

## Giants in Obstetrics and Gynecology Series: a profile of Judith Vaitukaitis, MD, who made possible the early detection of pregnancy



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**D**r Judith L. Vaitukaitis, one of the first female senior investigators at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), changed the practice of medicine and the lives of women with a seminal contribution: the first radioimmunoassay for the beta subunit of human chorionic gonadotropin (hCG).<sup>1</sup>

The assay, first described on the pages of the *Journal* in 1972, made possible the early and simple detection of pregnancy in the 20th century and beyond (Figure 1).<sup>1</sup> This assay measured the beta subunit of hCG in peripheral blood as early as 7–9 days after ovulation if conception took place in that cycle around the time of blastocyst implantation.<sup>2</sup>

Serial determination of hCG allows monitoring of patients with gestational trophoblastic disease,<sup>3–5</sup> the early diagnosis of ectopic pregnancy,<sup>6–19</sup> the identification of patients at risk for spontaneous abortion,<sup>15,20,21</sup> and tumors producing hCG (eg, choriocarcinoma, germ cell tumors, and other cancers of the lung, prostate, gastrointestinal tract, and the hematological and neuroendocrine organs, among others).<sup>22–27</sup> For a review of the methods for detection of hCG, the reader is referred to a review by Cole.<sup>28</sup>

Dr Vaitukaitis became Director of the National Center for Research Resources of the National Institutes of Health (NIH), which was the organization that established general clinical research centers, expanded the construction of research facilities in academic medical centers, and supported the expansion of training and mentoring opportunities for physician-scientists and patient-oriented research.

The assay to identify the beta subunit of hCG became the basis of all currently available pregnancy test kits that a



Judith Vaitukaitis, MD, circa 2005 (Wikipedia.com)

woman can utilize in privacy and know within minutes whether she is pregnant. For this reason, Dr Vaitukaitis is being recognized as a Giant in Obstetrics and Gynecology. Few discoveries and contributions have changed the lives of women such as this.

### Background

Born in Hartford, CT, Judith received a Bachelor of Science degree in chemistry and biology from Tufts University (Boston, MA) in 1962 and her medical degree from Boston University (Boston, MA). She completed a residency in internal medicine at Cornell Medical College (Ithaca, NY). Judith then went to the NICHD as a postdoctoral research fellow to study hCG (Figure 2).

The initial goal was to measure the concentrations of hCG as a method to diagnose cancer because some tumors secrete this hormone. However, given

that hCG is secreted for trophoblast, Judith and the team of investigators, which included Dr Glenn Braunstein (Figure 3) and Dr Griff Ross (Figure 4), realized that the assay they had developed could also be used for the early detection of pregnancy and complications of early pregnancy.

After her intramural work at the NIH, Judith returned to Boston and served as professor of medicine at Boston University School of Medicine while also directing the university's NIH-funded General Clinical Research Center (GCRC) and leading the Section on Endocrinology and Metabolism at Boston City Hospital.

Her focus at the time was on studying the mechanisms controlling hormone action at the cellular level. After 12 years at Boston University, she returned to NIH in 1986 as Director of the GCRCs. This was a network of centers in teaching hospitals that provided the infrastructure to conduct clinical research.

The National Center for Research Resources' GCRC program, which, at the time, was a nationwide network of more than 70 centers in major teaching hospitals, was instrumental in promoting clinical and translational research in the United States. This center was replaced by the National Center for Advancing Translational Sciences in 2011.

### Hormones as biomarkers of cancer: the context

Many of the pioneering studies about the role of hormones in cancer occurred in the Intramural Program of NICHD. The

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## FIGURE 1

**The 1972 Journal<sup>1</sup> publication of Judith, Dr Braunstein, and Dr Ross**

**A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone**

JUDITH L. VAITUKAITIS

GLENN D. BRAUNSTEIN

GRIFF T. ROSS

Bethesda, Maryland

*With antiserum to the  $\beta$ -subunit of human chorionic gonadotropin (HCG), we have developed a radioimmunoassay which selectively measures HCG in samples containing both human pituitary luteinizing hormone (HLH) and HCG. High HLH levels observed in samples obtained at the midcycle peak or from castrate patients do not cause significant inhibition in the specific HCG radioimmunoassay. The sensitivity of the assay is sufficient for distinguishing HCG from follicular and luteal phase HLH levels. This specific HCG radioimmunoassay is ideal for following serum HCG levels in patients undergoing chemotherapy for HCG-secreting tumors as well as for follow-up of patients after termination of molar pregnancies. In addition, the sensitivity of the assay will permit earlier diagnosis of pregnancy which, in turn, would permit earlier therapeutic intervention if desired.*

