CLINICAL TRIALS, CANCER, AND THE EMERGENCE OF HUMAN SUBJECT RESEARCH ETHICS IN CANADA, 1921-1980

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Saskatoon

by

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ABSTRACT

Clinical cancer trials in the 21st century take place only with the ethics review committee’s approval and the written informed consent of human subjects. How and why professionals reached these standards of a modern regulatory framework for clinical research by the late 1970s is the subject matter of this dissertation. An historical examination of burgeoning cancer care and clinical trial programs in Canada offers insight into socio-cultural factors that enabled the transformation of experimental treatment into clinical research. This dissertation is a history of the creation, coordination, and contestation of new practices in Canadian clinical settings wherein surgical, radio- and chemo-therapeutic procedures were devised, evaluated, and eventually regulated. Using historical epistemology and the constructivist methodology of science studies, this dissertation demonstrates that medical research ethics emerged through clinical investigation rather than philosophical speculation.

Since ethically questionable clinical trials usually provoked professional disapproval, public outcry, and official condemnation from the judiciary, clinicians continually modified their research protocols based on empirical evidence and ethical imperatives. Over the decades, new protocols induced changes in the ethical acceptability of human subject research (HSR) and in its regulation. This process culminated with randomized controlled clinical trials (RCTs) in the 1950-1960s, when their ethical rationalization became more problematic. As this dissertation shows, clinical investigators first raised these concerns in the late 1950s, which later resonated among medical professionals, patients, judges, philosophers and others, all of whom contributed to reshaping the ethics of HSR. Renegotiation and reinterpretation of the meaning of ethical HSR occurred through a series of critical junctures: institution-building, technological innovation, inter-professional struggle, exploitation of cancer patients, litigation, and challenges to the culture of clinical experimentation.

This dissertation concludes that both scientific and cultural factors interacted to produce a parallel development of clinical cancer investigation and its ethics, which became embodied in the RCT protocol. Facilitating both the conduct of RCTs and their ethical regulation, protocols generated a feedback loop between the RCT content and the codification of HSR ethics. Ultimately, RCT protocols made possible an increasing professionalization in oncology and an enhanced administrative oversight of clinical research.
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DEDICATION

To my family,
Misha, Vera and Viktor.
CONTENTS

Permission to Use i
Abstract ii
Acknowledgements iii
Dedication iv
Table of Contents v
List of Abbreviations vii
List of Figures ix
List of Tables x

Introduction: Ethics on Trial 1

Chapter I The Rise of Cancer Challenges Therapeutic and Organizational Standards 29
  1.1. Through Invisible to Noticeable: Radiation and Cooperation 33
  1.2. Radiotherapy and Anti-Cancer Initiatives 45
  1.3. Conclusion 58

Chapter II Shifting Sands of Organizing, Problematizing, and Rationalizing Cancer Research in Post-War Canada 60
  2.1. The NCIC: Origins and Objectives 64
  2.2. Betatron and Experimental Treatment 74
  2.3. Isotopes 85
  2.4. Cobalt-60 90
  2.5. Conclusion 105

Chapter III The Hard Way to Randomized Clinical Trials in Canada 108
  3.1. The Untouchables of Medical Practice Reaffirm their Status 111
  3.2. Professionalization of Radiotherapy and Diversification of Surgery 122
  3.3. Chemotherapy Finds a Haven in the Stronghold of Radiotherapists 134
  3.4. Strange Bedfellows 142
  3.5. Conclusion 149

Chapter IV Evolving Standards of Clinical Investigation and its Regulation 152
4.1. Randomized and Not Randomized Clinical Trials 163
4.2. Clinical Trials and Human Subject Research Ethics 179
4.3. Institutions and Regulation of Human Experimentation 199
4.4. Conclusion 209

Chapter V The Construction of Meaning: Ethics in Clinical Cancer Research 211
5.1. Two Uncommon Tumors and One Common Sense 218
5.2. Development of the NCIC Cooperative Program 236
5.3. Investigators’ Consensus, Institutional Regulations, Patient Consent 252
5.4. Conclusion 265

Conclusions 268
Bibliography 273
List of Abbreviations

AECB Atomic Energy Control Board (Canada)
AECL Atomic Energy of Canada Limited
ACS American College of Surgeons
ASCC American Society for the Control of Cancer (US)
BCCI British Columbia Cancer Institute
BCG Bacillus Calmette-Guérin
CAC Clinical Advisory Committee of the NCIC
CCI W.W. Cross Cancer Institute
CCNSC Cancer Chemotherapy National Service Center (US)
CCS Canadian Cancer Society
CDBS Canada Dominion Bureau of Statistics
CMA Canadian Medical Association
CSCC Canadian Society for the Control of Cancer
DCH Dominion Council of Health
DHEW Department of Health, Education, and Welfare (US)
DNHW Department of National Health and Welfare (Canada)
DRB Defense Research Board
FDD Food and Drug Directorate (Canada)
FDA Food and Drug Administration (US)
ICRF Imperial Cancer Research Fund (UK)
MCTRFL Manitoba Cancer Treatment and Research Foundation
MOPP Nitrogen Mustard, Oncovin, Procarbazine, Prednisone
MRC Medical Research Council
NCI National Cancer Institute (US)
NCIC National Cancer Institute of Canada
NIH National Institutes of Health (US)
NRC National Research Council (Canada)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>NSCC</td>
<td>National Study Committee on Cancer (Canada)</td>
</tr>
<tr>
<td>OCI</td>
<td>Ontario Cancer Institute</td>
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<tr>
<td>OCTRF</td>
<td>Ontario Cancer Treatment and Research Foundation</td>
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<tr>
<td>OIR</td>
<td>Ontario Institute of Radiotherapy</td>
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<tr>
<td>PHS</td>
<td>Public Health Service (United States)</td>
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<tr>
<td>PMH</td>
<td>Princess Margaret Hospital (Canada)</td>
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<tr>
<td>RCPS</td>
<td>Royal College of Physicians and Surgeons</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Clinical Trial</td>
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<tr>
<td>SCC</td>
<td>Supreme Court of Canada</td>
</tr>
<tr>
<td>SCF</td>
<td>Saskatchewan Cancer Foundation</td>
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<tr>
<td>SMA</td>
<td>Saskatchewan Medical Association</td>
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<tr>
<td>TGH</td>
<td>Toronto General Hospital</td>
</tr>
<tr>
<td>UICC</td>
<td>Union Internationale Contre le Cancer (International Union Against Cancer)</td>
</tr>
<tr>
<td>UN</td>
<td>The United Nations</td>
</tr>
<tr>
<td>USSR</td>
<td>Union of Soviet Socialist Republics</td>
</tr>
<tr>
<td>UWO</td>
<td>University of Western Ontario</td>
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<tr>
<td>VGH</td>
<td>Vancouver General Hospital</td>
</tr>
<tr>
<td>VLB</td>
<td>Vincaleukoblastine/Vinblastine</td>
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<tr>
<td>WMA</td>
<td>World Medical Association</td>
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</tbody>
</table>
List of Figures

Figure 1-1. Number of Deaths from Cancer for the Registration Area of 1921, 1921-1927.

Figure 1-2. Number of Deaths from Cancer in a Total Population of Canada, 1928-1935.

Figure 1-3. Cancer Clinics in Regina and Saskatoon: Cancer Admissions, Diagnoses, and Mortality, 1932-1937.

Figure 2-1. Number of Deaths from Cancer in a Total Population of Canada, 1936-1951.

Figure 5-1. Anthony Bernard Miller, c.1980.
List of Tables

Table 2-1. Cobalt-60 units in Saskatoon and London, 1951.

Table 2-2. Cancer Patients Treated by Radiotherapy Method, 1951-1955 inclusive.

Table 2-3. Completed Installations of Cobalt-60 Beam Therapy Units, Model A – Eldorado Unit, and Model B – Theratron, October 1951 – March 1955.

Table 3-1. Patient Statistics at the OCI/PMH in 1959.

Table 4-1. Canadian RCTs Reported to the UICC Committee on Controlled Therapeutic Trials

Table 5-1. Constituents of Cooperative Groups in the United States, 1968.
Introduction

_Ethics on Trial_

In early 1891, leading German exponents of scientific medicine aired the idea of patient consent requirement in medical research, formulated the concept of “experimental therapy”, and suggested a blueprint for ethical guidelines on clinical trials.¹ This was a consequence of the Tuberculin scandal. When the new substance, developed by the trained physician Robert Koch for the treatment of tuberculosis, did not meet expectations of several physicians to cure their patients, opponents of purportedly unwarranted large-scale therapeutic application of Tuberculin declared it human experimentation.² A wide use of Tuberculin as a miracle drug, created by the same Koch who had identified the cause of the epidemiologically most important nineteenth-century disease in the tubercle bacillus, revealed how epoch-making bacteriology led to ever-expanding human experimentation.

Like tuberculosis in the nineteenth century, cancer occupied the place of the most significant twentieth-century disease that defied treatment approaches of medical professionals. Similarly, innovations in anti-cancer therapeutic modes produced among physician-investigators waves of euphoria often resulting in reckless clinical trials. For one, in 1959, Canadian investigators, led by Robert Noble and Harold Warwick, used a novel substance Vincaleucoblastine to treat cancer patients unaware of their participation in the clinical trial of the experimental drug.³ When the boundary between treatment and medical experiment shifted, so did the discourse on ethical acceptability of clinical trials. Thus, advances in bacteriology and cancer medicine created an aura of legitimacy around the interference of experimental investigation in conventional medical practice. A debate on the justification of clinical trials and their ethical adequacy had begun earlier, however.

In the eighteenth century, some physicians and surgeons espoused the experimental method, based on testing a hypothesis, accurate observation, rational consensus on and disinterested validation of the observed anatomo-clinical phenomena, to improve their treatment. Medical professionals declared therapeutic experimentation a constituent part of practice as early as 1771. A British surgeon, John Aikin, wrote,

The healing art has its original foundation in experiment. Accident at first made known the virtues of a remedy in some particular disease. Upon the proper attestation of this accidental success, men were induced to try its efficacy in the next case of the same kind that offered. After repeated experiments of this sort, they went farther, and from analogical reasoning ventured to apply the remedy not only in the same disease, but others which either from their cause or symptoms appeared similar.4

The teaching hospital was the institution that allowed organized medicine to do clinical trials systematically. Michel Foucault identified the beginnings of clinical medicine in a shift of finding medical certainty from the observation of individual patients to the multiplicity of individual facts observed in pathological cases.5 Likewise, Ian Hacking argued that imperatives of counting, quantifying, creating norms, correlating, and medicalizing drove medicine since about 1800 and generated its functional principles characterizing interactions among physicians and patients.6 In this setting of looping effects, the medical practitioner, whose calling was to treat, and the investigator, inclined to pursue research, merged in one entity. Accordingly, the “objects of natural knowledge” overlapped with the “objects of moral discourse” intrinsic to clinical medicine.7

The hospital ward created an environment conducive to incremental improvements in therapeutics and surgery. Several reasons accounted for this. One reason was a continuous availability of patients for observation. Second, a relatively regulated regimen and diet allowed the physician to concentrate fully on the management of medical conditions. Third, senior

4 John Aikin, Thoughts on Hospitals (London: printed for Joseph Johnson, St. Paul’s Church Yard, MDCLXCI), 76-77. Italics in the original.
doctors could modify the accepted treatment to attend to unresponsive cases, which made physicians genuine experimenters. Fourth, a collection of observations and further discussions among the professionals afforded an opportunity to follow up on experimental procedures methodically. As John Aikin noted, hospitalized patients became “the most proper subjects of an experimental course,” and the physician-investigator could disregard conventional treatment norms to “exert his genius in any new thought for the benefit of his patient, though unsupported by precedent.”8 The conservative medical profession realized the value of experiments in improving treatments, but it denied that clinical trials constituted a scientific practice requiring a different kind of ethical regulation.

Although clinical trials were not rampant in teaching hospitals and there were seldom more than ten subjects in any given trial at the turn of nineteenth century, the fatal risks of highly experimental procedures proved real on occasion. Such situations occurred due to the inadequate evidence concerning tested remedies, the venturesome approach of investigators who focused much more on benefits of the intervention rather than on its dangers, and the general willingness of participants either to alleviate their suffering or to earn easy money. Considering these trying circumstances, gentlemanly medical practitioners and researchers undertook to devise ethical codes of conduct for human experimentation which could supplement the medical ethics in the tradition of the Greek physician Hippocrates of Cos.

Among the trendsetters in the codification of modern medical practice was John Gregory, a Scottish physician and moral philosopher. In Observations on the Duties and Offices of a Physician of 1770, Gregory provided a response to challenges in the practice of medicine and clinical investigation, compounded by the poor management of medical institutions.9 For Gregory, the utility and dignity of the medical profession required no justification, but what needed questioning was the experimental practice that “require[d] a greater compass of knowledge than [wa]s necessary in any other art […] and sufficiently establishe[d] the dignity of

8 Aikin, Thoughts on Hospitals, 79-81.
the science.” The practitioners’ occupation in this ample field necessitated not only “a strict attention to method”, but also humanity, since medicine was most beneficial to people when it was not converted into a trade that increased prosperity. The emphasis on humanity as a common ground for the physician-investigator and patient-subject shone through Gregory’s work:

Every man has a title to speak where his life or his health is concerned, and every man is entitled to suggest what he thinks may save the life of his friend. […] If a patient is determined to try an improper or dangerous remedy, a physician should refuse his sanction; but he has no title to complain of his advice not being followed, as he has no right to hinder any man from going out of the world in his own way. […] But, in all cases whatever, it is a physician’s duty never to conceal his [patient’s] real situation from the relations.

These propositions resonate with a modern notion of doctor-patient relationship and its focus on autonomy, nonmaleficence, beneficence, and justice, although they originated in a different historical context.

*Medical Ethics* of Thomas Percival, a British physician, was a response to the demand for public health reforms and a radical change in the medical practice within teaching hospitals. In 1803, Percival captured reverberations of the burden of clinical experimentation with new

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10 Gregory, *Observations on the Duties and Offices of a Physician*, 5-6 and 67-84. Gregory gave a broad spectrum of disciplines the basic competence in which was required for an appropriate practice of medicine: anatomy, physiology, natural philosophy (mechanics, hydraulics, optics, pneumatics), chemistry, pathology, surgery, materia medica, natural history (botany, comparative anatomy), mathematics, and the Latin, Greek, French languages.
substances and therapeutic techniques shouldered mainly by the poor admitted to teaching hospitals and infirmaries. As Percival noted:

Whenever cases occur, attended with circumstances not heretofore observed, or in which the ordinary modes of practice have been attempted without success, it is for the public good, and in an especial degree advantageous to the poor (who, being the most numerous class of society, are the greatest beneficiaries of the healing art) that new remedies and new methods of chirurgical treatment should be devised. But in the accomplishment of this salutary purpose, the gentlemen of the Faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trials should be instituted without a previous consultation of the physicians or surgeons, according to the nature of the case.15

This idea of preliminary consultation among specialists seems to be a progenitor of a contemporary committee review of medical research involving human subjects. Despite numerous benefits that the poor patients derived from their hospitalization, there were significant problems related to the hospital economy, such as crowdedness, insufficient ventilation, and improper hygiene, which caused the spread of infection and proved sometimes fatal. In the course of time, these issues were partially addressed through the classification of patients according to their chief complaints and the specialization of available hospital personnel.16 This practice made it possible to assign particular patients to separate wards and even to set up “hospitals for the small-pox, for inoculation, for cancers, &c. &c. […] in different places.”17

**Experimental Medicine in Teaching Hospitals**

In the clinical world of a hospital, reliance on the senses became less important for physicians as relatively controlled experiments gained in significance and physician-investigators secured their authority in the power to count, quantify, and normalize. The nineteenth-century hospital turned into a well-disciplined institution where knowledge accumulation and correlation became the

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16 George Weisz argued that medical specialization was concentrated in academic settings since at least the nineteenth century because it was mainly understood as a function of clinical research and training within teaching hospitals. See G. Weisz, *Divide and Conquer: a Comparative History of Medical Specialization* (Oxford; New York: Oxford University Press, 2006).
foundation for training of the medical discipline.\textsuperscript{18} Arguably, the state itself conferred the honor of self-regulation on the medical profession within the existent political and moral economy.\textsuperscript{19} In these circumstances, the guardians of public health had to take a step forward in modernizing their professional code of ethics by focusing on the rights and duties of the individual. The dignity of the person and of the professional undertaking along with the interests of society warranted that medical experimentation be reduced to the least dangerous activities. A teaching hospital became the institution that created quasi-laboratory conditions for the art of medicine and disciplined the performers in conducting experiments by establishing a hierarchy of relations.\textsuperscript{20}

Illustrating this trend, Max Simon’s \textit{Déontologie Médicale} of 1845 drew a close attention to the question of human experimentation in medicine and the need to delimit it. Covering major perils of improper medical experiments with humans, Max Simon pointed out that only genuine science and sincere love of humanity could save the physician-investigator from an adventurous spirit that did not reflect the link between valid principles and rational therapeutics understood at the time in terms of greater or lesser probability of success.\textsuperscript{21} He rightly asserted that the logic of science employed by the doctors working in hospitals made them the only professionals who operated in such conditions that contributed to the truly useful experimental results which guaranteed, at least on the basis of objectivity, the legitimacy of inferences derived therefrom.\textsuperscript{22} Thus, a new image of the hospital and the conduct of experimentation within its walls endowed the medical practitioners with a gloss of validated activity.

\textsuperscript{20} For secondary literature on the history of modern teaching hospitals, see Joel D. Howell, \textit{Technology in the Hospital: Transforming Patient Care in the Early Twentieth Century} (Baltimore and London: Johns Hopkins University Press, 1995); and David Wright, \textit{SickKids: The History of the Hospital for Sick Children} (Toronto: University of Toronto Press, 2016).
\textsuperscript{21} Max Simon, \textit{Déontologie Médicale ou des Devoirs et des Droits des Médecins dans l’Etat Actuel de la Civilisations} (Paris: chez J.B. Baillière, 1845), 113. This understanding was also manifest in John Gregory’s \textit{Observations} (1770).
\textsuperscript{22} My free translation of the passage from Max Simon’s \textit{Déontologie}, 332: “En considérant ainsi les choses du point de vue exclusif de la logique de la science, il est évident que les médecins chargés du service des hôpitaux sont les seuls qui soient placés dans les conditions qui rendent l’expérimentation véritablement utile, en assurant, sous le rapport objectif au moins, la légitimité des inductions auxquelles elle conduit.”
The addition of ethical norms restraining physicians’ latitude of action secured the pride of place for the hospital as an appropriate institution for carrying out clinical trials. Two principles underlay those norms. First, the experimenter was obliged to bear in mind the immediate interest of the human subject whatever his scientific concern and passion for finding a solution to a fundamental question or for enriching *materia medica*. The second principle, which dated back to the age of Galen according to Max Simon, urged the experimenter to mentally take the position of the human subject and try the suggested unproven course of action on himself.23 This growing visibility of the person’s value in experimental investigations from the perspective of a physician-researcher could be explained by the reasonable expectations to assure fiducial relationships and obviously desirable follow-ups on the ever-extending trials. The latter were undoubtedly more important, for the state bureaucracy was interested in the administrative quantification of health and disease, rather than particular individual demands. As Ian Hacking felicitously put it, “morality and health were always combined in the utilitarian mind,” thereby making possible a cross-fertilization of social policies and medico-scientific activities.24 Vital statistics gained increasing appreciation in the nineteenth century because the industrializing nations continued to lose indispensable human resources fueling economic growth due to epidemics.

Epidemiology alongside other medical research were already vigorously elaborated by leading clinical investigators. Claude Bernard postulated the tripartite coalition of pathology, therapeutics, and physiology as the essential combination for experimental medicine.25 Applying himself strenuously to physiology, Bernard could speak from experience that medical investigation was the most complicated among experimental sciences and, thus, it necessitated experiments “in hospitals, amphitheatres, or laboratories, [to] stir the fetid or throbbing ground of life.”26 For Bernard, the experimental method brought about the scientific revolution, which meant placing scientific criteria in the foreground of research and replacing personal authority

therefrom.\textsuperscript{27} It was possible for medicine to become scientific exactly because the experimental method in the sciences was uniform in the abstract: observation of phenomena showing facts, reasoning on the basis of given facts and their comparison, a hypothesis leading to devising controlled experiments with the aim to establish new facts. Bernard advocated parceling out of the experimental domain into simpler parts that could be better cultivated on their own, yet he gainsaid the claims that specialization in the theory of science was of any value.

A grave peril of medical specialization lay in therapeutics without knowledge of general physiology, when physicians used toxic or allegedly medicinal substances in an attempt to treat the ill.\textsuperscript{28} Bernard indicated that in his time “physicians already make too many dangerous experiments on man, before carefully studying them on animals. I do not admit that it is moral to try more or less dangerous or active remedies on patients in hospitals, without first experimenting with them on dogs…”\textsuperscript{29} He had demonstrated that knowing how and under what conditions to experiment with animals properly could supplement available evidence from the allied disciplines and provide results that would be so conclusive as to deter any poorly justified human trials. Bernard was engaged in discussing a right to carry out clinical trials as far as physicians made therapeutic investigations on their patients and surgeons performed vivisections on their subjects routinely. In delineating the limits of human experimentation, he stated, “it is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit.”\textsuperscript{30} Rejecting any human trials that might be highly advantageous to the advancement of science or to the health of others, Bernard made it clear that “performing experiments and operations exclusively from the point of view of the patient’s own advantage does not prevent their turning out profitably to science.”\textsuperscript{31} This proposition represents a summary of the preceding intellectual legacy on the benchmarks of human experiment and its

\textsuperscript{27} \textit{Ibid.}, 40.

\textsuperscript{28} \textit{Ibid.}, 65. Claude Bernard defines general physiology as “the basic biological science toward which all others converge [and which] problem is to determine the elementary condition of vital phenomena.” By comparison, “physiology – the science whose object it is to study the phenomena of living beings and to determine the material conditions in which they appear” (66). Finally, by referring to therapeutics, Bernard means a corpus of knowledge that “lead[s] us, on the one hand, to prevent the development of morbid conditions, and, on the other, to fight their results with medical agents, i.e., to cure the diseases” (1-2).

\textsuperscript{29} \textit{Ibid.}, 102.

\textsuperscript{30} \textit{Ibid.}, 101. Curiously, Bernard “consider[ed] it wholly permissible, however, and useful to science, to make investigations on the properties of tissues immediately after the decapitations of criminals.”

\textsuperscript{31} \textit{Ibid.}, 102.
ethics. Medicine was turning toward its durable scientific route in the second half of the nineteenth century.

Bernard’s contemporary, Louis Pasteur set the stage for the rise of the bacteriological phase in the evolution of medicine. A chemist by training, Pasteur realized early in his career that scientific questions could be the most effectively answered in the laboratory environment with controlled conditions. In the mid-nineteenth century, a fertile ground was prepared for tackling the pressing problems of contagion by extending the practices of hospital hygiene to the public domain. A fierce debate between the adherents of miasma and contagion theories of disease still raged, for the incontestable experimental proof of the correctness of either was lacking. The chemist’s outlook of Pasteur was decisive in enabling him to fathom that inorganic chemicals remained constant in amount and could not be responsible for the spread of disease. Public health campaigns, targeted at limiting epidemics at the time, served a good illustration for Pasteur that entities producing diseases were growing and multiplying, which suggested that the cause of illness was something with living powers. Medical reformer-hygienists induced Pasteur’s thinking along these lines. The hygienist movement, already well-organized in terms of public funding and human resources, found in Pasteur and his associates “a fulcrum” that justified the state strategies of making scientific hygiene a link connecting the laboratory with the hospital and the public.32 As Bruno Latour, a philosopher and sociologist of science, put it, “Pasteurians […] were like the first observation balloons [that] made the enemy visible.”33

Unlike physicians in hospitals and private practice, Pasteur was reluctant to indulge in human experimentation, yet human trials did take place in the face of an immediate need. This was the case in 1885, when Joseph Meister and Jean-Baptiste Jupille, two boys suffering from bites of mad dogs, received anti-rabies inoculations developed in Pasteur’s laboratory.34 These were publicly celebrated cases of scientific-medical success, but there were at least two less successful attempts to save victims of rabies which Pasteur recorded in his laboratory notebooks.35 Pasteur apparently chose to conceal equivocal aspects of his clinical trials so that

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33 Ibid., 34.
35 Ibid., 194-203.
his accounts of human experimentation raise no questions from the Academy of Science of Paris and the news about the validity of the germ theory of disease propagates.

In Berlin, Robert Koch refined Pasteur’s technique of culturing disease-causing organisms outside the body and demonstrated through pioneering work on a complete life cycle of anthrax a convincing proof of a causal relation between a specific disease and a particular microorganism. Not only did Koch bridge the gap between laboratory science and its applications, including in clinical medicine, by advancing the microbiological achievements of his forerunners, but he also made scientific hygiene a reality. Koch managed to find keys to two puzzles challenging public healthcare in the period of increasing industrialization and urbanization. Tuberculosis was one, and cholera – the other. By demonstrating the pathogens of those infectious diseases, he laid down a foundation for a new classification of diseases based on the identification of their specific causative agents in addition to clinical symptoms. The year of 1882, when Koch announced the discovery of the tubercle bacillus, marked a shift in the understanding of a complex interplay of science and medicine.

Claude Bernard’s proposition to consider as “the true sanctuary of medical science” a laboratory, rather than a hospital, where doctors should observe and study human diseases by therapeutic interventions, acquired a new meaning. It was a paramount accomplishment of Koch to bring laboratory experimental analyses of life in its normal and pathological manifestations together with clinical observations of diseases in the hospital ward. Bacteriological hygiene from its inception aimed at reproducing results obtained from cell cultures and from the animal models in humans, who initially provided the material for laboratory research. A relatively fast invention and introduction of Tuberculin – an agent designed to treat tuberculosis – resulted from these considerations.

37 Gradmann, Laboratory Disease, 70.
38 Bernard, An Introduction to the Study of Experimental Medicine, 145-146 and 225. Bernard suggested “medicine does not end in hospitals, as is often believed, but merely begins there. In leaving the hospital, a physician, jealous of the title in its scientific sense, must go into his laboratory; and there, by experiments on animals, he will seek to account for what he has observed in his patients, whether about the action of drugs or about the origin of morbid lesions in organs or tissues. There, in a word, he will achieve true medical science” (147).
The development of Tuberculin followed quite a standard pattern. A series of hypotheses based on the natural history of tuberculosis, a set of tests in a nutrient medium, studies on different animals, self-experimentation, trials in a small group of healthy individuals and a relatively large cohort of patients. In September of 1890, the Charité hospital in Berlin became the first site of a full-scale clinical trial, and already in November the preparation became available to physicians.39 Koch noted in the accompanying report on Tuberculin that human sensitivity to it was significantly higher than that of animals, yet he did not provide any details on the medication’s composition. The scientific-medical community issued a clarion call for action on the part of the state only by the end of the year, when a critical evaluation of Tuberculin started to outweigh the clinical value of the drug.40

At the end of the nineteenth century, the difference between treatment and medical research involving humans, as reckoned by the experts, impinged upon the therapeutic intentionality of experimental medications’ use. If the drug showed positive preliminary results after laboratory and animal tests, the criteria for labelling the practice of its clinical usage as therapy or experimentation were proportions of a therapeutic success – cured patients, and a therapeutic failure – patient mortality. In the case of Tuberculin, a gradually revealing number of successes was lower than failures, so the justifiability of its mass use became cast in doubt. Ethical issues entered the discussion of scientific-medical matters. On the one hand, the sensationalism of bacteriological advances prompted investigators and physicians to focus on the benefits of Tuberculin to the public at large and disregard its risks. On the other hand, the state and professional interests generated a trend of disinclination to keep a potentially valuable medication from the multitude of patients suffering from the epidemic.41

The convergence of experimental practices and therapeutics came to prominence not because the Charité hospital represented it, but because human experimentation went beyond its walls. On the background of this tarnished public image of the teaching hospital, members of the medical profession, scientific investigators, and public health administrators had to find a compromise. The principles of medical ethics were violated in the thrill of the chase for quick fixes to complex epidemiological phenomena. Increasingly sweeping epidemics in the virtual

39 Gradmann, *Laboratory Disease*, 97 and 123.
41 Gradmann, *Laboratory Disease*, 142-144.
absence of reliable treatments necessitated more clinical trials that smacked of human experimentation. In addition to tuberculosis, Koch’s identification of the cholera bacterium, among other pathogens, prompted the public health services to take prophylactic measures of disease control. Quarantine rules, the application of medical statistics to social determinants of health, and the promotion of bacteriological hygiene contributed to a reduction of the death toll in epidemics.

**Reportable Diseases and Epidemics**

Since the mid-1880s, the propagation of prophylactic measures in western knowledge economies was predicated on a doctrine of avoidable disease. The latter meant that it was possible to prevent an epidemic by reporting all potentially high-risk cases to physicians. Then health authorities determined the severity of illness and estimated the number of afflicted individuals, which in turn protected the healthy people. As Charles Rosenberg, a historian of medicine and science, rightly put it, “society received a measure of emotional reassurance and clinical efficacy in exchange for the increased status and autonomy of medicine.” Following this logic, national leaders of countries partaking in international trade were anxious to enact public health legislation regulating the course of action in epidemic emergencies. In Great Britain, for example, the *Infectious Disease Notification Act* of 1889 and the *Prevention Act* of 1890 stipulated that potentially ill persons could be “removed to a hospital” or any suitable place on the strength of a “certificate signed by a legally qualified medical practitioner”, and if not sufficient, “by order of any justice […] at the cost of the local authority.”

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communicable diseases were listed in the acts and the authorities formalized penalties along with enforceability measures to guarantee a proper execution of regulations.

Another consequential effect of making specific diseases notifiable related to the empowerment of the patient, however minimal, against the arbitrariness of the medical authority. Tuberculosis and cancer, like a multitude of other diseases, were incurable at the time, and hospitals, not to mention the general practitioners, tended to reject poor patients diagnosed with a medical condition for which no treatment existed. The official introduction of policies on notification of diseases aimed at providing incentives for both patients, who could get at least basic care, and doctors, who were remunerated for registering notifiable cases.

In the Dominion of Canada, by contrast, health care authorities enacted regulations that penalized medical officers who failed to report an outbreak of epidemic disease among patients in their constituency as early as 1884. Although the Canadian government undertook sanitary reforms patterned on the British model of 1875, medical officers in Ontario modified the first Public Health Act of 1882 to conform to local requirements. Having received news on the advances of bacteriology in Europe, the Canadian Medical Association exerted its influence on political circles, in particular on Prime Minister John A. Macdonald, to create an administrative hierarchy of responsibilities for public health maintenance. The legislation provided for the empowerment of local health boards to regulate sanitary conditions, and for bureaus of statistics, financed by the government with the stipulation that policies of the provincial agency were strictly adhered to. This healthcare model gradually became adopted by the majority of Canadian provinces.

Epidemic disease was a powerful driver that propelled rapid sanitary reforms in Canada. Wide-ranging measures were introduced to fight the notifiable ills, venereal diseases, and tuberculosis across the country. A degree of success in managing the spread of infections could be observed before long, but its inherent limitations struck the medical officer’s eye as the Spanish influenza made a visitation in 1918. Shortcomings of hygienic bacteriology surfaced in the face of an imminent peril impossible to avert. People’s trust in the omnipotence of medical

47 Christopher Rutty and Sue C. Sullivan, This Is Public Health: A Canadian History (Ottawa: The Canadian Public Health Association, 2010), 1.10-1.11.
48 Ibid., 1.3-1.9.
49 Ibid., 1.8.
science was eroded because of numerous physicians and investigators who had succumbed to flu. Established hygienic and therapeutic norms betrayed how powerless medicine might become in the absence of a firm scientific basis. Regardless of all substantial gains of medical science in the heroic period of “microbe hunters”, the science was enriched by its failures.\textsuperscript{50} Under the circumstances, the Spanish influenza possibly had a role in accelerating the creation of a Federal Department of Public Health.\textsuperscript{51} Following a period of public criticism, political apathy, and professional inaction in times of epidemic crisis, Canadian society responded by forming the agency that could make up existent deficiencies in health care.

With the Department of Public Health emerging on a national scale, three levels of government introduced a more coherent system of managing future epidemics by coordinated efforts, feedback mechanisms, surveillance and organization of community interventions.\textsuperscript{52} To complement this promising development, the Dominion Council of Health (DCH) was founded. The DCH served as an advisory body that provided a forum for discussing input from almost all stakeholders in public health.\textsuperscript{53} A symbol of the new order was the involvement of universities “representing academic and scientific expertise in medicine, public health and laboratory research.”\textsuperscript{54} Therefore, medical academicians were provided with opportunities to reshape healthcare policies so that they adhered to the emerging principles of scientific medicine.\textsuperscript{55}

More importantly, the two-agency organization facilitated standardization and classification within the scientific-medical domain. Federal commitments to invest in uniform

\textsuperscript{50} My free translation of a proposition by a Russian physician-investigator Vikenty V. Veresayev, “исторія медицины показываетъ, что теперешняя наука наша, несмотря на все её блестящія положительныя приобретения, всѣ‐таки больше всего [...] обогатилась именно своими потерями. Записки врача [Physician’s Notes] изд. 2‐ое (С. Петербургъ: Типографія А.Е. Колпинскаго, 1901), 115‐116.

\textsuperscript{51} Mark O. Humphries, The Last Plague: Spanish Influenza and the Politics of Public Health in Canada (Toronto: University of Toronto Press, 2013), 168-169. The bill on the Department’s formation was approved by the Royal Assent on June 6, 1919.

\textsuperscript{52} Ibid., 178.

\textsuperscript{53} Chaired by the federal Deputy Minister of Health, the Council comprised “the provincial chief officers of health, and five appointed members, including representatives from organized labour, women’s groups, social service agencies, agriculture, and universities.” See Rutty and Sullivan, This is Public Health: A Canadian History, 2.19.

\textsuperscript{54} Ibid., 3.2.

\textsuperscript{55} For historiography on a seemingly unavoidable tension between scientific medicine and clinical practice, consult Steve Sturdy, “Looking for Trouble: Medical Science and Clinical Practice in the Historiography of Modern Medicine,” Social History of Medicine, 24, no.3 (2011): 739-757.
health programs countrywide played a considerable part. The Federal Department of Public Health provided conditional grants-in-aid to the provinces to ensure a strict conformity to collegially agreed courses of action.\textsuperscript{56} Such allocation of funds channeled many initiatives into a predetermined, strategically planned course. For one, a public health infrastructure enhancement took priority after a general assessment of key operational capacities. Large projects to build more testing laboratories and all-purpose hospitals got underway in the 1920s.\textsuperscript{57}

The Federal Department of Public Health along with the DCH engaged in collecting vital statistics and classifying diseases according to a prearranged scheme. The importance of this scheme could not be overestimated in that the factor of comparability underlay it. In the early 1920s, provincial authorities started assembling numbers on mortality by causes of death – categorized in chronic conditions, communicable diseases, degenerative ills, and others – keeping to a uniform system.\textsuperscript{58} A list of notifiable diseases was standardized across the provinces and a report on their incidence reached the federal government in 1922.\textsuperscript{59} A compilation of numbers in reports on vital statistics indicated nearly regular patterns of disease incidence from year to year. Comparisons of tabulated data over longer periods, however, sparked a realization that a new epidemic was creeping into figures. Malignant diseases were on the rise, as mortality rates indicated.\textsuperscript{60} The second all-Canadian annual report on vital statistics of 1924 revealed that an epidemic of cancer was taking shape.

**Thesis Statement and Analytical Framework**

When the treatment methods were based on the expertise of several physicians or surgeons, the distinction between a therapy and a therapeutic experiment seemed to make little sense. As this dissertation shows, almost every treatment was to some degree experimental. Tuberculin marked the beginnings of rational therapeutics for specific disease entities. Essentially, rational

\textsuperscript{57} *Ibid.*, 293.
\textsuperscript{59} Humphries, *The Last Plague*, 179.
therapeutics implied that experimentally used treatments had properties that had been established provisionally in the laboratory. With the doctrine of rational therapeutics, a clinical trial acquired a broader meaning. Where physicians increasingly used investigative substances or procedures to treat patients without admitting the experimental side of this practice, the application of medical ethics became a concern. Even so, physicians tapped into the professional codes of ethics in their attempts to regulate human subject research. Over time, these many efforts resulted in both successes and failures. Medical ethics became less applicable to the practice of human research as medicine came to be more disease-centered and state-backed. By the early twentieth century, a tension between the increasing use of patients in clinical investigation and the use of medical ethics to regulate it became perceptible. Guidelines for medical research involving humans originated from this tension.

Contingent on the hope for cure and the statistics of survival, clinical trials seemed inextricable from medical ethics until analogous ethical principles for human research came into being.61 Imperatives of common morality and cultural norms dictated acceptability of a variety of ethical standards in human research.62 Since ethically dubious medical investigations usually provoked professional disapproval, even public uproar, and official condemnation from the judiciary, it may be argued that these very clinical trials indirectly induced the elaboration of adequate human subject research guidelines. To assess this argument, I examine how the practice of clinical trials evolved along with its ethical regulation in Canada. Specifically, I analyze the evaluation of new anti-cancer treatments in clinical investigation to demonstrate why its ethics changed and what factors contributed to these changes.

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62 Often used synonymously, the terms ‘ethical’ and ‘moral’, however, need to be distinguished. I am in accord with Lorraine Daston and Peter Galison who rightly put it, “… ethical refers to normative codes of conduct that are bound up with a way of being in the world, an ethos in the sense of the habitual disposition of an individual or group, while moral refers to specific normative rules that may be upheld or transgressed and to which one may be held to account” (italics in the original). Lorraine Daston and Peter Galison, Objectivity (New York: Zone Books, 2007), 40.
I associate the history of clinical cancer investigations with human research ethics because both of them are intertwined within the overall pattern of medical experimentation. As malignant tumors can develop in all four human tissue types, cancer medicine depends on collaboration in laboratory and clinical sciences, statistics, and epidemiology. Professionals in these fields, historically, have pursued not quite comparable avenues of research and their understanding of the ethical itself have had subtle nuances. Further, human research ethics in the realm of cancer therapy development has been and continues to be a controversial topic. Moral philosophers, health activists, lawyers, journalists, judges, and pharmaceutical industry representatives have increasingly mediated interactions among physicians and investigators in the public forum. In this respect, a medical historian Harry Marks noted that in cooperative clinical trials “potential for conflict was not confined to individuals with different scientific orientations or professional training,” but it also involved the “immorality of commerce” in its corporate undertakings and the “ideological base of support for such ventures.” Hence, a tension between the practice of clinical investigation and its ethical regulation grew during the twentieth century. However, this tension became more manageable as designs for clinical investigation, protocols, developed into instruments for the administration of research.

In western medicine, the word ‘protocol’ has two meanings that relate to the laboratory and clinical practice. The protocol as a detailed plan of an experiment or a treatment has

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64 I use the terms ‘cancer’, ‘malignant tumor’, and ‘neoplasm’ interchangeably in this dissertation to refer to what medical researchers, general practitioners, and health officers at the time called a number of diseases whose chief characteristic was a “rapid, uncontrolled division of the cell that constitutes the main difference between normal growth and cancer growth.” See John W.S. McCullough, the first Chief Provincial Health Officer of Ontario and a Secretary of the Cancer Committee under the Health League of Canada, used this definition in his article “What is Cancer?”, a part of the all-Canadian series The Cancer Crusade – a public campaign to contribute to health education on and the prevention of cancer. Article no. 2, 15 July 1937. In the Provincial Archives of Saskatchewan (hereinafter PAS), R-321.1 Saskatchewan Cancer Foundation, file 9.2. The German physiologist Karl Friedrich Burdach coined the term ‘neoplasm’ (literally a ‘new formation’) in the early nineteenth century. See Ernest Klein, A Comprehensive Etymological Dictionary of the English Language (Amsterdam, New York: Elsevier, 1966), 1039.


66 I use the term ‘western medicine’ to differentiate it from ‘non-western’ or ‘traditional’ medicine that are beyond the scope of this project. The Merriam-Webster’s Medical Desk Dictionary (Thomson Learning: Gale Research, 2003) defines ‘protocol’ as follows: “1. An official account of a proceeding; especially: the notes or records relating
accompanied the scientific method since the times of Hippocrates of Cos in Ancient Greece, which evidence is in the word’s etymology.67 From the Middle Ages to the Enlightenment, physicians were not averse to compile protocols for testing substances of potential therapeutic value.68 By the twentieth century, clinical trials turned into a relatively reliable mechanism for evaluating therapeutic efficacy through elaborated research protocols. Peter Keating and Alberto Cambrosio, historian-sociologists of science and medicine, argued that the emergence and development of randomized controlled clinical trials (RCTs) in cancer encapsulated a platform for scientific medicine and a new style of practice amounting to “the constitution and administration of protocols” and a network of relations underlying it.69 Keating and Cambrosio defined protocol as “a particular way of organizing and managing biomedical activities.”70 This interpretation of the clinical trials’ domain is plausible, but it de-emphasizes a cultural embeddedness of the style of practice.

In this dissertation, I consider protocols not as mere fine-tuning tools, nor as modes for ordering the style of practice, but as an elastic system of conventions open to a continuous collective negotiation. Investigators with insider knowledge of clinical trials negotiated their criteria of feasibility, proof, and of ethical acceptability in the context of external constraints on the conduct of medical research. In Canada, these constraints took the form of reconfigurations in government-backed programs of organized research, a reluctance of medical specialists to abandon the case-based method of knowledge production, challenges in the adaptation of medical ethics to human research regulation, conflicting disciplinary interests in using cancer

to a case, an experiment, or an autopsy; 2. A detailed plan of a scientific or medical experiment or treatment.” Another authoritative reference, Stedman’s Medical Dictionary (Philadelphia: Lippincott Williams & Wilkins, 2007) has only one definition for ‘protocol’ – “a precise and detailed plan for the study of a biomedical problem or for a regimen of therapy.”

67 Klein, A Comprehensive Etymological Dictionary of the English Language, 1259. Protocol, n. — Middle French prothocale (F. protocole), from Middle Latin protocolum, from Late Greek πρωτόκολλον, ‘the first leaf glued to the papyrus roll’, which is compounded of Greek πρωτός, ‘first’, and κολλα, ‘glue’.


70 Ibid., 32.
treatment modalities. Thus, I examine a conversion of human experiments into therapeutic research based on retrospective studies of cases and then into RCTs to shed light on changing meanings of human research ethics revealed through the emerging investigative practices.

I propose that research-minded physicians and surgeons in their quest for effective cancer treatments constantly overhauled study protocols by assimilating into them both empirical evidence and ethical imperatives to achieve the set objectives. Protocols, therefore, reflected a cultural milieu in which scientific-medical investigations were performed. Experimental designs became more complex over time, as did the ethical justification of clinical investigation. Innovators of medical experiment also spurred the progression of therapeutics and the formation of clinical science guided by professional ethics. At the turn of the twentieth century, William Osler stated of the conduct of human experiment:

The limits of justifiable experimentation upon our fellow creatures are well and clearly defined. The final test of every new procedure, medical or surgical, must be made on man, but never before it has been tried on animals. […] For man absolute safety and full consent are the conditions which make such tests allowable. We have no right to use patients entrusted to our care for the purpose of experimentation unless direct benefit to the individual is likely to follow. Once this limit is transgressed, the sacred cord which binds physician and patient snaps instantly.71

Osler outlined a bond between therapeutic research and medical ethics in 1907. By drawing his colleagues’ attention to this bond, Osler also suggested that it had already begun to disintegrate. Clinical trials gained momentum as disease entities, like cancer, and novel treatments for them generated both enthusiasm and concern among the medical profession.

In the first half of the twentieth century clinical trials and their changing designs developed through countless failures, while their underlying ethics centered on attempts at therapeutic progress. As a trial-and-error method involved failure of potential treatment as a necessary element in the randomized clinical trial, the ethical justification of human subject research became more problematic. This issue, I argue, found its initial expression in clinical investigators’ considerations, and then resonated in reflections among medical professionals,

patients, judges, and others, all of which contributed to reshaping the concept of ethical human subject research. Medical researchers often resisted this purported encroachment on their considerable latitude in professional activity by glossing over facts and making the outsiders’ demands seem unimportant. Still, discussions amid investigators on how to make clinical trials more acceptable, at least to an adequate standard of the time, stimulated a gradual renegotiation and reinterpretation of the meaning of ethical human subject research. Its ethics involved coming to grips with the uncertainty and failure inherent in clinical trials. The matter was how to communicate these probabilities and prepare both clinical researchers and patients for contingencies. To what extent was it possible to make the patient aware that the investigator cared about the individual subject as well as the collective object of clinical work?

My inquiry into the evolution of clinical cancer trials and the ethics of human research in Canada builds on constructivist studies in history of science and medicine. I adopt this methodological approach informed by ideas of Ludwik Fleck, Ian Hacking, Harry Marks, Peter Galison, and Jan Golinski to evaluate how scientific and cultural factors interacted to produce a parallel development of clinical cancer research and its ethics.

In *Genesis and Development of a Scientific Fact*, Ludwik Fleck, a progenitor of the constructivist approach, explains how a scientific ‘thought collective’ purposively directs the legitimization of a particular interpretation of facts by logically conforming them to the system of a ‘thought style’ in its cultural context.72 Hence, Fleck argues, the ‘thought collective’ manages the exoteric knowledge of the ‘thought style’ by a cooperative abstraction that determines what can be pragmatically applied in practice. This culture of thought collectives underlies the mechanisms of communication and the possibility of transfer of a sustaining fund

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of knowledge to new locations. In relation to my analysis of research protocols’ language, I accept Fleck’s proposition that “communication never occurs without a transformation, and indeed always involves a stylized remodeling, which intracollectively achieves corroboration and which intercollectively yields fundamental alteration.”73 Along these lines, I suggest that cancer investigators tried to keep their practices immune from externalities, including ethical impositions.

Addressing the problem of construction, Jan Golinski, a historian of science, discusses the scientists’ use of language as a dual activity encompassing the production of meaning and the act of persuasion.74 Golinski frames constructivism as a “methodological orientation” that articulates the role of humans as social actors in the making of scientific knowledge locally with material and cultural resources.75 Peter Galison adds to this understanding of constructivism that science is about local interests reflected in socio-economic and psychological forces operating at several levels. Echoing Fleck’s argument, Galison points out, “experimental knowledge should not be considered autonomous at all, so heavily is it ‘theory laden’.”76 Yet, my analysis of clinical trials as mechanisms for refining experimental knowledge builds on Ian Hacking’s claim that “Experimentation has a life of its own.”77 In connection with cancer treatment development, this meant that a medical experiment could have been the starting point of hypothetico-deductive method that researchers usually conceptualized as a sequence of hypothesis-calculation-experimentation.

Through a constructive process of creation, coordination, and contestation, experimental knowledge gains a wider acceptance and becomes exoteric eventually. This process takes prominence when an internal mismanagement or an external pressure leads to a clash of

71 Ludwik Fleck, Genesis and Development of a Scientific Fact, 111.
73 Ibid., 6.
interests. A need for mediation induces the formation of a ‘trading zone’ in which discrete realms of meaning are restricted and adjusted for the emergence of new meanings acceptable at a given time and place. Galison makes it clear that this exchange needs a coordination of action but it does not necessitate a complete translation of knowledge. According to Galison, “in the trading zone, where two webs meet, there are knots, local and dense sets of quasi-rigid connections that can be identified with partially autonomous clusters of actions and beliefs.”

This happened, for instance, when clinical investigators specialized in two different cancer treatment modalities developed protocols of combined therapy evaluation. A variant of this interaction may occur in a disagreement among investigators on the ethical acceptability of a treatment comparison within the clinical trial. To demonstrate that clinical research is a social process at its core, which inevitably involves the use of persuasion and power, I use the concept of ‘trading zone’ in this dissertation. A protocol, as a ‘trading zone’ for investigators and as an institutionally-supported plan of clinical procedure, became an indispensable part of medical research and practice following an erosion of trust in clinician-investigators during the twentieth century.

Placing this Dissertation

This dissertation contributes to historiography in the history of medicine and science, and its several sub-fields. These include Canadian human subject research, clinical trials, cancer treatment and investigation, medical and research ethics, technology in cancer surgery and radiotherapy, anti-tumor chemotherapy. To a lesser degree, this project adds to historiography on

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78 For a concrete example, see Christopher Lawrence, “Incommunicable Knowledge: Science, Technology and the Clinical Art in Britain 1850-1914,” *Journal of Contemporary History* 20, no.4 (1985): 503-520.


81 Marks, *The Progress of Experiment*, 240.

the organization of institutions for cancer treatment and investigation, governance of medical research and its legal foundations, and professionalization in oncology. The scope of this introduction allows me to discuss only a few histories representing a cross-section of literature relevant to themes covered in this dissertation.

In Canada, a medical research community emerged simultaneously with the discovery of insulin in the early 1920s, when several university-based scientists combined potentials of biology and chemistry with pre-clinical programs of investigation. The ensuing interdisciplinary field of biomedicine was conducive to uninterrupted studies. This also meant that private and corporate funding enhanced scarce university support of biomedical investigations, which gradually expanded the institutional core of medical research. Alison Li, a historian of science and medicine, explored how and why a small community of Canadian researchers “burgeoned into a systematic, large-scale enterprise involving teams of professional scientists and dozens of laboratories in universities, government, and industry” by 1950. Likewise, in this dissertation I trace how cancer research initiatives came to fruition with the formation of the National Cancer Institute of Canada in 1947. The exceptional few cancer specialists engaged in investigation transformed their sideline work into a professional occupation. A comprehensive program to manage the problem of cancer in Canada emerged as health officers declared an “epidemic” of the malignant disease, the public perceived its imminent threat, and the medical profession increasingly resorted to innovations in science and technology.

Innovations that worked at an atomic scale underlay this program. Radioisotopes became part of the mid-twentieth century “episteme of understanding life in molecular terms.” Angela Creager, a biochemist and historian of science, argued in Life Atomic that the use of

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83 Robert Ramsay Wright and Archibald B. Macallum, both of the University of Toronto, were early exponents of this field. See Alison Li, J.B. Collip and the Development of Medical Research in Canada: Extracts and Enterprise (Montréal and Kingston: McGill-Queen’s University Press, 2003), Chs. 1-2. See also Michael Bliss, The Discovery of Insulin (Chicago: University of Chicago Press, 1982), passim.


85 Li, J.B. Collip and the Development of Medical Research in Canada, 172.


radioisotopes spread to medicine, biology, and other non-military domains in the United States because of two mutually-supporting factors. One reason was that nuclear physicists tried to solidify their increased weight in the scientific community after World War II. The other determinant was the government’s strategy to represent its commitment to the civilian development of nuclear energy as important as its military mission in harnessing the atomic power. In this context, I analyze how medical uses of radioactive sources created favorable conditions in Canada to organize and centralize cancer care at least a decade prior to World War II. As this program continued unfolding in the 1940-1950s, some Canadian cancer investigators increasingly tapped resources designated for radiation research to promote specialization in radiotherapy and to create a counterbalance to cancer surgeons holding sway in the management of malignant disease. This dissertation, therefore, relates to Charles Hayter’s historical study of Canadian radiotherapy by looking into cancer control programs through the lens of disease-technology interaction.88 Hayter, a therapeutic radiologist and historian, argued that costly processes of designing experimental therapies and of delivering them to patients without a significant variation across Canada justified government intervention in medical practice, previously a free enterprise, by introducing radiotherapy in cancer programs.

Probing this complex relationship between government-funded research and duties of physician-investigators during the Cold War, Gerald Kutcher, a clinical physicist and historian of science, analyzed experimental radiation studies involving humans at the University of Cincinnati in the United States. Kutcher argued in Contested Medicine that investigators regarded radiotherapy trials with critically-ill cancer patients as ethically acceptable in the late 1950s and the 1960s since they ensued from a consensus on the need for radiation research by the political and the scientific-medical elites.89 Suggesting that medical research and its ethics changed in step with locally-adopted standards of investigators and with the war-effort demands of state officials, Kutcher demonstrated that arguments in favor of experimental studies underwent adjustments in response to political forces. This argument coincides with my

interpretation of cancer clinical trials as fluid media wherein researchers form a consensus allowing for institutional, political, and socio-economic factors.

According to Ilana Löwy, a historian of medicine and biologist, some medical researchers began strategically adopting a “science-laden” principle of randomized controlled clinical trial (RCT) by taking advantage of reforms in the organization of scientific investigation following World War II.90 As Löwy argued in Between Bench and Bedside, this adoption had a potential to consolidate the prestige of medical elite and to enhance the dominance of clinicians at teaching hospitals over other physicians and surgeons.91 In Canada, however, a close collaboration of the medical research establishment and the government culminated in the unique atmosphere that delayed the introduction of multimodal cancer RCTs until the 1960s. Although leading clinician-investigators secured the support of statisticians who added a gloss of objectivity to medical research, there was little need to justify the legitimacy of non-randomized clinical trials. As this dissertation shows, only when radiation specialists contested the therapeutic evidence of surgeons and chemotherapists did the enterprise of clinical experiments started changing toward RCTs. The other reason lay in Canadian cancer researchers’ involvement in RCTs conducted during the 1960s in the United States and Great Britain. Researchers, administrators, and politicians who allocated public funds scrutinized newly introduced RCTs as a technology to streamline cancer treatment. Proponents of both randomized and non-randomized clinical trials tried to protect themselves from criticism by increasingly embracing statistics.92 This was evident in the case of cancer radiotherapy.

Radiotherapists in Great Britain, and later in Canada, employed the RCT approach to the evaluation of novel therapeutic methods as a tool to further their professional interests in cancer treatment. In A History of Lung Cancer, Carsten Timmermann, a historian of science and medicine, discussed how surgeons’ inability to deliver the successful therapeutic results enabled

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91 Ibid., 53.
92 See Marks, The Progress of Experiment, 129. By comparison, Theodore Porter argued in Trust in Numbers that the prevalence of quantified information and statistical power was the result of insecure and contested disciplines operating in an environment of cultural diversity, rather than the product of a monolithic and constantly expanding scientific enterprise. Porter concluded that the constructed numerically objective knowledge had sway on the consent of a culturally diverse public. See T.M. Porter, Trust in Numbers: The Pursuit of Objectivity in Science and Public Life (Princeton, N.J.: Princeton University Press, 1995).
specialists in radiotherapy to initiate a series of RCTs in lung cancer.\textsuperscript{93} Timmermann argued that “ethical difficulties were integral to the whole enterprise of organizing clinical trials for cancer therapies.”\textsuperscript{94} In this dissertation, I propose that the ethics of clinical cancer research varied depending on a collective agreement of investigators, administrators, and of other interested parties on the ethical acceptability of trials under given circumstances. Thus, changeable ethical difficulties became integral to the process of conducting clinical research because they were one of the bargaining chips in negotiations on the adequacy of this or that cancer trial.

Even though narratives of progress appear to predominate in the historiography of medicine and its biomedical triumphs, this dissertation does not belong to the genre.\textsuperscript{95} Through a fine-grained analysis of investigative practices in oncology, this dissertation traces a conversion of experimental treatments for cancer patients into therapeutic research with human subjects. It examines, from a cultural and an epistemological perspective, why the Canadian medical research evolved from arguably unethical radio- and chemo-therapeutic experiments with cancer patients to the supposedly dignity-enshrining clinical trials of anti-tumor treatments in the late 1970s. By probing into this shift and its origins, I also consider how international trends influenced Canadian developments in cancer research and its regulation.

**Material**

In this dissertation, I draw on primary sources collated from major medical archives across Canada. The fonds consulted adequately represent record-keeping practices of the institutions, consistent with standards at the time, from which they have been derived, that is, the universities and government bodies. The sources range from research protocols to personal correspondence, institutional memoranda, patents, government documents, and transcripts of parliamentary debates, among others. Research protocols for cancer clinical trials and pertinent to them original


\textsuperscript{94} Ibid., 105.

documents, like project reports and correspondence among investigators, constitute the main primary sources for this study. Unpublished materials lend themselves to a qualitative historical analysis better than published works because they represent “tacit knowledge” about the experimental projects with their nuanced meanings of human research ethics. Furthermore, published texts contain largely polished versions of the “trading zone” negotiations, and the sensitive information (e.g. disagreements and conflicting positions on controversial issues) is only imperfectly reflected in them. The culture of medical research defies an in-depth critical analysis if it is presented in a refined form.

Moreover, I have looked into judicial repositories containing primary sources on medical malpractice in cancer treatment and clinical research. Considering the legal-medical domain as another prism through which to examine the ethical and the experimental, I scrutinize several Canadian court rulings on supposedly unethical and unlawful medical practices which informed the agencies issuing guidelines on ethically acceptable clinical research. As legal precedents from Provincial Courts, Courts of Appeal, and the Supreme Court of Canada represented major controversies in organized medicine, I use judicial decisions to contextualize how professionals delineated the boundary between medical practice and research, emphasizing their justificatory reasoning.

Law and ethics form a cluster of mutually complementary systems in public life. The ethical system ensures a fail-safe functioning of a community by demonstrating how to act appropriately, whereas the legal system codifies the acceptable standard of conduct and makes sure that any deviations from it are justly punishable. Human rights are constructed at the intersection of ethics and law, for the possibility of rights is contained within a chosen ethical paradigm the reality of which is embodied in a systematized arrangement of laws. Because legal entities have differing values and goals, recurrent conflicts of interest arise. To adjudicate these conflicts, the judiciary works toward preventing the unjust settlements of contentious issues. If

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96 See Michael Polanyi, *Personal Knowledge: Towards a Post-Critical Philosophy* (London: Routledge & Kegan Paul, 2005 [1958]), 62. Polanyi suggested, “When we accept a certain set of pre-suppositions and use them as our interpretative framework, we may be said to dwell in them as we do in our own body [...] They are not asserted and cannot be asserted, for assertion can be made only within a framework with which we have identified ourselves for the time being; as they are themselves our ultimate framework, they are essentially inarticulable. It is by his assimilation of the framework of science that the scientist makes sense of experience.” See also Thomas S. Kuhn’s *The Structure of Scientific Revolutions* (Chicago: University of Chicago Press, 1996 [1962]), 74 and 191.
there is a significant dispute between the parties, they resort to the courts in order to establish what is right and how to interpret it. The ethical system becomes much less relativist when a judicial decision makes it necessary for all right-holders to conform to it. Legal persons secure their rights against the claims of others by relying on the legally binding judgments of the court—the public institution in itself. Thus, the court is another “trading zone” wherein the adjudicative function of law is coupled with its constructive function—legislative.

The judicial domain reflects the most controversial debates taking place in the public arena. These debates surround issues impervious to one-time compromises, insofar as the public, the institutional, and political interests are at stake, especially when a norm favors any of them. I analyze in this dissertation how the ethical in medicine and research penetrates the realm of law, gets interpreted under the pressure of external conflicting interests, and becomes a legal standard that actuates changes in the sphere of scientific-medical practice.

By reconstructing the interaction of practices encompassing clinical trials and cancer care, I shed some light on how novel modes of doing things lead to new meanings and processes through which people make sense of them. As Michel Foucault once put it, “To be finite, then, would simply be to be trapped in the laws of a perspective which, while allowing a certain apprehension—of the type of perception or understanding—prevents it from ever being universal and definitive intellection. All knowledge is rooted in a life, a society, and a language that have a history.”

This dissertation excavates historical sites of medicine, ethics, and law to reveal how and why the development of cancer clinical trials created new meanings and contributed to the emergence of a modern regulatory framework for human subject research.

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Chapter I

The Rise of Cancer Challenges Therapeutic and Organizational Standards

Cancer featured prominently among the diseases affecting Canadians in 1921, which the first all-Canadian annual report on vital statistics revealed. Ranking third, alongside predictably common respiratory and heart diseases, cancer surpassed even tuberculosis.¹ The latter was under an unremitting attack of preventive and educational campaigns deployed by Canadian health boards, which resulted in a demonstrable reduction of its prevalence over a decade.² In contrast, the armamentarium available for a large-scale undertaking against malignant tumors was meager. A malignant tumor was juxtaposed with a benign one because the former inevitably spread through lymph and blood to other tissues and parts of the body where similar uncontrolled growths started from the invasive cancer cells.³ Moreover, my usage of the phrase ‘cancer epidemic’ implies only a steady numerical increase in mortality of people affected by different kinds of malignant tumors, so there is no implication that cancer is either infectious or transmissible.⁴

The etiology of cancer remained a major unknown factor. Among the potentially predisposing causes of malignant tumors were age – the older the individual, the higher the probability of developing the disease – and a range of irritants to which an individual was regularly exposed.⁵ In some cases, particular types of cancer could be associated with specific

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¹ Reported figures for the respective diseases were 6,021, 5,966, 4,826, and 3,989 out of 67,722 total of deaths in the Registration Area including PEI, NS, NB, ON, MB, SK, AB, and BC. See CDBS, Vital Statistics 1921: First Annual Report, (Ottawa: F.A. Acland, 1923), xvi.
² For instance, tuberculosis became a compulsorily reportable in Ontario since 1911, and in the same year the Anti-tuberculosis League was formed in Saskatchewan. See Jay Cassel, “Public Health in Canada,” op. cit., 294; and C. Stuart Houston, Steps on the Road to Medicare – Why Saskatchewan Led the Way (Montreal; Kingston: McGill-Queen’s University Press, 2002), 23.
⁵ Ibid. McCullough listed the following common irritants: tar, lubricating oils, tobacco smoke or the juice of tobacco, arsenic, strong sunlight, wind and dust, jagged and dirty teeth, ill-fitting dental plates, burns, too hot and improperly chewed foods, parasites. He also noted, “Diet, civilization, and race are not believed to be provocative of cancer. Cancer is not hereditary like diabetes and pernicious anemia, but undoubtedly some persons are more predisposed to cancer than others.” Statements like this might have prompted later medical researchers to produce evidence either in favor or against the underlying hypotheses.
agents and circumstances, but a reported mortality from malignancies among the general population, amounting to about seven percent, defied this reasoning.\(^6\) The incidence of malignant tumors in 1921 was about 0.075 percent of total registered population, while the numbers in 1924 and 1927 were, respectively, 0.083 and 0.086 (see Figure 1-1).\(^7\)

\[\text{Figure 1-1. CDBS, Vital Statistics 1921-1927: Annual Reports (Ottawa: F.A. Acland).}\]

\(^6\) CDBS, \textit{Vital Statistics 1921}, xvi. As early as 1700, an Italian physician Bernardino Ramazzini authored \textit{De Morbis Artificum Diatriba}, translated into Italian as \textit{Le Malattie degli Artefici [Diseases of Workers]}, wherein he explored occupational and lifestyle hazards that correlated with particular ills. Concerning cancer among women, Ramazzini wrote, “[…] we must admit this harmony between the breasts, and the uterus without the placenta, as in young women, in whose breasts milk is produced sometimes, of which we have sufficient evidence, due to persistent fluids from the uterus which rather soon lead to cancerous breast tumors, which are most recurrent in nuns than in other women, not because of the absence of menstruations, but, most probably I think, because of their chaste life; insofar as I have observed often that Vestal Virgins, with rosy cheeks, and with their bodies functioning well, but sensuous by nature, die miserably from dreadful cancers in their breast; therefore, since each city in Italy has many convents for religious women, rarely do we find any nunnery without such a pernicious disease” (my translation from Italian). See B. Ramazzini, \textit{Le Malattie degli Artefici}, transl. Chiari da Pisa (Venezia: appresso Domenico Occhi, 1745), 159-160. In addition, an English surgeon Percivall Pott noted in 1775 an increased rate of the cancer of the scrotum and testicles among chimney-sweepers. As Pott put it, “The disease, in these people, seems to derive its origin from a lodgment of soot in the rugae of the scrotum” (as in the original). See P. Pott, \textit{The Chirurgical Works of Percivall Pott, F.R.S. and Surgeon to St. Bartholomew’s Hospital} (London: printed for Hawes, W. Clarke, and R. Collins, in Pater-Noster Row: MDCCCLXXV), 735-736.

\(^7\) These seemingly small percentages correspond to 75, 83, and 86 deaths from cancer per 100,000 people.
The population size given for the Registration Area of 1921 during the indicated years constituted no more than 70 percent of the estimated total population of Canada. Indirectly, it means that for a variety of reasons consistent statistical data could be gathered only from the registration area in eight provinces. The category of cancer as a malignant tumor was undergoing a gradual epistemological extension, so registered cases, in all probability, represented only a part of the overall mortality due to the neoplastic disease. 8 Reports of medical officers relying on diagnostic manuals that included quite indeterminate diseases, such as cancer and influenza, possibly omitted borderline cases. However, non-cancerous growths were included in a separate category “benign tumours and tumours not returned as malignant” since 1921. 9 Pathology could resolve the majority of dilemmas concerning borderline cases, but a shortage of specialists, who were competent enough to perform required analyses, and a dearth of medical laboratories, which were located in hospitals and near urban centers, made a liminal classification designed for comprehensiveness unrealizable in terms of specificity. Nevertheless, the latter was even unnecessary in view of the breadth of obtained data.

By 1928, cancer was found responsible for 87 deaths per 100,000 of population, and three years later the figure rose to 92. 10 Having realized that the registration area approach to quantifying death rates from cancer was not rigidly structured, health care authorities adopted a more encompassing strategy of correlating all reported cases to the total population in Canada. To a medical officer who reviewed available statistics annually, tabulated numbers served as a dramatic proof of impending epidemic crisis. Figure 1-2 shows how appreciable the problem was.

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8 The classified malignant tumors constituted cancers of the buccal cavity, the stomach and liver, the peritoneum, intestines and rectum, the female genital organs, the breast, the skin, and the unspecified organs. Leukaemias and lymphadenomas (like Hodgkin’s disease) fell into a separate category that was not classified as cancer. See CDBS, Vital Statistics 1921, 127.

9 In 1921, 1924, and 1927, mortality tables recorded respectively 74, 61, and 127 deaths in this category. Benign tumors of female genital organs were excluded from this count because there were separate classificatory niches for them. See CDBS, Vital Statistics 1921, 127; Vital Statistics 1924, 131; Vital Statistics 1927, 151.

The above numbers suggest that cancer rates over the period of seven years indicate a well-marked upward trend, rising to 102 per 100,000 in 1935. There was also a noticeable increase in the category “tumours, non-malignant and not specified”, with a score of 811 cases overall for the same year. Accordingly, the diagnosis of malignant tumors was steadily improving since 1921. Yet, this positive development could not fully explain the demonstrated escalation of cancer incidence. Nor was the aging Canadian population a crucial factor, for a huge wave of predominantly young immigrants swept Canada in the 1920s. What was quite incontrovertible was that preventive measures approved by the Federal Department of Public Health, which were incrementally reducing the epidemiological pressure of major infectious diseases, had almost no effect on curbing the proliferation of cancer. Moreover, the development of a technological and a therapeutic arsenal for treating cancer was stagnating.

This chapter discusses how Canadian approaches to cancer management changed during the 1920-1930s in response to international developments in the field, such as a medical use of radiation (X-ray and radium) and public/state initiatives in a structural organization of cancer

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11 By comparison, this number was more than six times smaller (127 cases) in 1927. CDBS, Vital Statistics 1935, 32.
control. I argue that both fear-mongering interpretations of cancer statistics and the medical profession’s projection of radiation therapy as a life-saving technology created conditions conducive to the formation of cancer-care institutions. Since these institutions aimed mostly at cancer treatment and education, clinical research entered the therapeutic setting by default. Few clinicians paid attention to this combination of therapy with investigation when the odds to treat the dread disease were heavily against the patient.

Examining why the first provincial cancer committee in Canada, later known as the Saskatchewan Cancer Commission, came into existence, I analyze how this development induced a similar mobilization of major politico-economic and medico-scientific actors across the country. A prime example was the establishment of the Canadian Society for the Control of Cancer in 1938. Through its educational campaigns the CSCC not only heightened public awareness of the cancer problem, but also played a significant part in helping patients suspecting the disease to find a way to specialized clinics. Within cancer clinics, collaboration between the physician and the scientist contributed to a systematic therapeutic research.

1.1. Through Invisible to Noticeable: Radiation and Cooperation

Surgery as a treatment modality took the pride of place in removing tumors since the times of Ancient Egypt.\textsuperscript{13} It continued to be the treatment method of choice for cancers that were more or less amenable to surgical interventions at the turn of the twentieth century. The cure rate of surgery was relatively low, because malignant tumors usually would have spread in tissues so extensively by the time they were detected, that any excision was insufficient to eliminate all cancer cells causing new growths. Consequently, the curative effect of surgical operations in most cases should be understood in temporal, rather than absolute terms. At the time, however, only surgeons and those medical practitioners versed in the surgical art were in full knowledge of this limitation. Besides, as far as a significant number of tumors was hidden from the doctor’s eye in human bodies, only those diagnosticians who had vast experience were able to identify

\textsuperscript{13} Ann Rosalie David and Michael R. Zimmerman, “Cancer: an old disease, a new disease or something in between?” Nature Reviews Cancer, 10, no.10 (October 2010): 729-731. The authors noted that the Papyrus Kahun (c.1825 BCE) and the Papyrus Ebers (c.1538 BCE) included descriptions of putative cancers and their surgical removal by knife.
malignancies before performing an autopsy. The medical gaze in terms of diagnostic visibility became enhanced with the advent of an innovative technology at the close of the nineteenth century: X-rays.

Owing to a convergence of multidisciplinary knowledge and international experience, a German physicist Wilhelm C. Röntgen discovered “a new kind of rays” that made invisible things visible. In 1895, Röntgen called them X-rays because of their unknown nature. It was a mysterious radiation of energy to which physicists, and soon other researchers, directed their efforts. This field held immense potential for medical practice. Applications for diagnostic techniques could be improvised by the experimentally-minded surgeons and physicians, while other therapeutic designs were contemplated among medical innovators. Röntgen’s discovery shook the foundations of physics, chemistry, and anatomy, throwing light on formerly obscure junctures among the disciplines.

News about X-rays disseminated rapidly. Published pictures of Röntgen’s rays in action were tellingly illustrating a broad a range of possibilities to employ them. It ran the gamut from science and medicine to industry and artistry. The scientific intellectual ferment manifested itself earliest. French scientists were possibly the first to draw parallels among established facts and proposed hypotheses on X-rays. The effect of phosphorescence – a generation of light without heat – occasioned the physicist Antoine H. Becquerel to think that a prolonged exposure of some phosphorescent materials to visible light will make them emit rays themselves. Following this insight, Becquerel tested many phosphorescent metals. Having identified several compounds that produced a similar phenomenon to Röntgen’s rays, Becquerel chose uranium compounds as a particularly suitable material for his further experiments. Before long, Becquerel’s investigations led him to recognize and prove experimentally that uranium had a property of energy emission.

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independently of “any familiar source of excitation”, that is, spontaneously.\textsuperscript{17} This finding did not pass unnoticed.

Fascinated by Becquerel’s experiments with uranium salts and explanations on their spontaneous radiation, Marie Sklodowska Curie, and later Pierre Curie, engaged with the problem of this radiation’s nature. Painstaking laboratory testing of all known elements and compounds for spontaneous rays and then comparative examining of their characteristics yielded results.\textsuperscript{18} The Curies discovered that various uranium salts had dissimilar energy-emitting properties, which meant that other elements in the compounds might create the difference. This hypothesis proved correct. On the route to discovering new elements, the Curies postulated that all chemical substances “containing uranium or thorium were capable of emitting a substantial amount of the Becquerel rays [and] called such substances radioactive.”\textsuperscript{19} As far as the mathematically estimated discrepancy in radioactivity of uranium compounds still could not be explained by thorium, Marie and Pierre Curie undertook to analyze a uranium ore, pitchblende, for the presence of other unknown radioactive elements. Tons of the mineral processed, the Curies made two other substances known and subsequently named them polonium and radium.\textsuperscript{20}

Further experiments showed radium salts had “an enormous radioactivity of an order of magnitude 2 million times greater than that of uranium” and the “quantity of heat released by radium in several years was enormous if it is compared with the heat released in any chemical reaction with the same weight of matter.”\textsuperscript{21} The Curies observed that these characteristics

\textsuperscript{17} Becquerel, “On Radioactivity, a New Property of Matter,” 52.
\textsuperscript{20} The Curies wrote in a note read by Antoine H. Becquerel to the French Academy of Science, “L’intensité de cette raie augmente donc en même temps que la radio-activité, et c’est là, pensons-nous, une raison très sérieuse pour l’attribuer à la partie radio-active de notre substance […] auquel nous proposons de donner le nom de radium” (italics in the original). Pierre Curie and Marie Curie, “Sur une substance nouvelle radio-active, contenue dans la pechblende,” \textit{op. cit.}, 1216-1217.
\textsuperscript{21} Pierre Curie, “Radioactive Substances, Especially Radium”, 74.
contributed to profound physiological effects on the living matter. Radium disorganized tissues almost without sensation during their irradiation, but severe lesions developed afterwards. X-rays produced a comparable kind of action biologically, which was another confirmation of the radioactivity’s existence. Moreover, this dual phenomenon of imperceptible destruction of biological material prompted medical scientists to attempt using X-rays and radium as a treatment method for various cancers. However, there was a serious setback in utilizing radioactivity therapeutically. How much of radiation was enough to destroy a tumor and leave vital functions of the organism intact?

