TURNING POINTS

Robert J. Levine

"Life is what happens to you while you're busy making other plans." —John Lennon

To prepare for writing this paper I spent several pleasant hours reading some of those published by my predecessors in the Intellectual Trajectories volumes. Many start with detailed accounts of the authors' families beginning two or more generations before the authors' birth. I cannot do this because I know very few details of my family's origins. My parents each arrived as young children from Europe early in the twentieth century, my mother from Budapest and my father from Russia, and they rarely spoke of the life or the people they left behind.

In 1934 when I was born, my family lived in Wantagh, then a very small town on the south shore of Long Island, where my father was just beginning the general practice of medicine. Most of Wantagh's residents were farmers. During the Depression when almost everyone was quite poor, his fees were often such things as a watermelon or, from the patients who lived along the shore, a basket of oysters.

My mother was the only daughter among four siblings. Her family decided they could support the education of only two of their children and that the other two would have to quit school to seek employment to support those to be educated. In such circumstances, the choice of the girl to be a worker was automatic; she left high school at the age of fourteen to become a secretary. Eventually, she became my father's secretary and, shortly thereafter, his wife.

My parents were each born in Jewish families, but neither the religion nor the culture was an important component of their lives. As for me, I attended Protestant churches and Sunday schools. I believe my motivation for doing so was at first to have someone to play with on Sunday mornings. These institutions were, as it were, the "only game in town" in each of my two childhood hometowns.

During World War II, my father enlisted in the U.S. Army and was stationed in Daytona Beach, Florida. My family moved to Ormond Beach, then a very small

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town about ten miles north of Daytona Beach. After the war ended we moved back to Wantagh. Because many of my formative years were spent in Florida, I think of myself as a Floridian.

In the 1950s my mother passed the high school equivalency exam and enrolled in Hofstra University, earning a B.A. degree and a master's degree in special education. By the time of her graduation she had begun to lose her vision and eventually became almost totally blind. She pursued a satisfying career as a teacher in a school for blind children.

John Lennon was right: life is what happens while you are busy making other plans. As I tell the story of the development of my professional life, I will focus on the turning points—unplanned events that introduced substantial changes in the direction of my intellectual trajectory.

Early School Experiences

When I began first grade at the age of five, I was already able to read. This was not because I was notably brilliant. Because Wantagh had no kindergarten, every child began in first grade, usually at the age of six. But because my sixth birthday would occur before the year's end, and because my parents argued with apparent success that I was ready, I was admitted early.

As a preschooler I was often afflicted with minor illnesses associated with modestly elevated temperatures and therefore confined to my bedroom. My mother, wanting to keep me busy so that I would not, as she put it, "drive her crazy," taught me to read.

Early in the first month of school, the teacher observed that I was not paying attention as she was teaching the class the alphabet. She caught me looking inside my desk. She came to my desk and asked me in a very irritated voice what I was looking at. "Nothing," I replied. She opened the desk and found an open book. She asked, "What are you doing with that?" I said that I was reading it. She seized the book and insisted that I immediately accompany her to the principal's office.

She told the principal that I claimed to have been reading a book. He opened the book and asked me to begin to read aloud. I did so. He closed the book, handed it to me, and told me to return to class. As I was leaving the office I heard him say, "Miss Dominy, we have a problem."

The remedy was to put me in second grade, where the students were learning cursive writing and reading "Run, Spot, run." This was the beginning of a school career that I considered boring, tiresome, and something to be avoided if at all possible. I became adept at finding excuses to be absent.

My lack of enthusiasm persisted through high school. I did enjoy English and geometry classes but little else. I was a member of the high school's extraordinary wrestling team. My senior year was its sixteenth year of existence. In all those years it had lost only one dual meet and that was during an epidemic of some childhood illness. It was widely regarded as the best high school wrestling team in the country. The

first-string wrestler in my weight class was a Pan American champion. This record was largely due to its most capable and renowned coach, Sprig Gardner.

My academic record in high school was undistinguished; I was told that I was at the top of the middle third of the class. I had applied to several colleges, but as of March of my senior year I had not been accepted at any. I went to the coach and explained my situation and asked if he could help me. He asked me which school was my first choice; I told him Duke University. He opened a telephone book and looked at the first few pages. After he found what he was looking for, he asked me if I had $1.25. I said no but I could raise it. He then dialed the telephone and I could hear his end of the conversation. "Hello Ace. Sprig here. I've got a 127 pounder here who would like to go to Duke. [*pause*] No, he's not first string, but our second string is good enough for you." (He was talking with Ace Parker, Duke's athletic director.)

After engaging in a bit of small talk he hung up, turned to me, and said, "It's taken care of." Shortly thereafter I received a telegram from Duke explaining that my application had been misplaced and that I would soon get official notification of my acceptance. I did.

At Duke I enrolled as a premed major. But I was more of an academic dilettante. I took the courses that I believed I would find most interesting. Near the end of my third year I received a letter from the dean stating that if I wanted to graduate in four years, I would have to be an English major. There was no way for me to meet the requirements of any other major in just one more year.

