Biosketch

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George Washington Corner The rise of reproductive endocrinology, 1926–1940. Cyclic changes in the ovaries and uterus of the sow, and their relation to the mechanism of implantation. The ovarian cycle of swine. Ovulation and menstruation in Macacus rhesus. How rhesus monkeys became laboratory animals. Physiology of the corpus luteum I. The effect of very early ablation of the corpus luteum upon embryos and uterus. Physiology of the corpus luteum II. Production of a special uterine reaction (progestational proliferation) by extracts of the corpus luteum. Physiology of the corpus luteum III. Normal growth and implantation of embryos after very early ablation of the ovaries, under the influence of extracts of the corpus luteum. Physiology of the corpus luteum VII. Maintenance of pregnancy in rabbit after very early castration by corpus luteum extracts. The sites of formation of estrogenic substances in the animal body. Crystalline progestin. Nomenclature of corpus luteum hormone. Influence of the ovarian hormones, oestrin and progestin, upon the menstrual cycle of the monkey. The relation between menstruation and ovulation in the monkey: its possible significance to man. The first maturation division of the macaque ovum. The rise of medicine at Salerno in the twelfth century.
Zuckerman, L. George Washington Corner Ramsey, EM. George Washington Corner Parkes, AS. Corner, GW. Corner, GW. Corner, GW. Hanson, E. Maienschein, J M Glitz GE Allen The University of Rochester Medical College, New York Corner, GW. Corner, GW WM. Allen Allen, WM GW. Corner Allen, WM GW. Corner Corner, GW. Allen, WM O. Wintersteiner Corner, GW. Allen, WM A Butenandt GW Corner Corner, GW. Corner, GW. Hartman, CG GW. Corner Corner, GW. Corner, GW. Corner, GW. Corner, GW. Corner, GW. Corner, GW.

The Discovery of the Mammalian Ovum: Lectures by Dr. George W. Corner1 On the generation of animals. De semine libri ii. De Natis e semine genitali Animalculis. De quadrupedum utero, conceptu, et fetu. Experiments in which after impregnation the ova of rabbits were found in the fallopian tubes. An experimental inquiry on animal impregnation. Nouvelle théorie de la génération.
Aristotle, Platt, A Galen, Kühn, CG Harvey, W. Swammerdam, J. Stensen, N. Van Horne, J. De Graaf, R. Leeuwenhoek, A. von Haller, A. Cruikshank, W. Haighton, J. Prévost, JL JB. Dumas von Baer, KE.

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Biosketch

George Washington Corner

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George W. Corner (1889–1981) was a pioneer investigator of the menstrual cycle who played a key role in the discovery of progesterone. Regarded as the greatest living anatomist of his day in America and an international leader in reproductive endocrinology for decades, he achieved even more over a long career. Besides being a beloved teacher, popular author, biographer, administrator, and scientific statesman, he was a distinguished scholar of medical history, notably studying medieval medicine in Salerno and synthesizing science and philosophy about the origins of life from the time of Aristotle until von Baer's discovery of the mammalian ovum.

Born into a nonconformist, merchant family in Baltimore in 1889, George Washington Corner absorbed a work ethic and sense of duty, but his early years gave no inkling of future distinction in medical science [1, 2] (Fig. 1). Before switching to biology, he was enrolled as a classics student at Johns Hopkins University, where a lifelong interest in medical history was nurtured by the wonderful university archives and aided by his proficiency in Latin.

After graduating in 1909, he qualified in medicine at the same university instead of taking a Ph.D., despite a growing interest and aptitude for science. He joined the anatomy department in 1913 as an assistant to Franklin Mall, director of the new Department of Embryology of the Carnegie Institution of Washington, DC (C.I.W.). Corner was either lucky or had an uncanny knack of landing among some of the best minds in his field. Mall was building a world-famous research collection of human embryos (Fig. 2), but he directed the young scientist to study the female reproductive system of sows, hoping that a better knowledge of the corpus luteum would help to estimate the postconception age of his embryos.

In those days, the existence of gonadal and pituitary hormones was speculative, the timing of ovulation was controversial, and it was even unclear whether ovulation occurred spontaneously or only after mating. The field was ripe for revolutionary advances. The period between the mid-1920s and 1940 has been called the ''heroic age of reproductive endocrinology'' because sex steroid biochemistry and physiology were making enormous strides [3], and Corner was one of the doyens of that age.

After an interlude with Herbert M. Evans of pituitary fame in Berkeley, California, he returned to join the Hopkins faculty in 1919, where he continued working on swine ovaries. He had shown that the corpus luteum is formed from both granulosa and theca interna cells and, although uterine progestational changes had been described before, he was first to realize the causal nexus between uterine, ovarian, and vaginal cycles and cyclical running behavior in rodents [4, 5]. Although an anatomist by profession, his outlook was generally that of a physiologist. Understanding that menstrual and estrous cycles had fundamental differences, he established a research colony of rhesus monkeys, the first in the United States, which became a highly important model in his hands for studying the human menstrual cycle [6, 7].

But in 1923, at the early age of 34 years, he moved to Rochester, New York, to became head of anatomy at the new

FIG. 1. George Washington Corner, M.D. (1889–1981). (By courtesy of the Carnegie Institution of Washington, DC.)