The above question was both theoretical and empirical. Looking for evidence to corroborate the hypothesis of the transformation of matter through radioactivity, physicists demonstrated that radioactive elements emitted rays that differed in terms of their penetrating power. Ernest Rutherford and Robert Owens, both working at McGill University in Montreal, examined properties of thorium and found that it emitted types of radiation of different intensity. In consequence of further experimentation, they revealed that thorium formed a

22 Cecil W. Rowntree, “Hunterian Lecture on X Ray Carcinoma, and an Experimental Inquiry into Conditions which Precede its Onset,” The Lancet 173, no. 4464 (20 March 1909): 821-824. Rowntree noted that a prolonged exposure to X-rays resulted in dermatitis, burns and might lead to cancerous growths, a fact that had been registered in 1903. Through a series of experiments with mice, rats, and rabbits, Rowntree tentatively concluded that X-rays had some special action that predisposed tissues to degeneration. The latter could be a retardation of cell division and tissue atrophy when the X-ray doses were moderately high, whereas in the case of low doses X-rays stimulated hyperactivity of cell proliferation.

23 Louis F. Wickham, “L’Action Thérapeutique du Radium sur le Cancer,” Revue Générale des Sciences Pures et Appliquées, 20 (1909): 902-912. Director of the Laboratoire Biologique du Radium de Paris, established in 1906, and a physician at the Hôpital Saint-Lazare gave evidence in his article that radium was more effective in the treatment of a number of benign and malignant tumors than X-ray therapy. As Wickham suggested, radium therapy, better known at the time as Curietherapy, was an experimental treatment for patients with advanced cancers and an adjunct to surgery with which it could be used in different combinations. Importantly, Wickham pointed out that the outcome of Curietherapy depended largely on the experience and sagacity of the physician applying it.

radioactive substance in the form of vapor at its surface. This vapor could be captured in a reservoir, as any gas, but its radioactivity quickly disappeared when thorium was removed from the reservoir. Soon after, Marie and Pierre Curie observed the same phenomenon in the presence of radium.25 A similar observation could only indicate that both thorium and radium emitted a kind of radioactive gas. Rutherford suggested designating this process “emanation”. Needless to say, this effect had a potential practical application in view of the scarcity of thorium and especially radium.

At the same time, the Curies experimented with a number of solids under the influence of radioactive substances and their probable emanations. As anticipated, the solid substances acquired radioactivity temporarily in degrees characteristic of their inherent physical qualities. The Curies called this phenomenon “induced radioactivity”, to differentiate it from the spontaneous radioactivity postulated by Becquerel.26 Yet, to use emanation and induced radioactivity to their full potential, their underlying mechanism of action required further elucidation.

Radioactive processes became more intelligible after Marie Curie had proposed to conceptualize radioactivity as an atomic property that persists in all physical and chemical states of the matter.27 This property made it theoretically possible to estimate the amount of emitted radiation by quantifying air ionization that led to its better conduction of electricity. Using an electrometer to measure the electric current in a specially-designed apparatus, in addition to sensitive photographic plates, Eugène-Anatole Demarçay demonstrated that radium rays were

25 Pierre Curie and Marie Curie, “Effets chimiques produits par les rayons de Becquerel,” Comptes rendus, 129 (1899), 823-825. In this report, the authors suggested that the transformation of oxygen into ozone under the influence of rays emitted from radium constituted a proof that radium’s radiation represented a continuous release of energy (825).

26 Pierre Curie and Marie Curie, “Sur la radioactivité provoquée par les rayons de Becquerel,” Comptes rendus, 129 (1899): 714-716. In their words, “En étudiant les propriétés des matières fortement radioactives, préparées par nous (le polonium et le radium), nous avons constaté que les rayons émis par ces matières, en agissant sur des substances inactives, peuvent leur communiquer la radioactivité, et que cette radioactivité induite persiste pendant un temps assez long” (714). Interestingly, the Curies did this research at l’École municipale de Physique et de Chimie industrielles, which suggests that this work had a commercial significance already at the turn of the twentieth century.

27 As M. Curie put it, “Pour interpréter le rayonnement spontané de l’uranium et du thorium on pourrait imaginer que tout l’espace est constamment traverse par des rayons analogues aux rayons de Röntgen mais beaucoup plus pénétrants et ne pouvant être absorbés que par certains éléments a gros poids atomique, tels que l’uranium et le thorium.” Marie Sklodowska Curie, “Rayons émis par les composés de l’uranium et du thorium,” op. cit., 1103.
much more powerful than those of other known radioactive elements. One of the challenges to fathom the nature of radium’s radioactivity, however, was to characterize at least one type of its emitted rays – either alpha, beta, or gamma – through physical-chemical effects and their seemingly unmeasurable impacts in the experimental set-up.

Not only was there an international competition in search for the keys to unlock the secrets of atomic transformation, but there existed also an unconditional cooperation among researchers within the scientific community. Without such a conflation, reaching quick solutions to unwieldy problems underlying a new order of things was anything but achievable. Around the mystery of radiation in the form of X-rays and radioactive substances revolved scientific, medical, state, and business interests. One of the most powerful sources of radioactivity, radium, predictably attracted the ultimate powers of intellect and capital. This combination in a peaceful atmosphere generated a series of radical innovations that had no precedent in the history of science.

In the medical science, radioactivity rekindled an enthusiasm for addressing the cancer problem, among others. Healthcare administrators needed to demonstrate their capabilities through a scientific approach to diagnostics and treatment of cancer. Numbers of cancer-afflicted people, whose often incurable conditions also led to them being treated as pariahs, continued to augment. In the circumstances, medical authorities turned to soliciting funds from the public for the translation of theoretical possibilities into empirical probabilities of radiation treatment. Both

29 Ernest Rutherford, “The Chemical Nature of the Alpha Particles from Radioactive Substances,” 11 December 1908, in Nobel Lectures, Chemistry 1901-1921 (Amsterdam: Elsevier, 1966). Briefly explaining how the identification of helium particles as alpha radiation occurred, Rutherford revealed how multilevel and participatory the scientific environment was at the time. The effect of radium emanation contributed to the detection of helium no less than newly devised optical and electrical methods to investigate single atoms for the first time.
30 Transformation of matter theory, put forward by Rutherford and Frederick Soddy in 1903, along with Albert Einstein’s special theory of relativity of 1905 gave a new meaning to the equivalency of matter and energy. Virtually all spheres of human life dealing with matter-energy conversions utilize this principle. In cancer therapy, for instance, the exposure of a tumor to high-energy radiation contributes to its either disintegration or proliferation, depending on the irradiated dose.
in Europe and North America, such initiatives especially encouraged private patrons to contribute to the public good and strengthen its social ties.\footnote{Foundation of the New York State Pathological Laboratory of the University of Buffalo in 1898 marked one of the earliest successes in persuading the government to fund cancer research. Joint efforts by Roswell Park and Edward H. Butler, a surgeon and a publisher respectively, had led to a cancer research facility that later became a large treatment center. See Roswell Park Cancer Institute, \url{https://www.roswellpark.org/about-us/history} (accessed 17 January 2018). Also, Edwin A. Mirand, \textit{Legacy and History of Roswell Park Cancer Institute, 1898-1998} (Virginia Beach, Va.: Donning Company Publishers, 1998).}

The British launched the Imperial Cancer Research Fund in 1900, which gave rise to the eponymous Institute in 1902.\footnote{Joan Austoker, \textit{A History of the Imperial Cancer Research Fund, 1902-1986} (Oxford; New York: Oxford University Press, 1988), 1 and 26.} In Tsarist Russia, a family of industrialists, the Morozovs, donated a lump sum to create a cancer hospital affiliated with the Moscow University in 1903.\footnote{A chief-surgeon and director of the Moscow University Surgical Clinic, Leo L. Levshin, presented a motion to found a cancer hospital and to receive a donation amounting to 150,000 rubles (then equivalent to about 116 kg of gold) from the Morozovs for this purpose at a board meeting of the University in early 1898. Motion carried, Levshin organized a donation pool for the hospital’s construction and simultaneously opened a clinic-shelter for cancer patients. The Morozovs granted additional 100,000 rubles in gold, whilst donations from other patrons made the hospital a reality in five years. This cancer hospital, christened the Morozov Institute, laid a foundation for organized cancer research in Russia. In 1947, the Soviet authorities re-named the Morozov Institute as P.A. Herzen Central Cancer Research Institute, after a distinguished surgeon and cancer researcher Piotr (Pierre) Alexandrovich Herzen (my free translation). See A.D. Kaprin, V.I. Chisson, I.V. Droshneva, “History Pages of the P. Hersten Moscow Oncology Research Institute,” \url{http://www.mnioi.nmicr.ru/about/history.php} (accessed 17 January 2018).} As early as 1900, medical authorities in Germany formed the German Committees for Cancer Research, headquartered in Berlin, with associated cancer institutes in Heidelberg, Munich, and Karlsruhe.\footnote{Ernst Viktor von Leyden, “Verhandlungen der Internationalen Konferenz für Krebsforschung vom 25 bis 27 September 1906 zu Heidelberg und Frankfurt a. M.” \textit{Journal of Cancer Research and Clinical Oncology}, 5, no.1 (1907): 2-6. Von Leyden, a chairman of \textit{Deutschen Komitees für die Krebsforschung}, founded the first cancer research institute on the grounds of the Berlin Charité Hospital in 1903.} In 1906, Heidelberg introduced to the scientific world an interdisciplinary cancer research institute, affiliated with the university, by holding the first international cancer conference.\footnote{George Meyer, “Verhandlungen der Internationalen Konferenz für Krebsforschung vom 25 bis 27 September 1906 zu Heidelberg und Frankfurt a. M.” (1907): 24-25; and Harald zur Hausen \emph{et al.}, \textit{Deutsches Krebsforschungszentrum: Current Cancer Research} (Berlin; Heidelberg: Springer-Verlag, 1995), 200. A founder of the \textit{Institut für Krebsforschung ’Samariterhaus’} in Heidelberg, Vincenz Czerny, was a surgeon who pioneered irradiation during his operations. Czerny’s understanding of limitations of surgery prompted him to complement surgical techniques with adjuvants – radiation, serum therapy, vaccination, and electrotherapy. In all probability, this unconventional interdisciplinarity in clinical practice might have inclined Czerny to organize an international conference.”} This congress possibly galvanized medical innovators in France into a cooperative
action. The French Association for the Study of Cancer started its preparations for a comprehensive program in the same year.36

The Swedish society stood out for its philanthropy tending to humanitarian causes, particularly in the fields of science and medicine, to which the legacy of Alfred B. Nobel bore witness. Work on radiation as a possible therapeutic mode necessitated the foundation of Radiumhemmet in 1910, which transformed into the Cancer Society in Stockholm later that year.37 A similar philanthropic spirit ran through the American Society for the Control of Cancer that saw its creation in 1913.38 These developments suggest there was a common pattern for constructing a pyramid of institutions sponsored by governments and corporate philanthropists. Why did the large-scale sponsorship come to pass?

The optimism of the triumphant bacteriology years about the possibility to find a cure for cancer was unflagging. Scientists singing the praises of X-rays and radium’s potentialities to overpower the social scourge instilled hope in political leaders and business elites who, thus, invested heavily in research and development of these treatment modalities. Clinical investigations with X-rays and radium evidenced indirectly the scope of committed financial resources.39 The establishment of radium institutes as independent entities, including radiation therapy centers, meant that state healthcare needed to supply them with qualified personnel, costly equipment, and adequate funding. Radiotherapy centers provided a link with universities and medical schools in which basic research trickled into tangible practices.

38 James T. Patterson, The Dread Disease: cancer and modern American culture (Cambridge, Mass.: Harvard University Press, 1987), 71-72. The ASCC was re-named the American Cancer Society in 1935.
39 Roger F. Robison provided a table of fifty-two X-ray and radium therapy trials from 1900 to 1909, but the dates and the countries given suggest that this number constitutes only a part of the total during the period. See R.F. Robison, Mining and Selling Radium and Uranium (Springer; Heidelberg: Springer, 2015), 255-256.
In the context of increasing scientific-medical exchanges among countries, national achievements in radiotherapy gradually shifted to an international arena. The Vienna Radium Institute, inaugurated in 1910, served as a prototype for countries that could afford doing cutting-edge medical research and caring for their cancer patients. The Radium Institute in London went into operation in 1911. France unveiled the Institut du Radium de Paris in 1913, and the newly formed USSR created its cluster State Radium Institute in 1922. In due course, these national developments entailed joint undertakings internationally.

In the aftermath of World War I, the French-Anglo-American League Against Cancer came into being. The allies in military campaigns proceeded jointly in a peace offensive since 1918. This anti-cancer campaign proved to be so expensive that nations had to unite their forces. Yet, unification had also a peculiarly medical implication – that of professional conservatism. Despite the strides of scientists in radiation studies, a traditional teaching hospital was the domain of mainly surgeons, internists, pathologists, and hygienists. The evidence suggests that a

40 Wolfgang L. Reiter, “Stefan Meyer: Pioneer of Radioactivity,” Physics in Perspective, 3, no.1 (2001): 114. The construction of the Institute by the national Academy of Science became possible with a generous donation from a Viennese industrialist Karl Kupelwieser who was aware of the economic importance of St. Joachimstal natural reserves of uranium ores. Incidentally, Marie Skłodowska Curie obtained allegedly useless by-products of pitchblende from this part of the Austro-Hungarian Empire. Stefan Meyer, an Austrian physicist who became the first director of the Institut für Radiumforschung, played a major role in facilitating innovative research with radium across Europe by supplying it to leading scientists, including Ernest Rutherford.

41 On the insistence of King Edward VII, who developed a skin cancer, his two close associates, Sir Ernest Cassel and Viscount Iveagh, made a munificent donation for the establishment of the Radium Institute in England. See Anonymous representative of the BMJ, “The Radium Institute,” The British Medical Journal, 2, no. 2640 (5 Aug. 1911): 302. Plans for building the Radium Institute in Paris were approved at the end of 1909, when the Pasteur Institute announced that an industrialist, Mr. Osiris, had bequeathed his fortune to it. For details, consult Patrice Pinell, The Fight against Cancer: France 1890-1940, 37. In the USSR, Vladimir I. Vernadsky, a well-known scientist and thinker, took the initiative in forming the Radium Institute in Petrograd (present St. Petersburg) out of the Radium Laboratory of the Academy of Sciences, the Department of the State Institute of Röntgenology and Radiology, and the Laboratory of Radio-Chemistry (my translation). See The V.G. Khlopin Radium Institute, “History and Chronology,” http://www.khlopin.ru/?page_id=172 (accessed 17 January 2018). Similar institutions mushroomed elsewhere. In 1913, American entrepreneurs built the National Radium Institute in Denver, Colorado, which operated for only about three years. See Robison, Mining and Selling Radium and Uranium, 171. The same year, Marie Curie contributed to opening a Radium Institute in Warsaw (present Poland). See Reiter, “Stefan Meyer: Pioneer of Radioactivity,” 114.

handful of medical experimentalists who attempted to innovate with radiation as an anti-cancer method had a hard time winning the support of the above groupings in a hierarchical hospital system.

An International Symposium on Cancer Control organized by the American Society for the Control of Cancer (ASCC) in New York in 1926 provided a good illustration of those actualities. Bringing together medical professionals specializing in cancer research, treatment, and epidemiology, the symposium showed a crosscut of different national authorities in the field. On opening the symposium, Howard C. Taylor, a surgeon-gynecologist, George A. Soper, a sanitation engineer, William H. Welch, a pathologist-bacteriologist, formally greeted international guests, and Sir John Bland-Sutton, a surgeon-anatomist, replied with greetings on behalf of the foreign attendees. No wonder radiotherapy met with some opposition in England and the United States. However, years of clinical experimentation with cancer patients, considered by the surgical profession as incurables, rightfully induced practitioners of radiotherapy to express their views in public. At one of the symposium sessions, Bland-Sutton’s passing remark – “surgeons, baffled in their efforts to conquer cancer, appealed to the laboratories of pathology, bacteriology, biochemistry, and physics for enlightenment and guidance” – was echoed by viable propositions from the French delegates.

Claude Regaud, a histologist and medical investigator of radiation, pointed out that a desideratum of collaboration between the scientist and the physician, in addition to the need of centralizing expensive radiation-producing equipment with its accessories, required institutional changes. In other words, Regaud linked the increasing role of physicist in clinical medicine with the rise of X-ray and radium therapy. Regaud was among the first to apply radiation

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44 Taylor was President of the ASCC, Soper – Managing Director of the ASCC, Welch was the first Professor of Pathology and the first Dean of the Johns Hopkins University School of Medicine, and Bland-Sutton was Vice-President of the British Empire Cancer Campaign and President of the Royal College of Surgeons. Ibid.


techniques tested on animals to patients with inoperable cancers referred to him by colleagues. His therapeutic experiments led him to the directorship of the Radiophysics Laboratory in the Radium Institute of Paris in 1913.47

Regaud’s colleagues, Henri Hartmann and Théodore Marie presented evidence on how to induce a cooperation among surgeons, radiotherapists, and physicians with the aim to improve care for the cancer patient.48 The crux of the matter lay in organizing cancer centers independent from a hospital system. By then, this pioneering idea had turned into a realized project as the Franco-Anglo-American League gave an impetus to the anti-cancer campaign by attracting heavy patronage and financial aid.49 Owing to a merger of social, philanthropic, scientific, and business interests, the political establishment bent to public pressure and approved the construction of a number of specialized cancer centers.50 Thus, X-ray and radium therapy brought about a rearrangement in the national organization of cancer research and treatment.

Clearly, the rearrangement of French cancer control system hit the highlight of the international symposium. It was an organizational innovation that helped to overcome a conservative hierarchy in the teaching hospital. There was even a proposal to promote cancer research universally through an “international federation” for interchange of scientific literature and medical expertise, independently of national structures of the organized medicine.51 Such a federated body could also be useful for setting treatment standards, sharing clinical research achievements, and notifying members of troublesome issues. Some of the latter had already transpired in connection with a widespread adoption of X-ray and radium technologies.

Improper utilization of radiation sources, or even fraudulent pretense of using them, became a recurrent concern. It seemed as if a newly found mode of treating tumors in patients

50 The Curie Foundation spearheaded this development in 1921. Marie Curie and Claude Regaud became directors of, respectively, the Scientific and Therapeutic Sections of the Foundation in 1922. Earlier in the year, the government endorsed Jean-Alban Bergonie’s recommendations on the creation of a network of regional cancer centers. See Pinell, *The Fight Against Cancer: France 1890-1940*, 95-97.
generated an uncontrollably growing number of people practicing it. That growth was ostensibly malignant, since the big names of the medical establishment referred to those unscrupulous practitioners, including licensed doctors, as charlatans, quacks, and impostors. At the ASCC symposium, both the opening address and the closing dinner speech conveyed the acuteness of this situation. Declared George Soper, “The public sorely wants instruction and advice on the subject of cancer and, failing to get the genuine, it readily accepts the counterfeit. Ignorance, superstition and quackery nowhere cause greater misery.”52 During the final dinner, Stephen Leacock, a Canadian non-medical attendee of the symposium, delivered an address denouncing quackery.53 Leacock was a professor at the department of economics and political science of McGill University in Montreal, but became better known as a writer and humorist. After his wife, Beatrix, had fallen victim to irremediable breast cancer, Leacock dedicated himself to anticancer activism. His voice at the symposium was by no means a lone one.

A medical officer of health from Toronto, Charles Hastings, commented on what repercussions charlatanry entailed for the general population, “It is well to bear in mind that the uninformed public, or shall I say the more illiterate, become somewhat skeptical when the surgeon or the radiologist publicly advocates early operation or early treatment by radium or X-ray for these abnormal conditions.”54 To deal with apparently unacceptable patients’ skepticism, Hastings suggested, quite radically, instilling cancer-phobia in the public as a means to raise awareness of the cancer problem. As Hastings put it,

I should be very glad to be able to produce a “cancerphobia” [sic] if every person, on recognizing that he had any abnormal condition, any abnormal growth, or other danger signal, would immediately consult his family physician, fearing that he had cancer. It would be the means of saving very many lives from this dread scourge.55

There was probably a link between the medical profession’s need to create an intelligent cooperation of the patient with the physician and an educational campaign of the ASCC.

52 Ibid., 7.
53 Ibid., 335. A brief case study on S. Leacock is in Barbara N. Clow, Negotiating Disease: Power and Cancer Care, 1900-1950 (Montreal; Kingston: McGill-Queen’s University Press, 2001), 3-5.
55 Ibid., 57.
Considering that operations of the ASCC covered Canada, effects of the American influence on the Canadian medical establishment engaged in cancer control might be perceived already in the 1920s.\textsuperscript{56} Epidemiological and statistical initiatives in Canada, examined in the first part of this chapter, gradually supplemented the educational program to impart to the latter a factual basis. Systematized data on cancer incidence enabled administrators to assess how well the dissemination of information on cancer control actually worked. As far as early detection of cancer formed a cornerstone of the anti-cancer campaign, the primary objective of the ASCC was to bring the patient into contact with the competent doctor. The emphasis on competency carried a particular message. Proliferating quackery not only diminished patients’ prospects of recovery, but also interfered with assembling valid epidemiological data on cancer patients. The educational campaign targeting the exposure of quacks was only the first step on the path to forming an institutional stronghold from which further directives would be issued. In Canada, no such institutions charged with cancer control existed. Their creation, however, was a question of time. What expedited this process was the spread of radioactive sources among Canadian physicians.

1.2. Radiotherapy and Anti-Cancer Initiatives

Out of two radiation sources, radium and X-ray, the former was more convenient for small-scale use in a private practice. Bulky high-voltage X-ray machines fit well within a hospital, whereas tiny amounts of radium salts and its derivatives were easily adaptable to the working space of individual physicians. Moreover, X-ray equipment required somewhat higher investment than radium for a relatively equal output, though both forms of radiotherapy were expensive.\textsuperscript{57} On account of these two advantages, radium acquired a wider commercial significance and the market demand for it was rising year in year out. The research institutes, the medical profession,


\textsuperscript{57} Radium quantities were infinitesimal in quite rare uranium ores and the isolation of radium salts from admixtures necessitated a sophisticated process that added to the cost of the final product. One gram of radium had a price ranging from 75,000 to 120,000 US dollars over the period 1909-1922. Since 1923, when the Mineral Union of the High Katanga, a Belgian holding company, initiated selling radium isolated from rich uranium ores in colonized Congo, the price dropped to 70,000. The company monopolized the radium market around 1925. See Robison, Mining and Selling Radium and Uranium, 187-189 and 259.
and ingenious entrepreneurs found ways how to capitalize on radium with its derivatives. Having received massive publicity on the part of the scientific-medical world, radium descended into the realm of market forces beyond the pale of regulated use.

Beginning in major cities of Eastern Canada – Montreal and Toronto, the radium enthusiasm diffused quickly to Winnipeg, Regina, Edmonton, and Vancouver.\(^{58}\) Over the 1920s, the nodes of the radium network extended to other urban centers across the provinces. Annually published Canadian cancer statistics reached the majority of licensed physicians, making them mindful of the scourge, and radium became quite appealing as a treatment option. The Canadian Medical Association officers were cognizant of the radium proliferation, yet they appeared nonchalant. Nevertheless, one of the CMA affiliates changed its tack.

The possession of small amounts of radium by physicians and hospitals caused the Saskatchewan Medical Association (SMA) concern. The fact that owners of radioactive materials lacked special training to handle them and still used them for therapeutic purposes was at the heart of that concern. Ostensible misuse endangered not only patients’ health, but also the professional reputation of medical practitioners.\(^{59}\) To avoid this misuse, the SMA appointed a Cancer Committee in October 1929.\(^{60}\) It was the first Cancer Committee in Canada that aimed at inquiring into a cancer treatment capacity province-wide. The Committee concluded, “That it is desirable to organize the various factors in the province; vis., the profession, the laity and the government forces in an endeavor to provide the most modern scientific treatment for our cancer patients, and that a supply of radium should be made available for this purpose.”\(^{61}\) Importantly, the Committee recognized radium therapy as the most modern scientific one. Given that provincial inquiries revealed a meager 400 milligrams of radium salts owned by private

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\(^{58}\) Saskatchewan Medical Association, “Cancer Committee Annual Report 1930,” in Presentation to the Cancer Program Assessment Committee by the Saskatchewan Cancer Commission, 150. In the PAS, R-240, folder 1, file 2, Briefs and Presentations 1970.

\(^{59}\) On these issues in the British and American contexts, see John V. Pickstone, “Contested Cumulations: Configurations of Cancer Treatments through the Twentieth Century,” Bulletin of the History of Medicine 81, no.1 (2007), 171-173.

\(^{60}\) Report of the Saskatchewan Cancer Commission 1953, 8. In the PAS, PH-13, folder 2, Saskatchewan Cancer Commission Annual Reports.

practitioners scattered across the province, the Committee recommended requesting government funds to make radium therapy more accessible to patients and controllable by experts.62

Frederick D. Munroe, the Minister of Public Health of Saskatchewan, Earle E. Shepley, a roentgenologist at the Saskatoon City Hospital, and Ertle L. Harrington, a physicist at the University of Saskatchewan (and a former graduate student of Theodore Lyman, Albert A. Michelson, and Robert A. Millikan) had lengthy discussions on how to balance the interests of private practitioners and to use available radium efficiently.63 Harrington was a one of a kind member of the Cancer Committee composed of medical men: six physicians, two pathologists, and a surgeon.64 Based on Harrington’s expertise, the government and medical authorities agreed to use radium in two forms – as salts and as gas radon emanations.65 Such infiltration of physics into a medical domain symbolized a distinct dimension of solidifying scientific medicine. Consultation with a physicist enabled the medical professionals to create not only a public image of association between science and medicine, but also an exposure to an evidentiary paradigm steeped in experiment and measurement.

Another dimension of making medicine scientific related to quantifying cancer incidence in Saskatchewan. It was essential to undertake a survey to ascertain as correctly as possible the number of cancer patients that fell within the remit of the medical profession annually. The survey conducted, the Cancer Committee had enough evidence to recommend the Minister

62 Ibid., 150. See also Report of the Saskatchewan Cancer Commission 1961, 8. In the PAS, PH-13, folder 2, Saskatchewan Cancer Commission Annual Reports.
63 Minutes of a Meeting of the University Council, Saskatoon, 12 April 1956. In the USL, Faculty Biography Files, Ertle L. Harrington.
64 Summary of the First Meeting of the Cancer Committee of the Saskatchewan Medical Association, Regina, 27 November 1929. In the PAS, R-75 (F.D. Munroe), 1a Correspondence re Organization of Cancer Program in Saskatchewan, 1929-1931.
65 It emerged from Harrington and Shepley’s correspondence with major radium researchers – C. Regaud in Paris, J. Ewing in New York, G.E. Richards in Toronto, C.W. Prowd in Vancouver – that both forms had pros and cons. An emanation plant needed to be constructed initially and the distribution of radon in tiny containers, called ‘seeds’, necessitated maintaining laboratory technicians. By contrast, radium salts were ready-made in needles, tubes, and plaques. However, an accidental loss of radium salts products would cost hundreds of dollars, but lost radon seeds would only mean an inexpensive replacement of seeds because radon’s radioactivity was short-lived. Finally, seeds produced a uniform dosage of radiation and fewer cases of necrosis in patients, if compared with the same amount of radium salts in needles etc. See correspondence from E.S. Shepley to F.D. Munroe, 25 November 1929, in the PAS, R-75, 1a; and Shepley to Munroe, 4 February 1930, in the PAS, Saskatchewan Cancer Foundation Fonds (SCF) 321.1, file 9.2.
Munroe to address the Legislative Assembly. Munroe was anxious to present to the House a bill designed to deal with the cancer problem in the province. Underlying his prompt action was a statistical fact unearthed by the Cancer Committee. The report compiled out of questionnaires completed by all registered physicians estimated total cancer cases in the province at fifteen hundred in 1929, whereas the Dominion Bureau of Statistics characterized cancer mortality in Saskatchewan as the lowest in Canada, totaling 464 persons in 1928.66 Set side by side, those figures implied a discrepancy in reporting. Commenting on cancer incidence according to death certificates issued in Saskatchewan, Earle S. Shepley pointed out, “That the figures tell a poor story is evidenced by the fact that while eight cancer deaths from skin lesions are noted in Saskatchewan, I have treated practically dozens.”67 Over the 1920s, more than half of patients diagnosed with cancer usually had an advanced disease terminating their life within about year, but the Canadian federal statistics suggested otherwise.

Inadequate cancer statistics and the unregulated use of radium province-wide partly explained why the Legislative Assembly passed *The Saskatchewan Cancer Commission Act* summarily on 20 March 1930.68 The second part of the explanation lay in the political sphere of difficult negotiations about pooling resources with neighboring Manitoba to purchase high-priced radium.69 To forge into the lead, Manitoba adopted its *Cancer Relief Act* on 14 April 1930, which created a corporate body *The Cancer Relief and Research Institute*, though its legal

66 The tabulated cancer mortality rate was 55 per 100,000 of population. See CDBS, *Vital Statistics 1928*, lii and lviii. Also, *Report of Cancer Committee to the Executive of the Sask. Medical Association*, enclosed with Memo from R.O. Davison to F.D. Munroe, 24 January 1930. In the PAS, R-75, 1a.

67 E.S. Shepley to F.D. Munroe, 29 November 1929; in the PAS, R-75, 1a.

68 *Regina Daily Star*, “Dr. Munroe’s Cancer Bill Passes through All Stages in Legislature,” 20 March 1930. However, *An Act to Provide for the Establishment of a Permanent Cancer Commission* received the Royal Assent on 27 March 1930 and entered into force on 1 May of the same year. In the PAS, *Statutes of the Province of Saskatchewan*, 1930, Chapter 64.

69 R.O. Davison to E.W. Montgomery (Minister of Health and Public Welfare of Manitoba), Regina, 7 August 1930. In the PAS, R-75, 1c Correspondence re Organization of Cancer Program in Saskatchewan, 1929-1931. In particular, Munroe proposed to Gordon E. Richards of the Toronto General Hospital and to the newly formed Cancer Relief and Research Institute Board in Manitoba to put in a combined radium order from the Radium Chemical Company Incorporated of New York that offered a scale of lower prices for bulk purchases. Later, the decision-makers in Toronto and Manitoba resolved to act on their own, presumably because the New York company found out about the Canadian collusion. See correspondence from Richards to Munroe, Toronto, 21 June 1930; and Bruce Chown to Munroe, Winnipeg, 16 October 1930. Both in the PAS, R-75, 1d.
substance left much to be desired. In the Cancer Relief Act, an undefined Board was supposed to put into practice the Institute’s well-defined objects that somewhat resembled those of the Saskatchewan bill. To draw a parallel, The Saskatchewan Cancer Commission Act grounded its content in evidence elicited from a cooperative work of the medical profession, public health officers, and scientists engaged with the cancer problem. Moreover, as far as The Saskatchewan Public Health Act did not stipulate any cancer control measures, a separate statute seemed a better strategy than a series of amendments to the existing legislation. Generally relying on the opinion of the medical profession, the Minister Munroe, himself a medical doctor, proposed that the Commission’s creation shifted the focus from cancer prevention – the duty of the Department of Public Health, to cancer treatment, delineated under the Act.

The Saskatchewan Cancer Commission Act provided for collating statistics on the incidence and treatment of cancer, establishing specialized clinics for the treatment and diagnostics of cancer, and regulating radium and X-ray therapy by centralizing them in the clinics. These three major aspects of cancer control encapsulated the best practice internationally. On the one side, the establishment of regional cancer treatment centers in France since 1922 served a model. Montreal kept abreast of the French innovations by establishing the Radium Institute in 1927 and providing the Montreal General Hospital along with the Royal Victoria Hospital with radium for cancer therapy. On the other side, the British National Radium Trust and Radium Commission embodied a hub-and-spoke system of cancer centers.

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70 Manitoba King’s Bench publicly exposed the ill-conceived content of the Cancer Relief Act as early as 1939. Judge J. Dysart cited a number of inconsistencies, the major of which lay in the incorporation of the Institute that consisted of “nothing more than a name”, making its governance by the Board of Trustees questionable, for the latter was “entirely separate and distinct from the Institute.” See Manitoba King’s Bench [1939] 4 D.L.R. 191 Hague v. Cancer Relief & Research Institute, 192-194. For details on cancer control in Manitoba, see Hayter, An Element of Hope, 94-95.


72 The Saskatchewan Cancer Commission Act, Chapter 218 of The Revised Statutes of Saskatchewan, 1930 (effective February 1, 1931); Powers of Commission, 11.


74 Alfred T. Bazin to R.O. Davison, Montréal, 30 December 1929. In the PAS, R-75, 1a.
implemented in 1929. Either of these schemes could be adopted and adjusted to local settings in Western Canada.

The American Society for the Control of Cancer, informed of an incipient cancer control initiative in Saskatchewan, approached James Ewing, a pathologist and director of cancer research at the Cornell University Medical College, with a request to provide the SMA with relevant information on the organization of state-of-the-art cancer hospitals. Ewing, who knew the pathologist-commissioner W. Stewart Lindsay of the University of Saskatchewan, did his best in outlining how the Memorial Hospital of New York operated. Interestingly enough, it was the American College of Surgeons and Physicians that endorsed the cancer control program in Saskatchewan and suggested organizing cancer clinics within general hospitals. The Radium Commission in Britain had introduced the same idea as an alternative to the French system. The rationale behind incorporating cancer clinics in existing hospitals was two-fold. First, such organization provided “facility for the study of cancer”, meaning both the availability of a clinical set-up and the possibility for “any qualified physician to submit cases for study and take part in the proceedings.” Second, the cancer clinic thus organized secured a registry of valuable information on experimental alterations in treatment procedures.

The hospital system of recording medical histories complemented the existing method of collecting cancer patient data, mainly for vital statistics, through questionnaires completed by medical practitioners. This double-check arrangement probably ensured that cancer did not become a notifiable disease, commonly understood as any communicable disease on the officially approved list which had to be reported to medical authorities. Reginald O. Davison, Director of Cancer Service at the Department of Public Health of Saskatchewan, noted in a cover letter to dispatched cancer questionnaires, “While cancer could be made a reportable disease, it is felt that the physicians of the province realise the seriousness of the problem, and in justice to

76 Stressing the demand for specialization in diagnosis and treatment of cancer, Ewing referred to similar broadly organized research institutes within general hospitals in Boston, Buffalo, and Philadelphia. See R.O. Davison’s Reprint of J. Ewing’s “Cancer as a Public Health Problem,” Regina, 2 November 1929; and J. Ewing to C.M. Henry (Secretary of the SMA), 28 January 1930. Both in the PAS, R-75, 1a. W.S. Lindsay became the first Professor of Pathology and Bacteriology at the University of Saskatchewan in 1919 and he accepted the position of Dean of the newly formed School of Medical Sciences in 1926. In the USL, Faculty Biography Files, W.S. Lindsay.
77 Shepley to Munroe, 9 October 1931. In the PAS, SCF 321.1, file 9.2.
78 Ibid.
their patients and prospective patients, will be willing to submit this information voluntarily.”79 To keep on the safe side, however, the patients’ perspective and the doctors’ voluntariness demanded the letter of the law. Therefore, cancer came to be reportable by professional groups under The Saskatchewan Cancer Commission Act effective as of 1 May 1930.80 Davison also reviewed the College of Physicians and Surgeon’s resolution “That the Government make the necessary rules and regulations, that hereafter it will be compulsory to report all cases of cancer.”81 He recommended fulfilling this statutory requirement for hospitals by reporting on admitted and discharged cancer patients monthly, and for individual medical practitioners – on a case by case basis.82 This sound policy intended to kill two birds with one stone: to induce doctors and administrators to notify the competent body about possible cancer cases and to keep the general population relatively unaffected by anxiety about the cancer problem.

Following an enthusiastic approval of The Saskatchewan Cancer Commission Act from the professional and political authorities, a flurry of activity erupted to realize the cancer program. Where to purchase radium and X-ray apparatus at affordable prices? How to arrange a cancer clinic within a hospital hierarchy? What incentives to introduce to make cancer-related work a permanent occupation? These questions circulated among the Saskatchewan commissioners and other interested parties who engaged in an ever-expanding web of connections. Not only the volume of national and international correspondence grew

80 Relevant clauses in The Saskatchewan Cancer Commission Act read, “11. The commission shall have power, subject to the approval of the minister, to: (a) institute inquiries and collect facts and statistics relating to the incidence of mortality from and treatment of cancer”; and “18 (1) Every official of a public institution supported in whole or in part by the province, every medical health officer, every secretary of a board of health and every physician shall answer promptly communications from the commission, collect and tabulate facts according to instructions given them by the commission and supply correct information as to all matters submitted to them. (2) It shall be the duty of every clerk or secretary of a city, town, village or rural municipality to answer promptly communications from the commission and to supply correct information regarding any patient. (3) Any of the persons mentioned in subsections (1) and (2), who neglects or refuses to comply with the provisions thereof, shall be guilty of an offence and liable upon summary conviction to a penalty not exceeding $25” (as in the original). Statutes of the Province of Saskatchewan, Chapter 64, “An Act to Provide for the Establishment of Permanent Cancer Commission” (Regina: Roland S. Garrett, King’s Printer, 1930), 268-272. Also, R.O. Davison, “Memorandum on Compulsory Reporting of Cancer,” Regina, 11 February 1933; in the PAS, R-75, 2b.
82 Ibid.
substantially, but also exchange visits became more frequent. A trite turn of phrase by T. Clarence Routley, General Secretary of the CMA, “I am sure that if the [Saskatchewan] Bill becomes law, we shall all watch with keen interest the development of the plans” indeed turned into a reality in the spotlight. By the mid-1931, the completion of two major items on the cancer program agenda – the emanation plant at the University of Saskatchewan and two specialized clinics, in Regina and Saskatoon – was on the schedule. In this connection, R.O. Davison, the Deputy Chairman of the Cancer Commission, directed inquiries about the supplies of radon from the emanation plant to the Cancer Committee of the Alberta Medical Association and the Provincial Board of Health in British Columbia. It was indicative of the fact that an expeditious implementation of the ambitious program required a constant injection of money.

After unsuccessful attempts to secure grants from the Rockefeller Foundation or to raise funds through the Canadian Red Cross, a last resort was the CMA. Alfred Bazin, President of the CMA, suggested to the Minister Munroe affiliate the Saskatchewan Cancer Commission with the British Empire Cancer Campaign, but this course of action was temporarily postponed in view of designs to create a pan-Canadian anti-cancer organization. It was the Executive of the Saskatchewan Medical Association that introduced an initiative to form a Canadian Society for the Control of Cancer, but the CMA did not act upon it. A strong reason underlay this inaction.

The CMA was itself not united under a central organization. It constituted a token national body that did not form a single unit of affiliated provincial medical associations, which

83 See for example, R.O. Davison’s report on the visit to the USA and Eastern Canada, in the PAS, R-75, 1d, Davison to Munroe, 22 September 1930; and Harrington’s communication on his visits to cancer centers with emanation plants, in the PAS, R-75, 1g, Harrington to Davison, 10 November 1931. The Department of Public Health and the Cancer Commission under the guidance of F.D. Munroe arranged a visit of Joseph C. Bloodgood, an eminent American surgeon-pathologist, who participated in the Twenty-fifth Annual Meeting of the Saskatchewan Medical Association and other professional and public meetings in late August 1933. In the PAS, R-75, 2b – Bloodgood, J.C.: Correspondence, 1930-1933.
84 Routley to Munroe, Toronto, 2 March 1930. In the PAS, R-75, 1b Correspondence re Organization of Cancer Program in Saskatchewan (as in the original).
85 M.R. Bow (Chairman of the Cancer Committee in Alberta) to R.O. Davison, Edmonton, 15 October 1931; and H.E. Young (BC provincial health officer) to R.O. Davison, Victoria, 14 October 1931. Young requested Charles Wesley Prowd, Chairman of the British Columbia Cancer Committee, to “further the movement if possible through the B.C. Medical Association.” Both in the PAS, R-75, 1g.
86 Bazin to Munroe, Toronto, 3 March 1930. In the PAS, R-75, 1b.
87 Report of Cancer Committee to the Executive of the Sask. Medical Association, enclosed with Memo from Davison to Munroe, 24 January 1930. In the PAS, R-75, 1a.
were essentially autonomous. How could the CMA mobilize the medical profession across Canada to carry on the fight against cancer if there were neither formal regulations, nor working mechanisms to co-ordinate activities? Since the medical profession was in charge of applying scientific knowledge to the cancer problem, a coordinated all-Canadian cancer organization was beyond reach without the integrated national medical association.

No one understood this better than John S. McEachern who had rescued the CMA from its premature demise. Having established himself as a surgeon in Calgary, McEachern became an undeclared leader in the CMA when he reorganized the latter to obviate its bankruptcy in 1921. A decade later, McEachern observed how the Saskatchewan cancer initiative resurfaced in Alberta, where the Alberta Medical Association positively responded to the beginnings of a comprehensive cancer program in a neighboring province by following up with further developments. McEachern took up the challenge to translate the organizational momentum at a regional level into a national movement. Together with T.C. Routley, McEachern, as Inter-Provincial Relations chair of the CMA, traveled around Canada with the aim to federate provincial medical associations at the beginning of 1932. At the same time, discussions with key representatives of the provincial medical associations shed some light on a potential unification of local cancer agencies under the Canadian Society for the Control of Cancer.

Despite difficulties with this enterprise, McEachern demonstrated that he could form an alliance of the regional anti-cancer bodies. Therefore, McEachern volunteered to set up the National Study Committee on Cancer (NSCC) and the CMA Executive readily appointed him the chair of it. A formidable challenge of McEachern’s appointment lay in bringing representatives from every province to consensus on a centralized management and discretionary powers of the national organization. Among the few undisputed recommendations contained in

90 Bernard Mooney, a radiologist and professor of physics at the University of Alberta, served on the first Cancer Committee appointed by the Alberta Medical Association on 12 February 1930. Mooney to Shepley, Edmonton, 14 February 1929; in the PAS, R-75, 1b.
two reports of the NSCC were the creation of educational and research programs.\textsuperscript{93} However, a stumbling block to effecting both programs was a lack of stable influx of money that did not impinge on either changeable expenditures of provincial governments, or professional associations’ allocations. Members of the third NSCC, chaired by Alexander Primrose, and the CMA Executive, with McEachern as President, found themselves in a political \textit{cul-de-sac} of different regional priorities in the mid-1934.\textsuperscript{94}

Open-ended deliberations would proceed for years were it not for a pragmatic intervention from the Governor-General of Canada, the Earl of Bessborough, in 1935.\textsuperscript{95} Having received the approval of the King George V, the Governor-General inaugurated a fund for the purpose of the relief of cancer and the support of a Canadian cancer control campaign in commemoration of the twenty-fifth anniversary of His Majesty’s coronation. “The King George V Silver Jubilee Cancer Fund for Canada” thus became a nation-wide invitation to the public to donate for the organized effort to manage the cancer problem.\textsuperscript{96} The fund-raising was rather successful in collecting around half a million dollars over several months.\textsuperscript{97} It was high time to return to a frustratingly slow process of forming a national anti-cancer society, but a Board of Trustees, officially set up and charged with the administration of the fund, temporized.

The Board kept its options open presumably for two reasons. First, the fund at their disposal did not sufficiently cover the implementation of all recommendations produced by the third National Study Committee on Cancer. One of the principal recommendations called for a “survey […] of the whole of Canada to bring the cancer problem into full view” preceding any allocation of money by the board.\textsuperscript{98} This was a prudent suggestion encompassing both the

\textsuperscript{93} Lampard, \textit{Alberta’s Medical History}, 199. McEachern submitted one report in 1932, and the other – in 1933.
\textsuperscript{94} Primrose, a surgeon and professor of surgery at the University of Toronto School of Medicine, presented the report to the CMA Executive in Ottawa on 30 October 1934. Subsequently, the CMA Executive authorized to implement proposed recommendations and to establish a Department of Cancer Control in the Canadian Medical Association. See T.C. Routley, “The Conjoint Meeting of the American Medical Association and Canadian Medical Association, Atlantic City, June 10th to 14th, 1935,” \textit{Canadian Medical Association Journal}, 33, no.3 (Sept. 1935): 25.
\textsuperscript{95} The National Cancer Institute of Canada, “The Status of Provincial Programmes for the Diagnosis and Treatment of Cancer, Revised 1970,” in the PAS, R-240, folder 5.
\textsuperscript{96} \textit{Ibid.}, 1.
\textsuperscript{97} To be exact, 320,154 people, the Dominion Government, insurance companies, and undisclosed sources donated $489,066.92. In particular, the contribution from the people totaled $300,734.97. \textit{Ibid.}
\textsuperscript{98} Routley, “The Conjoint Meeting of the American Medical Association and Canadian Medical Association”, 25.
educational, clinical, and research components necessary for the baseline of a comprehensive cancer control program at a national level, though it was not feasible at the time. A reasonably calculated outlay on such cancer organization amounted to a sum considerably larger than the obtained one.99 Second, the Dominion Council of Health recommended to the Board of Trustees “that no allotment should be made for any new research activities” because the fund was quite moderate.100 The DCH was an influential advisory body consisting of major interested parties in public health, including medical schools and universities. Consequently, plans for a research program had to be shelved temporarily in favor of urgent matters.

In 1936, the Federal Government requested the Board of Trustees and the Canadian Medical Association take the necessary steps to use the fund for at least one of its intended purposes – professional and public education.101 Accordingly, the CMA assumed responsibility for the task and determined two priorities out of several NSCC recommendations: to set up a Department of Cancer Control and to organize a Canadian Society for the Control of Cancer. In early 1937, the Board of Trustees decided to grant the CMA $14,000 annually to support conceived projects.102 During that year, discussions on how to launch an economical but still comprehensive study of the cancer situation in Canada were taking place against the backdrop of a rather heated atmosphere in the USA. The Congress held a debate on the foundation of the National Cancer Institute (NCI). In July 1937, the congressional representatives passed the bill establishing the NCI, a federal body assigned with funding and organizing cancer research in the USA. Thus, the importance of scientific-medical investigations in a comprehensive cancer program could not be underestimated.103

The Canadian scientific-medical community interacted closely with its American counterpart in the overall scheme of things. The 1935 joint annual meeting of Canadian and

100 Routley, “The Conjoint Meeting of the American Medical Association and Canadian Medical Association”, 25.
102 According to the Board of Trustees’ recommendation, this grant was an annual interest from the capital sum of the fund. See R.E. Wodehouse (Honorary Secretary of the Board of Trustees) to Davison, “The King George V Silver Jubilee Cancer Fund for Canada,” Ottawa, 12 April 1937; in the PAS, J.M. Uhrich R-97, 9c: Cancer – General H-Z.
103 Patterson, The Dread Disease, 114.
American Medical Associations in Atlantic City (N.J.) reflected this trend well, to say nothing of common professional exchanges between Canada and the USA. For instance, a Canadian pathologist-surgeon Allan W. Blair became an associate director of the Toronto Institute of Radio-Therapy at the Toronto General Hospital in 1937, after he had worked as a cancer specialist at the Memorial Hospital of New York and at the University of Alabama. The NCI project apparently had a profound impact on Blair and his colleagues engaged in the organization of a comprehensive cancer program in Canada. Blair proposed to take stock of Canadian cancer institutions with their capabilities and then unite the independent cancer institutes and cancer clinics in hospitals under one organizational umbrella. In this connection, the foundation of the medical-lay Canadian Society for the Control of Cancer (CSCC) in March 1938 boded well for the future of organized cancer research in Canada.

The formation of the CSCC branches in each province constituted a series of opportunities to consolidate the research-minded in the medical profession. In Saskatchewan, for example, public and professional meetings accompanied the inauguration of the provincial division in September 1938. For this occasion, Edward B. Alport and Alfred T. Bazin, members of the CSCC Grand Council representing Saskatchewan and Québec respectively, expounded on the role of cancer clinics in improving therapeutic regimens through clinical research. Figure 1-3 demonstrates in outline how a steady increase in referral-based admissions to cancer clinics in Regina and Saskatoon correlated with the number of patients who died from cancer.

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104 Canadian Cancer Society, Saskatchewan Division, “Commemorating Forty Years of Progress, 1938-1978”, 41. In the USL, Harold Johns collection, MG 372, box 4, file 1. See also, Hayter, _An Element of Hope_, 110; and Houston, _Steps on the Road to Medicare_, 151.

105 Blair to Routley, Toronto, 15 June 1937; in the PAS, R-321.1, file 9.2. The CSCC became the Canadian Cancer Society in 1945.


107 The Saskatchewan Branch of the Canadian Society for the Control of Cancer was created exactly two months after the CSCC, on 27 May 1938, under the presidency of Justice W.M. Martin. See Canadian Cancer Society, Saskatchewan Division, “Commemorating Forty Years of Progress, 1938-1978”, 6-7.
No doubt, the CSCC’s educational campaign ran effectively, for patient referrals incremented consistently. The number of verified diagnoses had an upward trend overall, whereas fewer cancer patients succumbed to cancer each year. Therapeutic modalities, however, did not change so much as to fully explain a lowering cancer mortality in the clinics.

A plausible explanation behind the facts indicated in one direction: clinicians gradually rendered radiotherapy more efficient and cancer surgery more specialized through trial and error, which contributed to a longer-term survival or even recovery of patients. Out of 2,327 cancer patients with confirmed diagnoses (the dotted line), 1,012 or 43.5% (the double line) died as of February 1938.109 At least for cancer specialists, those figures heralded a positive outcome of their organizational efforts. What the survival rate might be in a decade if all Canadian cancer centers shared their therapeutic expertise and innovations? No easy answer could be offered,

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108 In the PAS, J.M. Uhrich R-97, 9c: Cancer – General A-G.
109 “Six-year Summary” enclosed with Memorandum from Davison to Uhrich, Regina, 15 September 1938; in the PAS, J.M. Uhrich R-97, 9c: Cancer – General A-G.
since a multi-level interchange of laboratory and clinical research results across Canada in the absence of a coordinating body was problematic at best.

1.3. Conclusion

Canadian public health officers considered declaring a continuous increase in malignant diseases during the 1920s an epidemic. Standardized vital statistics and the unknowns of the cancer problem, like etiology and transmission, served to justify this course of action. To recognize the cancer epidemic formally meant that medical authorities had to make malignancies notifiable and utilize the existing healthcare framework for managing epidemics. In the atmosphere charged with political indetermination in the wake of debates on influenza outbreaks, the rise of cancer was an unsettled issue. Hence, provincial and federal representatives of Canadian organized medicine, influenced by the international scientific-medical community, adopted a wait-and-see policy.

Given the situation, physicians dealing with cancer had leeway to introduce experimental procedures. A driver for this experimentation was a scientific discovery – the effect of radiation. As medical uses of X-rays and radium showed promise in treating otherwise incurable cancer patients, an optimistic mood revived among physicians who had witnessed triumphs of bacteriological hygiene. A new scientific-medical cluster of radiotherapeutic technology stimulated public and state initiatives in the organization of cancer control in Britain, France, and in the United States, which prompted Canadian healthcare officers to promote similar collaborative undertakings.

Despite resistance from the majority of surgeons and physicians, radiotherapy was blazing its trail to the frontline of treatment modes. What accelerated this process in Canada was an increasing use of radium by ingenious private practitioners, which conservative professionals regarded as a form of quackery, if not human experimentation. To resolve this dispute about a possibly harmful practice – in relation to the patient’s health and to the profession’s reputation – the medical community enlisted the help of physicists.

A scientific-medical conversation on radiotherapy actuated organizational changes in Saskatchewan. Faced with a putative epidemic of malignant disease and spurred by anti-cancer
activists, the Department of Public Health of Saskatchewan mobilized the Medical Association and the university in the province. Their joint efforts contributed to the formation of the first cancer committee in Canada – the Saskatchewan Cancer Commission, which marked the beginnings of a national cancer program in 1930. The three authoritative bodies acting in concert introduced a new cancer control regime without major difficulties. Several hundred medical professionals diffused across the province lent themselves well to regulation since they did not have firmly entrenched loyalty groups competing among themselves. By contrast, in Eastern Canada, especially in Ontario, opposition to the introduction of a comparable cancer-management regime was strong in view of the diversity of deep-rooted professional groupings with competing interests.

The example of Saskatchewan demonstrated how a statutory program in cancer control came into being when a public fear of the alleged epidemic, innovative radiation therapy, and uncertainty among medical professionals overlapped. It was a successful transformation that provided a blueprint for organizing major politico-economic and medico-scientific actors to reach a socially important goal. The success in Saskatchewan galvanized into action other provinces by triggering not only the formation of cancer committees, societies, and institutes across Canada, but also the federalization of Canadian Medical Associations. These organizational activities involved increasing numbers of laypeople and their growing support culminated in the foundation of the Canadian Society for the Control of Cancer in 1938. Its educational campaigns heightened public awareness of the cancer problem and encouraged patients suspecting the disease to visit physicians who referred them to specialized clinics. The latter played an important role in improving treatments through systematic research, in creating a space for teamwork of the clinician and the investigator, and in keeping reliable cancer records.
Chapter II

_Shifting Sands of Organizing, Problematizing, and Rationalizing Cancer Research in Post-War Canada._

One of the major consequences of World War II was a reassessment of consolidated scientific-medical research. Wartime circumstances showed how expendable humans might be in biomedical investigations serving as both objects and subjects of research. Ideologies of national utility and expediency trampled on human dignity. The post-war revelations of both military personnel and civil victims brought to light clear evidence on the abuse of humans for investigational purposes, not to mention a mass extermination of people due to National Socialist doctrine in Germany. These accounts of atrocities induced an international framework that could avert a recurrence of the inhumanity on a similar scale.

In 1947, a subdivision of the United Nations (UN), the Commission on Human Rights, drafted an outline of an International Bill of Human Rights. This document laid out the principles of universal human rights and duties the respect of which could preserve a lasting peace globally. The General Assembly of the UN involving major world powers approved the

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1 How the program of scientific experiment in changing cultural circumstances entered medicine and contributed to human experimentation in particular historical contexts is discussed in Erika Dyck and Larry Stewart, eds., _The Uses of Humans in Experiment_, 21-23.


3 A temporary working group assigned with drafting an International Bill of Human Rights noted “that ignorance and contempt of human rights have been among the principal causes of the sufferings of humanity and of the massacres and barbarities which outraged the conscience of mankind before and especially during the last world war; and [...] that there can be no true peace unless human rights and freedoms are respected; and only by abolishing war and the threat of war can human freedom and dignity be assured to all mankind.” See Drafting Committee on an International Bill of Rights, First Session, “Report of the Drafting Committee to the Commission on Human Rights,” 1 July 1947, E/CN.4/21, p.69: [http://research.un.org/en/undhr/chr/1](http://research.un.org/en/undhr/chr/1).
International Bill of Rights and affirmed unanimously “the dignity and worth of the human person” to be the basis of fundamental human rights and freedoms determined in the International Bill of Rights. The latter also provided that “Every one has the right […] to share in the benefits of science”, but “No person shall be subjected to […] medical or scientific experimentation against his will.” These propositions constituted a recurrent theme throughout a public Medical Trial in Nuremberg, Germany, at which the prosecuted Nazi officials attempted to justify their serial human experimentation. The triad of a mortal person, an ambivalent benefit, and an immortal science proved to be a highly intractable problem in the courtroom. What complicated the proceedings was a legal status of existing documents that stipulated the limits of scientific-medical experiments involving humans.

There were no international legal instruments to regulate human subject research, nor did an authoritative body competent to adjudicate on such matters exist. The Medical Trial, having generated a considerable publicity, turned out to be an appropriate venue to fill this gap. For instance, in *The Lancet*, a series of commentaries on the topic of Nazi doctors’ misuse of human subjects in scientific-medical experiments and subsequent publication of results therefrom provoked a lasting professional and public discussion in the press. Views on the above ethical

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5 As in the original. *Ibid.*, 21 and 82.  
6 For example, the German Circular of the Reich Minister of the Interior as of 1931, recognized at the Medical Trial as valid guidelines for human experimentation, formulated prerequisites for human subject participation in both therapeutic and non-therapeutic investigations. Importantly, what preceded the promulgation of this document was an unsuccessful BCG vaccination of children at Lübeck, Germany, in 1930. See Michael A. Grodin, “Historical Origins of the Nuremberg Code,” in *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*, ed. George J. Annas and Michael A. Grodin (Oxford: Oxford University Press, 1992), 129-131.  
dilemma were divided among the British medical profession. Likewise, parliamentary debates in Canada drew public attention to the reported abuse of science in the name of war exigencies. M.J. Coldwell, a leader of the Co-operative Commonwealth Federation party, declared in June 1946, “Let us bear this in mind, there can be no blackout of science. The Germans tried it, but did not succeed. We cannot blackout science. If we cannot black it out, then the thing to do is to have an organization through which scientific knowledge can be disseminated.

On this background, post-war clinical cancer research entailed a similar dilemma of rational organization of local investigations. On the one hand, a cancer patient more often than not faced the experimental approach of doctors who followed their empirical findings. Although there was a standard therapy for about one third of diagnosed malignant diseases, the better part of intractable cancers lent themselves to therapeutic experimentation. On the other hand, a grudging professional recognition of the epidemic of neoplastic disease implied a moral justification to introduce controlled human experimentation on a vast scale at least in specialized institutions. Within the compass of such organization of cancer investigations, comprising both laboratory and clinical work, fell institutions for medical research, universities, and teaching hospitals. All three epitomized systems of institutional governance and control by clinicians and scientists, which accorded with a war-imposed *modus operandi* in strategic branches of economy.

In this chapter, I situate the formation of the National Cancer Institute of Canada in the post-war context of scientific-medical cooperation and analyze several research projects supported by the NCIC and government agencies. Examining projects in nuclear medicine involving the betatron, radioisotopes, and the Cobalt-60 beam therapy units, I discuss the issue of indeterminacy of therapeutic clinical research. I argue that physician-investigators designated their clinical studies as experimental treatment, fundamental research, or something in between, to justify the conduct thereof in given circumstances. Their justifications were based on self-authenticated facts obtained in the process of therapeutic innovation by using novel technologies. The question of indeterminacy came into focus because pioneering investigators were the only

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arbiters of ethicality of their clinical research combined with therapy. Hence, the ethical acceptability of clinical trials was open to interpretation by a limited number of physician-innovators who adapted medical ethics to investigations of indeterminate therapeutic value.

The scientific-medical community that had gained access to new technologies faced the challenge of ascertaining whether some investigative practices put human subjects’ health at serious risk unnecessarily. This issue had received a fair hearing at the Medical Trial in Nuremberg, where a collective judgment defined what could be considered “permissible medical experiments” to provide a foil for instances of criminal human experimentation. Judge Harold Sebring pointed out that medical experiments on human beings were not justifiable by their results yielding benefits to society and “unprocurable by other methods or means of study” unless “certain basic principles [were] observed in order to satisfy moral, ethical, and legal concepts.” Those ten principles gained fame later under the name Nuremberg Code. Substantially, the principles tackled the conundrum of determining under what conditions medical experiments may be deemed unethical and criminal acts. This was problematic, since the war effort prompted groups of researchers to close ranks both at regional and international levels.

From a secret collaboration in atomic energy arose a strong association of Canada with the UK, France, and the US. The Eldorado mine on the Great Bear Lake in Northwest Territories of Canada and a refinery at Port Hope, Ontario, which produced enriched uranium and precious radium since the 1930s, supplied rare radioactive materials for nuclear research in the early 1940s. The British-Canadian scientific cooperation resulted in the establishment of the Montreal Laboratory in 1942, which involved over 340 collaborators in the atomic energy project – the largest research organization in Canada at the time. The UK, the US, and Canada formed a combined policy committee on atomic developments in 1943, a joint effort that made

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the construction of a unique nuclear plant at Chalk River possible a year later. American, British, and Canadian investigators collaborated on military-oriented projects through sharing otherwise classified information, which facilitated development of an efficient mode of operation tailored to particular objectives. Intensified interchange of knowledge and experience led to multi-member research teams performing complementary investigations in different places. These long-distance interchanges and mutually coordinated investigative activities set the pattern for establishing an organization in charge of cancer research in Canada.

### 2.1. The NCIC: Origins and Objectives

Within months of the opening of the Nuremberg Trials, the National Cancer Institute of Canada (NCIC) came into existence after its legal incorporation on 24 March 1947. Its unofficial launch, however, occurred in late January of the same year, when the Department of National Health and Welfare convened a two-day cancer conference in Ottawa to recognize publicly the extent of malignant diseases countrywide. That meeting was a culmination of a series of events that raised public consciousness on the issue of a cancer epidemic. In the Canadian Parliament, the scourge became tangible as two members of the House of Commons died from it within several days in 1946. On the second and the ninth day of May, Wallace R. McDonald and Harry

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16 Some Canadian scientists who engaged in solving practical problems of the army and navy, e.g. motion sickness, became leading cancer researchers in peacetime. See Robert L. Noble, Edward A. Sellers, Charles H. Best, “The Treatment of Motion Sickness: a Review of Therapeutic Studies Sponsored by the National Research Council of Canada,” Can. Med. Assoc. J., 56, no.4 (April 1947): 417-424. The authors wrote, “It was fully realized that even when subjects of proved susceptibility to swing sickness were selected for further therapeutic trials, and when such trials were controlled by placebo treatment, the results of the swing experiments could be used only as an indication of those substances which merited testing at sea” (418). There were only slight variations on this research design when experimental belladonna alkaloids, barbiturates, and other substances moved from the battlefield to the clinical domain subsequently.

17 Gordon E. Richards, “Report of Board of Directors of the First Year’s Activities of National Cancer Institute of Canada, 7-8 May 1948, p.3; in the Western Archives, Western University (hereinafter the WUA), the University of Western Ontario, Office of the President Fonds, Series 6: George Edward Hall, AFC 40 - 19/20, NCIC, 1947-1948.
Leader succumbed to cancer. Whereas McDonald was quite reticent about his illness, Leader openly admitted it and even delivered speeches on the importance of cancer research and new approaches to cancer treatment while suffering from the dread disease. Leader’s active role in reinforcing the message of struggle against cancer, in Parliament and beyond it, served well to draw attention to a nation-wide campaign for fundraising and furthering concerted efforts to meet the threat of cancer.

The loss of two parliamentarians united members of both the ruling and opposition parties in mourning. Associating with remarks of the Prime Minister W.L. Mackenzie King, the opposition leader John Bracken, among other members, pointed out unambiguously: “this disease [‘which all too often proves fatal’] still has secrets from medical science.” This statement regarding the two deaths seemed to indicate a virtual powerlessness of organized medicine against the scourge. As the news reached many Canadians through the radio and the press, activities of a newly created Department of National Health and Welfare came into focus, particularly through its minister – Brooke Claxton. Under the pressure of demands for accountability, Claxton had to report on cancer-related developments almost in every sitting of the Parliament. In late May of 1946, he informed the House that informal discussions with provincial ministers and their deputies on Canadian cancer control were underway. In Claxton’s words, “The objective will be a programme of work in cancer, using all means, which will mobilize all the resources that can be mobilized within Canada and to see to it that we do everything possible to find the cause and the cure of cancer.”

Drawing on the multilateral talks, Claxton conceived of four directions to employ potential resources efficiently: public education, training of cancer diagnosticians and radiotherapists, improving facilities for cancer treatment, fostering physicians and scientists’ interest in doing cancer research. A transition from war to peace in state governance made the potential to reconfigure coordinating and funding

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18 Wallace Reginald McDonald, aged seventy, and sixty-six-year-old Harry Leader represented the constituencies of Pontiac, Québec, and Portage la Prairie, Manitoba, respectively, in the Canadian House of Commons. See the DCORHC Debates, Twentieth Parliament, Second Session, Index Volume, March-August 1946, p. vii.
20 The DCORHC Debates, 31 May 1946, p.2070. The department was formed on 13 October 1944.
21 Ibid., 2072.
22 Ibid., 2073.
mechanisms underlying medico-scientific projects realizable. It meant that governments could repurpose a part of the war-effort funding to healthcare programs.

Until 1938, neither the Canadian government, nor other national agencies had played a role in encouraging cancer research across the country. That year, concurrently with the formation of the Canadian Society for the Control of Cancer, the National Research Council (NRC) created an Associate Committee on Medical Research. Its objective was to bring into correlation medical investigative work at Canadian universities and medical schools, which conducted the bulk of medical research, by supporting selected projects through grants and scholarships. The NRC adopted a mechanism of Associate Research Committees to supplement its existing system of National Research Laboratories that focused on such broad fields as agriculture, biology, chemistry, engineering, and physics. Research in more specific areas, like cancer, necessitated a more flexible approach to its coordination in view of the small number of investigators engaged in highly specialized work, and due to difficulties in aligning such projects with the operation of mainstream programs of research. Along these lines, the NRC made allocations of funds based on where the most suitable researchers and facilities were available for particular projects.

23 On the proposal of the NRC Honorary Advisory Council in 1936, its President Andrew G.L. McNaughton informed the CMA and the RCPS about a possibility to form an Associate Committee on Medical Research (ACMR). Subsequently, the CMA appointed a special subcommittee to consider the subject and discuss it with representatives from the NRC and the Department of Pensions and National Health. As a result, the NRC Preparatory Committee arranged a Conference on the Organization of Medical Research in Canada. On 18 February 1938, representatives from principal medical organizations engaged in research participated in this conference held in Ottawa. Already in March, the ACMR was established, and on 6 May 1938 Frederick G. Banting became its first Chairman. Soon after, he undertook a survey of medical research facilities in Canada by visiting investigators in major centers. See letters from A.G.L. McNaughton to Dr. J.S. Thomson (President, University of Saskatchewan), Ottawa, 6 November 1937; 18 July 1938; and 26 September 1939; in the USL, RG 2001, II, B119 (1), NRC. See also an enclosure to a letter from G. Edward Hall to F.T. Rosser (Vice-President Administration, NRC), 19 September 1957; in the WUA, AFC 40 – 36/2, NRC 1957-1958.

24 Acting President of the NRC and a former Dean of the College of Engineering at the University of Saskatchewan, Chalmers Jack Mackenzie, explained how the Associate Research Committees operated, “The National Research Council provides the Associate Committee with a yearly grant and the Committee then functions as an autonomous body with complete control over the distribution of the finances and is in no way subordinate in its operation to the main Council. At their meetings decisions are taken as to how the work of the various bodies can best be co-ordinated, what programmes shall be adopted, where additional work shall be done, and grants are made to various laboratories to carry on projects.” See C.J. Mackenzie, “Organization of National Research Council: An Address at Canadian Chemical Conference,” Toronto, 7 June 1944: 3. In the USL, RG 2001, II, B119 (3).
Grants targeted at cancer investigations were negligible in comparison with provincial allocations for the same purpose or the Canadian Society for the Control of Cancer expenditures on the educational campaign. The amount NRC-granted assistance indicated the dearth of experienced personnel and designated space for carrying out research into cancer. However, the Minister of National Health and Welfare, Claxton, explained it: “[…] fundamental medical research […] is usually best carried on in connection with clinical opportunities which are to be found most frequently in large centres where they have hospitals in association with teaching institutions.” His explanation was a fair representation of reality because therapeutic trials were the prerogative of teaching hospitals and specialized cancer institutions.

Spending on cancer research dwindled during World War II, since the majority of Canadian doctor-investigators had to be re-oriented to work on pressing problems of scientific-medical military research. Even the Cancer Committee of the Canadian Medical Association settled for a reduction of its annual grant of $14,000 from the King George V Silver Jubilee Cancer Fund by half. At the same time, the NRC activities expanded in diversity and magnitude owing to unprecedented rises in expenditure on targeted projects. The NRC annual expenditure increased from nearly one million to seven million dollars over 1939-1945. Those figures excluded an enormous financial support of various secret investigations by the Department of Munitions and Supply and the Department of National Defense.

A war-associated suspension of most cancer projects did not correlate with changes in cancer mortality. However, Figure 2-1 shows that cancer reporting diminished somewhat over the war years. As soon as non-emergency operations in the Canadian economy resumed, the government decreed that the extent of funding for investigative activities in science and medicine maintained in wartime remain the same because of exigencies of public health in peacetime. Military fear-mongering transmuted into civil phobias about disabilities and diseases, and the

25 Over the period 1939-1945, the grants amounted to mere 4,364.5 Canadian dollars. In 1939, the Associate Committee on Medical Research had $53,000 budgeted for funding of all projects, of which $1,277.16 was committed to cancer research, or 2.4 percent. See the DCORHC Debates, Twentieth Parliament, Third Session, Vol. IV, 29 May 1947, p.3565; and Alison Li, J.B. Collip and the Development of Medical Research in Canada, 154.
27 Ibid., p.2057.
28 The DCORHC Debates, 27 May 1946, p.1885.
29 Ibid. The NRC had at its disposal about $6,378,000 budgeted for 1946.
dread of cancer was second to none. As reports on battlefield casualties disappeared, cancer facts filled the void. An uninterrupted collection of data on malignancies in Canada showed that the epidemic was not abating. Death resided in numbers, making an abstract scourge quantitatively specific, so politicians wielded statistics as the most piercing of weapons. “Cancer kills one in every eight people in Canada,” declared William G. Blair, physician and member of the House of Commons, in his statement on the importance of health research. A representative of the medical profession, Blair repeatedly resorted to statistical data to portray, in his view, the greatest problem confronting medical research that received only a paltry amount of money for its investigation. Championing public subscription in anti-cancer endeavors, Blair was a vocal critic of the government’s inaction on the cancer front. He exalted a money-raising campaign for the Ontario Cancer Fund and at the same time deplored the King George V Silver Jubilee Cancer Fund sitting idle. At the time, those messages could not be easily dismissed.

![Number of Deaths from Cancer in a Total Population of Canada, 1936-1951](image)

*Figure 2-1. CDBS, Vital Statistics 1936-1951: Annual Reports.*

For the Dominion Council of Health (DCH), a rising public concern about the cancer problem found its way to particular recommendations when the trustees of the King George V Silver

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30 William Gourlay Blair was the member for the constituency of Lanark, Ontario. See the *DCORHC Debates*, Twentieth Parliament, Second Session, Vol. II, 31 May 1946, p.2057.
Jubilee Cancer Fund decided to put it to use entirely.\textsuperscript{32} At the fiftieth meeting in November 1946, the DCH recommended that the Department of National Health and Welfare convene a national conference on cancer control to formulate an action plan.\textsuperscript{33} The latter required resolutions not only on the disposition of the King George V Fund, but also on the role of existing fund-raising bodies, and on standardizing cancer reporting nationally.\textsuperscript{34} As suggested in Chapter 1, medical practitioners tended to cooperate more readily in cancer notification when the Saskatchewan cancer program was in place, and by analogy, the same trend was envisioned at a national level.

To arrive at a publicly acceptable consensus on the above three issues necessitated participation of delegates from key Canadian organizations, both voluntary and governmental, in the proposed conference. Thus, the DCH committee advised to invite chief health officers from all provinces, the trustees of the King George V Fund, representatives from the Canadian Cancer Society and its Divisions, delegates from the Canadian universities engaged in cancer research, and from the CMA Committee on Cancer.\textsuperscript{35} The only remaining thing was to act at that conducive moment.

Within weeks after becoming the Minister of National Health and Welfare, Paul Martin launched the machinery to set up the conference.\textsuperscript{36} On 27-28 January 1947, Ottawa hosted the

\textsuperscript{32} The board of trustees included the Prime Minister, the Leader of the Opposition, the Minister of National Health and Welfare, the Chief Justice of Canada, a representative from insurance agencies, the University of Toronto professor of pathology William Boyd, and the Dean of Faculty of Medicine at the University of Montreal – Edmond Dubé. See the DCORHC Debates, Twentieth Parliament, Third Session, Vol. IV, 10 June 1947, p.4004.

\textsuperscript{33} The Dominion Council of Health, 6-8 November 1946. In the DCH Fonds, MG 28 I 63, 100130, reel C-9816. In the Library and Archives Canada / Bibliothèque et Archives Canada (hereinafter the LAC).

\textsuperscript{34} The DCH recommended in its Resolution No. 6 that “the Department of National Health and Welfare undertake the necessary measures to have physicians in Canada acquainted with the necessity for adequate reporting to appropriate bodies of cancer cases; and [...] that the Dominion Council of Health endorse the principle of national reporting of cancer cases.” See The Dominion Council of Health, 6-8 November 1946, Appendix B, p.3; in the LAC, DCH Fonds. In Ontario, for instance, the agencies concerned with cancer care, which had different financial sources, comprised the Canadian Cancer Society, Ontario Division (1938), the Commission for the Investigation of Cancer Remedies (1938), and the Ontario Cancer Treatment and Research Foundation (1943). See “Report of the Ontario Health Survey Committee. Section H. Control of Cancer,” pp.138-149, enclosed with a letter from J.H. Broughton (Secretary-Treasurer) to G.E. Hall, Toronto, 27 June 1952; in the WUA, AFC 40 – 26/38, OCTRF 1952-1953.

\textsuperscript{35} DCH, 6-8 November 1946, Appendix G; in the LAC, DCH Fonds.

conference that cost $582 but was inestimably valuable for the coordination of cancer research in Canada. An immediate result of the conference was the formation of an Interim Committee to organize a scheme to support cancer projects and to incorporate the National Cancer Institute of Canada (NCIC). Another outcome of the conference was the agreement of the trustees of the King George V Fund to place at the disposal of the incorporated NCIC $450,000 in three annual grants. Paul Martin stressed that the Prime Minister had put forward a motion to allocate the fund in full and the Leader of the Opposition seconded it, which appeared to indicate that cancer research was a national concern that engaged a cooperative effort at all levels of government.