At this point the George Washington University School of Medicine had already accepted me. When I was accepted, I was advised to complete the courses that were prerequisite for enrollment in the medical school, but I declined to do so.

Medical Education

I entered medical school at the age of nineteen, lacking the scientific background I would have acquired in the premedical curriculum and surrounded by biology and chemistry majors, several of whom had advanced degrees in the sciences.

During the orientation week we were informed that we could expect our grade point averages to decrease about one point from what they had been in college. My college average was 3.01. If I wanted to maintain a C average in medical school, my margin of error was 0.01 point. That concerned me.

I found a roommate. He was a second-year medical student who had been elected to Phi Beta Kappa as a junior at a very good university. He was constantly very fearful that he would flunk out of medical school. He studied medicine virtually every hour he was not in class – during meals, on weekends, and late into every night. I figured that if he was fearful, given my record, I should be petrified. I studied almost as long and as hard as he did. At the end of the first year, my class standing was number one.

During the course of the first year I was delighted to find that fear was not my only motivation. I found the course work fascinating, and I was very eager to gain

a fundamental understanding of the various subjects. During the next three years, with my confidence bolstered by the success of my first year and with my continuing enthusiasm for the course work, I settled into a more reasonable schedule for studying. My class standing did not suffer; I continued to have the top average in the class throughout my time in medical school.

When I entered medical school I planned to return to Florida to become a general practitioner. I had even sketched the plans for a home I intended to build in Ormond Beach. My office was to be located in my home, just as my father's had been in Wantagh. In my second year in medical school I encountered Dr. Leland W. Parr, chair of the Department of Microbiology. He engaged me in several conversations in which he attempted to persuade me to pursue a career in academic medicine. He pointed out that by doing so I could magnify my contribution to peoples' well-being by a hundredfold each year by preparing one hundred students for the practice of medicine. I was dubious about this; his argument failed to take into account the fact that the contribution would have to be divided each year by the several hundred other members of the medical faculty. But in the course of our conversations he planted a seed of thought that germinated subsequently.

I spent the summer following my junior year as a clinical clerk at Memorial Sloan Kettering Center for Cancer and Allied Diseases. As a result of this experience I decided that I wanted to be a cancer surgeon. In those days the standard approach to the treatment of cancer was to excise it with a very large margin. The gallows humor of the time was that, after a major surgical procedure to remove a cancer, there was sometimes uncertainty as to which part of the patient should be returned to the hospital bed and which part should be sent to the pathologist.

My fourth year of medical school was largely devoted to work as an "acting intern." My service was required because one of the interns had developed an abscess on her foot and lanced it with a hatpin. Shortly thereafter she developed tetanus and was unable to complete her year as an intern. I enjoyed the work as an acting intern. However, in this role I was required to wear the starched white pants that were part of the uniform. As an intern one frequently has to awaken from sleep in the middle of the night and rapidly put on these pants. In such circumstances the buttons frequently popped off. I came to regard the wearing of these pants as a symbol of servitude. This, perhaps, influenced my decision to go into internal medicine. The period of servitude in internal medicine was only four years as compared with nine years for cancer surgery.

I applied for only five medical internships—those that I considered the four leading internships in the country and, to be safe, also George Washington. I reasoned that it was not worth the trouble of uprooting my family to travel to a distant city unless it was to enroll in a superior program. (My family at this point included my wife and a six-month-old son.) I was very fortunate to be accepted by my first choice of internships, a hospital in Boston that was then named the Peter Bent Brigham Hospital (now Brigham and Women's).

The program at the Brigham consisted of one year of internship followed by one year as a junior assistant resident. Then one was expected to enroll in a subspecialty training program during which one would be educated in the clinical aspects of the specialty as well as research in a related area. After at least two years in the fellowship, one could apply for appointment at the Brigham as a senior assistant resident.

In those days male graduates of medical schools could be certain that after completing their residencies, they would be drafted to serve in the military—usually the U.S. Army or Navy. Many of us applied for commissions in the U.S. Public Health Service (USPHS) with appointments as clinical associates at the National Institutes of Health (NIH). The USPHS was classified a "uniformed" service, and a two-year term was considered adequate to meet the obligation for "military" service in the army, navy, or Marines. An appointment to NIH as a clinical associate was the equivalent of a first-rate subspecialty fellowship with emphasis on research. Those of us who succeeded in getting these appointments were derisively called "yellow berets" (yellow being the color associated with cowardice) to distinguish us from the others who were sent to distant lands to face danger in combat zones. A famous group of military men in those days were called "Green Berets."

I was accepted as a clinical associate at what was then called the National Heart Institute, NHI (now the National Heart, Lung, and Blood Institute). I requested assignment to the laboratory of Dr. Robert W. Berliner, a distinguished nephrologist. But before I arrived, he was appointed associate director of the NHI. Because I believed he would not have much time to devote to his laboratory and the education of clinical associates, I requested and was granted two weeks to look around for a more suitable assignment. I selected the laboratory of Dr. Albert Sjoerdsma in the Experimental Therapeutics Branch.