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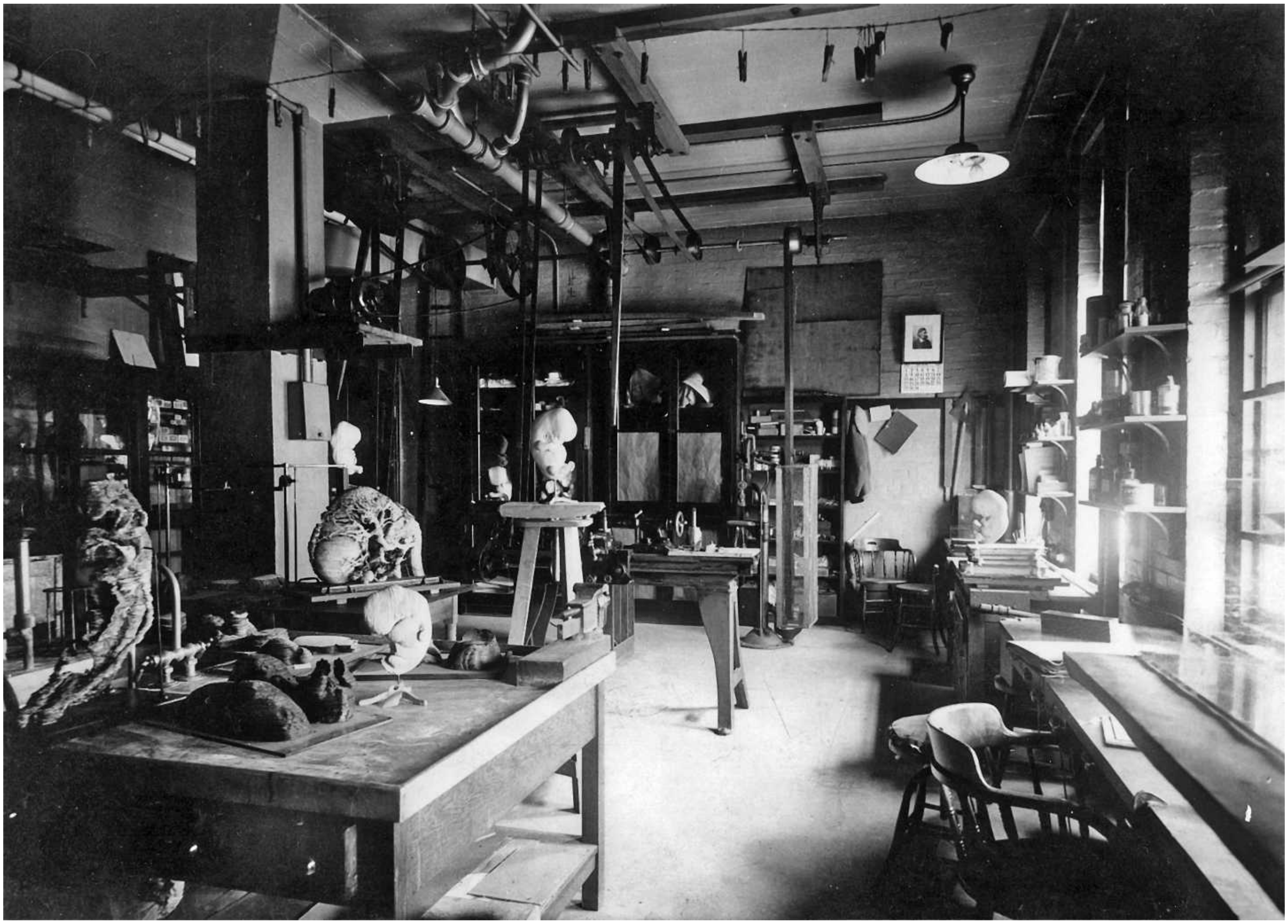

FIG. 2. Embryo modeling room in the Department of Embryology of the Carnegie Institution of Washington, DC, in Dr. Corner's time (1921). (By courtesy of the Carnegie Institution of Washington, DC.)

medical school after an intervening year spent abroad in London working with the leading physiologist, Ernest Starling, on uterine contractions, and with Charles Singer, an acclaimed medical historian. In the new institution endowed by the Rockefeller Foundation and George Eastman of Kodak, he hired new faculty and spearheaded innovations in medical education in line with the Flexner Report (1910), which had been based on the Hopkins model. As memorials to his influence, a dean's teaching fellowship and the Corner Society for medical history exist there to this day [8].

In experimental endocrine research, Corner adopted what became the classical strategy of observing the effects of organ ablation followed by replacement with purified organ extracts. He found that after blocking embryo implantation and progestational changes in rabbits by ovariectomy, they could be restored by injecting a ''mush'' of luteal tissue for 5 days [9–12]. With characteristic self-deprecating humor, he once admitted that his student, Willard Allen, was the better biochemist and that one day he had lost the entire world's supply of the corpus luteal hormone by stumbling on the steps of the animal house! [1] A few years earlier, Edgar Allen and Edward Doisy had isolated a purified preparation of estrogen from ovarian extracts [13], which was chemically characterized by Adolf Butenandt in Germany, winner of the 1939 Nobel Prize for sex steroid biochemistry. By the early 1930s, Corner and Willard Allen in Rochester in collaboration with Oskar Wintersteiner of Columbia University were making progress isolating the luteal hormone [14], but they faced stiff European competition, even for naming the new hormone. Corner had called it ''progestin'' but, after a diplomatic compromise with Butenandt and others, it was agreed by 1934 to be ''progesterone.'' International standards for the hormone soon followed [15, 16]. By then, the significance of steroid hormones in regulating the menstrual cycle was clear [17].

Corner's contributions to understanding ovarian cycles are difficult to properly appreciate so many years later. When he began, some authorities believed ovulation occurred at mid-cycle and others thought it coincided with menstruation, basing their claim on a false analogy with endometrial seepage during canine proestrus. The rhythm method of contraception was even more risky in those days! After meticulously monitoring cycles in monkeys and searching for ova in the reproductive tract, he stated in 1927 that ''ovulation is a periodic function occurring regularly at about the middle of the interval between the menstrual hemorrhages'' [18]. Vaginal bleeding coincided with luteolysis in ovulatory cycles [6], but because it also occurred in anovulatory cycles and was precipitated by ovariectomy or by withdrawing estrogen treatment it was argued that estrogen deficiency was the sole cause of menstruation. By treating monkeys with progesterone, Corner and his colleagues were able to throw light on how both types of cycle are regulated [15].

He returned to Baltimore in 1940 as the third Director of Embryology of the C.I.W., collaborating with Carl Hartman on endocrine and embryological projects while encouraging his department to embrace a more experimental approach to embryology [19]. After the war years, he was in demand again as a lecturer, administrator, and statesman for science. When the House of Representatives started to scrutinize funding of Alfred Kinsey's surveys of American human sexual behavior, Corner was one of his most articulate champions. He had already become a leading public communicator of science and had published two books explaining sex to adolescents when it was still a taboo subject. While balancing so many responsibilities, he still managed original research in medical history and wrote books and articles on a variety of topics [20–23].

During his final year in Baltimore, he became a visiting professor at Oxford and was elected a Foreign Member of the Royal Society of London, which added to a mounting number of awards and honorary degrees. But he never really retired after age 65. He was invited to New York to write the official history of the first 50 years of the Rockefeller Institute [24], and when that project ended, he moved to Philadelphia as the executive officer of the American Philosophical Society until reaching 88 years old. And as if he had a perfect sense of timing, he wrote his final autobiography shortly before his death in 1981 [25].

