Noyes, Hertig, and Rock revisited

It has been 70 years since the first issue of *Fertility and Sterility* was published. What has stood the test of time from that first issue? Among the eight articles was "A Twenty-Four-Hour Rat Test for the Diagnosis of Early Pregnancy and as an Aid in Predicting Abortion." Have you used that test recently? Did you even learn about it in your training? Doubtful. However, I'm sure you know about endometrial dating. And you may even use some form of endometrial testing in your clinical practice today. The reason you know about endometrial dating is because of a serendipitous event that changed the life of an Ob/Gyn resident, the lives of his professors, the lives of countless patients, and ultimately all of us who try to help people become parents.

The resident who serendipitously intersected with the endometrium was one Robert "Bob" Noyes. Born in Berkeley, California, in 1919, Noyes entered the combined BA-MD 6-year program at the University of California San Francisco at Berkeley in 1936, and in May 1942 he married Mary Nadine Holley, his childhood sweetheart, the weekend after they both graduated from Berkeley. Noyes was immediately drafted, sent to Alabama for basic training, and was stationed in Panama for the rest of the war, where he delivered the babies of expats and military dependents.

As time went on, Bob and Mary realized that they were having a problem achieving pregnancy. At the time, there were minimal tests that could be performed, but it appeared that they both had issues that together seem to preclude having a baby of their own. According to their daughter Martha H. Noyes, who was born in San Francisco on December 23, 1949, and adopted three months later, it was likely this early experience with infertility that motivated her father to not only do a residency in Obstetrics and Gynecology, but to seek a place where cutting-edge research on fertility and sterility was being performed. The obvious choice was Harvard with Dr. John Rock (a leader in obstetrics and gynecology and early pioneer of in vitro fertilization, sperm freezing, and hormonal contraception), Dr. Arthur Hertig (a pathologist who, with Rock, collected early human embryos and studied the endometrium and placenta), and Dr. Min C. Chang (who studied sperm capacitation at the Worcester Foundation for Experimental Biology—the laboratory that Margaret Sanger funded to create the contraceptive pill and where Gregory Pincus and Rock invented the first progesterone-based contraceptive). Despite a busy residency at Harvard, Noyes had time to discover that sperm capacitation could occur outside of the fallopian tube (1, 2). This was clearly fertile ground for the young Noyes to explore his personal interest in infertility, research which continued for the rest of his life. However, if this is all that had happened to Bob Noyes, we would not have had the seminal first article of Volume 1, Issue 1 of *Fertility and Sterility* (3, 4).

As told by Noyes himself on the 25th anniversary of the most cited article for all three authors—Noyes, Hertig, and Rock—a rash comment by him changed his life (5). It was the morning of October 9, 1948, when Hertig was reviewing an endometrial biopsy from an infertile woman. He asked the residents sitting at the multiheaded microscope "What's the dating?" Noyes, who was sitting a ways down the table, said in insufficiently confidential tones to one of his fellow Ob/Gyn residents, "What the hell, those endometrial dates don't mean anything anyway!" After taking some time to digest this whispered challenge, Hertig made a bet of $1.50 (equivalent to $16 today) with the residents about the dating, to be elucidated from the clinical facts: change in basal body temperature and date of next menstruation. The residents answered that it was day 2 (2 days after ovulation, or cycle day 16 in an idealized 28-day cycle, as we would say now) because they saw subnuclear vacuoles. Hertig said day 6 (6 days after ovulation, or cycle day 20) because, although there were in fact some vacuoles, there were no mitotic figures nor was there pseudostratification of the nuclei (Fig. 1). Hertig, undoubtedly owing to his many years of experience examining endometrial biopsies, was intuitively performing a multiplex analysis—that is, observing multiple characteristics at the same time—whereas the less experienced residents were focusing on only one characteristic: gland vacuoles. Hertig won the bet.