Clinical Pharmacology

I chose the Experimental Therapeutics Branch because it had a substantial commitment to clinical research as well as laboratory bench research. Given my unsatisfactory experience with science courses in high school and college, I was not confident that I would find two years in basic science research satisfying. If I did not, I could have concentrated on patient care in the clinical research division of the Experimental Therapeutics Branch.

Dr. Sjoerdsma put me to work in the laboratory under the guidance of Walter Lovenberg, who had recently received his Ph.D. in biochemistry. Research in the laboratory concentrated on biologically active aromatic amines such as norepinephrine (noradrenaline) and serotonin and on the enzymes that carried out their synthesis and destruction. I began my work with Lovenberg by studying monoamine oxidase, an enzyme that destroyed these amines, and a decarboxylase that was involved in their synthesis. I was surprised to discover that I greatly enjoyed the work. Looking back on my earlier attitude toward science, it was not science that I disliked; it was the way it was taught. Memorizing the results of science is boring. Doing science I found exciting.

I decided I needed to know more about science to better inform the design of my experiments. I was fortunate to have access to excellent courses presented at NIH by the U.S. Department of Agriculture. These courses contributed importantly to my ability to independently carry out a research program in the field of biochemical pharmacology.

After I had been at NIH for about a year, I received a letter from Dr. Paul Beeson, the highly distinguished chair of the Department of Internal Medicine at Yale School of Medicine. He invited me to come to New Haven to discuss with him the possibility that I might be appointed one of the two chief residents in internal medicine during the following year. I declined his offer. Yale was very highly rated but in my estimation not quite high enough to be among the top four to which I had applied for medical internship.

About three days later my friend Richard Kahler burst into my office and shouted at me: "What's the matter with you? You get a letter from the world's most outstanding leader in the field of medicine suggesting that you go to New Haven to discuss being his chief resident – he even offered to pay your train fare – and you say no. Apparently, you don't even want to discuss it." He then went on to explain that Beeson urgently needed to recruit a chief resident because the man he had appointed had been drafted into military service. Further, Kahler, who had accepted the other internal medicine chief resident position, was the one who recommended me.

I then wrote again to Dr. Beeson accepting his invitation to an interview. This, I thought, was primarily to mollify my friend Kahler. But Dr. Beeson turned out to be highly persuasive. I thought about it. Yale was clearly a very fine program. It would be my final year of residency. (I received one year of credit for my service at NIH.) I would be allowed to wear my own trousers, which closed with a zipper much more securely than the starched white alternative. And as a commissioned officer in the USPHS, I would be paid a salary about 2.5 times the standard chief resident's stipend. In exchange, I would be obliged to return to NIH for at least one additional year (something I planned to do anyhow).

The year of chief residency was entirely successful. I very much enjoyed the patient care responsibility and teaching Yale medical students. About halfway through the year Dr. Beeson teamed up with Dr. Arnold Welch, chair of the Department of Pharmacology, to offer me a joint appointment as an instructor in the departments of Medicine and Pharmacology. I accepted the appointment to begin after I had completed my obligation to return to NIH for one additional year of service.

During the year at NIH I concentrated my research efforts on histamine and serotonin. Serotonin was attracting a lot of attention in that year as an agent that contributed to multiple physiological and pathological processes. Lovenberg and I collaborated in a project that resulted in the first cell-free identification of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin. It is very important to be able to study the rate-limiting step in the biosynthesis of a biologically

active substance. If one could develop an inhibitor of this enzyme, one could, by depleting tissues of the substance, conduct studies of its physiological functions and treat manifestations of diseases that are mediated by this substance.

The success of our project attracted considerable attention and praise. Other scientists had tried without success to develop cell-free preparations of tryptophan hydroxylase. Lovenberg's mentor during his Ph.D. thesis work had recently published an account of his efforts to do this and concluded his paper with an assertion that tryptophan hydroxylase probably did not exist in mammalian tissues and that mammals probably had an as yet undiscovered method for using a different enzyme to accomplish the biosynthesis of tryptophan.

Several years later my daughter Liz's class was told they should drink a glass of milk at bedtime because milk contained tryptophan, which the brain converted to serotonin, which helps you sleep. Liz proudly announced, "Yes, that's my dad's enzyme."

At Yale I became a member of the section of Clinical Pharmacology. About two years later it was divided into two sections; one was devoted to cancer and was called Cancer Chemotherapy. I was appointed director of the other, which retained the name Clinical Pharmacology. The section flourished. And I became an associate editor of the journal *Biochemical Pharmacology,* responsible for the field of neurotransmitters and related substances.