My early memory of George Corner is fading, but I recall a sprightly old man for his years, and still an impressive communicator. Not until much later did I fully realize his role in laying foundations for future fertility treatment, women's health, and hormonal contraception. According to someone who knew him well, he believed the fruits of scientific knowledge should be devoted to the public good, not reserved for private profit, and one of his unbending principles was never to put his name to papers to which he had not materially contributed [2]. I guess that modesty about his own achievements was at least partly owing to his perspective as a medical historian, and nowhere is this attitude expressed more finely than at the end of his 1930 lecture on the discovery of the mammalian egg. This forgotten gem is republished below with new annotations and illustrations.

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Special Paper

The Discovery of the Mammalian Ovum: Lectures by Dr. George W. Corner[1]

I am here to tell you the history of the discovery of the mammalian ovum, not as a record of great scientific events past and done forever and now revived for old time's sake, but rather as the first chapter of a narrative of research which is still in progress in countless laboratories the world over. When the mammalian ovum was first seen, in 1827, the discovery solved a great problem, but at the same time it revealed an endless series of new questions in which we are still involved. Where history stops and the present begins, no one can say. In my own work, for example, it has often been necessary to use practically the same methods and materials as Harvey and de Graaf used in their investigations of early embryology. After such experiences, when one reads the descriptions which these men wrote, he feels a sort of practical sympathy with them, like the urge we have when watching a mystery play, of which we know the solution, to shout a little timely advice to the detective on the stage. At times I have caught myself wishing I could have sent Aristotle a little pocket magnifier, or have whispered to William Harvey that he would do well to give up studying deer and use rabbits instead. On the other hand, the achievements of our predecessors seen from this viewpoint win from us not the perfunctory admiration we accord to historical characters but the hearty cheers of men who themselves know what it is to work amid difficulty and confusion.

My story begins, as everything in the history of biology begins, with Aristotle, the first biologist whose written records we possess in complete form. I wish we could think of Aristotle, not as he looks in our picture on the screen—an image in an ancient carving—but rather as a living investigator (Fig. 3). Let us imagine him out with a few of his students on a collecting trip on the sandy beach of Phaleron. The teacher and his students have spent the day collecting the living creatures of the Mediterranean shore, and at the end of the afternoon when the fisherboats come in they purchase from the sailors a few fish to be carried back to Athens and dissected on the morrow. On the way back one of the students says to the teacher, ''We hear you are writing a book on the generation of animals,'' and with this hint Aristotle begins to expound to his enthusiastic listeners what he has been able to discover and to conjecture [1].

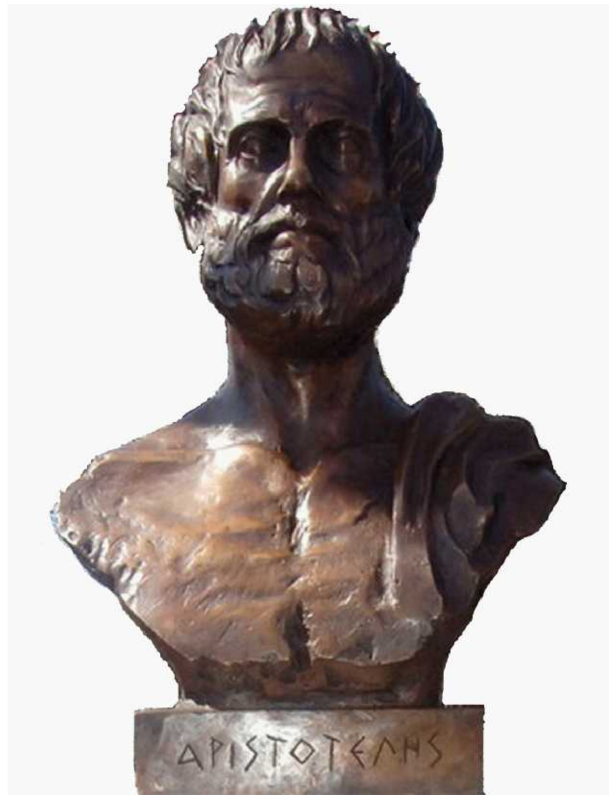

FIG. 3. Bronze sculpture of Aristotle (384–322 B.C.). Modified with permission. Photo credit: Malcolm Pinckney at NYC Parks.

Aristotle divided animals into two classes, those which develop without parents directly from unorganized matter by spontaneous generation, and those which are generated by sexual reproduction, each of the parents contributing something to the offspring. In this second group the male parent contributes seminal fluid, which is formed in the seminal ducts. According to Aristotle, the testes cannot be the site of formation of the sperm, for they are not present in the males of all species[a]; and moreover, castrated bulls sometimes are fertile for several hours after the testicles are removed. The true function of the testes is to bend or kink the seminal ducts (acting as weights) and thus to delay emission of the sperm until it has time to ripen. In female mammals it is the uterus, in birds, reptiles, and fishes the oviduct, which forms the maternal contribution to the embryo; the material which is contributed is menstrual blood. The process of reproduction consists in the admixture of the menstrual blood and the male semen, and in the development of an egg from this mixture. In the lower vertebrates the egg when formed is discharged to the outside, but in mammals it remains within the uterus during the period of gestation. The female seed contributes the substance of the embryo (as indicated by the fact that the earliest visible embryos are distinctly blood-filled), and the male contributes the formative impulse which initiates growth and determines the form.[b]

To us the idea that the embryo, even of our own species, develops from a blood-stained excretion, is unattractive and even disgusting; but we must remember that the biologists of Aristotle's day were quite accustomed to the thought that many creatures develop in decaying organic matter. From the spontaneous generation of worms in the barnyard or the dunghill to the conception of a mammalian or human embryo

[1]Lecture delivered at the Mayo Foundation, the University of Minnesota, the University of Wisconsin, Northwestern University, and the Des Moines Academy of Medicine in March 1930. *Lectures on the History of Medicine, 1926–1932*. Philadelphia & London: WB Saunders Co.; 1933. Compiled and Edited by Roger G. Gosden (E-mail: Roger.Gosden@cantab.net).

in a blood clot was not a long step. ''We are sown in corruption,'' says the Prayer Book, and in the hymnology of Isaac Watts man is but a worm. On this point, as on many others, Aristotle's biology seemed to accord with the religious outlook of those later Christians who gave him a large place in their philosophy.

As he watched the ever-marvelous differentiation of the embryo from its primitive beginnings,[c] and asked himself by what forces the successive steps of development are guided, Aristotle conceived that the process is like the movement of the parts of an automatic machine—when the first lever or wheel is started it sets another in motion, and so on. After long experimentation modern embryologists have reached about the same partial explanation with their theory of ''organizers,'' in which chemical stimuli are merely substituted for the mechanical parts of Aristotle's hypothesis.[d] Aristotle was quite certain that the early embryo is not a miniature preformed adult; he had the idea of epigenesis definitely in mind.