With state involvement, medical authorities and cancer agencies in Canada secured collaboration at the conference as they allied themselves under the burgeoning NCIC. This joint recognition was necessary to organize an all-Canadian specialized agency dedicated to support cancer research in institutions constituting units of autonomous provincial healthcare under provisions of The British North America Act. In this connection, Paul Martin stated in the House of Commons:


40 To administer affairs of the NCIC, the following organizations agreed to work together: Association of Medical Colleges of Canada, Canadian Cancer Society, CMA, Canadian Public Health Association, DNHW, DCH, Diagnostic and Treatment Agencies of the Provinces, NRC Medical Research Division (1946), National Federation of Canadian Universities, and RCPS. Sixteen representatives from the above bodies nominated another five medical scientists as associate members, which altogether formed a voting membership of twenty-one appointees for a three-year term. All appointees elected a five-member board of directors annually. See G.E. Richards “Report of Board of Directors of the First Year’s Activities of National Cancer Institute of Canada” (1948): 5-6; in the WUA, AFC 40 - 19/20.

41 According to a prototype of the Canadian Constitution, The BNA Act 1867, Chapter VI – Distribution of Legislative Powers, s.92, “In each Province the Legislature may exclusively make Laws in relation to Matters coming within [...] 7. The Establishment, Maintenance, and Management of Hospitals, Asylums, Charities, and Eleemosynary Institutions in and for the Province, other than Marine Hospitals.” Although the dividing line between provincial and federal division of powers is rather unclear in this section, a legal interpretation favors putting public health administration, including cancer care, under the provincial jurisdiction.
There was perhaps no legal authority to call that conference because, under the constitution, matters of health, except those referred to specifically in the British North America Act, came primarily under the provinces. Many of the provinces regard that particular field jealously; they regard it as a field in which they should have priority of interest in both administration and policy […, but] [e]very one of the provincial departments of health cooperated.42

This all-provincial agreement became possible because both the medical profession and the political establishment turned to considering cancer as a national problem.

A notable contribution to this interpretation of cancer as a threat to society came apparently from Great Britain and the United States, which also provided a model for the NCIC via the Imperial Cancer Research Fund and the National Cancer Institute, respectively. In keeping with these models, the NCIC became a non-governmental and a non-profit-making body.43 These features of the NCIC made it similar to the Dominion Council of Health and the Canadian Cancer Society, which had authority to recommend, facilitate, and execute courses of action, but not to enforce them. Besides, the NCIC aimed to ensure continuity of cancer research programs that otherwise fell within the purview of autonomous provinces having fluctuations in public health expenditure.

The NCIC allowed cancer researchers to bypass provincial constraints on funding projects not included in healthcare budgets. A clear signal that the NCIC Interim Committee got down to work was a notification to all universities and specialized institutions about the availability of financial assistance for cancer research and a call for applications. On 12 May 1947, shortly after the NCIC organizational meeting in Toronto, the only female parliamentarian, Gladys Strum of Saskatchewan, addressed a series of queries on Canadian cancer research to Paul Martin in the House of Commons.44 In reporting on the developments in question, the

42 The only matter that fell under the exclusive Legislative Authority of the Parliament of Canada pertained to Ch. VI, s.91, clause 11, “Quarantine and the Establishment and Maintenance of Marine Hospitals”. See The BNA Act 1867 and the DCORHC Debates, Twentieth Parliament, Third Session, Vol. IV, 10 June 1947, p. 4008-9.
43 See the DCORHC Debates, 28 May 1947, p.3513.
44 Gladys Strum was elected Member of Parliament for the constituency of Qu'Appelle, Saskatchewan, after she had defeated General A.G.L McNaughton, the-then Minister of Defense. From 1945 until 1949, the House of Commons comprised one woman and 244 men. Gladys Strum also was the first woman president of a Canadian political party – the Co-operative Commonwealth Federation of Saskatchewan – in 1944. See Celebrating Women's
Minister of National Health and Welfare indicated that requests for grants received from cancer research institutions amounted to about $200,000, and he projected that a total of requested assistance would rise to $300,000 by the end of the application period on 1 June 1947. Given that the NCIC assets consisted of $150,000 allotted yearly from the King George V Fund, which fell short of the requested funding, Paul Martin announced that the Medical Research Division of the National Research Council (NRC), which replaced the Associate Committee on Medical Research in 1946, had additional financial support readily obtainable. Importantly, the NRC Medical Research Division was also in charge of screening applications for cancer grants-in-aid. This fact alone suggested that atomized clusters of cancer specialists in Canada were not as efficient in assessing the feasibility of proposed projects as the NRC Medical Research Division experts were. To make those clusters cooperative was another reason to organize the body coordinating a national cancer research program.

A prompt formation of the NCIC, which in some ways resembled the coming-to-be of the Associate Committee on Medical Research in 1938, reflected a sense of urgency among major actors in the Canadian scientific-medical establishment who had participated in the mobilization of human and material resources to achieve otherwise unattainable results. During World War II, the combination of army services’ priorities with the work of civilian research teams under the state administration crystallized many a practical plan in military terms, and this optimism translated into the approach to the cancer problem. If concerted efforts of biochemists and


P. Martin suggested that this large sum would amount to “the annual recurring budget for research alone”, meaning operational costs excluding administrative expenses. See the DCORHC Debates, Twentieth Parliament, Third Session, Vol. III, 12 May 1947, p.2956.

Ibid. Paul Martin noted that the available cancer research funds were included in the “federal health grants under the health insurance section” of the dominion proposals to the provinces. In 1946, the NRC Medical Research Division had a starting budget of $200,000. See Alison Li, J.B. Collip and the Development of Medical Research in Canada, 159.

On the approval of cancer research applications, the NCIC stipulated provision of fellowships for the training of budding investigators, thus encouraging them to work full-time on their projects. See the DCORHC Debates, Twentieth Parliament, Third Session, Vol. III, 12 May 1947, p.2956.

Creation of additional Associate Committees on aviation, naval, and army medical research at the time probably expedited a consolidation in the form of the Medical Research Division under the NRC. As the NRC President, C.J. Mackenzie put it, “Those who are familiar with the work of the Medical Committees agree that, in no field of Canadian science, have the contributions been more generally appreciated, not only in Canada but in the United
nuclear physicists yielded effective means to sap the foundations of life, why could further explorations of these avenues not provide an improved armamentarium to restore health of cancer sufferers? The NCIC aimed at enabling researchers to answer this question among others.

“To coordinate and correlate the efforts of individuals and organized bodies with a view to reducing the morbidity and mortality from cancer” was the primary aim listed in the NCIC Letters Patent. Those efforts signified fundamental research activities facilitated by funding, training, and equipping investigators in the field of cancer. Importantly, out of ten clauses in the NCIC Letters Patent specifying its aims and objects just two related to clinical aspects of cancer research. This fact indirectly meant that the NCIC had a mission to create favorable conditions for securing continuity in basic research that could provide a stable foundation for diagnosis and treatment of tumors. Albeit, decades of investigative work in teaching hospitals and clinics had fostered a culture of medical research that focused more on clinical trials than on laboratory explorations of these avenues not provide an improved armamentarium to restore health of cancer sufferers? The parliamentarian Gladys Strum, a teacher by training, provided an insight into this culture from a lay perspective, “In the course of treatment we shall uncover better and newer methods of treatment and, finally, through a combination of

States and the United Kingdom.” The NRC Liaison Offices in London, Ottawa, and Washington D.C. served as access points for direct exchange of all scientific information of both military and civilian nature. See Mackenzie, C.J. “Organization of National Research Council” (1944), 4-6; in the USL, RG 2001, II, B119 (3), NRC.

49 Politicians and doctors often juxtaposed battlefield casualties with deaths from cancer to draw public attention to the scourge. Two examples will suffice. J. Llew. Little, a Guelph physician whom the DHC appointed as a full-time registrar of the NCIC, wrote, “During the period of World War II, that is, 1939-1945, close to 80,000 men and women died of cancer, contrasted with 38,834 war casualties, killed and missing. The war cost Canada close to $19,000,000,000. The amount spent on cancer control for the same period amounted to not more than $5,000,000. The comparison is obvious.” See J.L. Little, “Editorial: National Cancer Institute of Canada” (1947): 325. Gladys Strum, a parliamentarian, stated in the House of Commons: “I find that the cancer casualties during the war period were 95,627 as compared with 41,000 casualties in the theatre of war. So that actually here in Canada our losses were twice as heavy from the killer cancer as they were in the shooting war where our men were engaged in actual physical combat.” See the DCORHC Debates, Twentieth Parliament, Third Session, Vol. V, 11 June 1947, p.4055.


51 Ibid., 3-4. One of them read, “To operate and maintain facilities for the purposes of treatment and research.” The other was “To assist in the examination of any method of cancer prevention, treatment or cure, when so requested by any Dominion or Provincial Government body.”
clinical and research effort, I hope we shall get this disease under control.”52 Her statement implied that the clinical part in cancer therapy development took precedence over the research effort. To confirm or reject this speculation, it is necessary to look into experimental modes of cancer treatment introduced by innovations in technology.

2.2. Betatron and Experimental Treatment

The betatron was a prime example of technological expansion that hinged on wartime experimentation.53 An ingenious apparatus for producing high-energy X-rays, developed during World War II to check massive steel castings for defects, the betatron found a new application in medical physics as military needs had dwindled. Illinois investigators in Chicago and Urbana, two centers where the US Department of Defense sponsored its naval research in physics and radiobiology, put a 20 MeV betatron into operation for an experimental treatment of one cancer patient in the spring of 1948.54

After rigorous testing of the 20 MeV betatron in terms of its physical and biological effects, a scientific-medical group from the University of Illinois, the Carle Hospital Clinic, and the Tumor Clinic of Michael Reese Hospital used the betatron to treat a patient suffering from a malignant brain tumor – glioblastoma.55 The patient, a twenty-seven-year-old white male student, had undergone neurosurgery at the Mercy Hospital of Chicago and subsequently received postoperative radiation therapy with an 800keV X-ray machine over ten days at the Mercy Hospital Institute of Radiation Therapy in March-April of 1948. Those therapeutic efforts were relatively unsuccessful according to medical reports, and clinicians in consultation with

physicists decided to initiate radiation treatment with the betatron as the last resort on 30 April 1948.\textsuperscript{56} The following proposition may explain their reasoning:

> It seemed that the man had a small but not entirely negligible chance of cure if treated with the betatron. The moral issue was simple. We could let the patient die without disturbing him further, or he could be given a last chance. This could be done without much inconvenience either to him or to his family. There was little doubt as to which decision to make.\textsuperscript{57}

There was no mention, however, of a corresponding decision on the part of the patient and his family. Decision-making was in the hands of experts who were allegedly knowledgeable about the ethical side of the matter.\textsuperscript{58} The ethics in this case concerned not only the individual’s potential exposure to unknown harm, but also a probable collective benefit, as the Illinois investigators suggested: “The risk involved [in using the betatron therapeutically] seems smaller than the opposite risk which is incurred if the betatron is withheld for a long period of time from patients who might benefit by its use.”\textsuperscript{59}

Unlike conventional radiotherapy, the 20 MeV betatron treatment showed promise. For a week, the patient improved slightly, his vital signs stabilized, and there were no indications of radiation sickness. The latter did not occur because investigators proceeded with this treatment cautiously, as the daily irradiation regimen suggested.\textsuperscript{60} They even developed a special system of cross-firing beams that distributed a radiation dose from the betatron quite uniformly and efficiently. Albeit, the patient’s general condition deteriorated markedly at the end of the second week. In view of his increasing weakness, the radiotherapy was discontinued.\textsuperscript{61} This course of action indicated that the patient’s failing health was more important for clinical researchers than

\textsuperscript{56} Ibid., 618.
\textsuperscript{57} Ibid., 592.
\textsuperscript{58} Ibid. Interestingly, the experts initiated the institutional process through the University of Illinois authorities that cleared the machine for its use in therapeutic research, and via the Carle Hospital Clinic that accepted the medical responsibility for the experimental treatment.
\textsuperscript{59} Ibid., 595.
\textsuperscript{60} Ibid., 619.
\textsuperscript{61} Doctors stopped the betatron treatment “at the dose of 4,669 instead of reaching 6,000 r.e.b.a. as originally intended.” Allowing for clinical applications of the betatron, the research team purposefully created a ‘r.e.b.a.’ unit, which stood for “roentgen equivalent by bio-assay”, to correlate biological effects of a certain dose of radiation from a 200keV machine, expressed in ‘roentgen equivalent man’ or rem, with the same biological reaction produced by the betatron which radiation dose needed measurement. Ibid. 596, 619, and 622.
scientific or administrative interests. The patient died on 30 May 1948 and a retrospective evaluation of the experimental treatment followed with no less thoroughness than the preparatory work.\textsuperscript{62} Investigators’ considerations of further clinical research with the betatron loomed large.

In Canada, the University of Saskatchewan’s Physics Department had a similar betatron by August 1948.\textsuperscript{63} This expensive installation became possible owing to two factors. First, the Canadian Atomic Energy Project, a division of the National Research Council, continued to forward its research in nuclear physics.\textsuperscript{64} With investments in the astronomical range of about twenty million dollars as of July 1947, officers of the Atomic Energy Control Board (AECB) hesitated more about where to channel available financial resources than about the sums to be expended on designated projects.\textsuperscript{65} Canadian universities that had excellent credentials in physics were obvious destinations. Three academic institutions – the University of British Columbia, McGill University, and the University of Saskatchewan – had both personnel and facilities for research auxiliary to the atomic energy project. Those facilities became further enhanced, correspondingly, through a linear accelerator, a cyclotron, and a betatron, which received assistance for their installation from the AECB.\textsuperscript{66} Only the betatron was contemplated at the time.

\textsuperscript{62} For instance, the investigators admitted that they could have administered higher radiation doses because the glioblastoma was not radiosensitive enough and the betatron showed very efficient depth-dose distributions for the treatment of this deep-seated tumor. They also determined two factors that limited a successful clinical application of the betatron: relatively unknown outlines of the internal cancerous region of soft tissue and the spread of metastases. In their assessment of the betatron’s application, however, the investigators concluded, “the betatron offers good methods for tumor regions of any shape and in any position in the human body. In general, with high energy roentgen rays it will be possible to irradiate any tumor region without delivering high doses anywhere outside the tumor region.” The latter was of paramount importance in view of the limits of the lower energy X-ray machines. \textit{Ibid.} 623

\textsuperscript{63} Houston, \textit{Steps on the Road to Medicare}, 112-115.

\textsuperscript{64} Since the promulgation of the Atomic Energy Control Act of 1946, c.37, s.1, this investigative domain became, arguably, the most propitious for scientific work. The Act not only stipulated encouragement and facilitation of investigations in nuclear research, but it also empowered the newly constituted Atomic Energy Control Board to “appoint and employ such professional, scientific technical and other officers and employees as the Board deem[ed] necessary notwithstanding the Civil Service Act or any other statute” (8b and 9a). In the WUA, London Regional Cancer Centre fonds, AFC 328.1.2829, New Advisory Committee on the Clinical Uses of Radioactive Isotopes, 1952-1963.


\textsuperscript{66} \textit{Ibid.}
for applied research in the field of cancer in addition to experimental work in physics. Such a division of research activities was not haphazard, however.

No less important factor for the betatron’s installation in Saskatoon was a strong connection between the University of Saskatchewan and the Saskatchewan Cancer Commission. Physicists Ertle L. Harrington, R. Norman H. Haslam, Leon Katz and Harold E. Johns directed research both in experimental nuclear physics and in medical physics at the University of Saskatchewan. Physician Allan W. Blair, Director of the Regina Cancer Clinic and of Cancer Services for Saskatchewan, and Thomas A. Watson, a therapeutic radiologist heading the Saskatoon Cancer Clinic, had a keen interest in ameliorating the existing radiotherapeutic modalities by means of the betatron. Both groups supported this undertaking, as their statements suggest. A.W. Blair explained that Saskatoon was the best place for the betatron in Canada because of “… the rather unique and fortunate organizational set up in this province where there is a close liaison between members of the Physics Department at the University and the clinicians in charge of a large volume of cancer patients at the clinics, [which] provides an advantageous background for such a project.” After a meeting of the Committee on Nuclear Physics at Chalk River, Ontario, E.L. Harrington argued along similar lines referring to Saskatoon, “we know of no population center in which there is already established such a close co-operation between a group of physicists and a medical organisation both interested in high voltage X-ray.”

Given that the betatron project required a sizeable investment of about $120,000 and chances for obtaining substantial grants-in-aid for research in physics from external sources were realistic, the physical part of investigations took priority over the medical one. Thus, E.L.

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67 A.W. Blair was Director of the Regina Cancer Clinic from 17 October 1944 until 9 November 1948, when he died of a heart attack. In the PAS, SCF R-321.1, folder 5, Cancer Clinic Directors and Medical Staff, 1932-1976.
69 Report from E.L. Harrington to J.S. Thomson, University of Saskatchewan, 10 February 1947. Ibid.
70 This estimate included both the construction of a special building and the complete installation of the betatron. In June 1947, General A.G.L. McNaughton, Chairman of the AECB, notified the administration of the University of Saskatchewan that the AECB was willing to make an initial grant-in-aid of $30,000 if the government of Saskatchewan appropriated a matching amount for the execution of proposed nuclear research program. The AECB anticipated the same funding arrangement for the second year. A month later, Thomas C. Douglas, Premier of Saskatchewan, informed James S. Thomson, President of the University of Saskatchewan, that “the Cabinet
Harrington, who had pioneered a model of introductory physics course with focus on medical and biological applications as early as 1928, A.W. Blair, and H.E. Johns who had assumed a joint position of physicist at the university and the Cancer Clinic in Saskatoon in 1945, came to play a central role in bringing the betatron to Saskatoon. This combination of actors was instrumental in ensuring the support of the Saskatchewan Division of the Canadian Cancer Society and the NCIC. Even more, common interests of researchers, public officials, and doctors hastened the commencement of a series of experimental treatments of patients from the Saskatoon Cancer Clinic.

In March 1949, T.A. Watson, Director of Cancer Services for Saskatchewan, together with Charles C. Burkell, therapeutic radiologist at the Saskatoon Cancer Clinic, supervised the administration of experimental betatron treatments to patients with advanced cancers whom specialists regarded to be unsuitable for conventional surgery or radiotherapy. Less than a year had passed since the Illinois therapeutic experiment. Preparatory work for medical research with the only Canadian betatron had taken seven months in adjusting and testing it. Preliminary studies to determine its possible therapeutic value included tests of penetration and distribution of betatron radiation in a water medium, considered an approximation of human skin and body in

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concurred in the proposals” on the betatron project and requested to “proceed with all possible dispatch.” See letters from J.S. Thomson to T.C. Douglas, Saskatoon, 10 June 1947; and from T.C. Douglas to J.S. Thomson, Regina, 10 July 1947. Both in the PAS, R-33.1 (T.C. Douglas), V.225 (5-3-1), University of Saskatchewan – Betatron.

71 Additionally, Gerhard Herzberg, a German physicist-spectroscopist with international reputation, strengthened the Department of Physics over 1935-1945. He came to the University of Saskatchewan through a program for scientists and scholars in distress with aid provided by the Carnegie Foundation based in the USA. Because Herzberg’s wife, also a physicist, was Jewish, he fell under the Nazi racial hygiene policies preventing him to prolong his contract at the Institute of Technology in Darmstadt or to obtain another academic post in Germany. John W.T. Spinks, a chemist at the University of Saskatchewan, had spent a year working with Herzberg in Germany during 1933-1934. See J.W.T. Spinks to W.J. Murray, 30 January 1935; in the USL, Spinks Fonds 074, box 57, Science files – 1935; also box 55, Department of Chemistry Files – 1939-1945.

72 H.E. Johns received the NCIC support for his “Investigation of the possible therapeutic applications of ultra high energy X-rays and electrons” since 1948. The approved research application for 1948-1949 amounted to $6,945. See National Cancer Institute of Canada, Annual Report of 1948-1949 (Toronto: NCIC, 1949), 32.

terms of density. To examine the effects of betatron radiation biologically, researchers had conducted animal experimentation before medical research started.

Under Louis B. Jacques, head of the Department of Physiology at the University of Saskatchewan, a group of researchers irradiated dogs and then examined their blood and metabolic processes after each test to find out a threshold of radiation sickness and a lethal radiation dose from the betatron. A plausible explanation for experimenting on dogs, after successive tests with mice and rabbits, was that dogs served as large enough proxies for humans. This additional stage of experimentation enabled investigators to acquire supplementary data suggesting that the betatron could be safely used for cancer treatment. L.B. Jacques and his group did this work in cooperation with H.E. Johns, the results of which formed a sound basis for further plans to broaden the scope of radiotherapy by experimenting with animals. Besides, L.B. Jacques collaborated with T.A. Watson to investigate whether treatment with nitrogen mustards increased levels of heparin, a natural blood-clotting agent, in patients suffering from leukemia – a progressive proliferation of abnormal white blood cells. Focusing on nitrogen mustards constituted a new direction in treating non-localized tumors.

What made nitrogen mustards similar to radiotherapy was a highly toxic effect on blood-forming organs leading to dangerous systemic consequences. These substances, originating from modified compounds of a mustard gas that had emerged as a chemical weapon during World

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75 Researchers performed autopsies on all animals to determine the exact cause of their death after irradiation by the betatron. Al Penfold, “Experiments Started to Test Betatron Radiation Effects on Living Tissues,” The Sheaf, 18 February 1949. In the USL, Physics Fonds F2043, Memorabilia, Physics Scrap Book 1924-1960. Prior to joining the College of Medical Sciences in Saskatoon in 1946, L.B. Jacques had been a member of the research group headed by Charles H. Best at the University of Toronto since 1934. See L.B. Jacques to Wallace Graham (a founder of the Canadian Arthritis and Rheumatism Society), 16 September 1948; in the USL, Department of Physiology fonds, RG 2090, s.4, box 2, B8(h) Miscellaneous 1948-1960.

76 L.B. Jacques, Application for a Grant for Research, “Blood Heparin Levels in Leukemia and Radiation Sickness,” 5 February 1949; In the USL, RG 2090, s.4, b.2, B8 (e), NCIC 1949-1955.
War I, ushered in an anti-neoplastic chemotherapy age at the height of World War II. Groups of American and British chemists and pharmacologists attempted to develop an antidote for the poisonous mustard gas, which caused skin blisters and severely affected blood and lymph systems. Their work involved screening potential counter-poison compounds. In 1942, researchers at Yale University, Alfred Gilman and Louis S. Goodman, compared the toxicity of several derivatives of mustard gas through testing them on animals and, after repeated observations of their effects, suggested that those substances might be even more toxic to tumors of the hematopoietic system. Later that year, clinical trials started with patients suffering from advanced leukemia, lymphoma, and related neoplastic diseases to determine the therapeutic value of those derivatives. Although there were positive findings on indications and contraindications for the use of the nitrogen mustards therapeutically, a problem of optimal dosage schedules remained unsolved. Therefore, almost every discussion of clinical results obtained with nitrogen mustards in the late 1940s called for more trials, which essentially meant more therapeutic experimentation. In the words of Cornelius P. Rhoads, Chairman of the Committee on Growth of the US National Research Council, “The experimental use of the nitrogen mustards in the treatment of any active, extensive, neoplastic process is probably justified if other methods of control have proved to be without benefit.” Hence, further clinical trials followed.

In Canada, L.B. Jacques and his colleagues addressed the issue of optimal dosage in therapeutic regimens by examining the biological effects of overdoses of radiation and nitrogen mustards. The idea was to develop methods for measuring specific compounds, like heparin, in

79 Ibid., 575.
the circulating blood to determine a proper dosage through comparing baseline concentrations of the compound with the lows and highs after therapy in particular conditions. This research program dealt with radiotherapy to a greater extent than with chemotherapy since an accumulated clinical experience with the former served as a better basis for judging its value. The same could not be said about largely unexplored nitrogen mustards to which doctors resorted when the preferred options of surgery and radiotherapy had been exhausted. Considering that the number of patients developing cancers of systemic nature was relatively small, and the discomfort due to chemotherapy side-effects tended to be large, clinicians ventured to prescribe nitrogen mustards on indeed rare occasions. The situation with experimental high-energy radiotherapy by means of the betatron was different.

Radiotherapists could partially extrapolate necessary information for the betatron therapy from clinical evidence on the use of conventional X-ray machines already employed for treatment purposes. Since 1932, a few thousand patients treated at the Regina and Saskatoon Cancer Clinics allowed clinicians to ascertain the extent of therapeutic advantages and disadvantages of radiation therapy up to the range of 400keV. In the late 1940s, trends in using higher voltages in the treatment of cancer continued to grow. In this connection, H.E. Johns noted, “Whether such radiation [from the betatron operating at 25 million electron-volts] will prove to be of greater therapeutic value than the customary 200,000 and 400,000 volts which are used in many places, only experiments can tell.” Thus, Johns indicated that recurrent clinical research was essential to verify laboratory findings and to replicate one-time therapeutic experiments with the betatron, which might yield a useful addition to the standard therapy for particular malignancies.

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82 A research team at the Royal Cancer Hospital and the Brompton Hospital for Consumption and Diseases of the Chest in London (UK) carried out a pioneering clinical trial of nitrogen mustards in non-hematologic tumors as early as 1947. Following C.P. Rhoads’ lead on justified experimental therapy, the team attempted to treat 41 patients with a histologically proven lung cancer. Among the team members was a Nuffield Dominion Travelling Fellow from Canada, O.H. Warwick, who was possibly the first Canadian physician to have taken the opportunity to participate in conducting nitrogen mustard trials. See Eric Boyland, J.W. Clegg, P.C. Koller, E. Rhoden, and O.H. Warwick, “The Effects of Chloroethylamines on Tumours, with Special Reference to Bronchogenic Carcinoma,” The British Journal of Cancer, 2, no.1 (March 1948): 17-29.

By September 1949, eight cancer patients had received a complete course of treatments and a few others were proceeding with the betatron radiation therapy.\textsuperscript{84} The conduct of further therapeutic research soon proved to be beyond available financial means due to unforeseen operating costs of the betatron. Constituent parts of the betatron wore out faster than technical specifications stipulated thereby increasing the cost of treatments and, proportionally, the overall expenditure on the project. In November 1949, the total operating costs to provide a full course of the betatron treatments for eleven patients amounted to $14,133.\textsuperscript{85} Although the Government of Saskatchewan, the Medical Division of the NRC, and the NCIC granted funds for specific projects during the first year, a planned fivefold expansion of the betatron treatment program needed additional external support.\textsuperscript{86} Consequently, T.A. Watson had recourse to the NCIC for extra financial assistance. Quite expectedly, the Executive Director of the NCIC, O. Harold Warwick, referred to the aims and objectives of the NCIC that stressed its commitment to support fundamental research projects rather than clinical ones.\textsuperscript{87} Such a response apparently did not satisfy Watson whose retort succinctly characterized how particular exigencies of the scientific-medical practice re-formulated established norms. Stated Watson: “The distinction between fundamental and clinical research cannot be exactly defined and it could be argued that this [betatron] project is of the fundamental group in spite of the fact that living patients are used.”\textsuperscript{88} His proposition suggested that as far as therapy with the betatron was not an approved method of treatment, a clinical nature of the project did not substitute for its fundamental aspects. The latter involved determination of a therapeutic ratio of the dose required to kill cancer cells to the dose required to kill normal cells of the same type in humans.

\textsuperscript{84} Broadcast for CBC News Roundup, 15 September 1949, Interview of Harold E. Johns by Idabelle Melville in Saskatoon; in the USL, MG 372, 2008-009, oversize box, scrapbook.

\textsuperscript{85} T.A. Watson to O.H. Warwick, Regina, 10 November 1949; in the USL, MG 435, H.E. Johns, 1945-1957.

\textsuperscript{86} Ibid. This technological innovation in cancer therapy was expensive. Treatments cost on average a prohibitive $224 per patient and unless the SCC bore the brunt of the expense, only a few would be able to afford them. Since 1944, when the Legislative Assembly amended The Saskatchewan Cancer Commission Act, 1930, the Cancer Services of the province paid for treatment of all cancer patients residing in the province longer than six months. See Chapter 78 of the Statutes of Saskatchewan (1944).

\textsuperscript{87} In Warwick’s words, “As yet the Institute has not supported financially clinical investigation, as it is felt that this is the concern of the Provincial diagnostic and treatment agencies.” See O.H. Warwick (Executive Director, NCIC) to T.A. Watson (Director, Cancer Services for Saskatchewan), Toronto, 18 November 1949; in the USL, MG 435, H.E. Johns, 1945-1957.

Watson, who had worked as radiotherapist at the Holt Radium Institute of Manchester (1940-1944) and at the Liverpool Infirmary (1944-1946), reflected an international perspective on indeterminateness of clinical research. Presumably, clinical research was what clinicians said it was and agreed on generally. To O.H. Warwick, who had experienced the tense atmosphere of the Royal Cancer Hospital in London over 1947, Watson’s ostensibly controversial standpoint could not sound foreign. Moreover, both Watson and Warwick appreciated the national importance of the betatron project: its experimental results could benefit all Canadians in the long run and claim recognition from the international scientific-medical community.

In the wake of this exchange of views between two specialists, the Board of Directors of the NCIC approved a grant in support of Watson’s project entitled “Experimental Treatment of Advanced Carcinomata Using the 25 MeV Betatron.” However, the Board stipulated that funding could only be extended if the project addressed “a truly investigative problem” to establish “usefulness of the betatron for certain cancer cases.” Albeit, this grant was a significant departure from the NCIC’s sharp focus on basic research. Given the NCIC supported a continuation of H.E. Johns’ and L.B. Jacques’ work integrally related to the betatron, Watson’s project indicated a subtle shift towards making fundamental and clinical cancer research inseparable. Thus, a scientific activity guided by the question of biological effects of the betatron radiation in quantitative terms merged with a clinical practice involving its experimental use to treat selected cancer patients. This selection depended on two criteria: physicians’ consideration that any conventional therapy would offer certain patients in advanced or even terminal stages of malignant disease no more than the most temporary palliation, and patients’ agreement to undergo the experimental treatment. Doctors explained to the patients what experimental treatment meant, as indirect sources suggest. “Treatments were given with full

89 Faculty Biography Files, T.A. Watson; in the USL.
90 The actual requested estimate ranged from $5,000 to $7,500, but the NCIC saw fit to provide $5,000. See O.H. Warwick to T.A. Watson, Toronto, 29 March 1950; in the PAS, R-321.1, folder 10.
91 Ibid.
consent of the patients who had been informed of their experimental nature,” read one article by a news correspondent.93 The same author noted in another article, “Patients are forewarned that the treatment is experimental.”94 Yet, I have found no primary evidence on how or what doctors communicated to patients. In all probability, doctors personally approached patients with recurrent or inoperable tumors and suggested that they submit to treatment by the betatron. Since patients had to be highly cooperative during the therapeutic procedure consisting of exact positioning before every treatment session and keeping immobile in the course of it, they likely consented to treatments voluntarily after preliminary discussions on the betatron therapy technicalities.95 Medicine as art played its traditional role in an informal encounter of the doctor and the patient.

Forty-five patients went through the experimental betatron treatment during 1950.96 It was more than a threefold increase over the preceding nine months. A higher turnover of patients occurred mainly owing to a gradually accumulated expertise that enabled radiotherapists and physicists to optimize their operations. Other reasons behind the increase were less apparent. Adverse reactions, for one, did not let some of the patients, closely supervised by physicians, complete all prescribed treatments. Besides, the doctors tended to exclude patients with particular types of tumors that responded very poorly to the experimental therapy.97


94 Muriel Snider, “Twenty-five Million Volts of Hope,” Saturday Night, 18 October 1949. Snider described two initial attempts to treat deep-seated cancers with the betatron. The first patient, a 67-year-old woman, received fourteen treatments over two weeks, but died shortly after. “The experiment was clouded by failure.” The second therapeutic attempt involved a 71-year-old man who had a “serious rectum cancer.” After fourteen daily treatments, his tumor shrank to “less than a fifth of its original size”. This “experiment” might be regarded as successful considering that the patient was alive six months later.

95 H.E. Johns, E.K. Darby, T.A. Watson, C.C. Burkell, “Comparison of Dosage Distributions Obtainable With 400kVp X-Rays and 22 MeV X-Rays,” The British Journal of Radiology, 23, no. 269 (May 1950): 299. The authors also noted the doctors needed to explain to patients that the betatron produced “a loud whining noise”, and when they did, the patients “tended to be impressed rather than dismayed.”

96 T.A. Watson, “Co60 Telecurietherapy – after Five Years” (1959); in the WUA, AFC 328.1.2644.

97 For example, the doctors excluded carcinomas of the rectum after eight negative treatment outcomes. Interestingly, the first patient treated with the betatron on 29 March 1949 suffered from a post-operative recurrence of this type of malignancy. Without previous knowledge of the betatron’s effect on human tissues, radiotherapists administered a low dose of 3000 roentgens that was not lethal for the tumor. See Thomas A. Watson and C.C. Burkell, “The Betatron in Cancer Therapy – Part I,” Journal of the Canadian Association of
empirical approach led to the establishment of tolerance levels of high-energy radiation and overall treatment time in view of the adequate dosage.\(^9^8\) Moreover, radiotherapists determined what systemic, local, and skin reactions ensued from different radiation doses to particular tumor sites only after a series of comparative cases presented themselves.\(^9^9\) It was an experimental treatment indeed, but with every experiment the gamble became less and less fatal. A case in point was the betatron therapy of brain tumors. Out of the six patients who had completed treatment, five remained free from symptoms over an average duration of ten months.\(^1^0^0\) These positive results may have been difficult to achieve had the American researchers not provided a detailed report on their experimental betatron treatment of a cerebral cancer in 1948.\(^1^0^1\) However promising, the betatron treatments required an amount of work and resources per patient significantly larger than a conventional radiotherapy. Even if standardized, the betatron could not enter a general-use therapeutic armamentarium because of economic constraints.

2.3. Isotopes

Designs to introduce a more economical and efficient radiotherapeutic apparatus were in the making. They took roots in the program of nuclear research in Canada with the emergence of the Montreal Laboratory in 1942, which triggered both international and interdisciplinary collaboration. In 1946, William V. Mayneord, a British radiologist from the Royal Cancer Hospital of London, joined André J. Cipriani, a Canadian biophysicist who worked with the Atomic Energy Division of NRC, to collaborate on medical applications of possible by-products from the use of atomic reactors.\(^1^0^2\) Those by-products were artificial radioactive isotopes –

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\(^{99}\) Ibid.


\(^{101}\) Drawing on their findings, Canadian radiotherapists started treating patients with brain tumors by administering initially high doses of betatron single-field X-rays. Five patients received the tumor dose of 5500r in fifteen treatments. *Ibid.*

variants of the stable elements produced by altering their nuclear structure through bombardment with subatomic particles in machines such as a cyclotron or a chain-reacting atomic pile.\textsuperscript{103} W.V. Mayneord and A.J. Cipriani investigated many isotopes having characteristics of a suitable substitute for radium – availability, cost of production, and convenience of use – but only to confirm J.S. Mitchell’s finding that there was just one.\textsuperscript{104} Joseph Stanley Mitchell, a physicist and radiotherapist at the University of Cambridge in England, had led studies into the biological effects of radiation at the Canadian NRC laboratory during 1944-1945.\textsuperscript{105} It occurred to Mitchell that a metal, Cobalt-59, which through a sustained bombardment with neutrons could become a radioactive Cobalt-60 with a relatively long half-life of 5.3 years, had a potential value in the treatment of cancer.\textsuperscript{106}

In August of 1946, H.E. Johns attended a course of lectures on the physics of radiotherapy given by W.V. Mayneord at the Toronto General Hospital.\textsuperscript{107} Highlighting therapeutic potentialities of high-energy radiation from the betatron and the isotope Cobalt-60, Mayneord prompted Johns to think of a research program along those lines. Furthermore, Mayneord let Johns know that Cipriani was in the process of producing prototype cobalt discs to be irradiated at a future nuclear reactor.\textsuperscript{108} As a unique heavy-water reactor called the “NRX” (National Research Experimental Pile), came into operation under the direction of the NRC on 22 July 1947 in Chalk River, Ontario, a plan to produce Cobalt-60 became feasible.\textsuperscript{109} However, cobalt was not in as high demand as other isotopes that could be produced within a short time.

\textsuperscript{104} J.S. Mitchell, “Applications of Recent Advances in Nuclear Physics to Medicine,” \textit{The British Journal of Radiology}, 19, no. 228 (December 1946): 483. Mitchell wrote this paper as a report to the Montreal Laboratory of the NRC of Canada.
\textsuperscript{106} \textit{Ibid.}, 482-485. Also, Evelyn, “Medical Applications of Artificial Radioactive Isotopes” (1947): 550 and 553.
\textsuperscript{108} H.E. Johns to W.P. Thompson (President, University of Saskatchewan), Saskatoon, 15 July 1949; in the USL, MG 435, H.E. Johns, 1945-1957.
\textsuperscript{109} Initially, it was a joint British-American-Canadian project “to design, build and operate a 10 MW heavy-water-moderated, natural-uranium fueled reactor” to produce material for nuclear weapons. This reactor generated the highest flux of thermal neutrons ever recorded at the time, which was essential for producing isotopes. It was the only atomic pile in the world that could transmute a stable cobalt into a highly radioactive one in several months, rather than decades, of irradiation. See Hurst, “Overview of Nuclear Research and Development,” 4-5.
span. The Atomic Energy Division of the NRC made radioactive carbon, phosphorus, sulphur, iodine, among others, available to researchers on request by September 1947. The Isotope Branch of the NRC distributed a pricelist on radioisotopes along with pamphlets on their use to all potential customers. Universities received those packages expeditiously together with application forms for the use of radioactive isotopes. In its memoranda, the Atomic Energy Division indicated also that there was a possibility to irradiate materials supplied by the customer in the course of weeks or even months, which some elements, such as cobalt, required. Catalogue charges for the irradiation were quite modest. This relatively inexpensive way to produce radioactive isotopes en masse generated a growing scientific interest that went beyond investigations in physics.

The NCIC approved seven cancer research applications that focused entirely on radioisotope investigations out of a total of sixty-one successful applications for 1949-1950. Other agencies – the Defense Research Board, the Department of National Health and Welfare, the NRC, and the Department of Veteran’s Affairs – received requests for studies on radioisotopes that exceeded the NCIC budget. Those five organizations could not but address developments in a mushrooming use of radioactive isotopes since officers of the Chalk River Project were barely able to screen properly the increasing number of applications for radioisotopes and to visit radioisotope laboratories to ensure safe practices. Furthermore, the handling of readily available radioisotopes in clinical projects gave a more serious cause for concern to the officers than that related to fundamental research.

111 Pamphlets “Precautions When Using Radioactive Isotopes”, “Control of Radioactive Contamination in Laboratories”, and “Radiation Health Manual” contained information on the use of isotopes in supposedly safe and dangerous amounts that entailed various health risks if researchers worked continuously with them.
112 Quotes in dollars for a millicurie (3.7 x 10^7 beta emissions per second) of isotopes were as follows: P³² – 1.1, I¹³¹ – 1.7, S³⁵ – 2.0, C¹⁴ – 50.0. A weekly pile irradiation of materials cost $22, while a monthly – $43. In the USL, RG 2001, B119 (4), NRC 1947, Radioactive Isotopes.
113 Researchers from Edmonton, Kingston, Montreal, Toronto, Vancouver, and Winnipeg received grants varying from $800 (University of Alberta) to $8000 (McGill University). See National Cancer Institute of Canada, Annual Report of 1948-1949 (Toronto: NCIC, 1949), 31-34.
A Clinical Subcommittee of the NRC in charge of supervising clinical uses of radioisotopes had difficulties reviewing all pending applications. Its chair, Duncan A. Graham, and its secretary, James A. Dauphinee, proposed devolving their powers of supervision to lower levels of administration apparently in order to absolve themselves from moral blame for a cursory examination of piling projects that involved patients. The NRC President, C.J. Mackenzie, followed up on their suggestion and convened all five above-mentioned organizations interested in radioisotope projects for a meeting on 2 November 1949. As a result, representatives of those organizations adopted a resolution stating,

that radioactive isotopes for clinical, tracer or therapeutic use in medicine be made available as soon as possible throughout Canada only under the aegis of universities or medical schools to serve proper geographical areas, provided that these medical schools or universities have already established representative committees on radioactive isotopes and that they comply with all the standards and requirements established by the National Research Council and the Atomic Energy Committee.

Universities and medical schools with teaching hospitals acted immediately to establish necessary committees and to take advantage of the bottleneck in radioisotope research approvals by the NRC Clinical Subcommittee. Toronto and London in Ontario along with Montreal in Québec – the cradles of medical research in Canada – set the trend in securing access to isotopes for researchers and thus opening more funding opportunities for their investigations. More

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114 This Subcommittee functioned from 1946 until 1952. See “History of the Advisory Committee on the Clinical Uses of Radioisotopes” in the WUA, AFC 328.1.2829.

115 D.A. Graham chaired the Department of Medicine at the University of Toronto until 1947 and J.A. Dauphinee became Head of Pathological Chemistry Department at the same institution in 1947. See “Atomic Energy Project: Clinical Subcommittee,” in the University of Toronto Archives (thereafter, UTA), J.A. Dauphinee Personal Records, B1985-0006/031/02.


118 For instance, the OCTRF awarded two large continuous grants for 1949-1950. William Paul, Associate Professor of Pathological Chemistry at the University of Toronto, received a $9,000 grant for his project “Radioactive Isotopes in the Investigation and Treatment of Malignant Disease,” and F.C. Heagy, Assistant Professor of Biochemistry at the UWO, got a $7,000 grant for his project “Treatment and Diagnosis with Radioactive Isotopes.” See “Schedule of the Applications for Grants for Clinical Research Approved by the OCTRF” enclosed with a letter from J.H. Broughton to H.J.C. Ireton, 7 July 1960, Toronto; in the UTA. Office of Research Administration, OCTRF
importantly, medical uses of radioisotopes strengthened the argument that the distinction between basic research and clinical practice could not be exactly defined in experimental treatments.

On 12 October 1948, Dr. Eaglesham of Weyburn, Saskatchewan, referred a middle-aged female patient to the Regina Cancer Clinic. Clinicians diagnosed her with inoperable carcinoma of the thyroid and prescribed a palliative course of X-ray radiation consisting of eighteen treatments. Monitoring her condition, doctors examined the patient several times during 1949 and administered further X-ray therapy in November of that year. At the clinic rounds on 5 May 1950, attending doctors decided that the patient could derive no benefit from additional X-ray treatment, but at that time, a junior physician mentioned in the presence of the patient the possibility of treatment with radioactive iodine before the matter had been discussed by the medical staff of the Cancer Clinic. The patient, encouraged, communicated this to her husband who agreed to pay for the new therapy himself although cancer patients residing in the province were entitled to free treatment since 1944. The patient’s husband also contacted his friends who managed to get in touch with Premier T.C. Douglas. In his letter to Douglas, Austin Metheral wrote that the patient’s husband was “getting plenty of this propaganda [about ‘some radio-active cures’] from his Dr., seems [sic] his Dr. has told him that he has had a lot of dirty deals from up there [not specifying either the clinic or the government], but this one [ignoring the last resort therapy] is the worst yet.” During a medical conference in early June 1950, the clinicians waveringly decided to order a supply of radioactive iodine for the experimental therapy, as they considered there was little chance of producing beneficial results. An order for the radioactive iodine was sent to Chalk River, Ontario. It took about three weeks to process the


119 Frederick D. Mott (Acting Deputy Minister of Public Health of Saskatchewan) to T.C. Douglas, 23 June 1950; in the PAS, R-33.1, XIV 558a (1 of 2).
120 At that time, the regulations prohibited any discussion of the case in terms of diagnosis, prognosis and treatment in the presence of the patient. See Regulations Gover ning Consultative Diagnostic and Treatment Clinics as of 9 November 1931, section 4(6); in A.W. Blair, Cancer in Canada; Report of National Survey, 1947, edited by the National Cancer Institute of Canada (NCIC, 1949), Province of Saskatchewan, 11.
121 Blair, Cancer in Canada (1949), Province of Saskatchewan, 15-17.
122 A. Metheral to T.C. Douglas, Weyburn, 9 June 1950; in the PAS, R-33.1, XIV 558a (1 of 2).
order and deliver the radioactive iodine to Regina. In the meantime, the patient transferred from the Weyburn General Hospital to the Cancer Clinic of the Grey Nuns’ Hospital so that a qualified medical staff could administer the treatment.123 She started a course of radioactive iodine on June 26, but the secrecy of clinicians’ communications, because of their earlier unfortunate disclosure, shrouded the outcome of that experimental treatment.

The consensus of key research-funding agencies on a local vetting of clinical projects with radioisotopes suggests that officials at a federal level tended to take a more flexible approach when a technology promising better treatments entered discussions. In fact, the NCIC created the Advisory Committee on Radiation Therapy in response not only to the spreading use of isotopes and high-voltage radiation machines, but also due to pressure from the Department of National Health and Welfare.124 The latter insisted that the NCIC should approve projects aimed at improving and standardizing cancer patient care countrywide in an effort to complement the federal assistance to the provinces in the programs for the control of cancer. This assistance, officially known as the Cancer Control Grant, the DNHW introduced in mid-1948. The grant in the amount of $3.5 million recurred annually and was divided on the basis of population with the stipulation that the cost of any approved program for cancer control was to be matched by the province.125 Provision of these federal-provincial grants had the highest impact on actively developing radiation therapy.

### 2.4. Cobalt-60

Since 1950, the Advisory Committee on Radiation Therapy assumed a more prominent position because cancer research coordinated by the NCIC was supposed to complement cancer care

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123 T.C. Douglas to A. Metheral, Regina, 26 June 1950; in the PAS, R-33.1, XIV 558a (1 of 2).
125 The Prime Minister announced the National Health Program in the House of Commons on 14 May 1948. The program included a number of federal health grants among which was the Cancer Control Grant. The Order-in-Council governing federal grants for cancer control (P.C. 3410) became effective on 28 July 1948. See Minutes of the Fifty-Fourth Meeting of the Dominion Council of Health, Ottawa, 7-8 June 1948, in the LAC, DCH Fonds; and “Federal Grants Available for Cancer Control Programme,” *Canadian Cancer Society Newsletter*, August 1948, 1; in the PAS, R-599, file 7.
programs managed by the provinces. Acting as a mediator, the Committee set radiation therapy standards across Canada through consultations with specialists working in the field. The Committee also considered the development of a new source of radiation treatment, Cobalt-60, since the crown corporation Eldorado Mining and Refining Ltd. (1944) proposed to devise a beam therapy unit for mass production. Those units, in the company’s estimation, had a potential to standardize a part of cancer radiation treatment economically. The Committee recommended using the units initially “on a research basis and only at major centers connected with Universities.” Nonetheless, there was scarcely a reference to H.E. Johns’ research group in Saskatoon in the course of the Committee’s discussions, even though T.A. Watson was its member. Experimental research with the betatron seemed a logical prelude to investigating the appropriateness of Cobalt-60 for cancer therapy with its major advantage of radiation dose standardization in clinical institutions.

Watson did not want to give much publicity to the possibility of doing research with Cobalt-60 at Saskatoon because the Saskatchewan Cancer Commission together with the Saskatoon Cancer Clinic had already submitted a formal application to the NRC Atomic Energy Project, requesting the irradiation of Cobalt-60 in the pile, in August 1949. Wilfrid B. Lewis, Director of the Atomic Energy Division of NRC, and A.J. Cipriani, Director of the Biology Division in the Chalk River Laboratory, had agreed on H.E. Johns’ proposal to conduct fundamental physical investigations with Cobalt-60 that could be applied to clinical work subsequently, but they were unwilling to recognize this agreement officially in correspondence. Lewis and Cipriani did not want to have a clash of scientific and commercial

127 Ibid., 17.
128 T.A. Watson to F.D. Mott, Regina, 9 May 1950. The two institutions submitted the application for Cobalt-60 in the quantity of 1400 curies to the NRC AEP Isotopes Branch, Chalk River, on 13 August 1949. The Statement of Intended Uses read, “The cobalt 60 will be used in a Telecurie Unit for the treatment of cancer under the direction of Dr. T.A. Watson [...] The physical aspects of the problem will be under the direction of Dr. H.E. Johns. This involves considerable research on the construction of the unit and subsequent detailed investigations of the distribution of radiation produced in a scattering medium by cobalt gamma rays.” Both documents in the USL, MG 435, H.E. Johns, 1945-1957.
129 W.B. Lewis to H.E. Johns, Chalk River, 23 August 1949. W.B. Lewis received the application for Cobalt-60 that day and replied, “We need not, however, at this time commit ourselves or you on the application [...].” In the USL, MG 435, H.E. Johns, 1945-1957.
interests over the first irradiated cobalt. Had Eldorado officials known about the application and negotiations, they could have brought pressure to bear to obstruct an anticipated pile irradiation of cobalt destined for Saskatoon. As Watson put it, “Eldorado [was] pressing for early deliveries of Cobalt 60 so that they [could] sell these units on a commercial scale, and it would be most annoying for them to commandeer our material.”¹³⁰ No commandeering occurred, and the NRC supplied two identical sources of Cobalt-60 for experimental use in the summer of 1951.¹³¹ One source was transferred to Saskatoon and installed in a specially built room of the cancer clinic, while the other was transported to the Radiology Laboratory, Physics Division of the NRC in Ottawa, before its final installation at Victoria Hospital, London, Ontario.¹³²

On 27 July 1951, three days prior to the arrival of cobalt to Saskatoon, an engineer-physicist working with Eldorado, Donald T. Green, came from Ottawa to confer with H.E. Johns and T.A. Watson on publicity regarding Cobalt-60 units.¹³³ Green, Johns and Watson discussed how to avoid unnecessary competition in news releases among the three groups involved. The NRC and the Atomic Energy Project officials were interested in publicity on this subject presumably because they “wish[ed] to show that public money in the atomic energy project [were] being put to useful medical purposes as well as research concerned with war.”¹³⁴ Eldorado had commercial interests in building and selling Cobalt-60 worldwide, particularly in the United States, where General Electric Company had designs to enter this field by constructing similar units. General Electric was at a competitive disadvantage, for there was no US nuclear pile in 1951 that could irradiate cobalt to a required level of activity, and all

¹³⁰ T.A. Watson to F.D. Mott, Regina, 9 May 1950, op. cit.
¹³² Toronto General Hospital had a four-gram radium unit, unique in Canada, which could have been an argument in support of the Cobalt-60 installation in London. See Charles Coady, “Canada’s New Weapon Against Cancer,” The Star Weekly, Toronto, 15 December 1951. Interestingly, the officials in Saskatchewan had to revise their original plan to install a Cobalt-60 unit in the Regina Cancer Clinic because C.J. Mackenzie and his colleagues at the NRC indicated that it was necessary to place the unit near the Department of Physics of the University of Saskatchewan. Consequently, the unit found its permanent place in one of the rooms of the new Cancer Clinic in wing G of the University Hospital. See a letter from T.A. Watson to F.D. Mott, Saskatoon, 17 October 1950; in the USL, MG 435, H.E. Johns, 1945-1957.
¹³³ D.T. Green, a former graduate of the University of Saskatchewan, was a chief assistant of Roy F. Errington who had managed the Commercial Products Division of Eldorado since 1946. See T.A. Watson to F.D. Mott, Saskatoon, 8 August 1951; in the USL, MG 435, H.E. Johns, 1945-1957.
¹³⁴ Ibid., 1.
Canadian radioactive cobalt had to be sold through Eldorado.\footnote{Ibid., 2.} The third group of interests involved the Saskatchewan Cancer Commission and the University of Saskatchewan, which wanted to demonstrate continuity in their productive collaboration on experimental research and to get due credit for publicly supported projects. Watson was in favor of a “gentlemen’s agreement to the effect that one organization will not completely ignore the other in news releases.”\footnote{T.A. Watson clarified his statement, “We certainly would not, anyway, enter a publicity competition with London.” Ibid., 4.}

On behalf of the Saskatchewan group, H.E. Johns publicly acknowledged in his interview for the Canadian Broadcast Corporation that two radioactive cobalt sources would soon become available for the treatment of deep-seated tumors in Saskatoon and in London, Ontario.\footnote{Reporter, Idabelle Ness, introduced this as follows, “A similar source will be installed soon at the University of Western Ontario,” probably thinking that there was an arrangement with a hospital in London similar to that in Saskatoon. See CBC International Service, “Broadcast for Canadian Chronicle,” Saskatoon, 23 August 1951 (recorded 22 Aug.), p.1; in the USL, MG 372, 2008-009, oversize box, scrapbook.} When asked about the value of the cobalt units for the cancer patient, Johns conveyed a message from Watson stressing that “this [therapeutic] use of radio-active cobalt [was] NOT [sic] a new cure for cancer, […] it was] an improvement in the technique of cancer treatment.”\footnote{Ibid., 3.} Albeit, this technique was novel and it required testing by specialists. Physicists in Ottawa and Saskatoon measured the output of two units and their “results were in excellent agreement.”\footnote{Johns, et al. “1,000-Curie Cobalt-60 Units for Radiation Therapy,” Nature (1951): 1035.} In preliminary theoretical and empirical investigations with the sources, “there was close collaboration among Eldorado Mining and Refining (1944) Ltd., the University of Saskatchewan, and the National Research Council,” which indicated that the three parties honored their gentlemen’s agreement. And that agreement went even further, as Table 2-1 shows.

The opening of the Saskatoon Cobalt-60 Unit on 23 October 1951 was not grand – quite the opposite. Neither the Minister of Public Health of Saskatchewan, T.J. Bentley, nor Premier
T.C. Douglas attended the ceremony, to say nothing of federal officials. Instead, Dean of the Faculty of Law, Frederick C. Cronkite, presided over the ceremony that seemed to be of local magnitude rather than of a national one. Yet, the same day newspapers in Ontario published titles like *World’s First Cobalt Bomb to Fight Disease* referring to a newly installed beam therapy unit at the War Memorial Children’s Hospital in London. The Children’s Hospital formed a part of the complex of treatment institutions in London.

<table>
<thead>
<tr>
<th>Events in 1951</th>
<th>Saskatoon (SK)</th>
<th>London (ON)</th>
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<tbody>
<tr>
<td>Cobalt-60 unit installed</td>
<td>17 August</td>
<td>18 October</td>
</tr>
<tr>
<td>Official opening</td>
<td>23 October</td>
<td>12 November</td>
</tr>
<tr>
<td>First patient treated</td>
<td>8 November</td>
<td>27 October</td>
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*Table 2-1. Cobalt-60 units in Saskatoon and London.*

For the media, the cobalt story represented a sensational drama. Journalists used the term ‘cobalt bomb’ in describing the unit because its radioactive source was equivalent to about two kilograms of radium – a huge amount in terms of both strength of radiation and price. Preparing a launching pad for its commercial activity, Eldorado released these compelling facts about an allegedly novel weapon against cancer. The crown corporation’s high-powered publicity was not without tacit support from federal authorities and the Ontario government, which surfaced at the inauguration of the Cobalt-60 Beam Therapy Unit in London. On this occasion, representatives of state, science, medicine, business, and church congregated to celebrate, and even bless, a

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140 T.C. Douglas to T.A. Watson, Regina, 27 October 1951; in the USL, MG 435, H.E. Johns, 1945-1957. F.D. Mott, Deputy Minister of Public Health of Saskatchewan, was absent too. See The Star-Phoenix, “Cobalt Unit for Cancer Installed,” Saskatoon, 23 October 1951, *ibid.*

141 Only a few news pieces contained references, somewhat misleading, to the Saskatoon unit. “If the London experiment proves successful, Cobalt bombs will be built for the other clinics in Ontario and throughout the United States. One is also being installed at Saskatoon, Sask.” In the WUA, AFC 328.1.2874. Only in late November did stories on the Saskatoon unit surface in newspapers like *The Toronto Daily Star,* “Radioactive Cobalt for Cancer,” 24 November 1951. *Ibid.*

142 The Cobalt-60 unit found its temporary place in the expanded War Memorial Children’s Hospital as it got a new 63-bed addition in May 1951. See “Victoria Hospital Annual Report, 1951,” London, 1952, p.12; in the WUA, London Regional Cancer Centre, AFC 328.1.2765.

143 T.A. Watson to T.J. Bentley, 15 February 1956; in the USL, MG 435, H.E. Johns, 1945-1957; and “Cobalt 60 Beam Therapy Unit Completed Installations (Model A – Eldorado Unit),” in the WUA, AFC 328.1.2875, box 54, folder 15, Cobalt 60, 1952-1955.
second-to-none Canadian achievement. H.E. Johns attended as well, which indicated that the Saskatchewan research group obtained its Cobalt-60 for the project with strings attached, namely, to comply with the business-oriented project of Eldorado. Assuming that agreement was in place, to what extent did experimental therapy with patients fall under it? After “the installation ceremonies passed over, the cold facts remained, the Bomb was there, what would be treated and how would this be done?” – reflected Ivan H. Smith, Director of the Ontario Institute of Radiotherapy at Victoria Hospital, who was in charge of the Eldorado Unit Model A.

Ivan H. Smith had a burdensome task, but well-trained members of his team helped to shoulder it. On the one hand, a flow of cancer patient applications for the Cobalt-60 treatment grew every day following the publicity campaign. On the other hand, Smith’s team had to administer an undeniably experimental treatment to patients who at the same time needed to serve as ‘good’ statistics for commercial purposes of Eldorado. Unlike T.A. Watson, who had ample opportunity to employ the high-voltage betatron, I.H. Smith had little experience with high-energy radiation treatment. Otherwise, Smith’s professional record was strong. Having graduated from the University of Western Ontario as a medical doctor specializing in pathology, Smith received training in surgery (M.Sc.) and worked as an instructor in pathology over 1927-

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144 Incomplete list included C.D. Howe, Minister of Defence Production and Minister of Trade and Commerce; G.D.W. Cameron, Deputy Minister of DNHW; C.J. Mackenzie, President of the NRC; David A. Keys, Vice-President of the NRC and Head of the Atomic Energy Project; MacKinnon Phillips, Minister of Health for Ontario; G.M. Jarvis, Secretary of the AECC of Canada; A.R. Ford, Chairman of the OCTRF; J.B. Collip, Dean of College of Medicine at the UWO; J.C. Cody, Roman Catholic Bishop of London Diocese; William Loveday, Chairman of Victoria Hospital Trust; William J. Bennett, President and Managing Director of Eldorado. See The Free Press, “New Cancer Weapon Hailed,” London, 12 November 1951; and The Free Press, “Leaders of Church, State, Education at Cobalt Bomb Opening,” London, 13 November 1951, p.7. Both in the WUA, AFC 328.1.2874.


147 The main characteristic that distinguished a high-voltage from a conventional low-voltage radiation therapy was the near absence of superficial reddening of the skin that guided the doctor in terms of the patient’s response. As members of a special committee of the OCTRF, I.H. Smith and a physicist Jack Brown visited a number of US institutions utilizing equipment in the 1 to 2.5 MeV range to investigate and report on the place of high-voltage radiotherapy machines in 1949. See I. H. Smith, “An Estimate of the Future of Teletherapy with Radioisotopes” (1955): 1; in the WUA, AFC 328.1.2791.
1928. He became a resident at Howard A. Kelly Hospital in Baltimore (USA) during 1930-1931. Afterwards, Smith moved to Edinburgh to work as clinical assistant in surgery under David Wilkie and J.J.M. Shaw in 1935. The next year, Smith got a position of resident and assistant in radiotherapy at Christie Hospital and Holt Radium Institute of Manchester (UK) – one of the world’s top cancer treatment institutions. In the course of 1936-1937, Smith visited cancer centers in Paris, Hamburg, Brussels, Copenhagen, Stockholm, and London to acquaint himself with innovative therapeutic methods and apparatus used in the management of cancer. Offered the appointment of registrar at the Ontario Institute of Radiotherapy (OIR) directed by George McNeill, Smith returned to Canada in 1938. Three years later, Smith became director of the OIR at Victoria Hospital. Smith’s specialist qualifications in pathology, surgery, and radiotherapy made him an ideal candidate to manage the second largest, after Toronto, Cancer Clinic in Ontario. In November 1947, the Advisory Medical Board of the OCTRF recommended bringing the London Cancer Clinic more closely under the supervision of the Foundation by appointing I.H. Smith as its director. These two reasons – professional competence and institutional centralization – probably explain why the Cobalt-60 unit came to London, rather than to Toronto.

What is more difficult to explicate is the reverse sequence of the official opening of the Cobalt-60 unit and the first treatment of patients by the machine in London. I.H. Smith was under pressure to demonstrate that the Eldorado Unit Model A pioneered a new approach in

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150 George McNeill was Director of the OIR, Victoria Hospital, since its establishment in 1934. That year, the Legislature of Ontario adopted The Ontario Institute of Radio-Therapy Act, 1934. The Act validated “an agreement entered into between the Board of Hospital Trustees of the City of London and the Province of Ontario, dated the 15th day of January, 1934, regarding Radio-Therapy treatment.” The Legislature of Ontario passed a similar act validating agreements between the Toronto General Hospital, the Kingston General Hospital, and the Province of Ontario in 1933. See Chapter 37 of the Statutes of the Province of Ontario, Bill No. 57, in the WUA, AFC 328.1.2789. Also, The OCTRF Annual Report of 1954, p.42; in the WUA, AFC 328.1.2758.
151 “Report of a Meeting of the Committee on Cancer Centres of the Advisory Medical Board of the Ontario Cancer Treatment and Research Foundation,” Kingston, 21-22 November 1947, Appendix A; in the WUA, AFC 40-73, S13 (George E. Hall Advisory Medical Board of OCTRF Minutes).
cancer therapy, and he treated patients as soon as the apparatus was ready, without waste of time in anticipation of the inauguration. A competition between the London and the Saskatoon groups on this matter can be ruled out on account of the above-described tacit agreement. Besides, as radiologist C. Stuart Houston put it, “At Saskatoon [H.E.] Johns knew about the machine delivery in London, but he had Sylvia [Fedoruk] complete her depth dose calibrations and knowingly let London be first [in treating patients]. This was for science, not for vanity.”\textsuperscript{152} In London, science and vanity seemed more closely aligned than in Saskatoon, which indicated that the practice of experimental medicine varied according to local circumstances.

Treatment of patients with the Eldorado Unit commenced on 27 October 1951. The first patient was Mrs. Mary Watson, an eighty-three-year-old resident of London (ON), diagnosed with malignant melanoma of skin.\textsuperscript{153} Mary developed a primary symptom, a small lump on the right side of her neck, in December 1949. More than a year later, in February 1951, when her mass had grown to a few centimeters, she went to consult a physician. Her family doctor did a partial excision for biopsy. The histological report revealed a malignant melanoma. The doctor referred Mary to the London Cancer Clinic to which she was admitted in August 1951. Clinicians confirmed the diagnosis as a melano-sarcoma, 7.5 centimeters in diameter, involving neck lymph nodes.\textsuperscript{154} On request from the clinicians, pathologists examined the biopsy again and established a metastatic carcinoma that appeared to be a melano-sarcoma. The stage of disease in terms of clinical evaluation was four – a highly advanced malignancy. On 14 August 1951, radiotherapists began a palliative treatment with a conventional X-ray machine. The palliation lasted for ten days at the end of which a skin dose of 2,500 rads was reached. Within six weeks, Mary’s malignant neoplasm resumed growing and started bleeding. I.H. Smith noted, “because the exophytic growth [outward from skin surface] permitted a study of tumor regression and skin reaction, we selected this patient as the first to be treated by irradiation from a kilocurie source of cobalt-60.”\textsuperscript{155} It was a sincere acknowledgement from I.H. Smith that a study and a treatment

\textsuperscript{152} C.S. Houston, email message to author, 15 February 2015.
\textsuperscript{153} Mary Watson had no kinship with T.A. Watson. See Case No. L51/809, OCTRF London Clinic, in the AFC 328.1.2790, Cancer Centre – Cobalt 60 Beam Therapy, 1951-1952.
\textsuperscript{154} Ibid.
were inseparable in this case. Mary was both a patient who received the best available therapy and a research subject who provided necessary data to refine further treatments.

At the Saskatoon Cancer Clinic, a medical team headed by T.A. Watson prepared to use the Cobalt-60 unit for treatment considered novel in degree, but not in kind. In Watson’s words, “There [wa]s nothing revolutionary […] in the use of large quantities of radioactive cobalt in beam units, since the rays produced [we]re roughly equivalent to those generated by a 3 to 4 peak machine.”156 He stated this resolutely because cancer treatments with the betatron continued and data obtained therefrom correlated well with that on Cobalt-60 radiation tested in experimental media. The Cobalt-60 therapy was not so experimental in Saskatchewan as in Ontario. Still, clinicians were anxious to treat patients by means of a new technique, especially if their prognoses with other therapeutic modalities were gloomy. This was the case with forty-three-year-old Mrs. Molly Birtsch who was the first patient to begin treatment by the Saskatoon Cobalt-60 unit on 8 November 1951.157 Doctors diagnosed Molly with carcinoma of the cervix uteri, the disease being at clinical stage two, fairly advanced. Following examinations, clinicians determined that her malignancy was primary and it did not involve regional lymph node metastases, but there was invasion in parametrium, structures immediately adjacent to the uterus.158 After Molly had undergone a therapeutic course of radium implants, T.A. Watson suggested that she receive Cobalt-60 treatments. Molly agreed. Having first-hand knowledge about possibilities and limitations of high-voltage therapy, Watson devised a treatment plan and proceeded with allegedly routine fifteen courses over three weeks.159

In both Saskatchewan and Ontario, the relative simplicity of ionization chamber tests of Cobalt-60 units did not translate directly into treatments of complex human bodies. For I.H. Smith, this translation meant clinical research, while T.A. Watson viewed his work as

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experimental therapy. The numbers of patients treated by the two specialists differed, however, as shown in Table 2-2.

<table>
<thead>
<tr>
<th>Year</th>
<th>London (ON) Cobalt-60 Units</th>
<th>Saskatoon (SK) Betatron*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951</td>
<td>39</td>
<td>(since 8 Nov.) 7</td>
</tr>
<tr>
<td>1952</td>
<td>482</td>
<td>152</td>
</tr>
<tr>
<td>1953</td>
<td>405</td>
<td>194</td>
</tr>
<tr>
<td>1954</td>
<td>326</td>
<td>186</td>
</tr>
<tr>
<td>1955</td>
<td>356</td>
<td>213</td>
</tr>
</tbody>
</table>

* There was no betatron in clinical use in Ontario.

Table 2-2. Cancer Patients Treated by Radiotherapy Method.160

I.H. Smith rationalized his radiotherapeutic practice:

Selection of cases, although desirable, [was] badly stilted perforce of demands for palliative assistance to many advanced problems [;] nevertheless, an attempt [was] made to precisely carry dose higher and higher, fully utilizing the physical advantages offered by cobalt 60 in an effort to gather factual data on this new form of external irradiation.161

Considering every case treated by the Cobalt-60 Unit as a clinical research problem, I.H. Smith admitted that palliative care somewhat detracted from his team’s attempts to appraise the effectiveness of therapy on different groups of patients. Yet, a boundary between palliation and treatment was permeable in advanced cases of disease as the treatment plan of Mary Watson indicated. Her tumor at the skin surface received 5,400 rads between 27 October and 7 December 1951, but little change occurred in either skin or tumor.162 Over the next nineteen days of treatment break, Mary’s tumor diminished and there was only slight skin reddening in that area. Treatment resumed on 26 December and continued until 21 January 1952, adding a dose of 2,500 rads to a total of 7,900 rads received in the course of eighty-seven days. The exterior tumor

160 Edgar P. Furie, Administrative Director of The Jewish Hospital Association in Cincinnati, Ohio, contemplated purchasing an Eldorado unit and sent a detailed questionnaire on Cobalt-60 radiation treatment to Carman J. Kirk, Superintendent of the Victoria Hospital. See E.P. Furie to C.J. Kirk, Cincinnati, 2 December 1957; I.H. Smith to Edgar P. Furie, London, 23 December 1957, with enclosed “Questionnaire”; both files in the WUA, AFC 328.1.517. Also, T.A. Watson “Co60 Telecurietherapy – after Five Years”; in the WUA, AFC 328.1.2644.
162 Smith et al. Cobalt-60 Teletherapy, 370.
mass disappeared completely on 18 March, leaving a small pigmented area around which moist skin exfoliated. An induration appeared below Mary’s right lower jaw, probably due to radiation overexposure of tissues opposite the tumor. Mary died on 9 June 1952 and her post-mortem revealed residual tumor in the skin with ulceration and deep adjacent nodes, but distant metastases were absent. Was the use of Eldorado A unit in this case a palliative treatment, clinical research, or human experimentation?

Put into perspective, the prescribed dose of radiation (5,400r) delivered to Mary’s tumor over the six-week period could hardly count as palliative as far as it was more than a double of initial ten-day palliation by conventional X-ray radiation of 2,500 rads in August of 1951. Even on the assumption that the dose of 5,400r delivered by high-voltage radiation did not have the same biological effect as the same dose delivered by radiation of relatively lower energy, this dose was much higher than a palliative one. Rather, the dose of 5,400r was in the range of radical X-ray treatments for cancer of the neck, introduced in Manchester in 1935. In particular, Manchester radiotherapists administered radical whole-neck treatments with 5,000-6,000 roentgen in five to six weeks, the practice which bore a striking resemblance to what I.H. Smith’s team did with the Cobalt-60 unit. This second round of radical experimental treatment produced a visible effect on Mary’s tumor, but the medical decision was to continue irradiation with another 2,500 rads. From this point onwards, clinical research clearly tended towards human experimentation because the prognosis for the tumor elimination by radiotherapy contrasted sharply with the actual deterioration of Mary’s overall condition of health. In sum, Mary received about 10,000 rads in six months, which made her a survivor of radiation exposure, rather than of cancer.

During 1952, the London team went to fewer extremes. For instance, I.H. Smith and his colleagues recorded that a patient with a floor of mouth carcinoma, stage two, received a tumor

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163 Ibid.
164 Case No. L51/809, OCTRF London Clinic, in the AFC 328.1.2790; and Ivan H. Smith et al. Cobalt-60 Teletherapy, 370.
166 Ibid. 93. During the period in question, radiotherapists regarded radiation dosage in roentgen (R), a unit of X-radiation or gamma radiation in physics, as largely synonymous with radiation in rad (r), a unit of absorbed dose of ionizing radiation used in radiotherapy. Harold E. Johns, The Physics of Radiation Therapy (Springfield, Ill.: Charles C. Thomas, 1953), 180-185.
dose of 7,300r, which fell under “high dose observations.”¹⁶⁷ Palliative treatments with doses ranging from 2,500 to 4,000r for a variety of malignant tumors showed more promise than expected.¹⁶⁸ In this connection, Smith proposed that the Cobalt-60 unit opened an entirely new field in the palliative treatment of certain types of cancer. That matched Smith’s rationale for requesting the OCTRF to provide a minimum of twenty-five additional beds for the purpose of clinical cancer research and “for the active treatment of the disease.”¹⁶⁹ In support of his request, Smith referred to his experience in the clinic and stated that the Cobalt-60 unit operating sixteen hours a day could provide treatment to sixty patients at the maximum, or to about fifty patients monthly if both technical and human factors were conducive to work.¹⁷⁰ Figures on a number of patients treated in London over 1952-1953 reflect Smith’s proposition well. By contrast, did the Saskatoon group underuse their Cobalt-60 unit? Perhaps there was a lack of cancer patients suitable for this treatment?

Evidence suggests the Saskatoon Cobalt-60 unit operated at full capacity and, if there was any idle time, the machine was used to treat patients who came from other provinces.¹⁷¹ Out-of-province patients had to pay for their treatment, unlike the residents of Saskatchewan who received the complete treatment free of charge under The Cancer Control Act, 1944.¹⁷² Additional requests for the experimental treatment might have come through members of the Western Regional Group under the NRC Medical Research Division, wherein L.B. Jacques

¹⁶⁸ Ibid., 7.
¹⁶⁹ Minutes of a Meeting of the Committee on Cancer Centres of the Advisory Medical Board of the Ontario Cancer Treatment and Research Foundation, Ottawa 7 November 1952, p.2; in the WUA, AFC 328.1.2821.
¹⁷⁰ Ibid., 4.
¹⁷¹ As early as November 1951, correspondence about the possibility of Cobalt-60 treatment for cancer patients from different parts of Canada and elsewhere started arriving to Regina and Saskatoon. See, for instance, a letter from Mr. H. Gargrave (International Representative of the United Steelworkers of America) to Premier T.C. Douglas, Trail (British Columbia), 20 November 1951. In reply, T.J. Bentley (Minister of Public Health of Saskatchewan) wrote that the Cobalt-60 treatment had been administered to just four patients and, although there were no adverse reactions, a definite policy about the prescription and provision of this treatment did not take a definite form. Still, T.J. Bentley specified the approximate cost in the average case for a full course of therapy was $75.00 for fifteen treatments, excluding additional hospital charges. See T.J. Bentley to Mr. H. Gargrave, Regina, 4 December 1951. Both files in the PAS, R-33.1, XIV 558a (1 of 2).
¹⁷² Chapter 78 of the Statutes of Saskatchewan, as amended by Chapter 95 of the Statutes of 1945 and Chapter 83 of the Statutes of 1946.
Cancer researchers at universities and teaching hospitals in Winnipeg, Edmonton, and Vancouver could utilize this channel in referring patients from different parts of Western Canada to the Saskatoon Cancer Clinic. Thus, the discrepancy in patient numbers defies explanations based on the accessibility of Cobalt-60 units.