My laboratory work built on a line of research I had begun at NIH. This work entailed studies of histidine decarboxylase, the enzyme responsible for the biosynthesis of histamine from the amino acid histidine. I then studied the effects of inhibitors of histidine decarboxylase and found, among other things, that histamine was the mediator of gastric acid secretion and that depletion of histamine from the gastric tissue of the rat afforded a high degree of protection from stress-induced ulcers.

Shortly after I left the field of study of gastric acid secretion and ulcers, the drug cimetidine (Tagamet®) was introduced for the treatment of peptic ulcer; it acted by blocking the effect of histamine in the stomach. It was so successful that it became the best-selling brand name in the world. While that shows that I was on the right track, I must acknowledge that my work had almost nothing to do with the development of this drug.

Bioethics, National

In the mid-1960s I became active in the American Federation for Clinical Research (AFCR). The AFCR was, at that time, the largest organization of clinical researchers in the world. In 1971 I accepted an appointment as editor of its official journal, *Clinical Research*. At that time each issue of the journal was divided into two parts. The larger part consisted of abstracts of papers that were submitted for consideration for presentation at their meetings. The smaller, front part of each issue was largely devoted to publication of the presidential addresses of major organizations in the field of clinical research. (Currently, the organization is named the American Federation for Medical Research, and the journal, *Journal of Investigative Medicine*.)

I accepted this appointment on condition that I would be allowed to expand the front part of the journal to include peer-reviewed articles in what I then called the social, political, and economic ecology of clinical research. By 1974 the content of the journal was largely focused on the ethics of research involving human subjects. Dr. Kenneth Ryan, chair of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, commonly referred to it as the "Journal of Medical Ethics."

In the early 1970s the U.S. federal government began issuing proposed regulations for the protection of human subjects of research. These regulations, it asserted, were grounded in considerations of ethics. I thought the ethical positions the government set forth were faulty, unbalanced to sponsor the rights of the subjects over against those of the researchers, and unduly bureaucratic, and that they would, if promulgated as regulations, cripple the efforts of clinical researchers.

I used the editorial pages of *Clinical Research* as my "bully pulpit" for my critiques of these proposed regulations. I wrote the official position statement of the AFCR criticizing one set of proposed regulations. On the next set of proposed regulations, when I again wrote the position statement, it was countersigned by several other professional organizations that were devoted to research.

In July 1974 Congress passed the National Research Act, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). This showed promise of being a very important commission. It gave a group of eleven nonfederal employees the authority to identify the ethical principles that should underlie the conduct of research involving humans as subjects and to make recommendations for guidelines to assure that research would be conducted in accord with these principles. The secretary of the Department of Health, Education, and Welfare (DHEW), forerunner of the Department of Health and Human Services, was given 180 days to convert these recommendations into regulations or to explain why not. In effect, a group of nonfederal employees was given the authority to write federal regulations; this was unprecedented. The resultant regulations remain the central core of federal regulations in this field to this date.

I was offered an appointment to the staff of the National Commission. I declined because, as a federal employee, I would not be permitted to criticize the government. They came back with an offer to spend 95 percent of my time working as a "special consultant" to the commission; then, they said, if it did anything with which I disagreed, I could use the other 5 percent of my time to write a criticism. I asked the advice of Robert Berliner, who had left NIH and was now dean of Yale School of Medicine. He told me to accept the offer, as I would be more valuable to Yale in that role than if I continued my current activity. I thanked him for the vote of confidence in my teaching and accepted the appointment.

My primary responsibility as special consultant was to write what they called their "background theoretical essays." I was permitted to work at home in New Haven

and required to spend two days weekly in Bethesda meeting with the staff and an additional two days monthly attending meetings of the National Commission. I was expected to produce one background theoretical essay every two months. Each of the "bullets" in the general charter of the National Commission became the title of one of my essays. Here are some examples of these ungainly titles: "The boundaries between biomedical or behavioral research and the accepted and routine practice of medicine"; "The role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects"; "Appropriate guidelines for the selection of human subjects for participation in biomedical and behavioral research."

Each of these papers was referred to various relevant specialists, including philosophers, historians, ethicists, lawyers, social scientists, various medical specialists, nurses, biomedical researchers, and others. These reviewers, many of whom were distinguished thought leaders in their fields, provided criticism of the papers and offered consultation on how the paper could be improved. It is difficult for me to imagine a better postdoctoral fellowship in research ethics.

My writings had considerable influence on the language and concepts of the resultant regulations. I will give three examples:

(1) Before 1977 the use in the practice of medicine of therapeutic or diagnostic agents that were not suitably evaluated was referred to as "experimental" or as "research." Historically, this is related to the fact that the federal Food and Drug Administration calls drugs and devices that are not yet approved for commercial distribution "investigational." That, in turn, refers to the requirement that in order to secure FDA approval, it is necessary to conduct investigations (research) to establish the safety and efficacy of the drug or device. International standards, beginning in 1964 with the World Medical Association's *Declaration of Helsinki* (*DoH*), divided all research involving human subjects into two categories: "therapeutic research" in which the primary objective was to provide medical benefit for the patient/subject and in some cases to also develop data that would form the basis for evaluation of the safety and efficacy of an investigational drug or device, and "nontherapeutic research" in which the sole beneficiary was the cognate field of science. The *DoH* named these two categories "clinical" and "nonclinical" research, respectively.

