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Cancer Treatment Pioneers

The lives of two great physicians and pioneers of alternative cancer treatments were celebrated in New York City at the end of March. On March 28, the Foundation for the Advancement of Innovative Medicine (FAIM) presented its Pioneer Award posthumously to Josef Issels, MD, for a half century of work on diet and immunotherapy. The following evening, March 29, The Re- vici Foundation for Lipid Biomedical Research held a public memorial service at the Church of St. Paul and St. Andrew, New York City, to commemorate the life and work of Emanuel Revici, MD, originator of a lipid-based nontoxic cancer chemotherapy.

It was fitting that a further FAIM Pioneer Award was presented to Stanislaw Burzynski, MD, for his unrelenting efforts to make antineoplaston therapy available to cancer patients.

An obituary and appraisal of Drs. Issels and Revici replace the customary Photoessay for this issue of the journal.

An Appraisal of the Life and Work of
Dr. Josef Maria Issels
1907–1997

Dr. Josef Maria Issels

Dr. Josef Maria Issels, 90, was widely re- garded as the “Father of Integrative Medi- cine.” Nearly 50 years ago, his efforts to im-
pital. His unexpected death on February 11, 1998, was due to influenza-caused pneumonia.

Dr. Issels was born November 21, 1907, in Munchen-Gladbach, Germany. In 1932, at the age of 24, he received his medical doctorate from the University of Wurzburg in Germany. He first achieved international recognition at the age of 28 when, as a ship's physician, he defied orders from the vessel's owners and performed emergency surgery on a British woman who suddenly presented with acute abdomen pain. Under unimaginably difficult circumstances, in the poorly equipped and long-unused operating room of an ocean liner tossed on the waves of a stormy sea, the young physician operated with scalpels "as dull as a butter knife." The surgery was a success, and the press seized the story, which ran counter to the rising tide of international tension and conflict. The headlines read, "German Doctor Saves British Woman's Life!"

Dr. Issels' defiance of authority was never simple rebellion for its own sake. Despite incredible danger to himself and his family, when Nazi officials insisted that he stop treating his Jewish patients, he petitioned to resign from the Nazi Party. The petition was granted, but he was immediately drafted as an Army medic and sent to the Russian Front. He was captured and interred until the end of 1945 under cruel circumstances. Each day, as his fellow prisoners died of starvation and disease, he forced himself to stand and walk, subsisting on meager prison rations and consuming snow to augment fluid and mineral intake. This experience, more than any other, gave him a deep understanding and spiritual bond with the thousands of exhaustively pretreated cancer patients who would later seek his help. "Don't talk to me about survival," he would tell them, "I know about survival."

Dr. Issels is regarded as the Father of Integrative Medicine because as a classically trained German physician and surgeon, he boldly incorporated alternative and complementary therapies decades before their current popularity. In 1951, he opened the Ringberg-Klinik in Rottach-Egern, Germany, the first full-service hospital in Europe to offer treatment to cancer patients who had been rejected by other doctors. His comprehensive management consisted of standard care integrated with alternative, complementary, experimental, and traditional forms of treatment, including behavioral (mind/body) medicine. Combined management with surgery, radiotherapy, chemotherapy, naturopathic medicine, homeopathy, nutritional immunology, Coley's toxins, tumor vaccines, biological dentistry, and neural therapy marked his practice as thoroughly unique in the world.

In 1959, independent epidemiologist A.G. Audier concluded and published in the respected journal, Die Medizinische, the remarkable observation that Issels had cured nearly 17% of the exhaustively pretreated, refractory cancer patients admitted to his practice. Audier's exclusion criteria were extraordinarily rigorous, only allowing review of those patients with histologically verified, recurrent disease who simply could not be given any more standard treatments. Due to the relatively large sample studied, Audier's comparison with world data was statistically significant.

Ironically, in 1960, on the heels of the Audier publication, Dr. Issels was arrested on charges of fraud and manslaughter. The "cancer trial of the century" spanned 4 years and reached Germany's highest court, where, in 1964, Dr. Issels was acquitted of all charges. In the course of the trial, it came out that members of the German medical establishment had sent confederates to apply for jobs in Issels' medical practice. A worker whom Dr. Issels initially admired because he stayed until midnight every evening meticulously cataloging and reviewing charts, turned out to be a plant combing the cases for possible fodder for the impending lawsuit. Some of the top names in the German medical community were involved in the conspiracy, which ultimately backfired.