Herophilus, the first great anatomist of the Alexandrian school, took a step forward with his description of the mammalian reproductive organs. His writings are lost, but fortunately Galen copied paragraphs from them into some of his own books. Herophilus must be regarded as the first anatomist to describe the mammalian ovaries, but he had an incorrect idea of the ''seminal duct.'' The description of the ovary and its membranes suggests that the anatomist was dealing with the genitalia of a sow; perhaps Herophilus had by chance obtained a not very rare uterus of a sow in which the wolffian duct persists, on one side or both, as a small, ''much-folded'' canal (Gärtner's duct) running in the mesometrium, parallel with the uterus from near the ovary to the upper part of the vagina.[e]

When Galen himself took up the question in *De Semine*, he supposed that the male semen is made in the spermatic arteries and veins, and is strained out or elaborated by the testes [2]. The female semen is likewise made in the ovarian vessels, separated in the ''female testes,'' and carried by what we now know as the fallopian tubes to the uterus. On this point, Galen is in direct opposition to Aristotle. The male and female fluids, as Galen supposed, are mixed in the uterus, coagulate, become frothy, and evolve the embryo.

After Galen there was no progress for more than a thousand years. The later Greco-Roman writers accepted Galen's views on this subject, as on everything. In the Arabic period Aristotle's ideas of the formation of the embryo persisted along with Galen's and were transmitted to Europe once more in the anatomical texts prepared at Salerno.[f]

After the resumption of dissection, anatomists were too busy with the skeleton, the muscles, and the larger viscera to concern themselves with such difficult and recondite matters as the organs of reproduction. There were no new observations until after the Vesalian reform. Vesalius himself, in the *Fabrica,* came near announcing a discovery with his casual mention of vesicles and yellow cavities or bodies in the ''female testes,'' but his account of the reproductive organs of both sexes does not improve on Galen. His pupil and successor, Fallopius, clearly mentioned vesicles in the ''female testes'' and declared that he saw in them only a clear fluid. He wrote a fairly good description of what we now call after him the fallopian tubes, but he had no idea of their function in reproduction, and could offer as an explanation of their function only a guess that they might be vents serving to conduct noxious vapors from the uterus.

It is in the work of Hieronymius Fabricius, a pupil of Fallopius, that we find a truly systematic attack upon the problem of reproduction. Fabricius revived the ancient method of incubating hens' eggs through periods of known length. His pictures of embryos thus obtained are the first ever published. The text of *De formatione ovi et pulli* is not very original, for Fabricius was so close a follower of Aristotle that his ideas were often limited by his ancient master's viewpoints. Fabricius saw clearly, for example, what we now call the ovary of the hen, and indeed gave it the name *ovarium,* recognizing its importance as the site of formation of the eggs; but because Aristotle had believed the egg to be formed in the uterus, Fabricius considered the ovary simply a part of that organ.

William Harvey was a student of Fabricius at Padua in 1598–1602. It is an interesting fact that in both of his great investigations Harvey was influenced by the observations of Fabricius. *De motu cordis* had its remote beginnings in the demonstration of the valves in the veins which Harvey saw at Padua. *De motu cordis* appeared in 1628; within a few years of this time we know that Harvey was working on embryology. There is a record that he was seen incubating hens' eggs in his chambers at Oxford in 1642. From these observations he obtained a very full knowledge of the development of the chick as far as it could be seen with the unaided eye.

Harvey's position as personal physician to Charles I gave him an opportunity to transfer his studies to mammals. The king was an enthusiastic huntsman who took the field at least weekly during the season for deer hunting. Harvey was freely permitted to hold postmortem examinations on the female deer which were brought in by the hunters. He soon obtained a good idea of the bicornuate uterus, and saw the fallopian tubes, although he did not appreciate their importance. The ovaries he thought to be mere glands like the prostate gland or the mesenteric lymph nodes.

In the south of England the season of estrus or ''rutting'' of the deer begins about September 15 and continues until October 15. Only during this time do the animals mate, and therefore necropsy during the period of 6 or 8 weeks from September 15 should reveal in the uterus of the does the first embryonic rudiments. Since Harvey was a professed follower of Aristotle, we know what he expected to find in these animals; the first stage of generation should be visible in the form of blood (menstrual blood) mingled with sperm from the male; or if Galen were correct, the material in the uterus should be a mixture of male and female sperm. To Harvey's great surprise and confusion, what he actually discovered confirmed neither Aristotle's nor Galen's hypothesis, for the uterus was empty! At no time before November 12 in any of the years in which he studied the king's deer was anything found in the uterine cavity. Its lining was swollen and softened, but the lumen—was devoid of contents. This surprising finding was demonstrated to the king himself (Fig. 4).

> *This alteration in the Womb when I had often discovered to His Majesties sight (as the first assay towards impregnation) and having likewise plainly showed that all this while no portion of seed, or conception either was to be found in the Womb, and when the King himself had communicated the same as a very wonderful thing to diverse of his followers, a great debate at length arose.* [3]

This demonstration before the king was surely one of the most dramatic occasions in the history of science, but neither the Royal Presence nor the intelligence of the great physiologist availed to solve the mystery. King Charles permitted Harvey to have 12 does taken alive during the mating season and kept in a paddock at Hampton Court Palace. Some of these were killed soon after capture, and again nothing

FIG. 4. Painting by Robert Hannah depicting William Harvey giving a biology lesson to King Charles I using deer from the royal hunt. (By courtesy of the Royal College of Physicians, London.)

was found in the uterus; the others were kept for controls, and in due time gave birth to their fawns. The evidence seemed to be complete that for a fortnight or perhaps even a month after conception nothing exists in the uterus which the human eye can discover.

About the 12th to the 14th of November, however, something began to be found in the uterus: ''white filaments like spider-webs, becoming conjoined and presenting themselves as membranous or gelatinous sacs.'' A few days later a tiny embryo could be described amid the membranes.[g]

From these observations Harvey concluded that the male spermatic fluid does not reach the uterus, but merely sends up an effluvium which stimulates the uterus to secrete an egg, first as an incorporeal substance, then as a filamentous-membranous web, finally as an embryo in its chorion. The process of forming an egg in the uterus is comparable to the formation of an idea in the brain; just as an artist can paint a landscape from memory, or a bird can sing in springtime those songs it learned last summer, so the uterus can produce an egg. This hypothesis seems very mystical, even more so perhaps because it comes from the man who was able to reason precisely about the circulation.