I pointed out that research and practice, properly understood, were two entirely separate entities. Research is a class of activities designed to contribute to the development of generalizable knowledge; medical practice is a class of activities designed to contribute to the well-being of individual patients. I also identified a third class of activities, which I called "nonvalidated therapy" (subsequently named and more widely known as "innovative therapy"). Many activities such as the randomized clinical trial (RCT)—the research process most commonly used to evaluate the safety and efficacy of therapeutic or diagnostic agents—are complex in that they combine elements of research and practice (most commonly nonvalidated practice). They are properly understood as "research on practices." Before these conceptual clarifications,

RCTs were most commonly considered therapeutic research. Consequently, some dangerous nontherapeutic components of RCTs were improperly justified according to the relatively lax standards designed for therapeutic research. I referred to this unfortunate grouping of interventions and procedures as the "fallacy of the package deal."

The National Commission had these categories removed from federal regulations. Instead of categorization of entire research protocols as therapeutic or nontherapeutic, they adopted my recommendation of a process called "component analysis." This entails separate analysis of each component of the protocol to determine if the risk it presented was justified by the therapeutic or diagnostic benefit one hoped to achieve. In the language of the resulting regulations, interventions or procedures that "held out the prospect of direct benefit for the individual subject" are to be justified differently from those that did not hold out such benefit.

(2) About ten years ago, Henk ten Have, a Dutch physician/philosopher, telephoned me to inform me that he was writing a history of research ethics. He told me that I was the one who introduced the word "vulnerable" in the literature of bioethics. I told him that I doubted my priority. But I acknowledged that in my teaching I commonly pointed out that before the days of the National Commission I rarely, if ever, saw this word in the literature of bioethics and that since those days it was hard to find any paper in the field of bioethics that did not use that word. He gave me the reference to what he considered my first usage; it was one of my background theoretical essays. After reading it I returned his telephone call. I told him that I was not the first and that in my paper I credited John Rawls, who in his book *A Theory of Justice* provided me with the idea of using this word. Ten Have replied that Rawls was a political philosopher, not a bioethicist, and that his book could hardly be considered part of the literature of bioethics.

I conceded his point. And, I must admit that I feel good about having made this and several other contributions to the language of bioethics.

(3) The National Commission's most widely known publication is a small volume known as the *Belmont Report*. It contains the definitions of the fundamental ethical principles—respect for persons, beneficence, and justice—and some commentary on how they can be applied in the ethical justification and evaluation of research involving human subjects. It also contains the definitions of research, practice, and innovative therapy and some advice on how to decide if an Institutional Review Board should review any particular project. I coauthored the *Belmont Report* with the philosopher Tom L. Beauchamp. Shortly after it was published, the *Belmont Report* "went viral" (in contemporary parlance). It has had a major influence on virtually every national and international document designed to provide guidance for or regulation of research involving humans as subjects. This sudden widespread acceptance surprised me; I thought it would be necessary to undertake considerable revision to make it suitable for use outside the United States. (I will elaborate this point later in this paper.)

Bioethics at Yale

In 1978 the National Commission discontinued its operations, and I resumed my full-time work at Yale. This consisted of teaching, research, and chairing the Institutional Review Board (IRB) at Yale-New Haven Medical Center. IRB was the name given in 1974 by the federal government to committees that reviewed research involving human subjects for the purpose of protecting the subjects' rights and welfare. Since no one knew what IRB meant, we at Yale continued to use the name we gave it in 1969, the Human Investigation Committee (HIC). I chaired the HIC continuously from 1969 through my resignation in 2000 with the exception of two years (1971–73); until 1973 the term of office was two years. In 1973 I was informed by the dean that the term of office had been changed to life.

I had the great privilege and pleasure of teaching in collaboration with three of Yale's most eminent teachers: Margaret Farley, Jay Katz, and Angela Holder. Since these people are well known to most of you, I will not introduce them further. My favorite teaching activity was serving as thesis adviser to medical students. This was a labor-intensive activity, so I limited myself to one or occasionally two students in each class. In general, the students who worked with me did very well and continue to do well in their careers.

My teaching in partnership with Margaret Farley began in 1975 when she invited me to join her in teaching an elective course in medical ethics. She had been teaching this course for several years with Fritz Redlich, a psychiatrist who had been dean of the medical school. Replacement was necessary because Redlich left Yale for a position at another university. Enrollment in the class was limited to forty students, twenty each from the Divinity School and the School of Medicine. Occasionally I exceeded my limit, and on one occasion Margaret told the class that I appeared to be better at mercy than at justice. Margaret and I continued our partnership in various activities until 2007, when she became professor emerita. From 2002 through 2007 Margaret and I were founding codirectors of the Yale Interdisciplinary Center for Bioethics. In 2010 I became the chair of the executive committee of the center, a position I continue to hold.

