In this paper, I shall not attempt to list chronologically the advances which have been made in reproductive physiology but will merely discuss a few which happen to be of greater interest to me. Regrettably, modern biological textbooks provide little information on the historical background to the advances which have been made in various phases of biology. Obviously, teachers have had to choose between presenting students with a methodical step-by-step development of a given area of biology or presenting the results of current studies, many of which in the long run will prove to be trivial. To show how far this has gone, the 1966 edition of “General Endocrinology” by C. Donnell Turner provides no information on the discovery of the growth hormone, even though the book contains an introductory chapter on the Science of Endocrinology. It is clear that today’s teachers have “opted” for the “current status” concept. Though swimming against this tide, I am an advocate of the step-by-step approach of teaching leading up to our modern knowledge in a given area of science.

The science of reproductive physiology was born in the barnyard during antiquity rather than in the laboratory and the only piece of equipment required was a sharp knife. Aristotle described the effects of castration in birds in the fourth century before Christ, but certainly the effects of castration upon the temperament of domestic animals as well as upon their sexual behavior were known by husbandmen as far back as we can trace (cited by Turner, 1966). History does not tell us whether some fortuitous incident in which an animal was accidentally deprived of his testes brought the effect of castration to the attention of husbandmen, or whether deductive reasoning relating to the marked change of temperament occurring at sexual maturity stimulated the curiosity of a livestock producer to the point where he performed one of the earliest physiological experiments. No matter, certainly this primitive investigator possessed the following: 1. He was well informed on the behavior of the male; 2. He was a careful observer; and 3. He possessed sufficient drive to capitalize on the observations involved. Is there any way to better describe a good modern investigator: an inquiring mind, a good grounding in knowledge of the discipline, acute observation, drive and good judgment. This all adds up to his being able to display creativity. These are the elements we need in writing a letter of promotion for a faculty member.

Fertilization

Advances in reproductive physiology, as in many other areas of biology, depends upon advances in other fields. This is true concerning fertilization. As is well known (Austin and Walton, 1960), in many lower forms, especially insects, the development of a new individual from a male or female germ cell without participation of a germ cell from the opposite sex is a frequent occurrence. In higher forms, however, participation of germ cells from both sexes, excepting under extraordinary circumstances, is required. Loeb (1899) produced parthenogenesis in sea urchin eggs by combined treatment of the eggs with butyric acid and hypertonic solution.

To get back to the discovery of the fertilization process in mammals, the development of the microscope was a prerequisite. Although the Janssen brothers combined lenses into “microscopes” in the 1590’s, Galileo is usually credited with this invention a little later. Anton van Leeuwenhoek (1677) discovered and described spermatozoa in 1677. The mammalian ovum was not discovered until 1827 (von Baer, 1827), possibly because de Graaf (1672) had earlier mistaken the ovarian follicle for the egg. Then, of course, there was the problem of sectioning the ovary in a manner which would allow for identification of the ovum. Although Barry (1843) had observed the penetration of the sperm within the perivitelline space of the rabbit ovum, some 30 more years elapsed before Van Beneden (1875) showed that the nuclei of male and female gametes united to complete the fertilization process. A gap of 200 years elapsed from the time of discovery of sperm until their role in fertilization was
understood. Before von Baer had actually seen the ovum, a lively debate centered around the role of male and female gametes. Van Leeuwenhoek maintained that the sperm played the dominant role and suggested that the female merely functioned to receive and nourish the sperm. William Harvey, de Graaf and Swammerdam regarded the egg as the preformed organism and that the function of sperm was to provide "animal spirit" which caused conception (Sirks and Zirkle, 1964). But van Leeuwenhoek stuck to his point. I quote, "and had your Harvey and our de Graaf seen one hundredth part of what I have seen, they would doubtless have maintained with me, that the seed of the male only forms the fruit, whereas the female's contribution is to receive the male seed and nourish it." As late as 1784, Spallanzani reported that semen without sperm had the capacity to fertilize. His technique was faulty and he stuck with this thesis even though he later found that filtered semen did not fertilize. He concluded that the unfertilized egg already contained the fetus and thus the semen adds nothing to the fetus. Thus the understanding of fertilization suffered a painful birth.

Discovery of the Estrogenic Hormones

In my discussion of the discovery of estrogens, I make no apology for leaning heavily upon the excellent account given by Corner (1965) under the title, "The Early History of the Estrogenic Hormones," presented at the occasion in which he received the Marshall Medal.