Harvey kept the manuscript of *De generatione animalium* unpublished for several years, yielding it finally to his friend Sir George Ent with great reluctance. It was printed in 1651 [3]. By this time its author's reputation was so great that the book was received with interest and respect in all quarters. Possibly it retarded the study of early mammalian embryology by its idea of an immaterial stage in the development of the ovum; investigators would scarcely be tempted to waste time and animals to search the uterus for an invisible exhalation.

A generation elapsed, at any rate, before new discoveries were made. Then, as if to make up for lost time, things went rapidly, so rapidly indeed as to create friction. The story of the scientific events at Leyden in 1666–1672 is told us at length by one of the participants, Jan Swammerdam [4]. Swammerdam enrolled himself in the year 1666 as a pupil among the brilliant group then under the leadership of Franciscus Sylvius. He was assigned to the tutelage of Jan Van Horne, an anatomist of sound reputation, and the two men began to work together very actively in anatomical research, chiefly on the male and female reproductive tracts. Early in the course of their work they developed the idea that the human ''female testes'' are comparable to the *ovaria* of birds, serving to produce eggs. Van Horne intended to publish this idea, with the discoveries he and Swammerdam had made, but he put off the task of writing from month to month. In the next year (1667) the fellow workers received a copy of Stensen's *Myologia*, published at Florence in 1667, in which the Danish anatomist suggested the same idea about the ovary, and promised at a later time to expand it more fully [5]. Swammerdam and Stensen were acquainted, for the latter had recently been a pupil of Franciscus Sylvius, and therefore Swammerdam wrote a letter to Stensen, telling him that Van Horne had already conceived the idea that the ''female testis'' is an ovary, and asking Stensen for friendship's sake to postpone his elucidations until Van Horne could publish his views [6]. This rather presumptuous request was granted; but meanwhile a third student of the Leyden group, Regnier de Graaf, published in 1668 a book on the male genital organs, which anticipated in several points the still unwritten papers of Van Horne and Swammerdam [7].

Regnier de Graaf was 26 years old when the events of this story began. He had been a pupil of Sylvius at Leyden until 1663, then studied in France, and finally settled in the practice of medicine at Delft in 1666. As a student he had published an important work, *De succo pancreatico* (1663), which announced his discovery of the pancreatic juice.

Van Horne became excited when he found his work on the male reproductive system partially anticipated by de Graaf's book of 1668, and being unable at the time to consult with Swammerdam, he hastily published (in the same year) what we should now call a preliminary note, in the form of a four-page letter to a scientific friend, Rolfink. This letter contains, without any mention of Swammerdam, a brief statement of the hypothesis about the ''female testis.'' The book which this letter was intended to foreshadow never appeared, for Van Horne died in January, 1670.

Early in 1672 Regnier do Graaf published his third and most important book, *De mulierum organis generationi inservientibus* [7]. In this book, among other brilliant things to be discussed later, there is a chapter on the ''female testis,'' chiefly devoted to explanation and proof of the idea (for which credit is given to Van Horne) that this organ is an ovary.

Within a few weeks Swammerdam put out a pamphlet called *Miraculum naturæ* in which de Graaf's accuracy and honor are impugned, and the accusation made that credit due Swammerdam as the discoverer of the ovarian function of the ''female testis'' had been denied him. The tone of this book is remarkably bitter.

Let us consider de Graaf's book for a few minutes. It contains in the first place a full description of the human female genital tract, decidedly superior to the accounts of all previous writers, and illustrated with excellent figures (Fig. 5). Important parts of the reproductive system previously not well understood, as, for example, the fallopian tubes, are here described and illustrated with clearness and accuracy. The description of the ovary includes the first real account of the corpora lutea, and the ovarian follicles are so well described that they became known at once as ''the graafian follicles,'' although they had been seen and casually mentioned by other writers (Fallopius, Castro) as long as a century before.

It was de Graaf's opinion that the whole content of the follicle is the ovum. The considerations which led him to make this assumption were based chiefly upon the general resemblance between the protruding ripe follicles as seen in the ovaries (for example) of the pig, and developing eggs in the hen's ovary. When he heated the ovaries of swine or cows in boiling water the entire contents of the follicle coagulated and could be shelled out of the ovary as a spherical white mass, closely resembling boiled albumen of the hen's egg. De Graaf's ideas as to the physiology of ovulation were derived from observations on rabbits. He thought that the corpora lutea developed in the follicular wall before rupture of the follicle, and that rupture and the discharge of the egg are induced by the growth of the lutein tissue which he supposed to swell until it pushes the egg of out the follicle.

To all this novel and suggestive investigation of the ovary, Regnier de Graaf added a study of early mammalian embryology which made an even greater advance on the work of his predecessors. In this investigation he used the same method practiced by Harvey, namely, systematic examination of pregnant animals from the time of mating daily through the full term of gestation. That he succeeded where Harvey failed we must admit was due in large part to the fact that de Graaf made use of rabbits, in which (as we now know) the earliest embryos are spherical in shape and brilliantly distinct to the unaided eye, whereas the earliest blastocysts of the deer, like those of other hoofed animals, are elongated, collapsed strands closely resembling the threads of mucus which Harvey took them to be. While de Graaf was thus favored by chance in the selection of his animals, this was truly a case in which chance favored the prepared mind and the trained hand, for investigations of the sort which he made require even in our own time considerable technical facility and sharp observation.

De Graaf found nothing in the reproductive canals of those rabbits which he killed on the first and second day after mating, but on the third day he discovered tiny spherical bodies in the fallopian tube, and on the fourth day he found slightly larger spheres in the uterus (Fig. 6). In accordance with his previous conception that the whole contents of the follicle is the ovum, he supposed these tiny spherical bodies were simply the follicular contents, discharged and passing downward through the tubes as eggs, on their way to settle in the uterus and there hatch into embryos. Although this interpretation of the tubal ova was incorrect, de Graaf was, of course, right in assuming that the spherical structures which he found were the product of the ovary and the forerunner of the embryos. He had thus brought forward the first proof that the embryo or ovum is formed before reaching the uterus. Looking back upon the work we can see that the discovery of these tubal ova completely demolished the hypothesis which Harvey had so laboriously formed from his studies of the deer.

The excellence of de Graaf's observations is demonstrated by the fact that, in spite of attempts by able men, no one else found tubal embryos until 106 years later. If de Graaf had lived a few years longer he would have learned the use of the microscope from someone among the group of his fellow countrymen who introduced that instrument into biological research. It can hardly be doubted that given a microscope de Graaf himself would have discovered the actual mammalian ovum.