An overload of cancer patients treated by the Eldorado A unit boiled down to the institutional pressure on I.H. Smith and his team. It was not by coincidence that C.J. Mackenzie, David A. Keys, C.D. Howe, G.M. Jarvis, Arthur R. Ford, and William J. Bennett partook in the opening ceremonies of the unit at Victoria Hospital, London (ON). Key figures of the NRC, the AECB, the OCTRF, and Eldorado came into spotlight since the Cobalt-60 unit represented a gem of radioactive isotopes that became increasingly marketable. A crowning achievement of the government’s peaceful atomic research had to be useful not only socially, in cancer treatment, but also profit-wise. The establishment of Atomic Energy of Canada Limited (AECL) as a crown corporation on 1 April 1952 and its takeover of Eldorado four months later meant that radioisotope distribution was profitable and might become even more so if its publicity worked properly. The Cobalt-60 unit seemed an attractive advertising icon. Facts corroborating its utility, such as the spectrum of usage for cancer treatment and palliation along with some clinical successes made possible by it, could boost a market demand for the unit. Purchase orders for Eldorado units indicate that this commercial strategy worked quite well (see Table 2-3).

173 The Executive meeting of the Associate Committee on Medical Research (ACMR) on 16 September 1944, and the General meeting of the ACMR on October 23, 1944, approved the formation of Western Regional Group. The Group aimed to encourage medical research at universities and medical schools in Western Canada and to further its coordination, to survey research facilities periodically, and to review applications from the region to the NRC for grants-in-aid of medical research. The first annual meeting of the Group took place at the British Columbia Provincial Health Laboratories in February 1945. In attendance were members P.H.T. Thorlakson (MB), W.S. Lindsay (SK), C.E. Dolman (BC), J.W. Scott (AB), and visitors by invitation J.B. Collip (Chairman, ACMR), G.H. Ettinger (Honorary Secretary, ACMR). See “National Research Council Proceedings of the First Meeting of the Western Regional Group of the Associate Committee on Medical Research,” Vancouver, 23 February 1945; in the USL, RG 2090, box 5, I.B.26, Western Regional Group, 1945-1964.

174 See enclosures with a letter from L.B. Jacques (Secretary, Western Regional Group of the Division of Medical Research) to all Members of the Group, Saskatoon, 13 November 1951; in the USL, RG 2090, box 5, I.B.26.


176 This argument, that the radiation therapy specialty evolved together with the radiation device industry, is well elaborated in Barbara Bridgman Perkins, Cancer, Radiation Therapy, and the Market (London: Routledge, 2017), 7.
<table>
<thead>
<tr>
<th>Date</th>
<th>Hospital</th>
<th>Model</th>
<th>Radiologist</th>
<th>Physicist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951, Oct. 18</td>
<td>Victoria Hospital, London, Ontario (CAN)</td>
<td>A-1</td>
<td>Ivan H. Smith</td>
<td>Paul M. Pfalzner</td>
</tr>
<tr>
<td>1952, Sept. 10</td>
<td>British Columbia Cancer Institute, Vancouver (CAN)</td>
<td>A-2</td>
<td>A. Maxwell</td>
<td>Harold F. Batho Evens</td>
</tr>
<tr>
<td>1952, Nov. 30</td>
<td>Montefiore Hospital, New York, N.Y. (USA)</td>
<td>A-3</td>
<td>J.R. Fried</td>
<td>Lillian Jacobson</td>
</tr>
<tr>
<td>1953, June 12</td>
<td>Cook County Hospital, Chicago, Illinois (USA)</td>
<td>A-4</td>
<td>I. Hummon</td>
<td></td>
</tr>
<tr>
<td>1953, Mar. 10</td>
<td>Manitoba Cancer Institute, Winnipeg, Manitoba (CAN)</td>
<td>A-5</td>
<td>H. Walton</td>
<td>E.M. Campbell</td>
</tr>
<tr>
<td>1953, Mar. 30</td>
<td>University of Minnesota Hospital, Minneapolis (USA)</td>
<td>A-6</td>
<td>K.W. Stenstrom</td>
<td>J. Marvin</td>
</tr>
<tr>
<td>1953, May 28</td>
<td>Francis Delafield Hospital, New York, N.Y. (USA)</td>
<td>B-1</td>
<td>C. Braestrup</td>
<td>M. Lenz</td>
</tr>
<tr>
<td>1953, Sept. 30</td>
<td>Toronto General Hospital, Toronto Clinic, Ontario (CAN)</td>
<td>A-8</td>
<td>C.L. Ash</td>
<td>J. MacDonald</td>
</tr>
<tr>
<td>1953, Oct. 1</td>
<td>Mount Vernon Hospital and Radium Institute, Middlesex, England (UK)</td>
<td>B-2</td>
<td>B.W. Windeyer</td>
<td>D.E. Jones</td>
</tr>
<tr>
<td>1953, Oct. 8</td>
<td>Memorial Centre for Cancer and Allied Diseases, New York, (USA)</td>
<td>B-3</td>
<td>J.J. Nickson</td>
<td></td>
</tr>
<tr>
<td>1953, Oct. 11</td>
<td>Ospedale Civile S. Lorenzo, Centro Tumori del Trentino (ITA)</td>
<td>A-7</td>
<td>C. Valdagni</td>
<td></td>
</tr>
<tr>
<td>1953, Dec. 7</td>
<td>Lankenau Hospital Research Institute, Philadelphia, Penn. (USA)</td>
<td>B-4</td>
<td>T.C. Pomeroy</td>
<td>T. Sopp</td>
</tr>
<tr>
<td>1953, Dec. 22</td>
<td>Lovelace Clinic, Albuquerque, New Mexico (USA)</td>
<td>B-6</td>
<td>J.W. Grossman</td>
<td>J. Howarth</td>
</tr>
<tr>
<td>1954, Mar. 19</td>
<td>Hamilton General Hospital, Hamilton, Ontario (CAN)</td>
<td>A-9</td>
<td>Lloyd S. Green</td>
<td>R.J. Horsley</td>
</tr>
<tr>
<td>1954, Apr. 23</td>
<td>General Hospital of Port Arthur, Thunder Bay Clinic, Ontario (CAN)</td>
<td>A-10</td>
<td>W.A. Hargan</td>
<td>Harold S. Braun</td>
</tr>
<tr>
<td>1954, May 1</td>
<td>Edmonton Cancer Clinic, Edmonton, Alberta (CAN)</td>
<td>A-11</td>
<td>M. Marlborough</td>
<td>D.B. Scott</td>
</tr>
<tr>
<td>1954, July 23</td>
<td>Metropolitan Hospital, Windsor, Ontario (CAN)</td>
<td>B-7</td>
<td>Norman McCormick</td>
<td>P. Pfalzner</td>
</tr>
<tr>
<td>1954, Oct. 23</td>
<td>Hartford Hospital, Hartford, Connecticut (USA)</td>
<td>B-10</td>
<td>Ralph Ogden</td>
<td>T. Hutchison</td>
</tr>
<tr>
<td>1954,</td>
<td>Centro Italiano di Radio-</td>
<td>A-12</td>
<td>B. Allioni</td>
<td></td>
</tr>
</tbody>
</table>
By 1955, AECL had a flourishing business in Cobalt-60 beam therapy units and sources. Their sales grew steadily, not without the encouragement of agencies interested in cancer research. The NCIC Advisory Committee on Radiation Therapy, for instance, recommended to the AECL to supply Cobalt-60 units to important centers in other parts of the world in preference to Canadian centers that did not meet the required “Minimum Standards for Radiation Therapy Centres” to facilitate the clinical assessment of usefulness of the units. This assessment particularly concerned newly developed rotational models of Cobalt-60 units – Theratrons. They were more expensive than the original Eldorado A units, but as the production line standardized, and US competitors entered the market, prices lowered. Nonetheless, the volume of sales of the not so novel but affordable Eldorado A units did not decrease, to say nothing of a variety of Cobalt-60

177 “Cobalt 60 Beam Therapy Unit, Completed Installations (Model A – Eldorado Unit; and Model B – Theratron)” in the WUA, AFC 328.1.2875, box 54, file 15.
179 In 1953, the OCTRF paid $73,000 for a Theratron to be installed in the Windsor Cancer Clinic, while a quoted price for the unit was $59,000, excluding installation and accessories amounting to about $4,000, in 1955. See “The OCTRF Annual Report – 1954,” 43; in the WUA, AFC 328.1.2758. Also, “Price-list – A.E.C.L. Cobalt 60 Beam Therapy Sources and Equipment,” in the WUA, AFC 328.1.2875, Cobalt 60 – 1952-1955.
sources that could be encapsulated in independently designed units.\textsuperscript{180} In parallel with the increase in AECL sales, Canadian cancer researchers gained a reputation for their capabilities to do groundbreaking medical investigations. In its turn, this reputation transmuted in larger investments in cancer projects. How ambivalent such a rationalization of commercializing medical research appears is another matter, especially if this commercialization involves patients who turn into research subjects, willingly or not.

2.5. Conclusion

The war effort laid the foundation for the organization of cancer research in Canada. Specialists clustered across disciplines and spaces to form coordinated groups with well-defined research goals. Canada became an acceptable and convenient place for assembling scientists from the UK, France, and the USA, who could cooperate in their mostly military-oriented investigations. The Atomic Energy Project constituted a major research program that had significant ramifications in the medical field. In the wake of World War II, a constellation of Canadian interests found a new enemy – cancer – against which a part of the existing organizational framework was directed. To study complex effects of radiation from new sources, investigators explored phenomena at the interfaces between physics, biology, and medicine. This cross-disciplinary research had a considerable impact on forwarding radiotherapy as a promising cancer management modality.

As the high-voltage betatron entered the laboratory, investigators, who had been used to finding practical applications for their research, realized a therapeutic potential of the novel technology. It took not long for physicists to attract the attention of medical researchers who felt helpless against malignant tumors otherwise not amenable to surgery and conventional radiation therapy. To cancer specialists who had hard clinical data on the usefulness of radiotherapy for certain malignancies, an innovation in this field seemed a more useful therapeutic approach than burgeoning chemotherapy that had a rather patchy record. Still, the betatron, and later the Cobalt-60 unit, was no less experimental and lacking in convincing clinical evidence.

\textsuperscript{180} A standard Eldorado A unit cost \$26,500, while the price for sources differing in radiation output varied from \$10,000 to \$26,200. See “Price-list – A.E.C.L. Cobalt 60 Beam Therapy Sources and Equipment,” in the WUA, AFC 328.1.2875.
Unlike low-voltage X-ray machines (up to 400keV), the betatron required clinical trials because visible effects of skin exposure to highly penetrative rays – redness and other superficial changes – appeared only when the radiation dose was dangerously harmful. In this connection, the physicist acquired an important role in preparing the betatron for its therapeutic use through calibrating the apparatus and measuring radiation therefrom. However, particular radiation doses measured by the physicist served as a mere approximation for the radiotherapist who needed to adjust them to the response of cancer patients. The only way to determine a generalizable adjustment scheme was to experiment and to gather necessary clinical data in the process.

A contentious issue that clinical research with the betatron could be regarded as fundamental research induced officials at the National Cancer Institute of Canada to see its policy of supporting cancer projects in a new light. Wrote O.H. Warwick, the NCIC Executive Director, “Initially, I think it was felt that the Institute’s most important role might be in the field of fundamental research, but it was appreciated that it might also serve a useful function in coordinating the efforts being made provincially to facilitate and improve the standards of medical care for cancer patients.”\textsuperscript{181} This point arose because physician-investigators tried new methods of treatment – the betatron and radioactive isotopes – more or less experimentally on hospital patients and proposed that while the value of those methods was in the course of establishment, they should be considered fundamental research. Consequently, the NCIC placed itself on record as not opposing its members taking an interest in clinical research.

To the cancer patient suffering from an advanced malignancy the distinction between experimental treatment and clinical research seemed to matter less than a possibility of cure or a probability of palliation by a new technology. T.A. Watson chose critically ill patients for experimental treatment by means of the betatron and I.H. Smith did the same for the Cobalt-60 unit, but Smith preferred to call it clinical research. Patients’ choice to submit to this kind of treatment tended to follow from their trust in physicians’ medical knowledge and ethics. There were treatment plans, rather than clinical research protocols, which indicated that patients had no reason to question any procedures at the time. On the other hand, radiotherapists could not unequivocally explain whether they subjected patients to treatment or palliation, or clinical

\textsuperscript{181} O.H. Warwick, “Report of the Executive Director,” 28 May 1951, p.3; in the USL, RG 2090, s.4, box 2, B8(h) Miscellaneous 1948-1960.
research, since indications for using the betatron, radioisotopes, and the Cobalt-60 unit were uncertain.

More evidence from patients was essential to determine what truly constituted treatment. However, when this objective became two-fold – to help as many cancer patients as possible and to provide clear clinical data that sustained a commercial interest in the Cobalt-60 units – as in the case of I.H. Smith’s team, the utilitarian reasons behind experimental treatments began taking shape at the background of the humanitarian reasons. Yet, it would be erroneous to assume that utility prevailed over humanity when a “downright ornery” cancer afflicted the person.182 Some propositions of I.H. Smith implied this, such as the following, “A hollow viscus [the stomach] may be endowed with some natural reparative ability, but its restorative power as tumour melts away [during Cobalt-60 irradiation] is woefully lacking and is the constant mental check on our desire to carry dose to a lethal point. Be this as it may, the renewal of a patient’s interest in the T-Bone steak has its quiet compensations.”183

Chapter III

The Hard Way to Randomized Clinical Trials in Canada

Radiotherapy with Cobalt-60 units became a standard of treatment for a range of tumors following its effectiveness appraisals on different patient groups. In the second half of the 1950s, treatment outcomes of Cobalt-60 teletherapy yielded convincing evidence through the recognized index of five-year survival rates.¹ Both Thomas A. Watson and Ivan H. Smith, the pioneers of this treatment, documented their findings in a series of publications.² In the words of Ivan Smith,

Like all others using new therapeutic techniques against cancer, we rightly are serving that conventional five-year term assigned by statistical judges. We view our work as clinical research and on the basis of experience gained, we alter our dosage, overall treatment time, and techniques to fully utilize the physical advantages afforded by cobalt⁶⁰ [sic]; and thereby gather factual data on this new form of irradiation.³

This passage reveals two important implications. The first statement suggests that medical statistics not only reinforced credible boundaries of radiotherapy at the time, but also became a powerful shaper of expert opinion among representatives of the medical profession, however reluctantly they may have admitted it. Smith’s second proposition indicates that radiotherapists were primary agents in collecting and analyzing data, rather than statisticians who had gained ground on major scientific and medical research enterprises during World War II.⁴

¹ For details on the advantages of this statistical method of treatment evaluation in comparison with the ‘cure’ rate, see Ralston Paterson, Margaret Tod, and Marion Russell, The Results of Radium and X-ray Therapy in Malignant Disease: being the second statistical report from the Holt Radium Institute, Manchester (Edinburgh, UK: E.&S. Livingstone, 1946); and T.A. Watson, Results of Treatment of Cancer in Saskatchewan, 1932-44 (inclusive) (Regina, SK: Thos. H. McConica King’s Printer, 1951), 7.
⁴ A good example of this rise of statistical thinking is an article-reference for investigators of the Medical Division of the NRC prepared by Donald Mainland, “Statistical Methods in Medical Research,” Canadian Journal of Research, 26, Sec. E1 (February 1948): 1-166. On page 35, Mainland, Professor of Anatomy at Dalhousie University of Halifax
In radiation therapy, the diversification of methods increasingly influenced the management of cancer and, simultaneously, contributed to the recognition of radiotherapists as specialists. Prior to 1954, the same personnel at hospitals across Canada that conducted diagnostic radiology were in charge of radiotherapy.5 By the mid-1950s, radiotherapy could not be further carried on in conjunction with diagnostic radiology because of the amount of work required to treat patients whom physicians increasingly referred to cancer clinics with new equipment. Radiotherapy and diagnostic radiology separated as a consequence. Prudently choosing inoperable cancer cases for treatment initially, radiotherapists demonstrated that their therapeutic mode gave results at least as good as surgery, and in cases in which surgical measures were hardly applicable, high-voltage radiation techniques produced a number of successes. Patients who survived a five-year benchmark enhanced the status of the nascent field of high-voltage radiotherapy and most likely linked public perception of the radiotherapists’ sophisticated equipment with a potential to cure cancer. Although surgeons and radiotherapists had explored the strengths and weaknesses of their respective practices, they tended not to take a cooperative approach in the management of cancer. Yet, this cooperation was even more necessary when surgeons and radiotherapists confronted the rise of chemotherapy in cancer control during the 1950s.

Like the development of nuclear physics for defense purposes resulted in its increased use in medical research and treatment, chemotherapy gained importance in cancer management owing to the war effort since the 1940s. Clinical investigators found that nitrogen mustards, hormones, and metabolism-blocking agents had temporary effects on the growth of certain

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5 G. Frank Boult “Addition to History of Radiology in Manitoba Re: Radiotherapy,” in the University of Manitoba Faculty of Medicine Archives (hereinafter UMFMA), Department of Radiology, Series 2.23.2 – historical files, folder 1. Boult, who began as an Assistant Radiologist at the Winnipeg General Hospital in the 1950s and became a radiotherapist later, expounded on this national trend with an emphasis on regional repercussions. Exceptions to this dominant trend were radiotherapy centers, like the OIR, which employed certified radiotherapists, such as Gordon E. Richards, who had obtained their training and certification in Great Britain. See a report of the Director of the Ontario Institute of Radiotherapy, Clifford L. Ash, “Cobalt 60 Beam Therapy Unit, Toronto,” in the WUA, AFC 328.1.2758, The Ontario Cancer Treatment and Research Foundation Annual Report – 1953, p.29.
cancerous cells. Realizing that those agents used alone had less than satisfactory effects, they started using chemotherapy agents in combination. Before researchers studied physiological effects of chemical substances in the human organism, they had carried out extensive preliminary investigations with animal models in order to determine the safe levels of these compounds. Moreover, the human studies necessitated a controlled demonstration in a series of events that modelled experimental conditions by limiting the number of variables influencing the treatment outcome. A significant aspect of this combinatorial approach relied on the use of chemical agents in conjunction with radiation.

At the Banting Institute of the University of Toronto, for example, William R. Franks and his associates tested hundreds of different chemicals to discover which were most effective for particular therapeutic needs. Potential chemical enhancers of radiotherapy for cancer, such as oxygen and cysteine, received close attention because of substantial advances in the field of irradiation. Surgeons and radiotherapists soon embarked on interactive work with chemotherapists in the ‘trading zone’ of the cancer clinic. In view of the asymmetric power relationships among those three groups, their negotiations often led to an inevitable impasse, but changing priorities of provincial cancer care programs and shifting preferences of funding agencies nationally called for compromises on all sides.


7 “Cancer Research 1956-1957,” Canadian Cancer Society Newsletter, 9, no.3 (March 1956): 2; in the WUA, AFC 40 – 28/34.


9 For more details on the notion of “trading zone,” consult Galison, Image and Logic, 816.
Exploring the professional struggles in the domain of therapeutic innovations for cancer, I examine in this chapter the slow emergence of the randomized controlled trial as the method to test the efficacy of cancer treatment modalities in comparative terms. I argue that the rift between surgeons, radiotherapists, and chemotherapists contributed to hampering the development of randomized controlled trials of new treatments in Canadian teaching hospitals. This contestation unfolded against the national and the international backgrounds. Nationally, cancer surgeons upheld their interests in healthcare and in courts (e.g. Wilson v. Swanson judgement of 1956) despite opposition from other interested parties. International developments in clinical cancer research entered the equation as Canadian radiation specialists working with Cobalt-60 units and medical scientists developing cancer chemotherapy with vincaleucoblastine, among others, moved into the world arena.

Since the introduction of Cobalt-60 teletherapy units in 1951, radiotherapy in Canada emerged as a serious rival to surgery. A contributing factor to this rivalry was the National Cancer Institute of Canada that centered largely on radio- and chemotherapeutic aspects of cancer control, rather than on surgery. Novel chemotherapeutic agents and upgraded megavoltage radiotherapy machines catalyzed a reconfiguration of power relations among surgeons, radiotherapists, and chemotherapists, though it was not until the early 1960s that randomized controlled trials played a role in this process.

3.1. The Untouchables of Medical Practice Reaffirm their Status

By mid-1953, there were four Cobalt-60 beam therapy units operating in London (ON), Saskatoon (SK), Vancouver (BC), and in Winnipeg (MB). Working at full capacity, between twelve and sixteen hours a day, the units needed two full-time radiotherapists to treat all cancer patients admitted to the clinics who required high-voltage therapy, but usually only one was available. On average, a good month’s work would be with about fifty new patients per one Cobalt-60 unit. Patient numbers were growing also because radiotherapists saw an entirely new field in the palliative treatment of certain types of cancer with Cobalt-60 units. From the social perspective, the Canadian Cancer Society (CCS) and its Divisions spread the word about

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10 Minutes of a Meeting of the Committee on Cancer Centres of the Advisory Medical Board of the Ontario Cancer Treatment and Research Foundation, Ottawa, 7 November 1952, p.4; in the WUA, AFC 328.1.2821.
advances in cancer care concurrently with telling the public about the dreadful and insidious disease that could be prevented if detected early enough.

Like the American Cancer Society, the CCS promoted the early detection strategy of cancer care in view of the virtual absence of effective treatment modalities for late-stage malignancies. Disputing this course of action were a few widely respected medical professionals in both Canada and the United States. For instance, a well-known American surgeon, George Crile, perceptively noted, “It is quite likely that the propaganda about early detection of cancer has had as serious an effect on the medical profession as on the public. This is inevitable because the practice of physicians always reflects to some extent the opinions of their patients. Today many people believe that the slightest delay in treatment diminishes the chance of cure.” In other words, Crile pointed out that there seemed to be a feedback loop in how the message about early diagnosis of cancer percolated through specialists, healthcare officials, organized community-minded volunteers, and the public. The intermediary agents, such as the CCS, had a pivotal role in this interconnected process. Besides using the weapon of fear in cancer education, the CCS toned down its communications with news on the advances in technology that could alleviate anxiety of cancer sufferers. Radiation therapy enhanced its appeal with impressive Cobalt-60 units. Thus physicians, who were on the front-line of diagnosing patients suspecting malignancy, tended more and more to make referrals to cancer clinics.

These developments ran counter to the work schedules of cancer surgeons, however. In Saskatchewan, for instance, the College of Physicians and Surgeons notified the Department of Public Health in the spring of 1953 that members of the College of Surgeons intended to increase the cancer surgery fees and contract schedule by twenty percent. This intention apparently addressed a reduction of cancer surgeons’ workload associated with the hype surrounding radiotherapy. Therefore, the College decided that “failing agreement of the [Saskatchewan]
Cancer Commission to pay the 20% increase, the College [would] instruct all cancer surgeons to bill the patients for the extra 20%, this to become effective on July 1st [1953]."\textsuperscript{14} This meant there would be no longer “free” cancer services in Saskatchewan, which would likely imperil the provincial cancer care program. To oppose this course of action, the Minister of Public Health, T.J. Bentley, instructed the Chairman of the Saskatchewan Cancer Commission, C.F.W. Hames, to attempt to persuade the College to agree that cancer surgery should continue on the same schedule as in the past. Hames’s taking the matter up with the College did not produce any agreement until the Cabinet considered this issue. After difficult negotiations, which almost reached a Board of Arbitration, the Cabinet, headed by the Premier T.C. Douglas, agreed to offer an increase of ten per cent for cancer surgery fees to the College.\textsuperscript{15} The latter reluctantly accepted it, but surgeons operating on cancer patients seemed to perceive their work disadvantaged by comparison with occupations of other cancer specialists, especially radiotherapists.

In this connection, the overlap of government intervention in otherwise free enterprise in medical practice deserves a mention. Discussions on this matter began in Ontario as early as the late 1940s. A prominent radiologist and director of the Department of Radiology at St. Joseph’s Hospital in London (ON), M.C. Morrison, had debated this issue with a number of surgeons and radiotherapists associated with the Ontario Cancer Treatment and Research Foundation clinics. His conclusions found general agreement with suggestions of those professionals. Morrison put it as follows,

\begin{quote}
It is my firm conviction that if we must tolerate state intervention in medical practice by the invasion of radiotherapy in a cancer program, then this activity should be limited to cancer in so far as possible. Yet, we see a reluctance on the part of the clinic doctors to so limit their field of activity – some extending their practices to include the whole field of surgery (appendectomies, fractures, etc.), also all radiotherapy, benign and malignant – truly a most pretentious specialty.\textsuperscript{16}
\end{quote}

\begin{footnotes}
\item\textsuperscript{14} \textit{Ibid.}
\item\textsuperscript{15} Memorandum C.M.3816 Re: Cabinet Meeting of June 8\textsuperscript{th}, 1953, from H.S. Lee to Premier T.C. Douglas, Regina, 9 June 1953; in the PAS, R-33.1, file XIV 558a (14-12).
\item\textsuperscript{16} Blair, \textit{Cancer in Canada}, Province of Ontario, op. cit., 22-23.
\end{footnotes}
By the mid-1950s, the pretensions of radiotherapy transformed into a recognition of its new accomplishments in Saskatchewan, Manitoba, British Columbia, and Alberta. Moreover, cancer patients contributed to the recognition of radiotherapy as a standard of treatment.

Against all odds, some patients defied the professional judgement of the clinic doctors and decided on their own at critical moments in their lives. Even though it was the cancer specialist who, following the diagnosis of the patient, determined the course of recommended therapy, the patient could reject the recommendations by assuming full responsibility for the desired treatment, whatever it might be. This responsibility meant that the clinic transferred financial and legal obligations for the administered treatment to the patient. In Saskatchewan, Regulations Governing Consultative Diagnostic and Treatment Clinics, read:

Where a patient declines to accept the recommendations of the consultative staff and desires radi[o]therapy, without or instead of surgery, the staff may accede at its discretion, to the patient’s request, providing that a signed written statement is obtained from the patient, giving reasons for so declining, and accepting responsibility for the treatment administered.\(^\text{17}\)

Similarly, Regulations on the Cancer Treatment and Prevention Act in neighboring Alberta stipulated that, “When surgery has been recommended as being the treatment in the best interests of the patient and the patient declines to accept the recommendations of the Clinic in this regard but desires X-ray and/or radium treatments, the costs of such treatment will not be assumed by the Department.”\(^\text{18}\) Those two regulative documents, particularly their provisions disclaiming legal liability for malpractice, need some explanation in light of the recommended cancer surgery.

The case of Mr. Swanson reflects how tenuous the boundary was between a standard surgical intervention and radical cancer surgery.\(^\text{19}\) Mr. Swanson, born in British Columbia, was a miner and construction worker. At the age of sixty-seven, Swanson, who was still steadily employed in construction in Alberta, got a recurrent indigestion that he could not relieve. In January 1951, he saw a doctor in Lethbridge, F.J. Johnson, who after the usual medical

\(^{17}\) See Regulations Governing Consultative Diagnostic and Treatment Clinics as of 9 November 1931, sections 21 and 22; in Blair, Cancer in Canada, Province of Saskatchewan, p.15.

\(^{18}\) Regulations on the Cancer Treatment and Prevention Act came into force on 23 July 1946. See the document’s section 12 under “Preferences of Patients” in Blair, Cancer in Canada, Province of Alberta, p.6.

\(^{19}\) Wilson v. Swanson [1955], 3 Dominion Law Reports (D.L.R.) 171 [McInnes J.], British Columbia Supreme Court.
examination concluded that Swanson’s condition was serious enough to warrant further
diagnostic procedures. Dr. Johnson referred Swanson to the Galt Hospital in Lethbridge to have
an X-ray of his stomach taken. Having read a report of the hospital radiologist, Dr. Johnson
made a presumptive diagnosis of cancer and advised to make a laparotomy – a surgical cut in the
abdomen in order to establish the initial diagnosis as either accurate or incorrect. On hearing this,
Swanson decided to return to Vancouver for further medical and potentially surgical care.

In April of 1951, Swanson visited the British Columbia Cancer Institute (BCCI) to
confirm the diagnosis of his condition. Based on available records, which Swanson brought with
him from Alberta, and his medical history taken at the BCCI, Dr. Lambert, an attending
physician associated with the Vancouver General Hospital (VGH), examined Swanson again and
reported his patient’s condition as “a peptic ulcer, with probable gastric carcinoma and possible
gall bladder and chronic pancreatitis.”20 Cancer surgeon, Dr. Roger Wilson, read all the
supporting documentation, examined Swanson once again, and recommended an immediate
operation by arranging for the patient’s admission to the VGH on 23 April 1951. Swanson
agreed to submit to this operation at first, but then reconsidered, inasmuch as Dr. Wilson did not
explain to him the nature of recommended surgery, nor even indicated a likelihood of stomach
cancer that necessitated the operation. Swanson was also concerned about his inability to work
after the operation and a possibility to survive for only about four years if his stomach problem
resulted from a cancerous growth, about which Dr. Wilson had apparently let him know.
Ultimately, Swanson came to the VGH on the specified date and Dr. Wilson performed the
planned surgery. In the course of that operation, “about four-fifths of his stomach, about two-
thirds to three quarters of the pancreas and the entire spleen were removed.”21 It was a radical
surgical intervention, rather than an exploratory operation. Swanson suffered post-operative
complications, but recovered, and was discharged from the VGH on 31 May 1951.22 Later, he
developed diabetes due to the removal of the better part of his pancreas. On finding out that his
surgery did not expose any malignant disease, Swanson began legal action against the cancer
surgeon, Dr. Wilson. In particular, Swanson sued Wilson for negligence and consequent damage

20 Wilson v. Swanson (1955), 175.
21 Ibid.
to his body because of the surgeon’s failure to use reasonable care when there was a duty to do so.

On 4 April 1955, The British Columbia Supreme Court in the person of Judge H.W. McInnes arrived at a verdict denying any finding of negligence. Judge McInnes justified the radical operation since the surgeon intended to prevent the recurrence of a probable cancer by removing any cancerous growth in the abdominal area. According to Judge McInnes, Dr. Wilson demonstrated “a fair and reasonable standard of care and competence.”23 The reasoning behind this judgment was that Dr. Wilson did not want the patient’s condition to deteriorate to such an extent as to make it inoperable. Arguably, the cancer surgeon envisioned the worst scenario in view of his extensive previous experience that suggested a poor prognosis for advanced cancer cases. Judge McInnes summarized his position, “Can it be said in the case at bar that Dr. Wilson either undertook a case which he knew or should have known to be beyond his powers or that he made the plaintiff [Swanson] the subject of reckless experiment? In my opinion it is clear on the evidence that he did neither.”24 Such a ruling on a supposedly safe-bet legal action did not satisfy Swanson and he filed an appeal to the higher court of justice.

The British Columbia Court of Appeal started proceedings with a statement on the relevance of this case to the public awareness about cancer. Indeed, the disease became a public problem in the mid-1950s as the knowledge about its diagnosis and treatment spread through the media. In this connection, the strategy of the Court of Appeal judges was to reveal that cases like the one under consideration were quite infrequent occurrences that did not need to alarm the public. Consequently, deliberations of the court centered upon the doctor’s duty to the patient to subject him to a thorough clinical investigation before engaging in radical surgery. Judge Cornelius H. O’Halloran rightly put it, “the patient operated on for a cancer he did not have, has never been able to learn the reason why. He and people like him should not have cause to develop the belief that the conduct of a professional medical man in such a case is not open to full investigation in the Courts of British Columbia.”25 Correspondingly, the focus of the court shifted to the professional conduct of a cancer specialist in dealing with diagnoses of malignancies inside human bodies. In other words, the root of the matter was the ethics of the

24 Ibid., 180.
medical profession in respect to reaching a final diagnosis of cancer on the balance of the uncertainties of the different alternatives. In question was the legitimacy of radical surgery under the circumstances, which meant a removal of internal organs that should not have been removed unless cancer had been present.

Judge O’Halloran pinpointed a Halstedian trend in cancer surgery, “since cancer is so common, and its presence is so difficult to be sure of before opening up a person on the operating table, a surgeon cannot be criticized or held liable in damages, if [his] mistaken assumption that the patient has cancer [leads to unnecessary removal of body parts].”26 This kind of logic, clearly manifested in the submissions of respondent Wilson’s counsel, encountered a degree of learned skepticism on the part of the court. Therefore, the judges determined what procedures of other specialists should have reasonably preceded the “opening up a person on the operating table.” In determining this, the roles of a radiologist and a pathologist stood out.

Before proceeding with the operation, surgeon Wilson had failed to obtain both additional X-ray pictures and the radiologist’s report on them and on fluoroscopy. Although Wilson’s clinical information on the case was incomplete, his diagnosis was unqualified – “Ca. [cancer] stomach for resection” – despite the fact that the initial diagnosis on the medical examination was “probably cancer.”27 Admittedly, Wilson embarked upon radical surgery almost at the outset, but during the operation, he began doubting the correctness of his diagnosis and sent for the pathologist to clarify the issue. Dr. Fidler, a pathologist, made a requested quick examination of the excised stomach tissue and produced a short biopsy report saying, “this was […] probably a case of linitis plastica type of cancer.”28 With the pathologist’s intra-operative consultation supporting Wilson’s diagnosis, he continued the operation lasting for about five hours in total. After the surgery, pathologist Fidler, Head of Pathology at the VGH, did a paraffin wax test, a definitive pathological method designed to examine tissues, which showed that

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26 Ibid., 197. The approach to cancer surgery of American surgeon William S. Halsted, who became famous for his refinement of radical mastectomies in the late nineteenth century, not only continued to command respect from many a surgeon in the first half of the twentieth century, but also gained recognition of the surgical profession as the proper mode of action in operations involving tumor resection.


28 Ibid., 216.
Wilson’s tumor was benign. This meant that Fidler’s initial biopsy report was erroneous, in all probability due to his hasty assessment of the tissue specimen.

Most of the pieces of the puzzle appeared to fall into place for the court. Judge O’Halloran’s proposition deserves a citation in full,

In my opinion it would be a strange and unscientific approach when it is necessary to remove a large peptic ulcer that other organs which might perhaps be affected (but might not be) should also be removed on the mere speculation that cancer might exist in them. Such an attitude is too closely connected with a callous disregard of a patient’s rights and human dignity as a person, and more markedly so when as here it occurs without a thorough clinical investigation.

This strong statement explicitly contrasted the surgeon’s single-minded determination in his professional activity with the patient’s powerlessness in the face of specialists. Wilson showed bias against the authority of radiologists in their sphere of competence and he was prejudiced in favor of pathologists’ expertise. Such partiality on the part of Wilson seems to have contributed to the self-induced error and the resulting injury to patient Swanson. As Judge James M. Coady noted, “this preconceived and unjustified diagnosis made it difficult for him [Wilson] to reorient his mind when the doubt arose, and to properly weigh the pathologist’s report against the facts.”

Thus, the court ascertained a fait accompli of wrong diagnosis compounded by the failure to use additional valuable information in diagnosis, and ruled that the alleged negligence did take place. Even so, the College of Surgeons could not leave this interpretation of a professionally significant precedent as it stood. The reputation of cancer surgery in the growing cancer care program was at stake, so the ruling did not go unchallenged.

Surgeon Wilson’s legal counsel appealed expeditiously. Less than three months after the appeal decision, the Supreme Court of Canada (SCC) judges began their deliberations on this case of medical malpractice. In particular, the court focused on what constituted negligence in a

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29 Ibid., 217.
30 Ibid., 200. By referring to a disregard for human dignity, the judge supposedly meant the offence to the patient through the impingement upon his bodily integrity that happened without a proper antecedent explanation on the part of the surgeon. In the 1960s, this explanation took the form of a written informed consent. See Charles Fried, Medical Experimentation: Personal Integrity and Social Policy. Edited by Franklin G. Miller and Alan Wertheimer. New edition (New York, NY: Oxford University Press, 2016), 20-21.
31 Swanson v. Wilson (1956), 212.
surgical practice generally and how this standard applied to the case under consideration. The judges used the test of reasonable care that had to do with performance of a difficult surgery within the accepted limits of professional surgical opinion. In the words of Justice I.C. Rand, “What the surgeon by his ordinary engagement undertakes with the patient is that he possesses the skill, knowledge and judgment of the generality or average of the special group or class of technicians to which he belongs and will faithfully exercise them.”

33 What required demonstration to dismiss the alleged negligence was the substantiation that surgeon Wilson employed the degree of skill and professional judgement of an average specialist in his field. Other parameters of the case, like the incomplete diagnosis and the snap assessment of evidence, turned out to be beyond the scope of relevance. Accordingly, the judges proceeded to establish whether the steps taken by surgeon Wilson to do a radical surgery were reasonable enough under the circumstances for average specialists to think of them as such.

Given that Wilson completed the surgical intervention successfully and patient Swanson recovered, despite some complications, the court avoided any consideration of the substantial harm associated with the operation.

34 The issue in dispute, therefore, was the surgeon’s decision to perform a radical instead of a standard abdominal resection. That Wilson made a recourse to the experienced pathologist at a critical point of choosing one of the alternatives proved crucial in adjudicating the balance of competence and considerateness in this case. Even though pathologist Fidler committed a mistake in his examination, his level of expertise urged him to verify his hasty conclusion by conducting a more rigorous test after the operation. Without this longer test, neither the surgeon, nor the patient would have found out about the absence of cancer. Justice Rand pointed out, “If under the microscope – which reaches nearest to certainty in detecting malignancy – the interpretation could be erroneous, what significance could tests have which can give the same result in either type of tumour?”

35 This proposition elucidated why surgeon Wilson had relied so heavily on the intra-operative pathological report. The pathologist of recognized competence failed to provide corroborative evidence on the tumor’s benign nature,

33 Ibid., 119.

34 For example, Justice Rand was dismissive of this topic in writing, “The radical procedure was thereupon carried out […] this meant the removal of substantial portions of those three organs [spleen, stomach, pancreas] as well as a small and unimportant bit of the liver. The issue is on the decision to remove what would have been called for in the presence of carcinoma [a malignant tumor].” Wilson v. Swanson (1956): 115.

35 Ibid., 119.
which suggested that a radical operation was necessary. Justice D.C. Abbott, therefore, concluded, “[Wilson] made an admittedly difficult decision [sic] but the sort of decision which every surgeon must be called upon to make from time to time. In making that decision [sic] I am satisfied he exercised his best judgment in what he considered to be the best interest of his patient.” This purportedly best interest disabled Swanson, encouraged him to appear in court in 1955, and yet spared him the psychological burden during the appeal hearing in the Supreme Court of Canada. Swanson had died before the proceedings commenced.

The SCC judgment to dismiss this malpractice action was far from unanimous: two of the five justices dissented. Considering this three-to-two majority, it is noteworthy that the Chief Justice of Canada, Patrick Kerwin, was on the dissenting side. It seems more understandable on the authority of an influential manual, Malpractice Liability of Doctors and Hospitals, wherein the eminent lawyer, William C.J. Meredith, stated, “Since the science of medicine is not an exact science, a doctor is not as a rule liable for an honest error of judgment, provided he does what he considers best in the patient’s interests following a careful examination.” A bone of contention was, therefore, the scrupulousness of patient’s preoperative examination. This point becomes clearer on the background of another proposition by Meredith: “[…] it is important to recall that the right of a patient when consulting a doctor is to have an examination, a diagnosis, advice and consultation. Thereafter it is for the patient, and not for the doctor, to decide what, if any, treatment or operation shall be performed.” This notwithstanding, the social utility of what surgeons did in public health, to say nothing of cancer management, mattered more than random events of their malpractice. It explains sufficiently well why a legal precedent that recognized a right in the patient not to compromise his physical integrity yielded to another precedent, which prioritized reasonableness of professional groups that determined such contested issues.

36 Ibid., 125.
38 Italics in the original. The SCC Justice Abbott cited this work. W.C.J. Meredith was a Queen’s Counsel barrister in Montreal and Dean of the Faculty of Law of McGill University. See William C.J. Meredith, Malpractice Liability of Doctors and Hospitals (Toronto: Carswell, 1956), 63.
39 Ibid., 144. W.C.J. Meredith further supported his contention by a reference to a precedent ruling quoted as follows, “no amount of professional skill can justify the substitution of the will of the surgeon for that of his patient.”
One cannot deny that the SCC judgment grounded several claims of cancer surgeons nationally. First, a demand for higher fees for rendered services, as exemplified by Saskatchewan surgeons, could be justified on account of the specific cancer cases that were difficult to operate on and required appropriate surgical expertise. Other claims followed. On the suggestion of Walter C. MacKenzie, a surgeon and Dean of Medicine at the University of Alberta in Edmonton, the Council of the Royal College of Physicians and Surgeons of Canada (RCPSC) formed the Ad Hoc Committee that “acted as a disciplinary committee to recommend to Council appropriate action in cases of irregular behaviour on the part of Fellows or Certificated Specialists.”40 Under the leadership of MacKenzie, the so-called “Judiciary Committee” issued a memorandum listing instances of the-then common misconduct and proposed to penalize it under the by-laws of the RCPSC and the Canadian Medical Association Code of Ethics. These instances of misconduct included, among others, “Improper financial dealings, including the direct or indirect division of fees with other physicians, the payment or acceptance of rebates of fees for technical services or appliances, and the charging of exorbitant fees. […] Solicitation of patients. […] Performance of unjustified surgery.”41 Thus, practices of physicians and surgeons had also an ethical dimension that converged with providing care to patients.

Unjustified and especially unsuccessful surgeries made practitioners vulnerable to accusations of misconduct and legal liability. The number of malpractice lawsuits across Canada in the mid-1950s increased approximately seven times compared to the early 1940s.42 Medical malpractice litigation indicated a troublesome change in the relations between the patient and the doctor. According to Dr. Samuel Kling, Chairman of the Committee of Medical Ethics and Public Relations of the Edmonton Academy of Medicine, “in recent years [1954-1957] the practicing doctors have toppled precipitously from their previous favorable pinnacle [in public

40 James H. Graham (Secretary, RCPSC) to Donald R. Wilson (Professor of Medicine, University of Alberta Hospital, Edmonton), Ottawa, 6 September 1960; in the University of Alberta Archives (hereinafter the UAA), Acc. No. 86-65, box 8 (72) – Committee on Ethics and Judiciary Committee, 1960-61.
41 Walter C. MacKenzie (Chairman, Royal College Committee on Ethics), “Memorandum to: Members of the Ethics and Judiciary Committees, Royal College of Physicians and Surgeons of Canada,” 6 December 1960, p.2. ibid.
42 At a regular monthly meeting of the Edmonton Academy of Medicine, held at University of Alberta on 8 April 1959, Mr. J.H. Laycraft, a lawyer from Calgary, delivered a keynote speech on the topic “Medical Malpractice.” A key theme of his talk was that fear of legal action should not interfere with the good practice of medicine, such as refusals to treat patients. See the UAA, Acc. No. 69-121, box 2 (14) – Edmonton Academy of Medicine Minutes, 1959-1964, p.11.
relations].\(^{43}\) Albeit, this development was not so evident in teaching hospitals, where doctor-investigators tended to combine treatment with research, owing to a more adequate medical care and a partial, or even full, coverage of fees for medical services.\(^{44}\) Thus, the establishment of “an institution comparable to a teaching hospital” signaled to medical administrators in Canada that legal liability risks could be reduced and a distance between the bench and bedside may be shortened pending similar arrangements.\(^{45}\)

3.2. Professionalization of Radiotherapy and Diversification of Surgery

A newly built University Hospital in Saskatoon saw its official opening ceremonies on 14 May 1954.\(^{46}\) Although the Saskatchewan Legislative Assembly passed the University Hospital Act in 1946, the university lacked the proximity of teaching facilities to bond medical academics with clinicians.\(^{47}\) With the University Hospital in place, faculty members of the College of Medicine staffed the hospital. One of the results of this was a fully-fledged Medical School, which meant that it became possible for the university to offer the final years of the medical curriculum and consequently graduate medical students for the first time in 1956. Establishing a medical school, however, also meant supporting medical research, which involved human experimentation.

Similar events took place in London, Ontario, where Victoria Hospital remained the principal teaching center for clinical studies in collaboration with the Medical School of the University of Western Ontario (UWO). On 18 November 1954, the London Cancer Clinic

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\(^{43}\) *Edmonton Academy of Medicine Minutes, 1953-1958*, p.97. Meeting as of 2 October 1957; in the UAA, Acc. No. 69-121, box 2 (13).

\(^{44}\) See *The Western Assurance Company liability policy No. 5-401184, Toronto, 16 March 1954*; in the University Health Network Archives (hereinafter UHNA), Ontario Cancer Institute/Princess Margaret Hospital fonds, Series 5: Division of Clinical Services records, 94-00021, box 11B, 5.48.

\(^{45}\) For this purpose, the Board of Governors of the University of Toronto and the Board of Trustees of the OCI formed a University-Cancer Institute Joint Relations Committee in February 1955. See correspondence from Sidney Smith (President, University of Toronto) to Clifford L. Ash (Director, OCI), Toronto (ON), 6 December 1954; and Minutes of the Board of Trustees of the OCI held at Toronto General Hospital, 4 February 1955; both documents in the UHNA, 98-0001, box 34, SF1: 17D.2.

\(^{46}\) *The First Annual Report of the University Hospital, Saskatoon* (1955), p.5; enclosed with a letter from G. Edward Hall (President, UWO) to Carman J. Kirk (General Superintendent, Victoria Hospital, London, Ontario), 1 August 1956; in the WUA, AFC 40 – 33/23.

opened its doors on two floors of the newly constructed Y-shaped addition of Victoria Hospital.\footnote{Ivan H. Smith, “The Ontario Cancer Foundation London Clinic,” in The OCTR\F Annual Report – 1954, 36; in the WUA, AFC 328.1.2758.} The Ontario Cancer Treatment and Research Foundation (OCTRF) allocated 11,231 square feet of the hospital space for treatment coupled with teaching and research presumably to strengthen its alliance with medical academics at the UWO.\footnote{Ibid., 36.} There were ample grounds for this assumption. The next day after the hospital wing’s inauguration, an important meeting of the Committee on Cancer Centers of the Advisory Board of the OCTRF took place at the London Clinic. Key items on the agenda included a consideration of the report of the Special Committee on the Winnipeg Conference on Cobalt-60 Beam Therapy, held under the auspices of the NCIC, and a discussion of means by which Canadian physicians may be interested in making radiotherapy their future profession.\footnote{Minutes of a Meeting of the Committee on Cancer Centres of the Advisory Medical Board of the Ontario Cancer Treatment and Research Foundation, London (ON), 19 November 1954, p.2; in the WUA, AFC 328.1.2821.} Those were interrelated issues.

Cobalt-60 teletherapy units were a highly useful addition to the radio-therapeutic armamentarium. As their availability in Canada increased, it became clear to leading therapeutic radiologists that there was a shortage of trained radiotherapists. One solution to this problem was that radiologists acknowledged the qualifications of radiotherapeutic technicians who had had at least five years of full-time experience in a recognized radiotherapeutic department.\footnote{For instance, the Ontario Society of Radiographers arranged for a separate certification of technicians in radiotherapy and radiology on a recommendation from the Advisory Board of the OCTRF. Ibid., 1.} Moreover, as early as 1952, the NCIC Advisory Committee on Radiation Therapy organized a post-graduate training program for radiation physicists whose objective was to work in clinical settings. Up to mid-1954, thirteen medical physicists had received training sponsored by the NCIC, but not all were interested in proceeding with work in radiotherapy.\footnote{H.E. Johns, “Report of the Ad Hoc Committee for the Post-Graduate Training of Radiation Physicists in Canada,” 6 May 1955, in NCIC, Annual Report of 1954-1955 (Toronto: NCIC, 1955), 25.} The reason was not the absence of suitable positions, inasmuch as the certified radiotherapists and physicists numbered in double-digits across Canada. For instance, thirty-five Canadian radiation therapists and physicists working with Cobalt-60 units attended an NCIC-funded meeting on radiotherapy that convened during the First Canadian Cancer Research Conference on 16-19 June 1954 in Honey Harbour,
Ontario. Such low numbers of medical radiation specialists indicated that their professional status was not high enough.

The Advisory Board of the OCTRF recommended how to enhance the image of radiotherapy and make it more attractive to future specialists in radiation treatment. One member, W. Gerald Cosbie, expressed this idea thus, “if young men enter the field of radiotherapy merely to become medical technicians, there is not too much future for them. However, if they become medical scientists, they face an unlimited field of thought and endeavour.” Indeed, this course of action was most likely to prompt young medical graduates to consider radiotherapy as a specialty worth pursuing despite its uncertainties: a modest remuneration for occupation with health hazards, and work with patients who were mostly destined to die in spite of efforts in many cases. If the future of high-voltage machines, like Cobalt-60 units, was rather uncertain, the breadth of applications for radioactive isotopes in cancer treatment offered unlimited opportunities for medical research. Novice radiotherapists could make great strides in this budding field.

Creating conditions for this institution-building process, the NCIC appointed Robert W. Begg, an associate professor of biochemistry in the Department of Medical Research at the UWO, as the first full-time cancer researcher on 1 July 1954. This appointment had a symbolic significance – to convey a message to students and professionals in medical sciences that cancer research had career prospects. There were other indications too, particularly for those who thought of becoming radiation specialists. The Canadian Association of Medical Physicists came into being in Ottawa on 10 January 1955. It aimed at developing an effective liaison between the radiation physicist, the medical scientist, and the clinician. In this connection, the Department of National Health and Welfare (DNHW) undertook to consult the Atomic Energy Control Board on the clinical uses of radioisotopes in mid-1955, in addition to its previous function as the

54 W.G. Cosbie had worked as cancer gynecologist in radiotherapy with Gordon E. Richards at the TGH. Minutes of a Meeting of the Committee on Cancer Centres of the Advisory Medical Board of the OCTRF, London (ON), 19 November 1954, p.3; in the WUA, AFC 328.1.2821.
55 The NCIC directly funded Robert W. Begg’s employment. See R.B. Willis (Comptroller, UWO) to O.H. Warwick (Executive Director, NCIC), London (ON), 3 June 1954; in the WUA, AFC 40 – 26/27.
Board’s health advisor on all aspects of the use of radioactive material. It became known during the first meeting of the Executive Council of the Advisory Committee on the Clinical Uses of Radioisotopes that the Committee would consist of six members – a radiotherapist, a radiation physicist, a physician, an internist, a secretary, and a DNHW delegate – who had expertise in handling radioisotopes and who were “as fully geographically representative as possible.” This geographic distribution created local reference points for physician-investigators interested in projects involving the use of radioisotopes.

Therapeutic applications of artificially produced radioisotopes sat at the crossroads of professional interests. Like radiotherapists, surgeon-investigators realized that some types of malignant tumors were not amenable to surgical treatment alone, however refined their operative skills may be. As novel artificial radioisotopes became available, surgeons considered regaining a prerogative for some treatment claims contested by high-voltage radiotherapy. Brain tumors, especially malignant glioblastomas, presented one of those claims. With the advent of a new potent source of radiation, Iridium-192, on the scientific research market, surgeons could pursue their objective of employing radioisotopes to complement particularly delicate operations.

A neurosurgeon, Charles G. Drake, and a physicist, John G. Brown, employed by the UWO and the Victoria Hospital in London, received a grant from the OCTRF in 1953 to investigate the effect of gamma radiation in treating malignant brain tumors by using Iridium-192. The next year, they provided preliminary results in a progress report. Introducing the therapeutic problem, the investigators pointed out that “radiotherapy had little to offer in the

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58 Ibid., 5. The membership comprised Drs. D.H. Copp (University of British Columbia, Vancouver), H.E. Duggan (University of Alberta Hospital, Edmonton), J.P. Gemmell (University of Manitoba, Winnipeg), C.H. Jaimet (McMaster University, Hamilton), Chas. Plamondon (Laval University, Québec), I.E. Rusted (The General Hospital, St. John’s, Newfoundland), J.E. Stapleton (The Victoria General Hospital, Halifax), T.A. Watson (University Hospital, Saskatoon), Dr. J.A. Caskey (St. John General Hospital, St. John, NB).

59 For a brilliant account on the convergence of military and civilian interests in radioisotopes, consult Angela Creager’s Life Atomic. Creager argues that the politics of atomic energy exhibited a Janus-faced nature in nuclear medicine, mingling its humanitarian and utilitarian-military imperatives. See Creager, Life Atomic, 20 and 313.

60 The OCTRF Annual Report – 1953, p.88; in the WUA, AFC 328.1.2755.
treatment of malignant gliomas of the brain” and, therefore, there was a need to fill this therapeutic gap by other methods.\(^{61}\) Drake did precisely this when he inserted an applicator with Iridium-192 into the cavity created following a fairly complete removal of the tumor from the brain. The idea was to subject the tumor bed to intense radiation with a minimal irradiation to the surrounding healthy brain. When a small partially shielded pellet inside the applicator was surgically fixed in position in the brain, it remained in place for several days until the radiation dose reached a required threshold. A second craniotomy, a surgical opening into the skull, was necessary to take out the applicator. Thus, the team of researchers planned to give about 5,000 r, a supposedly lethal tumor dose, in two to five days. They also presumed that this amount of radiation would be within tolerance limits of the adjacent tissues.

Over the eighteen-month period, three patients underwent this experimental treatment, though the investigators never mentioned in writing that it was experimental.\(^{62}\) The first patient, a middle-aged farmer, R.T., had a tumor removed from the frontal lobe of his brain, which proved to be a malignant glioma after histological examination. He received 2,500 r during 40 hours to avoid the risk of extensive radiation damage to his cerebral blood vessels. Having received only half of the intended 5,000 r dose, the patient succumbed to recurrence of the tumor five months after his initial operation.\(^{63}\) The second patient, F.E., a thirty-seven year-old man, had an operation to remove his tumor, a glioblastoma multiforme, and to install the applicator with the Iridium-192 source that gave the full dose of 5,000 r to the bed of the tumor over 111 hours. In this case, however, “the applicator became detached from the bone flap, and, therefore, the exact distribution of the radiation wa[s] unknown.”\(^{64}\) This patient succumbed to a recurrent tumor eight months subsequent to the first operation. The third patient, a young man of seventeen, R.F., had his malignant astrocytoma removed, and received 5,000 r to the bed of the tumor during 132 hours according to the treatment plan. Following a three-month period since the radiation treatment, he remained in good health.\(^{65}\) This progression of experimental treatments showed that the intracavity irradiation of brain tumors with Iridium-192 was

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\(^{61}\) Ibid., 88


\(^{63}\) Ibid., 429.

\(^{64}\) Ibid., 430. A pathologist performed a post mortem in this and the preceding case.

\(^{65}\) The OCTRF Annual Report – 1953, p.88; in the WUA, AFC 328.1.2755.
practicable. A renewed interest of other neurosurgeons in this line of investigation ensued. For example, Thomas P. Morley, an associate in surgery at the University of Toronto and attending neurosurgeon at the Sunnybrook Hospital, received a grant from the OCTRF for “The Study of Gliomas in Vitro and in Vivo” in 1954.66

Encouraged by a positive outcome, after two disappointing results, the research team in London continued with their investigations.67 From mid-1954 till 1956, three more patients suffering from brain tumors had Iridium-192 applicators implanted as part of their treatment. The fourth patient, a man of fifty, received 7,000 r in 192 hours, which nevertheless resulted in a lethal outcome twelve months later. While the radiation dose given to another two patients, women aged forty-six and forty-eight, amounted to 7,200 r in just forty-eight and fifty-two hours correspondingly. They survived, respectively, for fourteen and nine months, though a description of quality of that survival escaped commitment to paper. What the researchers did publish in this regard was “The procedure was tolerated well in each instance” […] and] the radiation may have produced more widespread pathological lesions than those observed.”68 Thus, the last three cases evinced an experimental design of the investigation. This radiotherapeutic experiment proceeded in an incremental fashion: from a dose of 2,500 r to 7,200 r delivered in the period of 40-192 hours. As a result, the youngest patient in the series had reached his mid-twenties when the experimental results appeared in press.69 The researchers considered him a cure after eight years of no recurrence.

The above empirical study illustrates the limited progress in the surgical field of cancer research, not to say that a surgical treatment of cancer was in stagnation. Developments in cancer surgery were relatively gradual and comparatively subtle. On the background of high-voltage radiotherapy, which developed in leaps and bounds, the surgical profession in relation to cancer treatment innovation seemed to be stagnant. This putative inertia was mainly due to two factors: a qualitative appraisal of investigational procedures and an entrenchment in the tradition of

66 The OCTRF awarded 33,410 dollars for this study over the six years and it recommended the grant of $1,289 to continue research in 1960. See “Schedule of the Applications for Grants for Clinical Research Approved by the OCTRF”, Exhibit B, p.11, enclosed with correspondence from J.H. Broughton to H.J.C. Ireton, 7 July 1960, Toronto; in the UTA, A66-0009/023, Surgery 1960.


68 Ibid., 429 and 433.

69 Ibid., 433.
professional authority. Surgeons realized that a frequent performance of neoplastic operations improved therapeutic outcomes, meaning that skills and techniques of particular practitioners became better, which triggered further specialization. However, to compare specific surgical approaches employed by a few leading representatives of the profession pragmatically was not just a laborious and lengthy process, but an ambitious enterprise, since the majority of surgeons would have to re-evaluate their skills and to engage in debates, usually counterproductive, on the objective improvements of surgical treatment. Moreover, controlled surgical trials would entail the imposition of additional training for those professionals whose *modus operandi* could not qualify for the modified standard of practice. Why complicate an already complex practice? No more complexity was necessary, given that expanding domains of radiotherapy and chemotherapy could provide insights and tools to supplement surgical proficiency levels.

In the field of radiotherapy, by contrast, quantitative research was the driving force. Physical measurements of radiotherapeutic practice dealt with increasingly complex molecular chemistry, biology, and clinical medicine. Even more, comparative laboratory and clinical investigations were essential to justify public expenditure on high-priced equipment for radiotherapy. For instance, a confirmation of the Cobalt-60 units’ necessity for cancer care hinged on comparisons with existing technologies in terms of economy and multi-functionality.70 To ground the claims for a wide-ranging utility of high-voltage machines, more clinical findings had to be provided which could only happen when more radiotherapist-researchers engaged in this work. Inasmuch as the public recognized the importance of such a mission, mainly in response to patients’ voices amplified by the Canadian Cancer Society and media, the remaining priority was to organize radiotherapy along professional lines. This process was well underway.

At the 1955 Supervoltage Symposium in Chicago, Illinois, Ivan H. Smith, Director of the London Cancer Clinic, concluded his speech with a call for a “friendly competition among those [radiotherapists] trying different [supervoltage radiation] spectra to work to the betterment of the patient.”71 The unfolding of competitive investigations in radiotherapy was conspicuous at the

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70 T.A. Watson “Co60 Telecurietherapy – after Five Years,” in the WUA, AFC 328.1.2644.
Eighth International Congress of Radiology, held in Mexico City on 22-28 July 1956. For example, Vera Peters, a senior therapeutic radiologist at the Toronto General Hospital, presented a paper on the curability of allegedly hopeless Hodgkin’s disease by high-dose irradiation. Her report on the five-year survival of thirty-eight percent of patients and a ten-year survival rate of twenty-four percent over 1928-1954 caused something of a stir among the radiotherapists in the audience. After a barrage of probing questions and cutting remarks, which Peters skillfully parried, “the former prevailing attitude of skepticism gradually evolved into optimism [and] they [radiotherapists] all rushed home and analyzed their own experience.”

One of those radiotherapists was Henry Kaplan, an accomplished academic radiologist and a clinical investigator heading the Department of Radiology at the Stanford University School of Medicine. Kaplan responded to Peters’ report as a challenge to his non-aggressive treatment practice and set out to attempt more experimental approaches to cancer therapy. An international contest was building up from a series of overwhelming results achieved by investigative radiotherapy.

The 1956 Congress was also remarkable because presentations and discussions on radiation therapy occupied nearly a half of the sessions. Moreover, informal meetings focusing on “Supervoltage Therapy” and “Independent Status of Radiotherapy” continued over two days following the Congress as part of the program arranged by the International Club of Radiotherapists. The Club, which membership comprised exclusively clinical radiotherapists, inaugurated its first regular assembly with reports on the state of radiotherapy in Belgium, Brazil, Canada, Chile, Cuba, Denmark, France, Great Britain, India, Ireland, Mexico, the United States, and Uruguay. The Canadian representatives – Jean Bouchard, Ethlyn Trapp, and T.A. Watson – reviewed the situation with radiotherapy in the dominion and communicated to the forum that according to the questionnaire completed country-wide, there were “approximately 70 certified radiotherapists in Canada of whom 38 g[a]ve full time to radiation therapy. Twenty of these 38

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c[a]me to Canada from other countries, mainly Great Britain […] and there [were] 15 doctors in Canada who [we]re training in radiotherapy.”77 These numbers suggested that radiotherapists seemed to mushroom in Canada, for there were a handful of them at the turn of the 1950s. Highly qualified radiation specialists from overseas arrived in Canada to have the opportunity to work with megavoltage machines and research into their therapeutic capabilities. Furthermore, the creation of directorships and professorships in radiotherapy across Canada attracted more professionals, particularly those who possessed valued certifications from training institutions in Edinburgh, London, and Manchester in Great Britain.

In Winnipeg, for instance, Richard J. Walton, a New Zealander, became the Head of Radiotherapy and Medical Director at the Manitoba Cancer Treatment and Relief Institute in 1954.78 In this position, Walton supervised radiotherapy departments at the Winnipeg General Hospital and St. Boniface Hospital since 1955. David W. Smithers, a professor of radiotherapy at London University and a director of the Radiotherapy Department of the Royal Cancer Hospital, had trained Walton in the new specialty prior to his appointment. Interestingly, no Canadian radiotherapists were on staff in both hospital radiotherapy departments until the spring of 1957, when Walton became Executive Director of the Manitoba Cancer Treatment and Research Foundation (MCTRF). During that year, Ingrid Z. Strautmanis became the first appointed Resident in Radiotherapy to pursue her studies and work at the MCTRF. Walton rightly put it, “As Canada ha[d] been sadly lacking in Canadian trained radiotherapists, […] it [wa]s the exception rather than the rule for Residents in Radiotherapy to be available.”79 What prompted medical graduates to embark on the career in radiotherapy was the openness of this field to cross-fertilization with other disciplines concerned with cancer treatment. Endocrinology was one of them.

Hormonal therapy for particular neoplastic diseases, like carcinomas of the breast and prostate, provided insights into the possibility of inhibiting endocrine gland functions by

79 The Manitoba Cancer Treatment and Research Foundation Report, 1 April 1957 – 31 March 1958, p.8; in the Archives of Manitoba (hereinafter the AM), LA 0009, GR 0646, 57-20 Sessional Paper #25.
megavoltage irradiation, thereby leading to potential cancer remissions. For example, endocrinologist Earl R. Plunkett of the Department of Medical Research at the UWO, investigated whether the Cobalt-60 irradiation of the pituitary, a gland at the base of the brain controlling the production of hormones, was of therapeutic benefit to some patients with advanced stage hormone-dependent cancers. The OCTR-funded investigation that Plunkett conducted in cooperation with I.H. Smith, Stewart Lott, and Fred C. Heagy, at the London Cancer Clinic. The latter two collaborators designed, respectively, radiotherapy and radioisotope studies to make this investigation possible in terms of safety and adequate measurement. Thirty critically ill patients, aged twenty-three to seventy-two years, underwent the experimental treatment: twenty-five women with metastatic breast cancer, two men with advanced prostatic carcinoma, a man with disseminated malignant tumor of the testis, and two men with metastatic brain tumors. Although the high-energy radiation doses administered to the pituitary glands of most patients did not change the progress of their diseases significantly, six patients survived between twelve and twenty-two months. Plunkett concluded, however, “this therapeutic approach to breast and prostatic cancer [held] little promise” because the irradiation did not inhibit pituitary function sufficiently. Nevertheless, the clinical investigation cast some light on the endocrine functions in the human organism before and after pituitary irradiation.

The relationship between cancer and hormones did not escape the attention of surgeons either. In 1956, the NCIC awarded a grant to Gordon W. Bethune, a surgeon at the Dalhousie University School of Medicine, to continue his “Endocrine study in advanced carcinoma of the breast with special reference to hypophysectomy” at the Victoria General Hospital of Halifax in Nova Scotia. This grant-in-aid of research was one of the few given by the NCIC to cancer investigators in surgery.

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81 Ibid., 301. To do preliminary collaborative studies on clinical material from cancer patients, the NCIC provided a block grant to Robert L. Noble, Associate Head of the Department of Medical Research at the UWO, of which E.R. Plunkett’s research funding constituted a part. See NCIC, Annual Report of 1954-1955 (Toronto: NCIC, 1955), 41.
83 Ibid., 300.
Almost simultaneously with the Canadian clinical investigation that started in April 1954, a similar, but randomized trial began in Great Britain. Surgeons at Guy’s Hospital of London, supported by the Imperial Cancer Research Fund, decided to determine whether the surgical removal of adrenal glands (adrenalectomy) along with ovaries (oophorectomy) or the ablation of the pituitary gland (hypophysectomy) brought more benefits to patients with inoperable cancer of the breast for whom standard procedures of radiotherapy and hormone treatment had been exhausted.\(^8^5\) Thirty patients were randomly selected for each of the two treated groups. Even though the investigators “wanted a statistically valid answer rather than a clinical impression,” they consulted medical statisticians Peter Armitage and A. Bradford Hill only after the study had been completed.\(^8^6\) Having analyzed the results, Armitage and Hill reported that despite the trend in treatment outcomes favoring the pituitary removal, “the difference [wa]s not statistically significant in the conventionally accepted sense.”\(^8^7\) Put differently, this possibly first surgical randomized controlled trial did not give a definite answer as to the therapeutic advantage of either adrenalectomy or hypophysectomy because of a flawed experimental design.

Like his British colleagues, and similarly to Canadian radiotherapists, Bethune considered hypophysectomy, a surgical removal of the pituitary gland, a useful procedure because it could potentially alter the balance of hormones in the body and help treat patients suffering from a late-stage breast cancer. Before hypophysectomy, ten patients with “hopelessly far advanced breast cancer […] had been treated primarily by a routine radical mastectomy and post-operative x-irradiation [sic].”\(^8^8\) Three other breast-cancer patients had different medical interventions prior to hypophysectomy. Having performed thirteen operations on women whose age varied from thirty-nine to fifty-eight years, Bethune reported four preliminary “good results.”\(^8^9\) The latter meant that patients were living without the metastatic progression between six and twenty-six months after the operation, lost practically all symptoms of the disease, but required daily doses of cortisone and thyroid to maintain their hormone balance. In comparison


\(^8^6\) Ibid., 494-495.

\(^8^7\) Ibid., 494.

\(^8^8\) Gordon W. Bethune, “Advanced Breast Carcinoma Treated by Hypophysectomy,” in *Canadian Cancer Conference* (1957), 287.

\(^8^9\) Ibid., 288.
with radiotherapy, this surgical treatment was relatively more successful: about ten percent more patients had their lives prolonged. However, it induced little adjustment in the professional confrontation between the surgeons and radiotherapists.

Successes of radiotherapy allowed its leading practitioners to make strong statements on the extensive uses of it. As Ralston Paterson, a distinguished British radiotherapist declared at the 1956 Congress, “the primary function nowadays of radiotherapy in malignant disease is cure, and [...] much latitude is permissible where cure is a reasonable expectation.” Surprisingly, he did not promote the intensification of radiotherapeutic effort for therapeutic purposes. Otherwise, Paterson argued for a wider use of palliative radiotherapy for late-stage malignant disease because this domain of practice could make a substantial difference in cancer management that the surgical profession could not contest. “We have a duty in the interests of our specialty, as well as of our patients, to decide whether or not to treat, just as the surgeon decides for or against operation,” stated Paterson, who accentuated the professional struggle and downplayed the patient’s role in the whole process of medical care. His authoritative view on the primacy of doctors in decision-making reflected a contemporary trend in cancer care, but not the dominant disposition of radiotherapists who still had a hard time winning the patient over. It took too much of resourcefulness, and resources, on the part of radiotherapists to let the patient believe that all-pervading radiation was sometimes powerless in the fight against malignant disease. How many patients would approve of the doctor’s endeavors to alleviate pain rather than to seek a cure, however unlikely? Certainly not the majority of patients who wanted to see the power of scientific medicine reified in the restoration of health of every treated person.

90 Ralston Paterson, “The Use and Abuse of Palliative Radiotherapy,” Journal of the Faculty of Radiologists, 8, no. 4 (1957): 235 and 238. Paterson, Director of the Holt Radium Institute at the Christie Hospital in Manchester, became well-known internationally for the Manchester system of radiation treatment for cancer, developed in the late 1930s. The system featured standardization and physical measurement of radiotherapy, which allowed the transfer of scientifically and clinically proven techniques to different body sites and geographic locations. Paterson was also a pioneer of the randomized controlled trial in cancer radiotherapy that began in July 1948, a year after the initiation of the famous Streptomycin Trial of 1947. See Medical Research Council Streptomycin in Tuberculosis Trials Committee, “Streptomycin Treatment for Pulmonary Tuberculosis,” The BMJ, 2 (1948): 769-782; and Ralston Paterson and Marion H. Russell, “Clinical Trials in Malignant Disease: Part II – Breast Cancer: Value of Irradiation of the Ovaries,” Journal of The Faculty of Radiologists, 10, no. 3 (1959): 130-133. For a biographical piece on R. Paterson, consult Juan A. Del Regato, “Ralston Paterson,” International Journal of Radiation Oncology, Biology, Physics 13, no. 7 (1987): 1081-1091.
3.3. Chemotherapy Finds a Haven in the Stronghold of Radiotherapists

The Ontario Cancer Institute, incorporating the Princess Margaret Hospital (OCI/PMH) in Toronto, represented a materialization of the sway of radiotherapy over cancer care in Canada. A cancer hospital dedicated to the radiotherapeutic treatment of tumors saw its inauguration on 1 May 1958. Clifford L. Ash, a successor of Gordon E. Richards and the first director of the OCI/PMH, made every effort to enable radiotherapists and, to a lesser degree, chemotherapists to be in the frontline of patient care by sidelining surgeons who otherwise dominated the medical scene at other University of Toronto teaching hospitals. The Board of Trustees of the OCI ensured this by appointing suitable highly-trained cadres to key positions in the new establishment: Harold Warwick, Vera Peters, Harold Johns, Arthur Ham, William Allt, Walter Rider, and John Darte. Except for Warwick, a hematologist, and Ham, a histologist, all others in the above list were radiation specialists. Warwick provided a definite link between the NCIC and the OCI/PMH when he left the post of executive director in the former body and accepted the position of a full-time Consultant Physician in Internal Medicine in the latter. This link signified a strong likelihood that fundamental research and conventional treatment would merge into clinical research as soon as the internal and external conditions permitted.

The OCI/PMH prioritized cancer patient care as professionals established patterns of clinical and research practice. Since radiotherapy was the dominant treatment modality, the outpatient department had much more admissions than the inpatient one. Table 3-1 below shows patient statistics of the OCI/PMH during the last quarter of its first year of operation. Even though radiation treatment was a major function of the OCI/PMH, chemotherapy played an

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91 The Medical Advisory Board Minutes of the OCI, Toronto, 28 May 1958, in the UHNA, 98-0001, box 34, SF1: 17D.3. Edward L. Shorter, a historian of medicine, wrote that cancer surgery was “divided between TGH and the other teaching and community hospitals,” as very few surgeons received specialized training in cancer. Thus, general surgeons performed the lion’s share of operations involving tumors in the community hospitals. This also meant that high mortality rates and complications of such general surgeries for cancer generated a poor reputation for this treatment mode. See E.L. Shorter, Partnership for Excellence: medicine at the University of Toronto and academic hospitals (Toronto: University of Toronto Press, 2013), 326 and 336.

92 McCulloch, The Ontario Cancer Institute: Successes and Reverses at Sherbourne Street, 7-8.

93 Edward L. Shorter, A Century of Radiology in Toronto (Toronto and Dayton: Wall and Emerson, 1995), 46-49. As Shorter felicitously put it, “Ash did not recruit Vera Peters. He inherited her,” for both radiotherapists were Gordon Richards’ students.

94 Warwick commenced his duties as staff physician at the Toronto General Hospital in 1955. See “A Meeting of the Board of Trustees of the Ontario Cancer Institute,” TGH, 29 November 1954; in the UNHA, OCI SF1: 1.17.
increasingly important role in cancer management. Whenever malignancies became radio-resistant, disseminated, or had a systemic nature, the OCI/PMH physicians had recourse to using chemotherapeutic agents.

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<td>87%</td>
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<td>70%</td>
<td>87%</td>
<td>41%</td>
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Table 3-1. Patient Statistics at the OCI/PMH.\(^95\)

Physicians’ pharmaceutical armamentarium was limited at the time: nitrogen mustards, Endoxan (cyclophosphamide), Urethan, aminopterin and methotrexate, triethylene-melamine (TEM), Myleran (busulfan), triethylene-thiophosphoramide (Thio-TEPA), thioguanine, 6-

\(^95\) Attachment to the “Report of the Director, Clifford L. Ash, M.D., 7 May 1959,” in the UNHA, OCI SF1: 1.32.
mercaptopurine, prednisone and synthetic hormones. All these agents offered alternatives to radiotherapy when it served no further useful purpose after the patient had received a maximum exposure, or radiotherapy was contraindicated in particular cases of malignancy found in close proximity to the vital organs. The chemotherapeutic agents, however, had circumscribed applications. They triggered severe side-effects due to their toxicity that fairly quickly exceeded patients’ tolerance levels. This, in turn, led to early relapses possibly resulting from the defensive mechanisms of cancerous cells against the chemicals. Hence, a considerable number of agents induced only temporary remissions followed by unremitting tumor recurrences that hastened the course of the disease. Moreover, available chemotherapeutic drugs were rather similar in the modes of action – alkylating agents, metabolic antagonists, and hormones – which meant that if one substance did not halt the progression of cancer, the whole group to which it belonged had to be avoided. With every sequence of a chemotherapeutic regimen, a range of effective options for the patient narrowed down, and eventually palliative maintenance remained the only choice for the physician.