Aristotle, in his Historia Animalium (cited by Turner, 1966) reports that several centuries before Christ farmers removed the ovaries of sows to, I quote, "... quenching in them of their sexual appetites" as well as stimulating growth and fattening. This practice by swine growers extended into the 19th century. Nonetheless, the phenomenon of castrate atrophy of the uterus did not get into the medical literature until 1873 (Puech, 1873) and it was not until 1896 that Knauer reported the prevention of uterine atrophy following castration in rabbits by the transplantation of ovarian fragments. Now, you see, we have two common approaches used in determining the function of a presumed endocrine gland: 1, removal of the gland and noting anatomical, physiological or psychological changes; and, 2, transplantation of the gland into an animal in which the gland has been removed to note any affects of the transplant before nervous connections are re-established. Marshall and Jolly (1905) introduced a third approach by injecting saline ovarian extracts into at least one anestrous bitch (I have gone back to the original article and it is not clear from their account as to whether more than one animal was involved) and noting manifestations of estrus (sexual receptivity). This experiment would hardly meet present standards for a properly conducted investigation, but listen to then conclusions, I quote, "The ovary is an organ providing an internal secretion which is elaborated by the follicular epithelial cells or by the interstitial cells of the stroma. This secretion circulating in the blood induces menstruation and heat." Thus the widely accepted view reported by Aristotle and based on anecdotal evidence that the ovary controls the manifestations of estrus received experimental confirmation about 1,300 years after Aristotle's report. Marshall's forte was not as an experimentalist but rather as a philosoper and as a superb collater of information on the physiology of reproduction (Marshall, 1910). Marshall, however, was certainly one of the first to submit evidence relating to the endocrine function of the ovary by administering an extract of the gland. It is true that Brown-Sequard (1889) had previously reported revitalizing effects resulting from the injection of ovarian extracts into women. Almost certainly Brown-Sequard's revitalizing effects must have depended upon factors other than estrogenic hormones. The information provided by Marshall was too scant to make an appraisal. In any instance, the evidence of Knauer and of Marshall and Jolly suggests that the ovary secretes something which is concerned with uterine development and estrous behavior.

Incidentally, George Corner speaks of having an evening with F. H. A. Marshall in his rooms in Christ College at Cambridge University in 1923. He speaks of the "cozy fireside and the excellent tea." I enjoyed this same hospitality in Marshall's apartment in 1947, but wine was substituted for tea.

As Corner (1965) points out, four investigators discovered independently between 1910 and 1915 that an ovarian substance, soluble in ether or alcohol stimulated growth of the uterus: Henry Iscovesco, Ottfried Fellner, Edmund Hermann and Robert Frank. On what grounds, therefore, do Allen and Doisy generally receive credit for discovery of estrogens? In modern vernacular, they put it all together but, further, they had one significant additional tool at their disposal. I refer to the finding of Stockard and Papanicolaou (1917) in the guinea pig, of Long and Evans (1922) in the rat,
and of Allen (1922) in the mouse that the condition of the reproductive organs and, to some extent estrus, could be predicted by vaginal smear changes. Parenthetically, each of these authors recounted their findings using the terminology for the various phases of the estrous cycle proposed by Walter Heape (1900) and brought to more general attention by Marshall (1910).

In any instance, Allen and Doisy (1923) and Allen et al. (1924) showed that liquor folliculi from sows ovaries contained a substance which would stimulate estrous changes in the vagina and uterus of spayed rats, would induce what they incorrectly referred to as precocious puberty in infantile rats and mice and which would induce sexual receptivity. Although these “precociously” matured females showed estrous changes in the vagina and uterus and although they would mate, these authors did not recognize that any matings would be infertile because of the lack of ovulation. They also expressed the opinion that one needed to assume the existence of only a single ovarian hormone. They believed this hormone was produced cyclically by the developing follicles. One of their important contributions was the method of quantifying the amount of estrogen present in a fluid or tissue on the basis of the percent of spayed animals showing a cornified smear following the injection of a specified amount of an extract. They also went further in these initial studies in purifying the hormone than had previous investigators.

Following the studies of Allen and his coworkers and the additional discovery of a rich source of estrogenic activity in the urine of pregnant women and mares, only a relatively short period intervened before several estrogens were isolated and their structural formulae determined. A natural sequence of events was the production of many new synthetic estrogenic substances including diethylstilbestrol by Dr. E. C. Dodds in England (Dodds, Lawson and Noble, 1938).

Obviously the studies on the cyclical changes in the reproductive organs during the estrous cycle and the studies relating to the estrogenic hormones paved the way for the discovery of progestins, relaxin and the gonadotropins, but I will not go into the history of these developments. It should be pointed out here that the great increase in our knowledge of reproductive physiology made between 1915 and 1935 was in no small measure due to the superb collation of early studies by F. H. A. Marshall in his “Physiology of Reproduction” 1910.