In 1965, the Demographic Institute of Al lensbach polled Germans to test recognition of people in the news. Not even the current Chancellor of the Federal Republic of Germany was known to as many common people as Dr. Issels, who had become a national hero. His insight and leadership continue to be of interest to scholars and practitioners alike. Recent publications, including Michael Lerner's Choices in Healing from MIT Press, and David Hess' NYU Press publication, Can Bacteria Cause Cancer? Alternative Medicine Meets Big Science, continue to highlight his many contributions.
In 1970, the British Broadcasting Corporation’s (BBC) scientific investigators concluded a 6-month critical review of Issels’ methods and outcomes. With unprecedented enthusiasm, the BBC reported that a new independent epidemiological chart review had replicated the earlier findings of Audier—in fact, with a larger sample size and equally rigorous exclusion criteria, the new review demonstrated a statistically significant cure rate approaching 19%, even higher than the 1959 report. The documentary was entitled “Go and Climb a Mountain,” a reference to Dr. Issels’ undisguised psychotherapeutic techniques: he would revive depleted cancer patients so thoroughly that they were able to hike up the small peak near his hospital. Once they had done so, he would suggest, “Now that you have climbed the mountain, don’t you think you can conquer the cancer?” His acceptance at all levels was such that the BBC film depicted German Army helicopters delivering terminally ill cancer patients for treatment, and related that their care would be fully covered by both government and private insurance.

The lead researcher contracted by the BBC was Professor John Anderson, M.D., Chairman of the Department of Medicine, King’s College Hospital Medical School, University of London. A champion and defender of Issels, Anderson wrote:

He has contributed to our understanding of the whole-person approach to cancer therapy and the problems involved in controlling a serious whole-body disease. His patients have come from many countries and his extensive records have enabled him to produce data about his complete and long term remissions in seriously ill cancer patients who had been rejected by other doctors.


For more than 40 years, Issels labored on behalf of his patients. To his everlasting credit, he rose from adversity to become a coveted speaker for international medical conferences, at universities including Oxford and McGill, and prestigious institutions such as Memorial Sloan Kettering Cancer Center.

In 1981, capping his meteoric rise, Issels received an invitation to join the German Federal Cancer Commission, a post he held for nearly 7 years until his retirement from the Ringberg Klinik. Professor Anderson summarized his relationship with Issels:

I have known Dr. Issels for 12 years and been involved in an assessment of him both as a person and as a clinician. His reputation is international as well as national and he is known for this clinical work and research, not only in Europe, but in North and South America. His new ideas have aroused challenge and change and there is no doubt his approaches have forced others to reconsider theirs. He has had an impact internationally in the cancer field. He has as I know treated over 10,000 patients with proven cancer. His long term remission rate is still significantly greater than that of other physicians working in this field, and better than the standard cancer registry data.

After relocating to the United States, Dr. Issels lectured and traveled extensively, maintaining a schedule that would have been difficult for a considerably younger man. He and his wife, Ilse Marie, created the Issels Foundation to advance and promote his approach to cancer management through education and medical research. His final project, embarked on with his move to Rancho Santa Fe, California in 1996, was the merger of his own integrated set of medical managements with the well-known dietotherapy developed by former University of Münich tuberculosis division chief, Dr. Max Gerson. To accomplish this, at the age of 88, Issels became a coprincipal investigator and senior medical consultant to a three-way effort involving the Issels Foundation, the Gerson Research Organization (GRO), and Centro Hospitalario Internacional Pacifico, S.A. (Mexico) (CHIPSA). Until his unexpected
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illness, Dr. Issels worked daily with the Issels/CHIPSA/GRO Collaboration, writing, publishing, and teaching. Two full days a week, he engaged GRO researchers and CHIPSA physicians in technology transfer, teaching the theory of integrated practice and the practical issues of treatment delivery.