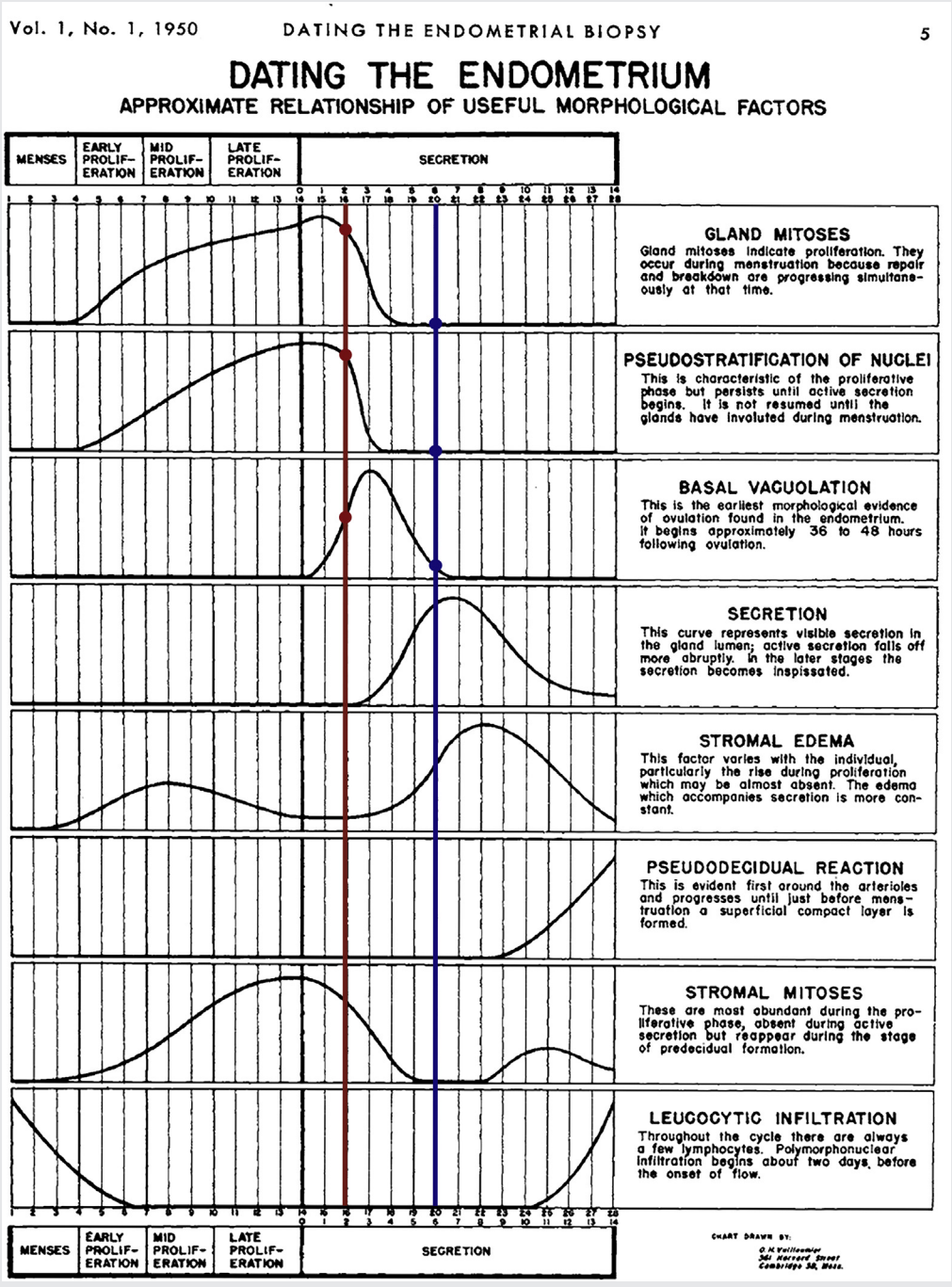
Maybe it was the potency of this teaching moment, maybe it was the fact that Noyes had a strong personal interest in infertility testing, or maybe he viewed this as another way to collect data from nature—we'll never know for sure. What we do know is that Hertig offered Noyes coauthorship of an article for what was to become the first article in the first issue of *Fertility and Sterility*. Having heard Hertig tell this Rashomon-esque story myself, I also know that Hertig did not take the solicitation for an article from Pendleton Tompkins, the inaugural editor for *Fertility and Sterility*, very seriously. However, Noyes clearly did. With his pasteurian prepared mind ("In the fields of observation chance favors only the prepared mind," Louis Pasteur, Lecture, University of Lille, 7 December 1854) and his core belief that—as recounted by his daughter—"Everything is the result of multivariate causality," Noyes went all in on this challenge.