The uses of natural and synthetic estrogens are manifold and their importance from a practical standpoint ranks, in my opinion, with the importance of insulin and thyroid hormone. There are some important differences both in the nature of the practical significances of estrogens as well as in the period of time elapsing between the discovery of the hormone and the development of its practical usages. Hypoinsulinism may, of course, be fatal unless the lack of insulin is corrected or strict dietary regimes followed. Hypothyroidism results in mental retardation in children as well as severe metabolic disturbances referred to as myxedema when thyroid deficiency occurs during adulthood. Hyperthyroidism likewise has marked characteristics. The effects of estrogen lack, or excess, are more subtle. In regard to the time interval between discovery and practical use of insulin only about a year elapsed whereas, with estrogens there was a lapse of 10 to 20 years. Some of the uses of estrogens which I consider most important are:

1. Alleviation of the distressing symptoms of the menopause. Though estrogens were used for this purpose soon after their discovery, it was not until after richer sources in the urine of pregnant women and mares were found, and the development of synthetic estrogens, that the amounts employed by physicians were large enough to be of significant help. Some of the earlier workers employed dosages of 100 rat units, whereas it later became known that about 50 times this amount was required to alleviate the symptoms. The alleviatism of the distressing mental as well as physical symptoms allowed many women to lead more useful lives. Though there are marked differences in the severity of menopausal symptoms, the instances are rare which do not benefit by estrogen supplementation.

2. Contraception. It was known about 16 years following the discovery of estrogens that high doses of estrogens would upset normal reproduction, but it was not until about 25 years after their discovery that extensive use of estrogens (with progestins) as contraceptives were made. Ball and Hartman (1939) reported that estrogens would delay ovulation in the monkey. Cole (1946) found that the ovaries of rats were stimulated with small and inhibited with large doses. In 1959, Pincus et al. reported that successful prevention of pregnancy in women using a combination of synthetic estrogens and progestins. In 1966, Pincus reviewed the evidence on their use and concluded that the adverse effects of their use do not offset their benefits.

The value of this use of estrogens cannot be overemphasized, because, in my opinion and
the opinion of many others studying the problem, overpopulation is reaching catastrophic proportions. As Hardin (1971) points out, many effects of overpopulation are blamed onto other factors: brown-outs in eastern cities are blamed onto negligent electrical companies, polluted streams are blamed onto profit-conscious manufacturers, the recent disaster in East Bengal was blamed onto floods whereas, if it were not for overcrowding, people would not have been living in that flood-prone area.

I should hasten to add that there are a number of other effective means of controlling population growth: rhythm method used in conjunction with progestins to stabilize the time of ovulation, vasectomy of the male, the intrauterine device (IUD), and abortion, all have their place; the method of choice will depend upon many factors which cannot be gone into here.

But Wylie (1971) believes we are headed for self-destruction by using our natural resources and contaminating our environment. He states, "The need to adjust our technologies and related lifeways to the ecological limits, to the capacity of the ecosphere, and the related need to husband and recycle our finite resources will merely appear as a growing menace to the very identity of the great majority."

"In that case, our immense and growing technological ability will simply terminate this civilization and after the shortest span on record. We may, indeed, have already arranged that fate and, if not, we soon shall for causes stated, and barring changes almost too immense to be credible. If so, it seems probable that not only civilization will perish but also all men, since the fatal fallacy that then will bring down the technical cultures will do so by rendering the ecosphere of the planet (not a single habitat or locale) unfit for our breed."

And again, "We shall not, in such a case be missed. For we shall no longer be here to miss ourselves and it is difficult to imagine that the surviving life forms (if any) would rue our passage."

3. The use of estrogens in stimulating growth in cattle and sheep. This use of estrogens is based upon a chance observation by Dinusson, Andrews and Beeson (1950) and represents, to my knowledge, the most important use of a hormone in livestock production. The use of estrogens was rapidly extended to steers (Andrews, Beeson and Johnson, 1951). I have two reasons for mentioning its use. First, it was a by-product of a study on the influence of estrogens on reproductive activity; secondly, it illustrates how important it is for an investigator to be a keen observer and to recognize the importance of what he has observed. Inasmuch as all earlier work with which I am familiar had indicated that estrogens inhibited growth in mammals, Dinusson et al., might have passed over this observation as a fortuitous result, but they were not prejudiced by this earlier information on rats.

Discovery of a Method of Storage of Semen by Freezing

The discovery of a successful method of freezing semen represents another chance discovery which might have been put aside as just one of those aberrant happenings had it not been for the persistent zeal of the discoverers, Christopher Polge, Audrey Smith and Alan S. Parkes (1949).