My participation in the elective course was suspended for four years in the 1990s. During this period I worked with Jay Katz to develop a required course for first-year medical students. The course, named "Professional Responsibility," focused primarily on medical ethics. After two years, Jay withdrew from teaching this course; I recruited Angela Holder to replace him. After two additional years I resigned from the course; it continues with new faculty to this day.

My research is in the field of research ethics; this is not what most people in the medical center consider research. I wrote a book, *Ethics and Regulation of Clinical Research,* which was highly successful. About half of the book was derived from my background theoretical essays. The other half was mostly devoted to special ethical issues that arise in research involving what the federal government called persons with "limited capacity to consent"—children, prisoners, persons "institutionalized as

mentally infirm," fetuses, and other individuals now included in the category I had labeled vulnerable. There were also chapters on research involving deceptive strategies and on RCTs. There were two editions.

I also founded the first peer-reviewed journal in the field of research ethics, *IRB: A Review of Research Ethics,* and served as its editor from 1979 through 2000. It was and continues to be published by the Hastings Center and has been renamed *IRB: Ethics and Human Research*.

Bioethics, International

In 1979 I was invited to participate in a working group at the World Health Organization in Geneva, the purpose of which was to develop ethical guidelines for research in the field of vaccines. When I arrived I discovered that I had been designated leader of a section called "Law, Policy and Ethics." The chairperson of the working group requested that I develop a piece for inclusion in the final document that presented the *Belmont Report*'s ethical principles. He asked me to have this ready for presentation to the group at the opening session the next morning. I refused, giving as my explanation that they were developed by Americans and reflected an American perspective. In my opinion, they required modification before they would be suitable for international guidelines.

The next morning he presented his own draft of the Belmont principles. I suggested that his draft contained several minor inaccuracies. He asked that I revise his draft and I agreed. And that is how I got the undeserved credit (or blame) for introducing the Belmont principles into international documents.

In 1989 I received a letter from Zbigniew Bankowski, secretary-general of the Council for International Organizations of Medical Sciences (CIOMS), inviting me to participate in a CIOMS regional roundtable to be held in Manila in 1990. (CIOMS divides the world into four regions. Each regional roundtable invites participants from one-quarter of the globe. The 1990 region was Asia and Oceania.) In his letter he provided the tentative agenda, a list of twenty-one topics. He asked me to select one topic on which I would present a primary paper and another on which I would present a commentary on another's primary paper. I wrote back that I would be glad to offer presentations on any of eighteen topics and invited him to choose. He replied that he knew I had already written papers on those eighteen and he would like to hear something new from me. For my primary paper topic he chose one of the other three: "The validity of the *Declaration of Helsinki*'s informed consent procedures in technologically developing countries."

Although I knew nearly nothing about the topic, I accepted the assignment. I spent much of the next three months reading about medical practice in technologically developing countries, concentrating particularly on anthropological studies. I concluded that the consent procedures set forth in the *DoH* were a product of Western civilization and did not reflect the concerns of most residents of technologically developing countries. I had great anxiety about presenting this paper to an audience that would include many of the authors of the most recent revision of the *DoH*—the

1975 Tokyo revision. I sent a copy of the paper to a friend and colleague, the eminent sociologist Renée Fox. She said the paper was accurate in most important respects and gave some good advice for its improvement.

When I arrived in Manila, I found a message advising me that my paper, which had been scheduled for the afternoon of the third day of a five-day meeting, had been moved to the first morning. When I asked Bankowski why, he said that my paper had generated considerable interest among the CIOMS members who were to chair the sessions, and they wanted to be sure there was adequate time to discuss it.

After my presentation, the first person to rise to comment on my paper was a pediatrician from Indonesia who said, "He's right." He went on to explain why he thought so. The next one to respond, a man from Tokyo, echoed the Indonesian's remarks. The chairperson pointed out to those and others who offered similar comments that they had been present at the meeting in Tokyo when the 1975 revision of *Helsinki* was presented and adopted. Why, he asked, had they not then raised their concerns? The pediatrician replied that this was the first time that someone with a white face had indicated that he was willing to listen to them.

Much discussion ensued.

I had been involved in various meetings of CIOMS since attending a regional roundtable in Mexico in 1980. The discussion in Mexico City contributed to the development of CIOMS's first set of guidelines on the ethics of biomedical research, *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects*. I offered several comments there, but as far as I can tell, they had no influence on the writing of the final draft of the document.

The purpose of the CIOMS *Guidelines,* printed in its introduction, was to "indicate how the ethical principles embodied in the Declaration (DoH) could be effectively applied in developing countries." In the 1980s there were several developments that suggested a need for revision of the CIOMS guidelines. For example, the AIDS epidemic gave rise to extensive research in vaccine development. This and other developments engendered a greatly increased use of RCTs. And during the 1980s the *DoH* was revised twice. In 1989 CIOMS decided to undertake a revision of its guidelines. Dr. John H. Bryant, the CIOMS president, and I were appointed cochairs of the steering committee of this project.