His meticulous analysis of 300 endometrial biopsies with known next menstrual periods—40 with ovulation date determined by basal body temperature—from 856 infertility cases made available to him from Hertig's collection of more than 8,000 specimens, formed the basis of the paper. The findings were illustrated with 26 photomicrographs from midproliferative to cycle day 27. The criteria for endometrial dating used by Hertig based on the standards then used at the Free Hospital for Women, Brookline, Massachusetts, were reduced to eight major histologic criteria in their now classic illustration (Fig. 1). Invariably, if you walk into a surgical pathology microscope room you'll see this figure taped to the microscopes or the nearby walls for the pathologists to refer to as they review endometrial biopsies.

Who was changed more by Hertig's serendipitous bet? For Noyes, it set the trajectory for the rest of his life. After his residency, he returned to California to join the faculty at Stanford (then in San Francisco). Shortly afterwards he and Mary adopted Martha, around the same time his seminal

H.J.K. has nothing to disclose.

FIGURE 1



Reproduction of Figure 1 from the first article of the first issue of the first volume of *Fertility and Sterility* (4), illustrating the use of multiplex analysis of the continuously changing endometrium. An accurate assessment of any specific endometrial biopsy is only possible if multiple characteristics are considered simultaneously. For example, if one uses only the criteria of basal vacuolation it would be easy to confuse a day 16 (*red line*) and a day 20 (*blue line*) biopsy because on both days basal vacuolation is present. However, if one adds the criteria of gland mitoses and pseudostratification, then the two dates can be easily distinguished (*red and blue circles* along the red and blue lines, which are very different between these two cycle dates). Reproduced from Noyes et al. (4), with permission.

Kliman. Noyes, Hertig, and Rock revisited. Fertil Steril Rep 2020.

paper was published in *Fertility and Sterility*. He spent most of his time in the laboratory, although he remained a consultant for "difficult" infertility cases throughout his academic life. Noyes continued to make important contributions to our field, including studies on sperm capacitation, in vitro fertilization, and embryo transfer. For Arthur Hertig the first *Fertility and Sterility* article was a source of frustration. What he thought would be a minor article in a journal with a nebulous future

turned out to be his most cited publication—and he was the middle author! (Let this be a lesson to you if asked by an editor to write an article for their new journal!)

The authors modestly concluded in their seminal paper that "We feel that examination of endometrium during the secretory phase gives more information about the time of ovulation, degree of progestational change, normality or abnormality of endometrium than any other single test done in sterility studies." Certainly all of these conclusions remained true for more than 50 years until it was shown that a hematoxylin and eosin–stained endometrial biopsy by itself was not helpful in a routine infertility evaluation (6). Nevertheless, 70 years after its publication, histologic endometrial dating is still done using the Noyes, Hertig, and Rock criteria. And even more importantly, all of the current tests to evaluate endometrial receptivity are ultimately based on the concepts laid out in the Noyes, Hertig, and Rock paper (7), namely, that the endometrium undergoes an orderly progression, with proliferation followed by differentiation of both the glands and stroma, and that abnormalities of this orderly progression are markers of abnormal endometrial function.

The Noyes, Hertig, and Rock paper was foundational to our field, giving physicians a standardized way to evaluate the endometrium from infertile patients. It also set the standard by which diagnostic tools should be developed and applied to patient care. With its seemingly simple summary figure (Fig. 1), the paper established multiplex analysis and the use of biological sampling as part of the standard workup for infertility. And the appreciation of the complex developmental changes that occur in the endometrium during the menstrual cycle remain a core tenet that we deal with every time we help our infertility patients. As we look toward the next 70 years of our specialty, we hope that other collaborations between pathologists, obstetrician/gynecologists, and scientists will yield as much to help people striving to be parents of healthy babies as did the Noyes, Hertig, and Rock paper.

Harvey J. Kliman, M.D., Ph.D.*
Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut
*Reprint requests: Harvey J. Kliman, M.D., Ph.D., Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University, New Haven, CT 06520-8063.

https://doi.org/10.1016/j.xfre.2020.04.004

REFERENCES

1. Noyes RW. The fertilizing capacity of spermatozoa. West J Surg Obstet Gynecol 1953;61:342–9.
2. Yanagimachi R. Germ cell research: a personal perspective. Biol Reprod 2009; 80:204–18.
3. Noyes RW, Hertig AT, Rock J. Reprint of: Dating the endometrial biopsy. Fertil Steril 2019;112:e93–115.
4. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril 1950; 1:3–25.
5. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Am J Obstet Gynecol 1975;122:262–3.
6. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004;82:1264–72.
7. Kliman HJ, Frankfurter D. Clinical approach to recurrent implantation failure: evidence-based evaluation of the endometrium. Fertil Steril 2019;111: 618–28.