Parkes (1966) has described both the initial studies on fowl spermatozoa and later ones on bull spermatozoa in a fascinating book, "Sex, Science and Society." Following World War II, Parkes and his coworkers had embarked on a study of preservation of tissues by freezing, including the freezing of fowl spermatozoa. The initial studies on sperm had been disappointing when, surprisingly, one vial of fowl semen contained motility after freezing. By accident, this semen had been placed into albumen fixative which contains glycerol. The researchers were hard put to explain the magical result until a small amount of the media had been turned over to a chemist who discovered that it contained glycerol. Dr. Parkes surmises that labels had fallen off and had been replaced on the wrong bottles. The important thing is that they persisted until the puzzle was solved.

Following this, attempts were made to freeze bull spermatozoa but about 3 years were required to modify the method employed for fowl sperm to make it adaptable to bull sperm (Polge and Rowson, 1952). Thus, one of the most significant advances was made in the development of the use of artificial insemination in cattle. This is a long step from the initial artificial insemination of a bitch by Spallanzani and the successful adaptation of AI to cattle by Milovanov and his coworker (1932).

In accordance with my introductory remarks, I have made no attempt to consider all of the important discoveries relating to reproductive physiology. Researchers in this country have made a host of discoveries relating to artificial insemination which have been responsible for the remarkable expansion of its use. This is a fantastic story in itself which can be told by others more authoritatively. I have not
discussed other gonadal hormones such as relaxin, progesterone and testosterone. Adolph Butenandt was offered, but refused for political reasons, the Nobel Prize in chemistry for his studies on the structure and synthesis of progesterone as well as for his many other significant contributions to our knowledge of the chemistry of androgens and estrogens (Koch, 1939; Doisy, 1939; Allen, 1939).

I have not discussed the anterior pituitary hormones which are concerned in controlling reproductive processes or the more recent studies on the releasing factors of the hypothalamus which control, in part at least, the secretion of anterior pituitary hormones. The early studies of Harvey Cushing reviewed in his book, "The Pituitary Body and its Disorders," did much to stimulate interest in the field of anterior pituitary function. The classical work of Smith (1930) in removing the pituitary in the rat without injury to the brain, as well as his replacement studies cleared up many uncertainties concerning pituitary function. The intriguing story of the first synthesis of naturally occurring polypeptides, oxytocin and pitressin, by Vincent du Vigneaud is the subject of an interesting book, "A Trail of Research" (du Vigneaud, 1952). This accomplishment of du Vigneaud and his associates rewarded him with the Nobel Prize in chemistry and culminated a long career on the chemistry of proteins. Rather remarkably, although two chemists, Butenandt and du Vigneaud, have been rewarded with the Nobel Prize for chemical studies of hormones controlling reproductive processes, no one working on the physiology of reproduction has been so rewarded.

Recent use of radioimmunoassay to determine the levels of gonadotropins and of gonadal hormones in blood plasma should serve as the basis for more intelligent use of these hormones in correcting abnormalities in the function of the reproductive organs. Also, mention should be made of the use of prostaglandins as contraceptives. Conceivably these are the substances produced by the uterus which may be involved in the uterine influence on ovarian activity. As you can see, I have discussed only a few discoveries, but I imagine by now you are beginning to feel weary. I'm reminded of the man attending a cocktail party who had imbibed too freely. His host found him sitting in the corner holding his head and asked how he felt. "Well," he replied, "I feel a lot more like I do now than when I came in."

I would like to close with a consideration of what lies ahead. Gunther Stent (1969), a geneticist, suggests that the major discoveries have been made and, therefore, we have about reached the plateau or as he calls it, "the golden age." Vannevar Bush (1946) on the other hand sees "endless horizons;" Bentley Glass (1971) believes, however, that the horizons are not endless, "Indeed, so awesome is already the accelerating rate of our scientific and technological advance that simple extrapolation of the exponential curves show unmistakably that we have at most a generation or two before progress must cease, whether because the world's population becomes unsufferably dense, or because we exhaust the possible sources of physical energy or deplete some irreplaceable resource, or because, most likely of all, we pollute our environment to toxic irremediable limits. Many scientists have in recent decades tried to flag the runaway express. The present more general outcry, daily growing stronger, against unlimited population growth and heedless pollution of the environment offers a slight ground for hope. The prime difficulty is that so many persons, not only in the highly industrialized countries but even more among the peoples of the under-developed countries, now see their hopes for the future bound up with the continuation and extension to all mankind of the progress hitherto limited to a few fortunate lands and people."

I quite agree that population excess, exhaustion of our natural resources and pollution of our environment will lead to the destruction of mankind if action is not taken at once to rectify these devastations. I do not agree that we are reaching the "golden age" as concerns our scientific horizons. When one considers how poorly we understand the working of the human mind, for instance, and how imperfectly we understand the integration of bodily processes there would appear to be endless horizons ahead. I would like to think that new horizons lie ahead for the physical sciences as well. Certainly endless horizons lie ahead for the political scientists in learning how nations can live peaceably together.

**Literature Cited**


