The content of the duty of care, i.e. the interventions recommended by the responsible physician, is necessarily determined (at least partly) by the relevant, best evidence.[4] Having a critically informed understanding of the relevant, best evidence, then, is partly constitutive of responsible medical practice; that someone has such an understanding is partly what we mean when we describe that person as a good physician. In this sense, the duty of care involves both moral duties, i.e. the provision of personal care justified by the evidence, and epistemic duties, i.e. the critical appraisal of the relevant, best evidence.

At this point, it should already be clear that contrasting research and practice in terms of the epistemic goals of the former and the pragmatic goals of the latter is problematic. The duty of care is not a purely moral duty. Rather, the duty of care involves both moral and epistemic duties. But the epistemic duties implicit in the duty of care are not exhausted by the epistemic demands explicitly imposed by EBM (i.e. critical appraisal of the relevant, best evidence). Though it is necessary, 'critical appraisal' is not sufficient for the epistemic justification of medical practice for the obvious reason that critical appraisal presupposes something to appraise, namely evidence. Since the relevant evidence is (ideally) provided by good clinical research, the epistemic duties implied by the duty of care include a duty to support the ongoing conduct of clinical research.

[4] Note: insofar as determinations of what counts as an "intervention…that [has] a reasonable expectation of success" involve the critical assessment of the relevant evidence from Applied POR, such determinations are necessarily comparative in nature because, as we saw in chapter three, questions proper to Applied POR are "questions about the comparative safety and efficacy of (experimental) interventions". Alternatively: "a reasonable expectation of success" is necessarily a judgment made in relation to current practice.

Without clinical research, medical practice would soon lapse into dogma. Indeed, insofar as modern medicine is defined in terms of its relationship to science, as I have argued above, modern medicine stands and falls with the ongoing conduct of research. It is good clinical research that provides the evidence that ultimately justifies a physician's belief in a particular diagnostic technique or therapeutic intervention. It is good clinical research that provides the physician with the knowledge that (ought to) guide his practice. Without research, there is no medical practice in the modern sense. Given a commitment to EBM (or a rational therapeutics in general), therefore, the duty of care implies a duty to support the ongoing conduct of clinical research.

To be clear, by a "duty to support the ongoing conduct of clinical research" I do not mean to suggest that all practitioners must actually be engaged in formal clinical research in order to satisfy their duty of care. Clearly, such a suggestion is both unnecessary and impractical. A division of labour is permissible and, no doubt, both more efficient and effective. So long as someone is doing the relevant research, and the results of that research are communicated and taken up in a timely fashion, a physician may satisfy his duty of care even if he is not engaged in formal clinical research.

On the other hand, precisely because the relationship between epistemological justification and therapeutic practice is internal, that relationship cannot be, and should not be, viewed as passive, or disinterested. Modern medical practice is deeply dependent upon clinical research. Indeed, if the above argument is right, modern medical practice is partly constituted by clinical research and is, thus, unavoidably implicated in its conduct. Thus, the duty to support the ongoing conduct of clinical research neither condones an uninterested attitude towards the conduct of clinical research, nor demands that every

physician be actively engaged in clinical research. Rather, the duty to support the ongoing conduct is something like a (Kantian) imperfect duty. Because every responsible physician depends on the evidence provided by clinical research, every physician is obligated to support or promote the ongoing conduct of clinical research, however, just how they do so is largely up to them.

Thus, a physician might fulfill this duty by, for example, actively pursuing a program of research herself, by offering her patients enrolment in someone else's study, by reporting adverse events experienced by her patients receiving the recommended intervention, or by suggesting hypotheses for future research. Practicing physicians are arguably uniquely positioned to notice anomalies in our current theories about diagnosis, prophylaxis and treatment, because they are exposed to a wide array of patients with different backgrounds, ages, co-morbidities, and preferences. As Dr. K. Shine has observed (along with many others), "...the physician scientist is uniquely positioned to ask the relevant questions that will redefine the therapeutic and preventive opportunities and to identify the human conditions, inherited or acquired, that offer new opportunities to advance health science" (Shine, 1998, 1442). Indeed, physician scientists have been a rich source of novel hypotheses in the past, a point much emphasized by both recent historical work and commentators concerned with the disappearance of the physician-scientist in recent decades (See, e.g., Williams, 2004; Wyngaarden, 1979; Goldstein et al, 1997; Schechter et al, 2004). Howsoever physicians choose to fulfill this duty, the point is that they are obligated to support the ongoing conduct of research. Each physician may choose how to fulfill this duty, but she cannot, without being epistemically irresponsible, choose to ignore this obligation. Precisely because medical practice derives its epistemic

credentials largely from clinical research, a physician is epistemically responsible if and only if she supports the ongoing conduct of clinical research.

In sum, then, the National Commission's definition of practice is problematic because it misleadingly presents a picture of practice as a purely pragmatic and morally unitary endeavour. We need a new understanding of the duty of care, and a less misleading definition of practice. I suggest the following definition of practice in the stead of the National Commission's:

> 'Practice' refers to interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.[5]

By omitting the term 'solely' from the National Commission's definition, the suggestion that the duty of care is morally unitary is removed. This is important because research and practice are frequently contrasted in terms of the moral unitarity of the latter and the moral plurality of the former. Second, by adding the phrase 'justifiably believed' to the definition, the fact that the duty of care involves both moral and epistemic duties is made explicit. This amendment, like the first, is crucial because research and practice are frequently contrasted along these lines as well: the goal of research is supposed to be epistemic in nature whereas the goal of practice is purely pragmatic, i.e., the enhancement of the well being of the patient. I hope I have shown why both of these contrasts are misleading and problematic.

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[5] Again, insofar as determinations of what counts as an "intervention…that [has] a reasonable expectation of success" involve the critical assessment of the relevant evidence from Applied POR, such determinations are necessarily comparative in nature. See the previous footnote (#4). Notice that, given the comparative character of such determinations, randomizing a patient to the placebo arm in a placebo-controlled trial (PCT) is consistent with this definition of practice when there is no accepted intervention for the disease in question. When there is no accepted treatment for disease X a placebo has "a reasonable expectation of success" relative to current practice precisely because, currently, there is no accepted treatment for disease X.

Conclusion

In Chapter Two I argued that the National Commission's definitions of research and practice are problematic because they both raise the specter of the central problem – how can theoretical knowledge be applied to concrete, individual persons with therapeutic results – and effectively eliminate the conceptual space required for its solution: a bona fide clinical research. I called for a more sophisticated analysis of 'research,' an analysis that carefully distinguishes clinical research from other kinds of research (e.g., basic or pre-clinical research), and sorts out the different categories of clinical research as well. I turned to this task in the next chapter.

In Chapter Three, building on Ahrens' analysis of "clinical research," I offered a contextualist analysis of Applied POR. This analysis revealed that Applied POR is constituted by very specific contextual commitments that only come into view when we are attentive to the particular interests at stake in this form of inquiry, commitments that are themselves revelatory of the epistemological, metaphysical, and ultimately moral, character of this form of inquiry. Once these commitments were made explicit, it became clear that we cannot even define Applied POR independently of the context of practice, let alone determine the justificatory status of its hypotheses. Far from being an accidental side-effect of the conduct of research, as the National Commission supposed, this analysis showed that practice (properly construed) is an essential feature of Applied POR.

These metaphysical and epistemological characteristics of Applied POR, revealed by close attention to the particular contextual interests at stake in Applied POR, have been obscured by talk of research simpliciter. It is necessary to be more specific. Thus, in

the stead of the National Commission's definition of research simpliciter, I offered a definition of Applied POR:

> Applied POR is research involving direct contact with patients or healthy volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.

This definition has the virtue of specificity. Unlike the National Commission's definition, this is a definition of a specific form of inquiry with its own questions and methods. Thus, this definition stresses the fact that Applied POR involves the controlled observation of actual patients in order to determine the optimal modality for the management of disease. Furthermore, given that the response of actual patients to interventions is more or less idiosyncratic, this definition implicitly acknowledges that the scope of the knowledge developed by Applied POR is rarely universal. Finally, this definition has the virtue of making more explicit the contextual constraints on justification implicit in Ahrens' analysis of Applied POR. Specifically, the inclusion of the phrase "a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease" invokes the three constraints on justification elucidated in Chapter Three, the third of which implicitly refers to the context of practice. This definition of Applied POR, thus, makes more explicit the tight connection between Applied POR and the context of practice.

In this chapter, Chapter Four, I argued that the National Commission's distinction between research and practice suggests a misleading picture of practice as well as research. Specifically, I argued that their definition of practice is problematic because it misleadingly presents a picture of practice as a purely pragmatic and morally unitary

endeavour. Practice is neither morally unitary nor purely pragmatic. Practice is not morally unitary because other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. Practice is not purely pragmatic because, given a commitment to a rational therapeutics, the content of the duty of care cannot be specified independently of evidence provided by good clinical research. The duty of care, thus, involves both moral and epistemic duties (i.e., it is not a purely moral duty). In an effort to forestall misinterpretation, I proposed a new, less misleading definition of practice that reflects our new understanding of the duty of care:

> 'Practice' refers to interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.

Again, by omitting the term 'solely' from the National Commission's definition, the suggestion that the duty of care is morally unitary is removed. Furthermore, by adding the phrase 'justifiably believe' to the definition, the fact that the duty of care involves both moral and epistemic duties is made explicit.

We now have revised definitions of "research" and "practice" in hand. It may be helpful to set them side by side:

> Applied POR is research involving direct contact with patients or volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.
>
> 'Practice' refers to interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.[6]

[6] Given that 'practice' is concerned with "interventions that are designed to enhance the well-being of an individual patient...," whereas 'Applied POR' is concerned with studies of "the optimal management of disease," it is particularly important to recall that studies of the management of disease are merely paradigmatic of this form of research. Applied POR is not restricted to studying the management of *disease*, but also concerns itself with managing well-being, conceived more broadly than disease, and with managing injury, disability, and the like, none of which can or should be categorized as diseases.

Notice, now, that these definitions, unlike those of the National Commission, do not raise the "specter" of the central problem, at least not directly, because Applied POR and practice are not contrasted in terms of generality and specificity. Furthermore, these definitions explicitly make room for clinical research, our best solution to the central problem to date. Gone is talk of "research" simpliciter and along with it talk of "generalizeable knowledge" simpliciter. Instead, as I have already emphasized, we have a definition of a very specific form of inquiry that implicitly acknowledges the specificity of clinically relevant knowledge. Furthermore, the inclusion of the phrase "a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease" in the definition of Applied POR makes (more) explicit the tight connection between Applied POR and the context of practice. Far from being an accidental side-effect of the conduct of research, practice is acknowledged as an essential feature of Applied POR.

Similarly, the revised definition of "practice" draws attention to the tight relationship between practice and clinical research. Given a commitment to a rational therapeutics, the content of the duty of care cannot be specified independently of the evidence provided by good clinical research; practice is partly constituted by the results of clinical research.

Clinical research is our best solution to date to the central problem. No doubt this is because both the questions and the methods of clinical research take us quite close to the realities of clinical practice. Of course, the problem still remains. Even clinical research can stray quite far from the messy complexity of practice. After all, even though clinical research and clinical practice are tightly related, they are not the same activity. Nonetheless, it is striking that when we do focus on clinical research (specifically

Applied POR) the question as to their relation simply appears wrong-headed. If we get specific, the epistemic problems posed by the metaphysical assumptions implicit in the National Commission's definitions of research and practice largely disappear.

But this result is not merely of metaphysical and epistemological significance. As I noted at the end of Chapter Three, it also of important because it paves the way for an adequate ethical analysis of Applied POR. As we will see in Chapter Five, much as the context of practice shapes the epistemological and metaphysical character of Applied POR, it also informs its moral analysis, providing a crucial constraint on the moral justification of human subjects research. Indeed, I will argue that a commitment to the contextual constraints implicit in Applied POR amounts to committing oneself to the principle of clinical equipoise, albeit for epistemological as opposed to moral reasons. Constraints on epistemic and moral justification converge.

Chapter Five: Rethinking Equipoise

Introduction

At the outset of this essay, I remarked upon a growing tendency in the research ethics literature to attribute substantive metaphysical, epistemological and, ultimately, moral significance to the National Commission's distinction between research and practice. Increasingly, I noted, the distinction is interpreted as a definitive description of the nature and goals of research and practice, rather than a conceptual tool designed to facilitate the implementation of a system of review. In Chapter Two, I worried that this picture of 'research' and 'practice' both raised the question as to their relationship – how can theoretical knowledge be applied to concrete, individual persons with therapeutic results – and effectively eliminated the conceptual space required for its solution: a bona fide clinical research.

My analysis of "practice" in the previous chapter showed that practice is partly constituted by the results of clinical research (particularly Applied POR) and that, given a commitment to a rational therapeutics, the content of the duty of care cannot be specified independently of the evidence provided by good clinical research. To this extent, the 'natures' of clinical research (particularly Applied POR) and practice are intimately intertwined, not sharply distinct. Furthermore, this analysis also showed that the goals of practice and research overlap. Contrary to the picture presented by the National Commission, wherein research and practice are contrasted in terms of the epistemic goals of the former and the pragmatic goals of the latter, practice, like research, also involves epistemic goals and obligations.

My contextualist analysis of (clinical) research led to parallel conclusions about the 'nature' and goals of Applied POR, showing that insistence upon a sharp distinction between research and practice is problematic because we cannot even make sense of Applied POR independently of the context of practice. Indeed, my analysis showed that, far from being sharply distinct, practice is an essential feature of Applied POR. More generally, my analysis showed that forms of inquiry are constituted by very specific contextual commitments that only come into view when we are attentive to the particular interests at stake in that form of inquiry, commitments that are obscured if we insist upon talking in terms of research in general. In the case of Applied POR, which is defined in terms of the improvement of the management of disease, neither its goals nor its 'nature' can be explicitly stated without reference to the context of practice. Again, far from being sharply distinct, Applied POR and practice are intimately intertwined.

In sum, then, my analysis showed that "practice" and "Applied POR" are deeply enmeshed, metaphysically, epistemologically, and, as we shall see, morally. But this analysis is apparently at odds with that of the National Commission, and certainly at odds with most contemporary interpretations of *The Belmont Report*. To some extent, however, contemporary commentators cannot be blamed for interpreting *The Belmont Report* as they do. By defining "practice" as they do, the National Commission presents a misleading picture of practice as a purely pragmatic and morally unitary endeavour. By talking in terms of "research" simpliciter defined in terms of "generalizeable knowledge" simpliciter, the National Commission presents a decontextualized picture of research that misrepresents the nature of scientific knowledge and inquiry, and obscures important differences between different forms of research. By defining "research" and "practice" as

they do, in other words, the National Commission presents a picture of 'research' and 'practice' that strongly suggests that the two activities are sharply distinct.

I believe this picture of 'research' and 'practice' has led to a host of problems in research ethics, some new, and others less so. One of the most worrisome is the dearth of serious critical work concerning the research agenda in the research ethics literature. In my view, this lack of critical attention can be traced back to conceptual mistakes implicit in this picture of 'research' and 'practice,' a picture that has encouraged an uncritical stance toward the research agenda by reinforcing problematic assumptions about the epistemology of clinical science. I will say more about this problem in Chapter Six. In this chapter I want to focus on an older problem (at least from the perspective of research ethics): the problem of the randomized controlled trial (RCT), or, the so-called RCT dilemma.

