The Legacy of Reinier De Graaf

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In the second half of the 17th century, a young Dutch physician and anatomist left a lasting legacy in medicine. Reinier (also spelled Regner and Regnier) de Graaf (1641–1673), in a short but extremely productive life, made remarkable contributions to medicine. He unraveled the mysteries of the human reproductive system, and his name remains irrevocably associated with the ovarian follicle.

De Graaf was born in Schoonhaven, Holland. After studying in Utrecht, Holland, De Graaf started at the famous Leiden University. As a student, De Graaf helped Johannes van Horne in the preparation of anatomical specimens. He became known for using a syringe to inject liquids and wax into blood vessels. At Leiden, he also studied under the legendary Franciscus Sylvius.

De Graaf became a pioneer in the study of the pancreas and its secretions. In 1664, De Graaf published his work, *De Succi Pancreatici Natura et Usu Exercitatio Anatomica Medica,* which discussed his work on pancreatic juices, saliva, and bile. In this work, he described the method of collecting pancreatic secretions through a temporary pancreatic fistula by introducing a cannula into the pancreatic duct in a live dog. De Graaf also used an artificial biliary fistula to collect bile.

In 1665, De Graaf went to France and continued his anatomical research on the pancreas. In July of 1665, he received his doctorate in medicine with honors from the University of Angers, France. De Graaf then returned to the Netherlands, where it was anticipated that he would succeed Sylvius at Leiden University. However, De Graaf's entry into the strictly Protestant University of Leiden was denied because he was Catholic. De Graaf thus settled in Delft, where he acquired a large practice.

In 1668, De Graaf published a classic account of the testicle, which he described to be made of a collection of small tubules. To defend his observations and his claim that the testis essentially consisted of tubules, De Graaf sent the testis of a dormouse preserved in spirits to the Royal Society. The testis had been stripped of its capsule and teased out to show the separated tubules. A drawing of this extraordinary specimen was published in the *Philosophical Transactions of the Royal Society of London* in 1669.

Reinier De Graaf. Illustration by Venita Jay, MD, FRCPC.

De Graaf also described the efferent ducts by which the spermatozoa left the testis.

De Graaf's authoritative 1668 work on the male regenerative organs, *Tractatus de Virorum Organis Generationi Inservientibus,* appeared in a volume that also included his brief essay on the syringe and the use of ''clysters'' (enemas), which had become enormously popular in Europe at the time.

While De Graaf's work on pancreatic secretions and the testis were in themselves remarkable discoveries, he is most renowned for his contributions to female reproductive anatomy and physiology. The doctrine of Aristotle stated that the egg was formed in the uterus as a result of activation of menstrual blood by the male semen. Even Galen questioned this view. The renowned anatomists Andreas Vesalius and Gabriel Falloppio of Padua, Italy, had observed fluid-filled structures in the female ''testes,'' but did not know their significance. In the latter half of the 17th century came a resurgence of the concept of the fe-

Accepted for publication March 30, 2000.

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The author acknowledges that the general biographical overview presented does not necessarily include all of the accomplishments or achievements associated with the person discussed. Dr Jay welcomes comments from readers concerning the ''A Portrait in History'' section.

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male testes, which were thought to be similar to the ovaries of birds, where eggs are formed. In the mid-1660s, Jan Swammerdam, Johannes van Horne, and Niels Stensen independently arrived at this hypothesis, but failed to publish their work immediately.

Then appeared De Graaf's brilliant publication on the female gonad in 1672, in which he gave due credit to van Horne. When this famous work, *De Mulierum Organis Generatione Inservientibus,* was published, a bitter confrontation ensued between De Graaf and Swammerdam, who accused De Graaf of taking credit for the discoveries of van Horne and himself. De Graaf published a rebuttal in his defense, but he continued to brood over the unpleasant allegations. This continued brooding is believed to have been a factor in his premature death.

In his *De Mulierum Organis Generatione Inservientibus,* De Graaf provided the first thorough description of the female gonad and established that it produced the ovum. De Graaf used the terminology *vesicle* or *egg* (ovum) for what we now call the *follicle.* Because the fluid-filled ovarian vesicles had been observed previously by others, including Vesalius and Falloppio, De Graaf did not claim priority to their discovery. Instead, he carefully pointed out that these structures had been seen by others long before him and were described under different names. But De Graaf was the first to observe changes in the ovary before and after mating and describe the corpus luteum.

De Graaf, working without the aid of a microscope, made the error of thinking that the fluid-filled follicles were the ova themselves. This incorrect assumption that the entire follicle represented the ovum was an understandable oversight in an era when microscopy was still in its infancy. Thus, De Graaf was indeed confounded to find that the rabbit embryos within the blastocysts in the oviducts, which he had traced to the third day after copulation, were smaller than the ovarian follicles themselves.

De Graaf studied the ovaries in animals before and after copulation and noted changes in their structure. He remarked that the vesicles disappeared to make room for a ''glandulous substance'' that projected from the surface. His erroneous assumption that the presence of corpus luteum implies impregnation was undoubtedly based on his study of rabbits, a species in which ovulation normally occurs only after coital stimulation.

After making exhaustive comparative studies of ovaries of many mammals and birds, De Graaf concluded that the function of the female testicles was to generate ova, to nourish them, and bring them to maturity; thus, female testicles served an analogous function to ovaries in birds. He concluded that all animals and humans take their origins from an egg, which exists in the female testicles before coitus. De Graaf proposed that the female testicles be referred to as *ovaries.* He correctly surmised that the ovaries were indispensable for reproduction and that sterility followed castration of females. He firmly disputed the view that the embryo originated from the male alone.

De Graaf also understood the true function of the fallopian tubes and recognized pathologic conditions of the tubes. He was aware of tubal pregnancies, and he surmised that the mammalian egg traveled from the ovary to the uterus through the fallopian tube.

It was Albrecht von Haller who named the ovarian follicles after De Graaf, calling them *ova Graafiana*; later they came to be called *Graafian vesicles* and eventually, *Graafian follicles.* The mammalian ovum was actually discovered by Karl Ernst von Baer in 1827.

In April 1673, De Graaf sent an appreciative communication to the Royal Society about the ingenious Antoni van Leeuwenhoek and his wonderful world under the microscope. But De Graaf was never able to use this instrument to further his own research, for he died on August 17, 1673, presumably of a virulent illness. Yet, in the very short life that was accorded to him, De Graaf left an indelible mark in the annals of reproductive medicine.