The resulting document, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* published in 1993, is very different in style and substance from the 1982 version. It departed in several important respects from the *DoH*. But in the light of its stated purpose—to facilitate the correct application of the *DoH*—it was necessary to include several circumlocutions. Here are two examples of such statements in the text of the *Guidelines:*

(1) "The requirement of the *Declaration of Helsinki* that 'subjects [of nontherapeutic research] must be healthy volunteers or patients for whom the experimental design is not related to the patient's illness' is not to be disregarded lightly."

This *DoH* statement that the subjects of nontherapeutic research "must be healthy volunteers or patients for whom the experimental design is not related to the patient's illness" is one of the serious adverse consequences of relying on the distinction between therapeutic and nontherapeutic research as an organizing principle. It is not a rational requirement. It is impossible to conduct any research on the pathogenesis or pathophysiology of diseases without studying persons who are afflicted with the disease. The results of such studies on the basic mechanisms of diseases are essential in the subsequent design of research to develop new therapies and diagnostic agents.

In the cited passage from the CIOMS *Guidelines* is the implicit statement that, while disregarding this *DoH* requirement is not to be done lightly, it nevertheless must be done.

> (2) "[*DoH*] does not provide guidance for [RCTs]. Rather it assures the freedom of the physician 'to use a new diagnostic or therapeutic method if it offers hope of saving life….' [T]here are customary and ethically justified exceptions to… *Helsinki*. A placebo, for example…."

This was written in response to the following statement in *DoH:* "The physician can combine medical research with professional care…only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient." The research components of an RCT are not justified by their medical value to the patient. The *DoH* provided authorization for what we, in the United States, call compassionate use of an investigational new drug, not for its evaluation in an RCT.

The 1993 version of the CIOMS *Guidelines* is intended to be applicable to all biomedical research involving humans as subjects, not simply to provide advice for the effective application of the *DoH* principles in developing countries.

In 1999 CIOMS decided to once again revise its *International Ethical Guidelines*. This time I was named chair of the steering committee. There are several additional major changes in the revised version, which was published in 2002. Among them are the following three: There are no circumlocutions regarding the separation from the requirements of the *DoH;* the 2002 document simply states its guidance and, when it differs from that of *DoH*, there is no flagging of the distinction. There is, moreover, a reduction in the number of aspirational guidelines and their replacement with pragmatic standards. And there is a less paternalistic stance with regard to research to be carried out in low-resource countries (previously called technologically developing countries).

In 1997 Nancy Dickey, then president of the American Medical Association (AMA), created a task force to propose a revision of the 1996 version of the *DoH*; I was a member of this group. She presented the proposed revision to the council of the World Medical Association (WMA). The council did not accept the proposal. Rather, it decided to consult with experts nominated by its constituent national medical associations to determine whether any revision was necessary and, if so, to make recommendations for such revisions.

Delon Human, then secretary-general of the WMA, formed the International Electronic Working Group for Revision of the *DoH* and called upon the national medical associations to nominate members of the working group. I was nominated by AMA, and Dr. Human then appointed me to chair the working group.

I presented an outline of my plan for a proposed revision to a meeting of the WMA Council. The major features of the plan were to remove the problematic distinction between therapeutic and nontherapeutic research and to update the guidance on the use of placebo controls in clinical trials. The distinction between therapeutic and nontherapeutic research had been removed from U.S. regulations in 1981 and from CIOMS guidelines in 1993.

In the late 1990s there were multiple, often strident demands for revision or clarification of international guidelines regarding the ethical acceptability of placebo controls in clinical trials. These demands, which were published in leading newspapers and scientific journals, were instigated by reports of placebo-controlled trials conducted in low-resource countries of an antiretroviral drug (zidovudine) to reduce transmission of HIV (human immunodeficiency virus, the causative agent of AIDS) from pregnant women to fetuses. In these trials the administration of zidovudine was for a much shorter duration than was customary in wealthy industrialized countries; the purpose of this abbreviation was to lower the cost of this prevention so that it would be affordable in the low-resource countries.

Critics of these trials objected to administering a placebo to some research subjects when there was a therapy established that was known to be safe and effective; they further objected to giving the research subjects a much smaller amount of zidovudine than was prescribed in the standard preventive regimen.[1]

The language used by some commentators to express condemnation of these clinical trials was intemperate to say the least. Marcia Angell, the editor of the *New England Journal of Medicine,* stated that the ethics of these trials was reminiscent of the Tuskegee Syphilis Studies. Tuskegee is the most powerful metaphor for evil in the field of research involving human subjects. I, on the other hand, published an editorial in which I argued that these particular trials ought to be considered ethical and that ethical codes ought to be clarified to define the grounds for ethical justification of placebo controls.