One of the central problems of research ethics has long been the so-called RCT dilemma: the supposed conflict between a physician's duty of care and her commitment to research (or, more specifically, to optimally informed action). Though there are many formulations of the dilemma, the following version is typical. Assuming (a) that the RCT is the best method for generating the reliable knowledge necessary for optimally informed clinical practice and (b) a commitment to being optimally informed (i.e., what I have referred to as a commitment to a rational therapeutics), prima facie, such a commitment entails the use of the RCT. However, the conduct of a RCT involves the randomization of subjects to one of two or more treatment arms. The treatment received by any particular participant in the trial, thus, is determined by the randomization scheme, not by the attending physician-researcher. By contrast, in the context of therapy it is the

patient's physician who recommends a treatment course according to what she believes to be in the best interests of the patient. Randomization, which is carried out for epistemic reasons, appears to violate the fundamental trust characteristic of the physician patient relationship, i.e., that a physician always acts with unqualified fidelity to each of her patient's health. The conduct of a RCT, more specifically the offer of enrollment in a RCT by a physician to her patient, appears to be inconsistent with the moral character of the physician-patient relationship.

Despite its prima facie plausibility, it is my contention that the RCT dilemma is a false dilemma. It is a false dilemma because it is generated by the same conceptual errors that inform the mistaken picture of "research" and "practice" that I have been at pains to criticize in the preceding chapters. Both that picture and the RCT dilemma are based on the assumption that the nature and goals of research and practice are fundamentally different. The RCT Dilemma emerges from the further inference that, because of these differences, there is a fundamental moral conflict between a physician's duty of care and her commitment to research (or optimally informed action). But, as I hope I have already convinced you, the root assumption is false (at least with respect to Applied POR). Precisely because Applied POR and practice are so intimately intertwined, other things being equal, there cannot be a categorical conflict between a physician's duty of care and her commitment to Applied POR, or so I will argue.

The aims of this chapter, then, are as follows. First, I will provide some background on the RCT dilemma, summarizing key versions of the dilemma articulated by Hill, Fried, Marquis, and Gifford. Second, I will review three important 'solutions' to the dilemma offered by Fried, Freedman, and Miller and Brody respectively. Third, I will

offer an extended critique of Miller and Brody's 'solution' to the dilemma. Fourth, I will offer a critique of the RCT dilemma itself, concluding that it is a false dilemma. Fifth, I will reframe the so-called historical question in epistemological terms, and situate the principle of clinical equipoise as a methodological constraint on the conduct of Applied POR.

The RCT Dilemma

As far as I know, the RCT Dilemma was first articulated, if not in name then in substance, by Bradford Hill in 1963. In his article, "Medical ethics and controlled trials," Hill noted the following problem concerning the conduct of controlled clinical trials (in this case he is considering, retrospectively, the ethical challenges posed by an RCT conducted in order to evaluate the efficacy of Streptomycin for the treatment of pulmonary tuberculosis conducted in 1948):

> ...the Tuberculosis Committee had nevertheless two ethical problems to resolve. About the first – the doctor's responsibility to the patient in his care – there was, of course, no real difficulty. In this trial, as in all controlled trials, it was implicit that the doctor must do for his patient whatever he really believes to be essential for that patient to restore him to health. If he believes that it is essential for the patient's well-being that he remove him from a comparative group on an orthodox treatment (or vice versa), then surely it is his basic duty to so remove him. While such removals may seriously weaken, or even destroy, the value of a trial... (Hill, 1963, 1043).

However, it was Charles Fried who, in his 1974 book *Medical Experimentation: personal integrity and social policy*, offered the first book length treatment of the problem. Fried articulates the dilemma as follows (part of this passage will be familiar from Chapter Four):

> The traditional concept of the physician's relation to his patient is one of unqualified fidelity to that patient's health. He may certainly not do anything that would impair the patient's health and he must do everything in his ability to further it. The conduct of a patient's doctor in an RCT appears to conflict with these traditional norms…
> In the RCT a physician (or group of physicians) determines each individual's precise therapy by considering not only that individual's needs, but also by considering the needs of the experimental design, that is the needs of the wider social group that will be benefited by a more definitive evaluation of the therapies concerned. Concretely, the actual therapy the patient receives is determined by the randomizing scheme. Does this not, then, clearly pose the dilemma of the physician's duty to the individual and his interest in serving the wider group that would be benefited by the results of the trial? (Fried, 1974, 50-1)

In the 1980s, the RCT Dilemma received further attention by philosophers like Don Marquis and Fred Gifford. In many ways, Marquis' and Gifford's articulations of the dilemma are superior to Fried's because they, unlike Fried (at least in the above passage), make the goal of research in this context explicit, i.e. the development of "scientific knowledge in medicine," or, "reliable causal knowledge necessary for optimally-informed action". Thus, Marquis frames the dilemma as follows:

> Consider this dilemma: according to an argument that is hard to refute, the procedures for conducting randomized clinical trials of anti-cancer drugs are incompatible with the ethics of the patient-physician relationship. If this problem cannot be resolved, then either a key procedure for achieving scientific knowledge in medicine must be given up or unethical behavior by physicians must be tolerated. (Marquis, 1983, 40)

Gifford's version is similar:

> The central dilemma concerning the randomized clinical trial (RCTs) arises out of simple facts about causal methodology (RCTs are the best way to generate the reliable causal knowledge necessary for optimally-informed action) and a prima facie plausible principle concerning how physicians should treat their patients (always do what is most reasonable to believe will be best for the patient). (Gifford, 1986, 347)

Their differences aside, all versions of the RCT dilemma canvassed here presuppose both that physicians must act with unqualified fidelity to their patient(s) and

that this obligation is inconsistent with the conduct of RCTs. Historically, then, the central moral question of the RCT has been "When [if ever] may a physician legitimately offer enrollment in a RCT to her patient" (Weijer, Glass, and Shapiro, 2000)? In the following section, I will examine three of the most prominent solutions to the RCT dilemma offered to date.

Solutions

Fried

The first important solution to the RCT Dilemma was proposed by Charles Fried in the same book quoted from above (*Medical Experimentation: Personal Integrity and Social Policy* (1974)). According to Fried, a physician may legitimately offer enrollment in a RCT to her patient if and only if *she* is genuinely uncertain as to the relative merits of the treatment alternatives under study in a proposed clinical trial (Fried, 1974, 153). Fried termed this state of uncertainty 'equipoise'.

There is significant controversy over how to interpret Fried (see for example, Miller and Brody, 2003; Miller and Weijer, 2003). One locus of interpretive dispute concerns whether or not Fried endorses an 'absolute evidentiary standard' (AES). Given the AES interpretation, equipoise is disturbed when the odds that treatment A will be more successful than treatment B are anything other than 50%, making equipoise a demanding standard indeed. Another interpretive controversy focuses on whether or not Fried intended equipoise to be a subjective principle. May equipoise be achieved and/or disturbed by an investigator's idiosyncratic hunches or perceptions?

Typically Fried has been interpreted as endorsing both a subjective version of equipoise, and an absolute evidentiary standard.[1] On this interpretation of Fried, however, equipoise is obviously fatally fragile. Indeed, if we take the absolute evidentiary standard seriously and combine it with the subjective interpretation of Fried's principle, it is unlikely that equipoise would survive even the earliest phases of research, e.g., hypothesis formation, let alone remain undisturbed long enough for the study to be completed. It is unclear, in other words, whether clinical research could proceed at all; so interpreted, Fried's principle looks impossibly demanding.

Freedman

These are points emphasized by Benjamin Freedman in his landmark paper "Equipoise and the Ethics of Clinical Research" (1987). In this paper, Freedman attempts to redress these problems, and others, by offering a novel concept of equipoise called 'clinical equipoise'. The principle of clinical equipoise requires that at the start of a trial "there must be honest, professional disagreement in the community of expert practitioners as to the preferred treatment," and that "the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed" (Freedman, 1987, 144). This alternative, argues Freedman, is suggested by recalling the basic reason for conducting clinical trials: "there is current or imminent conflict in the clinical community over what treatment is preferred for patients

[1] See, for example, Chalmers, 1978; Schafer, 1982; Marquis, 1983; and Freedman, 1987. I should add that I find this interpretation of Fried uncharitable. As Miller and Weijer (2003) have emphasized, Fried acknowledges the impracticality of the principle of equipoise so interpreted. Furthermore, he explicitly discusses the difference between individual and professional knowledge, and points out that, viewed in light of the latter, equipoise becomes significantly more plausible (Fried 1974, 153).

in a defined population P" (Freedman, 1987, 143). There is, in other words, no consensus within the expert community as to the comparative merits for population P of the alternative treatments in question, and a clinical trial is instituted in order to resolve this dispute.

Notice that Freedman's principle of clinical equipoise places the relevant moral and epistemic locus at the level of the community of expert practitioners not the individual physician. This is appropriate, argues Freedman, because "...competent (hence, ethical) medicine is social rather than individual in nature" (Freedman, 1987, 144). By shifting the moral locus in this way Freedman is able to satisfy the basic intuitions behind Fried's principle of equipoise (Freedman dubs Fried's principle 'theoretical equipoise'), i.e., the ethics of controlled clinical trials has *something* to do with what is known about the treatments in question, and also avoid many of its problems.

First, from the perspective of the principle of clinical equipoise it is neither necessary nor sufficient for the investigator to be genuinely uncertain as to the preferred treatment alternatives. A decided treatment preference on the part of the investigators, argues Freedman, is consistent with a state of clinical equipoise. The investigators need simply show that their less favoured treatment is preferred by colleagues whom they judge to be responsible and competent (Freedman, 1987, 144). Furthermore, since it is likely a matter of chance that a patient is being seen by a clinician with a treatment preference for B rather than A, randomization is also appropriate (Freedman, 1987, 144).

Second, there need not be a perfect 50/50 split of evidence favouring the two treatments in question. Rather, most interpreters of Freedman agree that it is sufficient for

a state of clinical equipoise if a 'significant minority' of expert practitioners disagree with the majority as to which of the treatment alternatives is preferable (See, for example, Miller and Weijer, 2003, 105). Freedman, in other words, rejects the absolute evidentiary standard often attributed to Fried. Furthermore, since the reason for initiating a clinical trial is the resolution of the dispute in question, even if interim results favour one treatment over the other, clinical equipoise persists until such a time when the evidence is judged sufficient to convince the relevant community of experts.

All of these features of Freedman's principle mean that the principle of clinical equipoise, unlike theoretical equipoise, is relatively robust; clinical equipoise is not necessarily an unreasonable obstacle to the conduct of clinical research. Finally, by emphasizing the social character of medical knowledge, Freedman rules out subjective treatment preferences and hunches. Precisely because a clinical trial is initiated in order to resolve a conflict in the community of expert practitioners, objective (at least inter-subjectively available) evidence is demanded:

> Progress in medicine relies on progressive consensus within the medical and research communities. The ethics of medical practice grants no ethical or normative meaning to a treatment preference, however powerful, that is based on a hunch or on anything less than evidence publicly presented and publicly convincing to the clinical community... (Freedman 1987, 144)

In this way, Freedman redresses the fragility of Fried's concept of equipoise. The principle of equipoise provides what looks like a satisfying solution to the RCT dilemma and an answer to the historical question, while avoiding the unreasonable proscription of clinical research resultant from the application of Fried's principle of theoretical equipoise.

Miller and Brody

Since its introduction, Freedman's principle of clinical equipoise has enjoyed widespread uptake in bioethics discourse. That being said, there have always been critics of the principle, particularly with respect to its implications regarding the use of placebo controls (e.g. Temple and Ellenberg, 2000). In a 2003 article, however, Franklin Miller and Howard Brody offer a critique of clinical equipoise that attacks the principle at its foundations, arguing that both the problem the principle is supposed to solve (i.e., the RCT dilemma), and the answer itself, are profoundly confused (Miller and Brody, 2003).

Miller and Brody challenge what they rightly identify as a key assumption underlying the RCT dilemma and both Fried's and Freedman's responses (2003). The assumption in question is that investigators have therapeutic obligations in the context of research. Clearly, the RCT dilemma assumes that investigators do indeed have therapeutic obligations. The RCT dilemma arises out of the apparent conflict between a physician's commitment to providing personal care on the one hand – her duty of care – and her commitment to a program of research on the other. Without the former commitment, the RCT dilemma would not arise. Furthermore, insofar as both Fried's principle of (theoretical) equipoise and Freedman's principle of clinical equipoise respond to the problem posed by the RCT dilemma, their responses also assume that investigators have therapeutic obligations in the context of research. Miller and Brody argue that this assumption is false.

Miller and Brody argue that "the basic goal and nature of an activity determines the ethical standards that ought to apply [to that activity]" (Miller and Brody, 2003, 22). Since research and practice differ both in terms of their nature and goals, or so they

contend, different ethical standards ought to apply in the two contexts. Specifically, they deny that what they call "the norms of therapeutic beneficence and non-maleficence" apply in the context of research.[2] Since the principles of theoretical and clinical equipoise presuppose that these norms do apply in the context of research, Miller and Brody conclude that both principles must be rejected as the appropriate moral standard for clinical research (indeed, their argument cuts against any solution that presupposes the assumption in question, though their immediate target is the principle of clinical equipoise).

Thus, Miller and Brody's solution to the RCT dilemma is really no solution at all; rather, they dissolve the dilemma itself, arguing that it arises from the faulty assumption that researchers have therapeutic obligations in the context of research, an assumption forming one horn of the dilemma. They do not provide an answer to the historical question for the same reason. The historical question emerges from the RCT dilemma and, like the latter, presupposes that physicians have therapeutic obligations to their patients in the context of research. Having rejected the latter assumption, Miller and Brody feel no need to answer the historical question. For Miller and Brody, enrolment is a decision made by a potential participant in discussion with a researcher, a researcher who does not have therapeutic obligations to that participant. Furthermore, for Miller and Brody, equipoise plays no part in the moral assessment of research, because equipoise (theoretical or clinical) presupposes the very assumption that they reject, i.e., that researchers have therapeutic obligations in the context of research. Instead, Miller and Brody argue, following Emanuel et al, that research involving human subjects is ethical if it satisfies the following requirements (which, for them, do not imply the principle of

[2] Miller and Brody draw a distinction between 'therapeutic beneficence' and beneficence *per se*.

clinical equipoise): (1) scientific or social value; (2) scientific validity; (3) fair subject selection; (4) favourable risk-benefit ratio; (5) independent review; (6) informed consent; and (7) respect for enrolled participants.[3]

A Critique of Miller and Brody

Schematized, Miller and Brody's argument looks something like this:

1. If the basic goals and natures of two activities differ, the ethical standards that apply to those activities ought to differ;
2. In terms of their goals and natures, clinical research and clinical practice differ.
3. Therefore,

   (C1) the norms of therapeutic beneficence and non-maleficence do not apply in the context of research (Miller and Brody, 2003, 25).

Prima facie, Miller and Brody's argument looks straightforward. Premise one is uncontroversial. Furthermore, premise two is generally supposed to be true. Most commentators agree that clinical research and clinical practice differ with respect to their goals and natures. Notice, however, that C1 does not follow from premises 1 and 2. Strictly speaking, modus ponens only gives us C2:

(C2): The ethical standards that ought to apply to clinical research and clinical practice ought to differ (MP from 1 and 2).