Swammerdam's charge of plagiarism against de Graaf caused him intense grief and led him to publish later in the year 1672 a pamphlet called *Partium genitalium defensio,* in which he countered the accusation very clearly by showing that in 1670 Swammerdam had actually written to him a friendly letter urging him to hasten the publication of his work on the female reproductive tract. There is no evidence, therefore, in favor of Swammerdam's claim that he deserved credit for originating

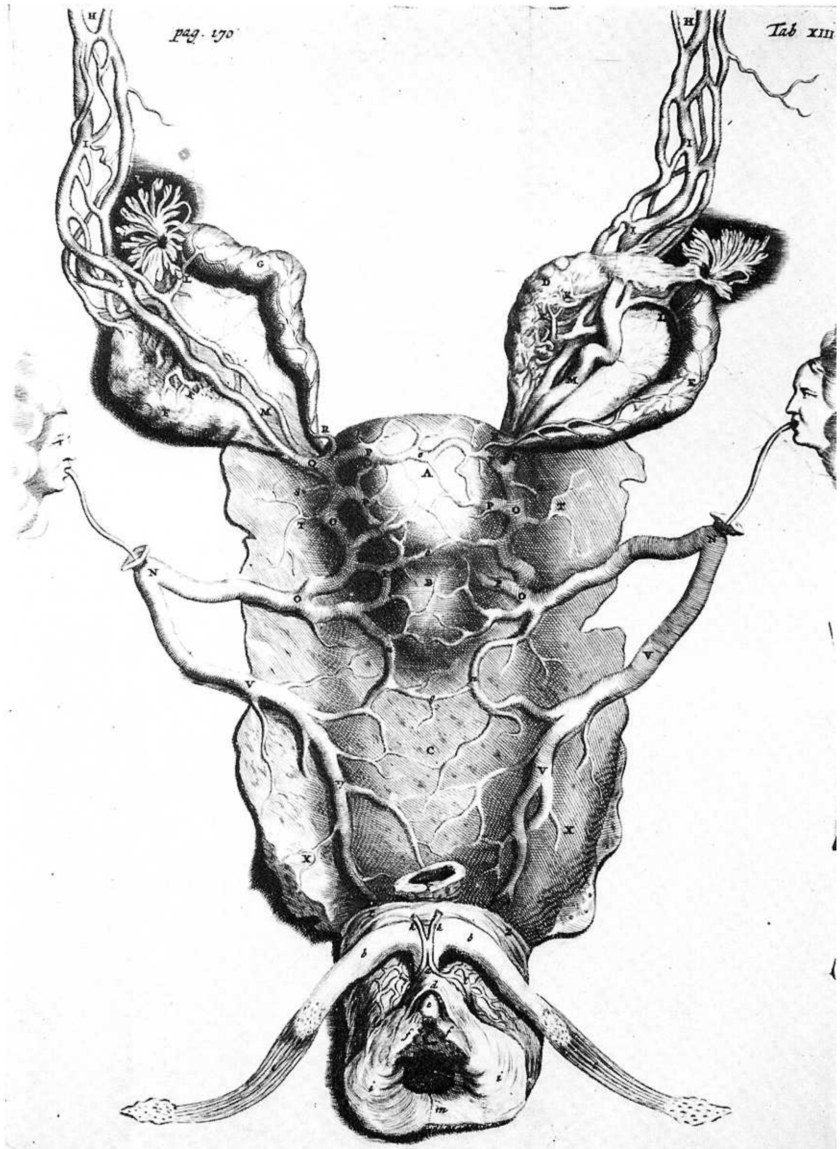

FIG. 5. Reproductive anatomy of the human female. From the New Treatise Concerning the Generative Organs of Women by Regnier de Graaf. Adapted from Jocelyn HD, Setchell BP. J Reprod Fertil 1972, Suppl 17. (By courtesy of the Society for Reproduction and Fertility.)

the idea that the mammalian ''female testis'' is an ovary, and in view of his subsequent mental disturbance we may assume that he was not fully in control of his judgment during the years 1671 and 1672. The idea in question was almost certainly first conceived by Van Horne and perhaps independently by Stensen[h]; it was de Graaf alone who expounded and amplified it, and (most important of all) he alone brought forward to support it evidence based on experimental observation. Van Horne had died in 1670; de Graaf's brilliant career was cut short by premature death in 1673 (hastened, according to his friends, by agitation over Swammerdam's charges); Swammerdam survived only to 1680. Thus within a decade all the participants in the affair were dead, a fact which may well lead us to reflect on the ultimate futility of contests for priority in scientific investigation. Time seems to have dealt fairly with the reputations of all concerned, and even Swammerdam, who played an ignoble part in this matter, has received ample honor and respect for his great work in other fields.

The story of the discovery of the spermatozoa in 1677 by van Leeuwenhoek is familiar to all. The first observation was made by the great microscopist on a drop of fluid obtained by the student Ham from a patient suffering with a urethral discharge. Observations made at once on other animals confirmed the existence of ''animalculæ'' in the seminal fluid of all of them, and the discovery was reported in a series of letters to the Royal Society of London, beginning in 1677. Van Leeuwenhoek immediately concluded that the spermatozoon is the whole material contribution to the embryo from its parents; the uterus is simply a place of incubation and nourishment for the spermatozoon while it develops into an embryo [8]. In a letter of 1683 van Leeuwenhoek denied the importance, even the existence, of eggs in mammals. The objects recently described (i.e., by de Graaf) in the ''ovaries'' seemed to him so large and so firmly seated in the organ that they could surely never drop from the ovary or pass through the tube.

Van Leeuwenhoek's view that the spermatozoon is a rudimentary embryo was carried to absurd lengths by some of his followers. Dalenpatius published in 1699 the picture of a *homunculus*—a miniature man—which he had observed in the seminal fluid, having the outward form of a spermatozoon,