Dr. Issels was a member of numerous professional and government medical associations, including the New York Academy of Sciences, the American Association for the Advancement of Sciences, the German Cancer Society, the Bavarian Cancer Society, the Royal Medical Society of Scotland, the Academia Teatina of Florence, Italy, and the German Federal Government’s Gesamtprogramm zur Krebsbekämpfung (Commission for the Fight Against Cancer).

Dr. Issels is survived by his widow, Ilse Marie, their sons Hellmut and Christian, two children from a former marriage, son Rolf and daughter Ruthild, and six grandchildren. Services were held at 2:00 PM Wednesday, February 18 in San Diego. It is requested that any donations be sent to the Issels Foundation, P.O. Box 676047, Rancho Santa Fe, CA, 92067, tel. 888-374-7757.

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—Gar Hildenbrand


Emanuel Revici, M.D., who died at the age of 101 on January 9, 1998, left two legacies. The first, and principal one, is research and treatment. He developed a system of individually guided lipid-based chemotherapy of negligible toxicity a generation before cytotoxic chemotherapy became a mainstay of cancer care, and he utilized this system to treat not
only cancer but acquired immunodeficiency syndrome (AIDS), narcotic addiction, radiation burns, arteriosclerosis, and arthritis, among many other diseases.

Revici's second, lesser legacy is health rights. It derives from precedent-setting opinions in several malpractice suits against him in the 1980s that are consistent with an important liberalizing trend toward assumption of risk by patients in choices of treatment.

Emanuel Revici was born in Bucharest, Romania, in 1896. He received his doctorate in medicine and surgery from the University of Bucharest in 1920 and his license to practice the next year. Subsequently, he was appointed "Preparator," then "Assistant," at the second Medical Clinic of the Faculty of Medicine, University of Bucharest.

In the mid-1920s, he began to concentrate on biochemical research, specializing in the relation between lipids and normal and abnormal cellular metabolism. From 1936 to 1941, after resettlement in France, he continued his studies at academic and hospital laboratories directed by prominent Parisian physicians. During this period, the sub-director of the Pasteur Institute deposited five papers by Revici in the National Academy of Sciences, a prestigious way of registering scientific innovations. These papers summarized observations Revici had made about the influence of lipids in pathological pain and cancer.

Revici's clandestine service with the French Resistance during World War II obliged leaders of the Underground to provide sanctuary for him outside of Europe. In 1941, he resettled in Mexico, advancing his studies in Mexico City for the duration of the war. Between 1942 and 1945, he established and directed a free clinic, staffing it with fellow physicians-in-exile and local physicians. The clinic, which contained over 100 rooms, mainly treated cancer patients.

In 1946, Dr. George Dick, dean of the medical school, Chicago University, invited Revici to continue his research in the United States. In recognition of both his assistance to the French Underground and the potential of his scientific discoveries, Sumner Welles, a high-level aide to President Franklin Roosevelt, arranged with the U.S. Consulate in Mexico to grant special visas to speed the entry of Revici and his family. (Mr. Welles, a diplomat, had served in the Roosevelt Administration as Undersecretary of State from 1937 to 1942.)

When the dean of the Chicago University medical school resigned, Revici accepted an invitation from physicians, businessmen, and civic leaders to open an experimental cancer clinic in New York City in 1947. The clinic, named the Institute of Applied Biology (IAB), became operational that same year. Revici served as scientific director, a position he held until the IAB ceased operations in 1990. He earned his medical license in New York by examination in 1947, and resided and maintained his dual career as a scientist and physician in New York City until his death.

**SCIENTIFIC FINDINGS AND MEDICAL APPLICATIONS**

Revici's medical insights derived from several different lines of intertwining investigation. Each one is simple enough by itself, but when woven together they form a complex body of knowledge that cannot be assimilated through a superficial examination of his writings.

During the early years of his clinical research, Revici noted that cancer patients presenting with pain showed a cycling in their levels of discomfort. Some patients felt more pain in the morning, others suffered more at night. Some patients had their pain relieved by eating, others found their pain so exacerbated by eating that eating became a fearful experience. Revici surmised that any cycling of this nature must be associated with an underlying cycling of the patients' physiology, and he set out to discover what such underlying fluctuations might be.