But the conclusion Miller and Brody need is C1.

Miller and Brody are not merely concerned with showing that different ethical standards ought to apply in the contexts of research and practice in some general sense;

[3] For a detailed discussion of these requirements, see Emanuel, E., D. Wendler, C. Grady, "What Makes Clinical Research Ethical?" *JAMA* 283 (2000): 2701-2711.

rather, they are concerned specifically with demonstrating that the norms of therapeutic beneficence and nonmaleficence do not apply in the context of research:

> The presumption that RCTs must be compatible with the ethics of the physician-patient relationship assumes erroneously that the RCT is a form of therapy, thus *inappropriately applying the principles of therapeutic beneficence and nonmaleficence that govern clinical medicine to the fundamentally different practice of clinical research.* (Miller and Brody, 2003, 25 – emphasis mine)

Precisely because clinical research and clinical practice are "fundamentally different" in terms of their goals and natures, Miller and Brody aver that there is what we might call a normative gap between the two activities. For Miller and Brody, the norms of therapeutic beneficence and nonmaleficence apply on one side of this gap (i.e., in the context of practice), but not on the other (i.e., in the context of research). In order to show that this is the case, however, it is not sufficient to show that the goals and natures of clinical research and clinical practice are different (though this may be sufficient for C2); rather, Miller and Brody must demonstrate that the goals and natures of clinical research and clinical practice are independent. But this they have not and cannot do because, in order to do so, it would have to be possible to specify the non-normative facts about clinical research and clinical practice (i.e., the facts about their respective natures and goals) independently. But, as I have shown in Chapters Three and Four, at least with respect to Applied POR, this is impossible.

The sorts of differences Miller and Brody point to in order to establish the normative independence of clinical research and practice are, by now, very familiar. They are the same differences, or contrasts, noted by the National Commission in *The Belmont Report*. Indeed, Miller and Brody cite *The Belmont Report* just prior to offering their own discussion of the differences between clinical research and clinical practice. Following, in

large part, the National Commission, Miller and Brody describe clinical research and practice as follows:

> Clinical research is … not a therapeutic activity devoted to the personal care of patients. It is designed for answering a scientific question, with the aim of producing "generalizeable knowledge." The investigator seeks to learn about disease and its treatment in groups of patients, with the ultimate aim of improving medical care. Scientific interest in any particular patient concerns what can be learned that is applicable to other patients. In view of the nature and purpose of clinical research, the principles of beneficence and nonmaleficence applicable to clinical research lack the therapeutic meaning that guides their application to medical care. Clinical research is dedicated primarily to promoting the medical good of future patients by means of scientific knowledge derived from experimentation with current research participants… (Miller and Brody, 2003, 21)

> Clinical medicine [i.e., clinical practice] aims at providing optimal medical care for individual patients. Ethically, it is governed by the principles of therapeutic beneficence and therapeutic nonmaleficence. Therapeutic beneficence directs physicians to practice medicine with primary fidelity to promoting the health of particular patients. According to therapeutic nonmaleficence, the risks of medical care to which a patient is exposed are to be justified by the prospect of compensating medical benefits for that patient. The physician uses scientific knowledge to care for the patient and engages in therapeutic experimentation with the aim only of finding optimal treatment. It is not part of the role of the physician to develop scientific knowledge that can help future patients. (Miller and Brody, 2003, 21)

The similarity between Miller and Brody's description of "clinical research" and "clinical practice" with the National Commission's definitions of "research" and "practice" should be obvious (despite the fact that Miller and Brody talk explicitly in terms of *clinical* research and practice while the National Commission does not). Thus, like the National Commission, Miller and Brody contrast the two activities as follows:

- whereas research is designed to produce generalizeable knowledge (an epistemic goal achieved using research methods), practice aims to provide optimal care to patients (a pragmatic goal achieved using clinical methods);
- whereas research is an activity concerned with groups of patients, practice is concerned with individuals; and
- whereas research aims to benefit future patients, practice aims to benefit individual patients in the here and now.

Miller and Brody, however, add another contrast that is not explicit in *The Belmont Report*, which they clearly believe to follow from the above:

- Ethically, [clinical practice] is governed by the principles of therapeutic beneficence and therapeutic nonmaleficence…In view of the nature and purpose of clinical research, the principles of beneficence and nonmaleficence applicable to clinical research lack the therapeutic meaning that guides their application to medical care. (Miller and Brody, 2001, 21)

Insofar as the first three contrasts are mistaken, however, Miller and Brody are mistaken when they infer from these alleged differences between clinical research and practice that the norms of therapeutic beneficence and nonmaleficence should not apply in the context of research. And in Chapters Three and Four I have taken issue with each of the first three contrasts.

Thus, in Chapter Three, I argued that defining "research" in terms of generalizeable knowledge is problematic because it is suggestive of a decontextualized picture of knowledge and knowledge seeking that gravely misrepresents scientific inquiry. Inquiry is inherently context-bound because justification is inherently context bound. Furthermore, I argued that we cannot even make sense of Applied POR independently of the context of practice. Indeed, far from being sharply distinct activities, as both the National Commission and Miller and Brody suppose, I showed that practice (properly understood) is an essential feature of Applied POR because questions proper to Applied POR are questions about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic *interventions*, and these questions can be answered only via the application of interventions designed to enhance the well-being of an individual patient (i.e., practice).

Finally, precisely because Applied POR necessarily involves practice, I noted that the knowledge developed by Applied POR is not only of a very particular sort, but of a very particular scope. Precisely because that knowledge is obtained via the controlled observation of the effects of an experimental intervention on individuals, that knowledge will only be as generalizeable as individuals are similar. Because individuals are idiosyncratic, the scope of the knowledge developed by Applied POR is rarely universal; rather, the scope of this knowledge is typically restricted to clinical subgroups of the population within which response to intervention is more or less homogeneous.

It is, thus, misleading to contrast research and practice, as both the National Commission and Miller and Brody do, in terms of generality and specificity (or individuality). Similarly, it is misleading to contrast research and practice in terms of the former's concern with the future benefit of groups of patients, and the latter's aim to benefit individual patients in the here and now. Precisely because Applied POR necessarily involves practice, it is necessarily concerned with benefiting individual patients in the here and now (as well as groups made up of similar patients in the future).

Turning to practice, in Chapter Four I argued that it is misleading to characterize practice, as both the National Commission and Miller and Brody do, in terms of unqualified fidelity to the patient. Practice, as I put it, is not morally unitary because other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. Indeed, the very knowledge to which physicians must appeal when determining how best to act with unqualified fidelity to their patient's health, i.e., clinically relevant knowledge, is itself qualified in the relevant sense. Due to the logic of clinical research (specifically Applied POR), clinically relevant knowledge is (and ought

to be) attuned to the social environment from the outset. It makes little sense, therefore, to characterize the doctor-patient relationship in terms of unqualified fidelity to the patient because determinations of what counts as unqualified fidelity – the content of the duty of care – are qualified (i.e., social) from the outset (or should be).

Furthermore, I argued that it is misleading to contrast practice and research (at least Applied POR) in terms of the pragmatic goals of the former and the epistemic goals of the latter. Practice, as I put it, is not purely pragmatic because, given a commitment to a rational therapeutics the content of the duty of care cannot be specified independently of evidence provided by good clinical research. Practice, in other words, is partly constituted by the results of clinical research (particularly Applied POR). The duty of care, thus, involves both moral and epistemic duties (i.e., it is not a purely moral duty). Thus, it is misleading to contrast research (at least Applied POR) and practice in terms of the epistemic character of the former and the pragmatic character of the latter. Practice is not a purely pragmatic activity; again, it is as much about knowing as it is about doing.

To this extent, our analyses in Chapters Three and Four show that, contrary to the picture presented by the National Commission and taken up by Miller and Brody, the natures and goals of clinical research (particularly Applied POR) and practice are intimately intertwined, not sharply distinct. The goals of practice and research (at least Applied POR) overlap. Both metaphysically and epistemologically, 'practice' and 'Applied POR,' are deeply enmeshed. Importantly, given our present subject, we cannot specify the relevant non-normative facts about clinical research and clinical practice (i.e., the facts about the respective natures and goals) independently. As our analyses have shown, Applied POR and practice are reciprocally constituted. You cannot define one

without appealing to the other. But, as we saw above, this is precisely what Miller and Brody needed to show: that you can specify the relevant empirical facts about clinical research and clinical practice independently. Only given the possibility of such an independent specification of these facts does it make sense to suppose that the norms supervenient upon these facts should be independent, or, more specifically, that the norms of therapeutic beneficence and nonmaleficence do not apply to the context of research. But we have shown that such a specification is impossible. Thus, Miller and Brody's argument fails. Though clinical research and practice may be different, and though the ethical standards applicable to these activities may differ accordingly, given the fact that Applied POR and practice are deeply enmeshed, there is little reason to suppose that the norms of therapeutic beneficence and nonmaleficence do not apply to the conduct of Applied POR. Furthermore, given that Applied POR is defined in terms of the improvement of clinical practice and, thus, necessarily involves the application of interventions designed to enhance the well-being of an individual patient (i.e., practice), there is every reason to suppose that the norms of practice (i.e., therapeutic beneficence and non-maleficence) do apply in the context of research.

The RCT Dilemma is False

While Miller and Brody are wrong to suppose that the norms of clinical practice and clinical research are independent, or that the norms of therapeutic beneficence and nonmaleficence do not apply in the context of research, they are right to point out that the goals and nature of research and practice differ in a weaker sense. Clinical research and clinical practice may be interdependent, but this does not entail that they are the same.

The two activities are interdependent, but they are nonetheless distinct. For example, participants in a research trial do not receive treatment that is exactly the *same* as they would receive outside of a trial. After all, at least some of them receive an *experimental* treatment. Furthermore, given the methodological requirements of research, treatment is not administered in exactly the same way as it would be outside of the trial, and is typically accompanied by nontherapeutic procedures administered solely in order to answer the study question. Finally, there is arguably potential for exploitation in the context of research that is not present, at least to the same extent, in the context of practice. Indeed, it is because of this risk that we insist upon external review of research involving human subjects.

Miller and Brody, I think, are also on the right track when they argue that the so-called RCT dilemma, for which both Fried's (theoretical) equipoise and Freedman's clinical equipoise are supposed to be a solution, is a false dilemma. Of course, they maintain the falsity of this dilemma because they believe that it is a mistake to suppose that researchers have any therapeutic obligations to their research participants, an assumption forming one horn of the dilemma. I believe Miller and Brody are wrong to reject this assumption. As the above argument suggests, I believe that researchers do have therapeutic obligations to their research participants. Nonetheless, I agree that the RCT dilemma is false, but for different reasons. The RCT dilemma is false, not because researchers do not have therapeutic obligations to their research participants, but because, contrary to common wisdom, the (proper) conduct of RCTs is not incompatible with the fulfillment of this obligation.

It is, of course, a fundamental presupposition of the RCT dilemma that the conduct of RCTs is incompatible with the ethics of the physician patient relationship. All of the authors canvassed above agree on this fundamental point. As Marquis puts it: "according to an argument that is hard to refute, the procedures for conducting randomized clinical trials of anti-cancer drugs are incompatible with the ethics of the patient-physician relationship" (Marquis, 1983, 40).

This argument may be hard to refute, but it is refutable nonetheless. The argument in question is essentially a special case of the argument I have been criticizing throughout this essay: that research and practice are so different in terms of their natures and goals that they are also ethically incompatible. Hill, Shaw et al, Fried, Marquis, and Gifford all apply this same basic argument to the RCT, appealing to the same familiar contrasts in order to make their point. Fried, for example, argues as follows:

> In the RCT a physician (or group of physicians) determines each individual's precise therapy by considering not only that individual's needs, but also by considering the needs of the experimental design, that is the needs of the wider social group that will be benefited by a more definitive evaluation of the therapies concerned. Concretely, the actual therapy the patient receives is determined by the randomizing scheme. (Fried, 1974, 50-1)

For Fried, then, the RCT dilemma emerges from the same contrasts between research and practice, now applied to the conduct of RCTs: whereas the aim of the RCT is a "more definitive evaluation of the therapies concerned," practice is concerned only with the "individual's needs"; whereas the conduct of an RCT is dictated by "the experimental design" and treatment in an RCT is "determined by the randomizing scheme," in practice "a physician determines each individual's precise therapy [only] by considering...that individual's needs"; and whereas practice is concerned with the present needs of particular patients, the RCT is concerned with the future needs "of the wider social

group." For Fried, it is because the conduct of RCTs and the conduct of practice differ in these ways that the conduct of RCTs is incompatible with the ethics of the physician-patient relationship.

But this argument fails for the same reasons that the more general argument concerning 'research' simpliciter fails. The conduct of RCTs (qua method of Applied POR) and clinical practice cannot be accurately contrasted in these terms. Indeed, once the contextual constraints constitutive of Applied POR are made explicit, it becomes clear that, far from being at odds with one another, the RCT (qua method of Applied POR) and clinical practice are deeply interconnected along these very axes. Thus (to repeat the same arguments in terms of the RCT), practice (properly understood) is an essential feature of the RCT (qua method of Applied POR); like practice, the RCT involves the application of interventions designed to enhance the well-being of an individual patient. Furthermore, the physician's relationship to the patient in the context of practice is qualified much as it is in the context of an RCT (qua method of Applied POR) because the very knowledge to which physicians must appeal when determining how best to act with unqualified fidelity to their patient's health, i.e., clinically relevant knowledge, is itself qualified in the relevant sense. Finally, and perhaps most pertinently, it is misleading to contrast practice and the conduct of RCTs (qua method of Applied POR) in terms of the pragmatic goals of the former and the epistemic goals of the latter. Practice is not purely pragmatic because, given a commitment to a rational therapeutics the content of the duty of care cannot be specified independently of evidence provided by good clinical research. Practice is partly constituted by the results of RCTs. Put another

way, the two activities (i.e., the conduct of RCTs and clinical practice) are internally related and, thus, cannot be in conflict with one another.

Of course, at this point the following objection might be raised. Even if we grant that the RCT (and/or Applied POR more generally) and practice are internally related in terms of content, the two activities may still come into conflict in terms of process; that is, the procedures required for the conduct of an RCT may conflict with the procedures required for the provision of good personal care. This objection is a good one and quite probably a charitable interpretation of the conflict presupposed by the RCT dilemma. Nonetheless, I believe this objection fails. It fails because it too is based on a faulty understanding of both the RCT (qua method of Applied POR) and clinical practice. In particular, this objection reveals both a failure to recognize the importance of context in the conduct of scientific inquiry and, ultimately, a failure to take seriously our commitment to a rational therapeutics. If we are attentive to the interests at stake in the conduct of RCTs (again, qua method of Applied POR) and, thus, to the contextual constraints constitutive of Applied POR more generally, it becomes clear that the proper conduct of RCTs is, and ought to be, compatible with the ethics of the physician patient relationship.