The 1996 version of *DoH* ruled out placebo controls except in studies of a new therapeutic agent for a condition for which there was no standard therapy. In my editorial, I referred to this proscription as an adverse consequence of relying on the spurious distinction between therapeutic and nontherapeutic research as an organizing principle.

The WMA Council accepted my plan for a proposed revision but added one additional requirement: there should be "a statement in the preamble that attests to the historical and philosophical importance of the distinction between clinical [therapeutic] and nonclinical [nontherapeutic] research." There were also to be references to

previous documents of historical and philosophical importance that had been promulgated by the WMA.

The proposed revision of the *DoH* was presented to the WMA Council at its meeting in Santiago, Chile, in 1999. The discussion was entirely unsatisfactory. The principal reason for this is that the members did not have sufficient time or guidance to understand it. They first saw the proposal shortly before the meeting began, when they found a copy of it on their desks in the meeting room. Because its central organizing theme had been removed and replaced by a novel concept, component analysis, the structure of the document was completely changed. Members could not easily find topics for which they were searching. The subject matter of what had been in the fourth paragraph might now be found as parts of the seventh and eighteenth paragraphs. One member correctly observed that there was no mention of the historical and philosophical importance of the distinction between clinical and nonclinical research. The proposal only presented the guidance for the conduct of research. Our plan was to add the preamble including the references to statements of historical and philosophical significance subsequently, after acceptance of the guidance.

The chairperson recognized that this was not going to be a productive discussion. He ended it by announcing that further discussion of the need for revision would be conducted "in house." This denouement was discussed extensively in periodicals addressed to the lay public and in professional journals. Most discussions portrayed this as a rejection of the working group's proposal.

A review of subsequent developments in revision of the *DoH* indicates a different assessment—that most of the working group's recommendations were accepted and incorporated into the *DoH*. The next iteration of the *DoH,* issued in 2000, removed the distinction between therapeutic and nontherapeutic research. This had been the main problem with the document.

In the 2000 version of the *DoH,* the proscription of placebo controls is identical to that in the 1996 version. This elicited sharp criticism from professionals in conversations that were not made public. In 2001 the WMA issued what it called a "Note of Clarification" of the intended meaning. This note was not merely a clarification; it was a substantial change in the meaning. It now permitted placebo controls in two large categories of research. In subsequent revisions of the *DoH,* the guidance on placebo controls is very similar to that proposed by the working group.

Not all of the working group's recommendations have been accepted. But with each revision of the *DoH,* the revisions bring it closer and closer to the working group's proposal. The working group's proposal is very similar to the 2002 version of the CIOMS *Guidelines* in its guidance. The main difference is a matter of style. The *DoH* consists of thirty-seven brief statements of guidance called "paragraphs" by the WMA. Most of these are one to four sentences in length. CIOMS *Guidelines,* by contrast, is made up of twenty-one guidelines, each of which is followed by a commentary that

provides advice on its application in various circumstances; many commentaries are several pages long.

I prefer the style of the CIOMS document.

One More Turning Point

In 2005 I contracted peripheral neuropathy, a disease of the nerves. Consequently, I have lost most of the sensory and much of the motor nerve function in both legs below my knees. My sense of balance is seriously impaired. In most people my age, peripheral neuropathy is a complication of diabetes. But mine is a complication of an adverse drug reaction. How ironic! I began my career at Yale working in the field of pharmacology and ended it afflicted with a drug toxicity.

Peripheral neuropathy has made it hard for me to get around. Before this I did a lot of traveling professionally. About five years ago I was asked to write a summary of my experience in international work. A sentence from the first paragraph of my response: "I have participated in the teaching of bioethics, in the development of teaching and research programs and in advising on the development of policy in every continent other than Antarctica." Often, my wife, Jeralea (Jerry), would accompany me, and we would spend an additional week or so touring the country in which I was working. I enjoyed the travel very much and accumulated a large number of frequent flyer miles. But my diminished sense of balance has limited my ability to travel.

In the summer of 2007 I decided the time had come to begin phased retirement from Yale. My phased retirement was interrupted by the financial crisis of 2008 and the ensuing Great Recession; it was not completed until June 2016.

In the time freed up during my prolonged phased retirement, I have gradually increased the amount of my consulting work in the field of research ethics. My clients have included universities, pharmaceutical firms, lawyers, and some international agencies. I have been able to limit my work to projects I find interesting.

My wife, Jerry, and I are now about to begin a new venture, working as a team as mediators. We recently completed an intensive course in dispute resolution and found it very interesting and challenging. We each have extensive experience working with people who are engaged in making difficult decisions, she as a clinical social worker in private practice and I as a physician.

Notes

1 The arguments over this clinical trial are much too complex to fully elaborate in this paper. For details see R.J. Levine, "The 'best proven therapeutic method' in clinical trials in technologically developing countries," *IRB: A Review of Human Subjects Research* 20, no. 1 (1998): 5–9.