Utilizing the techniques available to him during the first half of this century, he studied a variety of aspects of blood and urine. These simple studies led to the finding that healthy individuals characteristically showed daily rhythmic fluctuations in fundamental physical parameters, such as urinary pH and levels of free potassium in the blood. Cancer patients, in contrast, failed to show normal patterns of fluctuation, exhibiting either patterns of acidic imbalance or alkaline imbalance (Revici, 1961a).

The next steps taken by Revici typify his ability to penetrate directly to simple experiments.
First, he found that ingestion of a small amount of sodium bicarbonate by patients in acidic imbalance would ameliorate their pain temporarily, but would worsen the pain of patients in alkaline imbalance. Experiments with dilute phosphoric acid yielded approximately converse results. Knowing that such small amounts of dilute base or acid would not change body pH, he then placed platinum electrodes into painful loci of patients with superficial tumors, as well as into nonpainful regions of the tumor mass and into normal tissue. These experiments led to a remarkable conclusion: the pH of painful local lesions was not only different from the rest of the body, but could be rapidly and specifically altered by the ingestion of small amounts of acid or base. As a result of these initial studies, Revici proposed that a critical distinction be made between pathological pain and what he termed "physiological pain," a distinction supported by many subsequent years of research (Revici, 1961a).

Wishing to relieve pain in his cancer patients, he decided to develop lipidic means of altering pH, realizing that interventions based on ions, amino acids, or proteins would prove too short-lived to provide meaningful benefit. Before Revici could carry out this work, however, he determined that it was necessary to define lipids as more than greasy, water-insoluble substances extractable in ether (a definition still found in many present-day biochemistry books). Decades earlier than anyone else in the field, he redefined these important substances at a molecular level, accurately describing the relative importance of the polar and nonpolar regions of these molecules. This definition guided Revici's utilization of lipids for therapeutic purposes by providing a precise structural guide to the analysis of the compounds he would go on to create (Revici, 1961a).

While seeking to develop better means of analyzing the effects of lipids on the organism, and being intrigued by his observations that the mineral constituents of the nuclei and cytoplasm resembled the Earth's crust rather than sea water, Revici also initiated a systematic study of the effects of different elements on bodily function (Revici, 1961a). This research led him to categorize elements as to whether they primarily were inductive of anabolic or catabolic metabolism (terms that, to some extent, became interchangeable in his thought with categorization according to whether an element contributed to an acidic or alkaline state). Remarkably, Revici found that within a vertical series of the Periodic Table of the Elements, elements acted similarly; he deduced that their valency shell in part determined their bioactivity. Based on his analysis of elements in different levels of organismal organization (cell, tissue, organ, system), and the effects of specific elements on cellular pathology, he suggested that the concentration of an element in different organizational levels was both precisely regulated and a critical determinant of normal and pathological states (Revici, 1961a).

A further component of Revici's development stemmed from his observations on the molecular structure of carcinogens and other bioactive molecules. In contrast to the prevailing wisdom (expressed most forcefully by Linus Pauling), he observed that many bioactive molecules exhibited a charge structure in which adjacent carbon atoms could be predicted to carry identical charges. As with so much of Revici's work, examination of molecular structures makes one wonder why his peers resisted this discovery: Perusal of the Merck Index reveals example after example of bioactive molecules with such an energetic configuration. The concepts Revici evolved from study of these "twin formations" (as he termed them), or energetic centers, also played a crucial role in his design of medicaments (Revici, 1961a).

Time after time, his investigation of lipid function and chemistry opened the way to findings that predate ideas now widely accepted. For instance, 20 or more years before Bengt Samuelsson described leukotrienes (1987) and received a Nobel Prize for his work, Revici essentially described them, recognizing their crucial role in inflammation (Revici, 1950; Revici, 1961a).

Typically for him, though, Revici also saw these compounds as a small part of a much larger picture. Instead of choosing the traditional scientific path of focusing the next 10 years of his research on this one topic, he went on to describe presciently the capital role of
bioactive lipids in the early stages of cellular and systemic host defense processes, deducing that intervention by lipids at this level of the body's defenses might drastically alter outcome, and even the extent of mobilization, occurring at other levels (Revici, 1987).