The RCT in Context

The mistake most commentators have made is to fail to take adequately seriously the tight connection between the epistemological and ethical constraints on the conduct of RCTs (qua method of Applied POR). Most commentators have focused their attention on questions of ethical justification, ignoring, for the most part, the epistemic aspect of the

problem.[4] A central reason for this narrow focus, I believe, is a tendency to view 'research' in decontextualized terms, a tendency fostered by the National Commission (or, at the very least, by contemporary interpretations of the National Commission's work). This tendency has obscured both the important connections between the ethics and epistemology of RCTs (and clinical science more generally), and forestalled the development of a contextualized approach to the epistemology of the RCT (and clinical science more generally). However, as our analysis in Chapter Three showed, attention to context is absolutely essential if we hope to understand both the ethics and epistemology of Applied POR (of which the RCT is the principal method). Forms of inquiry are constituted by very specific commitments that only come into view when we are attentive to the particular context of that form of inquiry. These commitments, or constraints, are obscured if we insist on talking in terms of research in general. A decontextualized view of "research," thus, is deeply problematic because, insofar as "an ethical framework that provides normative guidance about a practice should accurately characterize the practice" (Miller & Brody, 2003, 20), talk of research simpliciter obstructs rather than facilitates the development of an adequate ethics for human subjects research.

Consider the process version of the RCT dilemma canvassed above. Commentators have long supposed that enrolment in an RCT poses an ethical problem because the RCT involves procedures that are incompatible with the ethics of the physician patient relationship, notably randomization. Thus, enrolment is seen to be

[4] Debate concerning the validity of active controlled trials in the context of the larger debate concerning the use of placebo controls in human subjects research stands as a significant exception to this tendency. See, for example, Freedman, B., C. Weijer, K.C. Glass, "Placebo orthodoxy in clinical research I: Empirical and methodological myths," *Journal of Law, Medicine, and Ethics* 24 (1996): 243-51; Temple, R., S.E. Ellenberg, "Placebo-controlled trials in the evaluation of new treatments. Part 1: Ethical and Scientific Issues," *Annals of Internal Medicine* 133 (2000): 455-63; Anderson, J. "The Ethics and Science of Placebo-Controlled Trials: Assay Sensitivity and the Duhem-Quine Thesis," *The Journal of Medicine and Philosophy* 31 (2006): 65-81.

unethical because enrolment in a RCT involves the possibility that patients will be randomly assigned a treatment that is unproven and, thus, inconsistent with the prevailing standard of care. But this is muddled. It is muddled because it fails to attend to the specific interests at stake in Applied POR and, thus, fails to recognize the contextual constraints on justification implicit in Applied POR.

Applied POR, recall, is defined in terms of the optimal management of disease:

> Applied POR is research involving direct contact with patients or volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.

This definition speaks to the general point that forms of inquiry are constituted by the particular angle of that inquiry, not the level. It is the interests (i.e., the angle) that drive a particular form of inquiry that allow us to (1) distinguish that form of inquiry from others, (2) to identify methods (norms of justification) appropriate to that form of inquiry and, ultimately, (3) to identify ethical norms appropriate to that form of inquiry. Of course, this definition also speaks to the specific point that Applied POR is driven by an interest in improving the management of disease, and this point is crucial in the present context because it allows us to identify the relevant question in this context.

Suppose that, given the available evidence (which, let us assume is credible), it is widely accepted in the relevant expert community that the preferred treatment for Y is Z. Now suppose that evidence emerges from pre-clinical research, animal modeling, and/or basic POR, that a novel treatment, X, is a legitimate rival candidate for the optimal treatment of Y (i.e., a significant minority of the community of expert practitioners justifiably believes X to be a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y). In this scenario, given the interests at stake in Applied POR,

the relevant question is not merely whether or not X is an effective treatment; rather, the relevant question is whether or not X is the preferred treatment for Y. Because Applied POR is concerned with the optimal management of disease, questions proper to Applied POR are questions about the *comparative* safety and efficacy of interventions, including (experimental) interventions. We are interested in whether or not X is preferable to Z, not merely whether X is effective.

Highlighting the comparative nature of questions proper to Applied POR also highlights the importance of the dialectical context with respect to the justificational status of its claims. Before X emerges as a legitimate rival, the proposition (P) 'that Z is the preferred treatment for Y' enjoys default status: until challenged by some plausible evidence to the contrary, the epistemic status of P is stable. However, as soon as new evidence emerges that Z may not be the preferred treatment for Y (i.e., evidence that treatment X is a legitimate rival candidate for the optimal treatment of Y), evidence that is convincing to at least a significant minority of the relevant expert community, P no longer enjoys default status. Given such a legitimate challenge, in other words, P is no longer justified unless the challenge can be met by, for example, demonstrating that, ceteris paribus, treatment Z differs from (i.e., is superior to) treatment X by more than D in a controlled trial comparing the two treatments. The crucial point is that the epistemic status of P changes as the dialectical environment changes.

The latter point, it seems to me, has been overlooked by most commentators, again, because they have tended to view "research" in decontextualized terms. But this point is absolutely crucial. The RCT dilemma, at least in its procedural form, turns on the supposition that enrolment is ethically problematic because it involves the possibility that

patients will be randomly assigned a treatment that is unproven and, thus, inconsistent with the prevailing standard of care. But this supposition ignores the role of the dialectical context in justification. Assuming that X is a legitimate rival, citing the relevant evidence concerning X acts as an epistemic defeater, undermining the justificatory status of P in this context. Once evidence (from pre-clinical research, animal modeling, and/or basic POR) for the efficacy of X emerges, evidence that is convincing to at least a significant minority of the relevant expert community, P is no longer 'proven'. Furthermore, until this question is resolved (i.e., whether X or Z is the preferred treatment for Y), belief in P remains unjustified. So, given a commitment to a rational therapeutics, it is a mistake to suppose that randomization to X is unethical because our epistemic situations with respect to X and Z are, at least in the relevant respect, identical. Both X and Z are 'unproven' in the relevant sense. What counts as the 'prevailing standard of care' is, at present, unclear.[5]

The RCT dilemma in its procedural form collapses into the substantive version. Randomization is only problematic given the alleged substantive contrast between the content of the care administered on the two arms of the study. However, if we are attentive to the role of the dialectical environment in this context, it becomes clear that the alleged contrast does not hold. In our example, patients would not be randomly assigned to one of two treatments, one of which was unproven. Rather, assuming that X

[5] Note: I am not denying that we have more evidence for the efficacy of Z than we do for the efficacy of X. If not for this asymmetry, there would be no point in initiating a trial. But, again, evidence for success is not sufficient here. We are concerned with identifying the preferred treatment, not simply a successful treatment. Note, furthermore, that this argument entails an account of 'preference' in this context that involves more than comparative judgments about efficacy based on the results of APOR. This is obvious enough. Legitimate disagreement about the preferred treatment for Y, when X is a novel treatment, must be based on credible evidence from pre-clinical research, animal modeling, basic POR, that suggests that X will prove to be more effective in general, that X will be more effective for some sub group or sub groups, that X will have fewer/less severe side effects, that X will be less expensive or easier to administer, etc.

is in fact a legitimate rival candidate for the optimal treatment of Y, citing the relevant evidence to that effect defeats the epistemic justification for believing P such that belief in P is no longer justified. In effect, both X and Y are unproven (as the preferred treatment) until such time that one or the other is shown to be preferable. Thus, the RCT dilemma in both its substantive and procedural forms emerges from a failure to recognize the importance of context in the conduct of scientific inquiry and, ultimately, a failure to take seriously our commitment to a rational therapeutics. If we are attentive to the interests at stake in the conduct of RCTs (again, qua method of Applied POR) and, thus, to the contextual constraints constitutive of Applied POR more generally, it becomes clear that the proper conduct of RCTs is, and ought to be, compatible with the ethics of the physician patient relationship. The RCT dilemma, therefore, is a false dilemma.

The Historical Question

The historical question, recall, is: "[w]hen [if ever] may a physician legitimately offer enrollment in a RCT to her patient" (Weijer, Glass, and Shapiro, 2000)? Given the falsity of the RCT dilemma, insofar as the historical question emerges from the dilemma, the question is misplaced. Historically, of course, the historical question was in fact raised in response to the RCT dilemma. If the above is correct and the proper conduct of RCTs is compatible with the ethics of the physician patient relationship, RCT enrolment does not pose an ethical problem and the historical question is misplaced. Furthermore, insofar as Fried's principle of (theoretical) equipoise and Freedman's principle of clinical equipoise are designed to respond to the historical question, they too are flawed because

both principles mistakenly presuppose that RCT enrolment poses an ethical problem that must be solved.

That being said, we need not read the historical question as it has normally been read; that is, we need not interpret 'legitimately' as meaning, at least first and foremost, 'ethically.' Instead, we could read the historical question in epistemological terms. So read, the historical question becomes, first, a question about the proper epistemic conduct of RCTs. The question as to whether or not it is ethically legitimate for a physician to offer enrolment to a patient arises later and turns, at least in part, on whether or not the RCT (qua method of Applied POR) in question has been properly designed. The historical question, in other words, becomes a question concerning method or design.

Determining what counts as the proper epistemic conduct (i.e., the proper design) of an RCT (qua method of Applied POR) turns, in large part, on identifying the interests that the RCT is supposed to serve. In the conduct of Applied POR, as we saw in Chapter Three, the central interest in question is an interest in improving the management of disease. In order for a researcher working in Applied POR to pursue this interest – in order for Applied POR to take the particular direction it does (and should) – various default entitlements must be conceded. First of all, given this interest, it must be conceded that there is such a thing as an experimental treatment; otherwise, questions concerning the preferred modality of disease management could not be posed. This is our first methodological constraint:

1) There is such a thing as a legitimate, yet incompletely tested, (rival) candidate for the optimal management of a disease (i.e., an experimental intervention).

Again this concession may seem trivial, but it is not. Since Applied POR is defined in terms of the improvement of the management of disease, a bona fide hypothesis in

Applied POR is necessarily a hypothesis concerning a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease.

In a particular study, furthermore, it must be the case that the intervention under study is in fact a legitimate, albeit incompletely tested, rival. Otherwise, the hypothesis in question would not be a question concerning the preferred modality of disease management and, thus, would not be a bona fide hypothesis in Applied POR. This gives us our second methodological constraint:

2) Intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease Y.

Finally, and most importantly, we must be able to identify a legitimate rival in order to ensure that, in this particular study, the intervention under study is in fact a legitimate, albeit incompletely tested, rival. Thus, the conduct of a particular study presupposes a standard or norm, the application of which allows for the identification of a treatment that is a legitimate rival candidate for the optimal treatment of a disease. Again, we could argue over the precise form of this norm, but, given an interest in the optimal management of disease, the following is a plausible candidate:

3) An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be.

The answer to the historical question in its epistemological form, then, turns on whether or not the RCT in which enrolment is being offered is designed in such a way that it satisfies these constraints. Commitment to the third constraint, once the variable is bound, implies commitment to the first two. Thus, enrolment in an RCT (qua method of Applied POR) is legitimate if and only if the study in which enrolment is being offered is

designed to determine whether or not a legitimate, yet incompletely tested rival candidate for the optimal management of disease Y, X, is in fact the preferred modality for the management of disease Y (where X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if a substantial minority of the community of expert practitioners justifiably believes it to be).

Again, this follows from the 'nature' of Applied POR. Since Applied POR is defined in terms of the *improvement* of the management of disease, questions proper to Applied POR are questions about the *comparative* safety and efficacy of (experimental) interventions. Bona fide hypotheses in Applied POR, thus, are always posed in relation to current practice; that is, hypotheses proper to Applied POR are hypotheses about whether or not an experimental intervention is preferable to an accepted intervention, or if there is not an accepted intervention for the disease or disorder in question, hypotheses about whether or not an experimental intervention is preferable to nothing. Given the 'logic of Applied POR,' therefore, a physician may legitimately offer enrolment in an RCT (qua method of Applied POR) to her patient if and only if the RCT in question is designed to test a hypothesis concerning the comparative safety or efficacy of a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease, where a rival is legitimate if and only if a substantial minority of the community of expert practitioners justifiably believes it to be.

Conversely, enrolment in an RCT (qua method of Applied POR) is illegitimate when the study in question fails to satisfy this constraint. But failure to satisfy this constraint does not merely mean that enrolment in this RCT (qua method of Applied POR) is unethical, though it means that too; first and foremost it means that the study

fails to count as a study in Applied POR. Such a failure is deeply problematic if the RCT in question is purportedly motivated by a desire to improve the management of disease and has been advertised as such to funders, physicians, and/or potential participants (I will say more about this in Chapter Six). Given that this constraint (and the first two constraints that the third implies) is constitutive of Applied POR, a study that fails to satisfy it is either a study in some other category of clinical research masquerading as Applied POR, or simply a poorly designed mess. In either case, given its ostensible aims, such a study is epistemologically problematic. Other things being equal, the study's ethical shortcomings follow from its epistemological shortcomings.

The Principle of Clinical Equipoise and the Identification of Legitimate Rivals

Significantly, though both Fried and Freedman conceive of their respective principles as ethical principles, both principles turn on epistemic considerations: principally, what is known by the relevant agent. Fried's principle of (theoretical) equipoise, recall, states that a physician may legitimately offer enrollment in a RCT to her patient if and only if *she* is genuinely uncertain as to the relative merits of the treatment alternatives under study in a proposed clinical trial (Fried 1974, 153). Thus, for Fried, the relevant agent is the physician herself. Freedman's principle of clinical equipoise, on the other hand, requires that "there must be honest, professional disagreement in the community of expert practitioners as to the preferred treatment" (Freedman, 1987, 144). In Freedman's case, the relevant 'agent' is the community of expert practitioners. Oddly, despite this clear emphasis on the epistemological in both

Fried and Freedman, the principles of (theoretical) and clinical equipoise are viewed, both by their authors and by later commentators, at least primarily, as ethical principles.[6]

No doubt, this view of the principles is urged upon both their authors' and later commentators by the role played by these principles in their author's respective responses to the historical question, a question which has, historically, been interpreted as an ethical question. However, once we have recognized the falsity of the RCT-dilemma, we are in a position to see that the historical question is first and foremost an epistemological question. Furthermore, viewed from this perspective, the principles of theoretical and clinical equipoise reveal themselves for what they are: epistemic (methodological) constraints on the conduct of Applied POR.

For reasons already adduced above, I believe that the principle of clinical equipoise is the better principle. As Freedman pointed out in his 1987 article, "medicine is social rather than individual in nature" (Freedman, 1987, 144). Judgments as to whether or not a rival is in fact preferable to the currently accepted treatment cannot be based on a particular physician's idiosyncratic hunches, as Fried's principle of theoretical equipoise suggests. Again, as Freedman says:

> Progress in medicine relies on progressive consensus within the medical and research communities. The ethics of medical practice grants no ethical or

[6] As noted above, debate concerning the validity of active controlled trials in the context of the larger debate concerning the use of placebo controls in human subjects research stands as a significant exception to this tendency. In fact, Freedman explicitly recognized that the principle of clinical equipoise had epistemological implications. Thus, he argued that the principle constrained design, e.g., requiring that second-generation interventions be tested against first-generation interventions, and that studies be designed in such a way "as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed" (Freedman, 1987, 144). However, he does not seem to view the notion of clinical equipoise itself as an epistemological constraint because, insofar as he interprets the historical question as an ethical question, he allows for the possibility of a RCT (qua method of Applied POR) that is properly designed but unethical (because it does not satisfy the principle of clinical equipoise). For Freedman, perhaps, the principle merely implies epistemological (i.e., design) constraints. On my view, however, clinical equipoise itself is an epistemological constraint on the conduct of Applied POR). Thus, a RCT (qua method of Applied POR) that fails to satisfy the principle of clinical equipoise is not merely unethical, but improperly designed (more, it fails to count as Applied POR at all).