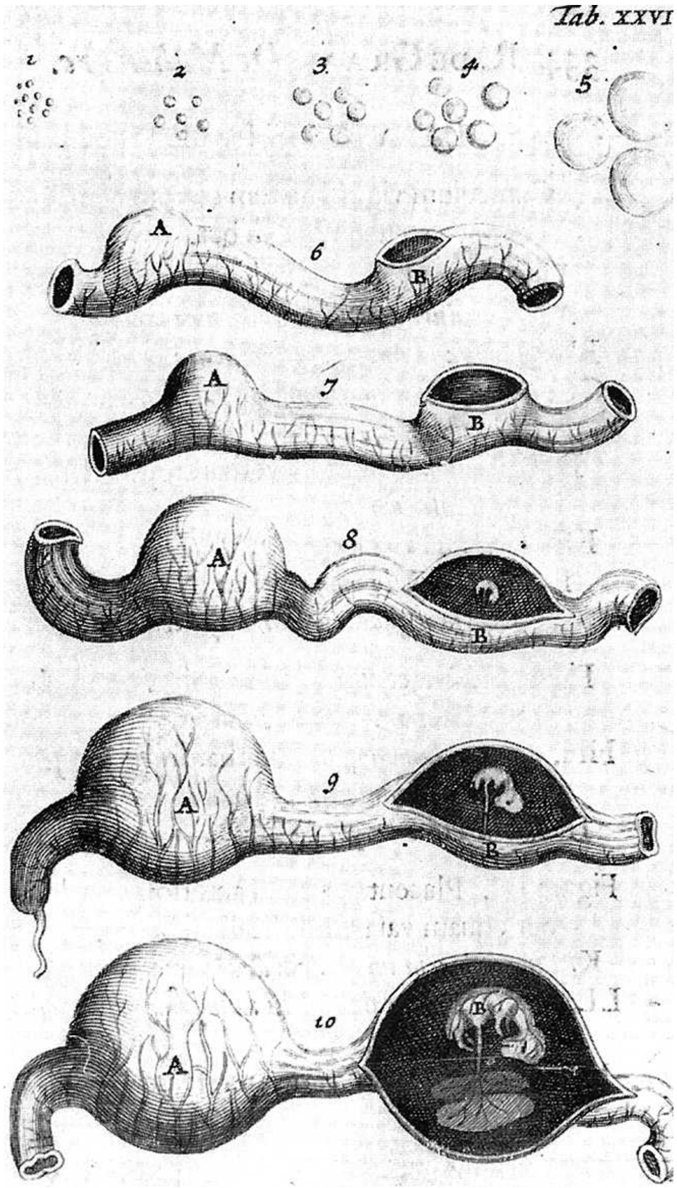

FIG. 6. Rabbit embryos from day 3–14 postcoitum. From the New Treatise Concerning the Generative Organs of Women by Regnier de Graaf. Adapted from Jocelyn HD, Setchell BP. J Reprod Fertil 1972, Suppl 17. (By courtesy of the Society for Reproduction and Fertility.)

with folded limbs and human lineaments. This observation seemed to prove that the spermatozoon contains all the structures of the man in reduced size; from this it may be deduced that the testes of the homunculus contain smaller homunculi and so ad infinitum. Father Adam, therefore, contained in his reproductive system the whole race of man, encased one generation within another like Chinese boxes, simply waiting to be removed and to expand in their turn. The philosopher Leibnitz even applied the same idea to the soul.

The observations of van Leeuwenhoek were easily confirmed by anyone who had a microscope; those of de Graaf required a high order of skill and the use of specially bred animals, and were not confirmed during van Leeuwenhoek's lifetime nor indeed for long afterward. The "spermatists" therefore held the field without difficulty against the "ovulists."[i]

In 1752 Albrecht von Haller and one of his students, Kühlemann, undertook to make embryologic observations on sheep after the manner employed by Harvey and de Graaf [9]. They carried out systematic examinations of 51 ewes killed serially at known dates after mating. The results were similar to those of Harvey (because, as we now know, the early blastocysts of the sheep resemble those of the deer); nothing which the observers could recognize as an embryo was found in the uterus until the 13th day. Haller seems to have concluded that something corporeal, of undefined character and perhaps in a fluid state, passes from ovary to uterus and there slowly coagulates into an ovum. Such a view was put forward in his great textbook, *Elementa Physiologiæ*, of 1766.

Because of Haller's position of absolute dominance in the medical world of his day, his views on this subject completed the eclipse of de Graaf's observations, and it was not until 1778 that any effort was made to reopen the question. In the spring of that year one of the assistants of Dr. William Hunter's Great Windmill Street School of Anatomy in London, William Cruikshank, proposed he undertake a repetition of de Graaf's experiments. The experiments prospered from the start, and Cruikshank had no difficulty in finding blastocysts in the fallopian tubes on the third day, and in the uterine canals on subsequent days [10]. This was a complete confirmation of de Graaf, 106 years after the publication of his work.

It is a curious circumstance that in the same volume of Cruikshank's paper, a surgeon named Haighton reported experiments on reproduction in rabbits which seemed to deny de Graaf's findings and to reaffirm Haller's position [11]. These experiments of Haighton were the very first in which surgical methods (ligation of tubes and uterus by laparotomy) were applied to study of mammalian embryology. It is a good exercise in scientific logic to check them over one by one until it appears how Haighton was misled by one unproved and actually false assumption borrowed from de Graaf, which underlies his whole argument, that is, that the presence of corpora lutea implies impregnation. Although Cruikshank had confirmed de Graaf's embryological observations, he did not advance beyond them, and after his work there was still a dark period of 3 days between ovulation and the first discovery of blastocysts (or eggs, as they were thought to be) in the fallopian tube; and the nature of the ovarian egg remained completely obscure. In 1821 the Göttingen Academy of Sciences offered a prize for the discovery of the site of formation of the mammalian ovum; in 1824 this prize was awarded to Hausmann for a paper in which he upheld the Harvey-Haller theory that the ovum is formed in the uterus.

While the savants of Göttingen were thus misspending their prize money, two young men in Geneva, Jean Louis Prévost and J. B. Dumas, were beginning an ambitious effort to solve the problem of mammalian generation.[j] With the confidence of their years, the coworkers undertook in their first memoir, somewhat pompously entitled *Nouvelle théorie de la génération,* to apply exact methods and a logical procedure (derived from the chemical laboratory) first to the seminal fluid, then to the ovum, then to the united egg and sperm [12]. In their first paper, they reinvestigated a great many questions which had been studied before their day only in the original, if sometimes crude, experiments of Abbé Spallanzani. The most important new finding, made by Prévost and Dumas in this first work, was that anatomically complete spermatozoa are found in the testes; thus the male germ cells were traced beyond all doubt to their actual site of formation. In the second memoir they studied the eggs of the frog and (again repeating Spallanzani) were able to produce artificial fertilization in vitro by mixing eggs and sperm. In experiments on dogs they found

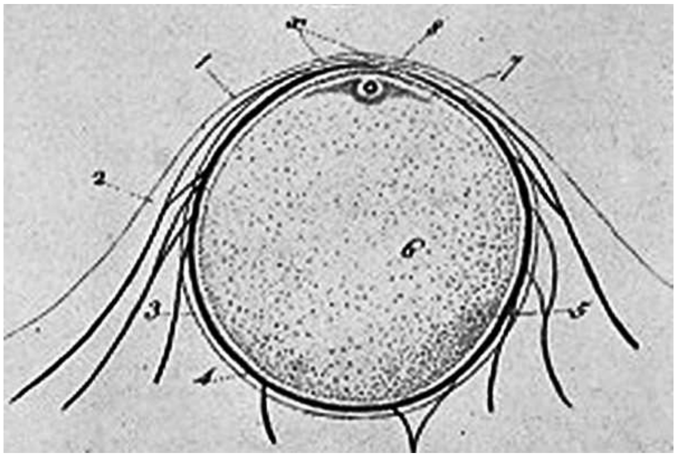

FIG. 7. Drawing of the mammalian ovum by Ernst von Baer (1827).