At the OCI/PMH, a few patients foreseeably reached the nadir of treatment options in early 1959. The clinical staff faced a dilemma: either to let those patients go on palliative regimen, or to undertake a trial of a new investigative drug if there were any. The prestige of a unique cancer hospital demanded an uncommon course of action. Harold Warwick and his team were prepared for the challenge. They arranged that a novel substance, vincaleukoblastine, had its pioneering clinical trial at the OCI/PMH. In March 1959, Robert Noble and Charles Beer brought ten vials with vincaleukoblastine from the Collip Medical Research Laboratory in London, Ontario, to Warwick’s office in the OCI/PMH. Warwick and Noble knew each other well through their association with the NCIC. Beer was a British Empire Cancer Exchange Fellow and Medical Research Associate of the NRC in Ottawa who along with Harry Cutts, a NCIC Research Fellow, collaborated on the project exploring the chemical and biological effects of extracts from a periwinkle plant that presumably had anti-diabetic properties. Cutts together

with Beer and Noble observed that the periwinkle extracts experimentally injected into laboratory animals brought about effects comparable to those exhibited by rats receiving high doses of cortisone. Since the latter hormone found ample application in cancer chemotherapy, the researchers concluded that one of the active principles in the periwinkle might be useful as an anti-cancer agent. This observation prompted further research that continued at the UWO Department of Medical Research until 1961.99

Unlike the American screening programs that fueled the cancer drug development along the lines of rational therapeutics, the project that led to producing vincaleukoblastine was trailblazing.100 When researchers extracted the active principle from the periwinkle and tested it on cancer-bearing mice and rats, they realized that the extract was dissimilar in its mechanism of action from existing therapeutic substances. The next step was to make enough of the substance for a clinical trial. Seemingly by coincidence, Noble and his research team presented their findings at a 1958 meeting of the New York Academy of Sciences in which participated Irving S. Johnson and Gordon H. Svoboda – investigators representing the pharmaceutical giant Eli Lilly and Company of Indianapolis, USA.101 While leading a screening program for compounds that could be developed into profitable drugs, Svoboda and Johnson came across an intriguing chemical activity of the periwinkle extracts. Without much delay, their research teams tested a few extracts against leukemia in mice and obtained promising results. Having heard Noble’s report on the biological effects of the periwinkle extract, Johnson and Svoboda offered the Canadian group to join their investigative efforts with support from Eli Lilly and Co. It was a tempting offer given that the company had manufacturing capabilities to supply the

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100 By rational therapeutics I understand, following Harry M. Marks, the application of drugs made through a systematic search for scientifically established properties of substances which may be adapted for particular medical needs. See Marks, The Progress of Experiment (1997), 21. In April 1955, the NCI of Bethesda (MD) formed the Cancer Chemotherapy National Service Center to streamline screening programs for anti-cancer drug development across the US. The CCNSC coordinated and administered the US national cancer chemotherapy program that involved the NCI, the Food and Drug Administration, the Veterans Administration, the Atomic Energy Commission, the American Cancer Society, and the Damon Runyon Memorial Fund for Cancer Research. The US clinical trials network emerged from this concerted effort approved by the US Congress. See Kenneth M. Endicott, “The National Cancer Chemotherapy Program,” *Journal of Chronic Diseases*, 8, no.1 (1958): 172; and Charles G. Zubrod, “Historic Milestones in Curative Chemotherapy,” *Seminars in Oncology*, 6, no.4 (1979): 493-494.

pharmaceutical preparation in necessary quantities. Noble, Cutts, and Beer moved cautiously in the direction of dealings with the company, however. Before an official collaboration commenced, they had filed Canadian and American patent applications for the invention relating to novel compositions (the investigators named the substance vincaleukoblastine, or VLB) as well as to methods for their use.\footnote{Patent applications US 777627 and CA 653005, entitled “Vincaleukoblastine and Salts Thereof,” were filed on 2 December 1958. This priority date warranted the issuance of Canadian and American patents within three years to protect the invention under the intellectual property law. Canadian Patents and Development Limited issued the patent on 27 November 1962, and the United States Patent Office published its patent 3097137 dated 9 July 1963. For details, consult, respectively, the Canadian Intellectual Property Office database and the USPTO database PatFT.} Shortly, a medical-grade compound in the crystalline form of sulfate became available from Eli Lilly and Co. for clinical trials at three centers: the Indiana University Medical Center in Indianapolis, the National Cancer Institute in Bethesda, Maryland, and the OCI/PMH of Toronto.\footnote{Warwick et al. “Some Biological Effects of Vincaleukoblastine” (1960): 1033, note 1. Also, R.L. Noble “Symposium on Vincaleukoblastine (VLB),” in \textit{Canadian Cancer Conference. Proceedings of the Fourth Canadian Cancer Research Conference}, ed. R.W. Begg \textit{et al.} (New York; London: Academic Press Inc., 1961), 339, 373, 383.}

As \textit{Table 3-1} above shows, inpatient and children’s ward occupancy at the OCI/PMH increased during March 1959 by several admitted patients, some of whom began their VLB experimental treatments then. Patients suffering from late-stage malignant disease received VLB only after conventional therapy regimens had failed and their diagnoses had a histological confirmation. Another quite significant criterion of patient selection was a possibility to measure any beneficial effects of the investigational drug by patients’ specific symptoms evident at physical and biochemical examinations.\footnote{Warwick et al. “Some Biological Effects of Vincaleukoblastine” (1960): 1032.} This meant that just twenty-two patients whose medical conditions were relatively clear-cut underwent VLB treatment over ten months.

Objectivity of clinical researchers apparently was a single standard guiding the implementation of the new treatment. According to Warwick,

Strict regulations governing the introduction of new medicinal agents did not then exist. We knew, however, that the dosage in animals and the biological effects had been well documented and hence, with informed consent, felt justified in

\begin{thebibliography}{10}
\footnote{Patent applications US 777627 and CA 653005, entitled “Vincaleukoblastine and Salts Thereof,” were filed on 2 December 1958. This priority date warranted the issuance of Canadian and American patents within three years to protect the invention under the intellectual property law. Canadian Patents and Development Limited issued the patent on 27 November 1962, and the United States Patent Office published its patent 3097137 dated 9 July 1963. For details, consult, respectively, the Canadian Intellectual Property Office database and the USPTO database PatFT.}{102}
\footnote{Warwick et al. “Some Biological Effects of Vincaleukoblastine” (1960): 1032.}{104}
\end{thebibliography}
giving VLB to patients with advanced disease, which had not responded or was no longer responding to established forms of treatment.105

Warwick’s statement of 1983 seems to be self-exculpatory because there actually were regulations stipulating the procedure of introducing new drugs – the Food and Drug Regulations of 1954.106 Yet, no regulatory framework existed in 1959 that obliged physicians to get informed consent from patients under the circumstances of the VLB trial. Considering that neither Canadian, nor American publications on the VLB trials noted anything indicative of patients’ consent, one may suggest that the selected patients, or their guardians, agreed to the last resort chemotherapy thanks to physicians’ powers of persuasion. Likewise, it could be argued that doctors acted in good faith without written consents, since they published somewhat compromising accounts of deaths supposedly correlated with VLB. For example, a six-year-old boy afflicted with acute myeloid leukemia died the next day after administration of the experimental drug, although he had had partial remissions taking prednisone and 6-mercaptopurine over a four-month period prior to a complete relapse.107 No legal action on the part of his parents or guardians followed. After all, his fatality was not that exceptional: sixteen out of twenty-two patients treated with VLB had no improvement and their death physicians ascribed to the disease rather than to the experimental drug.108

Clinicians from Toronto and Indianapolis conducted a screening for therapeutic effects and dosage schedules of VLB by treating cancer patients. Animal studies were good indicators for the drug’s potentialities, but diverse human malignancies provided the real testing ground. Rational therapy at the turn of the 1960s involved the rationality of scientists, who attempted to

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107 On autopsy, the pathologist revealed that this boy and another two children who succumbed to acute leukemia after receiving VLB had “degenerative changes in lymphoid tissue and hypoplasia of bone marrow [that were] of much greater degree than [wa]s usually seen in untreated cases of these disorders.” See Warwick et al. “Some Biological Effects of Vincaleukoblastine” (1960): 1034 and 1039. Another publication communicating the results of treatment of the second group of twenty-four patients with VLB also had a reference to a ten-year-old boy suffering from acute stem cell leukemia who died ten hours after the administration of the experimental agent. Harold Warwick, J.M.M. Darte, and J.S. Olin, “Some Further Observations on the Effects of Vincaleukoblastine with Special Reference to Hodgkin’s Disease,” in Canadian Cancer Conference (1961), 374 and 376.
establish VLB’s mode of action before clinical trials, and that of clinicians, who partially overwrote those findings through determining patients’ responses to the experimental agent. American investigators from Eli Lilly and Co. laboratories concluded their discussion of experiment-based hypotheses on how *Vinca* alkaloids, to which VLB belonged, acted biochemically with an extreme proposition: “VLB and related active compounds, regardless of mechanism of action, [we]re examples of clinically active substances of new chemical compositions which provide[d] a new and heretofore unknown lead in cancer chemotherapy.”

In other words, the scientists suggested that clinical work would help untangle the mystery of VLB’s activity *in vivo*. This was a far cry from the scientific quest for biochemical structure-activity relationships on which supporters of rational therapeutics premised clinical trials.

Even though scientists admitted VLB was not a broad-spectrum antitumor agent, the clinicians used it in practice as extensively as the range of cancer patients allowed. By mid-November of 1959, Marion E. Hodes and his clinical team at the Indiana University Medical Center experimentally treated thirty-two patients with VLB, only a part of whom “were far along in the course of their disease and had been treated with numerous medications” to which their tumors became resistant. For twelve patients with different types of leukemia, out of twenty-seven patients evaluated in the report, VLB proved to be the first-line chemotherapy agent. It was a stark contrast to the Canadian clinical experimentation led by Warwick who employed VLB only after all established forms of treatment had left no options. Yet, unlike his American colleagues, Warwick had neither pressure, nor incentives from the pharmaceutical company attempting to weigh the pros and cons of investing more money in VLB.

What encouraged Eli Lilly and Co. managers was a consonance between scientific and clinical findings on VLB’s low levels of toxicity. Apart from considerable adverse effects on the bone marrow, VLB had few severe side-effects and they were reversible. A virtual absence of

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111 Ibid., 1042-1043.

cumulative toxicity with consecutive courses of VLB was another piece of good news. That VLB produced sporadic, but efficacious, regressions in some neoplastic diseases resistant to conventional forms of treatment greenlighted further work on the bench and at the bedside.\textsuperscript{113}

For instance, Lyonel G. Israels, a hematologist at the University of Manitoba and the Manitoba Cancer Treatment and Research Foundation, began a clinical trial of VLB at the Winnipeg General Hospital in early 1960.\textsuperscript{114} It was a clear indication that VLB had characteristics of a useful agent vitally needed in the management of some drug- and radiotherapy-resistant solid tumors and Hodgkin’s disease.

Minimization of unfavorable systemic reactions to chemotherapeutic agents was on the agenda of physicians for a long time. As clinicians reached a plateau in their efforts to make durable remissions possible without pushing to toxicity the dosage of utilized drugs, new agents became a lifeline for chemotherapy to remain as a practical method for cancer control. At the

\begin{footnotesize}
Research, 20 (August 1960): 1050-1051. Hertz, Lipsett, and Moy, who worked at the Endocrinology Branch of the US NCI, assessed the therapeutic potential of VLB in eight women with advanced-stage cancers of the uterus. The clinicians had used a variety of chemotherapeutic agents, including methotrexate, to which the patients’ tumors gradually developed resistance, before they resorted to the experimental agent. Interestingly, the NCI investigators administered VLB intravenously to tolerance, which was for them 36 mg per course of three successive days, whereas the clinical researchers in Indianapolis gave their patients up to 90 mg over nine consecutive days and considered this regimen to be within tolerance limits. A twenty-four-year-old man suffering from acute monocytic leukemia for one month received the latter dosage of VLB as primary therapy, had reportedly no evident toxicity, and died on the nineteenth day following the treatment. This was another facet of clinicians’ objectivity. See tables in the above articles.

\textsuperscript{113} Emil Frei, Ill \textit{et al.}, “Clinical Studies of Vinblastine,” \textit{Cancer Chemotherapy Reports}, 12 (June 1961): 125-129. Frei, a physician-investigator at the NCI, led VLB investigations within the Eastern Cooperative Cancer Chemotherapy Group that had been one of the first to conduct a collaborative multicenter randomized comparative clinical trial of methotrexate and 6-mercaptopurine against leukemia, which started on 16 May 1955 and ended on 15 October 1956. Frei also was a member of the Eastern Cooperative Group in Solid Tumor Chemotherapy that had undertaken a multicenter RCT of two alkylating agents – nitrogen mustard and thio-TEPA – in cancers of the breast and lung, melanoma, and Hodgkin’s disease, over 1955-1958. Still, Frei and his research team did not attempt to carry out a comparative randomized trial of VLB, but empirically studied 112 patients with various malignancies who were refractory to alkylating agents. See E. Frei, “A Comparative Study of Two Regimens of Combination Chemotherapy in Acute Leukemia,” \textit{Blood}, 13, no.12 (1958): 1129; and C.G. Zubrod, “Appraisal of Methods for the Study of Chemotherapy of Cancer in Man: Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide,” \textit{Journal of Chronic Diseases}, 11, no.1 (1960): 7 and 24.

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same time, surgeons took the baton of optimizing treatment efficiency of chemotherapeutic agents already in use without crossing threshold levels of toxicity.

### 3.4. Strange Bedfellows

Surgery combined with chemotherapy made for a symbiosis in cancer management. It was a mutually-beneficial relationship occasioned not only by patients in dire straits, but also by professional aspirations. Tumor chemotherapy practitioners were fledglings in their field who needed to prove themselves, whereas surgeons, who continued to play a major role in the treatment of cancer over the late 1950s, were willing to keep their ascendancy through bringing in more innovation. This became possible when rudimentary chemotherapeutic approaches to cancer control induced systemic toxicity due to high dosages of drugs required for increasingly recalcitrant tumors.

A number of resourceful surgeons considered employing existing anti-tumor drugs locally as adjuvants to operations. Their rationale was two-fold. As Michael B. Shimkin, a physician-investigator who headed the NCI Biometry and Epidemiology Branch, and George E. Moore, a surgeon who directed the Roswell Park Memorial Institute, explained,

1. Moral and ethical considerations preclude[d] the use of chemotherapy as the sole form of treatment when curative techniques [we]re available. 2. Early tumors comparable to those utilized in animal experiments [we]re diagnosed but rarely in man. Therefore, surgical excision of the gross tumor followed by chemotherapy for the residual cells appear[ed] to be the appropriate clinical experimental situation.\(^{115}\)

The first proposition also cast light on the-then scheme of introduction of new drugs, like VLB, into clinical practice, which necessarily followed from customary treatments for manageable cancers to experimental agents in resistant or intractable malignancies. In this sequence, adjuvant therapy took an intermediary position. Its aim was to get a therapeutic effect by producing a large enough drug concentration regionally, at the site of surgical intervention, and to restrict a damaging systemic exposure to the drug. American surgeons Oscar Creech and Edward T.

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Krementz utilized this technique with the application of nitrogen or phenylalanine mustards to the tumor-affected areas. In June 1957, they first treated patients by this method at the Charity Hospital and Touro Infirmary in New Orleans, Louisiana. The study included twenty-four patients suffering from a variety of malignancies at advanced stages. Their clinical trials demonstrated that body parts and organs invaded by tumor growths could be isolated from the systemic circulation and perfused with alkylating agents for both therapeutic and palliative purposes. Those dramatic results gained approval of the originator of prophylactic and adjuvant use of nitrogen mustard in surgery, Warren H. Cole of the University of Illinois School of Medicine who said, “This modification of the use of alkylating agents represent[ed] a definite improvement over the conventional method of administration because the toxicity of most of these agents [wa]s so high.” Yet, the determination of the extent to which this method was valuable as an adjunct to surgery when the isolation of a tumor-affected area proved difficult demanded more investigations.

Further experimental studies came from a somewhat unanticipated alliance. Radiation specialists that enabled radiotherapy to make intermittent encroachments on the home turf of surgeons played a part in the evaluation of adjuvant therapy. At the University of Western Ontario, the surgeon John A. McCredie teamed up with the biophysicist W. Rodger Inch to appreciate the value of using nitrogen mustard during operations to remove locally-advanced malignancies in patients. Their initiative was galvanized with encouragement from the radiotherapist Ivan H. Smith along with Professor and Head of the Department of Surgery at the UWO, Angus D. McLachlin. Smith and McLachlin came to terms with the inter-professional cooperation that brought not only experimental work opportunities, but also research funding.

The OCTRF supported McCredie and Inch’s investigations during 1959-1961. McCredie, who had collaborated with Warren H. Cole and his group for a year in Chicago, yielded to temptation of an OCTRF research fellowship and a post of Instructor in Surgery at the UWO. Besides, Rodger Inch, who straddled clinical work at the London Cancer Clinic and research at the department of biophysics of the UWO, seemed the optimum professional to be associated with in such a ground-breaking project.

In line with expectations, McCredie and Inch devised clinical perfusion and infusion studies using radiobiological techniques through which they could compare the therapeutic efficiency of three routes of adjuvant chemotherapy administration: that is, systemic intravenous, intra-abdominal, and local intra-arterial. McCredie had already performed preliminary laboratory experiments on rats to determine the feasibility of clinical trials. Together with Inch, McCredie employed radioactively tagged albumen, a protein occurring in egg white, to measure how much of given nitrogen mustard leaked from the isolated tumor-bearing site, and what amount of it was present in the patient’s systemic circulation. The investigators also utilized a Cobalt-60 unit to give a course of radiotherapy to the patient’s tumor before or after the perfusion with nitrogen mustard to estimate whether it improved the treatment outcome. Initially, it was a pilot investigation involving eight patients. In the course of it, McCredie and Inch developed two clinical research protocols to enter further patients in a larger trial. One of the protocols was for patients with intra-abdominal malignancies of the gastrointestinal tract, pancreas, kidney, bladder, ovary, body and cervix of the uterus, while the other protocol dealt with tumors located outside the abdomen, such as cancer of the breast, lung, lymph nodes, etc.

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fact, both protocols constituted a unified whole because the former protocol had two sections that also referred to the latter protocol.\textsuperscript{125}

A section on patient eligibility stipulated that, “cases to be included [were in] good enough general condition to merit use of the drug.”\textsuperscript{126} This stipulation suggested that patients were not hopeless cases and they were amenable to the proposed therapeutic approach. Another section called “Procedure” set forth the randomization instructions. Accordingly, the attending surgeon decided during the operation to place the patient in the ‘attempted curative’ or ‘palliative’ series. […] It is then determined whether or not the patient should be treated with nitrogen mustard by consulting a treatment book kept in the operating room. In this book the tumour sites are listed and further divided into ‘attempted curative’ and ‘palliative’. Successive cases are listed alternately as ‘treated’ and ‘not treated’ thus giving a random selection. The patient’s name should be entered immediately into the book.\textsuperscript{127}

On this fairly simple randomized basis, thirty-five patients with intra-abdominal cancer and fifty patients with malignancies outside the abdomen either received adjuvant chemotherapy or not.\textsuperscript{128} The clinical trial objectives were to determine whether the use of nitrogen mustard decreased the incidence of cancer recurrences and to establish if the occurrence of any serious complications related to a particular way of the agent’s administration. In the intra-abdominal category, patients in the treatment group received a nitrogen mustard irrigation of the tumor area before its removal and they had another freshly prepared solution of the agent left in the abdominal cavity to act locally after the operation. Patients with cancer outside the abdomen had an equal amount of nitrogen mustard solution injected systemically over two to three days following the surgical procedure.

McCredie and his team simultaneously performed an experimental investigation in rats to compare the effects of administering nitrogen mustard by the systemic venous and intra-abdominal routes. The animal study results approximated those found in human subjects. As the

\textsuperscript{126} \textit{Protocol for the Use of Nitrogen Mustard at the Time of Surgery for Intra-Abdominal Cancer}, p.1; \textit{Ibid}.
\textsuperscript{127} \textit{Ibid}., 1.
researchers wrote, “findings in the rat confirm[ed] the clinical observation that the systemic venous administration of nitrogen mustard cause[d] a greater toxicity and decrease in the white cell count than its administration by the intraperitoneal route.”\textsuperscript{129} Nonetheless, the clinical trial revealed that rats differed to a certain degree from humans: the animal approximation of intravenous dose of nitrogen mustard given to patients led to a considerable general toxicity manifesting itself in a drop of hemoglobin and leucocytes. Several patients received antibiotics and blood transfusion to prevent fatal consequences.\textsuperscript{130} This experience prompted the investigators to lower the chemotherapeutic dose by a third for new patients entering the trial.

McCredie and Inch presented interim results of their research program at the 18th Annual Meeting of the Central Surgical Association in St. Louis, Missouri, on 18 February 1961.\textsuperscript{131} Their paper stimulated a lively discussion that ranged from an allegation that the clinical trial apparently was “just doing something” to an admonition not to overdo it with the adjuvant therapy. In his statement to the surgical forum, Claude R. Hitchcock, chief of the department of surgery of the Minneapolis General Hospital, addressed “those in the audience who [we]re interested in the problems of chemotherapy concomitant with surgery that [they] should approach this area with caution in the human.”\textsuperscript{132} Hitchcock referred to the-then ongoing US cooperative studies on the adjuvant use of chemotherapy in the surgical treatment of cancer that had a checkered history. Particularly, his criticism targeted a nearly indiscriminate use of certain agents as adjuvants to surgery in the Veterans Administration hospitals. Such practices, in Hitchcock’s view, unnecessarily increased mortality in patients with cancer of the stomach thus treated as compared to the patients operated on without receiving the adjuvant chemotherapy. It was a delicate subject at the time since Rudolf J. Noer of Louisiana, a chairman of the Breast Study Group within the US Adjuvant Chemotherapy Program, stiffly retorted that the mortality rate was not higher among other groups of patients who had received adjuvant Thio-TEPA and that more factors needed consideration to discuss the topic.\textsuperscript{133} Indeed, this episode of public

\begin{footnotes}
\footnote{\textsuperscript{129} Ibid., 3.}
\footnote{\textsuperscript{130} McCredie and Inch, “Further Experiences with the Use of Nitrogen Mustard as an Adjunct of Operation in the Treatment of Cancer” (1961): 486-487.}
\footnote{\textsuperscript{131} J.A. McCredie and W.R. Inch, “Nitrogen Mustard (HN2) Toxicity: Comparison of Effects of Administration by the Systemic Venous and Intraperitoneal Routes,” \textit{Archives of Surgery}, 83, no.4 (October 1961): 597.}
\footnote{\textsuperscript{132} Ibid., 603.}
\footnote{\textsuperscript{133} Ibid., 604.}
\end{footnotes}
intra-professional quibbling elucidated how McCredie and his team came up with their experimental design for a clinical study.

In the US, the Cancer Chemotherapy National Service Center (CCNSC) of the NCI began the Surgical Adjuvant Chemotherapy Programs to study human malignant tumors of the stomach, lung, colon and rectum, and breast as early as July 1957. Over the preceding year, the CCNSC developed the cooperative study plan to do clinical research on the usefulness of particular chemical agents as adjuvant therapy to cancer surgery. Twenty-seven university surgery departments and twenty-one surgery departments of the Veterans Administration across the US participated in devising statistically controlled clinical trials categorized into four group studies according to the above cancer sites. The Clinical Studies Panel headed by Isadore S. Ravdin, the Surgeon in Chief at the Hospital of the University of Pennsylvania, proposed to start with investigations on Thio-TEPA as the adjuvant chemotherapy for cancer of the stomach, and on nitrogen mustard as the adjuvant agent for carcinoma of the lung. Those were pragmatic decisions because lung cancers had usually poor prognoses and nitrogen mustards might affect their progression, while stomach cancers reportedly had a low therapeutic response to most available drugs and Thio-TEPA was a potent drug promising to overturn the established clinical opinion.

Underlying the protocols for adjuvant therapy with Thio-TEPA and nitrogen mustard for stomach and lung cancers was a research program originated by the aforementioned Warren H. Cole. CCNSC clinical investigators draw heavily on Cole’s experimental designs and findings to develop a pilot protocol for the treatment of stomach carcinoma, which served as a prototype for three other adjuvant therapy trials. Key features of the pilot protocol included the classification of patients into curative and palliative categories, the sequential randomization of eligible patients, and the statistical analysis of parameters under study. This approach was hard to miss in McCredie’s clinical research protocols. However, they had significant modifications. Unlike the CCNSC investigators, McCredie and his group opted for a more justifiable adjuvant use of the well-researched nitrogen mustard in a variety of cancers. Moreover, in view of evident

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136 Ibid., 1711-1712.
toxic effects of the nitrogen mustard initial dosage, which was identical to that given under the
CCNSC lung cancer protocol (0.3 mg/kg of body weight), McCredie reduced it to 0.2 mg/kg and
continued the clinical trial.\textsuperscript{137} The CCNSC investigators proceeded with the cooperative study as
indicated in the protocol regardless of the patients’ morbidity. Still, both American and Canadian
clinical researchers arrived at the same conclusion that most patients were relatively unaffected
by nitrogen mustard as adjuvant to surgery. McCredie and Inch summarized their clinical
experience with a challenging proposition, “Radiotherapy, however, produce[d] better results in
the majority of patients than either infusion or perfusion [with nitrogen mustard].”\textsuperscript{138}

Hundreds of patients entered the CCNSC cooperative investigations. While dozens of
patients were subjects in the clinical trials of McCredie and Inch, just one cancer patient proved
sufficient for William N. Kemp of Vancouver, British Columbia, to call “a new approach to
treatment” efficacious.\textsuperscript{139} Kemp, a general practitioner, reported in the \textit{Canadian Medical
Association Journal (CMAJ)} that he successfully treated a forty-year-old woman with an
advanced carcinoma of the cervix by a regimen of hormone-, chemo-, and radiation-therapy
culminating in a complete removal of her uterus. About seven month later, the patient did not
show any symptoms of the disease, and Kemp decided to share his remarkable treatment
combination with his fellow Canadian doctors.

Readers of the \textit{CMAJ} might have appreciated Kemp’s venturesome therapeutic approach,
if it were not for Thomas A. Watson, a radiotherapist and director of Cancer Services for
Saskatchewan. In his letter to the editor, Watson noted that Cobalt-60 teletherapy, which the
patient received, alone may have brought a positive treatment outcome, and he listed point by
point all relevant details missing from Kemp’s report. Watson reasoned, “Surely such a
conclusion [on the efficacy of treatment by Kemp] could only be reached after a large series of
patients had been treated with the magic combination and compared with an adequate control
series treated by radiation therapy alone.”\textsuperscript{140} Having pointed out further that the patient’s follow-

\begin{itemize}
\item\textsuperscript{137} See \textit{Protocol for the Use of Nitrogen Mustard at the Time of Surgery for Intra-Abdominal Cancer} and \textit{Protocol for
the Use of Nitrogen Mustard for Cancer Outside the Abdominal Cavity}; in the WUA, AFC 328.1.2194. Also, Moore,
\item\textsuperscript{138} McCredie and Inch, “Chemotherapy of Cancer in Surgical Patients” (1961): 1240.
\item\textsuperscript{139} William N. Kemp, “Inoperable Carcinoma of the Cervix: preliminary report of a case and a new approach to
\end{itemize}
up period was not long enough for concluding anything at all, Watson suggested that single case reports, like that of Kemp, misled medical practitioners.

A week before the case report appeared in press, the CMAJ featured a special article on the proper conduct of clinical investigations. Alex J. Phillips, the NCIC statistician, expounded on why doctors must nip in the bud their bias toward uncontrolled clinical research that misinformed colleagues on the usefulness of particular treatments. In doing so, Phillips explained and instantiated how important the size of the research sample was for making valid inferences from the available evidence. Through the elucidation of main criteria of a “good experimental design,” such as randomization and common statistical tests, Phillips urged the research-oriented doctors to “always bear in mind the limitations imposed on the evidence by the manner in which it was obtained.” For Kemp, evidence was present in the patient’s state of health rather than in the procedure of getting to that point. The therapeutic end justified the means, however excessive. Kemp ignored most of the principles made plain in Phillips’ article, which possibly prompted Watson to give a second thought to the neglect of a scientific approach to practicing medicine.

Having taken notice of this neglect, Watson represented a view of proponents of medical science who learnt from their bitter experience. Case-based reports perpetuated damaging stereotypes in cancer control rather than expedited the expert assessment of new treatments. To demonstrate that a treatment modality was indeed a “magic combination” a physician-investigator required something more than a patient and a therapeutic technique. The need was in a reproducible procedure to evaluate how patients responded to a particular technique and to what extent the technique was better or worse than existing modes of treatment.

3.5. Conclusion

In the clashes and intermittent truces among the established surgeons, the entrenching radiotherapists and chemotherapists there ultimately emerged the randomized clinical trial on the Canadian cancer research horizon. It was a protracted process marked by struggles against the

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142 Ibid., 377.
convention and the norm. Conventions of general surgery confronted the ill-defined variability of cancer which, in turn, necessitated the elaboration of diversified treatment approaches to neoplastic diseases. Radiotherapists branched out from radio-diagnostics in view of the scientific-technical challenges of nuclear medicine. The norm of introducing new forms of treatment when the customary procedures came to naught proved difficult to alter, but not impossible.

In the late 1950s, surgeons only seemed to be losing their dominant position in cancer management in Canada against the backdrop of booming radiotherapeutic investigations within university-based teaching hospitals. The reason for this was a long-standing place of surgeons high up in the institutional cancer treatment hierarchy, which allowed them to hold sway in community hospitals and in private practice. The situation was changing, however. Among catalysts for this change was the competition of professionals with the wishes of cancer patients. Yet, the courts of law judged the practices of expert surgeons working at the specialized institutions according to standards of the general surgical practice. Professional solidarity of doctors and utilitarian considerations of judges overshadowed occasional disregard for the patient’s human dignity.

Therapeutic cancer research was situated in this context. As the number of clinical trials and their size gradually increased, the impingements on patients’ bodily integrity seemed to grow concurrently. It happened behind the scenes, veiled in the medical jargon. Attending surgeons, radiotherapists, and physicians had more opportunities to speak the same language of clinical investigations within institutions than beyond their walls. Institutional incentives, like research funding and better career prospects, also played a role in the creation of professional alliances which would have otherwise been inconceivable. Although sporadic, collaborations between the surgeon, the radiation specialist, and the physician did occur. At such periods of convergence, promising avenues of enquiry opened for improvements in cancer management by obtaining new evidence along with the reassessment of available findings through interdisciplinary lens.

A multi-focus on particular difficulties of cancer control, like over-exposure to radiation and chemotherapeutic toxicity, induced a growing cooperation. It was conducive to groundbreaking studies and to enviable patents for inventions, which further enhanced the willingness to cross the professional lines. This cooperation apparently stemmed from lingering
doubts about the effectiveness of certain cancer treatment modalities in comparison to others. As the empirical evaluation of therapeutic procedures and agents reached its limits, a need arose for an alternative method to analyze their effectiveness or the lack of it. Clinical investigations involving fewer than a hundred patients were most common at the time, but such sample sizes proved impractical when differences in the efficacy of treatments were subtle. Such less-than-ten-percent differences were fairly common in clinical studies, which presented the doctor-researchers with problems of determining superiority of one treatment over the other.

Indistinguishably low margins of therapeutic benefit had a twofold effect. On the one hand, the cancer specialists representing one professional group could argue that their particular treatment approach was no worse, or perhaps even better, than a new approach developed by another professional group. On the other hand, the attempt to demonstrate a slight gain in treatment outcomes could contribute to more appreciation of the clinical research effort and its increasing value in the cancer control program. To neutralize the inter-professional controversies and to augment the weight of investigational activities, clinician-researchers introduced a technique for judging the significance of both incremental improvements and breakthroughs. That technique was a randomized controlled clinical trial.
Chapter IV

Evolving Standards of Clinical Investigation and its Regulation

Canadian clinical research flourished in the 1960s while a regulatory framework for it was in the making. The number of medical investigations grew exponentially in teaching hospitals, to the extent that volunteers were welcome to join the ranks of patients. In the domain of clinical studies in cancer, surgeons and therapeutic radiologists opposed this trend in view of a greater legal liability for non-therapeutic interventions. Their increasingly aggressive approaches to cancer treatment found applications in clinical research with patients, since therapeutic investigations were relatively immune to charges of human experimentation. Moreover, interest in medical uses of radiation somewhat overlapped with possibilities to employ it for military purposes, which purportedly discouraged physician-investigators from attracting volunteers.

Chemotherapeutic trials, by comparison, could hardly do without volunteers not only because there was a growing supply of new investigational drugs to be tested, but also because there were more chances to avoid unforeseen adverse effects and complications in healthy people. The US cancer chemotherapy cooperative research groups suggested that both therapeutic and non-therapeutic clinical studies had more merits than demerits. Leading Canadian investigators, such as surgeon Norman C. Delarue and physician-hematologist Ernest A. McCulloch, were involved in the American collaborative studies.

As the NCIC extended its web of connections across Canada, both procedural and ethical standards of acceptable clinical investigations became pressing. These standards emerged through an overly optimistic performance of risky human subject research. Litigation followed some unsuccessful clinical trials, as the case of W. Halushka demonstrated, which will be discussed in this chapter. This resulted in a gradually augmenting institutional oversight of research involving humans. However, the ethical review of clinical studies remained under a local control of principal investigators who interpreted both the international guidelines on human experimentation and the national requirements of funding agencies according to their own conventional frame of reference. Admittedly, conventions were not readily amenable to changes. Nonetheless, from Halifax in Nova Scotia to Vancouver in British Columbia, the cancer research community sensed the tide of change in 1961.
Investigators engaged in clinical work had sensed a shift for at least a decade. Changing conditions related to the conduct and assessment of clinical trials of chemotherapeutic agents for cancer treatment. Director of the Nova Scotia Tumour Clinic and a surgeon at the Victoria General Hospital in Halifax, Norman H. Gosse, requested that Robert M. Taylor, Executive Director of the National Cancer Institute of Canada, establish a position of the NCIC Research Professor to lead a clinical trial program. Gosse justified this by a unanimous decision of faculty members of Dalhousie University Medical School “to reorganize [their] resources so as to do better work in Chemotherapy [sic] in the case of patients with advanced disease, [which] required that any such reorganization must be entirely on a research basis.”

Gosse pointed out that a close affiliation between the university and the hospital made the Victoria General virtually a university hospital. A direct liaison with the NCIC, Gosse noted, could also contribute to associating the Department of Pharmacology with the cancer research effort. Overall, Gosse argued for a more effectively integrated laboratory and clinical work in cancer chemotherapy. One of the assumptions underlying Gosse’s request was that an unmediated access to the NCIC would ensure that novel chemotherapeutic agents for clinical trials were more readily available to patients at the Victoria General. At the time, the NCIC consulted the Food and Drug Directorate of Canada on newly introduced investigational anti-cancer drugs. This assumption had its roots in the developments initiated by the NCIC in Western Canada.

The NCIC had appointed Robert L. Noble in early 1960 to direct a newly set-up Cancer Research Centre on the campus of the University of British Columbia in Vancouver. Noble,

2 Ibid., 2.
3 The Food and Drug Directorate of Canada (FDD) in many functional respects resembled the US Food and Drug Administration. As the administrative unit in the Department of National Health and Welfare, the FDD had responsibility for enforcing the Food and Drugs Act and the Proprietary or Patent Medicine Act. To fulfill this responsibility, the FDD conducted research and provided advice on the products under its jurisdiction through the Laboratory Services Division. See R.A. Chapman, “Statement of Research Activities of the Food and Drug Directorate,” attached to Minutes - Special Session of DACOFT, Ottawa, 13 November 1959; in the in the USL, MG 074, b.72, Science files – DRB, 1958-1960.
4 Although an official opening of the Cancer Research Centre occurred on 19-20 March 1962, the unit saw its formation in April 1960. See Administrative Committee of the Cancer Research Centre chaired by John F. McCreary, “Minutes,” 18 October 1960; and R.L. Noble’s Report to the Management Committee of the Cancer Research Centre, p.4, enclosed with its “Minutes,” 30 September 1961; both documents in the University of British Columbia.
who brought Vincaleucoblastine (VLB) from the bench to the bedside in Ontario, organized a research group that continued to work on periwinkle alkaloids and the role of hormones in malignancy. Moreover, Noble’s expertise in the field made it possible to accelerate the translation of suitable chemical agents into medical preparations that potentially had anti-cancer properties. Affiliation of the Cancer Research Centre with the university enhanced the interdepartmental collaboration in special lines of cancer work, including clinical studies.

At the same time, the NCIC became more engaged in local investigations, which enabled it to facilitate a better coordination between the different research groups nationally. Such a hub-and-spoke model originated in July 1957, when the University of Saskatchewan formed a Department of Cancer Research after the NCIC had offered to create and maintain a cancer research unit. Robert W. Begg, the first full-time NCIC Professor of Medical Research at the University of Western Ontario, was appointed director of the unit and head of the Department of Cancer Research at the University of Saskatchewan. Like Begg in Saskatoon, Noble in Vancouver became an essential link in the NCIC chain of coordination after a period of

Columbia Library Rare Books and Special Collections, Vancouver (hereinafter the UBCL), Faculty of Medicine fonds (1947-2009), box 8, file 25.


6 Over 1961-1962, Noble insisted on the development of a clinical research program in cancer. Envisioning a full-scale unit for clinical research, he suggested that it was “imperative to obtain a person orientated in both clinical and basic research, who might have a full-time appointment for comparative studies.” He was concerned because D.M. (Mac) Whitelaw, who had conducted extensive clinical studies with VLB, left for Toronto to take an appointment of Head of Medicine at the OCI/PMH. Additionally, it was a matter concern for Noble since Eli Lilly and Company had already supplied a new VLB-like substance, Leurocristine, to have it tested both experimentally and clinically in Vancouver, but there was no competent enough chemotherapy specialist to do the work. Noble felt strongly, therefore, that the cancer authorities needed to establish facilities and personnel in Vancouver for further studies with VLB and its derivatives. According to Noble, there was “a pressing need not only from our own point of interest, but also for the possible benefit of the citizens of British Columbia who ha[d] contributed to the Cancer Research Centre.” Moreover, Noble’s participation in the US National Cooperative Chemotherapy Program under the NCI led him to become a regular Consultant to Collaborative Research in February 1965, which contributed to more cooperation with American investigators. He was the only Canadian investigator on the list. See Robert L. Noble (Director, Cancer Research Centre) to J.F. McCreary (Dean, Faculty of Medicine, UBC), Vancouver, 19 February 1962; in the UBCL, Faculty of Medicine fonds, 8/25. Also, Charles G. Zubrod, “The Chemotherapy Program of the National Cancer Institute: History, Analysis, and Plans,” Cancer Chemotherapy Reports, 50, no.7 (October 1966): 402.

7 Robert W. Begg, “Annual Report to the President, University of Saskatchewan: The Saskatchewan Cancer and Medical Research Institute, 1 July 1957 - 30 June 1958,” p.1; in the USL, College of Medicine Dean’s Office fonds 2087, MR. 7(8).
cooperative research in London, Ontario. It was no coincidence that views on a double-blind randomized controlled clinical trial (RCT) as an innovation in cancer treatment assessment disseminated via cancer researchers in Ontario to other medical centers across Canada.⁸

Not unlike any novelty in medicine, the RCT began gaining ground somewhat sluggishly in Canada. At the turn of the 1960s, just a few Canadian leaders in clinical research were in the process of adapting and applying this new technique to investigations within a local environment of inter-professional struggle and resource scarcity. A considerable value of the RCT in expediting valid conclusions on the effectiveness of treatments under investigation seemed a collateral benefit. I argue that physician-researchers in Canada gradually adopted the RCT methodology through their association with American and British standards of clinical investigation, which set off comparable, but locally conditioned, developments in response to human subject research.

A pragmatic borrowing of the technique was explicable. It spared Canadian investigators difficulties in designing research protocols from scratch and in funding the trials. At the same time, there were undeniable advantages in collaborating with British and especially American cancer researchers, such as access to investigational new drugs and to expertise in administering concurrent RCTs. While participating in the RCTs coordinated by American investigators, Canadian cancer specialists continued doing their own original therapeutic experiments, but mostly of non-randomized kind. What prompted this activity was a significant factor of patients’ limited availability for particular clinical investigations. Considering that there were relatively few patients even with frequently occurring malignancies, such as breast and lung cancers, sequential clinical trials seemed expedient to investigators. Moreover, doctor-researchers tended to obviate the need to deal with ethically controversial RCTs that involved treated and untreated patient groups. Thus, the emergence of RCT was a mixed blessing for Canadian cancer investigators.

In large medical centers, Canadian doctor-researchers engaged in RCTs opportunistically, mainly when their American colleagues organized such cooperative investigations and invited a

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⁸ The attribute ‘double-blind randomized’ meant that any expectations or biases of physician-researchers and patients had virtually no influence on the clinical trial results because the subjects were randomly allocated, unbeknownst to the investigators, into groups that either received, or not, an experimental drug or procedure.
wider participation. For example, Norman C. Delarue, assistant professor of surgery at the University of Toronto, spearheaded a research program on adjuvant chemotherapy in cancer of the lung and implemented it at the Toronto General Hospital (TGH) in conjunction with the Princess Margaret Hospital and the Wellesley Hospital.9 This project became possible because Delarue joined the second cooperative adjuvant chemotherapy study administered and sponsored by the US Cancer Chemotherapy National Service Center (CCNSC) of the National Cancer Institute from 1956 to 1963.10 Delarue had participated in the CCNSC cooperative study since 1958, the year when the CCNSC double-blind RCTs commenced. A key part of his research program concerned a comparison of lung cancer patients at the TGH treated in three modes: by surgery alone, surgery with adjuvant chemotherapy, and chemotherapy with radiotherapy. In his progress report of 1960, Delarue noted that this cooperative trial used

the double blind scheme of assessing the potential value of nitrogen mustard […] in the treatment of resectable bronchogenic carcinoma [and …] the actual statistical assessment of patients [wa]s carried out by the statisticians at Roswell Park Memorial Institute in Buffalo in association with the study of similar cases from other teaching centres [sic] on the North American Continent.11

In addition to this concurrent RCT coordinated by the CCNSC, Delarue proposed to undertake a complementary sequential trial. He suggested evaluating the use of chemotherapy simultaneously with radiotherapy in the treatment of non-operable lung cancer. To Delarue this evaluation appeared feasible by means of a Cobalt-60 unit and a full course of nitrogen mustard or other chemotherapy.12 In his view, such a sequential study had the potential to shed light on the pros and cons of this combination in terms of its curative rather than palliative effects. At the same time, Delarue planned to test safety limits of combined treatment dosage: a tolerable amount and possible route of administration of chemotherapy in relation to an optimal schedule and duration of radiotherapy. Yet, his plan was not entirely original inasmuch as the Toronto group of investigators led by Delarue already took part in a project assessing chemotherapeutic

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agents alternative to nitrogen mustard in the series of patients with advanced lung cancer. One such alternative was Benzcarbimine (AB-103), a product of the expanding CCNSC drug development program.

Together with American cancer research groups in Buffalo (NY), Chicago (IL), and Philadelphia (PA), Delarue’s team undertook an initial evaluation of AB-103.\textsuperscript{13} The Toronto group drew on the clinical experience with the agent of investigators from Roswell Park Memorial Institute and the University of Buffalo who experimentally treated twenty-eight patients with far advanced, inoperable, carcinoma of the lung.\textsuperscript{14} The American team tentatively demonstrated a potential effectiveness of AB-103 and its suitable dose schedules to treat bronchogenic carcinoma. Their rationalization for this pilot study was simple, “Advanced carcinoma of the lung [was] so hopeless a disease and existing treatment [was] so often ineffective that trials of new chemotherapeutic agents [were] justified.”\textsuperscript{15} Further studies of AB-103 continued in Toronto.

By March 1961, twenty patients at the TGH received AB-103.\textsuperscript{16} Like in the American clinical trial, there was no randomization in Delarue’s investigation. What differed in those two pilot trials was that in the Canadian study all potentially curable, \textit{i.e.} operable, patients received the drug. This course of action allowed Delarue to reach a conclusion regarding efficacy of AB-103 in a greater number of patients, which could qualify the agent for a large-scale study. In this case, AB-103 was a candidate to replace nitrogen mustard in the RCT of adjuvant chemotherapy.\textsuperscript{17} Albeit, AB-103 did not enter a crucial stage of the double-blind randomized clinical trial, since the agent’s statistical evaluation indicated its therapeutic unsuitability for the RCT in lung cancer.

\textsuperscript{15} \textit{Ibid.}, 860.
\textsuperscript{17} Rudolf E. Falk, \textit{Progress Report No.3} “A Study of Adjuvant Chemotherapy in Lung Cancer,” enclosed with \textit{The OCTRF Application for a Grant for Clinical Research}, Toronto, 29 January 1962; in the UTA, A66-0009/023, Surgery 1962. Falk stressed the significance of a cooperative approach to clinical investigations by noting, “Initial results do not demonstrate any convincing evidence of value of Adjuvant Chemotherapy [sic] currently available but the group evaluation technique is so important that it is felt this centre should continue in the study indefinitely.”
Delarue did not overlook critically-ill patients with inoperable carcinoma of the lung in his expanding clinical research project. Although the patients did not meet criteria for receiving AB-103, they had another experimental treatment option – a combination of nitrogen mustard and radiotherapy. Between 1960 and 1962, about fifty patients underwent this combined therapeutic regimen that grew in intensity as findings about its effects amassed. For instance, doctor-researchers modified the dose of nitrogen mustard from 0.2 milligrams per kilogram of body weight given intravenously on each of two successive days to 0.4 mg/kg administered at once. To cope with the workload, Delarue secured funding from the Ontario Cancer Treatment and Research Foundation in 1961 to recruit Rudolf (Rudy) E. Falk as a Fellow in Surgery at the TGH. Falk became responsible for the major part of Delarue’s clinical research project that assumed increasingly experimental features. Wrote Falk in an annual report,

23 additional cases [were] treated by a single dose of 0.4 mg per kg of body weight of nitrogen mustard given immediately before a course of radiotherapy in which no attempt [was] made to adjust the dosage of radiation on the basis of the hazard to the hemopoietic [blood-producing] system. These cases [we]re followed closely and since of advanced stage an evaluation of potential value of this form of combination therapy may become possible soon due to the rapid accumulation of final results.

Delarue’s combinatory therapeutic approach was a form of human experimentation. In fear of under-treatment that made doctor-researchers powerless against the progression of lung cancer, they resorted to over-treatment that could lead to either cure or death. This modus operandi prevailed at the time when the inability to treat advanced cancer provided a rationale for the advancement of treatment capabilities through trial and error. For example, the Pacific Veterans Administration Cancer Chemotherapy Group in the US included this principle in their experimental design to test AB-103. Their protocol had a requirement to administer AB-103 “at a maximum tolerated dosage for a minimum of 6 weeks for a trial to be considered adequate,”

18 An additional alteration of the regimen included a substitution of intravenous cortisone, which relieved patients’ nausea and vomiting, for less effective anti-emetic drugs in suppository form. The reason behind this decision was that cortisone supposedly affected patients’ resistance to infection. See R.E. Falk, Progress Report No. 4B, “A Study of Therapeutic Chemotherapy in Conjunction with Radiotherapy for Non-resectable Bronchogenic Carcinoma,” in The OCTRIF Application for a Grant for Clinical Research (1962).
19 See “Summary of Proposed Responsibilities to be Assigned to the Fellow Supported by the OCTRIF for the Academic Session 1962 to 1963,” in The OCTRIF Application for a Grant for Clinical Research (1962).
which seems ethically unjustifiable given that it was a relatively large clinical trial, involving 206 patients, based on previous pilot studies.\textsuperscript{21} This was suggestive of the extreme scientific-medical practices to which investigators inured through the exigencies of wartime.

The post-war military-industrial complex continued to exert its inconspicuous impact on medical investigations. The Defence Research Board under the Department of National Defence of Canada supported a number of projects that had relevance to military interests. One such project on radiation developed under the auspices of the Ontario Cancer Institute (OCI). A physician-hematologist Ernest A. McCulloch and a physicist James E. Till, affiliated with the departments of Medicine and Physics of the University of Toronto, respectively, collaborated to explore how ionizing radiation affected living matter and what exactly happened in this process.\textsuperscript{22} Their objective was to determine the best ways to deal with the hazards of total-body irradiation that could be warranted in the treatment of metastatic cancers, leukemia, and other systemic medical conditions. As the investigators explained, the survival of animals following a total-body exposure to radiation had a low threshold due to a high susceptibility of blood-forming tissue in the bone marrow to irradiation.\textsuperscript{23} By extrapolation, humans had the same constraining factor of a total-body irradiation that needed elucidation in order to overcome it.

The investigations of McCulloch and Till moved relatively fast from the cell culture to the animal model, and then to the human system between 1958 and 1961.\textsuperscript{24} They studied radiation sensitivity \textit{in vitro} and the effects of bone marrow transplants on mice that had received lethal doses of radiation. The investigators gave mice total-body radiation doses no less than twice as large as those required to kill the animals, in the range of 500-1000 rads, and immediately after the irradiation transplanted non-irradiated bone marrow cells to the radiation-

\textsuperscript{22} Ernest A. McCulloch and J.E. Till, \textit{Final Report to the Defence Research Board}, Grant DRB 9350-14, “Studies on Repair Processes Occurring in Hemopoietic Tissue Following Total-Body Radiation,” September 1973; in the UTA, B1991-0004/020(21) – Canada. Department of National Defence. DRB Grant no.9350-14. On page 1 of their report, the authors wrote: “For thirteen years, with the support of the Defence Research Board, we have been studying marrow function after whole-body radiation and its relationship to survival.”
\textsuperscript{23} \textit{Ibid}.
exposed mice. In doing so, McCulloch and Till worked towards determining the radiation sensitivity of bone marrow along with its protective effects in animals and, by analogy, in humans.

As soon as McCulloch and Till’s animal research findings showed that a total-body radiation coupled with bone marrow transfusion was practicable, the investigators turned to a pilot clinical trial. In early 1959, the initial laboratory research into the problem of systemic effects of irradiation led to the application of a new technique of bone marrow transplantation in three patients. McCulloch and William E.C. Allt, a radiotherapist at the OCI, performed “autologous marrow replacements […] where it was known that supra-maximal amounts of trunk or whole body radiation (or chemotherapy) would be necessary to control widespread disease [in patients with] carcinoma of ovary, embryonal carcinoma of testis, [and] Hodgkin’s disease.”

The NCIC and the OCTRF funded, respectively, fundamental and clinical research phases of the project. The Defence Research Board generously supplemented those allocations in mid-1959. Studies on the effects of whole-body irradiation interested not only the clinicians treating

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25 Defence Research Board Application for Grant in Aid of Research, Renewal Grant No. 9350-14, 18 October 1965, by E.A. McCulloch; J.E. Till; L. Siminovitch; in the UTA, B1991-0004/020(21).
27 J.M.M. Darte and E.A. McCulloch received from the OCTRF a joint grant for two projects – “Immune Mechanisms in Hodgkin’s Disease and Bone Marrow Transplantation” – in the amount of $7,300 in 1959, and another one totaling $4,200 in 1960. Whereas the NCIC awarded a block grant for projects under a general direction of Arthur W. Ham over 1959-1960. The sum of $127,000 was distributed among twelve projects and E.A. McCulloch along with Louis Siminovitch developed one of them – “Effects of Whole Body Radiation and the Transplantation of Isologous, Homologous and Heterologous Marrow on Radiated Animals and the Nature of Secondary Disease.” See “Schedule of the Applications for Grants for Clinical Research Approved by the OCTRF,” Exhibit B, p.6, enclosed with correspondence from J.H. Broughton to H.J.C. Ireton, 7 July 1960, Toronto; in the UTA, A66-0009/023, Surgery 1960. Also, NCIC, Annual Report of 1958-1959 (Toronto: NCIC, 1959), 39.
28 In June 1959, the DRB granted $9,400 for “Studies on Protection Afforded against Total Body Radiation by Isologous, Homologous and Heterologous Fetal and Adult and Frozen and Fresh Marrow.” The next year this project received another $11,700. The DRB continued to support this research program until 1974. See Stanley L.W. Mann (Grants Officer, Defence Research Board), DRB 240-1(G&C), “To Distribution: Grants-in-Aid of Research 1959/60,” p.7, Ottawa, 12 June 1959; and Defence Research Board, “Forty-Second Meeting of the Standing Committee on Extramural Research,” DRBS 171-80/S6(G&C), Ottawa, 11 April 1960, p.8; in the USL, MG 074, b.73, DRB – Meeting Agenda, 1959-1961.
malignancies, but also the military personnel considering the implications of nuclear test explosions or atomic bomb strikes for humans.²⁹

The clinical radiation research gathered momentum, as evidenced by the diversification of studies owing to the technique of bone marrow replacement. For instance, Walter D. Rider, a senior radiotherapist at the OCI, took an active interest in studying acute radiation syndrome in humans after the whole-body irradiation of patients.³⁰ Rider’s engagement in exploring systemic biochemical disturbances induced by whole-body irradiation attracted collaboration with the MRC National Institute for Medical Research in Great Britain.³¹ British investigators were also interested in studying the human physiology of acute radiation syndrome.

Further clinical experience with bone marrow transplantation made radical radiotherapy a possible course of action in the absence of alternative treatment. Patients suffering from acute leukemia received total-body irradiation followed by bone marrow transfusions when conventional treatment options – steroids, antimetabolites, and folic acid antagonists – became exhausted. Even critically ill children were included. During 1960, E.A. McCulloch and John M.M. Darte, a radiotherapist at the OCI and a clinical teacher in pediatrics at the University of Toronto, administered whole-body irradiation in the supra-lethal range with subsequent bone marrow transplantation to six children. In their words, “Following the sedation with chlorpromazine and barbiturates the patient received a midline dose of 800-950 rads from a Co⁶⁰ [Cobalt-60] source, given to the whole body including extremities and head. The total time of exposure varied between 29 and 290 mins. [sic], the later treatments requiring less than 1 hour for administration.”³² Experimental treatment outcomes proved less than satisfactory. Only one child had an eight-month complete remission, while the other five children survived between

³⁰ The syndrome manifests itself in fatigue, nausea, and vomiting within a short time after receiving a large radiation dose. See the OCTRF, Annual Report 1959-1960, p.107; in the USL, MG 404, box 11.
³¹ Ibid., 107.
³² As the investigators wrote, “Prior to the administration of the massive dose of irradiation, small doses of 25 to 75 rads were administered to five of these patients for control of pain, to reduce the total amount of leukaemic tissue present and to accustom the child to the procedure.” Italics added. See the OCTRF, Annual Report 1960-1961, pp.86-87; in the USL, MG 404, box 11.
nine and seventy-five days. It should be noted, however, that a number of adult cancer patients underwent similar, but probably more trying, therapeutic experiments before 1960. Harold E. Johns, who headed the Division of Physics of the Ontario Cancer Institute since July 1956, put it thus,

Dr. McCulloch and others in the [Ontario Cancer] Institute [gave] super-lethal doses of whole body radiation to a few patients suffering from very acute leukaemia [sic]. After this very severe radiation these patients [we]re given a bone marrow transplant preferably from a twin or if this [wa]s not possible then from a brother, a sister or foetal [sic] liver cells. The results appear[ed] somewhat encouraging.\(^{33}\)

Those “somewhat encouraging results” obtained during 1959 likely contributed to the later inclusion of children in the clinical research program. Johns’ considered assessment had no particulars, but it revealed that human experimentation clearly did take place. What remained undisclosed, however, was a spectrum of factors that motivated McCulloch and his research group to resort to the experimental treatment of patients so readily. Was it the scientist’s curiosity or the clinician’s desperation to do something useful for the patient? How determinant was the involvement of the Defence Research Board (DRB)? Whereas these factors lend themselves to speculation about their importance, the role of the DRB appears more clearly defined in the context of Canadian-American relations. Cooperation of Canada with the USA on atomic energy and related national defense projects bridged the scientific-medical communities engaged in them across the border. One concrete example may suffice.

At the end of the 1950s, Eugene L. Saenger, a physician-radiologist at the University of Cincinnati School of Medicine in Ohio, launched a research program of total-body irradiation of patients with disseminated cancer.\(^ {34}\) The US Department of Defence granted funding for the program in addition to the university hospital allocations. The whole-body radiation that Saenger administered by means of a Cobalt-60 unit to patients with advanced malignancies had both a therapeutic and a scientific value. For the military, Saenger’s studies could answer some of the urgent war-related questions on unidentified radiation exposure of soldiers. Yet, the usefulness of such therapeutic approach for critically ill patients was apparently underdetermined, since the


criteria for measuring patients’ improvement were not part of the clinical trial’s design.\textsuperscript{35} Despite this incommensurability, with patients acting as proxies for soldiers, Saenger’s program was embedded in the practices of the time. The environment of active therapy development through clinical cancer research and the interests of government officials favored a utility-oriented frame of reference.

The research program of Saenger bore a striking similarity to therapeutic investigations of McCulloch’s group. It is instructive to draw a parallel between those two studies with human subjects so as not to overlook significant factors affecting the scientific-medical domain. Ties between the American and Canadian Departments of Defence possibly contributed to a common denominator in those clinical trials. In the same vein, participation of Delarue’s group in the US cooperative chemotherapy program connected the Canadian group to a network of American scientific-medical investigators interacting within particular socio-political forces.

**4.1. Randomized and Not Randomized Clinical Trials**

Enthusiasm among Canadian cancer investigators for randomized clinical trials developed as their involvement in the US cooperative group studies deepened over the 1960s. Yet, this collaboration did not prompt organization of cooperative RCTs in cancer throughout Canada. Unlike in the US, there was no relatively formalized research group framework with regular meetings when the members had the opportunity to be involved in formulating policy concerning the direction of collaborative activities and the elaboration of research protocols. Moreover, the number of doctors willing to make a major research commitment to cooperative clinical trials was insufficient. Participation of those few Canadian investigators in the cooperative RCTs with the US groups was less burdensome in terms of financial and administrative responsibilities. A continuity in the American cooperative program was another feature that attracted Canadian cancer specialists. New RCTs spun off from the active studies, which created a self-perpetuating

\textsuperscript{35} Eileen Welsome, The Plutonium Files: America’s Secret Medical Experiments in the Cold War (New York: Dial Press, 1999), 340.
cycle of protocol generation limited only by the validity of objectives in experimental designs and the availability of patients.\textsuperscript{36}

Canadian investigators outside the US cooperative network had two alternatives: to conduct no RCTs at all, or to attempt clinical studies in areas that other research groups overlooked. The latter option was not an easy one because the investigator had to keep abreast of contemporary trials relevant to the proposed study. For keeping the interested persons informed of on-going investigations, the NCIC promoted the establishment of cancer research centers under its auspices. In May 1963, Edmonton (AB) joined the ranks of Saskatoon (SK), London (ON), and Vancouver (BC) by hosting another NCIC cancer research unit.\textsuperscript{37}

Coordination and consolidation of the cancer research effort facilitated by the NCIC across the country produced results. Although the NCIC focused on the promotion of cooperative projects in basic research, the proportion of its budget allocated to clinical research grew since 1961.\textsuperscript{38} Cancer research centers associated with university hospitals created feedback loops between the laboratory investigators and clinicians. For instance, a research program on the mode of action of vinblastine (VLB), developed by Robert L. Noble at the NCIC unit in Vancouver, encouraged Peter Coy, a radiotherapist at the British Columbia Cancer Institute (BCCI), to carry out a RCT involving the chemotherapeutic agent. Before joining the staff of BCCI in 1963, Coy had successfully completed a three-year radiotherapy training at the Christie Hospital in Manchester, England, where the eminent radiotherapist Ralston Paterson continued to conduct RCTs in the field.\textsuperscript{39} Small wonder Coy took initiative in applying his knowledge and new insights from the laboratory to clinical investigations. Coy’s objective in the trial was to

\textsuperscript{36}This argument is developed well in Peter Keating and Alberto Cambrosio, \textit{Cancer on Trial: Oncology as a New Style of Practice} (2012).


evaluate the advantage of giving patients with inoperable carcinoma of the lung Cobalt-60 irradiation and VLB. In late 1963, Coy suggested that patients with a relatively advanced lung cancer localized to the chest and adjacent lymphatic nodes might benefit from the addition of VLB to their radiotherapy regimen. This RCT was one of the eight studies that the NCIC executives registered at the Information Office on Clinical Therapeutical Trials of the International Union Against Cancer (UICC) headquartered in Geneva, Switzerland. Table 4-1 details all eight RCTs, initiated between 1959 and 1967, which the NCIC reported to the UICC.

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Investigators</th>
<th>Sites</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cobalt-60 radiation vs. 22 MeV betatron radiation; both supplemented by a standard radium therapy. Carcinoma of the uterine cervix (stages IIB and III).</td>
<td>William E.C. Allt</td>
<td>The Ontario Cancer Institute / Princess Margaret Hospital, Toronto</td>
<td>1959 – 1964</td>
</tr>
<tr>
<td>4. Placebo vs. Patients’ own diazotized tumor cells (antigen); both preceded by conventional surgery and radiotherapy. Carcinoma of the uterine cervix (stages II, III and IV).</td>
<td>Bernhard Cinader and J. William Meakin</td>
<td>The OCI/PMH, Toronto</td>
<td>1964 – 1971</td>
</tr>
<tr>
<td>5. Mastectomy vs. Mastectomy + Surgical oophorectomy; both followed</td>
<td>Arthur J.S. Bryant</td>
<td>The Allan Blair Memorial Clinic,</td>
<td>1964 – 1973</td>
</tr>
</tbody>
</table>

40 Over several years, 194 patients were randomized into two groups that received either chemotherapy and irradiation or irradiation alone. The trial’s termination in 1969 brought definite but disappointing results: the length of patients’ survival did not differ significantly in the two groups. See Peter Coy, “A Randomized Study of Irradiation and Vinblastine in Lung Cancer,” Cancer, 26, no.4 (1970): 803-804.

41 Members from nine countries (Belgium, France, Japan, Italy, Norway, UK, USA, USSR, and West Germany) formed the Committee on Controlled Therapeutical Trials that established the Information Office of l’Union Internationale Contre le Cancer (UICC) at Villejuif, France, in March 1968. The Information Office served to provide investigators planning to start a RCT with information about similar trials in progress elsewhere. See Report of the Meeting of the Committee on Controlled Therapeutical Trials (UICC), Paris, 27-29 March 1968; enclosed with correspondence from Robert Flamant (Secretary to the Committee on Clinical Therapeutical Trials) to A.J. Phillips (NCIC statistician), Villejuif, 21 August 1968; in the UTA, A1986-0035/03(07).
by conventional radiotherapy.
Operable carcinoma of the breast (stages I and II)

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| 8. Mastectomy + Post-operative Co-60 Irradiation of the breast region +
  - Series 1 (age 35-44, stages II and III) Ovarian Co-60 radiation vs. no further therapy (control);
  - Series 2 (age 45-59, stages I, II, III) Ovarian Co-60 radiation (OvR) vs. OvR + prednisone vs. control;

| Table 4-1. Canadian RCTs reported to the UICC Committee on Controlled Therapeutic Trials.\

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At first sight, the number of Canadian RCTs seems less than impressive. However, Canada ranked fourth among twenty-eight countries that had registered the RCTs at the UICC Information Office over 1959-1967. Only the United States, Great Britain, and Japan had more RCTs underway during the period – sixty-three, twenty-two, and eleven, respectively. Besides, evidence suggests that the NCIC executives reported RCTs selectively, reserving information on some trials for internal use. For example, the Ontario Cancer Treatment and Research

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42 Protocols of the given RCTs; correspondence from Miss R. Wiley (secretary to the NCIC statistician A.J. Phillips) to D.E. Cannell (Medical Director, OCTR), Toronto, 31 August 1970; in the UTA, A1986-0035/03(07); Robert Flamant, ed., *Controlled Therapeutic Trials in Cancer* (Geneva: International Union Against Cancer, 1972).

43 See “Appendix 2: Analysis of Registered Trials according to Countries, 31 December 1974,” enclosed with the *UICC Report of the Meeting of the Project on Controlled Therapeutic Trials*, Geneva, 5-7 May 1975; in the UTA, A1986-0035/03(07).
Foundation reported to the NCIC two similar RCTs – one, conducted in Toronto, comparing fractionation techniques in the Cobalt-60 radiotherapy of advanced malignant brain tumors and the other RCT that ran at the London Clinic in Ontario – but only the former trial was registered at the UICC Information Office. Investigators in London assessed the same treatment mode in patients with metastatic cerebral malignancies through administering Cobalt-60 irradiation in the treated group, and not giving any radiotherapy in the control group. The London RCT complemented the Toronto study that evaluated the length of survival along with the duration and the degree of improvement of patients with histologically proven disseminated astrocytomas randomized in three groups that all received 3000 rad of radiotherapy in different ways.

The underlying idea was to alter the time intervals between repeated radiation doses, which could increase the destruction of rapidly dividing tumor cells without increasing the damage to normal cells in the brain. Correspondingly, one patient group received 146 rad once every day over three weeks, the second group had 49 rad three times a day during three weeks, and the third group received 146 rad three times a day over one week. Although the third radiotherapy regimen was somewhat severe, it was less radical than the experimental Iridium-192 irradiation of advanced glioblastomas employed by C.G. Drake and P.M. Pfalzner to treat patients at the London Clinic in the mid-1950s, as explained in the preceding chapter. Investigators learned their lessons through trial and error, and acted accordingly to refine their approaches to treatment of intractable malignancies. To manage this intractability, doctor-researchers were on the lookout for new solutions, such as immunotherapy and radiation sensitizers.

Immunization of patients with a diazotized extract of their own tumors appeared feasible to the immunologist Bernhard Cinader and the physician-endocrinologist William Meakin, both of the OCI/PMH. After experiments on rabbits demonstrating the antibody-antigen reactions to human proteins, like albumin, they found that a prolonged exposure to a chemically modified, 44 “Clinical Trials being conducted at OCF Clinics or in conjunction with a Trial being conducted at a Particular Clinic or Institution,” p.1; enclosed with a letter from A.J. Phillips to Douglas E. Cannell, Re: Clinical trials information for UICC, Toronto, 2 December 1970; in the UTA, A1986-0035/03(07).
“diazotized”, albumin provoked an immune response to a normal albumin as well. With further animal studies done on the basis of this finding, Cinader and Meakin decided to try this technique with human cancer antigens. Patients with late-stage carcinoma of the uterine cervix seemed to investigators a reasonable choice for planning a RCT because of a relative ease to get tissue material necessary for making diazotized extracts. In February 1964, the first twenty-six women who received a standard treatment of radiotherapy and surgery, if possible, were randomized into a control group and an experimental group that received injections of the antigen monthly for at least a year. The objective of this investigation was to determine whether patients immunized in this manner could have positive changes in terms of recurrence rate and survival.

The concept of radiation sensitization found its way to validation or falsification in a Canadian RCT initiated in 1964. This RCT evaluated the effect of breathing oxygen in potentiating the curative irradiation of bladder cancer. Surgeon-urologist A.G. Keresteci and senior radiotherapist Walter D. Rider collaborated at the OCI/PMH to study whether a randomly chosen experimental group of patients who breathed oxygen for two hours before radiotherapy and during the sessions had any benefits over the control group that had the same radiation treatment alone. Interestingly, it was through involving both patients and healthy volunteers in measurement tests, which included the use of microelectrodes in large veins, that the investigators determined a two-hour period of oxygen breathing was optimal for the desired result. Thus, it was an attempt to enhance the therapeutic effect of radiation without risking a higher exposure, but there were also clinical efforts to boost the defensive mechanisms of human organism so that it could endure more intensive radiotherapy.

Harold Warwick, who was promoted from a staff physician at the OCI/PMH to a Consultant in Medicine and Dean of Faculty of Medicine at the University of Western Ontario, arranged an RCT to assess the possible value of selachyl alcohol, an ester derived from fish liver oils, in reducing systemic effects of ionizing radiation. Warwick found out about selachyl alcohol from publications by a physician-investigator, Astrid Brohult, of the Karolinska

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48 Ibid., 155.
University Hospital in Stockholm, Sweden. Results of Brohult’s RCT, conducted at the Radiumhemmet, suggested that selachyl alcohol as an adjuvant to radiotherapy increased survival of patients with stage II cervical cancer by approximately fifteen percent. These statistically significant findings appeared to Warwick worthy of confirmation, or otherwise. Hence, Warwick designed a double-blind study with a plan to sample randomly no fewer than 400 patients.

To include in the RCT such a large number of patients from the London area required several years. Aware of this fact and impatient to satisfy his curiosity about the interesting finding, Warwick considered following the American example by organizing a cooperative study in Ontario. He invited to participate in his RCT all seven OCTRF clinics. The RCT had a two-fold objective: to evaluate the protective effects of selachyl alcohol on the elements of the blood and to determine whether the agent contributed to increased survival rates among patients with cancer of the uterine cervix who underwent a conventional radiotherapy. Five of the Ontario clinics agreed to cooperate in Warwick’s RCT, but there were two refusals. University hospitals in Toronto were engaged in two other trials entering patients with cervical cancer in the protocols – one comparing Cobalt-60 radiotherapy with that by a 22 MeV betatron, and the other appraising immunotherapy against a placebo. The Windsor Clinic staff also declined participation because their treatment plan differed from those in the other clinics. Still, in less than three years, between September 1964 and February 1967, Hamilton, London, Kingston, Ottawa, and Thunder Bay clinics enrolled 440 patients in the study. This RCT set a Canadian record in terms of patient enrollment and time to study completion.

Brohult performed a series of laboratory and animal experiments with alkoxyglycerol esters and showed that one of its main constituents, selachyl alcohol, reduced the deficiency of cellular elements in the circulating blood associated with exposure to radiation or toxic chemical agents. She obtained selachyl alcohol in quantity from Western Chemicals Ltd., a Canadian company based in Vancouver, which isolated the compound from shark and cod livers. During 1955-1956, Brohult investigated the therapeutic effect of an alkoxyglycerol mixture with selachyl alcohol in a group of about 300 patients suffering from cancer of the uterine cervix, who received a standard treatment of radium and X-rays in Stockholm. See A. Brohult, “Alkoxyglycerols in Irradiation Treatment,” Nature, 193 (31 March 1962): 1304; and A. Brohult “Alkoxyglycerols and their Use in Radiation Treatment: an experimental and clinical study,” Acta Radiologica, 1, Supplement 223 (1963): 7-99, esp. 45.

Brohult, “Alkoxyglycerols in Irradiation Treatment” (1962): 1304.


Within six months after the trial’s termination, however, Warwick concluded, “under the conditions of the experiment, no protective effect [of selachyl alcohol] on blood [was] demonstrated […] Blood studies produced no positive findings and it remain[ed] to be seen whether one group [would] fare better than the other in the matter of survival.”54 In other words, Warwick and his colleagues in Ontario failed to replicate an important part of the RCT done by A. Brohult in Sweden. To repeat the therapeutic experiment from a published account once again proved to be not a straightforward matter. The unsuccessful replication indicated that something was amiss about the trials’ constituents: the quality of administered selachyl alcohol due to differences in its manufacturing process, or the assumption that selachyl alcohol was indeed an active medical ingredient.55 Even so, the main value of Warwick’s RCT was the demonstration that several clinics could cooperate effectively to conduct a clinical investigation of this type.