At this stage in his development, Revici incorporated another important foundation principle: that frequently, the damage done to any organism by disease is caused not by the pathogenic focus alone but by the body's defense mechanisms as well. Although he may not have been the first to codify this key principle, Revici again seems to have been decades ahead of others in applying this understanding of pathology in his treatment (Revici, 1961a; 1961b).

Because he believed that these defense mechanisms, activated into disequilibrium, may do more harm than the pathogenic focus itself, he therefore devoted himself to devise medications that would restore normal bodily function. Based on his earlier studies, Revici chose to utilize the properties of elements to alter different levels of function, and the ability of lipids to cause longer lasting alterations, to create a large series of therapeutic compounds in which elements were conjugated into lipids (Revici, 1961a). He thereby anticipated, again by decades, interest in lipids as carriers of pharmaceutically useful compounds (Mizushima et al., 1986). As already noted, his research on "twin formations" also heavily influenced his thought on the structure of useful therapeutic agents.

Taken altogether, the different paths of research explored during his life facilitated the development, with foresight and intention, of a great number of therapeutic compounds designed to have particular effects on the function of normal and diseased tissues. It may be said, then, in summary and without exaggeration, that Revici developed a theory of rational drug design decades before the concept entered the imagination of the larger scientific community. And this theory helped Revici discover, among other therapeutic agents (again, many years before anyone else), such compounds as organo-selenium drugs for treatment of cancer, AIDS, and other terminal or chronic degenerative diseases.

**EXPRESS ASSUMPTION OF RISK**

In the last two decades of his life, Revici struggled desperately to remain in practice. In November 1983, two negligence suits, the first major negligence actions against him in 63 years of continuous practice, commenced in the Federal Court. In January 1984, the New York State Health Department initiated a disciplinary proceeding against him, alleging gross negligence and gross incompetence (among other charges, all of which basically reduce to departures from community standards resulting in claims of injury to patients). Each proceeding could have ousted him from practice and closed the IAB.

The story of how he kept, lost, and regained his license in the New York State proceedings is eminently worth recounting, especially for the instrumental role played by his patients in saving the license in the first proceeding. However, it is too lengthy (stretching over a period of 14 years), and too complicated by different circumstances that necessitated different strategies for each proceeding, to tell here. The victories won by Revici in court comprise his "second, lesser legacy," and they can be recounted concisely.

The cases went to trial before juries, and in both cases the juries returned verdicts against him and awarded damages in monetary amounts totally beyond his ability to pay. His attorneys filed appeals with the appellate court, and the appellate opinions reversed the lower court verdicts, remanding both cases for retrial (Schneider v. Revici, 1985, 1987, and Boyle v. Revici, 1989, 1992). The second case went to retrial, and the jury verdict this time was for Revici (Boyle v. Revici, 1994).

The reason for reversal in each case was the same. The appellate justices ruled that the lower court judges had failed to instruct the juries to consider whether the patients had expressly assumed the risk of unconventional care that departed from community standards. The appellate rulings set a legal precedent, "Express Assumption of Risk" (technically speaking, an affirmative defense). Under this precedent, if a defendant physician proves to a jury that a patient expressly assumed the risk of unconventional care, this bars recovery of any damages.

To quote the appellate opinion in the first case:
Appellees contend that it is against public policy for one expressly to assume the risk of medical malpractice and thereby dissolve the physician’s duty to treat a patient according to community standards. We first note that the ‘public policy’ referred to . . . is defined solely by statute . . . and appellant points to no statute imposing limitations upon such express agreements. Moreover, we see no reason why a patient should not be allowed to make an informed decision to go outside currently approved medical methods in search of an unconventional treatment. While a patient should be encouraged to exercise care for his own safety, we believe that an informed decision to avoid surgery and conventional chemotherapy is within the patient’s ‘right to determine what shall be done with his own body’ (Schneider v. Revici, 1987).

The two sentences that end this quote firmly place a significant development in the judicial branch of government, a matter of relatively narrow interest, into a much more general trend toward liberalization of attitudes about the risks patients (and the public) may take in choices affecting health.