FIG. 8. Celebrating a national hero of science, the Estonian state printed Ernst von Baer's image on the 2-krooni banknote (obsolete since the country converted currency to the euro).

spermatozoa in the uterus after copulation—the first observation of this fact and a definite refutation of Harvey's notion that no material or substance passes from the male into the upper female reproductive tract.

At first Prévost and Dumas could not find any trace of the ova in the tubes or uterus. They were looking for large structures representing the entire contents of the follicles, but finally, on the eighth day, they found in the uterus very small vesicles like those seen in the rabbit's uterus on the third day by de Graaf and Cruikshank. Surprised by the small size of these ova (about 2 mm in diameter), the investigators formed a hypothesis that the ''large ova of the ovary'' (i.e., the graafian follicles) contain small ovules inside them. Following up this hypothesis they looked at the contents of a few follicles of the bitch, but did not find any small clear vesicles such as they expected to see. They did see on two occasions little opaque round bodies about 1 mm in diameter, but they dismissed them from consideration and thus threw away, out of their very hands, the objects for which they had sought with such great effort and trouble. In 1827, Dumas concluded:

> *Although we have easily cleared up many minor problems, the fundamental point of the whole question escapes us, and when we reach the crux of the matter, truth eludes our every effort, and all we do serves only to attest our weakness and ignorance.* [12]

Karl Ernst von Baer, who succeeded in the search which had baffled Harvey, Haller, Prévost, and Dumas, was born in 1792 on Russian territory, in what is now Estonia. He completed his medical studies at Würzburg, becoming professor extraordinarius and finally professor of zoology and anatomy at Königsberg, where he remained for many years pursuing a long succession of quiet and profitable work, rewarded early by one great discovery. Baer said in later life that his discovery of the mammalian ovum was due to luck more than to his merits as an investigator, but this was a modest untruth; the fact is that his work in early mammalian embryology was based on long studies of the chick embryo.

Baer was about 33 years of age when he began to study the early embryology of the dog. A seemingly trifling variation from the procedure of previous workers proved to be of great value; he worked backward, taking the later stages first, so that each stage examined made it easier to recognize the next earlier. The published account of the work begins with embryos of about 24 days and then proceeds to discuss a stage of about 12 days, at which time the embryos are still free spherical blastocysts in the uterus. From this stage it was but a short step to discover still earlier free blastocysts and then to find embryos in the fallopian tubes [13]. In his own words:

> *I opened one of the follicles and took up the minute object on the point of my knife, finding that I could see it very distinctly and that it was surrounded by mucus. When I placed it under the microscope I was utterly astonished, for I saw an ovule just as I had already seen them in the tubes, and so clearly that a blind man could hardly deny it. It is truly wonderful and surprising to be able to demonstrate to the eye, by so simple a procedure, a thing which has been sought so persistently, and discussed ad nauseam in every text-book of physiology, as insoluble!*

This observation was made about May 1, 1827 (Fig. 7), and was soon confirmed by the finding of closely similar bodies in the ovarian follicles of many other species, including the human. The discovery was written out for publication in the form of a letter, in Latin, addressed to the St. Petersburg Academy of Science.[k,l] But in Berlin in September, 1828, hoping to hear his work discussed, no one even spoke to him of it until the last day of the meeting, when one of the foreign visitors, Anders Retzius, asked him if it would be possible to have a demonstration of the mammalian ovum. More than willing, Baer obtained a bitch from the janitor of the laboratories where the society was meeting, and set to work to find and demonstrate the ova. Among the group of men who gathered about him as spectators were some of the rising younger biologists: Johannes Müller, Ernst Weber, and Purkinje. Displayed to minds like these, the truth about the ovum was carried to all the laboratories of Europe, and the world of science knew that the problem of 2000 years was solved (Fig. 8).

The greatest reward of the scientific investigator is that no matter what his success or failure he knows that he can serve by merely keeping on asking questions; if he cannot answer them someone else will, and in the end truth is achieved, and mankind advanced a little farther toward the light.

NOTES

a. Aristotle may have been misled from observing fish with elongated testes. The main clues available to ancient authorities that pointed to the role of the gonads in reproduction were the obvious effects of castration, which was widely practiced in domesticated animals of both sexes from early times.

b. Aristotle used a piece of furniture as a graphic analogy: the substance is contributed by the wooden boards while the carpenter determines the form and supplies the energy.

c. Aristotle made detailed observations of the development of chicks in ovo.
d. The author is probably referring to the work of Spemann and Mangold published in 1924.
e. Herophilus had a false view of what were later recognized as fallopian tubes, which he regarded as "seminal ducts." Corner was familiar with genital abnormalities in swine, which was his main research model for many years.
f. The medieval Schola Medica Salernitana was the world's first medical school, the subject of several of Corner's scholarly publications on medical history.
g. Judging from his description, Harvey was studying fallow deer and red deer, not the European roe deer, which is the only artiodactyl with delayed implantation.
h. Stensen might have achieved greater fame in science had he not become a Catholic bishop (beatified in 1988), and his name is now mainly remembered from "Stensen's (parotid) duct."
i. In the debate about the role of eggs versus spermatozoa, the mule should have served as a familiar demonstration of the inheritance of characteristics from the mother (Short RV. In: Biology and Pathology of the Oocyte. Trounson AO, Gosden RG (eds.), pp. 3–10. Cambridge: Cambridge University Press, 2003.)
j. They possessed an early achromatic microscope.
k. After the discovery of the ovum, almost 50 years passed until fertilization was first observed in mammals by van Beneden and Hertwig, finally putting paid to the old controversy between ovists and spermists. Pinto-Correia C. The Ovary of Eve. Chicago: University of Chicago Press, 1997.
l. von Baer was disappointed when his paper was not published in time for a conference in the fall of 1827 in Paris, and afterwards when it passed unnoticed in Germany.

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