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Scientific Director of NICHD in 1965, Dr Roy Hertz, was the first to successfully treat and cure metastatic choriocarcinoma, a cancer derived from trophoblast.<sup>22</sup> Prior to this achievement, only leukemias and lymphomas had been successfully treated with chemotherapy alone, so Dr Hertz was the first to prove that solid tumors could also respond to chemotherapy.<sup>29,30</sup>

To promote research in endocrinology at NICHD, Dr Hertz recruited Dr Mortimer B. Lipsett and Dr Griff T. Ross. Dr Lipsett worked on steroid hormones, Dr Ross on gonadotropins.<sup>30</sup> They were both committed to clinical investigation and embraced the bench-to bedside culture of the NIH.<sup>3,22,23,29–34</sup> Indeed, Dr Lipsett was appointed Director of

## FIGURE 2

**Judith, circa 1971, at NIH**

Photo courtesy of [Wikipedia.com](https://en.wikipedia.org/wiki/Judith_L._Vaitukaitis).

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the Clinical Center (Building 10) in Bethesda and Griff as Associate Director.

Having expressed a desire to study reproductive endocrinology, Judith's mentors in Boston advised that if she wanted to advance the field, she should work with physician-scientists at NICHD, specifically, Dr Lipsett and Dr Ross. Dr Glenn Braunstein, a major protagonist in this story, also trained in Boston at the Peter Bent Brigham Hospital/Harvard University before joining NICHD.

Dr Braunstein and Judith both began as postdoctoral fellows and were coauthors with Dr Ross on the pioneering paper in the Journal reporting the development of the radioimmunoassay for the beta subunit of hCG.<sup>1</sup>

**Why hCG?**

The studies in hCG at NIH did not begin with a focus on pregnancy but rather on the measurement of this hormone as a reliable tumor marker for choriocarcinoma. Griff was treating male and female patients diagnosed with choriocarcinoma with methotrexate and actinomycin D. Response to treatment was being measured with a bioassay for hCG (the hypothsectomized mouse uterine weight test); however, the bioassay was insensitive and nonspecific and required the maintenance of animals under appropriate environmental and dietary conditions to have reliable results.

The team at the Reproductive Research Branch of NICHD decided to generate a radioimmunoassay against the beta subunit of hCG. Dr Ross had a well-planned experimental approach, and he divided the work between Judith and Dr Braunstein: Judith was responsible for generating the antibody and harvesting the sera, and Dr Braunstein for developing and validating the radioimmunoassay. The plan was that Judith would be first author if the antibody was generated; Dr Braunstein would be the first author for subsequent clinical studies describing the use of the radioimmunoassay in the assessment of patients.

Judith immunized rabbits by administering the subcutaneous beta subunit of hCG. Multiple subcutaneous injections led to high titers of antisera (the first rabbit to produce antibodies was called SB6 and was a baseline for future experiments). Dr John B. Robbins, also at NICHD and a subsequent recipient of a Lasker Award for his work in vaccination, helped with the planning and execution of the experiments to generate the antibody. Once the antibody was at hand, Dr Braunstein developed the radioimmunoassay, given that there was very little cross-reactivity with luteinizing hormone and other gonadotropins.

**Long hours, hard work, discoveries, and productivity**

Judith recalled working in a small laboratory in Building 10, the Clinical Center of NIH, often staying from 6:00 AM until 11:00 PM. Her nearly six-year stint of intramural research at the NIH, she said, "was probably the most fun time of my life. It was the kind of scenario that, if I were independently wealthy, I would have done it for nothing."

**FIGURE 3**  
**Dr Glenn Braunstein**



Photo courtesy of Dr Glenn Braunstein.

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The success of the Intramural Program of NICHD/NIH was the result of talented people, a stimulating environment, funding, stability, and access to newly developed technologies, such as the radioimmunoassay. Dr D. Lynn Loriaux noted, in an article celebrating 25 years of the Reproductive Endocrinology Branch of NICHD, that the Intramural Program encouraged “aspiration to greatness and that its germination was carefully nurtured, and when realized, it was never resented or envied.”<sup>35</sup>

Judith commented that this extraordinary environment allowed her to publish upwards of 25 articles during one year of her time at NICHD, in an era with no computers, when papers required a typewriter and carbon paper.