Meanwhile, mainly small-scale and non-randomized clinical trials took place at the London Cancer Clinic. Through them, Warwick and his medical colleagues tapped into the American chemotherapy program and its pool of investigational new drugs. The Canadian investigators gained access to the US system of drug development and cooperative trials by using experimental agents in trials designed to test their toxicity and antitumor activity. For instance, Thomas A. Watson, who succeeded Ivan H. Smith as Director of the London Clinic in November 1962, expanded the clinical research project of McCredie and Inch on the adjuvant use of chemotherapy and radiation with surgery. On learning about a possibility of treating neoplastic disease in the liver by a prolonged administration of a novel chemotherapeutic agent, FUDR, Watson took the initiative to study it clinically in London.56

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54 Ibid., 9-10.
55 O.H. Warwick admitted that his study did not “correspond exactly with that of Brohult who […] gave to her patients in varying quantities a mixture of the esters of these compounds [alkoxyglycerols]. We used selachyl alcohol for several reasons. It was readily available [from the John Labatt Company Ltd., London, Ontario] in a form easily given [capsules]. It constitute[d] about 60 per cent of the concentrates containing these alcohols and it seem[ed] to be the most effective biologically of this group of alcohols.” Ibid., 2-3.
56 T.A. Watson participated in the fifty-fourth annual meeting of the American Association for Cancer Research, held in Toronto (ON) on 23-25 May 1963, at which Robert D. Sullivan gave a paper on a new method of treatment for cancer of the liver. Sullivan reported on the management of twenty-one patients with primary or metastatic cancer of the liver by the prolonged intra-arterial administration of two antimetabolites: 5-fluorouracil (5-FU) or 5-fluoro-2'-deoxyuridine (FUDR). The latter, in Sullivan’s experience, had a higher therapeutic activity when continuously infused into the liver. Several years earlier, in 1957, two research teams – one led by Charles
Hepatic cancer and secondary tumors in the liver were not amenable to treatment by surgery or radiotherapy, and Watson was concerned about this medical problem. In preparation for the FUDR investigation, he contacted a research group led by an internist Robert D. Sullivan of Lahey Clinic in Boston, Massachusetts, who developed a method of continuous infusion of chemotherapeutic agents.\(^5^7\) Under the auspices of the OCTRF and with Sullivan’s support, Watson obtained the experimental drug FUDR (5-fluoro-2’-deoxyuridine, NSC 27640) with permission of the US Food and Drug Administration from the National Cancer institute (NCI) in June 1965.\(^5^8\) The FDA assigned the drug for clinical investigation to Bruce Barton and David White, attending surgeons of Victoria Hospital in London, who had received training under Sullivan’s guidance in Boston.\(^5^9\)

Conforming to the FDA’s supporting documentation, Barton and White had to use the drug only for a specific purpose stated in the research protocol of a pharmaceutical company, Hoffmann-La Roche Inc., which produced FUDR in Nutley, New Jersey (US). The protocol read,

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\(^5^9\) They received training on a technique for the installation of a continuous infusion portable pump and on particularities of the 5-FUDR administration. In 1963, Elton Watkins, a surgeon at the Lahey Clinic in Boston (MA), invented a Chronofusor, chronometric infusion pump, which allowed a protracted treatment on an outpatient basis and thus made it an almost indispensable piece of chemotherapeutic equipment. See correspondence from T.A. Watson to W.C. Cosbie (Medical Director, OCTRF), London (ON), 23 March 1965; and a Manual of Instructions for Watkins – U.S.C.I. Chronofusor model 5-24, 1965, produced by the United States Catheter and Instrument Corporation of Glens Falls (NY); both documents in the WUA, AFC 328.1.1269. Also, E. Watkins, Jr. “Chronometric Infusor – An Apparatus for Protracted Ambulatory Infusion Therapy,” The NEJM, 269, no.16 (1963): 850-851.
In some types of localized inoperable cancer which show[ed] little or no response to conventional administration of standard chemotherapeutic agents, the therapeutic margin of several drugs [was] increased by continuous 24-hour arterial infusion. 5-Fluoro-2’-deoxyuridine [was] one of these compounds. The purpose of these studies [wa]s to enlarge the clinical experience in regard to the therapeutic and toxic effects of FUDR by continuous arterial infusion.\textsuperscript{60}

Accordingly, Watson drew up another protocol for the clinical investigation of FUDR locally. In a brief to the surgical staff of St. Joseph’s Hospital and Westminster Hospital of London, who joined surgeons at Victoria Hospital in this investigation, Watson explained that it would not be possible to run a control series and that the observed remission would be adequate proof of the effect of the drug. Moreover, Watson recommended, “Initially it would be better to treat only liver metastases and to use a single drug to obtain adequate knowledge about the toxic effects.”\textsuperscript{61} Nevertheless, Watson’s study outline indicated that patients suitable for selection included not only those with liver metastases originating in primary malignancies elsewhere, but also with inoperable cancer of the liver. In general, Watson followed the script of the research protocol provided by the NCI.

In the experimental treatment protocol distributed to the three participating institutions, Watson wrote, “Certain criteria for patient selection, method of therapy, and follow-up [we]re implied in the [FDA] assignment of this drug.” Among those criteria was one that stated, “Moribund patients should not be included in these studies.”\textsuperscript{62} Watson adapted this criterion to the new protocol for London surgeons by adding certain qualifications. Hence, the London protocol stipulated that patients considered for FUDR treatment should have “average intelligence […] should be psychologically stable and not moribund.”\textsuperscript{63} More importantly, Watson specified that the patient should have “where practical, knowledge of his disease, its extent, and the ramifications of this type of therapy.”\textsuperscript{64} Put differently, Watson urged the doctor-

\begin{footnotesize}
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\item 60 No author, \textit{Protocol for the Study of Continuous Arterial Infusion of FUDR}, June 1965; in the WUA, AFC 328.1.1269.
\item 61 T.A. Watson, “Treatment of Hepatic Metastases by Continuous Intra-arterial Infusion,” p.1; in the WUA, AFC 328.1.1269.
\item 64 \textit{Ibid.}
\end{itemize}
\end{footnotesize}
researchers to seek informed consent from his patient-subjects. This was significant because the surgical operation of inserting a catheter (flexible tube) to administer 5-FUDR into the liver artery and the administration of the drug itself posed a high risk of a fatal outcome.

Informing patients of their disease and the potential implications of treatment that bordered on clinical research seemed to be a matter of relative importance among Canadian investigators in the mid-1960s. It was the case especially in the RCTs that aimed at assessing subtle changes in the standard treatment for particular malignancies. Those marginally new approaches to treatment jeopardized patients’ health almost to the same extent, according to the doctor-researchers, as conventional therapy. A controlled trial of preoperative Cobalt-60 irradiation in the surgical treatment of patients with cancer of the rectum illustrates this well.

Walter D. Rider, a senior radiotherapist at the OCI/PMH, launched this clinical study drawing on experimental work of American radiologists W.E. Powers and L.J. Tolmach, both of the Edward Mallinckrodt Institute of Radiology in St. Louis, Missouri.65 They showed that a single radiation dose of 500 rad followed immediately by surgical removal of the tumor in mice contributed to the animals’ survival more than surgery or radiotherapy alone. To Rider, this therapeutic approach appeared not just useful for the cancer patient, but also convenient in terms of the duration of hospital care. A conventional course of radiotherapy before surgery required a few visits to the hospital or a short-term hospitalization, whereas radiotherapy and surgery administered in one day eliminated the latter requirement. Limited resources of equipment-time and hospital-space could be used more economically in addition to possible therapeutic benefits for patients.

After due considerations, radiotherapist W.D. Rider and two surgeons, J.A. Palmer of the Toronto General Hospital and L.J. Mahoney of St. Michael’s Hospital in Toronto, prepared a protocol for the clinical investigation of the operable cancer of the rectum.66 All surgeons who operated on rectal cancer in the Toronto area received the protocol with an invitation to admit

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65 Powers and Tolmach suggested in their conclusion that “relatively small doses of radiation administered pre-operatively may be useful in increasing the cure rate in those clinical situations in which surgical extirpation of a tumour is expected to be followed by a significant incidence of local recurrences or metastases resulting from operative dissemination of tumour cells.” See William E. Powers and L.J. Tolmach, “Pre-operative Radiation Therapy: biological basis and experimental investigation,” *Nature*, 201 (18 January 1964): 273.

eligible patients into the study. To answer the question on the merit of single pre-operative irradiation in a statistically significant manner required the admission of no fewer than two hundred patients.\(^{67}\) This meant that the patient enrolment in the RCT needed to have no unnecessary hindrances, since the incidence of that type of cancer was rather low. One such hindrance was a documented consent of the patient to participate in the trial, so the doctor-researchers informed patients only verbally, “this treatment was being given in the hope of improving their chances of cure.”\(^{68}\) Asserted Rider, “At the time this trial was started [in July 1965] consent, informed or otherwise, was not in vogue.”\(^{69}\) He seemingly stated the obvious, but not all investigators followed the fashion of the day in clinical investigations.

Arthur Bryant, a therapeutic radiologist and director of the Allan Blair Memorial Clinic in Regina, Saskatchewan, affirmed the wide acceptance of a fashion for the RCT, but not for the substitution of the doctor-researcher’s will for that of his patient-subject. In January 1964, Bryant undertook to study the value of prophylactic oophorectomy (a surgical removal of ovaries) in patients with operable carcinoma of the breast.\(^{70}\) Together with his co-workers in the Grey Nuns’ Hospital, Bryant conducted the trial that randomized patients into two groups: the first group of premenopausal women had their ovaries surgically removed and the second – had not. Surgeons performed oophorectomy at the time of hospital admission for initial breast surgery. Radiotherapy of the breast region, which differed in extent depending on cancer stage I or II, followed surgical operations in both groups of patients. A.J.S. Bryant and James A. Weir, a chief surgeon for this study, described the procedure of randomization thus,

Those patients assigned to the oophorectomy series were at liberty to decline oophorectomy, on the basis of informed consent and after due explanation. The family practitioner or the surgeon could also decline on behalf of the patient. If oophorectomy was declined, the card [of the control or oophorectomy series] was

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\(^{69}\) *Ibid*.

Although the number of patients declining oophorectomy were few, a measure of bias was introduced, but this inevitable on ethical grounds.71

This passage suggests that Bryant loosened the standards of ethics of the scientific-medical community, which stated that not strictly observing the randomization rules was unethical, in favor of some patients’ subjective preferences. Permission of the patient in this case may have interfered with objectivity of the clinical study. Patients’ preferences could also contribute to a slow progress of trial enrolment. This happened to a second RCT under Bryant’s direction. The trial’s objective was to assess comparatively the therapeutic use of surgical oophorectomy and the administration of testosterone (a male steroid hormone) in the treatment of advanced and disseminated breast cancer. In contrast to the admission of 213 patients into the first RCT during a four-year period, there were just twelve patients entered into the second trial over three years, which led to its abandonment.72

It is noteworthy that Bryant initiated both RCTs at the suggestion of Ralston Paterson.73 Paterson reported five-year survival results of two RCTs in breast cancer – one on the value of ovarian sterilization by irradiation in a menopausal group of women and the other evaluating a prophylactic postoperative radiotherapy of the breast region following surgery – which provided leads that Bryant pursued to design follow-up clinical studies. Importantly, Paterson began his discussion on the RCTs with a few comments about the ethics of conducting controlled trials.

There was a proven way to avoid dealing with ethical issues of the RCTs and to make a fast-track completion of clinical studies possible. It was not to engage in randomized trials, but to continue using an empirical method for testing treatments, which disregarded a random selection of patients. In Saskatoon, for instance, Charles C. Burkell, a therapeutic radiologist and director of the Cancer Clinic, carried out a non-randomized trial of surgical and radiological oophorectomy in premenopausal patients with stage II breast cancer who had a primary

73 Ralston Paterson, “Breast Cancer: A Report of Two Clinical Trials,” Journal of the Royal College of Surgeons of Edinburgh, 7, no.4 (July 1962): 252-253. Paterson proposed that other investigators explore whether surgical oophorectomy could do more than ovarian irradiation and whether the planned use of androgens (male sex hormones) in tolerable dosage could further enhance survival of patients with advanced cancer of the breast.
mastectomy. For patients with advanced malignancies, including carcinoma of the breast, Burkell and his co-workers had chemotherapeutic agents that required further clinical evaluation. As the Department of Therapeutic Radiology was a member of the Western Division of the Clinical Drug Evaluation Program funded by the US NCI, access to new investigational drugs was open. Over 1962-1965, physicians at the Saskatoon Cancer Clinic used Vincristine, 5-Fluorouracil, and L-Sarcolysin to treat patients and to investigate the agents’ corollary effects. There were no controls in the breast cancer trials that Burkell coordinated at the same time as Bryant led similar randomized studies. In all probability, Burkell wanted to validate results from the American and British controlled trials, whereas Bryant’s aim was to find out something previously unproved by means of RCTs.

Ralston Paterson’s insights into the potentially testable treatments for breast cancer were also consequential for doctor-researchers in Toronto who followed the developments of the American National Surgical Adjuvant Breast Project (NSABP) that had launched a series of controlled cooperative trials in the management of breast carcinoma since 1961. At the OCI/PMH, a physician-endocrinologist William Meakin and a number of his colleagues undertook an elaborate and ambitious RCT. Succinctly named “Ovarian Irradiation and Prednisone Following Surgery for Carcinoma of the Breast,” the trial evaluated whether a prophylactic suppression of the female hormone production could delay cancer recurrence and prolong the duration of patients’ survival. The experimental design of this RCT, which began

74 The NIH grant of $10,200 was the largest among the other three operational grants in 1962-1963, and this trend continued during the indicated years. See Charles C. Burkell’s annual reports of the Department of Therapeutic Radiology for 1962-1966, enclosed with memoranda from C.C. Burkell (Professor and Head of Therapeutic Radiology) to R.W. Begg (Dean of Medicine, University of Saskatchewan), between 25 July 1963 and 6 July 1966; in the USL, College of Medicine f2087, Ad.7, 18B(3).
75 David G. McGowan, a Lecturer in Therapeutic Radiology at the University of Saskatchewan, launched a RCT comparing the treatment of glioblastomas with Cobalt-60 radiotherapy and Vincristine against radiotherapy alone in 1966, at which time Peter Coy continued a similar controlled trial in lung cancer in Vancouver (BC). There was an obvious connection between them. See “Report to the President for 1966-67, Department of Therapeutic Radiology,” p.3; ibid.
in June 1965, comprised three series of patients randomly selected after a primary breast surgery and a conventional post-operative radiotherapy. Series one had patients aged 35-44 with breast cancer of stages II and III who were assigned into a treated group receiving Cobalt-60 irradiation of the ovaries in the amount of 400 rad daily for five days, and a control group that had no further treatment beyond their initial surgery and radiotherapy. In series two, 45-59 year-old patients who had breast cancer of stages I, II, and III were randomized into three groups: the first group received ovarian radiation as in series one, the second group – the same irradiation along with 2.5 mg of prednisone every eight hours, and the third group was control. Series three included patients aged sixty and over with breast cancer of stages I, II, and III, randomly divided into three groups as in series two.79 Such a stratification of patients was necessary to determine if any adjuvant treatment regimen had benefits, or otherwise, for patients.

This study became possible through surgeons’ patient referrals from the Toronto area to whom Meakin and his co-workers distributed informative memoranda on the clinical study. To ensure that this RCT met the contemporary ethical norms, Meakin included in the protocol a few criteria of non-eligibility for the investigation, among which stood out “lack of consent from the referring doctor, the patient or the spouse.”80 The order of importance in the latter wording seems no less surprising than the use of conjunction ‘or’ instead of ‘and’, but those meaningful details lend themselves to an explanation in light of another aspect of the study.

Among investigators participating in this RCT were surgeon John L. Hayward of Guy’s Hospital and biochemist Richard D. Bulbrook of the Imperial Cancer Research Fund (ICRF) in London, England. They collaborated with Canadian doctor-researchers in an effort to find a test of hormone dependence in breast cancer patients. By separating patients into two groups – one with hormonally responsive and the other with hormone-independent tumors, the investigators could potentially demonstrate a more marked effect of therapy inhibiting the secretion of

hormones in one group. Moreover, such a diagnostic test might spare the hormone-independent fraction of patients from the useless additional treatments. The ICRF sponsored this part of the clinical study and therefore required that the research protocol conformed to the guidelines of the Medical Research Council (MRC) in Great Britain. In its 1963 statement on investigations with human subjects, the MRC executives emphasized that “any doctor taking part in such a collective controlled trial [was] under an obligation to withdraw a patient from the trial, and to institute any treatment he consider[ed] necessary, should this, in his personal opinion, be in the better interests of his patient.” It is likely for this reason the research protocol foregrounded the consent from the referring doctor in place of the patient’s consent.

Building on the MRC recommendations, J.L. Hayward, a co-investigator in Meakin’s trial, formulated five ethical principles relevant to the RCTs of cancer treatment innovations. Hayward publicly presented the principles to the scientific-medical community at the Ninth International Cancer Congress held in Tokyo on 23-29 October 1966. In his paper, Hayward also explained why the patient’s consent should be secondary to that of physicians or surgeons referring the patient to a particular RCT. Hayward noted,

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81 With this aim, investigators correlated urinary hormone excretion with the clinical course of the patients. Urine collections from all patients admitted into the RCT were done at the OCI/PMH, but the specimens underwent required analyses at the ICRF. See the OCTRF, *Annual Report 1965-1967*, p.166; in the USL, MG 404, box 11.

82 Both the OCTRF and ICRF funded this RCT. See Meakin et al., “Ovarian Irradiation and Prednisone Therapy Following Surgery and Radiotherapy for Carcinoma of the Breast” (1979): 1229.


84 John L. Hayward, “Ethics in Clinical Trials,” in *Proceedings of the 9th International Cancer Congress*. UICC Monograph Series 10, ed. R.J.C. Harris (Berlin; Heidelberg: Springer-Verlag, 1967), 208. The principles Hayward proposed were: “1. It is unethical to attempt to analyse the effect of a treatment by the haphazard and uncontrolled administration of that treatment. 2. It is unethical not to carry out a clinical trial when there is doubt whether a new treatment is better than an established treatment. 3. It is unethical to conduct a clinical trial unless the clinical and statistical design of the trial is appropriate. 4. It is unethical to carry out a clinical trial without due responsibility for the patients’ care and, if the procedures do not contribute to the benefit of the patients, without their understanding and permission. 5. It is unethical to terminate a clinical trial unless a meaningful result has been obtained.”
This perhaps is the nub of clinical experimentation – that it is the investigator’s own belief – or preferably that of a group of investigators – that what is being done is justified on moral grounds. The acceptance by the patient himself is not sufficient, because it is only too easy to persuade him to undergo almost any procedure the doctor suggests, due to the special relationship between them.  

The statement shed light on two significant and interrelated ethical issues in the RCTs: manipulation and justification. Through manipulation of specialized information, doctor-investigators could justify almost any clinical trial to patient-subjects. Moreover, a consensus among doctor-investigators on what was acceptable as the RCT could render manipulations legitimate in a particular place and time, but unjustifiable in others. For this purpose of reaching a group consensus on the appropriateness of investigations, granting institutions, like the MRC in Great Britain and the NIH in the United States, encouraged a peer-review process that warranted apparently irreproachable clinical studies deserving of the public support. The MRC in Canada arose from similar considerations: first concentrating research expertise to assess the projects and, second, delegating the implementation of investigations to clinicians in the framework of a local best practice.

4.2. Clinical Trials and Human Subject Research Ethics

A formal establishment of the Medical Research Council of Canada (MRC) in November 1960 indicated that the number and diversity of investigations in medicine and related fields reached unmanageable proportions. The Division of Medical Research under the National Research Council (NRC) could not process a barrage of grant applications satisfactorily which thus necessitated its re-organization.  As an autonomous body within the NRC, the MRC had more capacity for an adequate review of applications for support of medical research, especially in the domain of clinical investigation. The MRC came into being as NRC executives realized that no one province in Canada had enough experts in medical sciences to evaluate the pros and cons of

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85 Italics added. Ibid., 207.
87 The MRC Executive Committee formed four sub-committees: bacteriology and pathology, biochemistry, clinical investigation, physiology and pharmacology. Ibid., 1198.
projects. A more flexible evaluation through co-opting investigators was necessary for administering grants-in-aid of research by the MRC. Accordingly, a referee-report system enabled the MRC to decide more efficiently whether to approve requests for research funding or not. For instance, the MRC provided a reduced grant to Gordon M. Wyant, Professor and Head of the Department of Anesthesiology at the University of Saskatchewan, in March 1961, while the same project, entitled “The Effect of Different Anesthetic Drugs and Techniques upon Cardiac and Circulatory Dynamics in Anaesthetized Man,” had raised no objections a year earlier. Wyant proposed to expand his investigative program on new anesthetic agents developed for use in different surgical interventions.

The MRC executive committee “encumbered $3,000 pending approval of the University [of Saskatchewan] faculty of use of volunteers on this project.” Out of $8,000 requested, Wyant reserved $3,000 to pay approximately fifty volunteers needed for clinical studies of anesthetics. Inasmuch as the MRC had no regulations on human subject research in 1961, it sought an institutional approval to do this kind of clinical investigation from a local committee. As Joseph Auer, the MRC Secretary, wrote to Wyant, “The Council was somewhat reluctant to approve the use of volunteers on this project, but agreed that this would be permissible if it were sanctioned by the Medical Faculty of your University.” There was little delay with approving the project by the ad-hoc faculty committee because hardly any extramural bodies required an official confirmation that proposed investigations were within acceptable limits of human experimentation.

Moreover, the university hospital policy on human experimentation was established since September 1956. At the time, the Committee on Scientific Affairs (CSA) brought up the topic of responsibility of investigators and of the university for the risks involved

88 John B. Armstrong “Whither M.R.C?” 29 June 1965, p.4, enclosed with a letter from J.B. Armstrong (Executive Director, Canadian Heart Foundation, Toronto) to R.W. Begg (Dean of Medicine, University of Saskatchewan), Toronto, 12 July 1965; in the USL, R.W. Begg, f054, MRC – 4a.
89 Medical Research Council, Proceedings of the First Meeting, Ottawa, 8-10 March 1961, E-25; in the USL, Begg f054, 4b. Also, correspondence on the approval of G.M. Wyant’s NRC of Canada (Division of Medical Research) application, Saskatoon, 24 November 1959; in the USL, College of Medicine f2087, Ad.7/2(4).
91 J. Auer to G.M. Wyant, Ottawa, 22 March 1961; in the USL, f2087, Ad. 8/2(7a).
92 Dean of Medicine J. Wendell Macleod endorsed an ad-hoc committee decision-making on clinical research not only because this way “in most cases it could be done very speedily,” but also because “it would have the value of acquainting a larger number of people with work that [wa]s going on in one or another department.” See a memorandum from J.W. Macleod to G.M. Wyant, Saskatoon, 18 July 1955; in the USL, f2087, Ad. 7/2, 2/1.
in experiments carried out on human volunteers.\footnote{On motion of Irwin Hilliard, Professor and Head of Faculty of Medicine, seconded by G.M. Wyant, the committee asked the Faculty of Medicine to approve that “Research projects, which include human volunteers, be submitted to the Committee on Scientific Affairs for approval before the project is undertaken. This Committee should also be empowered to consult outside experts.” See \textit{Minutes of the Meeting of the Committee on Scientific Affairs}, Saskatoon, 28 September 1956; in the USL, f2087, Ad. 8/2(7b).} Within a year, the CSA elaborated a registration procedure for research projects involving humans.\footnote{The grounds for completing the registration forms for such clinical investigations were manifold: special insurance protection, faculty support of the investigator in adverse circumstances, possibilities for collaboration, Dean’s familiarity with ongoing projects. Concerning the latter, Dean J.W. Macleod noted in September 1957 that he was aware of all research applications to the NRC, NCIC, and Public Health Grant, but on the projects funded from private sources and the DRB he was uninformed. See \textit{Minutes of the Meeting of the Committee on Scientific Affairs}, Saskatoon, 25 September 1957 and 17 April 1959; in the USL, f2087, Ad. 8, 2/7b.} The procedure was as follows. The department head in charge of any project including experiments with humans in which there seemed to be a possibility of risk presented the project to Dean of the College of Medicine. Then, the Dean discussed the matter with an ad-hoc committee, comprising at least two clinicians from other departments who were competent to assess the project, and interview the investigator. Next, the committee’s recommendation would be cleared by the hospital and university administration.

Following this procedure, the project proposed by Wyant received approval of the ad-hoc committee assembled by Dean J. Wendell Macleod.\footnote{The committee, which included R.W. Begg (Director, Saskatchewan Cancer and Medical Research Institute), L.B. Jaques (Head, Department of Physiology and Pharmacology), and J.W. Macleod (Dean, College of Medicine), reviewed the proposed clinical study of anesthetics in male subjects between the ages of 21 and 35 who were not medical students. Importantly, Begg and Jaques asked the Dean at the end of the review “to check with the Controller’s Office on the point of whether our liability insurance was properly in effect.” Later, the Controller John A. Pringle reported that the university maintained its liability policy covering to certain limits the university employees in case of their negligence. See a memo from J.A. Pringle to J.W. Macleod, 26 May 1961, and enclosed with it J.W. Macleod’s note on “Meeting of Ad Hoc Committee to Scrutinize Research Applications Entailing the Use of Human Volunteers,” 20 April 1961; in the USL, f2087, Ad. 8, 2/7a.} Accordingly, the MRC released Wyant’s annual grant of partial encumbrance and awarded $3,000 by the executive action in May 1961.\footnote{MRC, \textit{Proceedings of the Second Meeting}, Ottawa, 8-10 June 1961, A-3; in the USL, Begg f054, 4b. Also, J. Auer to G.M. Wyant, “Re Annual Grant MA-1137,” Ottawa, 24 May 1961, in the f2087, Ad. 8, 2/7a.} Why did the MRC become suddenly alert to the possibility of assuming legal liability for the human subject research funded by it? This circumspection likely issued from the contemporary developments in the United States, where public disclosures on the ethics of clinical investigations entered the mass media.
Since the American ruling on *Salgo v. Leland Stanford Jr. University Board of Trustees* by the California Court of Appeals in 1957, the theme of human experimentation in teaching hospitals gained public currency. This case revealed the “conspiracy of silence” among members of the medical profession on the subject of clinical research without adequately informed consent of the patient. Still, the court had no intention to “hamstring the development of medical science.” By doing so, the judges could alienate enterprising physicians and surgeons who did not want any obstruction of their investigational practices with an exact requirement to disclose potential dangers of particular experimental treatments. Wrote Justice A. Francis Bray, “… each patient presents a separate problem, that the patient’s mental and emotional condition is important and in certain cases may be crucial, and that in discussing the element of risk a certain amount of discretion [on the doctor’s part] must be employed consistent with the full disclosure of facts necessary to an informed consent [of the patient].” The implication was that the doctor-investigator still had a prerogative to decide what amounted to a fully-informed consent.

Stories about allegedly widespread suspicious medical practices multiplied through news reports that provoked the popular imagination. Likewise, in the specialized literature, professionals discussed analogies between medical research and experiments on humans. One of such influential discussions appeared in the *Journal of the American Medical Association*, wherein Henry K. Beecher, Professor of Research in Anesthesia at Harvard University and Anesthetist-in-Chief of the Massachusetts General Hospital in Boston, published a report to the US Council on Drugs “Experimentation in Man” in 1959. The article was reprinted in book

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97 *Salgo v. Leland Stanford Jr. University Bd. of Trustees*, 154 Cal. App. 2d 560 (22 October 1957): 569. This judgment concerned the liability of Stanford University Hospital personnel for an unsuccessful experimental treatment of a fifty-five year-old Martin Salgo who consented to it without knowing important details of the procedure. Having received a preliminary diagnosis of an advanced arteriosclerosis aggravated by a block in his abdominal aorta, Salgo underwent a relatively new procedure of arteriography. The latter included insertion of the needle to inject a contrast medium into the abdominal aorta and a radiographic visualization of the artery by X-rays to discover the blocked area. An anesthesiologist, a surgeon, and a radiologist were involved in the procedure that resulted in the paralysis of the patient’s lower extremities. Following this, Salgo initiated a malpractice action in which he claimed that his injury would not have happened without negligence and that necessary facts to form the basis of his consent to the performed procedure had been withheld.

98 Ibid., 570.


format and received an extensive coverage in the press. A physician-investigator himself, Beecher reviewed controversies involving medical research and its ethics in Great Britain and the United States over the 1950s. On several occasions did Beecher stress the significance of professional group decision-making supported by an appropriate and independent consultative body. According to Beecher, clinical researchers should follow this two-step procedure in addition to obtaining the patient’s consent because in the event of a negative outcome of the experiment, even without obvious negligence, the judicial arbiters may have less doubt as to its ethical grounds.

Beecher’s publication did not escape the attention of the Canadian MRC members. They probably noticed some points of convergence in the clinical research program of physician-anesthesiologist G.M. Wyant of the university hospital in Saskatoon and the issues of human experimentation considered by anesthetist-researcher H.K. Beecher. Wyant was more than familiar with the American practices in clinical and experimental medicine. Before his appointment as Professor at the University of Saskatchewan and Department Head of Anesthesia at the newly-opened university hospital in 1954, Wyant spent his four formative years of clinical research in Chicago, Illinois. Having worked in the rank of assistant professor at the Division of Anesthesia at the University of Illinois during 1950-1952, Wyant was appointed Professor and Head of Anesthesiology, at Stritch School of Medicine, Loyola University, and Director of

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102 Ibid., 26 and 64-68. In his argument, Beecher drew upon the authoritative views of Michael B. Shimkin, an American cancer specialist heading the NCI Biometry and Epidemiology Branch, and James M. Mackintosh, a British Professor of Public Health at the University of London who consulted the United States Public Health Service.
103 In 1961, the MRC invited H.K Beecher, Dorr Professor of Research in Anaesthesia, Harvard University, to one of its annual meetings in Canada. Sponsored by the MRC, Beecher participated in the Sixteenth Annual Scientific Meeting of the Western Regional Group held at Suffield Experimental Station, Ralston (AB), on 28-31 January 1962. Both the MRC and the NCIC funded the meeting that provided a discussion forum for more than 120 medical scientists from Western Canada. Beecher gave a guest lecture on “Non-specific Forces Surrounding Disease and the Treatment of Disease,” in which he argued that a placebo action in medicine indicated that therapeutic effects of a drug or a procedure correlated significantly with a mental state of the patient; thus the physician’s approach, the doctor-patient relationship, and the environment of treatment should be considered in every case of disease. See “Report of the 1962 Meeting of the Western Regional Group of the Medical Research Council of Canada and the National Cancer Institute of Canada,” enclosed with correspondence from Murchie K. McPhail (Defence Research Board, Suffield Experimental Station) to R.W. Begg (Dean of Medicine, University of Saskatchewan), Ralston (AB), 5 April 1962; in the USL, f2087, MR. 4, 4/1.
Anesthesia at Mercy Hospital of Chicago in 1953.104 Both universities constituted a part of the Research and Educational Hospitals in the Chicago area and had strong connections with pharmaceutical companies that supplied promising drugs for clinical evaluation.105 Thus, Wyant brought to Saskatoon not only his clinical expertise in anesthesia, but also his academic network and corporate connections.

In his major project on the effects of anesthetic agents and techniques on humans, Wyant collaborated with John E. Merriman, Director of the Cardio-Pulmonary Laboratory at the Department of Medicine of the University of Saskatchewan.106 Merriman joined the medical college as assistant professor in Physiology and Pharmacology also in 1954. His appointment followed a two-year stint as Instructor at the Department of Physiology at the University of Western Ontario over 1952-1954 and a year in the capacity of Research Fellow in Medicine at Harvard Medical School in Boston.107 From July 1951 until August 1952, Merriman worked simultaneously as Assistant in Medicine at the Peter Bent Brigham Hospital in Boston and as Research Fellow in Medicine at the Boston Lying-in Hospital. Equipped with this clinical experience, Merriman found himself on common ground with Wyant.

Cooperation between Wyant and Merriman in the clinical studies of newly developed anesthetics proved fruitful. In late May 1961, Wyant received an annual operating grant from the newly formed MRC. Together with Merriman, Wyant proposed to “study the effect of different anaesthetic drugs, techniques and respiratory patterns upon pulmonary circulation in volunteers at different depths of anaesthesia with incidental observations on cardiac output, peripheral

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104 Interestingly, Warren H. Cole, Professor of Surgery, and Max S. Sadove, Professor of Anesthesia (both of the University of Illinois) provided references for the candidacy of G.M. Wyant for the senior appointment at the University of Saskatchewan. See “Curriculum Vitae of Gordon Michael Wyant,” p.2; in the USL, f2087, Ad. 7/2, 2/1.
105 Ibid., 3. Wyant noted that much of pharmacology and clinical evaluation work involved controlled experiments on human volunteers.
106 G.M. Wyant, National Research Council of Canada Application for Grant in aid of Research (Division of Medical Research), Saskatoon, 30 November 1960; in the USL, f2087, Ad.7/2, 4.
107 The NRC of Canada awarded Merriman a Graduate Medical Research Fellowship to pursue studies in physiology at the UWO. See Merriman, John Edward. Curriculm Vitae and Publications, enclosed with “Nomination of Dr. J. Merriman for a John & Mary R. Markle Scholarship in Medical Science from the Department of Physiology & Pharmacology, University of Saskatchewan,” L.B. Jaques to J.W. Macleod, 26 October 1954; in the USL, f2087, Ad. 7/7, 2/2.
circulation and circulation time.” The investigators’ objective was to find the anesthetic drug and technique that affected heart and lung function, particularly the pulmonary circulation, in the least harmful way. What constituted a danger was a marked rise in a mean pulmonary artery pressure concurrently with a deepening level of sedation effected by the anesthetic agents in use. Trying to obviate this problem, Wyant and Merriman had already performed twelve pilot studies and forty-five clinical experiments using a number of new drugs and techniques for light and moderate anesthesia before launching a series of trials with volunteers to test anesthetic agents at deeper levels of anesthesia.

The procedure was quite complicated, however. Without pre-medication, a volunteer had a cardiac catheter passed through the vein of the arm and into the heart to reach the pulmonary artery. The investigators then made necessary determinations of the blood pressure along with the cardiac output and advanced the catheter further along the pulmonary artery with simultaneous and continuous recording of the electrocardiogram. To monitor levels of sedation and maintain a necessary depth of anesthesia constant, electroencephalograph leads were connected to the volunteer’s head. Next, the volunteer received a low dose of anesthetic and a muscle relaxant to introduce a tube via mouth and down the windpipe into the lung. This tube traced pressures inside the lungs. The entire trial, which included some technical preparations and a post-study observation, would take about three hours in the hospital. For this, each volunteer was eligible for a remuneration of fifty dollars, transportation and meal on the day of the trial.

By August 1961, Wyant and Merriman successfully completed a number of clinical tests with volunteers who had found out about the study through the city employment office. Also at this time, the pharmaceutical companies E.R. Squibb & Sons of Canada Ltd. and Ohio Chemical Canada Ltd. of Montreal, which supplied experimental anesthetics, provided respectively $500 and $300 as grants-in-aid of research under Wyant’s direction. Additionally, the Ohio

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109 Ibid., 3. At the time Wyant’s research group investigated the technique of administering nitrous oxide anesthesia with muscle relaxants (atropine) and the effect of methoxyfluorane, supplied by Abbott Laboratories Ltd. of Montreal, Québec.
110 Ibid.
111 Memorandum from G.M. Wyant to J.W. Macleod, Saskatoon, 14 August 1961; in the USL, f2087, Ad.7/2, 4.
Chemical Canada Ltd. made available a novel trifluoroethylvinyl ether registered under the trademark Fluoromar for a clinical evaluation. Although Fluoromar had undergone preliminary clinical investigations in the United States, it did not have a detailed pharmacological assessment until Wyant and Merriman performed it in Saskatoon. Consequently, the Ohio Chemical and Surgical Equipment Company of Madison, Wisconsin, authorized its Canadian branch to fill this gap in clinical knowledge about the anesthetic agent.

In a series of investigations at the university hospital in Saskatoon, just one unforeseen contingency in a relatively well-tested procedure of a complicated clinical trial sufficed to cause harm to the human subject’s health and to draw in the court of law. Between a medical and a judicial intervention, a human drama unfolded. On 21 August 1961, a second-year engineering student at the University of Saskatchewan, Walter Halushka, presented himself at Wyant’s office on advice from the “Unemployment Commission” where he had enquired about employment availability. Having explained in general terms the essence of the new drug test to Halushka, Wyant assured him that it was a safe test that had been conducted many times previously and that he should not worry about anything. Yet, Wyant did not mention that he had had little experience with using Fluoromar. Nor did he tell Halushka details on the invasive procedure, specifying only that the tests would involve the catheterization of arteries and veins under local anaesthesia, with monitoring of those parameters by means of electronic equipment and injection of a dye; that after these base line investigations had been completed an anaesthetic would be administered for approximately ½ hour to 45 minutes and the same parameters measured again under anaesthesia.

A general consent form that Halushka had to sign prior to the study named “Heart & Blood Circulation Response under General Anaesthesia” did not contain particulars of the procedure.

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113 By this phrase Wyant meant the government’s Unemployment Bureau. See G.M. Wyant, “Report on Cardiovascular Experiment Carried Out on Mr. Walter Halushka, Aug. 23, 1961,” 30 August 1961, p.1, enclosed with a memorandum from J.W. Macleod to J.A. Pringle, 1 September 1961; in the USL, f2087, Ad. 8, 2/7a.
114 Ibid. Wyant used the cardio-green dye dilution method to determine cardiac output. See G.M. Wyant, National Research Council of Canada Application for Grant (1960), 3.
either. On reading the form, Halushka asked Wyant about the meaning of the word “accident” in the text. As an answer, Wyant offered the example of “falling down the stairs at home after the test and then trying to sue the University Hospital as a result.” Provided with this information on the clinical experiment, Halushka signed the form in the presence of a witness and agreed to report to the university hospital on 23 August 1961.

The test with Fluoromar started that day according to plan. Wyant followed the well-known procedures without a problem until it was time to increase the agent’s concentration to reach a deep level of anesthesia. This was necessary for the determination of possible physiological aberrations due to the circulating drug. In the course of this final experiment, Halushka suffered a heart arrest for ninety seconds. He had to experience resuscitation by a close-chest heart massage and then a surgical intervention to perform a direct manual cardiac massage. The administration of emergency drugs stimulating the heart and decreasing the brain swelling followed. Halushka was unconscious for some time and remained in hospital over fourteen days. In addition, a brain damage ensued from a temporary heart stoppage, which amounted to Halushka’s diminished mental ability in terms of concentration and reasoning. As a result, Halushka had to leave the university.

In view of his physical and mental injuries, Halushka went to court and claimed for damages on the grounds of trespass to his person and negligence. The rationale for Halushka’s decision was the absence of his truly informed consent based on a full disclosure of the nature of conducted clinical research. Put differently, the investigators failed to fulfill their duty to explain potential risks and consequences of the experiment. Justice Reginald M. Balfour of the

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115 The form read, “The tests to be undertaken in connection with this study have been explained to me and I understand fully what is proposed to be done. I agree of my own free will to submit to these tests, and in consideration of the remuneration hereafter set forth, I do release the chief investigators, Drs. G. M. Wyant and J. E. Merriman their associates, technicians, and each thereof, other personnel involved in these studies, the University Hospital Board, and the University of Saskatchewan from all responsibility and claims whatsoever, for any untoward effects or accidents due to or arising out of said tests, either directly or indirectly. I understand that I shall receive a remuneration of $50.00 for each test [next line] a series of One tests.” See Halushka v. University of Saskatchewan et al., Saskatchewan Court of Appeal (1965), 53 D.L.R. (2d), 438.

116 Ibid., 438.

117 G.M. Wyant, “Report on Cardiovascular Experiment Carried Out on Mr. Walter Halushka, Aug. 23, 1961,” 2-3. The drugs administered intravenously were phenylephrine (0.5 mg), atropine (0.4 mg), and urea (90 mg).

118 Halushka v. University of Saskatchewan et al. (1965), 441.

119 Ibid., 440.
Saskatchewan Court of Queen’s Bench found this case actionable and proceeded to adjudicate it sitting with a jury. The validity of Halushka’s consent to the medical experiment under the circumstances was the major issue before the jury. That Wyant and Merriman admitted the causative relation between the use of Fluoromar and the heart arrest made the jury’s task somewhat easier. Further, the expert testimony of internist-nephrologist Marc A. Baltzan of St. Paul’s Hospital and the University Hospital in Saskatoon, who reckoned that Wyant and Merriman performed the clinical test well and without obvious negligence, allowed the jury to focus on the issue of consent. Having considered pertinent aspects of this issue, the jury arrived at a verdict that the defendants Wyant and Merriman were guilty not of malpractice, but of negligence in explaining fully the details and dangers of the proposed test, which compromised the obtained consent. The jury awarded the plaintiff Halushka damages of $22,500. This compensation was significant, but even more so was the damage to the reputation of the investigators, and, by extension, the image of the institution that employed them.

As soon as the court delivered its judgement in October 1963, Wyant sent a confidential letter to J.W.T. Spinks, President of the University of Saskatchewan. In this letter, Wyant wrote that “much adverse publicity in the news-media” had resulted from a “fairly severe judgement” against him as one of the defendants in the lawsuit. Therefore, he was “particularly concerned that this publicity involved to a marked degree the University also, and that it may well have damaged the reputation of the University and the College of Medicine in the eye of the public.” In this connection, Wyant humbly suggested to Spinks that he could resign if this action was in the best interests of the University of Saskatchewan and its hospital.

Having received a copy of Wyant’s letter to Spinks, the new Dean of Medicine R.W. Begg forwarded one note to Wyant and another to Spinks. In a communication to Wyant, Begg assured him of a personal support in anything needed to vindicate himself and the Department of

120 See Judgment of the Honourable Mr. Justice R.M. Balfour, with a Jury, 18 October 1963 (Q.B. 146 of 1962), attached to the Judgment in the Court of Appeal for Saskatchewan on Appeal from the Court of Queen’s Bench Judicial Centre of Regina, 29 September 1964; in the PAS, Court of Appeal, 5249, University of Saskatchewan et al. vs Walter Halushka.
121 Ibid., 5.
122 G.M. Wyant to J.W.T. Spinks (President, University of Saskatchewan), Saskatoon, 21 October 1963; in the USL, f2087, Ad. 7/2, 2/1.
123 Ibid.
Anaesthesia.\textsuperscript{124} In a memo to Spinks, Begg pointed out that Wyant had discussed this matter with him and sincerely considered that giving an opportunity to President Spinks to demand Wyant’s resignation would contribute to less embarrassment for all involved parties. Besides, Begg expressed his view on the case, “My own feeling is that Dr. Wyant is a victim of circumstances, rather than any improper or negligent conduct.”\textsuperscript{125} At the suggestion of Begg, Spinks and Wyant talked the whole matter over and agreed to let it rest pending hearing of the appeal against the decision in a higher court. Spinks confirmed his considerations in writing:

> It also seemed to me that you [Wyant] had met the requirements of the College of Medicine Committee on Scientific Affairs for this particular experiment. I should add, however, that I feel that if the appeal goes against us, some sort of enquiry will be necessary so that the [university hospital] Board may be informed of the adequacy or otherwise of the present rules and regulations relating to research involving humans.\textsuperscript{126}

Unwilling to face any decision of the Saskatchewan Court of Appeal unprepared, Begg initiated an enquiry into the state of affairs regarding human experimentation in teaching hospitals across Canada. He wrote to ten major Canadian Colleges of Medicine to find out whether their faculty carried out clinical research with volunteers and how it was regulated.\textsuperscript{127} It was not just curiosity that prompted Begg to make enquiries. The debate on medical experimentation with humans raged after the court judgment on the case of Halushka, but the controversy on the matter had arisen among the MRC members earlier. Soon after the accident at the university hospital in Saskatoon, Ray F. Farquharson, Chairman of the MRC, visited the University of Saskatchewan. In his discussions with President Spinks and Dean Macleod, Farquharson disapproved of work that Wyant did on human subjects. Specifically, Farquharson was opposed to clinical

\textsuperscript{124} As early as 1955, Wyant requested that the Dean of Medicine or a special committee appointed by the Dean should give some sort of authority to the clinicians engaged in human experimentation. This policy of giving a sanction to the project would allow the investigators to share responsibility with the authorizing body in the event of possible litigation. See a memorandum from G.M. Wyant to J.W. Macleod (Dean of Medicine, University of Saskatchewan), Saskatoon, 12 July 1955; and R.W. Begg to G.M. Wyant, 22 October 1963; both files in the USL, f2087, Ad. 7/2, 2/1.

\textsuperscript{125} R.W. Begg to J.W.T. Spinks, 22 October 1963; in the USL, f2087, Ad. 7/2, 2/1.

\textsuperscript{126} J.W.T. Spinks to G.M. Wyant, Saskatoon, 21 November 1963; in the USL, f2087, Ad. 7/2, 2/1.

\textsuperscript{127} Begg requested information from Dalhousie University, McGill University, Université Laval, the University of Montreal, the University of Ottawa, the University of Toronto, the University of Western Ontario, the University of Manitoba, the University of Alberta, and the University of British Columbia. See correspondence between R.W. Begg and Deans of Medicine at the indicated institutions during November 1963; in the USL, f2087, Ad. 8, 2/7a.
investigations on volunteers because in his view “knowledge of new drugs should be gained from the observation of patients who must have them in any case for their own welfare.”

Macleod thought otherwise. From his perspective, if a patient had a health hazard due to a disease or surgical intervention, it could be no less reprehensible to add further to the patient’s risk by a drug trial. The same ethical polemic applied to trials of experimental agents in cancer treatment. In the aftermath of the accident, Wyant reflected,

> It [wa]s a rather fine point of ethics whether this [test of Fluoromar] should have been done on patients in whom the risk would have been considerably greater with a lesser return in terms of scientific data, or whether this should be done on healthy persons who have volunteered for the experiment. If one accept[ed] Dr. Farquharson’s view, one would submit patients to an increased risk and if the response to a drug were [sic] not favourable, [sic] resuscitative efforts may not be anywhere near as successful as in healthy individuals. Also some of the data which we hoped to obtain could not have been got in the operating room for technical reasons.

Despite Wyant’s strong emphasis on a scientific value of the clinical experiment, his position represented a counterargument to the claim that patients should bear the brunt of experimentation since they may benefit from new drugs. It could also be argued, therefore, that clinical trials with patients afforded the doctor-investigator more protection from liability in case of an accident than in a similar situation that involved healthy individuals. Begg wanted to clarify this issue by seeking information about activities and procedures regarding human experimentation at teaching hospitals across Canada.

By mid-April 1964, Begg received reports on medical experimentation from all but one Faculty of Medicine in Canada. These reports revealed that the University of Saskatchewan was ahead of the other Colleges of Medicine in terms of consideration of human experimentation, supervision procedures, and liability insurance. A general reaction from the Deans of Medicine to Begg’s inquiry was that regulation on the matter should be given serious

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128 See a note attached to the memo from J.W. McLeod to G.M Wyant, 8 November 1961; in the USL, f2087, Ad. 8, 2/7a.
129 G.M Wyant to Dr. J. Wendell Macleod, Saskatoon, 11 December 1961, p.1; in the USL, f2087, Ad. 8, 2/7a.
130 R.W. Begg to J.W.T. Spinks, 13 April 1964; in the USL, f2087, Ad. 8, 2/7a.
thought in view of the existing precedent.\textsuperscript{131} As Begg aptly described the situation, “It [wa]s ironic that the group who ha[d] considered the matter the most seriously should be the ones to end up in court.”\textsuperscript{132}

A year later, the Saskatchewan Court of Appeal reached a verdict on the case. The appeal of the University of Saskatchewan \textit{et al.} was based on several grounds, one of which seemed quite notable. The appellants suggested that the consent process had gone through properly because the investigators and the subject of the clinical experiment entered into a contractual relationship, rather than a doctor-patient one.\textsuperscript{133} This proposition meant that the scope of liability for a possible accident in the course of the test was limited by the contract terms given in the consent form, but not by the fiduciary duties of the medical practitioner toward the patient. Justice of Appeal, Roy N. Hall, interpreted the circumstances of this case thus,

the duty imposed upon those engaged in medical research, as were the appellants, Wyant and Merriman, to those who offer themselves as subjects for experimentation, as the respondent [Halushka] did here, [wa]s at least as great as, if not greater than, the duty owed by the ordinary physician or surgeon to his patient. […] The example of risks being properly hidden from a patient when it [wa]s important that he should not worry c[ould] have no application in the field of research. The subject of medical experimentation [wa]s entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent.\textsuperscript{134}

Justice Hall made it clear that the appellant Wyant was in a fiduciary position that necessitated a reasonable and fair explanation of the experimental procedure with its potential effects and risks to Halushka. The latter, in Justice Hall’s opinion, gave no valid informed consent to the investigators since they failed to reveal facts that might have influenced the judgment on which the consent was founded. In forming his opinion on the case, Justice Hall referred to a number of

\begin{itemize}
\item \textsuperscript{131} O.H. Warwick, Dean of Medicine at the UWO, wrote: “Your letter served a most useful purpose in my opinion, in letting the Department Heads know just how seriously they must accept their responsibilities if any new drug or other agent is to be used on a patient. I have had some personal experience in this same field and appreciate just how thin is the ice on which we skate.” See correspondence from O.H. Warwick to R.W. Begg, London (ON), 20 November 1963; in the USL, f2087, Ad. 8, 2/7a.
\item \textsuperscript{132} R.W. Begg to J.W.T. Spinks, 13 April 1964; in the USL, f2087, Ad. 8, 2/7a.
\item \textsuperscript{134} \textit{Ibid.}, 443-444
\end{itemize}
American court rulings, including *Salgo v. Leland Stanford Jr. University Board of Trustees*. Particularly, Justice Hall considered to what extent a professional judgment might circumscribe the disclosure of medical information to the patient or research subject and not compromise obtaining an effective informed consent. In consultation with two other Justices of Appeal – Merwyn J. Woods and Russell L. Brownridge – Justice Hall concluded that the consent given by Halushka was not adequately informed and the appellant investigators were guilty of trespass to his person. Thereby, the Saskatchewan Court of Appeal dismissed the appeal with costs. The court upheld the original decision.

Wyant and Merriman’s conduct of trials and its critical analysis in the Saskatchewan courts had local and national implications. For example, Wyant and Merriman’s tests of *Fluoromar* demonstrated that the agent was not safe for anesthetic use. Another result was that the question of ethics in human experimentation was broached at the Eighteenth Meeting of the MRC in Ottawa on 28 February 1966. R.W. Begg enquired during the session on recommendations for grants-in-aid of clinical investigations whether the MRC adhered to the code of ethics of the Canadian Medical Association or to any other guidelines concerning human experimentation. Surprisingly, the MRC Secretary, Joseph Auer, who was then Assistant Dean of Medicine and Professor of the Department of Anatomy at the University of Ottawa, reported that “the point [of human experimentation] had not to his knowledge been raised before.” Begg suggested that the MRC executive committee looked into this issue because some of the applications for funds had proposals that needed an ethical review and the MRC of Great Britain had already issued a statement on the subject.

The MRC ultimately proposed that universities establish an Institutional Committee on Clinical Research to appraise projects as to ethical acceptability. In other words, the MRC

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137 MRC, *Proceedings of the Eighteenth Meeting*, Ottawa, 28 February 1966, pp.14-16; in the USL, Begg, MG 54 S1, 4b.
139 The Executive Committee of the MRC consisted of five members: Joseph Auer (Secretary, MRC), G. Malcolm Brown (Chairman, MRC), C. Fortier (Professor and Head, Department of Physiology; Director, Endocrine Laboratory, Laval University, Québec), R.V. Christie (Dean of Medicine, McGill University, Montréal), J.A. McCarter.
devolved the responsibility for an ethical assessment of proposed projects to the local committees. Malcolm Brown, President of the MRC, had consulted with the MRC in Great Britain and the US Public Health Service before he took this course of action. Brown’s proposal constituted a middle ground between the American and British grant policies, but it tended to the former in view of the increasing funding of clinical investigations across the border. As background information for the MRC executive committee’s discussion on human experimentation, Brown circulated a copy of the memorandum on “Clinical Research and Investigation Involving Human Beings” by William H. Stewart, Surgeon General of the US PHS, which read, “The wisdom and sound professional judgment of you [grantee] and your staff w[ould] determine what constitute[d] the rights and welfare of human subjects in research, what constitute[d] informed consent, and what constitute[d] the risks and potential medical benefits of a particular investigation.”

Along those lines, the MRC executive committee proposed a recommendation on the position of the MRC in relation to clinical research at its Nineteenth Meeting in May-June 1966.

Following the ethical standards of clinical investigation endorsed by the British MRC, the US PHS, and the World Medical Association, the MRC of Canada recommended that projects involving experiments with humans meet certain ethical requirements. Accordingly, the

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(Director, Cancer Research Laboratory, UWO, London). See MRC, “Minutes of the Meeting of the Executive Committee,” Ottawa, 18 May 1966, pp.1-4; in the USL, Begg MG54 S1, MRC, 4c.

140 The US PHS grant policy formulated in December 1965 and effective as of 8 February 1966 was as follows, “No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: 1) of the rights and welfare of the individual or individuals involved, 2) of the appropriateness of the methods used to secure informed consent, and 3) of the risks and potential medical benefits of the investigation. A description of the committee of the associates who will provide the review shall be included in the application.” See a policy statement “Clinical Research and Investigation Involving Human Beings” by W.H. Stewart issued to the “Heads of Institutions Conducting Research with Public Health Service Grants,” 8 February 1966, attached to the MRC’s “Minutes of the Meeting of the Executive Committee,” Ottawa, 18 May 1966, Appendix B; in the USL, Begg MG 54 S1, MRC, 4c.


142 Those requirements reproduced a description of the review committee procedure offered by W.H. Stewart, Surgeon General of the US Public Health Service. See MRC, “Minutes of the Meeting of the Executive Committee” (1966), Appendix B. Ibid.
approval of a project by a local institutional committee convened for the purpose of ethical review was required. The committee had to include the head of the department in which the project was to be conducted, the Dean of Medicine or his counterpart, and at least two other members not associated with the project. Further, it was necessary that any application for the MRC funding of such a project be accompanied by a special form, signed by the committee members, with a statement that the proposed clinical investigation was ethically acceptable to the committee.\textsuperscript{143} Thus, a few medical professionals who achieved a consensus locally then determined the acceptability of human experimentation from an ethical perspective.\textsuperscript{144} It is instructive to illustrate this consensus-formation by analyzing the ethical review process at the College of Medicine of the University of Saskatchewan in the light of the continuation of G.M. Wyant’s clinical research program.

In July 1967, G.M. Wyant forwarded a protocol for a clinical investigation of Teflurane and an information booklet on this anesthetic agent to Donald F. Moore, Dean of Medicine of the University of Saskatchewan.\textsuperscript{145} Wyant was well aware that Moore had to appoint a committee for an ethical assessment of the Teflurane study. Produced by Abbot Laboratories of Chicago under the trademark Teflurane, tetrafluoro-bromoethane had been investigated clinically in the United States since 1960, but its evaluation in patients discontinued until 1966 due to unsuspected toxicity.\textsuperscript{146} Then clinical studies of Teflurane resumed in several American university hospitals. In 1967, the Food and Drug Directorate (FDD) in Ottawa authorized its use for clinical studies by qualified investigators in selected Canadian institutions. The University of

\textsuperscript{143} The MRC accepted those recommendations by voting on the motion. The executive committee created a form to be completed for grant applications involving clinical investigation and circulated it to the universities for the use of institutional review committees in the fall of 1966. See MRC, \textit{Proceedings of the Twentieth Meeting}, Ottawa, 24-25 November 1966, Appendix B; in the USL, R.W. Begg f054, MRC, 4b.

\textsuperscript{144} In this connection, R.W. Begg wrote to G.M. Brown, “I will be interested to see how the new form for clinical investigation goes concerning the ethics of clinical investigation. I am somewhat troubles [sic] by the statement that if local committee finds the proposed project unacceptable the application should not be forwarded to Council […] It is possible that a bright person might be unduly restrained by somewhat reactionary colleagues, though I suppose we might hear about it one way or another if such incidents do happen.” R.W. Begg to G.M. Brown (Chairman, MRC), Saskatoon, 24 August 1966; in the USL, Begg MG 54 S1, MRC, 4a – Correspondence 1961-1966.

\textsuperscript{145} Memorandum from G.M. Wyant to D.F. Moore, Saskatoon, 27 July 1967; in the USL, College of Medicine Committees, 1111-245, A.3.

Saskatchewan was with McGill University, Université Laval, and the University of British Columbia to which the FDD made Teflurane available. Wyant proposed to study the cardiovascular properties of the agent on young patients, diagnosed as free from any systemic disease, who needed to undergo a planned operation. According to Wyant’s protocol, “the patient w[ould] be informed that an experimental agent w[ould] be used and that certain observations w[ould] be made during the course of the operation after [a] prior discussion with the appropriate surgeon.” Unlike in the Fluoromar study of 1961, Wyant provided a list of proposed tests and made the investigation of Teflurane coupled with a pre-determined therapeutic surgery. The use of healthy volunteers for non-therapeutic studies involving invasive procedures was no longer justifiable in the university hospital setting.

By September 1967, Dean Moore organized the committee of five members from the College of Medicine. Its chairman, Robert G. Murray, a Professor and Head of the Department of Ophthalmology, called a meeting on 27 October 1967 to have Wyant acquaint the members with the details of the proposed study. Only R.G. Murray, C.C. Burkell, and A.W. Taylor attended the meeting at which Wyant discussed the proposed Teflurane investigation. As a result, the Committee approved the study under the following conditions:

1. The study to be performed in young adults over the age of 21. The patient is to be fully informed of the use of the anaesthetic [sic] and a special consent form to be signed. 2. Permission of the surgeon to be obtained before the anaesthetic agent is used. 3. The agent would only be used where an anaesthetic is required, that is the anaesthetic would not be given in isolation as an experiment in itself.

Two more conditions and four specifications pertained to the procedure of the Teflurane study. One of the specifications stipulated that cardiac catheterization was not allowed even though the investigation focused on arrhythmias effected by the agent. Failure in the Fluoromar

148 The members were Robert G. Murray (Chairman, Ophthalmology), Allan A. Bailey (Medicine, Neurology), Charles C. Burkell (Therapeutic Radiology, Cancer Clinic Director), Eric M. Nanson (Surgery), and A.W. Taylor (Medical Director, University Hospital); ibid.
149 R.G. Murray to D.F. Moore, “Re: Committee to examine the proposed Teflurane Study by the Dept. of Anaesthesia,” Saskatoon, 31 October 1967; in the USL, College of Medicine Committees, 1111-245, A.3.
150 ibid.
investigation, therefore, had repercussions for the implementation of similar clinical experiments.

Confident in the exhaustive assessment of the proposed investigation, R.G. Murray reported the committee’s endorsement to Dean Moore to have it registered by the Medical Advisory Committee of the University Hospital Board and to R.W. Begg, Principal of the University of Saskatchewan at the time. Quite unexpectedly, however, Begg suggested adding a member of the faculty outside the College of Medicine. In Begg’s view, it was worthwhile considering as an extra committee member someone from the College of Law.\footnote{Memorandum from R.W. Begg to D.F. Moore, 9 November 1967; in the USL, College of Medicine Committees, 1111-245, A.3.} The implication of this suggestion was clear – a lack of trust in the objective evaluation of clinical research left to medical professionals.\footnote{This proposition resonates with what David Rothman discusses in his book on the emergence of American bioethics. See D.J. Rothman, \textit{Strangers at the Bedside} (2003).} By including in its composition a layperson, both Spinks and Begg wanted to strengthen the position of the institutional committee in case of another court action.

The committee disagreed. From the chairman’s perspective, an extra member complicated and prolonged a project’s evaluation. Defending a sound judgement of the committee, Murray wrote, “If the University wishe[d] to have a lawyer examine the Committee’s report that [wa]s its prerogative. I would point out, however, that the last time this was done the consent document that was drawn up would not have been signed by anyone and the whole project was shelved.”\footnote{Memorandum from R.G. Murray to D.F. Moore, 21 November 1967; \textit{ibid}.} The last time was in June 1967, when at the Medical Advisory Committee (MAC) meeting, Thomas B. MacLachlan, Head and Professor of the Department of Obstetrics and Gynecology, initiated a discussion on the problems that could arise with the drawing up of a consent form. Particularly, MacLachlan pointed out that a clinical investigation consent form could be so detailed because of the legal counsel “that it would be extremely difficult to get a volunteer to agree to it.”\footnote{Medical Advisory Committee, \textit{Minutes}, Saskatoon, 1 June 1967, p.3; in the USL, f2087, H.3, 2/6a.} Likewise, Murray reckoned that any further protection from possible legal proceedings operated as a disincentive for initiating clinical investigations.
To bolster this argument, Murray invoked international guidelines on clinical research adopted by the World Medical Association as the Declaration of Helsinki, stressing that the investigator’s responsibility counted much more than the patient’s consent. Referring to the Canadian MRC’s requirement to form a local institutional committee for an ethical evaluation of the clinical investigation, Murray noted that it did not state explicitly that a non-medical member had to be part of the committee. Overall, Murray seemed to be inflexible on the subject. In his view, “the best protection against unethical clinical research and lawsuits against the Research [sic] worker and the University [lay] in a free and frank discussion of the proposed project by a Committee of Medical [sic] members.”

Confronted with Murray’s adamant attitude, Dean Moore persuaded the Medical-Dental College Committee of the University of Saskatchewan’s Board of Governors to waive its requirement for an extended ethical review committee in Wyant’s case. Hence, Wyant received the authorization to proceed with the Teflurane study. Still, the Board of Governors reported to the MAC of the University Hospital Board its proposal to involve an individual from other than medical faculty in the review process of clinical projects. In doing this, the university administration let the medical professionals know that they needed to bring up to date their approach to the ethical assessment of clinical investigations. Charles C. Burkell, Head of Therapeutic Radiology and Director of the Saskatoon Cancer Clinic, presented the MAC recommendations concerning human experimentation to the University Hospital Board (UHB) in January 1968. In three out of five recommendations, the MAC’s concern revolved around

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155 Ibid. Murray quoted section III, item 3c, of the Declaration of Helsinki that read, “Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.” See World Medical Association, “Human Experimentation: Code of Ethics of the World Medical Association (Declaration of Helsinki),” Can. Med. Assoc. J., 91 (12 September 1964): 619.

156 R.G. Murray to D.F. Moore, 21 November 1967. Although the MRC’s “Clinical Investigation Form” did not dictate the inclusion of a non-medical professional in the institutional review committee, it required that the committee consisted of “the Dean of Medicine or a representative of the university’s administrative office (or his counterpart in other institutions), two individuals knowledgeable in the field of the proposed research but not associated with the proposed project and not necessarily from the same department, and such other individuals as may be considered appropriate.” See MRC, Proceedings of the Twentieth Meeting, Ottawa, 24-25 November 1966, Appendix B; in the USL, Begg f054, 4b.


litigation rather than the ethics of conducting proposed investigations. Correspondingly, the role of the review committee altered. “This committee must be prepared to support the investigator if a suit [wa]s initiated,” read the primary recommendation, which meant the committee had to share responsibility with the investigator for an alleged misconduct in case of its failure to determine foreseeable risks of the clinical project. Nonetheless, the UHB requested the MAC to consider those recommendations further in terms of the suggested make-up of the ethical review committee.

In charge of the MAC’s reconsideration of the policy on human experimentation was none other than R.G. Murray. Following discussions among the MAC members, he prepared a report on clinical research and human volunteers. In its introduction, Murray noted that the MAC scrutinized the Declaration of Helsinki, a similar report prepared by the Faculty of Medicine of the University of Western Ontario, the requirements of the Canadian MRC and the US Department of Health, Education and Welfare for approval of clinical research projects. Although Murray claimed that the report’s recommendations met the requirements of the above regulations, one recommendation did not comply with standards of the Declaration of Helsinki. This recommendation related to the clinical investigation combined with professional care. Wrote Murray,

In this category of clinical research it would not normally be required that the [Review] Committee approve[d] individual diagnostic and therapeutic procedures which [we]re of potential value for the patient concerned. For studies of this type “group consideration” or “group consent” as provided at ward rounds or conferences from discussion amongst the physician in charge and his colleagues should suffice. The principal investigator must supply documentary evidence to the Head of the Department that such a discussion ha[d] been held and such approval ha[d] been given.

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159 The University Hospital Board, Minutes, Saskatoon, 12 January 1968, p.14; in the USL, Begg, MG S1, 5 – UHB, JA 1968.
161 Ibid., 2. Murray also made an astute and important qualification, “However, when in the opinion of the Department Head such studies represent a significant deviation from accepted practice or are associated with unusual hazards, they will be reviewed in a formal manner and documented by the Departmental Review Committee.”
It follows from this proposition that the professional judgment continued to determine the acceptability of human experimentation without patient’s consent. Such a course of action ran counter to the guidelines of the Declaration of Helsinki, but it was practicable, in both senses of the word, within a teaching hospital.\textsuperscript{162}

The Medical Advisory Committee approved the recommendations of R.G. Murray and the University Hospital Board followed suit in March 1968. Subsequently, they proceeded to the Board of Governors. When Wyant asked for an ethical review of the next project involving human subjects in August 1968, the Board of Governors still deliberated on R.G. Murray’s submission.\textsuperscript{163} By mid-November 1968, the Board of Governors requested that, in addition to the faculty members of the review committee formed by Dean Moore, Vice-President (Research) of the University, then Balfour W. Currie, joined the committee.\textsuperscript{164} Currie was a physicist-meteorologist by training, not a lawyer. The Board of Governors accepted all of the MAC recommendations on the condition that membership of further review committees at the College of Medicine included the Vice-President (Research).\textsuperscript{165} R.G. Murray conceded this interference in the medical affairs, for it was quite inconsequential by comparison with the allowed latitude of clinical research-practice formulated in the MAC recommendations.

4.3. Institutions and Regulation of Human Experimentation

Canadian clinical investigators in cancer constituted a significant part of the medical profession engaged in human subject research over the late 1960s. Their \textit{modus operandi} hinged on the relationship between the local and, to a lesser extent, national factors. Correspondingly, the ethics of conducting clinical trials evolved through the pronouncements of authoritative doctor-

\textsuperscript{162} The Declaration of Helsinki, section II – Clinical Research Combined with Professional Care, item 1, read, “If at all possible, consistent with patient psychology, the doctor should obtain the patient’s freely given consent after the patient has been given a full explanation.” See WMA, “Human Experimentation: Code of Ethics of the World Medical Association (Declaration of Helsinki)” (1964).
\textsuperscript{163} D.F. Moore to R.W. Begg, 16 August 1968; in the USL, College of Medicine, 1111-245, A.3.
\textsuperscript{164} William A. Allen (Assistant Dean of Medicine) to G.M. Wyant, 18 November 1968; \textit{ibid}.
\textsuperscript{165} The University Hospital Board, \textit{Minutes}, Saskatoon, 10 January 1969, p.5; in the USL, Begg, MG 54 S1, 5 – UHB, J-M 1969.
researchers, its application in concrete situations and its further re-conceptualization in view of the correlation between the general dicta and specific uses.

A prominent English physiologist and cancer epidemiologist, Richard Doll, who worked at the Medical Research Council in Great Britain, concluded a session on “Controlled Clinical Trials and their Evaluation” of the 1966 International Cancer Congress in Tokyo thus, “The interests of the patient [we]re best protected by the collective concern of the medical profession in maintaining its own ethics and not by legislation; […] and by insisting that new trials [we]re begun only after the doctors immediately concerned consulted with their colleagues.”166 This proposition found its realization in Saskatchewan, which led to a shift in the regulation of medical research across Canada. A collective medical judgement on a risky clinical investigation without the individual’s informed consent proved insufficient for the judiciary to deem the human experiment ethical. This precedent induced research administrators to update rules for the conduct of clinical investigations. Albeit, the investigative ethos of the medical profession yielded to outsider demands for change only gradually. In this instance, human experimentation tested the public confidence in the medical profession and expedited a deliberate action to ensure against the weakening of such confidence.

Besides requirements to control the ethical propriety of clinical research, which materialized in the form of institutional review committees, there was another development aimed at the surveillance of cancer trials’ investigators. The review committees became a means for establishing adequate standards to govern the use of human subjects, which thus represented a measure of the values of a local scientific-medical community. They were a response to the court that questioned those values and attempted to devise new ones reflecting the medical needs of an individual, rather than the scientific desiderata of interested groups. The other layer of regulation came into being at the national level.

The Department of Justice and the Department of National Health and Welfare issued updated rules on the introduction of new investigational drugs for trials in 1967. According to the departments’ review, the challenging task of obtaining evidence with respect to safety, dosage,

and effectiveness of new drugs necessitated a restriction of qualified clinical investigators to a small number.\textsuperscript{167} This group of NCIC-recognized clinical investigators needed to be limited because the US National Institutes of Health allowed it a regular access to the minutes of the task force meetings, like that of the NCI. With that insider scientific information on hand, the selected Canadian investigators provided necessary clinical data through preliminary trials with a particular chemotherapeutic agent. Next, they received a Notice of Compliance from the Food and Drug Directorate (FDD) for that agent based on the obtained evidence before making it available to physician-investigators in Canada for comparative clinical trials.\textsuperscript{168} In this manner, the FDD intended to provide a measure of protection to the public and the doctors in the clinical testing of investigational drugs.\textsuperscript{169} Having a statutory obligation under the Canadian Food and Drugs Act and Regulations, representatives of the FDD were also “concerned that legislative and administrative rulings d[id] not hinder the progress in the development of anti-neoplastic agents.”\textsuperscript{170} This concern ensued from an increasing spread of new chemotherapeutic drugs, which spiraled out of governmental control, not only to doctor-researchers in teaching hospitals, but also to physicians in general practice.

Studies of new investigational agents involving human subjects extended widely since a fair amount of progress in treating diseases was demonstrated over just two decades. In the span of three years, however, the Thalidomide disaster and the Fluoromar accident provoked the FDD to attend to potential dangers associated with new drugs. Newly developed anti-cancer agents drew close attention of the FDD too because “most of these agents were distributed through the National Cancer Chemotherapy Service Centre of the National Cancer Institute (Washington) and some [were] sponsored directly by private pharmaceutical firms.”\textsuperscript{171} The FDD did not want

\begin{itemize}
  \item \textsuperscript{167} A.C. Hardman (Director, Bureau of Scientific Advisory Services, DNHW, Ottawa) to R.M. Taylor (Director, NCIC), Ottawa, 5 April 1967; in the WUA, AFC 328.1.2176.
  \item \textsuperscript{168} By July 1965, the FDD had produced a revised \textit{Guide for Completing Preclinical Submissions on Investigational Drugs}, under section C.08.005 of the Food and Drug Regulations. Importantly, the document contained a clause on “double blind studies”. See Food and Drug Directorate (DNHW), \textit{Guide for Completing Preclinical Submissions on Investigational Drugs}, Ottawa, July 1965, p.22; in the UTA, A1986-0035/024(03).
  \item \textsuperscript{169} It is noteworthy that this caution about new drugs stemmed from the Thalidomide scandal in early 1962. See the Dominion Council of Health, \textit{Minutes of the 82nd Meeting}, 7-9 November 1962; in the LAC, the DCH fonds, MG 28 I 63, 100130, reel C-9817, pp.28-29.
  \item \textsuperscript{170} A.C. Hardman to R.M. Taylor, Ottawa, 5 April 1967, \textit{op.cit}.
  \item \textsuperscript{171} L.G. Israels and D.E. Bergsagel, “A Report to the Clinical Advisory Committee, NCIC”, 18 September 1968; in the WUA, AFC 328.1.2176.
\end{itemize}
to indiscriminately distribute substances that provided meagre descriptions of their characteristics. Hence, the FDD devolved this responsibility to expert cancer investigators, working in institutions with adequate facilities, who could assess the therapeutic merits of experimental agents.

The only body capable of accepting these special responsibilities was the National Cancer Institute of Canada. The NCIC Clinical Advisory Committee assisted the FDD in the development of methods for subjecting new cancer chemotherapeutic agents to clinical trial. In 1968, a sub-committee of the NCIC Clinical Advisory Committee, comprising Lyonel G. Israels of Winnipeg and Daniel E. Bergsagel of Toronto, considered the issue of drug distribution for clinical investigation and drew up the terms of reference governing the participation in this programme of institutions and investigators suited to undertake chemotherapeutic trials. The policy, agreed on between the FDD and the NCIC, enabled select cancer investigators to get new chemotherapeutic agents for clinical trials through government channels. Quite noticeable in this policy was the role of “a human experimentation committee to review the procedures used by investigators to inform patients about their use in clinical trials and the obtaining of informed consent.” It was the emergence of a new institutional structure – a research ethics committee – that indicated a change in the assessment of clinical trials. Even more, it was a revolutionary development in the field of human experimentation at the teaching hospital, for, as Ian Hacking argued, a fundamental feature of such a revolution was the “new kinds of institution that epitomize[d] the new directions created by the revolution.”

172 R.M. Taylor (Executive Director, NCIC), “Summary of the Minutes of the 108th Meeting of the Board of Directors,” 30 September 1968; in the USL, Cancer Research Unit RG 20 S9, II.5/1(2).
175 Israels and Bergsagel, “A Report to the Clinical Advisory Committee, NCIC” (1968), section II, item 4.
Between 1966 and 1972, every major teaching hospital in Canada set up a research ethics committee and laid down general principles governing its functions. However, differences emerged, like the inclusion of a lawyer or a layperson in the committee’s composition. Reasons for not including representatives of the law and the community in the ethical review process ranged from “a problem of logistics” and unbudgeted payments at the University of Alberta, to an interference in and a possible complication of the assessment procedure at the University of Saskatchewan. Such matters were of lesser importance to the university administrators in Toronto and Vancouver, where optimum protection for the investigators doing clinical research was a sine qua non.