This trend is discernible in actions and policies of the legislative and executive branches of government (U.S. Congress, notably, The Access To Medical Treatment Act, pending before both Houses since 1994, and notably the report delivered to President George Bush by the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, 1990). It also is traceable in medicine, where mainly the patient-centered school of outcomes research supplies impetus (Wennberg, 1988, 1990; Reiser, 1993).

**SUMMARY**

During the early, European years of Revici’s career (1920 to 1941), his medical theories attracted support, notably in France, where academic physicians who witnessed the results of his clinical applications thought his protocols had the potential to revolutionize the treatment of numerous pathological conditions. After he established himself in New York City in 1947, the United States medical community, for the most part, dismissed or reacted indifferently to his findings.

Since congressional establishment of the Office of Alternative Medicine (OAM) in the National Institutes of Health in 1992, the OAM and the Food and Drug Administration (FDA) have cooperated in developing a protocol to test Revici’s therapeutic agents. Recently, the Center for Alternative Medicine at the University of Texas (Houston) agreed to assist in this endeavor.

Independent validations of his findings about lipid structure and function have accumulated over the past 20 years. The section on his scientific discoveries in this article singles Revici out as the first medical scientist to elucidate the bioactivity of leukotrienes, the first to develop a safe, effective means of lipid transport. Certainly, he pioneered in the use of selenium in a virtually nontoxic form to treat cancer (Revici, 1961a; Schrauzer, 1981). It now also appears that he predated his peers in administering 0-3 fatty acids derived from marine fish oil to shrink tumors (Revici, 1961a; Simopoulos et al., 1998).

Reflecting on Revici’s life, on the obstacles he encountered in advancing his career and striving to earn recognition as a seminal figure in 20th century medical science, certain questions arise about his temperament, about the ways he conducted research, and how he applied laboratory findings to clinical practice. In short, how much did the personal factor count in building resistance to his theories and method of treatment, precipitating the trials that buffeted him mercilessly toward the end of his days?

Revici’s approach to research was conventional: observation first, next hypothesis, then experiment. Theory seems to have appealed to him more than experimentation did. (He repeated experiments to test his hypotheses and data, but as soon as his experiments convinced him that he was correct, he wasted no time repeating them again.) Still, he clearly realized that both weighed equally in discovering and perfecting treatment (Revici, 1961a).
Temperamentally, though, Revici had little tolerance for the time generally required to bring new treatments from breakthroughs in the laboratory to approval by the FDA. He felt very strongly that gravely ill patients whose conditions were resistant to accepted modes of therapy could not wait for the approval process to run its course. Once his own careful experiments confirmed to him that a therapeutic agent he developed was safe and effective, he gave it to patients regardless of regulatory agency policy. Recovery, or relief for his patients, was his primary, overriding rule. The medical community and regulatory agencies, of course, adhere to a different, opposing rule. The stubborn insistence in guiding his clinical practice in accord with his rule was likely to engender suspicion, hostility, and eventually administrative investigation and civil prosecution.

When the Office of Professional Medical Conduct succeeded in revoking his license in 1993, on charges of probation violation amounting to inadequate record keeping, they severed the ties to treatment and patients that had challenged him intellectually and nourished him emotionally throughout his career. Too proud to admit that the revocation had dispirited and devitalized him, Revici merely subsisted during his remaining years, until his appetite for life and food waned. He died shrunken in body, painfully burdened at last by great age, a vestige of the constitutionally sturdy, supremely optimistic and confident man he had been prior to loss of his license. (New York State had restored his license in September 1997, a few months before his death.)

At the end of Shakespeare's King Lear, immediately after Lear dies, two loyal subjects speak the following lines:

Edgar. He is gone, indeed.
Kent. The wonder is he hath endur'd so long.

Now that Emanuel Revici is gone, how long will his medical legacy endure? The answer depends on how soon objective studies corroborate the bulk of his lifework.

ACKNOWLEDGMENTS

Mark Noble, PhD, Professor of Oncology, University of Utah Health Sciences Center, prepared the section on Dr. Revici's scientific findings.

This appraisal of Revici's career is dedicated to Nita Revici Taskier, and to the memory of J. Robert DeBragga, founder and first director of Project CURE.

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