> normative meaning to a treatment preference, however powerful, that is based on a hunch or on anything less than evidence publicly presented and convincing to the clinical community. (Freedman, 1987, 144)[7]

The principle of clinical equipoise, unlike Fried's principle of theoretical equipoise, captures this aspect (i.e., the social aspect) of medicine. For this reason, I believe the principle of clinical equipoise is the better epistemic principle: the principle of clinical equipoise better captures the 'nature' of Applied POR.

It is no accident that the principle of clinical equipoise so accurately reflects the nature of Applied POR. Freedman explicitly 'derives' the principle of clinical equipoise from what he rightly takes to be the "basic reason" for conducting clinical trials in this context. This is precisely what I attempted to do in Chapter Three. First, I identified the fundamental interest at stake in the conduct of Applied POR (i.e., the basic reason for conducting clinical trials in Applied POR) and, then, I identified various propositions to which we must be committed if Applied POR is to take this particular direction. Thus, following Ahrens, I argued that Applied POR is defined in terms of an interest in the improvement of the management of disease. Having identified various methodological constraints on Applied POR so defined, I (ultimately) argued that enrolment in a RCT (qua method of Applied POR) is legitimate if and only if the RCT in question is designed to test a hypothesis concerning the comparative safety or efficacy of a legitimate, yet incompletely tested, (rival) candidate for the optimal treatment of disease, where a rival is legitimate if and only if a substantial minority of the community of expert practitioners justifiably believes it to be.

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[7] I would expand on this sentence as follows: The ethics [and epistemology] of medical practice grants no ethical or normative [including epistemological] meaning to a treatment preference, however powerful, that is based on a hunch or anything less than evidence publicly presented and convincing to the clinical community.

Freedman adopts the same procedure, 'deriving' the principle of clinical equipoise from the "basic reason" for conducting clinical trials in this context. For Freedman, this "basic reason" is:

> ...current or imminent conflict in the clinical community over what treatment is preferred for patients in a defined population P. The standard treatment is A, but some evidence suggests that B will be superior (because of its effectiveness or its reduction of undesirable side effects, or for some other reason... A clinical trial is instituted with the aim of resolving this dispute. (Freedman, 1987, 143)

The principle of clinical equipoise restates this 'basic reason,' with the caveat that the conflict in question must be honest and professional. Thus, the principle of clinical equipoise requires that, in order for enrolment in a RCT to be legitimate, "there must be honest, professional disagreement in the community of expert practitioners as to the preferred treatment" (Freedman, 1987, 144). But this requirement is not, first and foremost, an ethical requirement. Rather, as Freedman explicitly asserts, it is a re-statement of what Freedman takes to be the 'basic reason' for conducting a clinical trial in this context. Furthermore, the 'basic reason' in question is, at least primarily, epistemological in character. The conflict in the clinical community is, first and foremost, an epistemological conflict. Given the current state of knowledge, some practitioners believe that the standard treatment A is preferable, while other practitioners *believe* that novel treatment B is preferable. A clinical trial is instituted with the aim of resolving this *epistemological* dispute. Of course, precisely because the practitioners in question are committed to a rational therapeutics, their epistemic circumstances are ethically charged. But, the primary problem at hand is epistemological. Thus, the principle of clinical equipoise is as accurately described as an epistemological (specifically methodological), as it is an ethical, constraint on the conduct of clinical trials.

The latter point is crucial, but largely unappreciated. It is crucial because, interpreted as a methodological constraint on the conduct of clinical trials, the principle of clinical equipoise increases both in scope and importance. It is not only an ethical constraint on the conduct of clinical trials, though it is that too, but a criterion for bona fide Applied POR: an RCT (qua method in Applied POR) that fails to satisfy the principle of clinical equipoise is not merely unethical, but something else altogether – such a study fails to count as Applied POR. Much as we must accept the proposition that the Earth existed in the past in order to conduct historical inquiry, in order to conduct Applied POR we must accept the proposition that there is such a thing as a legitimate, yet incompletely tested, (rival) candidate for the optimal management of a disease (i.e., an experimental intervention). Furthermore, in order to conduct a particular study in Applied POR, we must accept the proposition that a particular intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of disease Y. Finally, in order to (justifiably) accept the latter proposition, we require a norm or standard by which we may identify a legitimate rival. In Chapter Three, I came up with the following norm:

> An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be.

But this norm implies clinical equipoise. Recall that Freedman defines clinical equipoise as "honest, professional disagreement in the community of expert practitioners as to the preferred treatment" (Freedman, 1987, 144). If a significant minority of the community of expert practitioners justifiably believes that X is a legitimate rival for the optimal management of Y, while the rest of the community of expert practitioners

justifiably believes that Z is the preferred intervention, this implies that there is "honest, professional disagreement in the community of expert practitioners as to the preferred treatment." Thus, the definition of clinical equipoise may be substituted for the definiens in the above such that:

> An intervention X is a legitimate, yet incompletely tested, (rival) candidate for the optimal management of Y if and only if, on the basis of good but incomplete evidence, there is honest, professional disagreement in the community of expert practitioners as to [whether X is] the preferred treatment.[8]

Clinical equipoise, in other words, becomes (part of) a norm used to identify legitimate rivals and, thus, enable the pursuit of Applied POR. Furthermore, precisely because the *principle* of clinical equipoise (which requires both that at the start of a trial clinical equipoise obtain and that the trial be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed) is 'derived' from the 'basic reason' for conducting clinical trials (in Applied POR), the *principle* of clinical equipoise is not merely regulative, but (partly) constitutive of Applied POR. The *principle* of clinical equipoise tells us what Applied POR *is*: it is research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Furthermore, precisely because it is (partly) constitutive of Applied POR, the principle applies in all cases of bona fide

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[8] First, I am assuming that "honest, professional disagreement" implies that the beliefs of both parties involved in the disagreement are justified. Second, if a significant minority of the community of expert practitioners justifiably believes that X is a legitimate rival, there is honest, professional disagreement in the community of expert practitioners as to whether X is the preferred treatment. The former principle canvassed above, in other words, implies the latter. But it might be objected that the converse implication does not hold such that we cannot substitute the principle of clinical equipoise for the definiens in the former norm. This objection is a good one. However, as I've pointed out previously, for the purposes of this discussion I have defined honest, professional disagreement as follows: there is honest professional disagreement in the community of expert practitioners as to whether X is the preferred treatment if and only if, on the basis of good but incomplete evidence, a significant minority of the community of expert practitioners justifiably believes it to be. Obviously this is somewhat arbitrary. We could change this definition. If we did change it, however, the definiens in the former norm would change as well, so the substitution would still be valid.

Applied POR including Phase I studies, not just studies of effectiveness. (I will say more about this in Chapter Six).

Conclusion

Even Freedman, it seems, failed to grasp the full significance of the principle of clinical equipoise. Though Freedman recognized that the principle had epistemological implications, he did not seem to view the notion of clinical equipoise itself as an epistemological constraint, because he allows for the possibility of a RCT (qua method of Applied POR) that is properly designed but unethical (because it does not satisfy the principle of clinical equipoise). On my view, however, clinical equipoise itself is an epistemological constraint on the conduct of Applied POR). Thus, a RCT (qua method of Applied POR) that fails to satisfy the principle of clinical equipoise is not merely unethical, but improperly designed (more, it fails to count as Applied POR at all).

No doubt, Freedman's failure to grasp the full import of his principle can be traced to his preoccupation with the so-called historical question in its ethical form: when may a physician legitimately (i.e., ethically) offer enrollment in a RCT to her patient? Having recognized the falsity of the RCT-dilemma, however, we are in a position to see that the historical question is first and foremost an epistemological question. Viewed from this perspective, the principle of clinical equipoise reveals itself for what it is: an epistemic (methodological) constraint on the conduct of Applied POR. The principle of clinical equipoise does not merely tell a physician when offering enrolment in a RCT is ethical, though it does that too. Nor does it merely apply to RCTs testing the effectiveness of a novel intervention, though it also does that. Rather, the principle of

clinical equipoise tells us what Applied POR *is*: it is research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment.

If this is right, as we shall see in the next chapter, the principle of clinical equipoise is both more important and broader in scope than previously believed, and its role in the regulation of clinical research is other than previously understood. For one, research that fails to satisfy the principle of clinical equipoise fails to count as bona fide Applied POR. Such a failure is deeply problematic if the RCT in question is purportedly motivated by a desire to improve the management of disease and has been advertised as such to funders, physicians, and/or potential participants. Here, I believe, is the real source of the so-called therapeutic misconception. In the next chapter, I will argue that clinical researchers are faced with a choice: either they must own up to the fact that their research is not about improving the management of disease or they must show that their research satisfies the principle of clinical equipoise (i.e., that it is bona fide Applied POR). Our new understanding of the constitutive role of clinical equipoise has two important consequences. First of all, it raises the epistemic bar, ensuring that we are asking the relevant questions and providing grounds for rejecting many research proposals that are currently approved by REBs. Furthermore, it explains away the so-called therapeutic misconception. Applied POR necessarily involves practice thus most forms of the therapeutic misconception simply cease to be an issue.

Chapter Six: Misconceptions

Introduction

If the foregoing analysis is right, our current understanding of a number of key notions in research ethics must be revised. First of all, we must come to terms with the fact that the role of the principle of clinical equipoise (qua epistemic constraint) is more basic than previously supposed. The principle of clinical equipoise, recall, requires that at the start of a trial "there must be honest, professional disagreement in the community of expert practitioners as to the preferred treatment," and that "the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed" (Freedman, 1987, 144). If my analysis is correct, however, the principle of clinical equipoise does not only tell a physician when offering enrolment in a RCT is ethical. Rather, it tells us what Applied POR *is*: it is research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Thus, the principle is broader in scope than previously believed, and its role in the regulation of clinical research is other than previously understood.

For one, precisely because the principle of clinical equipoise is (partly) constitutive of Applied POR, the principle applies in all cases of bona fide Applied POR including, for example, Phase I studies involving healthy volunteers (i.e., not patients). Given the historical understanding of the principle, however, this makes little sense. Historically, the principle has been interpreted in light of the historical question (qua ethical question). The principle has been used to operationalize the norms of therapeutic beneficence and nonmaleficence in a manner consistent with the ethics of the doctor-

patient relationship. In its historical role, therefore, the principle of clinical equipoise is necessarily tied to the notion of therapeutic benefit and is, thus, appropriately applied only in RCTs involving patients. Properly understood, however, the principle of clinical equipoise (qua epistemic constraint) is more embracing, applying to all Applied POR.

In order to make sense of this new, broader, role for the principle, it is necessary to draw a distinction between the epistemic benefits (i.e., knowledge) and the therapeutic (for present purposes, I will use "therapeutic" as a catchall term for prophylactic, diagnostic, and bona fide therapeutic interventions) benefits that flow from a study. In its role as an epistemic constraint, the principle of clinical equipoise tells us what counts as epistemically valuable in this context: the principle points the way toward clinically relevant knowledge.[1] In its role as an ethical constraint, the principle performs a more familiar service. When patients are involved in a study, the principle (qua ethical constraint) ensures that, with respect to the therapeutic procedures offered, patient/subjects are treated in a manner consistent with the ethics of the doctor-patient relationship.[2] When the study involves healthy volunteers, however, the principle (qua ethical constraint) applies subjunctively, ensuring that, if there were patients involved, they would be treated in a manner consistent with the ethics of the doctor-patient relationship. On my view, then, the principle of clinical equipoise applies to all Applied

[1] The principle of clinical equipoise tells us both what Applied POR *is*, and what counts as epistemically valuable in this context (i.e., clinically relevant knowledge). Indeed, because Applied POR is defined in terms of the improvement of the management of disease, these roles are essentially equivalent. Clinically relevant knowledge *is* knowledge produced by research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Applied POR, likewise, *is* research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment.

[2] It is not my intention to suggest that the principle of clinical equipoise is a stand alone ethical standard. The risks associated with the non-therapeutic procedures undertaken in a trial must be minimized. Determinations of what count as appropriately minimal risks in this context need not always be relative to the standard of care (and thus to the principle of clinical equipoise), though frequently they will be.

POR, playing two interrelated roles which apply either directly or subjunctively depending on the circumstances.

Another closely related implication of the foregoing is the need for a reassessment of the concepts of 'therapeutic research' and 'non-therapeutic research'. Since, on my view, all Applied POR involving patients necessarily involves practice (properly understood), all Applied POR involving patients is accurately characterized as 'therapeutic research.' Given our new definitions of 'research' and 'practice,' furthermore, the National Commission's concerns with these terms disappear. Therapeutic research simply is Applied POR (i.e., research involving direct contact with patients or volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge). Non-therapeutic research is everything else.

Finally, the foregoing requires reconsideration of the so-called therapeutic misconception. On my view, research that fails to satisfy the principle of clinical equipoise fails to count as bona fide Applied POR. In and of itself, such a failure is unproblematic. If the RCT in question is purportedly motivated by a desire to improve the management of disease and has been advertised as such to funders, physicians, and/or potential participants, such a failure is deeply problematic because it creates a therapeutic misconception. However, if researchers working in Applied POR conduct bona fide Applied POR, i.e. their research satisfies the principle of clinical equipoise, patients participating in a trial of a novel therapy are right to expect therapy in the context of that trial. If we are asking the right questions, in other words, the "therapeutic misconception"

largely disappears. The therapeutic misconception, thus, is primarily a problem with the research agenda rather than a problem with informed consent: i.e., when research participation is advertised (directly or indirectly) as a therapeutic modality when in fact the research in question is not bona fide Applied POR.

The Scope and Role of Clinical Equipoise

Historically, the principle of equipoise was developed in response to the historical question in its ethical form. The historical question, recall, is: "[w]hen [if ever] may a physician legitimately offer enrollment in a RCT to her patient?" (Weijer, Glass, and Shapiro, 2000) Historically, "legitimately" has been read as "ethically". Because this question arises out of the RCT dilemma, a dilemma that presupposes both that physicians must act with unqualified fidelity to their patient(s) and that this obligation is (ceteris paribus) inconsistent with the conduct of RCTs, a desideratum of any satisfactory response to this question is that it tell us when, if ever, an offer of enrolment in a RCT is consistent with a physician's unqualified fidelity to their patient(s). Setting aside the fact that no physician ever acts with unqualified fidelity to her patient(s) in the relevant sense, the (historical) problem is to figure out when, if ever, randomization to the experimental arm of a RCT promises to provide a ratio of therapeutic benefit to risk that is consistent with the standard of care in everyday clinical practice. The principle of clinical equipoise is supposed to provide a solution to this problem, telling us when the ratio of therapeutic benefit to risk is consistent with the standard of care: just when there is honest, professional disagreement in the community of expert practitioners as to the preferred treatment.