The University of Toronto set the trend in addressing the issue of a formalized ethical review of clinical investigations shortly after the Saskatchewan Court of Appeal judgment. In January 1966, the university Research Board approved the “Procedure of the University of Toronto for Review and Decision on the Propriety of Plans of Research Involving Human Subjects.” It was a detailed document that stipulated among procedural particulars a representation of the institutional administration by a person who was “to have legal training whenever possible.” Such a requirement seemed legitimate, since the number of clinical trials,

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177 See Frank A. Forward (Consultant, Research Administration, UBC) to Deans, Directors and Department Heads, and Mr. A. Myers (Director, Information Services, UBC), Interdepartmental Memorandum, Vancouver, 5 May 1972, with enclosure University Policy on Procedures in Research and Other Studies Involving Human Subjects; in the UBCL, Ceremonies Office fonds (1931-2014), box 2, file 9.
178 Bernard Snell, Executive Director of the University of Alberta Hospital explained the problem of logistics thus, “there are a fair number of Ethical Review Committee meetings and it might be unrealistic of us to expect to be able to have a lawyer available to attend these meetings in the same way as members of the medical and administrative staff of the Hospital and Faculty do. [...] A way around this could, of course, be found if we were to agree to pay these individuals. This, however, would cause concern as it would constitute a further drain on the Special Services and Research Committee’s budget.” See a memo from B. Snell to W.C. MacKenzie (Dean, Faculty of Medicine, University of Alberta), Edmonton, 15 December 1972; in the UAA, Acc. No. 80-162-242, 6-B-51.
179 In addition to medical faculty members, both a lawyer and a layperson had to be on the institutional committee of the UBC in Vancouver. See correspondence from W. Douglas Armstrong (Department of Pathology, University of Alberta) to W.C. MacKenzie, 6 December 1972; in the UAA, Acc. No. 80-162-242, 6-B-51.
180 According to the institutional regulations, a review was required whether the research project received funding from within the University of Toronto or its teaching hospitals, or where no grants were involved, as in cancer drug trials. See Committee of the Research Board of the University of Toronto, “Review Committee on Research Involving Human Subjects” (1966), p.1; in the UTA, B1991-0004/008(18).
181 See “Procedure of the University of Toronto for Review and Decision on the Propriety of Plans of Research Involving Human Subjects,” 1966, 3(ii); in the UAA, Acc. No. 80-162-242, 6-B-51.
especially in the field of cancer studies, increased substantially in the second half of the 1960s. The risk of litigation augmented proportionally. Moreover, cancer investigators at the university hospitals of Toronto forged ahead in the cooperation on clinical projects with their American colleagues.

Beginning from a sporadic participation in preliminary trials of anti-neoplastic agents subsidized by the US National Cancer Institute’s chemotherapy program, some Canadian clinical researchers progressed to comparative RCTs jointly organized with American investigators. Such was a RCT that compared local with regional radiation in patients with stage I/II Hodgkin’s disease.\textsuperscript{182} This co-operative study involved twenty centers in the United States and Canada. The Canadian centers were all based in Ontario and the coordinating institution was the OCI/PMH of Toronto. Vera Peters, a therapeutic radiologist at the OCI/PMH, supervised the implementation of this RCT since April 1967. That trial was an extension of a preliminary small-scale RCT in the management of patients with advanced Hodgkin’s disease by radiotherapy alone or combination chemotherapy undertaken at the Princess Margaret Hospital.\textsuperscript{183}

The Canadian-American collaboration in administering large cooperative RCTs evaluating treatments for Hodgkin’s disease necessitated that ethical standards on the conduct of clinical investigations had a common denominator in their institutional assessment. And it was the US NCI that determined this baseline. In exchange, American cancer chemotherapy study groups provided current research protocols and made it possible for the investigators to participate in the group projects with an additional benefit of receiving certain new investigational drugs.\textsuperscript{184} American regulators required that Canadian cancer investigators obtain institutional approval for the use of human subjects in clinical trials by the mechanisms established in the institution which the US National Institutes of Health had approved according to directives promulgated by the Surgeon General of the US Public Health Service in February

\textsuperscript{182} M. Vera Peters, “The Value of Local or Regional Radiation in Early Hodgkin’s Disease,” OCTRF Project No.181 (Grant 41-13), 30 April 1967; in the OCTRF, \textit{Annual Report 1968}, pp.178-9; in the USL, MG 404, box 11.
\textsuperscript{183} The combination chemotherapy consisted of Methylhydrazine, Cyclophosphamide, Vinblastine, and Prednisone. OCTRF, \textit{Annual Report 1968}, p.149.
\textsuperscript{184} Taking into account those considerations, Abdul Khaliq and Pierre R. Band, who both worked at the Chemotherapy Department of the University of Alberta Hospital of Edmonton, became members of the Southwest and Northeastern Cancer Chemotherapy Study Groups, respectively. See Provincial Cancer Hospitals Board, Meeting No. 6, item C-5, 16 October 1969; in the UAA, Acc. No. 81-70-358, 13-A-10.
1966.185 Significantly, those directives served as a template for Malcolm Brown, President of the MRC of Canada, to shape a policy on institutional review of human experimentation over 1966. Thus, access to the American system of institutional clinical research and its regulation was an important driver in the Canadian implementation process.

By 1970, experience recorded by institutional committees entered the realm of the media. Leading representatives of the medical profession proclaimed that an institutional ethical review of clinical investigations, further enhanced by government oversight, offered a reliable protection for the human subject and, concomitantly, a better standard of care for the patient.186 Underlying this proposition was a message that the public should accept medical research as an essential part of improving healthcare and participate in clinical investigations as stakeholders. The proposition also indicated that a professional credibility of doctor-investigators needed a restoration through increased social acceptability of clinical research. A crisis of enrollment in an ever-increasing number of RCTs was looming ahead because of the length of time necessary to build up a statistically adequate series of patients. Cooperative studies multiplied in an attempt to tackle this problem. Still, available patients for particular RCTs were more often than not reluctant to enroll in the trials after doctor-investigators had properly informed them and they understood the gist of proposed procedures, according to the consent process requirements. As the editor of The New England Journal of Medicine, Franz J. Ingelfinger, aptly put it,

Although it may prove impossible to define absolute standards of ethical human research, shoddy standards of performance by those [members of the institutional


186 Kenneth L. Melmon, Michael Grossman, and R. Curtis Morris, “Emerging Assets and Liabilities of a Committee on Human Welfare and Experimentation,” The New England Journal of Medicine, 282, no.8 (19 February 1970): 427 and 431. The authors examined the operations and effectiveness of the Committee on Human Welfare and Experimentation of the University of California at San Francisco over two years since its formation. Particularly, they analyzed the ad-hoc committees selected for each research protocol under review. Their analyses suggested that one of the most difficult tasks for the committees was “to disseminate convincing information that there is a legal as well as a moral obligation for investigators [...] to submit protocols on investigations in human beings for peer-group evaluation.” Put differently, the investigators resisted the trend for a tightening of their standards in human subject research.
committee] who must accredit ethicality are inexcusable. One man’s ethical conduct may be another’s impropriety, and the informed consent of this patient may be that one’s confused acquiescence. But there is no credible reason why this certifying mechanism should be an agonized appraisal of a colleague’s endeavor, and that one a perfunctory exercise of easy accommodation among peers.187

Ingelfinger described the concern among medical professionals. Like a protocol design for a new clinical trial, a properly working mechanism of the research ethics committee required test runs leading to a long-term consistency and development. Ultimately, an improved functioning of the committee was a key to safeguard the rights of the patient-subject before the court of law intervened to attest to their infringement. Nonetheless, even clinical investigations done by the exemplars of research ethics propriety underwent an evolution that involved variability in their practices.

The University of Toronto review committee on research involving human subjects examined a research proposal by Ernest A. McCulloch, a Professor of Medical Biophysics at the OCI/PMH, in November 1971.188 McCulloch’s project comprised laboratory studies of human blood and bone marrow cells obtained from patients with leukemia and other blood-forming disorders.189 Since 1959, the twists and turns of McCulloch’s research program on the mechanisms of renewal, damage and repair of cellular elements of the blood, which continued to be partially supported by the Defence Research Board, brought him to investigations on leukemia.190 By growing blood cancer cells in culture and using a newly developed colony-formation method, a group of researchers led by McCulloch explored the workings of neoplastic diseases in the laboratory and experimented with feasible models in cancer treatment protocols.

189 Protocol for the Human Experimentation Committee, University of Toronto, “The Biology of Blast Cells in Acute Myeloblastic Leukemia of Man,” by E.A. McCulloch (Principal Investigator, Department of Medical Biophysics), November 1971; in the UTA, B1991-0004/008(18).
190 Between 1959 and 1966, the DRB granted $111,500 for the project “Studies on Repair Processes Occurring in Haematopoietic Tissue Following Total-Body Radiation,” carried out by E.A. McCulloch, J.E. Till, and L. Siminovitch. The DRB funding amounted to $23,000 per year from 1966 to 1969, and remained in the same ballpark until the project’s termination in late 1973. See Defence Research Board, Project D50-93-50-14 (1959), Radiation Protection and Treatment, Financial History, p.3; in the USL, Cancer Research Unit RG 20 S9, l. Primary. E.1/4(4).
Inasmuch as the first phase of McCulloch’s project included only multiple blood and bone marrow aspirations from patients, with minimal risk to their health, the review committee approved the research protocol.

A second phase of McCulloch’s project involved testing the devised laboratory models of leukemia treatment in patients to ascertain which determinants of inducing remissions in leukemia correlated with certain modes of its treatment. Anticipating suitable patients for the proposed trial, McCulloch submitted another request to the human experimentation committee. Although cancer patients were under the care of McCulloch’s clinical colleagues, who exercised complete discretion over their treatment, cooperation of these colleagues with McCulloch made it possible to find suitable patients promptly. One likely candidate for the use of an experimental therapy based on laboratory research findings was forty-year-old Henry Dube who had acute myeloblastic leukemia. First diagnosed with the disease in July 1967, Dube went through a succession of chemotherapy treatments over four years. Beginning his therapy with 6-Mercaptopurine and Vincristine, Dube then received BCNU, a combination of Cyclophosphamide, Cytosine Arabinoside, and Vincristine. This therapeutic cycle was repeated continuously, but in different permutations depending on the disease progression or regression. To manage the side-effects of the drugs, physicians administered a series of transfusions and antibiotics to protect Dube from blood deficiencies and attendant infection. In view of the steadily deteriorating condition of Dube’s health, doctors referred this case to McCulloch who in turn requested permission from the institutional review committee to use an experimental treatment in the management of Dube’s disease.

In his submission to the committee, McCulloch outlined Dube’s case in terms of the clinical evidence, its interpretation, and possible courses of action. Among the latter, McCulloch suggested an experimental therapy that was as follows,

We propose that either frozen and thawed white cells or CSA [colony stimulating activity material from cell culture] be employed. The plan is to give a small test dose of either substance. If there is no adverse reaction to the test dose, the cells or CSA will be infused. The effect of the treatment will be monitored using not

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191 E.A. McCulloch (Professor, Department of Medicine, University of Toronto) to members of the Human Experimentation Committee, 29 August 1972; in the UTA, B1991-0004/008(18).
only standard hematological procedures but also culture techniques for detecting remission-induction. The actual protocol would evolve using either white cells first followed by CSA or the order might be reversed. In either case [sic] conventional therapy would be initiated at the first sign of clinical deterioration. The review committee decided that McCulloch’s research proposal met the institutional requirements on the use of human subjects. As the committee members wrote, “With the understanding that as clear an explanation as possible would be made to the patient, and his verbal consent obtained, the project was therefore approved.” Such an approval indicated to what extent the ethics committee policed the procedure requiring the patient-subject to give an adequately informed consent rather than a confused acquiescence. What evidence showed the clarity and completeness of the explanation on the experimental treatment given to the patient?

The physician-investigator embodied the evidence and his trustworthiness was seemingly beyond doubt. The review committee did not attempt to discern a credibility gap between the ideals and practices of medical investigators. Moreover, the lawyer’s participation in this ethical review suggested legitimacy and legality of the approved consent process whatever the consequences of the experimental treatment. In this case, a merger of professional care with clinical research made the physician-investigators virtually immune to potential allegations of malpractice. A traditional medical ethics of doctors benevolently subjecting patients to experimental treatment smoothly transitioned to an institutional regulation of ethics in research involving human subjects.

Clashes of expert opinion among clinical investigators participating in cooperative clinical trials and a lot of cancer patients’ engagement made a difference. Already in 1971, some patients who experienced both conventional treatments and clinical trials struggled to make themselves heard by medical professionals. When the opportunity came to speak to their assembly at grand rounds in a teaching hospital, one patient seized it to express her state of mind.

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192 *Ibid.*, 3. The committee comprised W.R. Bruce of the Department of Medical Biophysics, J.H. Crookston of the Department of Medicine, E.R. Alexander of the Faculty of Law, and S. Dymond, Director of the Office of Research Administration.

193 Italics added. See a communication from the Review Committee to E.A. McCulloch, Medical Biophysics, 21 September 1972; in the UTA, B1991-0004/008(18).
This is the first time I've faced a group of surgeons who haven’t had me anesthetized. [...] I’m a patient who has lived with active cancer for a little more than 2 years. I’ve been through most of the available treatment, and my chances of living out my life span are not great. I’m aware of it, but in spite of my serenity and acceptance, very few doctors have ever asked me, and I would like you to know, how I feel about it. [...] What I want to impress upon you is that whether I live 2 years or 20, every day is precious to me and I want to be encouraged to fight and to live each day and to be treated like an intelligent human being.194

A careful explanation of a proposed clinical investigation to patients and their special written informed consent to it constituted a significant aspect of treating patients as intelligent human beings, with dignity. The latter was about having a free choice, a so-called “autonomy of the will”, by means of which patients could purposefully act on the basis of their intellectual ability to affirm what was valuable to them unconditionally in the given circumstances.195 The respect for human dignity, or otherwise, was a touchstone for the assessment of ethical validity of human experimentation.

4.4. Conclusion

Cancer clinical trials in Canada were a euphemism for human experimentation at least until 1967. Investigations developed alongside conventional therapy, which meant to its practitioners that patients had to be treated as experimental subjects. This conversion of the patient into the subject occurred inconspicuously, inasmuch as a regulatory framework existed only for therapeutic interventions. With the emergence of randomized clinical trials as a gold standard for cancer treatment assessment over the 1960s, the patient-subject gradually came into the view of physician-investigators.

As accidents due to the experimental medical procedures became more frequent, and some of them entered deliberations of the courts of law, the ethics of research involving humans received more consideration on the part on medical professionals. The ethical dimension of RCTs generated among physicians and clinical investigators discussions on the legitimacy of using patients as research subjects without informing them appropriately. Accordingly, the medical profession reacted with a formalization of regulations necessitating an institutional review of clinical investigations in terms of their ethical acceptability. The establishment of institutional review committees served a twin purpose: to ensure that the risks of the investigation did not far outweigh its potential benefits and that an appropriate means to secure informed consent of the human subject were used. However, it was a consensus of the very clinical investigators within the review committee that determined the criteria of ethical acceptability for approving clinical study proposals. Thus, the committees reviewed the ethics of proposed investigations according to clinical research conventions predominant at the time and place.

Increased emphasis of the institutional review on the need to obtain a reasonably-informed consent issued from a growing threat of legal liability. Still, the informed consent procedures varied in different institutions in Canada over the late 1960s and the early 1970s. Participation of Canadian cancer investigators in the American cooperative RCTs and their requests for funding from American institutions, which imposed strict controls on the conduct of human subject research, induced the institutional committees and cancer researchers to adopt a more standardized approach to the ethics review. Likewise, collaboration among the Canadian and British medical investigators contributed somewhat to this process. International guidelines on clinical research played a less significant role in this respect, but they came under the scrutiny of both investigators and reviewers. Albeit, physician-investigators continued to follow the trend towards emphasizing a therapeutic side of clinical trials and understating their experimental side. This course of action made it possible for both the institutional committee members and the investigators to turn a blind eye to guidelines on human subject research, and to leave the patient in a limbo. The medical professional still decided what informed consent meant, but the institutional committee tended to clarify its meaning with increasing frequency.
Chapter V

*The Construction of Meaning: Ethics in Clinical Cancer Research*

Cancer represented the number one health concern for Canadians in the early 1970s. Organized campaigns to educate people about the problem were high on the agenda of a cancer control program that constituted a noticeable section of public healthcare.¹ The neoplastic disease, formerly an issue of scientific-medical professionals primarily, came increasingly into public focus as a medical problem that acquired a social, an economic, and a political element. Simultaneously accumulating bits of knowledge from laboratory work, clinical investigation, and epidemiological research made the cancer problem a less perplexing scientific puzzle. An interdisciplinary approach to the problems of cancer management became possible through a close association between research and clinical practice that had gained growing provincial and federal support. Without a multilevel involvement of concerned parties, both economically and politically, further initiatives of the cancer control program could hardly move beyond basic preventive and therapeutic measures that had remained its cornerstones over the previous decades.

Although chemotherapeutics somewhat enhanced surgery and radiotherapy, the latter two therapeutic methods continued to dominate the selection of treatment for most forms of cancer.² Inasmuch as the background of the surgeon and the radiotherapist was remote from that of the physician who was knowledgeable in the use of chemotherapy, there was a considerable delay in accepting this approach to therapy as valuable. Physicians tended to accept only well-tested drugs after several years of experience with them, and clinical research into the effects of new chemotherapeutic agents occurred mainly at university hospitals and medical centers. However, cancer specialists’ increasing ability to treat cancer gravitated towards more intensive strategies

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¹ Medical officers in Edmonton (AB), for example, noted, “Because cancer is a common disease, the loss of human dignity and human resources which may result is well known to the public.” See “Position Paper on Cancer Services, Province of Alberta,” 31 August 1972; in the UAA, ref. no. 51 (80-162-200), 6-A-107.1.
in using chemotherapy, rather than relying on surgery or radiotherapy.\textsuperscript{3} This inclination lent itself to a reasonable explanation: numerous drug combinations and permutations in their schedules had a theoretical potential to improve chances of survival, especially in patients with advanced cancer, while the range of applications for surgery and radiotherapy was comparatively limited to achieve the same objective. Moreover, cancer drug development kept a faster growth pace than innovations in surgical technique or irradiation technology. In practice, controlled clinical trials were requisite for establishing a relative effectiveness of given treatment options.

Physician-investigators had already begun waging an undeclared war against cancer by performing radical surgeries, administering high doses of radiation and massive amounts of toxic chemotherapeutic agents. For example, in view of an increasing number of legal suits for mutilating surgical interventions that had bordered on clinical experiments, the American College of Surgeons (ACS), to which many well-qualified Canadian surgeons belonged, used a subtle tactic of making concessions to the regulatory agencies in order to lessen the exposure to public scrutiny.\textsuperscript{4} In 1970, the ACS Board of Regents called for a wide adoption by clinical investigators of the guidelines on human experimentation enacted by the National Institutes of Health in the United States and by the Medical Research Council in Canada. They also proposed an institutional mechanism to manage the publicity related to innovative procedures in an effort to avoid reportedly unwarranted disclosures of experimental results.\textsuperscript{5} By resorting to the advocacy of ethical regulation on clinical trials, the ACS demand would afford protection to surgeons against charges of unprofessional conduct within the same institutional regulative framework.

The medical profession justified their unrestrained proliferation of human subject research in the field of cancer as an incessant fight against the implacable enemy. As the cancer-phobia gradually gave way to the fear of debilitating anti-tumor treatment, it was high time to

\begin{thebibliography}{9}
\bibitem{4} Although surgeons of the USA and Canada founded the American College of Surgeons in Chicago in 1913, only certified medical schools were entitled to the membership. See correspondence from Colin C. Ferguson (Professor and Chairman, Department of Surgery) to L.G. Bell (Medical Faculty, University of Manitoba), Winnipeg, 4 July 1957; in the UMFMA, Department of Surgery, 2.24.1, folder 1.
\end{thebibliography}
legitimate a war on cancer in political proclamations. This was the origin in the United States of *The National Cancer Act of 1971*, which assured the public that a more concerted effort of cancer specialists and institutions was needed to mitigate the plight of cancer patients.6 The solution was to provide more funding for research that hopefully translated into therapy and thus improved the well-being of both current and future cancer patients.7 Specialized institutions and teaching hospitals were most suitable to accomplish this goal.

Leading Canadian clinical investigators espoused a symbiotic relationship between hospital investigators and laboratory researchers, for many of them had done graduate training in the US medical centers that established such a doctrine. For example, Ronald Neil MacDonald, Executive Director of the Provincial Cancer Hospitals Board of Alberta and director of the W.W. Cross Cancer Institute (CCI) in Edmonton, had trained as Fellow in Cancer Chemotherapy under David A. Karnofsky, one of the foremost American pioneers in anti-tumor chemotherapeutics, at Memorial Hospital—Sloan-Kettering Institute in New York.8 MacDonald pointed out that one of the most important roles of the W.W. Cross Cancer Institute, which opened in September 1968, was to translate the results of laboratory research in therapeutic schedules into the treatment regimens of patients.9

In order to realize the objective of linking the experimental work at the University of Alberta NCIC cancer research unit with the clinical projects at the CCI and local teaching

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7 Ilana Löwy argued that this implication encapsulated the “culture of clinical experimentation in oncology [that] was and is shaped by the combination of belief in a future science-based solution to the “cancer problem” and the pressure of the currently insoluble problems of numerous cancer patients suffering from incurable, fatal disease.” Löwy, *Between Bench and Bedside* (1996), 37.

8 See *Curriculum Vitae* of R.N. MacDonald, enclosed with correspondence from R.N. MacDonald (Professor, Department of Medicine) to D.F. Cameron (Dean of Medicine, University of Alberta), Edmonton, 28 August 1975; in the UAA, ref. no. 51 (81-70-83), 6-B-85. MacDonald’s mentor, David A. Karnofsky, worked on planning high-dosage chemotherapy regimens for patients with advanced cancer and on developing evaluation criteria of their adequacy in terms of the therapeutic response and the level of toxicity. For details, consult D.A. Karnofsky, “Meaningful Clinical Classification of Therapeutic Responses to Anticancer Drugs,” *Clinical Pharmacology & Therapeutics*, 2, no.6 (1961): 709-712; D.A. Karnofsky, “Rationale for Aggressive or Extraordinary Means of Treatment of Advanced Cancer,” *CA: A Cancer Journal for Clinicians*, 12, no.5 (1962): 166-170; and D.A. Karnofsky “Problems and Pitfalls in the Evaluation of Anticancer Drugs,” *Cancer*, 18 (Dec. 1965): 1524-1527.

hospitals, a pharmacologist-biochemist, G.A. LePage was appointed director of the unit in 1972. LePage’s recruitment from the University of Texas M.D. Anderson Hospital in Houston was not fortuitous. During his negotiations with Walter C. MacKenzie, Dean of the School of Medicine at the University of Alberta, Robert A. Macbeth of the Department of Surgery and Pierre R. Band of the Department of Medicine, G.A. LePage had discussed “the extent to which he would be able to collaborate in chemotherapy studies with clinicians and the accessibility of clinical material for his research.” One of LePage’s aims was to streamline his long-standing research program on the mechanisms of action of chemotherapeutic agents and their targeted application in cancer patients. Thus, LePage planned a major expansion of the investigative activities at the cancer research unit into the clinical area.

To obtain a cancer specialist such as G.A. LePage, a member of an influential network of the US NCI-supported cooperative groups, meant to solidify the position of the CCI as a major cancer research institution in Canada. This resulted from access to the NIH funds, investigational new drugs and their study protocols. This strategic move allowed the Provincial Cancer Hospitals Board of Alberta to culminate initiatives of pioneering chemotherapists, such as Abdul Khaliq and Pierre Band, in securing more involvement in studies of American cooperative clinical cancer research groups. The latter were organized to form a comprehensive program of caring for cancer patients, especially those with advanced malignancies. Table 5-1 shows all

10 W.C. MacKenzie (Dean of Medicine, University of Alberta) to R.M. Taylor (Executive Director, NCIC). Edmonton, 12 July 1971, p.1; in the UAA, Acc. No. 81-70, box 7, item 78.
11 Before his appointment as Professor of Pharmacology at the University of Texas, G.A. LePage had worked at the University of Southern California, Stanford Research Institute, and the University of Wisconsin in Madison. In the course of his research career, LePage focused on the issue of cancer resistance to a single-drug therapy and developed schedules of drug combinations, mostly involving antimetabolites, based on laboratory experiments following pharmacological and biochemical principles. See correspondence from G.A. LePage to W.C. MacKenzie, Houston (TX), 4 August 1971; ibid.
12 A. Khaliq and P.R. Band made it possible for the W.W. CCI to partake in the US Eastern Cooperative Oncology Group, Southwest and Northeastern Cancer Chemotherapy Study Groups since 1969. Before commencing work in Edmonton, both Khaliq and Band had received training in cancer medicine under James F. Holland, Chief of Medicine at Roswell Park Memorial Institute in Buffalo, New York. J.F. Holland had been the first attending physician at the NCI Clinical Center in Bethesda, who developed a groundbreaking combinatorial clinical cooperative trial of methotrexate and 6-mercaptopurine to treat childhood acute leukemia in the mid-1950s. See Provincial Cancer Hospitals Board, Meeting No. 6, item C-5, 16 October 1969; in the UAA, Acc. No. 81-70-358, 13-A-10. Also, Pierre R. Band, Therapeutic Revolution: The History of Medical Oncology from Early Days to the Creation of the Subspecialty (Sharjah, U.A.E.: Bentham Science Publishers, 2014), 7, 50, and 65.
twenty-one cooperative groups across the US which worked on making presumably incurable malignancies more manageable through the assessment of various anti-cancer treatments.

<table>
<thead>
<tr>
<th>US Cooperative Groups</th>
<th>Participating Institutions</th>
<th>Supervised Care</th>
<th>Medical Consultations</th>
<th>Protocol Studies</th>
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<td>3. Central Clinical Drug Evaluation Program</td>
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<td>6. Southwest Chemotherapy</td>
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<td>72,222</td>
<td>38,715</td>
<td>12,808**</td>
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Table 5-1. Constituents of Cooperative Groups in the United States.\(^{13}\)

\(^{13}\) Compiled from responses of 250 principal investigators (PI) to a questionnaire sent to 376 PIs partaking in the US cooperative groups as of 1968. These data represent a 66% sample. *Institutions usually engaged with several
These cooperative groups also pursued improving standards of training in intensive cancer care for the general medical staff involved in protocol studies. As a result, a spillover effect occurred in cancer management by chemotherapy – information about the use of investigative agents disseminated by means of sharing expertise.

A constantly-expanding domain of clinical chemotherapy in hospital facilities became available to large numbers of patients. At the same time, this required an increase in the medical personnel to attend to a significant proportion of cancer patients desperate for new therapies because their disease no longer responded to conventional treatments anymore. Investigators partaking in the cooperative groups initiated clinical trials not only at their own discretion, but also under pressure from both the public and the laboratory scientists, mainly biochemists. The latter were enthusiastic about testing their novel compounds in humans, even though the results from animal experiments were less than satisfactory. It is worth noting that physicians were also eager to have new biochemical innovations, sponsored mostly by the US Cancer Chemotherapy National Service Center (CCNSC), tried in clinical studies, since there was a dearth of drugs that brought about relatively long regressions of the disease in patients.

As new compounds underwent human trials and yielded preliminary data, flashy announcements and premature reports came out on how promising drugs produced supposedly high percentages of remissions. Such communications not only enlivened patients and their families, but also restored confidence of the general population in the power of scientific medicine, which ensured a growing financial support for cancer research. The purported progress made physician-investigators virtually immune to both external and internal critiques that were vital for generating tangible results. Therefore, the government introduced measures to regulate human subject research in order to build public awareness of clinical investigations. The underlying assumption was that patients and research volunteers should have no hesitation about their participation in trials because they had adequate protection by the law.

*cooperative groups. **This number included clinical studies of the whole spectrum: Phase I, II, and III. I adapted this table from “Care and Training Tabulation for Cooperative Groups,” stamped by the University of Alberta Dean of Medicine’s Office, Edmonton, 2 October 1969; in the UAA, Acc. No. 81-70-358, 13-A-10.*
Given that the system of cancer research depended on mutually supportive relationships of the scientific-clinical community, government agencies, and non-governmental organizations, which all drew on public funding, state administration adopted an accommodating attitude to its regulation. Doctor-investigators and the supporting infrastructure for human research were on top of the pyramid aimed at developing the “means to reduce the incidence, morbidity, and mortality of cancer in humans.” Even a principal US regulatory document on human experimentation, prepared by the NIH in December 1971, *The Institutional Guide to DHEW Policy on Protection of Human Subjects*, declared to clinical scientists that its normative character was open to interpretation.

In the guide’s foreword, D.T. Chalkley, Chief of Institutional Relations Section in the Division of Research Grants, explicitly stated that a policy to safeguard the human research subject needs to be ‘flexible’ for the sake of the public interest. Medical professionals within institutional ethics review committees were in charge of making this flexibility practical. Committee members were to determine an appropriate protection of the human subject. This included their welfare, balance of risks and benefits in relation to the importance of knowledge to be gained, and the informed consent process. Only the investigators who engaged in similar clinical studies could adequately perform this task. Study protocols submitted for such reviews had to pass muster with the quorum of like-minded colleagues subscribing to the same research ethos. Their threshold of what clinical research could expose subjects to harm arose from the style of experimental practice to which the investigators were accustomed.

Clinical investigators applied their professional judgment to cancer studies in question to a greater degree at the stage of protocol design and development than in the phase of institutional review. More was at stake when cancer specialists commented on or even criticized research protocols written by their peers. It was about collegiality and the professional status of individual

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16 *Ibid.*, iii. D.T. Chalkley wrote, “A flexible policy is essential. Research, development, and the reduction to practice of new ideas are not carried out in a practical, ethical, or legal vacuum. The public interest obviously would not be served by an inflexible approach to what can or should be done.”
exponents of a particular therapeutic modality. Clinicians’ ethical considerations on certain procedures of the investigation were part of a larger process of intra-professional consensus that involved recognition of moral and technical competences amid colleagues, reputation, and a shared responsibility for anything untoward. Thus, investigators’ exchange of expert opinion on proposed and ongoing clinical studies produced a fair amount of discussion on aspects of their ethics. I argue that protocol-related discussions among investigators, notably on aggressive experimental approaches to cancer treatment, clarified the meaning of human subject research ethics. This followed from a correlation of challenges inherent in clinical studies with ethical principles formulated in human experimentation guidelines. How did this ethical consensus on particular procedures of the RCTs emerge in the community of Canadian cancer specialists? Why did this consensus acquire cultural dimensions through the seemingly extraneous factors of international cooperation, political expediency, and inter-professional competition?

5.1. Two Uncommon Tumors and One Common Sense

Unlike in the United States, there were no cooperative clinical cancer research groups in Canada except those in Ontario. This followed upon The Ontario Cancer Treatment and Research Foundation that had launched an effective collaboration among seven cancer clinics and a number of teaching hospitals since 1964, as discussed in Chapter 4. Still, the NCIC had a desideratum of the Canadian clinical cancer trial program as early as 1962, when the Institute’s Clinical Advisory Committee recommended not to embark on such a program in view of “the difficulties envisaged and the immense cost of setting up a National organization and the relatively small gain.”17 The difficulties probably concerned a shortage of well-qualified clinical investigators and adequate facilities, which were successfully surmounted less than a decade later. As to the requisite expenditure on the clinical trial program, the introduction of a comprehensive health insurance with universal coverage across Canada in the late 1960s substantially reduced the financial burden that the NCIC had to assume.18 Moreover, as cancer researchers in Canada forged closer ties with the US colleagues and pharmaceutical companies,

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access to investigational new drugs improved. A growing participation of Canadian clinicians in American cooperative trials made it imperative to organize certain units necessary for a systematic assessment and coordination of large-scale investigative activities. Some doctor-researchers working in major Canadian medical centers called for the organizational innovations. For example, Walter D. Rider, a senior radiotherapist at the OCI/PMH, noted in late 1965, “it [wa]s important that large scale collaborative studies be carried out and the results therefrom be analyzed statistically and therefore effectively. One wonders if the offices of the National Cancer Institute of Canada should not be promoting studies of this kind.”

Alex J. Phillips, assistant executive director and statistician of the NCIC, admitted in his correspondence with Stella Booth of the US National Cancer Institute that neither collaborative clinical trials, nor cancer epidemiology in Canada received due consideration in the late 1960s. The reason was, Phillips explained, the absence of properly trained Canadian medical professionals to manage those two interrelated aspects of the NCIC program. Things changed in 1971 when the NCIC recruited Anthony B. Miller, a British physician-epidemiologist, to direct a newly formed Epidemiology Unit. Miller’s duties involved coordination of cooperative randomized trials of treatment and screening in the field of cancer. Until 1971, Miller had worked in the capacity of a designer and coordinator-supervisor of clinical trials and epidemiological studies of tuberculosis and lung cancer at the Medical Research Council in London, England. A decade-long experience as a member of scientific staff of the MRC Tuberculosis and Chest Diseases Unit made him a sought-after candidate for the NCIC position. Further, Miller provided a fresh look at the organization of the cooperative clinical trials program in Canada. It was a tactical move on the part of the NCIC executives who wanted

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20 A.J. Phillips to S. Booth (Coordinator of Cooperative Clinical Activities, NCI, Bethesda), Toronto, 11 July 1968; in the UTA, A1986-0035/03(07).
21 Application form for a fellowship in the American College of Epidemiology, enclosed with correspondence from A.B. Miller (Director, NCIC Epidemiology Unit) to Curtis Mettlin (Director, American College of Epidemiology), Toronto, 28 November 1984; in the UTA, A1986-0035/034(08).
22 Canadian Who’s Who Biographical Data Form, A.B. Miller, 29 March 1985; ibid.
to distance their initiative from the politics of American cancer campaign unfolding since 1970.\textsuperscript{23} The latter provided the perfect foil for the inauguration of Canadian cooperative clinical trials program in cancer.

\textbf{Figure 5-1.} Anthony Bernard Miller.\textsuperscript{24}

Leading cancer specialists in Canada had had informal talks on the possibility of setting up a collaborative program in clinical chemotherapy before 1971, since this area of treatment

\textsuperscript{23} Rettig, \textit{Cancer Crusade} (1977), 17 and 296-301.

\textsuperscript{24} Courtesy of A.B. Miller, email message to author, 19 November 2017. According to A.B. Miller, this photograph, one of his favorite, was taken in the early 1980s.
development produced new drugs at a rather high rate. Many pilot trials of them, however, generated data that were not evaluable according to certain criteria due to inadequate study designs. In consequence, decisions concerning a potential role of new drugs in clinical use were often made without comparable efficacy-controlled studies. This situation necessitated the conduct of large-scale RCTs for at least some of the chemotherapeutic agents that had yielded positive results in a series of preliminary studies by different research groups.25 In addition to the clinical investigators’ concerns, there was also pressure from the general practitioners who kept up with contemporary innovative practices described in specialized literature. On the one hand, premature reports on new drug applications seemed to provide desired answers to therapy-oriented questions. On the other hand, such reports on small-scale studies failed to provide information immediately useful to physicians because their patients were not selected on the basis of particular trial eligibility criteria.26 Thus, the overlap of scientific and practical issues in cancer therapy further complicated the ethical status of clinical trials and methodology underlying them.

Scarcity of human and material resources did not permit to carry out all possible RCTs necessary to test all the available new agents or their combinations. Allowing for this, Robert M. Taylor, Executive Director of the NCIC, and Lyonel G. Israels, Chairman of the NCIC Clinical Advisory Committee, initiated a discussion on the desirability and feasibility of establishing cooperative clinical trials program in Canada in late 1970.27 Already on 26 February 1971, all six members of the Clinical Advisory Committee met with R.M. Taylor to discuss the role the NCIC could have in the organization of nationwide collaborative trials. The primary item on the agenda read, “Is there a place for a Canadian-based cooperative clinical trial system to answer certain questions regarding therapeutic regimens in malignant disease [?] This may be considered analogous to the MRC trials in Britain or the CCNSC trials in the U.S.A.”28 The seven

25 International Union Against Cancer (UICC), Report of the Meeting of the Committee on Controlled Therapeutic Trials, p.2, Paris, 3-5 April 1973; enclosed with correspondence from R. Flamant (Secretary to the Committee on Clinical Therapeutic Trials) to A.B. Miller, Villejuif (France), 26 June 1973; in the UTA, A1986-0035/03(07).
27 R.M. Taylor to L.G. Israels (Professor, Department of Internal Medicine, University of Manitoba), Toronto, 2 December 1970; in the UTA, A1986-0035/03(01).
28 The Clinical Advisory Committee consisted of D.E. Bergsagel (chemotherapy; Chief Physician, the OCI/PMH), Thomas C. Brown (Pathologist-in-Chief, the OCI/PMH), L.G. Israels (hematology-chemotherapy; Director of
discussants reached a consensus on the need for such a system. Their recommendations launched the Canadian cooperative clinical trials program that was feasible through

1) a clinical research function to determine the value or relative values of various forms of treatment; 2) an educational function related to the disease and to patient care; 3) increased communication between physicians caring for the same types of malignant disease in various parts of the country; 4) the establishment of a central organization with the potential to set up with relative ease across Canada studies of malignant disease as to etiology, diagnosis and treatment. 

Deliberations on potential collaborative investigations were next on the agenda. L.G. Israels had circulated before the meeting two tentative protocols for possible cooperative trials. One protocol, prepared by Daniel E. Bergsagel, Professor of Medicine at the University of Toronto and Chief Physician at the OCI/PMH, was on the treatment of advanced Hodgkin’s lymphoma. The other protocol, drafted by Gerald J. Goldenberg, Associate Professor at the Department of Medicine of the University of Manitoba and Clinical Research Associate of the NCIC, dealt with the prophylactic therapy for carcinoma of the kidney. Members of the Clinical Advisory Committee (CAC) agreed that each trial should have its own committee and chairperson accountable to the CAC. To make both scientific and ethics review more formal, the CAC amended the NCIC grant application form by introducing a requirement for a signature of the CAC chairperson. Following the approval of relevant protocols by the CAC, its chairperson submitted them to an ad-hoc committee of the NCIC Board of Directors “for consideration of their ethical justification.” Therefore, two stages of ethics review aimed to ensure against

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30 Agenda for a meeting of the NCIC Clinical Advisory Committee, Toronto, 26 February 1971; in the UTA, A1986-0035/03(01).
31 Therapeutic radiologist and pediatrician, John M.M. Darte, who after about four years at the OCI/PMH of Toronto moved to St. John’s in Newfoundland to become Professor and Chairman of the Department of Pediatrics at Memorial University in 1962, had offered this amendment by correspondence with R.M. Taylor who presented it at the CAC meeting. See “Policy of National Cancer Institute of Canada re Human Experimentation,” ibid.
unacceptable human experimentation. What procedure determined that proposed clinical trials were important in terms of healthcare priorities and scientifically appropriate?

There was no such procedure initially. Why did Hodgkin’s disease and kidney cancer become candidates for the inauguration of the Canadian cooperative clinical trials program? At the time, neither of the malignancies was among most frequently occurring or death-dealing forms of cancer. In 1970, mortality rate from Hodgkin’s disease was four in 100,000 Canadians, and seven – from carcinoma of the kidney.33 The incidence of Hodgkin’s disease in Canada amounted to 375 among males and 264 among females, while the incidence of cancer of the kidney and other urinary organs was 714 and 388 cases, respectively.34 In comparison, mortality rate from cancer of the lung in men was approximately 55 per 100,000, and from breast cancer in women – about 30 per 100,000.35 In terms of incidence, respectively, there were 4,737 new cases of cancer in the respiratory organs and 6,981 new malignancies of the breast registered in 1970.36 Thus, the NCIC decision to organize two trials involving Hodgkin’s lymphoma and carcinoma of the kidney had little to do with healthcare priorities. Did this decision pivot around the scientific interest of leading investigators?

The recommendation of the NCIC to do cooperative trials evaluating treatments for Hodgkin’s lymphoma and carcinoma of the kidney was probably based on the assumption that these malignancies were potentially more curable.37 Long-term studies of these two malignancies produced some advances in their management, but they required corroboration by large-scale RCTs that were likely to yield results convincing to both investigators and physicians. As the

34 These numbers corresponded to 3.5 male and 2.4 female new cases of Hodgkin’s disease per 100,000 Canadians and, respectively, 6.7 and 3.3 new cases of cancer of the kidney and other urinary organs in 1970. Ibid., 13, 16, 32, and 35.
35 Ibid., x.
36 Ibid., 9 and 52.
37 In this respect, therapeutic radiologist and director of the British Columbia Cancer Institute, J.M.W. Gibson authoritatively noted, “ [...] it is essential that the general public – the potential patients – should be confident that cancer can be cured at the present time, and that cancer research work is now not looking for a cure for cancer but for the ideal cure for cancer, one that will cope with a cancer at any stage, regardless of how widespread it may be in a patient’s body.” Italics in the original. See J.M.W. Gibson, “The Radiotherapist’s Hopes for Radiobiology,” in Proceedings of the Ninth Canadian Cancer Research Conference, ed. P.G. Scholefield (Toronto: University of Toronto Press, 1971), 219.
NCIC Executive Director, R.M. Taylor, pointed out to G.J. Goldenberg, “It [was] particularly important that these first attempts of the NCI[C] to develop Canadian trials be successful.” Accordingly, the extensive cancer research underlying these attempts needed two effective clinical trials to demonstrate how it could turn into a better treatment for patients. The proposed protocols for Hodgkin’s disease and kidney cancer trials originated in the scientific-medical environment that boded well for their implementation: Daniel E. Bergsagel of Toronto and Lyonel G. Israels of Winnipeg were high-caliber investigators who had experienced failures of clinical research and knew how to avoid them.

D.E. Bergsagel had worked at the Department of Medicine of the University of Texas M.D. Anderson Hospital and Tumor Institute and participated in investigations of the Southwest Cancer Chemotherapy Study Group for three years before the OCI/PMH recruited him to become Chief Physician in 1964. He designed the Hodgkin’s disease protocol with the benefit of scientific insights from Vera Peters, Associate Professor of Radiology at the University of Toronto and therapeutic radiologist at the OCI/PMH, and Donald M. Whitelaw, Professor of Medicine at the University of British Columbia and a senior research physician to the B.C. Cancer Institute. Owing to controlled trials in radiotherapy and chemotherapy over the late 1960s, according to Peters, cancer specialists gradually turned to accepting that clinical cures of Hodgkin’s disease were possible. This growing acceptance generated further clinical studies, which indicated that radiation therapy had limitations in the management of this malignancy. The limitations of radiotherapy meant that combinatory chemotherapeutic approaches to Hodgkin’s

40 Vera Peters was the only Canadian investigator among 42 leading cancer researchers invited to partake in the international conference “Obstacles to the Control of Hodgkin’s Disease” held on 13-15 September 1965 in New York, N.Y. This meeting convened clinicians of authority from the Unites States (Paul P. Carbone, Sidney Farber, Emil Frei III, Henry S. Kaplan, David A. Karnofsky, Robert J. Lukes, Saul A. Rosenberg, Philip Rubin, etc.), France (Raymond Latarjet, Maurice Tubiana), and the United Kingdom (Eric C. Easson) to discuss achievements and new treatment strategies in the management of Hodgkin’s Disease. See American Cancer Society and the NCI, “Symposium on Hodgkin’s Disease,” Cancer Research, 26, no.6 (June 1966): 1045-1046, and 1232. Also, Ruth E. Alison and D.M. Whitelaw, “A Comparison of Nitrogen Mustard and Vinblastine Sulfate in the Treatment of Patients with Hodgkin’s Disease,” CMAJ, 102, no.3 (14 Feb. 1970): 278-280.
disease were on the rise. Between 1968 and 1970, D.E. Bergsagel and his research group engaged in pilot RCTs evaluating a range of anti-cancer drugs and radiation therapy for Hodgkin’s lymphoma. Preliminary evidence suggested that patients with advanced Hodgkin’s disease fared better on a regimen of combination chemotherapy and radiotherapy. A logical development in 1971 was, therefore, a design of the protocol to compare combined therapeutic modalities for late-stage Hodgkin’s disease in a large collaborative RCT. D.E. Bergsagel drafted such a protocol for “Hodgkin’s Disease, Stages IIIB and IV” with an emphasis on the assessment of intensive chemotherapeutic combinations, rather than on the benefit of additional extensive radiotherapy.

Bergsagel’s rationale was that medical-scientific problems addressed in the protocol should balance out the practical issues pertaining to outpatient treatment. He reasoned that if two proposed drug combinations proved to be equally effective, the physician “would prefer PCV [Procarbazine, Cyclophosphamide, and Vinblastine] because this schedule permit[ed] patient visits to be reduced to once every three weeks, versus two to three times in four weeks for MOPP [Nitrogen Mustard, Oncovin (vincristine), Procarbazine, and Prednisone].” It seemed a valid comparison for a single-institution RCT, but not for a multi-center one. Donald M. Whitelaw of Vancouver explained the reason why Bergsagel’s trial needed to center on the role of radiotherapy as an addition to one combination of drugs. He stated, “I think we can probably

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45 The protocol had two objectives: “1. To compare the effectiveness of PCV and MOPP in the treatment of randomly assigned patients with Stage IIIB and IV Hodgkin’s disease. 2. To determine whether the addition of radiation therapy for a randomly assigned group of patients who achieve a satisfactory remission with combination chemotherapy, prolongs the disease-free interval significantly.” *Ibid.*, 1-2.
achieve a consensus among the chemotherapists more readily than we can among the radiotherapists.”

Since radiotherapy was the main treatment mode for Hodgkin’s disease, the position of its leading practitioners was decisive in getting the cooperative trial off the ground. In L.G. Israels’ view, the Hodgkin’s disease RCT became a prototype for the Canadian cooperative clinical trials program because it “involve[d] clinicians with radiological as well as chemotherapeutic interests.” Collaborative work of radiotherapists and chemotherapists on one large-scale trial could settle some inter-professional disagreements. It also had the potential to create a domino effect of increasing stimulus to use RCTs as the method of choice to investigate available and new therapeutic approaches to neoplastic disease in Canada. Thus, it was quite important to bring radiotherapists and chemotherapists together in the Hodgkin’s disease trial.

To reach a general agreement on this trial, the NCIC Executive Director, R.M. Taylor organized a meeting of select cancer specialists in Vancouver on 15 May 1971. The consultation was among three chemotherapists – D.E. Bergsagel, L.G. Israels, Donald M. Whitelaw, and three radiotherapists – Vivian Basco, John M.W. Gibson, both of the British Columbia Cancer Institute, and Ray S. Bush, Head of Therapeutic Radiology at the OCI/PMH. They considered what question should be the basis of the first clinical trial supported by the NCIC. Their decision gravitated towards one objective for the trial: to assess the value of supplementing the combination chemotherapy MOPP with radiation therapy.

During the Ninth Canadian Cancer Research Conference in June 1971, the Coordinating Committee on a clinical trial in advanced Hodgkin’s disease reviewed the study design at length and approved the above single objective. The committee members agreed that D.E. Bergsagel along with A.B. Miller draw up a final protocol. Further, the members decided to launch the

46 Whitelaw suggested to get rid of unnecessary complexity of the trial by limiting its scope to one research question, “Does the addition of extensive radiation, after a patient has achieved a remission with intensive chemotherapy, result in prolongation of life as compared with intensive chemotherapy alone?” See D.M. Whitelaw to L.G. Israels, Vancouver, 12 March 1971; in the UTA, A1986-0035/03(01).
48 Minutes of the meeting of CAC Coordinating Committee on a Clinical Trial in Advanced Hodgkin’s Disease, Honey Harbour (ON), 8 June 1971, enclosed with correspondence from A.B. Miller to D.E. Bergsagel, 11 June 1971; in the UTA A1986-0035/03(02).
study after the centers represented on the committee – Toronto, Winnipeg, and Vancouver – had provided feedback on the reviewed protocol. Although in discussions on this trial the committee deemed it not advisable to attempt getting input from the country as a whole, this meeting was a means to ensure that the NCIC obtained expert opinion across Canada on the later proposed studies. The NCIC planned to approach other Canadian cancer treatment centers, bringing them into the cooperative Hodgkin’s disease trial as soon as necessary arrangements could be made. A major arrangement concerned the nomination of at least one radiotherapist and one physician-chemotherapist as local coordinators of the study in each participating institution.

Gerald J. Goldenberg participated in the Coordinating Committee meeting as well, but he saw the Hodgkin’s disease trial through the prism of his proposed study on kidney cancer. Its protocol, *Prophylactic Therapy of Hypernephroma with Medroxy Progesterone Acetate (Provera)*, had no apparent similarities to the Hodgkin’s disease protocol.\(^{50}\) A renal tissue tumor had to be surgically operable and the efficacy of a synthetically prepared hormone was evaluated against a placebo. In other words, Goldenberg’s proposed trial involved patients with a non-advanced kidney cancer who did not undergo intensive treatment by a combination of toxic drugs. Why did the NCIC Clinical Advisory Committee recommend developing it as a second cooperative clinical trial? There were two likely reasons.

First, Goldenberg had used *Provera* since 1964 to treat metastatic renal cell carcinoma and a series of other cancers amenable to control by hormonal substances. A partnership formed between the University of Manitoba and the *Upjohn Company*. Second, the company tried to nudge investigators to use *Provera* in a variety of animal studies that could further lead to experimental therapeutic investigations with patients. For instance, the Ontario Cancer Treatment and Research Foundation awarded a grant in May 1962 to C.P. Vernon, Clinical Teacher of Obstetrics and Gynaecology at the University of Toronto, Toronto General Hospital, and Consultant in Gynaecology at the OCI/PMH, to assess the use of *Provera* in the treatment of carcinoma of the endometrium.\(^{51}\) Vernon carried out this three-year study in local teaching hospitals in collaboration with Douglas E. Cannell, Professor and Head of Obstetrics and

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\(^{50}\) Protocol enclosed with the agenda for a meeting of the NCIC Clinical Advisory Committee, Toronto, 26 February 1971; in the UTA, A1986-0035/003(02).

Gynaecology at the University of Toronto, to evaluate progestational steroids clinically in the management of advanced carcinoma of the endometrium that was inoperable and resistant to available options of radiotherapy and chemotherapy. The specific treatment was Provera, administered in large doses of 50-100 mg daily over several months and sometimes combined with chemotherapeutic drugs.\(^{52}\) A year later, Vernon and Cannell referred to this administration of Provera in thirty-two patients as “massive doses of the progestational steroid,” and they reported that “approximately one-third of patients have shown significant tumour [sic] remission.”\(^{53}\)

Similar laboratory and clinical investigations of Provera proliferated in other Canadian medical centers. Alexander Meisels, Professor of Pathology and Head of the Cytodiagnostic Laboratory at Laval University, Québec, studied effects of medroxyprogesterone, among other synthetic and natural sex hormones, on a model of experimental carcinogenesis of the lung and the uterine cervix in mice.\(^{54}\) In Winnipeg, a research program unfolded using Provera in a range of settings. Over 1966-1971, C.R. Bradford, T.M. Roulston, and H.A. Toews, all professors at the department of Obstetrics and Gynaecology of the University of Manitoba, examined different aspects of Provera’s use: from the interaction between the drug and the pituitary or adrenal glands, to its clinical application in patients with hormone-dependent tumors.\(^{55}\) In a sense, G.J. Goldenberg’s proposal to conduct a cooperative trial employing Provera to assess whether it could prevent a recurrence of kidney cancer appeared to fit within contemporary developments. Even more so because the Upjohn Company provided investigators with the drug free of charge if they concluded formal agreements on legal liability for any clinical accidents.

As soon as G.J. Goldenberg accepted chairmanship of the organizing committee on kidney cancer in March 1971, he contacted Edward L. Masson, Medical Director of the Upjohn Company of Canada. Goldenberg inquired about the availability of Provera and the possibility to

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52 Protocol, Carcinoma of the Endometrium, by C.P. Vernon, p.3, enclosed with “The OCTRF Application for a Grant for Clinical Research” (1962). Interestingly, Vernon noted in the application that his grant expenditure involved travel to the University of Western Ontario to correlate results and to the National Institutes of Health of the United States, but without stating the purpose. In all probability, the NIH provided the investigational new drug that the Upjohn Company supplied. Ibid.


55 Previous [Inactive] Research Grants, Department of Obstetrics and Gynecology, University of Manitoba, April 1977; in the UMFMA, Department of Obstetrics and Gynecology, 2.15.2.
produce suitable placebo tablets for the proposed double-blind trial.\textsuperscript{56} Pending the decision of the \textit{Upjohn Company} board of directors on the cost of necessary supplies and the study duration, E.L. Masson provisionally agreed to collaborate on the trial. The manufacture of placebo tablets identical to \textit{Provera} ones was a practical challenge, since a random allocation to the prophylactic therapy aimed to ensure the trial was ethically acceptable: that neither attending physicians, nor patients knew which tablets they received. To get an independent review of the proposed protocol, G.J. Goldenberg approached A.B. Miller, the NCIC Assistant Executive Director, who was to coordinate the cooperative trial.

In Miller’s estimation, the trial population had to be no fewer than 200 patients to show a statistical significance of obtained results and several medical centers needed at least two years to enroll this number.\textsuperscript{57} Miller agreed with Goldenberg that the trial’s objective was to “determine whether the administration of provera [\textit{sic}] earlier in the course of hypernephroma had a beneficial effect on the course of the disease and on survival time” of patients treated initially by a surgical removal of the kidney.\textsuperscript{58} According to the trial design, patients underwent randomization into a \textit{Provera} or a placebo group following surgery and a series of medical examinations. Based on his previous experience, Goldenberg indicated that patients needed to receive 100 mg of \textit{Provera} or placebo four times a day for a minimum of three months, so Miller could roughly calculate how many tablets of each type to request from E.L. Masson. In the course of fine-tuning the trial protocol particularities, Goldenberg and Miller also considered whether a four-times-a-day dosage was feasible in the clinic and how often to monitor patients for a regular intake of drugs and for any related untoward side-effects.

Another factor of importance was a likely extended period of enrolment in the trial, for carcinoma of the kidney occurred quite rarely. According to the protocol reviewed by Miller, men of any age and women aged fifty or over were eligible for the trial.\textsuperscript{59} Goldenberg questioned the exclusion of women under the age of fifty presumably because of the concern that women in the reproductive age group could receive contraceptive agents and thus distort the clinical results.

\textsuperscript{56} R.M. Taylor to G.J. Goldenberg, Toronto, 11 March 1971; and G.J. Goldenberg to R.M. Taylor, Winnipeg, 15 March 1971; both in the UTA, A1986-0035/03(01).

\textsuperscript{57} A.B. Miller to E.L. Masson, Toronto, 23 July 1971; in the UTA, A1986-0035/038(03).

\textsuperscript{58} Protocol, \textit{Prophylactic Therapy of Hypernephroma} (July 1971), 3.

\textsuperscript{59} \textit{Ibid.}, 3-4.
due to the cross-interaction of drugs.\textsuperscript{60} There were other recognized treatment options for patients who had their renal cell carcinoma removed surgically, such as post-operative radiotherapy, and Goldenberg realized that it may not be ethically appropriate to request surgeons and radiotherapists to withhold it.\textsuperscript{61} This added a further complication that could diminish the number of patients otherwise eligible for the trial.

Miller, however, disagreed on the inclusion in the trial of women under fifty because a possible induction of amenorrhea with high doses of \textit{Provera} could make women of reproductive age infertile. Concurring with Miller’s expert opinion, E.L. Masson of the \textit{Upjohn Company} expressed a different reason for excluding female patients under fifty. In Masson’s words, “…any woman who [ook] large doses of Provera w[ould] become amenorrhoeic \textit{sic}. This in itself [wa]s no great problem \textit{sic} but Provera orally [wa]s not 100\% effective as a contraceptive and therefore, these women would have [had] to use other methods of contraception to insure that they d[id] not become pregnant at this late age.”\textsuperscript{62} Consequently, the above specialists weighed the pros and cons of a larger trial intake of patients and decided against it and against a possible contamination of clinical data. At the same time, this meant that women under fifty afflicted with renal carcinoma were ineligible for the proposed trial.

No less significant in terms of ethics was Miller’s protocol amendment concerning the continuation of randomly allocated prophylactic therapy or no-treatment. In Goldenberg’s draft protocol, if any unfavorable changes in laboratory findings or in physical symptoms indicating the recurrence of disease took place during the trial, “those patients previously on placebo therapy [were] switched to Provera 100 mgs. \textit{q.i.d} [four times a day] and those previously maintained on Provera continue[d] on therapy.”\textsuperscript{63} Miller rectified this by noting that both treatment with \textit{Provera} and placebo had to be maintained either until the appearance of metastases or for two years, whichever was the shorter period. On obtaining evidence of definite relapse of the disease, the attending physician had discretion to place the patient on whatever

\textsuperscript{60} G.J. Goldenberg’s comments on the protocol \textit{Prophylactic Therapy of Hypernephroma} (July 1971) reviewed by A.B. Miller, enclosed with correspondence from G.J. Goldenberg to A.B. Miller, Winnipeg, 10 August 1971; in the UTA, A1986-0035/038(03).
\textsuperscript{61} \textit{Ibid}.
\textsuperscript{62} Amenorrhea is an abnormal absence of the menses. See E.L. Masson to A.B. Miller, Don Mills (ON), 8 September 1971, p.2; in the UTA, A1986-0035/038(03).
therapy was considered necessary.\textsuperscript{64} While G.J. Goldenberg had general comments on the revised protocol and A.B. Miller accepted them, E.L. Masson drew attention to a potential problem of using \textit{Provera} in this particular cooperative trial.

The Medical Director of the \textit{Upjohn Company} of Canada, E.L. Masson, queried his corporate colleagues about the availability of data on the tolerance of a 400 mg single-dose \textit{Provera}.\textsuperscript{65} In response, Masson received an unexpected communication from Grant Reist of the UK subsidiary about \textit{Provera}'s possible untoward effects when used as a prophylactic drug in lower doses than 400 mg daily. He transmitted this message, which essentially called in question the assumption that \textit{Provera} was a relatively harmless and non-toxic agent that could only help the cancer patient, to G.J. Goldenberg. The latter let Miller know about this word of warning from overseas and asked to postpone preparations on the trial until further information was at hand.\textsuperscript{66}

H.J.G. Bloom, a consultant radiotherapist at the Royal Marsden Hospital and Institute of Cancer Research in London, advised against the prophylactic use of \textit{Provera} in renal cell carcinoma because the drug might aggravate the disease.\textsuperscript{67} Since 1959, Bloom was an investigator who had employed \textit{Provera}, supplied via the UK subsidiary of the \textit{Upjohn Company}, in the treatment of metastatic hypernephroma.\textsuperscript{68} Summarizing his decade-long experience with using \textit{Provera} in clinical work that included 80 patients with advanced carcinoma of the kidney, Bloom observed that acceleration of tumor growth had occurred in

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\textsuperscript{64} Protocol \textit{Prophylactic Therapy of Hypernephroma} (July 1971), 3 and 8.
\textsuperscript{65} E.L. Masson to A.B. Miller, Don Mills (ON), 3 August 1971, p.4; in the UTA, A1986-0035/038(03).
\textsuperscript{66} G.J. Goldenberg to A.B. Miller, 10 August 1971, Winnipeg, Manitoba; \textit{ibid}.
\textsuperscript{67} H.J.G. Bloom read a paper at the Upjohn Symposium “Provera in Treatment of Some Malignancies” at the Royal Society of Medicine, on 27 October 1970, and later published an article in which he noted: “The possible stimulation of renal cancer during hormone treatment must be borne in mind, and patients should be seen at short intervals in the early stages of such treatment. For this reason we have waited for clear evidence of advancing disease before embarking on endocrine therapy. Renal cancer metastases may occasionally remain latent for a time, or progress only very slowly, and in such patients no treatment at all may be preferable to a regime which may disturb a satisfactory tumor-host relationship. This concept is particularly important if hormone administration is ever considered in a prophylactic role as part of the curative treatment of primary renal carcinoma.” H.J.G. Bloom, “Medroxyprogesterone Acetate (Provera) in the Treatment of Metastatic Renal Cancer,” \textit{British Journal of Cancer}, 25, no.2 (1971): 259.
\textsuperscript{68} G.J. Goldenberg to A.B. Miller, 10 August 1971, \textit{op. cit}.
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three patients treated with Provera.69 As Bloom’s four articles featured in a nine-reference bibliography of the revised protocol for a Canadian cooperative trial, A.B. Miller acted on this notification immediately.

To find out details about the reported data, Miller called Bloom.70 His main purpose, of course, was to seek Bloom’s advice on the value and usefulness of the proposed trial of Provera as a prophylactic therapy for kidney cancer. Bloom explained the particularities of his clinical evidence and reiterated that he would not use the drug for this kind of trial. Bloom’s position prompted Miller to reconsider expediency of the trial and discuss it again at the NCIC Clinical Advisory Committee meeting. Before any further action, however, Miller consulted local cancer specialists involved in the management of kidney cancer. His first contact was William K. Kerr, a urologic surgeon and Assistant Professor of Surgery at the University of Toronto. Kerr told Miller that he was aware of a possible renal carcinoma exacerbation due to Provera because his colleague, Willet F. Whitmore of the Memorial Sloan-Kettering Cancer Center in New York, was engaged in studies of progestational steroids and had some negative results.71 It was worth a try to follow this lead.

A.B. Miller wrote to W.F. Whitmore, Chief of Urologic Service at the Memorial Hospital for Cancer and Allied Diseases and the Clinical Unit of Memorial Sloan-Kettering Cancer Center in New York, to get details of his experience with using Provera. This information could allow the NCIC Clinical Advisory Committee to make a more informed decision on whether to proceed with the second cooperative trial or not. Miller’s major concern was to ask Whitmore for his opinion on the ethical justifiability of the trial comparing a placebo with Provera as prophylactic therapy after surgery for carcinoma of the kidney. Miller explained that in view of new evidence that some patients treated with Provera for metastatic renal carcinoma had shown

69 Among the British patients were 54 males and 26 females. See Bloom, “Medroxyprogesterone acetate (Provera) in the treatment of metastatic renal cancer” (1971): 251-253.
71 In this connection, Kerr suggested a clinical trial protocol evaluating post-operative radiation, no radiotherapy, and pre-operative radiation in patients with cancer of the kidney. See notes of a conversation between A.B. Miller and W.K. Kerr, Toronto, 5 October 1971; in the in the UTA, A1986-0035/038(03).
exacerbation of the disease, the NCIC was “faced with the ethical decision of weighing a doubtful benefit against a possible aggravation in some patients.”

It appeared from Whitmore’s answer that he had treated in excess of 40 patients with metastatic renal carcinoma by administering either oral Provera or intramuscular Depo-Provera over the 1960s. Still, Whitmore replied somewhat evasively. Although he could not give a precise number of favorable responses, Whitmore noted that this incidence had been substantially short of that described by H.J.G. Bloom and his colleagues in the UK. However Whitmore added, “the patient mentioned by Dr. Kerr in whom it seems possible that provera [sic] may have aggravated the disease [had] the rate of progression of disease prior to the institution of provera not so clearly established that one c[ould] be confident that the growth rate was enhanced by provera.” Whitmore’s non-committal reply to Miller’s inquiry on the ethics of conducting a cooperative nationwide trial with Provera seemed to have roots in a legal obligation of non-disclosure that agreements on university-industry partnerships entailed.

Propositions of H.J.G. Bloom and W.F. Whitmore were significant enough factors for a critical appraisal of the Provera protocol by the NCIC Clinical Advisory Committee that had to reconsider the ethical basis of the proposed trial. There was a prolonged discussion on both the substantial issues of this cooperative study – the risk-benefit ratio of the prophylactic therapy, and the technical matters – a disagreement among investigators on the hormone-dependency of the renal cancer and a difficulty in making urological surgeons cooperate. In anticipation of a tough debate at the CAC meeting, Miller had contacted biochemist-endocrinologist Robert L. Noble, Director of the Cancer Research Centre at the University of British Columbia in Vancouver, to clarify the points open to question. Noble was “surprised to learn that hormones ha[d] an effect in cancer of the kidney.” He also told Miller that metastatic renal carcinomas, unlike other tumors, were known to have spontaneous regressions after a surgical removal of the

74 Italics in the original. *Ibid.*
75 Notes of a conversation between A.B. Miller and R.L. Noble, 3 November 1971; in the in the UTA, A1986-0035/038(03).
primary growth. When asked whether there was any reason not to try Provera in a cooperative study, Noble answered that the proposed trial was “not likely to demonstrate anything.”

There was a preponderance of expert opinion on the futility of organizing the Provera trial. Accordingly, the CAC decided that the NCIC could not be associated with supporting this trial in view of the risk of tumor growth acceleration following Provera therapy. Lyonel G. Israels, the CAC’s chairman, stated, “it was not judged ethical to permit the use of the drug in asymptomatic patients,” and referred to the available data indicating the possibility of aggravation of the neoplastic disease by Provera. He considered it unethical to conduct this trial with patients having the disease at its initial stages because conventional surgery and postoperative radiotherapy offered better prospects for recovery and had a very low probability of causing cancer exacerbation, unlike the prophylactic treatment with Provera. Yet, Israels’ colleague, G.J. Goldenberg, had a different view, “I would have no reservations about the ethics of conducting such a trial because the risk of tumor acceleration [wa]s sufficiently small and not so clearly established to rule out a double-blind randomized trial of the nature that we ha[d] proposed. A close tie between G.J. Goldenberg and E.L. Masson of the Upjohn Company probably had a role. Nonetheless, the NCIC Board of Directors accepted a recommendation of the CAC that the trial of Provera following surgery for cancer of the kidney be not proceeded with.

At the same November meeting, the Clinical Advisory Committee discussed a final draft of the Hodgkin’s lymphoma protocol. Although the cooperative trial sub-committee modified the

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76 Ibid.
78 G.J. Goldenberg to E.L. Masson, Winnipeg, 10 November 1971; in the UTA, A1986-0035/038(03).
79 In late November, Goldenberg held a meeting with Masson who had expressed his willingness to see the Provera trial implemented on a private basis under Goldenberg’s supervision. In their discussion on the protocol, Goldenberg pointed out that it was imperative for ethical reasons to eliminate patients with early stage A of the kidney cancer and to do the study on the stages B and C. Afterwards, Goldenberg even asked A.B. Miller if he was interested in participating in this trial privately. Miller declined. See. G.J. Goldenberg to A.B. Miller, Winnipeg, 1 December 1971; and A.B. Miller to G.J. Goldenberg, Toronto, 10 December 1971; both letters in the UTA, A1986-0035/038(03).
80 The Clinical Advisory Committee adopted the following resolution: “Further consideration of a trial of the prophylactic therapy of Hypernephroma with medroxy progesterone acetate (Provera) [sic] be abandoned for the time being.” See A.B. Miller to W. Kerr, Toronto, 16 November 1971; and A.B. Miller to E.L. Masson, 15 November 1971, Toronto; both letters in the UTA, A1986-0035/038(03).
protocol in terms of the disease staging and the radiotherapy technique because of an international standardization of cancer treatment assessment, the design of the study did not change in principle.81 The discussion on ethics was brief and it chiefly concerned a plan for adjusting chemotherapy and radiotherapy doses to tolerable levels in patients who had adverse reactions to drugs in the MOPP combination and to intensive radiation exposure.82 In this connection, the protocol specified that the “patient must be willing to take part in this study after learning of the study plan and the objectives.”83 This formulation stood for implied consent of the patient, for there was no defined procedure to inform the patient, nor a consent form appended. The protocol highlighted that the responsibility for the clinical management of patients rested with the individual investigator.84 This meant that diverse local requirements for ethical acceptability of clinical investigation continued to govern the process of human subject research despite a national scope of the cooperative trial.

The CAC recommended finalizing the protocol. In December 1971, the sub-committee activated *A Cooperative Clinical Trial Comparing MOPP Alone Versus MOPP Followed by Radiation in Stage IIIB and IV Hodgkin’s Disease*.85 A.B. Miller distributed the protocol to thirteen teaching hospitals in seven Canadian provinces which had initially expressed interest in participation.86 Clinical cancer research in Canada entered a new phase.

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81 NCIC Protocol, *A Cooperative Clinical Trial Comparing MOPP Alone Versus MOPP Followed by Radiation in Stage IIIB and IV Hodgkin’s Disease*, December 1971, pp.5-6; in the WUA, AFC 328.1.2654. Also, the NCIC Clinical Advisory Committee, “Minutes of the Meeting,” Toronto, 5 November 1971; and A.B. Miller to Clinical Advisory Committee, 29 October 1971; both in the UTA, A1986-0035/03(02).

82 Radiation dose ranged from a minimum of 2000 rad in 15 fractions over 3 weeks to 3000 rad in 20 fractions over 4 weeks for both abdominal and the upper trunk field, separated by a four-week interval. The maximum radiation exposure, therefore, could be a massive dose of 6000 rad delivered in about twelve weeks. See NCIC Protocol (Dec. 1971), 10, 19-21, and addendum.


84 At least two similar wordings along those lines were included in the protocol. *Ibid.*., 4 and 12.


86 BCCI, Vancouver (BC); CCI, Edmonton (AB); Allan Blair Memorial Clinic, Regina (SK), University Hospital, Saskatoon (SK); MCTRF, Winnipeg (MB); PMH, Toronto (ON); Victoria Hospital, London (ON); Kingston Clinic (ON); Ottawa Clinic (ON); Windsor Clinic (ON); Royal Victoria Hospital and Jewish General Hospital, Montreal (Québec); St. John’s General Hospital (Newfoundland). See “Centres Participating in the Hodgkin’s Disease Clinical Trial,” enclosed with correspondence from A.B. Miller to Clinical Advisory Committee, 3 February 1972; in the UTA, A1986-0035/03(02).
5.2. Development of the NCIC Cooperative Program

The Canadian cooperative clinical trials program commenced officially when the first patient with advanced Hodgkin’s lymphoma registered for the study at the Princess Margaret Hospital in January 1972. As the patient intake increased in participating centers, so did the rate of communication between physician-investigators responsible for the protocol treatment and the NCIC coordinating unit. This direct link served as a feedback loop not only for consultation among the trial participants, but also for stimulating interest among clinical researchers in new or follow-up collaborative studies. Investigators with similar views on particular approaches to cancer management had a possibility to initiate further trials by forming a critical mass of group expertise. Any medical center in Canada with a proposal for a trial could send a draft to the NCIC Epidemiology Unit and get a fair hearing for ideas therein. This proposal then came to the Clinical Advisory Committee for consideration and, if approved, interested investigators created a trial subcommittee to draw up a detailed protocol. The latter went into circulation for a general review by interested clinical researchers in major teaching hospitals before the trial subcommittee prepared a final protocol of the study.

By the middle of 1972, A.B. Miller and his colleagues had a variety of proposed trials to consider. They involved possible studies on malignancies of the breast, lung, ovary, colon, cervix, uterus, Hodgkin’s disease and non-Hodgkin’s lymphomas. Those proposals largely reflected the-then scientific and practical needs of physician-researchers and included all available therapeutic modes. The proposed list underwent necessary paring based on two factors. First, there were active US cooperative clinical trials in which the main Canadian treatment centers collaborated, like breast cancer studies directed by the American surgeon and medical scientist Bernard Fisher. Second, disagreements among clinicians on the comparability of

87 Hodgkin’s Disease Trial: Dates of Registration for Eligible and Not Eligible Patients, 4 March 1974, enclosed with Agenda of the Third Meeting of Participants in NCIC Clinical Trials, Edmonton, March 1974; in the UTA, A1986-0035/038(04).
88 A.B. Miller to R.N. MacDonald, 6 January 1972; in the UTA, A1986-0035/25(05).
89 “Possible Future Clinical Trials,” item 6 on the Agenda for the Clinical Advisory Committee Meeting on 18 February 1972; enclosed with correspondence from A.B. Miller to the CAC, 3 February 1972; in the UTA, A1986-0035/03(02).
90 Bernard Fisher and Paul P. Carbone, “A Cooperative Protocol for Prolonged Therapy of Mammary Cancer with L-phenylalanine Mustard as an Adjuvant to Surgery,” activated 22 September 1972, enclosed with a memo from A.B. McCarten (Director, Department of Surgery, W.W. Cross Cancer Institute) to the CCI surgical staff, therapeutic
certain treatments for malignant tumors, e.g. colorectal cancers, were obvious deterrents to collaboration. Accordingly, the NCIC research advisory group members deemed that potential national RCTs needed to include the use of immunotherapy as an adjuvant in the management of intractable cancers, evaluation of treatments for neoplasms of the bone marrow and for ovarian cancer, and prophylaxis for disseminated infections resulting from intensive chemo- and radiotherapy. The first and the fourth proposals issued from clinicians experienced in long-term care for cancer patients undergoing aggressive treatments. Since the application of nitrogen mustards as anti-tumor agents in the 1940s, systemic toxicity of different chemotherapeutic regimens was a serious obstacle to their effective use. The cooperative Hodgkin’s disease trial was no exception: it was important to adhere to the protocol in terms of prescribed drug and radiation doses, but about half of enrolled patients were unable to remain on full dosage due to various side-effects.