In 1972, Judith described her research and the development of the new assay in a paper titled “A radioimmunoassay which specifically measures human chorionic gonadotropin in the presence of human luteinizing hormone.”<sup>1</sup> She and her

**FIGURE 4**  
**Dr Griff Ross with Dr Judith Vaitukaitis, circa 1971**

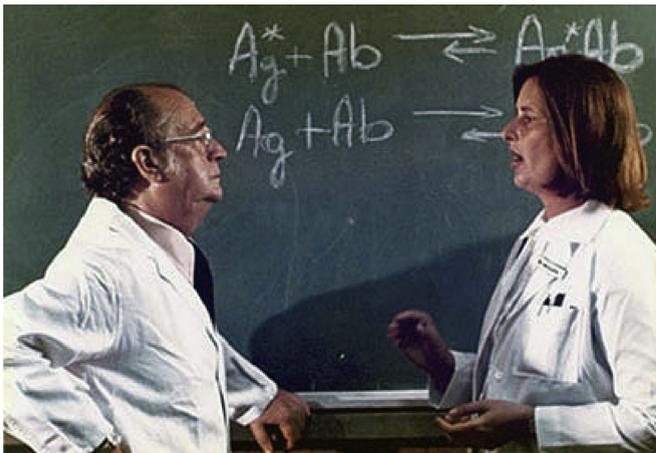


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coauthors, Dr Braunstein and Dr Ross, concluded that the specificity and sensitivity of the assay were ideal for following the course of the disease in patients undergoing chemotherapy for hCG-secreting tumors as well as for follow-up of patients after the termination of molar pregnancies. In the abstract, however, they hinted that the sensitivity and specificity of the assay “will permit earlier diagnosis of pregnancy, which, in turn, would permit earlier therapeutic intervention if desired.”<sup>1</sup>

### Publication of translational research in AJOG

Most of the papers published by Judith, Dr Braunstein, and Dr Ross were published in endocrinology journals, but they decided to submit their manuscript to the Journal because they believed that the assay would be particularly useful to gynecologists treating hydatidiform moles and patients with gestational trophoblastic disease. The Editor-in-Chief at the time, Dr John Brewer, along with Editors Dr Frederick Zuspan and Dr Edward Quilligan, welcomed translational research on the pages of AJOG.

The seminal 1972 paper is an example of the potential of translational research to transform the lives of women. Editors and readers tend to prize randomized controlled trials and observational clinical studies as the epitome of influential research, but many clinical papers do not have the transformative impact of the paper by Judith, Dr Braunstein, and Dr Ross.

The value of this important contribution and the wisdom of the editors of the Journal at the time only deepen my commitment to welcome translational research submissions to AJOG because I am convinced that progress in the diagnosis, prediction, prevention, and treatment of diseases of women will follow the application of state-of-the-art technology to address clinical problems.

### The decision not to patent the assay for the rapid diagnosis of pregnancy

Judith, Dr Braunstein, and Dr Ross understood the potential commercial value of a test for cancer and drafted the documents for a patent application. However, when they met with government attorneys to discuss protecting their intellectual property, they were told that Department of Health and Human Services policy did not allow intramural investigators to file patents on their discoveries. The argument was that the research had been funded by the public purse, and therefore, the work should go back into the public domain without any financial benefits to NIH or the scientists.

While not patenting the assay was consistent with prevailing views at the time, today NIH allows and encourages physicians and scientists funded by the extramural and intramural programs to patent their inventions. Had the assay for the beta subunit of hCG been patented by NIH, as would be allowed today, a substantial stream of income could have benefitted NICHD, NIH, and its programs to promote women’s health.

## Director of the National Center for Research Resources

As Director of the National Center for Research Resources, Judith relished her mission of making biomedical research happen all over the country. She felt great pride in supporting physician-scientists, ensuring safety in clinical research, and funding advanced research tools. In an interview with NIH, she quipped that the research tools available to her and others in the 1970s compared to those supported by the National Center for Research Resources in the late 1980s/early 1990s were like “Neanderthal [compared] to modern man.” Judith pioneered the establishment of what are now called the Clinical and Translational Research Centers.

## A Giant

In the earlier part of the 20th century, the diagnosis of pregnancy involved in vivo bioassays in which a woman’s urine was injected into animals; a frog would produce sperm upon testicular stimulation by hCG, and a rabbit would develop a corpus luteum. Pregnancy testing evolved over the decades, but it was the research of Judith, Dr Braunstein, and Dr Ross that made the detection of pregnancy simple, fast, and private. The first early pregnancy test kits became available for purchase in pharmacies in 1978.

In 2003, when NICHD celebrated its 40th anniversary, Institute Director Dr Duane Alexander called Judith’s research some of the most seminal work ever done by the Institute. Judith was inducted into the NICHD Hall of Honor for her work in developing a radioimmunoassay for the beta subunit of hCG, which became the earliest marker of pregnancy, leading to its development as the standard pregnancy test and a monitor for response to cancer treatment. The Journal is proud to honor Dr Vaitukaitis, an endocrinologist from the Intramural Program of NICHD, as a Giant in Obstetrics and Gynecology whose discoveries and research profoundly changed the lives of women and the landscape of clinical research in the United States.

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