So interpreted, of course, the applicability of the principle of clinical equipoise is much more limited than it is on my view. Broadly speaking, the principle only applies to trials involving patients because only patients, as opposed to healthy volunteers, are in a position to receive therapeutic benefit from trial participation. Furthermore, because RCTs of novel therapeutic (again, for present purposes, I will use "therapeutic" as a catchall term for prophylactic, diagnostic, and bona fide therapeutic interventions) interventions involve both "therapeutic procedures" and "non-therapeutic procedures," the applicability of the principle of clinical equipoise is of limited scope even within such RCTs: the principle only applies to the "therapeutic procedures" administered in the trial.[3]

The latter is a point much emphasized by Charles Weijer. In the following section, partly because I believe Weijer's approach to the ethical analysis of risk is the best produced to date and I want to borrow from it, and because it so clearly illustrates the historical understanding of the role of clinical equipoise, I will briefly review his approach to risk analysis.

Weijer: The Ethical Analysis of Risk

Weijer's approach to the ethical analysis of risk in research involving human subjects is commonly referred to as "component analysis". Weijer's approach has come to be called this because he, following what he takes to be the National Commission's ultimate position on risk analysis, endorses an approach that treats the "therapeutic procedures" and "nontherapeutic procedures" separately. "Therapeutic procedures," on

[3] The terms "therapeutic procedures" and "non-therapeutic procedures" will be defined in the following section.

Weijer's view, are "those interventions in research – drugs, surgical procedures, devices, or psychological procedures – administered with a therapeutic warrant" (Weijer, 2000, 354). "Non-therapeutic procedures," by contrast, are the remaining procedures administered in a clinical study that are "not administered with a therapeutic warrant" (Weijer, 2000, 355). Examples of non-therapeutic procedures given by Weijer range from the innocuous – randomization, chart review, filling out a questionnaire – to the risky – blood draws, genetic testing, or organ biopsy.[4] Such procedures, says Weijer, are "administered solely for scientific purposes – to answer the research question at hand" (Weijer, 2000, 354-355). According to Weijer, the risks posed by these two "components" of a clinical study must be analyzed separately, and according to different standards.

On Weijer's view, then, the first step in assessing the ethical acceptability of a research protocol is to distinguish the therapeutic procedures from the non-therapeutic procedures. Once the therapeutic procedures have been identified, their ethical acceptability is assessed by subjecting them to the test of clinical equipoise. Let's suppose that the protocol in question proposes to assess a novel second-generation selective serotonin reuptake inhibitor (SSRI) against a first-generation SSRI (SSRIs are a class of drugs that are currently the accepted treatment for clinical depression). The therapeutic procedures in question, then, are the administration of these two SSRIs. These

[4] Randomization is often characterized as a non-therapeutic procedure (see, for example, Weijer, 2000, 355). In this context, however, this designation is question-begging. Consider the example discussed below. If a second-generation SSRI is a legitimate rival to the first generation SSRI, citing evidence to that effect acts as an epistemic defeater such that we are no longer justified in believing that the first-generation SSRI is preferred. The two treatments, in other words, are in clinical equipoise. Since the standard of care is unclear in this scenario, given a commitment to a rational therapeutics, randomization is both the most rational and the most ethical course of action. Randomization, in other words, is not merely consistent with the standard of care, it *is* (at least ideally) the standard of care. Randomization, in this sense, *is* a therapeutic procedure, or so I would argue.

procedures are ethically acceptable, says Weijer, only if "[t]here exists...an honest, professional disagreement among expert clinicians about the preferred treatment" (Weijer, 2000, 354); that is, at least a significant minority of the community of expert practitioners justifiably believe that the second generation SSRI is the preferred treatment for clinical depression. By contrast, the non-therapeutic procedures proposed by the protocol need not pass the test of clinical equipoise. Indeed, the test of clinical equipoise is inappropriate here because, by definition, non-therapeutic procedures do not hold out the prospect of benefit to individual research subjects (they are procedures administered *solely* for scientific purposes). Thus, a risk-benefit calculus, which is implicitly at work in the principle of clinical equipoise, makes little sense.[5] Instead, Weijer argues that the risks posed by the non-therapeutic procedures must be assessed against different standards. First of all, says Weijer, the risk posed by the non-therapeutic procedures must be minimized. This can be done by, for example, "...using procedures already being performed on the subjects for diagnostic or treatment purposes" (Weijer, 2000, 355). Second, the research ethics board (REB) must determine whether or not the risks posed by the non-therapeutic procedures are "reasonable in relation to the knowledge to be gained" (Weijer, 2000, 355). The ethical analysis of risks associated with the non-therapeutic procedures in the study, in other words, involves a "risk-knowledge calculus" as opposed to a risk-benefit calculus (Weijer, 2000, 355). Enrollment in an RCT is ethically acceptable, then, only if "[the] ethical tests for both therapeutic and non-therapeutic procedures have been passed" (Weijer, 2000, 353).

[5] I am assuming that clinical judgment involves, among other things, weighing the risks of treatment against the benefits of treatment. Given this admittedly simplistic picture of clinical judgment, clinical equipoise can be seen as an expression of the expert community's uncertainty concerning the relative risk/benefit profiles of the treatments under comparison.

For our purposes, a number of features of Weijer's approach to risk analysis are particularly significant. First of all, notice that the principle of clinical equipoise is tied to the notion of therapeutic benefit. For Weijer, the principle is appropriately applied only when, in the context of a clinical trial, care is being provided. Given Weijer's historical understanding of the principle, this is unsurprising: Weijer, following Freedman, interprets the principle primarily in ethical terms.[6] Clearly, given this understanding of the principle, it is only applicable when patients, i.e., persons with an illness who are in a position to benefit from a therapeutic intervention, are involved in the study. Given this understanding of the principle, in other words, the principle is not appropriately applied to Phase I trials involving healthy volunteers because it is not relevant in these circumstances.

Second, notice that the principle plays no part in the assessment of a study's epistemic value. This follows from the structure of "component analysis". Whereas therapeutic procedures are subject to a risk-benefit calculus and, thus, to the test of clinical equipoise, non-therapeutic procedures are subject to a risk-knowledge calculus and, thus, need not pass the test of clinical equipoise. "The knowledge that may result from a study," says Weijer, "is essentially its scientific value … [and] the proper assessment of the scientific value of a study requires not only the opinion of experts from relevant disciplines, but also the opinion of representatives from the community at large" (Weijer, 2000, 355). Assessments of the scientific value of a study proceed independently of our assessment of the ethical acceptability of the therapeutic procedures in question,

[6] That being said, Weijer more than anyone else in the literature, has emphasized the epistemological implications of clinical equipoise. See, for example, Weijer, C. (1999). "Placebo-controlled trials in schizophrenia: Are they ethical? Are they necessary?" *Schizophrenia Research* 35: 211-18.

and according to different standards. According to Weijer, the principle of clinical equipoise plays no role in the assessment of a study's scientific (epistemic) value.

But how, I am inclined to ask, do the relevant experts determine whether a study is of scientific value? Despite the fact that every set of guidelines for research involving human subjects since the Nuremberg Code stipulates "scientific value" as one of the necessary conditions for the ethical acceptability of research involving human subjects, "scientific value" is rarely, if ever, spelled out. Furthermore, explications of this term that appeal to the further requirements that a study begin with "an honest null hypothesis" or a "non-trivial" research question are not particularly helpful, because these explications beg the question. The problematic term "value" has simply been replaced by the equally problematic terms "honest" or "non-trivial". What does "honest" or "non-trivial" mean in this context?

I believe that the principle of clinical equipoise provides the right sort of explication of "scientific value" in this context precisely because the principle is indexed to the context of practice. As noted in chapter two, insofar as Applied POR is defined in terms of the improvement of the management of disease, questions proper to this form of research are questions concerning the preferred modality of disease management. Clinical judgments as to whether one modality of disease management is preferable to another are highly complex, involving consideration of a host of factors, including effectiveness, consistency, side effects, cost, availability, and many others besides. Given the complexity of these judgments, it seems very likely that persons situated in the clinical context – the community of expert clinicians – are in the best position to make such judgments (in consultation with their patients). The principle of clinical equipoise reflects

this reality, placing the locus of epistemic agency in the community of expert practitioners. Clinicians and their patients are in the best position to identify legitimate rivals for the optimal management of disease.

Furthermore, the principle of clinical equipoise provides the expert community with a standard by which they can identify research of scientific value in this context. In the context of Applied POR, a proposed research project is scientifically valuable if and only if it is a research project designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. In the context of Applied POR, in other words, knowledge of scientific value is knowledge about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic interventions, knowledge that is directly relevant to the management of disease, or, simply, clinically relevant knowledge.

Operationalizing the Principle of Clinical Equipoise (qua Epistemic Constraint)

On my view, then, the principle of clinical equipoise tells us what counts as epistemically valuable in this context. Functionally speaking, it also tells us what Applied POR is; indeed, because Applied POR is defined in terms of the improvement of the management of disease, the answer to these questions is the same. Research of scientific value in this context *is* research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Applied POR is, likewise, research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment.

So understood, of course, both the scope and the role of the principle differ from that delineated by Weijer. However, in order to see how this new understanding of the principle is operationalized, we must rely on a distinction drawn by Weijer between the epistemic benefits (i.e., knowledge) and the therapeutic benefits (i.e., prophylactic, diagnostic, or therapeutic benefits) promised by a research protocol. Weijer, recall, notes that it makes no sense to speak of the therapeutic benefits of the non-therapeutic procedures in a research protocol since, by definition, non-therapeutic procedures are procedures administered *solely* for scientific purposes. On Weijer's account, therapeutic procedures promise therapeutic benefits, whereas non-therapeutic procedures promise epistemic benefits (i.e. knowledge). Furthermore, the principle of clinical equipoise is the relevant test for the ethical acceptability of the therapeutic procedures involved in a research protocol, and a reasonable ratio of risk to knowledge is the relevant test for the ethical acceptability of the non-therapeutic procedures involved (with the caveat that risks be minimized).

Given the wide scope my view accords the principle of clinical equipoise, Weijer's approach will not work. On my account, the principle applies to all Applied POR, not merely to Applied POR that involves patients. However, we can mobilize Weijer's distinction between epistemic and therapeutic benefits in order to spell out an alternative framework for research review. As in Weijer's account, we maintain a distinction between therapeutic and non-therapeutic procedures. Furthermore, as in Weijer's account, the risks associated with the non-therapeutic procedures must be minimized. However, on my view, the principle of clinical equipoise applies to both therapeutic and non-therapeutic procedures. On the therapeutic side, the principle

performs the same role it does in Weijer's account, ensuring that the ratio of risk to therapeutic benefit is consistent with the standard of care, or that it would be if patients were involved. On the non-therapeutic side, the principle acts as a standard against which the ratio of risk to knowledge is assessed. Quite simply, assuming that risks are appropriately minimized, as long as the study satisfies the principle of clinical equipoise (qua epistemic constraint) the risks posed by the non-therapeutic procedures are reasonable in relation to the knowledge to be gained.

To return to our example above, a protocol that proposes to assess a novel second-generation SSRI against a first-generation SSRI is both epistemically and ethically acceptable if the risks posed by the non-therapeutic procedures are minimized and the study satisfies the principle of clinical equipoise in both its epistemological and ethical forms; that is, the risks posed by the protocol are reasonable in relation to the knowledge to be gained, i.e., the protocol passes the test of clinical equipoise (qua epistemological constraint) and the therapeutic procedures under study pass the test of clinical equipoise (qua ethical constraint).

In the case of a Phase I trial involving healthy volunteers, the procedure is the same, except that the principle (qua ethical constraint) only applies subjunctively. The principle ensures that, if there were patients enrolled in this study, they would receive therapy consistent with the prevailing standard of care. The principle of clinical equipoise (qua epistemological constraint) ensures that the study is bona fide Applied POR; that is, the principle (qua epistemological constraint) ensures that it is a study of a legitimate rival for the optimal management of the disease in question, albeit a study designed to determine whether that intervention is safe, or how it is metabolized. In this context, the

principle of clinical equipoise acts as a standard by which we can determine whether or not the novel intervention in question is in fact a legitimate rival and, thus, whether or not the research project is scientifically valuable in this context (i.e., clinically relevant).

On my view, then, the principle of clinical equipoise plays two interrelated roles, an epistemological role and an ethical role. Furthermore, the principle applies to all Applied POR, not just Applied POR involving patients. When patients are involved, the principle (qua both epistemological and ethical constraint) is directly operative. When patients are not involved, the principle (qua epistemological constraint) operates in the same way. However, the principle (qua ethical constraint) operates subjunctively; that is, the principle (qua ethical constraint) ensures that, if there were patients enrolled in this study, the therapeutic procedures on offer would be consistent with the ethics of the doctor-patient relationship.

Rehabilitating "Therapeutic Research"

An implication of the foregoing is the need for a reassessment of the concepts of "therapeutic research" and "non-therapeutic research". As we saw in Chapter Two, by the time of *Research Involving Children* (1977) the National Commission had rejected these concepts, preferring the unqualified term "research" instead. Again, the National Commission's argument for this change of terminology as given in Chapter 8 of *Research Involving Children* is:

> Research, by definition, is intended to develop general knowledge. Therapy, by definition, is for the benefit of an individual and therefore does not inherently involve any generalizable component. The term 'therapeutic research' thus mixes together two quite different ingredients, and it remains unclear what 'therapeutic research' could mean. (*Research Involving Children*, 1977, 97)

This argument, of course, turns on the supposition that it makes sense to contrast research and practice (therapy) in these now familiar ways; that is, first, in terms of the individualized or particularist character of practice (therapy) and the generalized or universalist character of research and, second, in terms of the pragmatic character of practice and the epistemic character of research.

In Chapters Two, Three, and Four, however, I showed that these contrasts are problematic. In Chapter Two, I argued that the National Commission's definitions of research and practice are problematic because they both raise the specter of the central problem and foreclose the conceptual space required for its solution. In Chapters Three and Four, furthermore, I showed that the National Commission's distinction between research and practice suggests a misleading picture of research and practice respectively.

In Chapter Four, I argued that their definition of practice is problematic because it misleadingly presents a picture of practice as a purely pragmatic and morally unitary endeavour. Practice is neither morally unitary nor purely pragmatic. Practice is not morally unitary because other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. Practice is not purely pragmatic because, given a commitment to a rational therapeutics, the content of the duty of care cannot be specified independently of evidence provided by good clinical research. The duty of care, thus, involves both moral and epistemic duties (i.e., it is not a purely moral duty).

In Chapter Three, building on Ahrens' analysis of "clinical research," I offered a contextualist analysis of Applied POR. This analysis revealed that Applied POR is constituted by very specific contextual commitments that only come into view when we

are attentive to the particular interests at stake in this form of inquiry, commitments that are themselves revelatory of the epistemological, metaphysical, and ultimately moral, character of this form of inquiry. Once these commitments were made explicit, it became clear that we cannot even define Applied POR independently of the context of practice, let alone determine the justificatory status of its hypotheses. Far from being an accidental side-effect of the conduct of research, as the National Commission supposed, this analysis showed that practice (properly construed) is an essential feature of all Applied POR.

In light of these findings, I offered revised definitions of both 'research' and 'practice.' Abandoning the notion of "research" simpliciter as hopelessly decontextualized, I offered a definition of Applied POR:

> Applied POR is research involving direct contact with patients or volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge.