Intensive treatment and radical radiotherapy suppressed the immune system, which led to an increased susceptibility to opportunistic infections and medical conditions of viral origin. This had prompted numerous studies on the normal and the impaired immune functions in animals. Given that medical researchers understood tumor development as an uninhibited cell multiplication, they realized that studying cell growth factors might help characterize mechanisms underlying this process. In humans, disturbances of the immune system associated with either artificial or natural means, i.e. chemotherapy or pathogens, appeared to cancer specialists to trigger a range of neoplastic diseases: leukemia, Hodgkin’s lymphoma, and

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91 See protocols of the US National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) and their analyses by M. Vera Peters; in the UTA, B1996-0019/1(3).
92 A.B. Miller to the Clinical Advisory Committee, 18 July 1972; in the UTA, A1986-0035/03(02).
93 Hodgkin’s Disease Trial: Toxicity to MOPP and Radiation Dosage Achieved, 4 March 1974; in the UTA, A1986-0035/038(04).
94 As patients in the Hodgkin’s disease trial had their immune system weakened by the administered therapy, they were vulnerable to herpesviruses that caused different kinds of skin inflammation, including cold sores and shingles. Medical investigators from the University of Manitoba – William M. Hryniuk, John Foerster, and L.G. Israels – proposed a trial to evaluate using Cytosine Arabinoside (Ara-C), a drug that affected the development of leukemia and a series of viruses, to inhibit the growth of herpesviruses in cancer patients receiving intensive chemotherapy. See a draft protocol Cooperative Clinical Trial to Assess the Value of Cytosine Arabinoside as a Prophylactic Agent to Prevent the Dissemination of Herpes Zoster in Patients with Lymphoreticular Neoplasms,” enclosed with a letter from A.B. Miller to T.A. Watson, Toronto, 28 November 1972; in the WUA, AFC 328.1.2654.
multiple myeloma among others.\textsuperscript{95} Investigators also recognized that protracted courses of chemotherapeutic agents had negative effects, such as enhanced tumor growth if the anti-cancer drug concentration was insufficient in the short-run, or induction of tumor of a different kind in the long-term.\textsuperscript{96} To reduce those possibilities to a minimum, clinicians collaborated with researchers in the quest for chemotherapy combinations that allowed medium-duration courses of treatment involving a many-pronged attack on the tumor by drugs that had somewhat complementary cytotoxic effects. Another approach to diminish chemotherapeutic toxicity was the administration of substances-antidotes, like folinic acid, and hourly biochemical monitoring of patients’ blood.\textsuperscript{97}

A second strategy to enhance the immune system responsiveness involved the use of bioactive agents that could potentially induce its higher sensitivity to foreign bodies, including tumors. Clinicians experimented with immune stimulators, like Bacillus Calmette-Guérin (BCG) that had been originally utilized as an anti-tuberculosis vaccine, to try to augment a relatively-weak immune response to a cancerous growth.\textsuperscript{98} BCG seemed to have a potential to increase immune surveillance through stimulating the immune mechanism, which might inhibit cancer proliferation.

Although the idea to apply BCG for priming the immune system for resistance to disease-causing organisms originated in the scientific community, it migrated to medical practice sooner than laboratory work provided statistically meaningful results. It was the case in the field of cancer therapy, for the ease of obtaining BCG and experimenting with it in patients was no less


\textsuperscript{96} Third Clinical Cancer Research Conference Summaries, in \textit{The OCTRF Annual Report 1971}, pp. 57 and 60.


encouraging than its relative safety record as a prophylactic agent. This situation was troubling for public health officials who observed how the number of general practitioners requesting BCG for cancer treatment steadily rose in the early 1970s. Norman R. Stephenson, Director of the Drug Advisory Bureau of the Health Protection Branch, Department of National Health and Welfare (DNHW), reported that requests of physicians in private practice to obtain BCG from both government distribution channels and pharmaceutical manufacturers in Canada mushroomed. Such developments indicated that the Health Protection Branch had to consider BCG as a new drug for use in the immunotherapy of cancer and control its release for this purpose according to regulations pertaining to experimental agents.

Cancer investigators were responsible for generating among medical professionals a considerable excitement about a novel application of BCG. Their pilot studies of BCG and public discussions on preliminary results, usually emphasizing therapeutic successes, contributed to this. The studies took place in at least half of all university hospitals in Canada, so there were reasons for private practitioners to believe that they followed scientific medicine at the cutting edge. In September 1972, the Medical Research Council of Canada organized a workshop *Immunotherapy for Cancer* that convened thirty-one investigators interested in using immune stimulators in both laboratory and clinical settings. It was at this meeting that the majority of participants recommended that the MRC create a working committee to advise on advances in

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99 In Germany, Georg Deycke, Director of the Lübeck General Hospital, used Calmette’s method to vaccinate against tuberculosis 251 newborns during 1929-1930, and for at least 68 of them these vaccinations proved fatal. This tragedy prompted a public debate about human experimentation and gave rise to the Reich’s Circular of 1931, issued by the German Ministry of the Interior, which provided guidelines on the conduct of ethically acceptable experiments with human subjects. See Christian Bonah and Philippe Menut, “BCG Vaccination around 1930 – Dangerous Experiment or Established Prevention? Practices and Debates in France and Germany”; and Daniel S. Nadav, “‘The Death Dance of Lübeck’: Julius Moses and the German Guidelines for Human Experimentation, 1930” in *Twentieth Century Ethics of Human Subjects Research: Historical Perspectives on Values, Practices, and Regulations*, ed. Roelcke and Maio (2004), 117 and 129.

100 Two major Canadian producers of BCG were Connaught Medical Research Laboratories (CMRL) in Willowdale, Ontario, and Institut de Microbiologie et d’Hygiène (IMH) de Montreal, Québec. See *Minutes of the MRC Meeting on Immunotherapy for Cancer*, Ottawa, 12 January 1973, p.2; in the UTA, A1986-0035/030(01).


102 Hal E. Taylor, Director of the MRC Awards Programs, noted that a decade earlier “one could not have formed such a large group of Canadians with the immunological expertise represented at this workshop.” See H.E. Taylor, “MRC Report on Workshop ‘Immunotherapy for Cancer’,“ Ottawa, 14-15 September 1972,” 18 Sep. 1972; in the UTA, A1986-0035/030(01).
immunotherapy and on the development of clinical trials in this domain. The workshop was not only the MRC’s initiative, however. Both the NCIC and DNHW actively participated in its organization. All three bodies had interests in using the momentum of BCG’s growing popularity. The DNHW with the Food and Drug Directorate strove to demonstrate that the federal government was in charge of regulating experimental use of medical agents across the country. The NCIC wanted a successful continuation of its cooperative clinical trials program in cancer. The MRC had occasion for contributing to the development of the NCIC program and thereby joining the collaborative RCT campaign.

Several individuals galvanized the above bodies into action. Rudolph E. Falk and F. Griff Pearson, both associates in surgery at the University of Toronto, along with Michael A. Baker, physician-hematologist at Toronto Western Hospital, came up with a plan to use BCG experimentally in treatment schedules for intractable cancers, and therefore approached the OCTRF and the NCIC for support. Among the three, only R.E. Falk had both laboratory and clinical experience in utilizing BCG to manipulate the immune response, which yielded some positive findings. Over more than a decade Falk was engaged in developing therapeutic regimens for a range of cancers, with varied success, but malignancies of the chest cavity, especially bronchogenic carcinoma, increased the failure rate most. BCG therapy seemed a promising approach to tip the balance in favor of success. Thus, Falk, Pearson, and Baker joined their efforts to assess BCG scientifically as an immunotherapeutic method in lung cancer.

A.B. Miller had been involved in the MRC lung cancer studies in the UK, so he was glad to know that the above trio contemplated organizing a trial of BCG in operable carcinoma of the

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103 Ibid., 3.
104 In the spring of 1973, the MRC of Canada achieved this by forming a Cancer Research Coordinating Committee (CRCC) comprising initially two representatives from each of the following bodies: the MRC, Health and Welfare Canada, the NCIC, and the OCTRF. The CRCC further created two sub-committees: on immunotherapy for cancer and on clinical trials. See NCIC, Annual Report 1972-1973 (Toronto: NCIC, 1973), 11.
105 Minutes of the Medical Research Council Meeting on Immunotherapy for Cancer, Ottawa, 12 January 1973, p.3; in the UTA, A1986-0035/030(01).
107 See Chapter 4.
In their further discussions, they recognized the potential importance of immunotherapy and were convinced that the correct method to employ to study such a question was the randomized controlled trial. Moreover, this trial could help attract surgeons to the NCIC clinical trials program through incorporation of their interests into a national collaborative effort. It was important since surgeons practiced largely outside cancer treatment centers. Moreover, as one of the leaders of the surgical profession, Robert A. Macbeth of the University of Alberta, pointed out, surgery had already evolved from a method of treatment to “a reasonably well defined and sizable segment of medical practice, encompassing the total spectrum of patient care in that area, including diagnosis, treatment, and the acquisition of anatomical, biochemical, physiological and pathological knowledge relevant to ‘surgical disease’.” Lung cancer fit this category of surgical disease precisely and it contributed heavily to the death toll.

Inasmuch as cancer of the lung was a prominent public health issue, N.R. Stephenson of the Department of National Health and Welfare referred A.B. Miller to H.E. Taylor, Director of the MRC Awards Programs and Professor of Pathology at the University of Ottawa. H.E. Taylor was instrumental in mustering support among the MRC Board of Executives for the organization of immunotherapy trials. Already in January 1973, Taylor informed Miller about the MRC decision to proceed with immediate development of the trial protocol. This expedited preparation was necessary in view of the protracted protocol review process that comprised two stages: first, assessment by members of the Immunotherapy for Cancer Working Committee; second, comments on the protocol by external experts in the field. After the Working Committee had amended and accepted a modified protocol, its second draft moved on to the MRC and NCIC committees for their approval. Lastly, representatives from Canadian universities interested in participating in the proposed national trial had an opportunity to discuss the given protocol and to provide further input before the protocol activation.

109 Personal communication from A.B. Miller to author, 20 November 2017.
Having prepared a draft proposal for *The Cooperative Clinical Trial of BCG Immunotherapy in Resectable Carcinoma of the Bronchus*, in consultation with R.E. Falk and F.G. Pearson, A.B. Miller presented it for consideration of the Immunotherapy for Cancer Working Committee.\(^{113}\) The protocol concerned patients who had an apparently complete removal of their tumor and regularly received a high dose of BCG, or a placebo, for eighteen months or until relapse.\(^{114}\) In this protocol, BCG was referred to as a prophylactic agent that could prevent or postpone lung cancer recurrences in patients. The trial’s objective was to evaluate whether “BCG given orally can increase the survival in patients with carcinoma of bronchogenic carcinoma who had a complete resection of their tumor as assessed by the surgeon at the time of the operation.”\(^{115}\)

In late March 1973, the Immunotherapy for Cancer Working Committee, chaired by physician-hematologist J. Wallace Thomas of the BCCI in Vancouver, reviewed the proposed trial.\(^{116}\) Major points of this discussion included the options for the trial’s experimental design, feasibility of a double-blind trial using a placebo, and the route of BCG administration. The members agreed that the oral route of BCG administration was preferable to injections or scarification because it seemed to be more acceptable to patients. They also concurred that a single-blind trial designed according to a “fixed sample” methodology was suitable to achieve the trial objective of comparing the survival rate and time of recurrence for both groups of patients.\(^{117}\) As A.B. Miller explained, a fixed sample trial allowed a sufficiently rapid intake of patients to avoid early results influencing the enrollment rate or the decision to terminate the study due to interim analyses that showed a significant difference between the treatment and

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\(^{117}\) Ibid., 2-3.
placebo groups. In other words, the protocol developers – R.E. Falk, A.B. Miller and F.G. Pearson – eschewed the ethical side of the matter by choosing a fast-track enrollment in the trial.

At the final stage of protocol review, when the Working Committee held a meeting with seventeen clinical investigators representing Canadian university hospitals, R.E. Falk and A.B. Miller gave further details on its background. Drawing on his own and international studies of BCG, Falk discussed the pros and cons of administering the BCG by the oral rather than intracutaneous route that was a standard among the research groups in the US. Falk noted that his findings showed that giving a massive 1000 mg of BCG per week orally did not entail any evident toxicity. Yet, some patients had infrequent complaints related to the stomach and intestines, such as heartburn, cramps, or diarrhea, even if the BCG dose was comparable to that proposed in the trial, namely 120 mg weekly. Falk attributed such adverse reactions to BCG on the basis of his evidence from animal experiments. In his expert opinion, BCG absorption through the gastrointestinal tract into the lymphatic system stimulated the lymph tissues and provoked the immune response in the organism overall.

A few reviewers commented on the chosen dose of BCG, specifically that it was relatively low. For instance, T. Alex McPherson, Director of Medicine at the W.W. Cross Cancer Institute in Edmonton, called attention to the lower BCG dosage used by investigators at the M.D. Anderson Hospital in Houston (TX) in their anti-cancer studies of BCG, which was “600 million organisms per dosage by scarification.” It turned out that the bronchogenic trial protocol proposed to use as much as 1200-2400 million BCG viable units by oral administration when 120 mg of active ingredient were converted according to the scale of measurement provided by the manufacturer, the Connaught Medical Research Laboratories in Willowdale, Ontario. A.B. Miller calculated that, according to the protocol, each patient required for the entire course of treatment 2.76 grams of BCG, which equaled 69 vials. The MRC agreed to cover the considerable costs of treatment supplies and

120 Ibid., 3.
121 Ibid.
124 Minutes of the MRC Subcommittee Immunotherapy for Cancer meeting, Ottawa, 5 April 1973, p.2; in the UTA, A1986-0035/030(01).
the expenditure on the logistic assistance, while the NCIC and the OCTRF shared the responsibility for receiving data and analyzing statistics from participating institutions.\textsuperscript{125}

As to the statistical features of the trial, A.B. Miller recommended that at least 300 patients be enrolled in the trial, half of whom to receive BCG. Given that representatives of the participating institutions had presented estimates of the number of eligible patients treated yearly in their hospitals, Miller reckoned that the trial enrolment could be completed within eighteen months. In view of time considerations, the meeting participants unanimously agreed that this trial had to be a single-blind study of the fixed sample design.\textsuperscript{126} An intense discussion followed on the issue of stopping placebo administration and starting either radio- or chemotherapy when there were symptoms of the disease relapse. Because of its relative indeterminacy, this issue was left to the discretion of attending physicians, without any specification in the protocol. In the light of US cooperative groups’ \textit{modus operandi}, some clinicians from Canadian participating institutions suggested to use a different type of immunotherapy instead of placebo in the second group of 150 patients.\textsuperscript{127} Yet, A.B. Miller rejected this suggestion as impractical on account of difficulties in the interpretation of statistical significance of BCG benefit or harm when compared with other agents, rather than with placebo. It was characteristic of the British style of clinical trial development that stood in contrast to the American practices of cooperative groups.

Concurrently with deliberations on the BCG trial, the NCIC Clinical Advisory Committee reviewed another proposal for a cooperative investigation that had to do with immunology, though somewhat indirectly. Daniel E. Bergsagel, Chief Physician at the OCI/PMH in Toronto, wanted to determine by means of a cooperative RCT which mode of administration – the sequential, alternating, or concurrent – of three different drugs of proved efficacy in the treatment of multiple myeloma was the least detrimental to the immune system of the patient.\textsuperscript{128} Multiple or plasma cell myeloma was an uncommon malignant neoplasm that

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\textsuperscript{125} Minutes of the MRC Subcommittee Immunotherapy for Cancer meeting, Ottawa, 29 May 1973, p.2-3; \textit{ibid}.
\textsuperscript{126} Minutes of the MRC Clinical Meeting, “BCG Immunotherapy for Resectable Lung Cancer,” p.3, April 1973; \textit{op.cit}.
\textsuperscript{127} John S. Penta, Head of Drug Liaison and Distribution Section at the US NCI, reported that the NCI sponsored 37 protocols using BCG in the treatment of malignant disease, 19 protocols “for the methanol extraction residue of BCG (MER BCG), and 18 protocols which utilize[d] C. Parvum, Burroughs-Wellcome.” See J.S. Penta, “Summary of Immunotherapy Clinical Trials,” enclosed with correspondence from Derek Jenkin to A.B. Miller, Toronto, 28 April 1975; in the UTA, A1986-0035/010(08).
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originated in the bone marrow and was formed of any one of its cells, but for D.E. Bergsagel it had become a common research pursuit. Over more than ten years did D.E. Bergsagel study this disease entity at the bench and at the bedside.\textsuperscript{129} A research trajectory from no effective chemotherapeutic agents to treat multiple myeloma in the early 1960s to some accepted forms of therapy at the beginning of the 1970s was one of Bergsagel’s main professional achievements that he continuously tried to improve. A protocol for a \textit{Cooperative Clinical Trial Comparing the Administration of Melphalan, Cyclophosphamide, and BCNU in Sequential, Alternating, and Concurrent Schedules in the Treatment of Plasma Cell Myeloma} was his attempt to demonstrate how a vast knowledge of the malignancy and a competent handling of powerful drugs could yield a more efficient treatment.\textsuperscript{130}

D.E. Bergsagel argued that chemotherapists’ aggressive treatment of malignancies was predicated on the advances in knowledge about particular forms of the neoplastic disease.\textsuperscript{131} Bergsagel’s participation in the US Southwest Cancer Chemotherapy Group during the formative years of his clinical career likely had an impact on his view of chemotherapy comprising high-dose multi-drug schedules as curative. Accordingly, Bergsagel employed this way of thinking to find an optimal treatment for multiple myeloma. Leading his research group at the OCI/PMH in this direction, Bergsagel had shown some promising results by combining several drugs, which necessitated verification in a large-scale trial.\textsuperscript{132} Bergsagel’s protocol also proposed to use experimentally BCNU (1,3-Bis(2-chloroethyl)-1-nitrosurea) as a new investigational drug to treat multiple myeloma.\textsuperscript{133} Unlike the other three drugs used in the protocol – Melphalan,


\textsuperscript{130} This study also proposed to use the detection of M-proteins, myeloma-proteins commonly known as monoclonal immunoglobulins, in the blood serum or in the urine to track the progression of the disease and to identify which of the several immunoglobulins correlated with better treatment outcomes. See Protocol, \textit{Cooperative Clinical Trial Comparing the Administration of Melphalan, Cyclophosphamide, and BCNU in Sequential, Alternating, and Concurrent Schedules in the Treatment of Plasma Cell Myeloma}, April 1973; in the WUA, AFC 328.1.2652.


\textsuperscript{133} The US NCI supplied the drug “free of charge on the understanding that it w[ould] be used only for patients included in the trial and that regular reports w[ould] be submitted to Bethesda, taking the form of summary information sent every 3 months by the NCIC Epidemiology Unit.” Besides, the NCI required that special
Cyclophosphamide, and Prednisone, which were available in Canada, BCNU was supplied under regulations of the US NCI Cancer Therapy Evaluation Branch. Previous involvement of Bergsagel in clinical investigations of the US Cancer Cooperative Groups increased the probability of obtaining access to this novel drug.

D.E. Bergsagel submitted a protocol for a cooperative study on multiple myeloma to A.B. Miller who in turn offered it for consideration of the NCIC Clinical Committee. The latter reviewed the scientific merit and ethical acceptability of the proposed protocol. The next stage was an external review by several Canadian clinical investigators with expertise in the use of new drugs. In October 1972, A.B. Miller sent out Bergsagel’s protocol to four cancer centers. Experts in Nova Scotia, Ontario, Saskatchewan, and Alberta returned mixed reviews, however.

Having perused the protocol prepared by D.E. Bergsagel, A.J. Bailey of the Allan Blair Memorial Clinic in Regina and G.R. Langley of Dalhousie Clinical Research Centre in Halifax expressed their unqualified approval of it and their willingness to participate in the trial. In contrast, a review by physician-hematologist at the London Clinic of Victoria Hospital in Ontario, D.P. White, based on his discussion of the protocol with a therapeutic radiologist T.A. Watson and a physician Reinhard Lohmann, had some reservations about the trial design. These reservations concerned four aspects of the study. First, the London cancer specialists regarded the inclusion of a third patient group (alternating therapy) as unnecessary because of “a dilutional factor and a delay in getting significant answers.” Second, they suggested substituting CCNU for BCNU since the latter drug was a readily available analog of the former and the administration of BCNU by intravenous injection, unlike CCNU, already created unforeseen problems. In other words, the London group tried to avoid dependence on the US NCI for BCNU supplies and to minimize the risks of immediate adverse side-effects associated with specific requirements for BCNU administration. Third, the London group recommended more

arrangements be made for BCNU’s distribution: the NCIC had to disclose the names of pharmacists and clinical investigators who were involved in the trial. See Appendix of the Protocol, Treatment of Plasma Cell Myeloma, April 1973.

134 A.J. Bailey to A.B. Miller, Regina, 17 October 1972; in the UTA, A1986-0035/12(06).
136 David F. White to A.B. Miller, London (ON), 27 October 1972, p.2; in the UTA, A1986-0035/12(06).
137 ibid., 1.
frequent blood work, weekly rather than every twelve days, and highlighted that criteria of
patient relapse needed modification due to their under-determination. Finally, White along with
Watson and Lohmann asked for reasons why the use of prednisone was required only for six
months, rather than for the entire period of treatment.138 Although White called these objections
to several points of the protocol minor, he noted that without Bergsagel’s consideration of them
the London group could not approve the final protocol.

A review of Bergsagel’s protocol undertaken by Neil MacDonald and his colleagues in
Edmonton was a more wide-ranging and friendly critique than that of the London group. This
was little wonder, for not only was MacDonald’s clinical research team separate from the circle
of experts in Ontario and their institutional affiliation, but it also partook in several US
cooperative groups and employed their anti-tumor armamentarium for experimental
treatments.139 In addition to their quite numerous comments, investigators from Edmonton
provided a perceptive analysis of the treatment schedules and toxicity of proposed drugs.

Abdul Khaliq, a senior chemotherapist at the W.W. Cross Cancer Institute who had used
the drugs included in the protocol, expressed serious reservations about a large initial dose of
melphalan, a nitrogen mustard. As Khaliq explained, his experience showed that the majority of
patients with myeloma could not tolerate a 12mg/m²/day dose of melphalan during four days,
which the protocol proposed.140 Instead, Khaliq recommended reducing melphalan dose to
9mg/m²/day with a possibility to increase it for patients who had a higher tolerance of the
drug.141 Khaliq’s colleagues shared this reservation because there was no specification in the
protocol about a reduction in a 12mg/m²/day dose for patients who were too sensitive to
melphalan or had undergone a prior therapy that interfered with the function of the blood-

138 They stated that the use of prednisone required standardization because it had “a specific, not just a non-
specific effect as far as this tumor [was concerned].” Ibid., 2.
139 See notes 8 and 12.
140 Khaliq calculated that a proposed total four-day dose was “roughly equivalent to 72-80mg for an average
female and 80-90 mg for an average male,” which was overly toxic in his view. See Abdul Khaliq to R.N.
MacDonald, Edmonton, 30 October 1972, p.1; in the UTA, A1986-0035/012(06); and Protocol, Treatment of
141 According to Khaliq, this calculated total dose amounted to 54-60mg for women and 64-70mg for men, or
approximately 1 mg/kg. Ibid.
forming organs. Following Khaliq’s advice, MacDonald suggested to include a reduced dose in Bergsagel’s protocol so as patients did not suffer from undue toxicity.

Another major reservation of Abdul Khaliq concerned the proposed continuation of the assigned treatment for patients, even if their disease progressed indefinitely until death. As Khaliq put it, “In all sincerity and honesty to the patients I do not think that it is appropriate to continue a non-effective form of therapy. A time period should be defined.” His colleagues fully agreed that any patient on the protocol should move on to the next treatment following a relapse, or, if the options were exhausted, the investigator should discontinue further protocol therapy and decide on the next line of treatment: a new agent trial or palliation. Khaliq concluded his critical comment with an ethical proposition, “In good conscience I cannot continue a non-effective form of therapy (after a reasonable trial time) for those patients who have progressive disease.

It took a while to attain a consensus on the final protocol. An opportune moment for a general agreement came in March 1973 with the first meeting of participants in clinical trials sponsored by the NCIC. Its main subject was an interim analysis of the Hodgkin’s disease trial, but there was also a discussion on the proposed trials because the NCIC Clinical Advisory Board intended to utilize the existing infrastructure developed through the implementation of the first cooperative trial. Among more than sixty participants – investigators engaged in the Hodgkin’s trial and possible contributors to future trials – was an invited speaker from the US NCI Chemotherapy Branch in Bethesda, Robert Young. Young’s recurrent theme was the inevitability of high toxicity of novel chemotherapeutic methods and the desideratum to administer the drugs to a maximum tolerance. There were some objections, however.

142 MacDonald’s group also indicated that they preferred to see a statement in the protocol that “therapy should not be resumed at four weeks unless a demonstrated rise in value from the nadir [wa]s demonstrated.” See R.N. MacDonald to A.B. Miller, Edmonton, 6 November 1972, p.3; in the UTA, A1986-0035/012(06).
143 ibid.
144 Khaliq to MacDonald, Edmonton, 30 October 1972, p.3, op.cit.
145 MacDonald to Miller, Edmonton, 6 November 1972, p.3, op.cit.
146 Khaliq to MacDonald, Edmonton, 30 October 1972, p.2, op.cit.
147 NCIC, Minutes of the First Meeting of Participants in Clinical Trials (Draft), Toronto, 5 March 1973; in the UTA, A1986-0035/003(03).
A senior research physician to the British Columbia Cancer Institute, Donald M. Whitelaw, remarked that patients with Hodgkin’s disease receiving vincristine complained bitterly about spontaneous unpleasant sensations, like pins and needles, which led to their refusal to continue this therapy. Commenting on this, R. Young warned that if there was too much interference with the treatment regimens for seemingly inadequate reasons, the response rate was liable to be unsatisfactory, which could affect the trial results. Allowing for unavoidability of such refusals, D.M. Whitelaw called for a proactive approach on the part of investigators: to explain to patients in detail possible side-effects of the drugs at the beginning of the trial and to ensure they agreed to accept the treatment. Remarkably, neither the Hodgkin’s disease protocol, nor the Multiple Myeloma one contained a requirement for the patient’s informed consent.

In this context, participants in the meeting discussed Bergsagel’s protocol for the plasma cell myeloma trial and a number of proposals for other cooperative studies. Reviewers of the protocol raised the points open to debate, such as redundancy of the alternating regimen and toxicity of melphalan in the defined dosage. Even though R. Young drew investigators’ attention to difficulties of diagnosing a range of toxic effects of intensive chemotherapy and noted an increased probability of developing other malignancies related to the radical treatment, the majority of participants decided to proceed with Bergsagel’s protocol as designed. The NCIC Clinical Advisory Committee agreed to activate the protocol as soon as A.B. Miller arranged with the US NCI to secure a supply of BCNU for the trial. This happened in late June 1973 and the admission of patients to the protocol began within two weeks.

After 140 patients endured the high dosage level of melphalan, namely 12mg/m²/day, the multiple myeloma study group led by D.E. Bergsagel modified the protocol by reducing the dose

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149 Donald M. Whitelaw used the term paresthesia. NCIC, Minutes of the First Meeting of Participants in Clinical Trials (Draft), 5 March 1973, p.2.
150 Interim statistics on the trial showed that twenty patients entered on the protocol refused to take the drug for these reasons. Ibid.
151 R. Young emphasized that the diagnosis of liver disease was problematic, especially if maintenance therapy with agents characterized by marked toxicity, e.g. BCNU, was a part of the experimental treatment plan. Ibid., 3, 6-7.
152 A.B. Miller to T.A. Watson, Toronto, 30 April 1973; in the WUA, AFC 328.1.2652. Also, Minutes of the Thirteenth Meeting of the Clinical Advisory Committee of the NCIC, Toronto, 5 March 1973; in the UTA, A1986-0035/003(03).
by one-fourth. A severe toxicity of melphalan required this reduction and a corresponding amendment of the research protocol in October 1974. Abdul Khaliq and the team of investigators in Edmonton had predicted this turn of events at the stage of protocol review, but the majority of clinical researchers ignored their suggestions because of their conviction that they should administer a maximum tolerable dose. Consequently, as A.B. Miller put it, “the problem of acute life threatening toxicity [had arisen] prior to the decision to reduce the dose [of melphalan].” The investigators took more than a year to modify the protocol despite clinical evidence of overtreatment.

First and foremost, the chief purpose of any protocol study was not to alter the prescribed plan of experimental treatment. That the protocol underwent revision halfway to its completion was a rare occurrence that ensued from a clash of investigators’ scientific objectives with the clinical reality of bringing cancer patients to the brink of death. Second, there were sporadic attempts to determine the threshold of drug toxicity during the initial phases of treatment, but variable results of such evaluations among individual patients did not indicate a consistent trend. Finally, A.B. Miller suspected that some investigators participating in the trial did not administer the doses of chemotherapy defined in the protocol, but gave the drugs to the extent that their toxic effects in patients were under control. What caused Miller’s suspicion was his analysis of reports on the purportedly acceptable toxicity of melphalan at several medical centers, while the reports from institutions that had raised the alarm stated otherwise. Obviously, it was almost impossible to identify protocol violations, but this situation delayed the protocol revision based on evidence of severe toxicity.

Revision of the plasma cell myeloma protocol also meant that at least 200 more patients had to be enrolled in the study to achieve the planned sample size on a new drug regimen and make the assessment of treatments statistically significant. Accordingly, the trial duration

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154 The reduced dosage was 9mg/m²/day. See A.B. Miller, “Survey on the Size of Clinical Trials,” enclosed with correspondence from Stuart J. Pocock (Director, Medical Computing and Statistics Group, University of Edinburgh, Scotland) to A.B. Miller, Edinburgh, 23 November 1976, pp.3-4; in the UTA, A1986-0035/013(01).
156 Even D.E. Bergsagel admitted that evaluation of drug toxicity was “hard to do, since leukopenia and thrombocytopenia could be caused by the disease.” See D.E. Bergsagel, “Analysis of the Myeloma Trial for the ASCO Meeting,” p.3, enclosed with correspondence from D.E. Bergsagel to A.B. Miller, Toronto, 14 January 1977, in the UTA, A1986-0035/013(01).
157 Miller to Bergsagel, 26 January 1977, pp.2-4, op.cit.
extended by about two years. There were 364 evaluable patients at the termination of trial accrual in late February 1977.\textsuperscript{158} As the data on patient survival accumulated, it showed a not entirely unexpected trend. Protocol patients died increasingly of acute leukemia, though the percentage of those who were in the early intake of high-dose melphalan was unspecified. By November 1978, twelve patients developed acute leukemia and for ten it was the cause of their death.\textsuperscript{159} D.E. Bergsagel indicated that 6.6\% of the patients had acute leukemia by the third year of the follow-up, and the incidence of leukemia might amount to approximately 20\% by the fifth year.\textsuperscript{160} Three years later, the final analysis of the trial revealed that the incidence of acute leukemia grew to seventeen patients and the probability of developing it increased with the length of patient’s survival after the last protocol treatment for multiple myeloma.\textsuperscript{161} As A.B. Miller explained, the risk of developing secondary leukemia in myeloma patients was cumulative.\textsuperscript{162}

Did the investigators inform patients with multiple myeloma of a potential risk to develop acute leukemia in addition to serious side-effects of the aggressive chemotherapy? Likely not, since the principal investigators asserted in their first publication on the multiple myeloma trial that it was “not possible to decide whether treatment with leukemogenic agents (x-irradiation and alkylating agents) increase[d] the risk of developing acute leukemia, because [they did] not know what the incidence [wa]s in untreated [myeloma] patients.”\textsuperscript{163} This proposition was equivocal because the investigators recognized particular chemotherapeutic agents as leukemia-causing,

\textsuperscript{158} Table I – Study Population, in “Myeloma Trial 1: Updated tables and figures of the manuscript handed out at the 12\textsuperscript{th} Meeting of Participants in NCIC Clinical Trials,” enclosed with correspondence from Amina Jindani to T.A. Watson, Toronto, 24 November 1978; in the WUA, AFC 328.1.2652.

\textsuperscript{159} See Table VII – Causes of Death, and Table VIII – Acute Leukaemia in Myeloma Patients; in “Myeloma Trial 1: Updated tables and figures of the manuscript handed out at the 12\textsuperscript{th} Meeting of Participants in NCIC Clinical Trials,” \textit{ibid}.

\textsuperscript{160} Minutes of the Twelfth Meeting of Participants in NCIC Clinical Trials, Toronto, 13-14 November 1978, p.9; in the UTA, A1986-0035/037(03).

\textsuperscript{161} A.B. Miller to J. Pedersen-Bjergaard (Assistant Head, Department of Internal Medicine, The Finsen Institute, Denmark), 12 February 1982; in the UTA, A1986-0035/044(04).

\textsuperscript{162} According to Miller, the intermediary figures of leukemia incidence at two, three, four, and five years following therapy for plasma cell myeloma were, respectively, 0.45, 2.8, 9.1, and 12.8\%. Even one long-term survivor developed acute leukemia at ninety-three months, or in about eight years. \textit{Ibid}.

but at the same time they questioned the correlation between the agents’ use and the disease occurrence after intensive therapy for myeloma.

Another important ambiguity in the same article concerned the stated acceptability of the plasma cell myeloma trial on ethical grounds. The investigators noted that they kept to the Medical Research Council of Canada guidelines on the ethics of human subject research to design and implement the cooperative trial. The puzzling issue was that the guidelines referred to the MRC of Canada report *Ethical Considerations in Research Involving Human Subjects* of 1978, whereas the trial actually began in 1973. In this connection, it is necessary to clarify why the investigators claimed that the-then nonexistent code of ethics governed their clinical research.

### 5.3. Investigators’ Consensus, Institutional Regulations, Patient Consent

The Medical Research Council of Canada did not modify its policy on human subject research and on requirements for institutional ethics review between 1967 and 1978. Local committees at university hospitals regulated clinical investigation according to the standards of medical research defined by their members. Investigators participating in the cooperative cancer trials had to inform the NCIC coordinating unit that they had achieved clearance from their local ethics committees before they could register any patients for the investigation. The trial protocol development along with the assessment procedure by the NCIC investigators, as discussed above, was the main testing ground for determining both the scientific importance and the ethical acceptability of a proposed collaborative clinical investigation. In fact, A.B. Miller argued in 1973 that it was more ethical for investigators to participate in national cooperative trials than to conduct clinical research individually.

It was difficult for investigators to refute Miller’s argument when they introduced experimental therapies or new regimens combining conventional treatments in clinical practice. The experience of individual medical researchers was often insufficient to encompass the range of adverse effects that might emerge during the treatment, immediately after it, or over a longer

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165 A.B. Miller to Claude Labrosse (Director, Department of Cardiovascular and Thoracic Surgery, Centre Hospitalier Universitaire, Université de Sherbrooke), 31 May 1973, p.3; in the UTA, A1986-0035/011(04).
period. By contrast, a rapid pooling of data on unexpected toxicity or other harmful effects from a number of investigators in different medical centers could help detect latent dangers that the experimental treatment posed to patients. By collecting and analyzing this information, the NCIC coordinators were able to identify potential risks for patients early and to prevent them later. This indeed took place in the course of the plasma cell myeloma trial, when the investigators reconsidered the administration of high-dose melphalan. Drawing on this valuable experience, the NCIC investigators designed a Protocol for the Treatment of Patients with Advanced Ovarian Carcinoma with Melphalan, 5-Fluorouracil and Methotrexate in Combination and Sequentially.\textsuperscript{166} The protocol developers took necessary precautions against the exposure of patients to life-threatening toxicity of the drugs used in the trial.

The approval of the first cooperative trial in ovarian cancer by the NCIC Clinical Committee in 1974 was another advance in the Canadian clinical cancer trials program.\textsuperscript{167} It was important not only because such malignancies were difficult to treat and were relatively common in Canada, but also because the medical specialty of gynecology was necessarily involved.\textsuperscript{168} With support from leading gynecologists across the country, the better part of patients referred for further therapy to cancer clinics could enter the trials. To ensure this collaboration, the NCIC officially invited department heads of gynecology from each Canadian medical school to the third meeting of participants in the NCIC cooperative clinical trials in Edmonton.\textsuperscript{169} It was the first such gathering in Western Canada.

\textsuperscript{166} The protocol specified the dosage of Melphalan – 8mg/m\textsuperscript{2} per 24 hours during four days, 5-fluorouracil – 600mg/m\textsuperscript{2} on day one, and methotrexate – 360 mg/m\textsuperscript{2} infused over the first day and immediately followed by folinic acid (leucovorin) to avoid highly toxic systemic effects of the chemotherapy in patients. See the NCIC Protocol for the Treatment of Patients with Advanced Ovarian Carcinoma (Stages III and IV) with Melphalan, 5-Fluorouracil and Methotrexate in Combination and Sequentially, April 1974, p.3; in the WUA, AFC 328.1.2655.


\textsuperscript{168} In 1973, ovarian cancer afflicted 1430 women, which translated into the incidence rate of about 13 cases per 100.000 of Canadian female population. Mortality from this malignancy approximated 10 per 100.000 Canadian women. Ray S. Bush, a therapeutic radiologist at the OCI/PMH, reported that survival of patients with advanced ovarian cancer (stage III and IV) was around 30 percent at one year after treatment and only 10 percent at two years. See Gaudette and Lee, Cancer Incidence in Canada: 1969-1993 (1997), xii, 10, 29, 58, 59 and 96; also, Minutes of the Fifth Meeting of Participants in NCIC Clinical Trials,” Quebec City, 5 March 1975, p.14; in the WUA, AFC 328.1.2641.

\textsuperscript{169} A.B. Miller to participants in the NCIC trials and to the directors of the participating institutions, 7 February 1974, p.2; in the UTA, A1986-0035/038(04).
In the course of March 1974 meeting, leading Canadian gynecologists discussed the above protocol with the NCIC ovarian cancer trial study group chaired by David J. Klaassen, a Professor of Medicine and Pathology at the University of Ottawa and a staff chemotherapist at the Ottawa Civic Hospital, who had designed the protocol. An open exchange of expert opinion on the proposed protocol among the discussants contributed to a substantial input from gynecologists, which D.J. Klaassen later incorporated into the final protocol. Without this feedback and a consensus of gynecologists to proceed with the trial, the NCIC had slight chances to complete the planned cooperative investigation. Gynecologists’ agreement on the protocol also meant that they generally approved its contents, including the absence of the patient consent clause in it. There was only a formulation that the “patient should be willing to take part in the trial after learning of the study plan and objectives.” Interestingly enough, the Hodgkin’s disease trial protocol of 1971 had almost the same wording that instead of should had must. This modification seemed to indicate that the necessity of confirming the patient’s willingness to participate in the trial became less absolute. In other words, to get the patient consent was the right thing to do, but not strictly necessary.

In May 1975, the NCIC launched a second cooperative clinical trial in ovarian cancer. Like the first one, the trial protocol for the treatment of early-stage carcinoma of the ovary did not contain a note that required the investigator to get written patient consent. The wording that the patient should be willing to participate in the trial was identical to that in the first protocol. As collaboration between the NCIC investigators and the gynecologists involved in the ovarian cancer trials became more active, new ideas about further trials came into being. A realization of one such idea was the endometrial carcinoma trial. Its protocol, activated in July 1976, had a substantially different approach to the patient consent. This protocol included a distinct section “Registration and Consent” in its table of contents and a clear statement in the body text, which read, “Consent will be obtained according to local requirements prior to

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170 Italics mine. This was under “Patient Selection” section 3.7; see Protocol for the Treatment of Patients with Advanced Ovarian Carcinoma (Stages III and IV), April 1974, p.2, op.cit.
171 NCIC, Protocol for a Clinical Trial of Radioactive Chromic Phosphate and Chemotherapy with Melphalan following Surgery for Patients with Limited (Stages I, II and IIIa) Carcinoma of the Ovary, 20 May 1975, enclosed with correspondence from T.A. Watson to E.R. Plunkett (Professor and Chair, Department of Obstetrics and Gynaecology, UWO); in the WUA, AFC 328.1.2655.
This statement indicated that investigators had to get patient consent to assign the patient to one of the treatment groups through registration at the trial-coordinating center. Why did patient consent become imperative in the endometrial carcinoma protocol, but it did not appear so in the previous NCIC protocols?

An answer may be found in two changes in the context of regulatory environment of human experimentation internationally. In March 1975, the World Medical Association (WMA) circulated a significantly reviewed draft of the Declaration of Helsinki to country-member medical associations. The Canadian Medical Association (CMA) disseminated the draft to the deans of medical schools for comments in order that its representatives offered their views on the ethics of human subject research to the WMA Assembly later that year. This draft of the Declaration of Helsinki generated a lively discussion among the leading medical researchers in Canada, since it recommended that adequate investigative protocols include a clause on obtaining informed consent and that a competent authority had to review the protocol and the consent form. In addition to outlining the procedure of obtaining informed consent, the draft stated that the responsibility for clinical research always rested with the investigator, never with the human subject who consented to it. A reaction to the WMA ethical recommendations followed immediately at the institutional level. For instance, the Screening Committee for Research Involving Human Subjects at the University of British Columbia amended its submission form for ethics review by covering experimental procedures that did “not necessarily go beyond the subject’s needs for prophylaxis, diagnosis or therapy.” Even though this decision again introduced an underdetermined category of investigative treatment, it was more important to monitor all medical investigations for ethical acceptability.

After the WMA had approved the Declaration of Helsinki at the Tokyo General Assembly in October 1975, the CMA distributed a memorandum informing the deans of medical

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172 Underlined in the original. NCIC, Advanced Endometrial Carcinoma Clinical Trial: Chemotherapy of Stage IV, Metastatic and Recurrent Carcinoma of the Uterine Corpus, 16 June 1976; in the WUA, AFC 328.1.2643.
174 John S. Bennett (Director, Scientific Councils, CMA, Ottawa) to D. Bates (Dean, Faculty of Medicine, UBC, Vancouver), 21 April 1975; in the UBCL, Faculty of Medicine Fonds, 9(12).
176 The UBC, Faculty of Medicine, Screening Committee for Research Involving Human Subjects; Minutes of the Meeting, 19 June 1975, p.3; in the UBCL, Faculty of Medicine Fonds, 9(12).
schools that the position submitted on behalf of the Canadian medical profession was at variance with the adopted declaration on two relevant issues. First, the CMA had suggested that functions of the ethics review committee include approval of the research protocol and the informed consent form. Second, the CMA recommended that the WMA insert in the 1975 Declaration of Helsinki a clause on the requirement of informed consent for any investigative procedure involving human subjects. The WMA disregarded these two recommendations of the CMA, but the latter made efforts to let the Canadian clinical investigators know of its research ethics standards. A changing framework of human subject research regulation in the United States played a significant role in this as well.

The US government imposed strict legal requirements on clinical research institutions following two developments. They were the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in July 1974 and the enactment of a revised Code of Federal Regulations in April 1975. George A. Higgins, Chairman of the Veterans Administration Surgical Adjuvant Cancer Chemotherapy Group at Washington, D.C, reported at the meeting of the International Union Against Cancer (UICC) that a growing movement towards the protection of patients’ rights in the US had side-effects: the institutional review committees considered aspects of patient protection more important than the scientific evaluation of treatments through RCTs. As a consequence, numerous problems arose. They involved a protracted approval of research protocols by the ethics review committees and a falling enrolment of patients in the approved investigations due to fairly detailed informed consent forms. Specifics of these consent forms magnified patients’ fears.

177 J.S. Bennett (Director, Professional Affairs, CMA) to D.F. Cameron (Dean, Faculty of Medicine, University of Alberta, Edmonton), Ottawa, 27 January 1976; in the UAA, Acc. No. 80-162-242, 6-B-51.
180 International Union Against Cancer (UICC), “Report of the Meeting of the Project on Controlled Therapeutic Trials,” Geneva, 5-7 May 1975, p.4; in the in the UTA, A1986-0035/03(07).
For the Canadian investigators who participated in the US Cooperative Groups, the increasing government surveillance of clinical research meant excessive administrative work to comply with the US regulations on the protection of human subjects. For instance, it took Pierre R. Band of the University of Alberta several months to resubmit required documents to continue his ongoing clinical research within the Eastern Cooperative Oncology Group to the US Department of Health, Education and Welfare in Bethesda, Maryland. By contrast, for individual clinical researchers engaged in the investigation of new anti-cancer treatments in Canada, stringent rules in the US contributed to an influx of funding and experimental drugs from American colleagues who attempted to evade regulatory difficulties related to the institutional review boards and the informed consent requirements. Accordingly, outsourcing partnerships between American and Canadian investigators emerged, which caused tension between the NCIC, the Drugs Directorate of Canada (FDD), and the US NCI.

Since at least 1974, there was a growing reluctance on the part of the US NCI to supply necessary data on the experimental agents to the FDD to permit the latter body to assess independently whether particular drugs could be released for trial evaluation in Canada. With the appointment of John S. Penta as a new Head of Drug Liaison and Distribution Section of the US NCI in 1975, this situation worsened. Penta took an attitude that if the US NCI approved a new drug and the FDA authorized its use, then there was no reason for the FDD to review the drug in accordance with a similar procedure in Canada. Even more, Penta suggested setting up a Canadian distribution center for the US NCI-endorsed drugs, which could potentially improve the supply of investigational agents for use in Canada. Underlying his reasoning was a seemingly managerial approach: to decrease the workload of US NCI officials who had to deal with increasing amounts of paperwork for the customs and drug shipment purposes. However,

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181 The documents included Assurance of Compliance with DHEW Regulations on Protection of Human Subjects, Certification of Review and Special Implementation of Institutional Assurance, and Informed Consent Form for the Eastern Cooperative Oncology Group Studies. See enclosures with correspondence between D.T. Chalkley (Director, Office for Protection from Research Risks, NIH, US DHEW) and D.F. Cameron, Bethesda (MD), 12 September 1975; in the UAA, Acc. No. 80-162-242, 6-B-51.

182 Minutes of the Eighth Meeting of Participants in Canadian Clinical Trials, Montreal, 13-14 September 1976, p.13; in the UTA, A1986-0035/037(01).


184 Memorandum from C.P. Scott (Director, Bureau of Drugs, Drugs Directorate, Health Protection Branch) to John Murphy (Consultant, Research Programs Directorate), Ottawa, 9 February 1976; in the UTA, A1986-0035/038(02).
A.B. Miller of the NCIC considered Penta’s suggestion in a different light, “it [wa]s becoming increasingly clear that they [US NCI] [we]re anxious to test new drugs in Canada because they [we]re finding difficulties in testing [them] in the United States. Thus, […] we should be careful not to relax our requirements and insist on the appropriate submission of information from the U.S. NCI.”185 In this communication to Harold Taylor of the Medical Research Council of Canada, Miller also insisted that the MRC steer clear of a Canadian center for the US NCI drug distribution because this activity came under the FDD jurisdiction. Miller’s other likely concern was an interference of the distribution center with the NCIC cooperative clinical trial program. Because of a direct access to experimental drugs, Canadian individual investigators could resume their non-randomized clinical trials and significantly reduce the pool of cancer patients available for the NCIC-coordinated RCTs.

As the MRC of Canada did not have regulations in relation to patient consent until 1978, the NCIC did not demand from cooperative trial participants to spell out the ethical requirements. That the NCIC had no prescription for a uniform consent form for the approved trials seemed to be a strategy aimed at encouraging diverse groups of investigators to partake in the cooperative clinical trial program.186 In each center participating in the collaborative trial, local university regulations applied and an appropriate ethics review committee provided clearance for the proposed investigations. Thus, the NCIC left decision-making on the compilation of patient consent forms suitable for use in particular trials to the institutional committees in consultation with the local investigators. The culture of human experimentation was in the making locally, through a group consensus on the ethical acceptability of certain clinical investigations and on the extent to which research subjects were informed of this ethicity.

To contextualize the above, two examples may suffice. First, members of the endometrial cancer trial committee chaired by Alan H. Gerulath, a gynecologist at St. Michael’s Hospital in Toronto, agreed in early 1976 that it was appropriate to give melphalan as a last-resort therapy to patients with a progressing carcinoma of the endometrium in both treatment groups who had failed to benefit from the two evaluated regimens. Their reasons for using this chemotherapeutic

185 Miller to Taylor, 25 February 1976, op.cit.
186 A.B. Miller to T. Glen Stoddart (Director, Ontario Cancer Foundation, Ottawa Clinic, Civic Hospital), 23 July 1976; in the UTA, A1986-0035/010(06).
agent were that melphalan had proved somewhat effective in treating patients with advanced ovarian carcinoma and that it was useful to evaluate the efficacy of this drug when administered alone.\textsuperscript{187} It is noteworthy that the investigators were aware that carcinoma of the endometrium differed substantially from carcinoma of the ovary because of the two distinct tissues in which these malignancies originated. In all likelihood, the researchers did not have any better treatment options, so they decided to try melphalan, which was effective in treating ovarian tumors, as an anti-cancer therapy for neoplastic disease in the adjoining organ, the uterus. The committee members regarded this use of melphalan as “a Phase II type study [that determined] the response rate” of human subjects to the agent. It stands to reason that this investigation should have been conducted prior to the NCIC Phase III cooperative trial that required at least 140 patients to complete it, according to statistical considerations.\textsuperscript{188} Obviously, the investigators did not inform patients on the above and the patient consent form for the trial participation did not contain this information.\textsuperscript{189}

Second, A.B. Miller provoked a controversy among American participants of the International Symposium on BCG in Cancer Immunotherapy in Estérel, Québec, on 22 April 1976 when he discussed the design and challenges of the 1973 cooperative clinical trial without giving a preliminary analysis of its results. The trial, which assessed the use of BCG in operable lung cancer, closed the intake of patients in May 1975, with 310 evaluable patients, yet Miller along with his NCIC colleagues deemed it inappropriate to make hasty conclusions.\textsuperscript{190} Almost disappointed with this turn of events, Donald L. Morton, Professor of Surgery and Chief at the Division of Oncology of the UCLA Medical School in Los Angeles, asked A.B. Miller, the trial

\textsuperscript{187} As A.H. Gerulath explained, “melphalan, which was generally well tolerated, had not yet been assessed in endometrial carcinoma.” The forum of NCIC clinical trial participants agreed on minor revisions to the protocol and voted to activate it when amended. The final NCIC protocol \textit{Advanced Endometrial Carcinoma Clinical Trial} had melphalan at the last stage of treatment regimens in all four arms of the study. See “Minutes of the Meeting of the Sub-Committee on Endometrial Carcinoma of the Clinical Committee of the NCIC,” Toronto, 30 January 1976, p.1; in the UTA, A1986-0035/10(11); and NCIC, \textit{Advanced Endometrial Carcinoma Clinical Trial: Chemotherapy of Stage IV, Metastatic and Recurrent Carcinoma of the Uterine Corpus (1976)}, Schema, \textit{op.cit.}

\textsuperscript{188} Minutes of the Seventh Meeting of Participants in NCIC Clinical Trials,” Winnipeg, 1-2 March 1975, p.5; in the WUA, AFC 328.1.2641.

\textsuperscript{189} Consent Form, enclosed with correspondence from A.H. Gerulath to Barbara J. Merkens (Office of Research Administration, University of Toronto), “Re: The Advanced Endometrial Carcinoma Clinical Trials,” Toronto, 9 January 1978, p.2; in the UTA, A1986-0035/10(11). A.H. Gerulath wrote, “Melphalan, which is widely used in other gynaecologic cancers and effective, may be found to be useful in carcinoma of the endometrium.”

\textsuperscript{190} Frappier \textit{et al.}, \textit{BCG in Cancer Immunotherapy} (1976), xi-xvi and 202.
director, to present interim results of the trial. To justify his request, D.L. Morton noted that investigators in the US had to analyze clinical trial data every four months and report them to the institutional review board for approval. Government regulations on informed consent dictated that patients should have the option of the better therapy as soon as the investigation showed a statistically significant difference in favor of one of the evaluated treatments.\textsuperscript{191} Miller’s reply was straightforward, “In the beginning, the agencies [MRC, NCIC, OCTRF, Health and Welfare Canada] agreed they would not get themselves into the sort of bind which individuals here, I think, are getting into, reporting the results in a preliminary way, in a favorable way.”\textsuperscript{192} Miller explained that the trial statisticians assessed the results periodically and there was no substantial difference between the treatment regimens at any time, so the final analysis had to wait until the planned endpoint of the trial.

A.B. Miller also stated that an induced reporting of preliminary results in the US had wrong underlying reasons, such as acting seemingly in the best interests of patients, while in fact patients received unproven treatments that in the long term might be less effective. Moreover, this practice could lead to a premature termination of trials without producing valid scientific data, which not only halted an efficient treatment development, but also exposed patients to unnecessary risks.\textsuperscript{193} In response to Miller’s well-substantiated position, D.L. Morton commented, “… it is nice if you can do the type of trial you want. You can do them for those of us who have more stringent requirements in terms of our informed consent.”\textsuperscript{194} In support of Morton’s view, Jordan U. Gutterman, Associate Professor of Medicine at the Department of Developmental Therapeutics of the M.D. Anderson Hospital and Tumor Institute, pointed out, “I do not see how anyone can offer a patient with lung cancer [after a tumor-reduction surgery] a card that says \textit{placebo} or no treatment, when we have so many exciting leads to follow.”\textsuperscript{195} This

\textsuperscript{191} \textit{Ibid.}, 257.
\textsuperscript{192} \textit{Ibid.}
\textsuperscript{193} Knut Magnus and A.B. Miller, “Methodology of Controlled Prophylactic Trials in Cancer,” in \textit{Methods and Impact of Controlled Therapeutic Trials in Cancer: Part I}, UICC Technical Report Series – Volume 36, ed. Peter Armitage \textit{et al.} (Geneva: IUAC/UICC, 1978), 124. The authors wrote, “Ethically it is just as wrong to terminate a trial prematurely resulting in an indefinite result as to continue without taking note of possible hazard and induce substantial morbidity or mortality.” This was a double-bind situation.
\textsuperscript{194} Frappier \textit{et al.}, \textit{BCG in Cancer Immunotherapy} (1976), 257.
\textsuperscript{195} Emphasis in the original. \textit{Ibid.}, 258.
statement clearly indicated that the Canadian cooperative trial was relatively unethical in relation to American standards.

This clash of expert opinion on the ethics of human subject research was not unique. It was one among many, which signaled to the Canadian clinical investigators and officials responsible for regulation of medical research that reform was overdue. In July 1976, the MRC of Canada established a Working Group on Human Experimentation to review the existing clinical investigation practices, reassess their regulation, and recommend updated ethical guidelines for research involving human subjects. On behalf of the Working Group, Francis S. Rolleston, Assistant Director of the MRC, invited A.B. Miller and other specialists in the area of controlled clinical trials to share their views on ethical issues related to human research.

In his submission of materials for consideration of the Working Group, Miller emphasized that a re-evaluation of the approach to patient consent was necessary. Miller’s main concern was the doctrine of informed consent advocated in the United States. According to Miller, “there [wa]s a danger that attempts to obtain informed consent may not be possible, but that the onus to ensure that high standards of ethical conduct [we]re followed, may be passed from the physician to the patient, releasing the physician from taking the decisions he should take, and in fact resulting in a lower standard than would otherwise be achieved.” This proposition suggested that a knowledge asymmetry in the doctor-patient relationship could not easily turn into a parity of decision-making capabilities in the subject-investigator relationship. In the case of RCTs, some information relevant to the patient-subject was just not available, so Miller rightly questioned the possibility of a “true informed consent” on the part of the patient-subject and he recognized the correlated likelihood of the physician-investigator’s abdication of responsibility.

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196 Francis S. Rolleston (Assistant Director, Grants Program, MRC) to A.B. Miller, Ottawa, 25 October 1976; in the UTA, A1986-0035/002(06).
197 Pierre R. Band, Ernest A. McCulloch, and J. William Meakin were among the other consulted cancer specialists; see Medical Research Council of Canada, Ethical Considerations in Research Involving Human Subjects, MRC Report No. 6: Ethics in Human Experimentation (Ottawa: Supply and Services Canada, 1978), 49-51.
199 Ibid., 1.
200 Ibid., 2.
Ernest A. McCulloch of the University of Toronto, who also submitted a brief note to the MRC on informed consent in randomized clinical trials, expressed similar reservations. According to McCulloch, it was disturbing to patient-subjects to find out that their physician-investigators were “not confident as to the correct treatment for their condition.”201 Moreover, this situation induced patients to determine whether a random treatment allocation was the proper course of action in the process of decision-making on their own therapy. In practice, as McCulloch put it, “these problems of consent […] greatly inhibited randomized clinical trial, although this [wa]s the most generally accepted method for establishing the efficacy of treatment modalities.”202 Further, the by-products of this decision-making process could involve the patient-subjects’ unwillingness to participate in the RCTs, which had already induced American investigators to abandon trials with poor patient accrual. As this trend developed, a corresponding probability of lowering clinical care standards increased in the long-term.

The question of informed consent became less hypothetical when the NCIC requested supplies of investigational drugs unavailable in Canada from the US NCI.203 Without compliance with the American regulations on human subject research, which involved vetting of the proposed research protocol and of the informed consent procedure, the US NCI denied access to new drugs that Canadian investigators intended to use in their RCTs. Since the Canadian officials declined to establish a drug distribution center operated by the US NCI, this institutional verification of full compliance with US laws tightened. Hence, the NCIC had little choice but to reform its process of the protocol review and implementation when the investigators wanted to obtain drugs from the US NCI. Beginning from March 1977, the NCIC Clinical Trials Committee introduced this reform by requiring two written assurances from institutions

201 Ernest A. McCulloch, “Contentious Issues in Human Experimentation,” 4 January 1977, enclosed with correspondence from E.A. McCulloch to B.M. Dickens (Faculty of Law, University of Toronto); in the UTA, B1991-0004/008(18).
202 Ibid., 1.
203 For instance, the Investigational Drug Branch of US NCI supplied free of charge 500 mg vials of methotrexate for the 1974 NCIC trial of the treatment of advanced ovarian cancer. See Protocol for the Treatment of Patients with Advanced Ovarian Carcinoma (Stages III and IV) with Melphalan, 5-Fluorouracil and Methotrexate in Combination and Sequentially (April 1974), 8; op.cit.
participating in the cooperative trials: one on the appropriate local review procedures and the
other on the acceptable approach to informed consent.204

A research protocol for a second-generation trial of the treatment for advanced ovarian
cancer evaluating three new chemotherapeutic agents and melphalan, already a standard therapy,
clearly stated the existing requirements.205 Because two of the agents – Hexamethylmelamine
and cis-Platinum – were available only as investigational drugs through the US NCI, the latter
required a copy of the protocol and other supporting documents to review their scientific and
ethical acceptability according to American regulations.206 This process of verification took
about a year between the approval of the protocol by the NCIC Clinical Trials Committee and
the confirmation of compliance by the US NCI in March 1978.207 In the meantime, the MRC of
Canada adopted the report of the Working Group on Human Experimentation – Ethical
Considerations in Research Involving Human Subjects.208 Although these guidelines seemed to
lay the groundwork for governance of human subject research in Canada, local features of the
culture of human experiment interfered.

After the NCIC approved the 1978 advanced ovarian cancer protocol, Alan H. Gerulath, a
gynecologist at St. Michael’s Hospital in Toronto, sent it along with a consent form for
consideration by the University of Toronto Human Experimentation Committee.209 A member of
this committee, Alon J. Dembo, a radiologist at the OCI/PMH, returned a letter of criticism
regarding both the protocol and the consent form.210 A reaction of A.B. Miller was inevitable. He
contacted Barbara L. Merkens, an official at the Office of Research Administration of the
University of Toronto, to discuss the ground rules for the institutional ethics review of NCIC

204 Minutes of the First Meeting of the Clinical Trials Committee (formerly the Clinical Committee) of the Clinical and Epidemiological Research Advisory Group of the NCIC, Ottawa, 6 and 8 March 1977; in the UTA, A1986-0035/037(02).
205 Protocol, NCIC Second Cooperative Clinical Trial on Treatment of Advanced Ovarian Carcinoma (OV.3), March 1978, pp.3 and 17-18; enclosed with correspondence from Donald J. Dodds (Clinical Trials Coordinator, NCIC) to Directors of Cancer Treatment Centers, Toronto, 17 March 1978; in the WUA, AFC 328.1.2655.
206 Ibid., 1 and 26-29.
207 Minutes of the Eleventh Meeting of Participants in NCIC Clinical Trials, London, Ontario, 6-7 March 1978; in the UTA, A1986-0035/037(03).
208 MRC, Ethical Considerations in Research Involving Human Subjects (1978), 1-3.
209 Memorandum from D.J. Dodds to A.B. Miller, 6 July 1978; in the UTA, A1986-0035/015(03).
Miller’s main point was the criticisms from A.J. Dembo “fell outside the jurisdiction of an Ethics Committee and in fact could be regarded as quibbles or opinions rather than appropriate ethical or scientific comment.” Inasmuch as the majority of the NCIC Clinical Trials Committee members agreed to proceed with the protocol implementation, any change in the design of the trial or amendment to the protocol had to follow the same NCIC review procedure.

Institutional ethics committees did not have the authority to suggest modifications to the protocol, but they had a duty to approve, or not, participation of local investigators in the cooperative clinical trial. If the ethics committee approved the trial protocol, its task was to assist investigators in designing a consent form that represented ethically acceptable principles of human subject research. Did the MRC guidelines on the ethics of human experimentation enable the institutional review committee to appropriate the above authority in the context of inter-professional rivalry? It was likely, given that a struggle burgeoned between the administrators of research and the investigators. Marc A. Baltzan, Professor and Head of the Department of Medicine at the University of Saskatchewan, offered some insight into this complex problem. It was Baltzan who had given expert testimony before the Court of Appeal for Saskatchewan in 1965 about the appropriate conduct of medical research and the corresponding requirement for informed consent, but his major concern was different in 1979:

The situation at the present time is made particularly difficult by the fact that the managerial revolution is now sweeping through the health care field. The basic law of the managerial revolution is that management is everything and knowledge of the field is nothing. Thus, we find ourselves in the position of having to justify our activities to managers who know nothing about what we are doing.

In this light, the Canadian clinical cancer trial program acquired a distinctly political dimension. Since 1978, mechanisms for conducting clinical investigation embodied in the RCTs became inseparable from the policy on human subject research. Whether this change was for the better, or worse, is arguable. However, the number of those who considered themselves competent

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212 Ibid., 1.
enough to interpret the ethics of medical research steadily increased. Did therapeutic innovation fare any better as institutional review committees made human experimentation complicated?

5.4. Conclusion

As the issues of cancer management increasingly entered public affairs in the 1970s, exponents of scientific medicine did not miss the opportunity to make their contributions to cancer care more visible. It was important for investigators to gain popular acceptance of the major contribution that they brought to medicine – the randomized controlled clinical trial (RCT) that placed safe and effective treatment methods at general practitioners’ disposal. With this acceptance, the patients legitimized the conduct of RCTs on terms that investigators set. Given that there were no officially adopted guidelines on ethically appropriate human subject research in Canada, the modus operandi of investigators, including its ethics, was essentially open to determination by a consensus of leading cancer specialists.

The National Cancer Institute of Canada created a forum of investigators interested in clinical trials. This cooperative process was embedded in a matrix of interactions that conditioned both the direction of its development and the means of its activation. A cross-section of the organization of collaborative RCTs showed to what extent the research interests and values of leading investigators initially outweighed not only priorities of healthcare, but also needs, and sometimes rights, of patient-subjects. In the second half of the 1970s, however, a successful continuation of the well-established NCIC cooperative clinical trials program demanded that investigators applied a more patient-oriented approach to their research. This somewhat abrupt shift in the ethics of human subject research occurred when the international medical community reviewed the Declaration of Helsinki and the US government enacted a series of institutional regulations to enhance protection of research subjects and accountability of clinical investigators. Yet, it would be an exaggeration to claim that in the Canadian context of human subject research external pressures induced the shift. What happened was a formalization of the acceptable ethics of clinical investigation on the basis of a consensus achieved in the course of cooperation in the NCIC-coordinated clinical trials.
In making uncertainties of oncological RCTs and their ethical controversies clear, this chapter examined why investigators developed and approved particular cooperative trials. The NCIC investigators played a gambit with the collaborative trials in Hodgkin’s disease both to bring influential radiotherapists into the fold and to demonstrate that clinical research facilitated cancer management. A cooperative chemotherapy group in the US had already shown positive results with the MOPP drug combination and the NCIC investigators just added to it a regimen of radiotherapy to find out whether it still improved treatment outcomes. From the American perspective of twenty-odd cooperative groups that conducted hundreds of clinical trials, a Canadian initiative was a drop in the ocean. To compensate for an already significant American influence on the program, the NCIC officials appointed a British physician-epidemiologist with long experience in trial design and organisation, A.B. Miller, who proved instrumental in getting Canadian cooperative clinical trials off the ground. To a certain extent, the second NCIC-coordinated cooperative trial in plasma cell myeloma reflected the strong American impact that correlated with some grave consequences for patients. At the same time, the myeloma trial encouraged hematologists to collaborate in a joint project that utilized insights from a burgeoning immunology, which made the trial quite innovative.

An early success of the NCIC in the organization of the Hodgkin’s disease trial prompted the Canadian Department of National Health and Welfare, the MRC of Canada, and the Ontario Cancer Treatment and Research Foundation to support the cooperative trial in the treatment of operable lung cancer with BCG immunotherapy. Not only was this trial a priority of public health authorities, but it also involved surgeons in the NCIC program. An additional indirect benefit of the trial was a reduction in the indiscriminate use of BCG by general practitioners. Although American investigators insinuated suspect ethics of this placebo-controlled trial, Canadian cancer specialists representing the four agencies dismissed such insinuations as unsubstantiated. The power of community consensus on the ethics of human subject research had a role therein.

Through organizing a series of cooperative RCTs to evaluate treatments for gynecologic malignancies, the NCIC obtained recognition of its program from yet another medical specialty. Two opening trials in ovarian cancer set the stage for a fruitful collaboration between the NCIC and the leading Canadian gynecologists, but the next two trials were not so successful. The
inclusion of requirements for an informed consent and for an institutional ethics review clearance in the research protocols since 1976 seemed to make a difference to the patient enrolment for these trials. The NCIC completed all of the cooperative trials analyzed in this chapter, apart from the last two. There were no substantial changes in participating investigators, nor modifications in the NCIC procedure of a two-stage scientific and ethical review of research protocols. It was likely that the extra administrative workload imposed by the new regulations interfered with the investigators’ willingness to register patients for the protocols. The managerial revolution came to medical science, but there was a dearth of competent managers.
Conclusions

The tension between an institutional autonomy of Canadian cancer research and a demand for its accountability to the public was palpable by the end of 1970s. Institutional ethics review committees comprising both investigators and non-medical members received a mandate to regulate the activation and conduct of clinical trials. The administrative culture of control was pitted against the scientific-medical culture of trust. Underlying this was a burgeoning codification of human subject research ethics. An ever-closer link between cancer studies in the laboratory and clinical applications of experimental findings increasingly exposed patients to risks inherent in new forms of treatment. Yet, a shift in thinking about the ethics of human experimentation at the time did not occur because of administrative impositions. Rather, these impositions followed from a self-regulating mechanism of clinician-investigators’ peer-review established at least a decade prior to a 1966 official requirement for ethical assessments of clinical trials. The MRC of Canada introduced this regulation after cancer investigators had already achieved a consensus about principles of ethical adequacy of human subject research. Legal precedents triggered a reaction of research administrators to claims of unconsented clinical trials that investigators had regarded as common practice in experimental medicine. This practice was part of a culture of human experimentation that manifested itself locally through procedures and conventions of doing cancer research approved by a community of experts.

Several publicly revealed failures in medical research, among many undisclosed others, indicated how complicated clinical investigations became in the post-war period. Although these failures arose not from a lack of professionalism, a poor ethical judgement, or excessive incentives, they drew intense attention. At issue was the authority of investigators to decide on their own whether the clinical trial could do more good than harm. The 1965 ruling of the Supreme Court of Canada, representing contemporary public debates on human experimentation, reflected the wish to involve research subjects directly in the decision-making about their participation in clinical investigations. A set of requirements ensuring that research subjects gave an appropriately informed consent for their participation in medical investigations seemed to empower subjects and constrain the researchers’ latitude in experimentation. At the same time, investigators secured more protection from legal liability through sharing responsibility with
subjects for unforeseen consequences of medical research. Cancer clinical trials in Canada during the 1960-1970s contributed to the recognition of the concept of human dignity as the moral imperative essential to carry out human subject research. This meant that the investigator and the subject acted purposefully by maintaining what was unconditionally valuable for both of them in a particular clinical encounter. Human dignity, therefore, made a voluntary participation in medical investigation possible and set adequate limits for this activity. This was a necessary course of action when a growing number of researchers turned to experimental evaluations of anti-tumor agents in increasing quantity.

The formidable cancer problem induced investigators to consider ethically acceptable a greater than moderate risk to the research subject if their colleagues determined that scientific merits of certain clinical studies offered a significant contribution to therapeutics. Until the late 1970s, the majority of clinician-investigators concurred with the idea of comparative trials and considered them valid only if evaluated treatments presupposed a maximum allowable dosage. Such developments often led to over-treatment and excessive investigation of patients who believed their physicians’ preaching that the invasive disease needed an aggressive therapy. Still, some cancer specialists appreciated limitations of aggressive treatment, notably when they administered it in concurrent or sequential regimens. A few leading radiotherapists and chemotherapists, whose expertise had evolved through clinical practice to research, distrusted the establishment views about the quantity of therapy as a correlation to better treatment outcomes, to say nothing of the patient-subject’s quality of life. Their therapeutic failures were evident proofs of existing concerns. Results from cooperative randomized controlled trials further heightened these perceptions among the investigators. Collaboration in the multimodal investigations prompted experts to find a common ground for divergent views on the optimal treatment for a number of malignancies. Once investigators engaged in doing RCTs, they had to accept that they were doing research, not simply providing care, which needed some updated version of ethical review.

As approaches to clinical trials and their justification changed, so did the ethics of medical investigation. These conversions occurred through a series of critical junctures involving technological innovation, institution-building, inter-professional struggle, changing doctor-patient and investigator-subject relationships, lengthy litigation, and the contestation of a
research ethics paradigm. In bioethical discourse, however, the proposition that human research ethics evolved along with the practice of clinical investigation received little consideration. Debates about the meaning of ethical acceptability in clinical investigation ignored the historical epistemology of this issue. Without appreciating the past trajectory and uses of this notion of ethically acceptable clinical investigation, attempts to analyze it in a meaningful way are often misguided. To deepen our understanding of interactions among socio-cultural factors conditioning the construction of ethical judgements and frameworks at their basis, this dissertation examined the emergence of human subject research codification as an integral part of the development of Canadian cancer care and clinical trial programs.

Research ethics seemingly emerged from the exploitation of human subjects for the purpose of medical investigation. Indeed, intensifying human experimentation eroded clinical researchers’ credibility, but advances in cancer treatment could not have happened without therapeutic experiments. During the twentieth century, therapy development in oncology provided illuminating examples of successive clinical studies, varying in degrees of experimentalism, representative of medical research in other fields. Malignant tumors were seldom amenable to available treatments, so physicians and surgeons tried to use experimental approaches to treat their patient-subjects case-by-case, in small groups, and in large clusters, as was practicable under the circumstances. Accordingly, designs for such clinical trials differed across a wide spectrum of clarity and complexity. As experimental designs became more elaborate over time through specification and diversification, investigators engaged in this work promoted the use of research protocols for clinical trials. This made investigative practice increasingly systematized and open to collective review and criticism.

To investigators, protocol-creation in clinical research meant reproducibility, standardization, and improved accuracy of therapeutic evaluation, which seemingly contributed to a better quality of care for patients in the long term. At the same time, an increasing clarity of protocols allowed research administrators to gain an insider’s knowledge about a step-by-step implementation of clinical trials and to manage supposedly problematic aspects of them. The accessibility of protocols, therefore, facilitated both the conduct of RCTs and its ethical regulation. Protocols made a shift from medical ethics to that of human subject research possible. This shift, however, only occurred following a series of changes in the organization of cancer
control. Quantification of neoplastic diseases led to fearmongering about a possible epidemic, which induced medical authorities to utilize the infrastructure of bacteriological hygiene regimes. This prompted the formation of cancer charities, the establishment of specialized treatment institutions for cancer patients, and the organization of agencies to foster public awareness of the malignant disease, its prevention, early detection, and treatment. The inflow of public funds into cancer research precipitated the centralization of investigative activities in university hospitals and cancer clinics, which offered access to state-of-the-art therapeutic technologies and new medicinal agents. For example, a rapid transition of radioisotopes from a research tool in the laboratory to a therapeutic modality in the cancer clinic occurred through their commercial production and targeted distribution through a network of investigators.

The next stage in the organization of cancer control involved forging strategic links among the investigators, which the NCIC realized through its coordination of research initiatives. The development of synergy between government-backed programs and the NCIC-supported cancer research projects created favorable conditions for specialization in therapeutic radiology and chemotherapy. Facing a stronger competition for scarce public funding and professional growth opportunities, cancer specialists turned to re-evaluating the evidentiary base underlying assessments of new treatment modalities. Advocates of the RCT as the most reliable standard for testing efficacy of treatments redrew boundaries among the specialties and, concomitantly, problematized the practice of using patients as research subjects. A feedback loop between the content of RCT protocols and the ethics of human subject research came into being. There were challenges to the ethical adequacy of RCTs, however.

Statistical probability lay at the root of RCT methodology of investigative drug evaluation, while a factual assessment of the institutional ethics review centered on avoiding uncertainty in the consent form designed to inform the research subject. As investigators devised increasingly complex RCT protocols, ethics review committees developed more detailed informed consent forms. This generated disagreements among investigators and a growing perplexity among research subjects. As a result, some clinical investigations did not get off the ground, or if they did, a poor accrual of subjects led to their premature closure. Providing safeguards against harm to the research subject and securing the protection from liability of the investigator contributed to a more expensive maintenance of the cooperative clinical trial
program. This also meant that fewer treatment options for the cancer patient became available and affordable in the long run, since the number of RCTs evaluating new therapeutic modes tended to diminish and those in progress took more time to complete. There was an interdependence among scientific-medical, socio-cultural, and political-economic factors in this dynamic equilibrium of doing clinical research and providing cancer care. The Canadian development of the cooperative clinical trial program along with its ethical regulation demonstrated how interdependent these practices were and why.
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