I then offered a revised definition of "practice":

> 'Practice' refers to interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.

With these definitions in hand, it is clear that the National Commission's above argument fails. Since, on my view, all Applied POR involves practice, the term 'therapeutic research' does not "mix together two quite different ingredients," nor is it "unclear what 'therapeutic research' could mean"; rather, the meaning is quite clear: 'therapeutic research' is "research involving direct contact with patients or volunteers in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease [e.g., an

experimental treatment] in order to develop clinically relevant knowledge". In short, "therapeutic research" simply is Applied POR. Non-therapeutic research is everything else (e.g., Basic POR, pre-clinical research, animal modelling).

At this point, I anticipate an objection. The objection might proceed as follows: even if we grant that practice, albeit experimental practice, occurs in the context of Applied POR involving patients, it is difficult to make sense of the supposition that practice occurs in the context of a Phase I trial involving healthy volunteers. This objection is a good one. Throughout this essay I have repeatedly maintained that practice is an essential part of *all* Applied POR. However, healthy volunteers are not in need of treatment and, thus, are not usually in a position to benefit therapeutically from a novel intervention. Insofar as "practice" refers to "interventions that are designed to enhance the well-being of an individual patient," then, in what sense does practice occur in a Phase I trial involving healthy volunteers?

In order to answer this question we must, once again, appeal to the distinction between therapeutic (in the broad sense) and epistemic benefits. Given that Applied POR is defined in terms of the improvement of the management of disease, questions proper to Applied POR are questions about the (comparative) safety and efficacy of (experimental) prophylactic, diagnostic, and/or therapeutic *interventions.* But such questions can be answered only by actually intervening. In order to determine whether or not an experimental intervention is safe for human beings to use, for example, it is necessary to administer that intervention to actual human beings. To put it plainly, in order to test the safety of a practice, we must engage in that practice. Thus, insofar as the study satisfies the principle of clinical equipoise (qua epistemological constraint), even healthy

volunteers enrolled in a Phase I study (if the trial is randomized, those who end up on the experimental arm of the trial) receive an (experimental) intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success." The intervention is offered to them, however, for the sole purpose of obtaining epistemic benefits, i.e., clinically relevant knowledge concerning the safety of that experimental intervention. That being said, the principle of clinical equipoise (qua ethical constraint) ensures that, if there were patients enrolled in this study, they would receive therapy consistent with the prevailing standard of care. In this somewhat novel sense, practice is involved even in a Phase I study involving healthy volunteers (I will say more about this in a moment).

When patients are enrolled in a study, however, practice is involved in both the novel sense just canvassed and in the standard sense; that is, an experimental intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success" is given to participants randomized to the experimental arm of the study in order to obtain epistemic benefits (i.e., in order to determine whether or not that intervention is preferable to the standard) and to provide those participants with therapeutic benefits. As long as "practice" is understood in this dual sense, practice is an essential part of *all* Applied POR.

No doubt some readers will find this response unsatisfactory, arguing that the novel sense of 'practice' I have introduced distorts its meaning beyond recognition; that, by detaching 'practice' from the notion of direct therapeutic benefit, I have simply changed the subject and created another term. To this objection I respond as follows. Consider, again, the definition of practice I offered in Chapter Four (note: my definition

and the National Commission's are identical with respect to the features I discuss in the following):

> 'Practice' refers to interventions that are designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.

Notice the ambiguity associated with two key terms in this definition: 'intervention' and 'designed'. First consider the term 'intervention'. By 'intervention' we may mean one of at least two things. We may mean a particular action, as in "we carried out an intervention...," or a particular thing or strategy, as in "we administered intervention X." Similarly, by 'designed' we may mean a particular intention on the part of an agent, as in "her designs were clear, she was after his money…," or the particular function or end for which something was devised, as in "the drug was designed to lower blood pressure".

It seems clear enough that the standard reading of 'practice' relies on the former meanings of both terms respectively. If we substitute the corresponding terms, the standard reading runs as follows:

> 'Practice' refers to *actions* that are *intended* to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.

Given this reading, it is no surprise that the novel interpretation of 'practice' canvassed above raises eyebrows. 'Practice' in this sense is clearly not an action that is intended to enhance the well-being of an individual patient because the intervention in question is being administered to a healthy volunteer who, typically, is in no position to benefit from treatment. 'Practice' in the standard sense simply does not make sense in this context.

'Practice' in the novel sense canvassed above connotes the latter meanings of 'intervention' and 'designed' respectively. Substituting in the corresponding terms, this reading of 'practice' runs as follows:

> 'Practice' refers to a particular thing or strategy, e.g., a drug or regimen that is devised to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success.

Given this interpretation of 'practice,' notice, it makes perfectly good sense to suppose that practice occurs in a Phase I trial involving healthy volunteers because the status (qua practice) of a "drug or regimen that is devised to enhance the well-being of an individual" is stable across a range of intentions. A drug devised to lower blood pressure remains a drug devised to lower blood pressure even if it expires in the medicine cabinet unused. A treatment regimen devised to increase bone density remains a treatment regimen devised to increase bone density even if it is never followed. Analogously, an (experimental) intervention offered in the context of a Phase I trial remains an intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success," even if it is not intended to enhance the well-being of individuals enrolled in the trial.

Now notice the extent to which the novel reading of 'practice' undergirds our intuitions about clinical practice. First of all, it would be a mistake to suppose that an action counts as clinical practice only if that action is *intended* to enhance the well-being of an individual patient or client. We can readily imagine a physician who administers treatment without this intention. Imagine, for example, a profound misanthrope who believes that life is suffering. A physician with these beliefs might prescribe standard treatment to his patients with the intention of prolonging their suffering by prolonging

their lives. Insofar as he prescribes standard therapy to his patients, however, he is clearly engaging in clinical practice despite his intentions. If we were to discover his true intentions we might be horrified but surely we would be wrong if we judged him negligent. More mundanely, we can readily imagine a physician who acts as he does simply to get his patients out the door. Again, we might be horrified by such intentions; however, insofar as he continues to act in accordance with accepted standards he continues to engage in practice despite these intentions. Having the right intentions is not a necessary condition for an action counting as clinical practice. Indeed, intentions are far too unreliable a criterion for what counts as practice. No doubt this is why the National Commission avoided reference to intentions in their definitions of research and practice respectively.[7]

Intending to enhance the well-being of one's patients is not sufficient for an action to count as clinical practice either. A physician may intend by his actions to enhance the well-being of an individual. Unless his actions are in fact of the appropriate sort, however, his actions will fail to count as clinical practice. Imagine a well-intentioned physician whose prescribing habits were terribly out of date. Despite his intention to enhance the well-being of this or that patient, his actions are in fact useless or harmful; his actions fail to count as clinical practice.

In all of these examples, the novel reading of 'practice' is at work. The misanthropic physician is engaged in practice despite his intentions because he continues to offer drugs or treatment regimens that are 'devised to enhance the well-being of an

[7] Indeed, in an interview conducted as part of an *Oral History of the Belmont Report and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, Robert Levine notes that the National Commission avoided reference to intentions because one of the members of the National Commission, Dr. Joseph Brady, was a radical behaviorist and "radical behaviorists don't concede that there is any such thing as intent" (Belmont Oral History Project, 2004, 9).

individual patient or client that are justifiably believed to have a reasonable expectation of success.' Similarly, the actions of the well-intentioned physician fail to count as clinical practice because he fails to prescribe drugs or treatment regimens that are 'devised to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success.'

Now notice that the standard reading of 'practice' actually presupposes the novel reading. On the standard reading, as on the novel reading, it is necessary that the 'intervention' in question is justifiably believed to have a reasonable expectation of success. Insofar as our justification for believing that this or that action has a reasonable expectation of success derives from Applied POR, the standard reading of 'practice' presupposes the 'novel' reading because in Applied POR we are not typically evaluating the physician's intentions. On the contrary, we go to great lengths to control for the physician's intentions by employing design strategies like the double blind. In Applied POR we are typically evaluating the safety or efficacy of a drug or regimen, and it is on the basis of the results of such research that we come to be justified in believing that a particular intervention has a reasonable expectation of success. Notice, however, the sense of 'intervention' in the previous sentence: here 'intervention' means a particular thing or strategy, e.g., a drug or regimen, not an action. Of course, the administration of a drug is also an action. But one of the central aims of modern study design is to isolate the effects of the drug or regimen from the actions (and thus the intentions) of the acting physician/researcher. Applied POR, as exemplified by the RCT, is designed to evaluate the safety or efficacy of practices in the novel sense I identified above. Indeed, I doubt we

can even make sense of Applied POR as it is conducted today without relying on 'practice' in this sense.

That being said, it would be a mistake to draw a sharp distinction between these two notions of practice, or to suppose that research is exclusively concerned with 'practice' in the novel sense. Indeed, if we did draw such a sharp distinction we would simply be replacing one invidious distinction (i.e., the distinction between research and practice) with another (i.e., the distinction between 'practice' in the novel sense and practice in the standard sense). These two notions of practice are interdependent in much the same way as Applied POR and practice are interdependent: we cannot make sense of one without the other.

First of all, consider 'practice' in the standard sense. Insofar as we are committed to a rational therapeutics, 'practice' in the standard sense is necessarily connected to 'practice' in the novel sense precisely because the results of Applied POR supply the content of 'practice' in the standard sense. As we saw in Chapter Four, given a commitment to a rational therapeutics we cannot determine what counts as an "intervention…that [has] a reasonable expectation of success" without an informed (i.e., critical) understanding of the relevant evidence, evidence provided by good clinical research. Put in terms of the standard reading: given a commitment to a rational therapeutics we cannot determine what counts as an 'action that is intended to enhance the well-being of an individual patient or client that [is] *justifiably believed to have a reasonable expectation of success*' without relying on evidence provided by good clinical research. To this extent, 'practice' in the standard sense presupposes 'practice' in the novel sense.

Now consider 'practice' in the novel sense. The 'novel' reading of 'practice' runs as follows:

> 'Practice' refers to a particular thing or strategy, e.g., a drug or regimen that is devised to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success.

It would be a mistake to infer from the above discussion concerning the role of intentions in the definition of 'practice' that intentions are irrelevant to the status of an intervention qua 'practice' in the standard sense. A physician need not intend to enhance the well-being of his patient for his actions to qualify as practice. As long as his actions are consistent with accepted standards, his intentions may be irrelevant. Clearly, however, some intentions will be incompatible with acting in accordance with accepted clinical standards. It is hard to see, for example, how a physician who intended to kill his patient could possibly act in accordance with accepted clinical standards.

Similarly, the intentions with which an intervention is administered in the context of a study, or the interests a study is designed to serve, are not irrelevant to the status of an intervention qua 'practice' in the novel sense. After all, I have defined Applied POR in terms of an *interest* in the improvement of the management of disease. The status of an intervention, qua 'practice' in the novel sense, is stable across a range of intentions, but not across all or any intentions. Administering an intervention "designed to enhance the well-being of an individual patient or client that [is] justifiably believed to have a reasonable expectation of success" in the context of a study designed to test its effectiveness on healthy human subjects as a biological weapon effectively transforms that intervention into a weapon. Crucially, the conduct of such a study is incompatible with the norms of therapeutic beneficence and non-maleficence and, thus, with the

principle of clinical equipoise. No responsible, competent clinician could believe (at least not justifiably) that this intervention, as administered in the context of this study, is a legitimate rival for the optimal treatment of a disease. There is not 'honest, professional disagreement in the community of expert practitioners' as to whether or not this intervention, as administered in this study, is the preferred treatment for anything at all. This protocol neither satisfies the principle of clinical equipoise (qua ethical constraint), nor promises to produce clinically relevant knowledge (i.e., it fails to satisfy the principle qua epistemic constraint as well). This study, in short, fails to count as Applied POR; it is something else altogether.

But a study designed solely to test the safety of a legitimate experimental intervention (i.e., a Phase I trial involving healthy volunteers) is compatible with the norms of therapeutic beneficence and non-maleficence and, thus, with the principle of clinical equipoise, despite the fact the participants are not typically in a position to benefit therapeutically from the intervention. Why? Because, insofar as the experimental intervention in question (as it is administered in this study) is a legitimate rival, by definition there is "honest, professional disagreement in the community of expert practitioners as to the preferred treatment" of the disease in question. This study satisfies the principle of clinical equipoise (qua epistemic constraint), promising to produce clinically relevant knowledge. Furthermore, the study satisfies the principle (qua ethical constraint) subjunctively: if there were patients enrolled in this study (suppose, for example, that this is a Phase I study of an experimental cancer treatment), they would receive therapy consistent with the standard of care (i.e., the ratio of risk to therapeutic benefit would be consistent with that standard).

The Therapeutic Misconception

If the above is right, all Applied POR involves practice in one or both of the senses described. If the above is right, furthermore, all Applied POR is "therapeutic research," though experimental interventions "designed to enhance the well-being of an individual patient or client that are justifiably believed to have a reasonable expectation of success" are offered in order to provide participants with therapeutic (as opposed to epistemic) benefits only in the context of Applied POR involving patients.[8] If the above is right, finally, we need to reconsider the so-called therapeutic misconception.

The so-called 'therapeutic misconception' was first identified by Paul Appelbaum and colleagues 25 years ago. In that 1982 article, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," the authors characterize the therapeutic misconception in various ways. Their explicit definition of the 'therapeutic misconception' seems to be the following: "[the assumption on the part of research subjects] that decisions about their care are being made solely with their benefit in mind" (Appelbaum et al, 1982, 321). Later in their article, however, they characterize the therapeutic misconception as follows: "...many subjects entering research projects...carry strong expectations that the research, like the therapy they have received previously, is designed and will be executed in a manner of direct benefit to them" (Appelbaum, 1982, 327-8). Furthermore, in the course of explaining the results of their empirical study, the authors note that the therapeutic misconception manifests itself in two ways. First of all, they note that "[i]n the absence of information concerning the

[8] Whenever I refer to studies involving patients, the assumption is that they are participating in a study that is relevant to the treatment of their specific complaints.

means by which the project will be carried out…subjects tend to assume that the methodology will advance their therapeutic interests." Second, "[e]ven in the face of comprehensive disclosure…subjects often appeared not to hear, to distort, or to deny what was revealed to them" (Appelbaum, 1982, 328).

These characterizations differ in crucial ways. For example, in their 'definition' of the 'therapeutic misconception,' the authors characterize the misconception in terms of the assumption that "decisions about their care are being made *solely* with their benefit in mind" (emphasis mine). However, in the second version canvassed here, the misconception is characterized in terms of the "strong expectations that the research…is designed and will be executed in a manner of direct benefit to them." But the latter version is much weaker than the former (hereafter, I will refer to the former version of the therapeutic misconception as the "strong version" and the latter as the "weak version"). Given the strong version, a potential subject who believed that research participation would be of direct benefit to her would not be suffering from the therapeutic misconception because she does not believe (at least, not necessarily) that decisions about her care are being made *solely* with her benefit in mind. The same can be said about the third characterization: the fact that research subjects "tend to assume that the methodology will advance their therapeutic interests" does not mean that they assume that "decisions about their care are being made *solely* with their benefit in mind". The final characterization of the misconception is different altogether. On this version, subjects do not merely fail to understand the facts concerning research participation, they actively "distort, or deny what is revealed to them" due, the authors suggest, to a powerful psychological need to believe that study participation will be of benefit to them.

In a more recent paper, Sam Horng and Christine Grady attempt to clarify the concept of therapeutic misconception by distinguishing between 'therapeutic misconception,' 'therapeutic misestimation,' and 'therapeutic optimism.' According to the authors, a research subject who 'suffers from' therapeutic optimism is a subject who "hopes for the best personal outcome" (Horng & Grady, 2003, 12). The authors argue that therapeutic optimism is "[a]lways tolerable because hope does not compromise the autonomy of a decision to participate in research" (Horng & Grady, 2003, 12). A research subject who suffers from therapeutic misestimation, however, is a subject who "underestimates risk, overestimates benefit, or both" (Horng & Grady, 2003, 12). The authors argue that therapeutic misestimation is "[s]ometimes tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate in research" (Horng & Grady, 2993, 12). Finally, a research subject who suffers from therapeutic misconception, according to the authors, is a research subject who "conflates research with clinical care" (Horng & Grady, 2003, 12). The authors contend that therapeutic misconception is "[r]arely tolerable because understanding the nature of research is necessary for an autonomous decision to participate in research" (Horng & Grady, 2003, 12).

Horng and Grady's paper is very helpful in that it teases apart the various notions at work in the Appelbaum paper above and, indeed, the literature on therapeutic misconception more generally. Thus, according to Horng and Grady, a research subject's psychological need to believe that study participation will be of benefit to her is not necessarily problematic. Indeed, insofar as that need is accurately characterized as hope, it can be a good thing. Furthermore, Horng and Grady distinguish between a subject's

failure to accurately understand the specific facts about participation, like the probability of benefit and/or risk, and the more global misunderstanding which leads a research subject to conflate research with clinical care (i.e., the therapeutic misconception).

That being said, there is a major problem with Horng and Grady's definition of the therapeutic misconception. Their definition implies that a belief on the part of a research subject that clinical care will be provided in the context of a research study is, in and of itself, a therapeutic misconception. But this is too strong. It only makes sense to suppose that a subject's belief that she will receive care in the context of a research study is, in and of itself, a therapeutic misconception if we make the further assumption that in clinical care, as opposed to research, decisions are made solely with the patient's interests in mind (an assumption made explicit in Appelbaum et al's first definition of the therapeutic misconception above). But I have shown that this assumption is false. In the context of practice, as in the context of research, other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. For this reason, the "strong version" of the therapeutic misconception must be rejected. But the weak version is problematic as well. Participation in research often provides therapeutic benefits to participants. Indeed, on my view, all bona fide Applied POR involving patients is designed (indeed must be designed) to provide therapeutic benefits to participants that are consistent with the standard of care. Thus, insofar as the research in question is bona fide Applied POR (involving patients), participants are right to have "strong expectations that the research…is designed and will be executed in a manner of direct benefit to them." We must, therefore, reject the weak version as well.

On my view, subjects suffer from a therapeutic misconception whenever they mistakenly believe that they are participating in Applied POR. As long as they are participating in bona fide Applied POR, they are right to assume that "the research…is designed and will be executed in a manner of direct benefit to them" because all bona fide Applied POR must satisfy the principle of clinical equipoise. Problems arise when the research in which they are contemplating participation fails to satisfy the principle of clinical equipoise and, thus, fails to count as bona fide Applied POR. Of course, in and of itself, such a failure is unproblematic. If, however, the study in question is purportedly motivated by a desire to improve the management of disease and has been advertised as such to funders, physicians, and/or potential participants, such a failure is deeply problematic because it creates the false impression that "the research…is designed and will be executed in a manner of direct benefit to them".

On my view, then, the therapeutic misconception arises when subjects entering research projects mistakenly believe that they are enrolling in a study in Applied POR (and, thus, mistakenly assume that the research is designed and will be executed in a manner of direct benefit to them due to misleading advertising, or poor disclosure). On my view, however, the fault lies not with the subjects but with researchers who propagate this false belief, misrepresenting the character of the research in which they are engaged, and with REBs who approve protocols that fail to satisfy the principle of clinical equipoise (qua epistemic constraint). On my view, then, the therapeutic misconception is, ultimately, a problem with both the content of the research agenda and with how that content is represented. If we are asking the right questions (i.e., clinically relevant questions), if we stop misrepresenting the character of non-therapeutic research (i.e.,

research other than Applied POR), and if REBs stop approving protocols masquerading as Applied POR, the therapeutic misconception will cease to be a problem. Of course, subjects will continue to suffer from therapeutic misestimation and, thus, unrealistic therapeutic optimism. REBs will have to pay careful attention to these phenomena. However, as long as researchers working in Applied POR conduct bona fide Applied POR, i.e. their research satisfies the principle of clinical equipoise, patients participating in a trial of a novel therapy are right to assume that "the research…is designed and will be executed in a manner of direct benefit to them."

Conclusion

If my analysis in this essay is right, our current understanding of a number of key notions in research ethics must be revised. First of all, we must come to terms with the fact that the principle of clinical equipoise is broader in scope than previously believed, and its role in the regulation of clinical research is different than previously understood. On my view, the principle does not only tell a physician when offering enrolment in a RCT is ethical, it also tells us what Applied POR *is*: it is research designed to resolve honest, professional disagreement in the community of expert practitioners as to the preferred treatment. In this chapter, I began to flesh out the implications of this new understanding of the principle. Building on Weijer's approach to the analysis of risk, I argued that the principle applies to both therapeutic and non-therapeutic procedures. On the therapeutic side, when patients are enrolled, the principle performs the same role it does in Weijer's account, ensuring that the ratio of risk to therapeutic benefit is consistent with the standard of care. When patients are not enrolled, i.e., when the research subjects

are healthy volunteers, the principle (qua ethical constraint) applies subjunctively, ensuring that, if there were patients enrolled, they would receive therapy consistent with the standard of care. On the non-therapeutic side, the principle (qua epistemic constraint) acts as a standard against which the ratio of risk to knowledge is assessed. As long as risks are minimized, and the study satisfies the principle of clinical equipoise (qua epistemic constraint), the risks posed by the non-therapeutic procedures are reasonable in relation to the knowledge to be gained.

Second, I attempted to rehabilitate the discredited concepts of therapeutic and non-therapeutic research. Since, on my view, all Applied POR necessarily involves practice (in one of the two senses of that term), all Applied POR is accurately characterized as "therapeutic research." Indeed, on my view, Applied POR simply is therapeutic research; non-therapeutic research is everything else.

Finally, I argued for a new understanding of the so-called therapeutic misconception. On my view, the therapeutic misconception arises when subjects entering research projects mistakenly believe that they are enrolling in a study in Applied POR. On my view, then, patients participating in bona fide Applied POR are right to expect therapy (experimental therapy) in the context of that trial. Problems arise when the research in which they are contemplating participation fails to satisfy the principle of clinical equipoise and, thus, fails to count as bona fide Applied POR. Of course, in and of itself, such a failure is unproblematic. If, however, the study in question is purportedly motivated by a desire to improve the management of disease and has been advertised as such to funders, physicians, and/or potential participants, such a failure is deeply problematic because it creates the false impression that "the research…is designed and

will be executed in a manner of direct benefit to them". On my view, then, the therapeutic misconception is, ultimately, a problem with both the content of the research agenda and with how that content is represented. Fault lies not with the subjects who suffer from the misconception, but with researchers who misrepresent the character of the research in which they are engaged, and with REBs who approve research protocols that fail to satisfy the principle of clinical equipoise (qua epistemic constraint). If we are asking the right questions (i.e., clinically relevant questions), if we stop misrepresenting the character of non-therapeutic research (i.e., research other than Applied POR), and if REBs stop approving protocols masquerading as Applied POR, the therapeutic misconception will cease to be a problem.

Chapter Seven: Conclusion

We can't (and shouldn't) draw a sharp distinction between research (Applied POR) and practice. The supposition that we can (and should) only makes sense given the further supposition that scientific research can be isolated from the context of its development and application. Contemporary philosophy of science soundly rejects this view of scientific inquiry. Precisely because it encourages a radically decontextualized view of (clinical) science, the National Commission's distinction between research and practice has encouraged an outmoded, uncritical, and misleading picture of the epistemology of (clinical) science. This view of clinical science has, in turn, exacerbated the historical tendency in both the theory and practice of research ethics of focusing exclusively on the protection of the human subjects of research, encouraging an uncritical stance towards the research agenda. Even the logical positivists admitted that hypothesis selection was subject to the influence of contextual values and, thus, the complexities of ethics and politics. Many commentators working in contemporary research ethics, however, appear reluctant to admit even this much. Research, on their view, has its own goals and its own ethical norms, which are supposed to be sharply distinct from the goals and norms of clinical practice.

In this essay, however, I have shown that we can't even define Applied POR independently of the context of practice, let alone determine what counts as appropriate norms of justification (i.e., methods). Unless we're attentive to the particular interests at stake in this form of inquiry, interests that are and should be firmly located in the context of practice, the various contextual commitments constitutive of Applied POR are

obscured from view. Once these commitments are made explicit, however, it becomes clear that both the 'nature' and 'goals' of Applied POR are necessarily indexed to the context of practice. Far from being an accidental side-effect of the conduct of research, as the National Commission supposed, my analysis shows that practice is an essential feature of Applied POR.

My analysis of clinical practice led to analogous conclusions: much as we can't define Applied POR independently of the context of practice, we can't define clinical practice independently of Applied POR. Contrary to the picture of 'practice' presented by the National Commission, I argued that 'practice' is neither morally unitary nor purely pragmatic. Practice is not morally unitary because other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. Practice is not purely pragmatic because, given a commitment to a rational therapeutics, the content of the duty of care cannot be specified independently of evidence provided by Applied POR. The duty of care, thus, involves both moral and epistemic duties.

Contrary to the picture of 'research' and 'practice' presented by the National Commission (or, at the very least, by its contemporary commentators), my analysis shows that 'research' and 'practice' are intimately interdependent epistemologically, metaphysically and, therefore, ethically. The contrary picture of 'research' and 'practice,' wherein these activities are seen to be sharply distinct, has led to a host of problems in research ethics, problems that largely disappear once we understand the close relationship between research (specifically Applied POR) and practice.

In Chapters Five and Six I argued that two major problems in research ethics – the RCT dilemma and the therapeutic misconception – arise as problems only given

erroneous assumptions about 'research,' 'practice,' and their relationship. Despite its prima facie plausibility, I argued that the RCT dilemma is a false dilemma because it is generated by the same conceptual errors that inform the mistaken picture of 'research' and 'practice' endorsed by the National Commission. Both that picture and the RCT dilemma are based on the assumption that the nature and goals of research and practice are fundamentally different. The RCT Dilemma emerges from the further inference that, because of these differences, there is a fundamental moral conflict between a physician's duty of care and her commitment to research (or optimally informed action). But the root assumption is false (at least with respect to Applied POR). Precisely because Applied POR and practice are so intimately intertwined, other things being equal, there cannot be a categorical conflict between a physician's duty of care and her commitment to Applied POR.

The therapeutic misconception emerges from a similar mistake. It only makes sense to suppose that a subject's belief that she will receive care in the context of a research study is, in and of itself, a therapeutic misconception if we make the further assumption that in clinical care, as opposed to research, decisions are made solely with the patient's interests in mind. But my analysis of 'practice' showed that this assumption is false. In the context of practice, as in the context of research, other interests and commitments necessarily mitigate a doctor's commitment to enhancing the well-being of her patient. Furthermore, on my view all bona fide Applied POR involving patients is designed (indeed must be designed) to provide therapeutic benefits to participants that are consistent with the standard of care. Thus, insofar as the research in question is bona fide

Applied POR (involving patients), participants are right to have "strong expectations that the research…is designed and will be executed in a manner of direct benefit to them."

On my view, then, the therapeutic misconception arises when subjects entering research projects mistakenly believe that they are enrolling in a study in Applied POR. Patients participating in bona fide Applied POR are right to expect therapy (experimental therapy). Problems arise when the research in which they are contemplating participation fails to satisfy the principle of clinical equipoise and, thus, fails to count as bona fide Applied POR. The therapeutic misconception, thus, is ultimately a problem with both the content of the research agenda and with how that content is represented. If we are asking the right questions (i.e., clinically relevant questions), and stop misrepresenting the character of non-therapeutic research (i.e., research other than Applied POR), the therapeutic misconception ceases to be a problem.

This last point highlights one of the central lessons of this essay: we cannot successfully protect research subjects from undue harm without attending to the questions we're asking and, thus, to the research agenda. But we cannot make responsible decisions concerning the clinical research agenda without attending to context of practice precisely because determinations of scientific value, or clinical relevance, are themselves morally laden. These determinations shape the content and, therefore, the ethics of clinical practice. Thus, these determinations should be shaped by the norms we deem appropriate in the context of practice: the norms of therapeutic beneficence and non-maleficence.

To the extent that clinical research has provided a solution to the central problem – successfully bridging the epistemic divide between medical theory and practice – it has done so because it is sensitive both to the needs and specificity of clinical practice. When

Applied POR is addressed to the right questions, using the right methods, Applied POR is capable of developing genuine therapeutic knowledge. But this capacity is dependent upon both the methods and the content of the research undertaken. The ethical and epistemological status of Applied POR turns upon both the methods and the content of its activity.

One of the implications of this result is that we must move away from a one-size fits all approach to ethics review. There are many different forms of research involving human subjects, forms of inquiry that are conducted for different reasons, using different methods. Given the different interests served by these diverse forms of human subjects research, and their correspondingly different methods, they are (or should be) governed by correspondingly different ethical and epistemological norms.

In this, of course, I disagree with both the National Commission and others (including the authors of Canada's Tri-Council Policy Statement) who essentially ignore the distinctions between different forms of research involving humans and/or human tissue (including distinctions between medical/biological research and social science and humanities research, between so-called basic research and clinical research, and between different forms of clinical research), presumably because they did not believe that these distinctions were relevant to their ethical analysis. There have been many vocal opponents to this strategy, particularly within the social sciences, and I believe they are right to oppose this strategy. We must develop a system of ethics review that is sensitive to the important epistemological and methodological differences between forms of inquiry. Appreciation of these differences is essential for their ethical analysis.

A second implication is that research ethics must concern itself, not only with the protection of the human subjects of research, but with the protection of patients and, thus, with the research agenda itself. Again, my intention is not to suggest that clinical research or Applied POR should be prioritized over other forms of health research such as research into public health and prevention. Arguably, these forms of research deserve a much larger share of the available resources. That being said, I do maintain that in the case of Applied POR, the crucial question is whether or not the research agenda is responsive to the realities of clinical practice. The best way, I believe, to ensure that it is, is to ensure that determinations of scientific value in this context are consistent with the principle of clinical equipoise (qua epistemic constraint) because the principle of clinical equipoise is indexed to the context of practice. The supposition on the part of the National Commission (and their contemporary commentators) that 'research' and 'practice' are sharply distinct has forestalled rather than facilitated criticism of the research agenda from within the research ethics literature. Insofar as the protection of the human subjects of research is necessarily connected to the content of Applied POR and, thus, to questions about the content of the research agenda, this supposition has also forestalled the development of adequate protections for the human subjects of research. It is my hope that this essay will take us some way toward addressing this problem.

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