several times the amount of serum which a single fatal dose requires, since in the case of very virulent living bacteria whose virulence is due to their ability to increase, it is not the organisms which are introduced that kill but the millions that develop from them. As a rule, the serum has to be given before the bacteria introduced into the body have multiplied greatly. After that period has elapsed the serum usually fails to act. The immunity conferred on a person from serum lasts from a few days to several months, according to the amount of serum injected. As in animals, it is strongest immediately after absorption. An injection of bacterial poisons or the contraction of actual disease usually confers immunity in from one to three weeks after the infection, which lasts, according to the nature of the infection, from one month to a year or more. The serum loses all appreciable protective value as measured in test animals in the usual doses before the person is liable to infection. Repeated injections of serum continue this condition of immunity indefinitely.

The use of sera having specific protective properties has been tried in both animals and man as a preventive of infection. In susceptible animals injections of some of the very virulent bacteria, as pneumococci, streptococci, typhoid bacilli, and cholera spirilla, can be robbed of all danger if small doses of their respective sera are given before the bacteria have increased to any great extent in the body. If given later they are ineffective. For some bacteria, such as tubercle bacilli, no serum has been obtained of sufficient power to prevent infection. Through sera, therefore, we can immunize against an infection, and even stop one just commencing; but as yet we cannot cure an infection which is already fully developed, though even here there is reason to believe that we may possibly prevent an invasion of the general system from a diseased organ as by the pneumococcus from an infected lung in pneumonia. On the whole, the sera which simply inhibit the growth of bacteria have not given, as observed in practice, conclusive evidence of great value in already developed disease. This is partly due to the difficulty of determining early enough the exact nature of the bacteria causing the infection. Although the serum of animals which have been infected with any one of many varieties of bacteria is usually both antitoxic and bactericidal, still one of these protective substances may be present almost alone; thus antitoxic substances are present almost exclusively in animals injected with two species of bacteria which produce powerful specific poisons—the bacilli, namely, of diphtheria and of tetanus. When the toxins of either of these are injected in small amounts the animals after complete recovery are able to bear a larger dose without deleterious effects, and these doses in the more suitable animals can be gradually increased until a thousand times a previously fatal dose may be administered without any serious results whatever. To Behring and Kitasato we owe the discovery that this protecting substance accumulates to such an extent in the blood that very small amounts of serum are sufficient to protect other animals from the effects of the toxin.

Some other important parasitic bacteria produce toxins and in the body antitoxins, but all to a far less extent than those of tetanus and diphtheria. Following them is the plague bacillus, and then, but far behind, the cholera spirilla, the typhoid bacilli, the streptococci, etc. These latter bacteria produce more of the substances which inhibit bacterial growth than of those which neutralize their toxins.

Inherited Immunity.—Natural immunity pertains more to species than individuals, and such immunity is handed down by the parents to their offspring. If the immunity of one or both parents has been acquired by them during their lifetime previous to the birth of the offspring the immunity conferred is slight or none at all. This is especially true of the male side. In the case of the female parent another factor comes into play after the fructification of the ovum,—viz., the absorption of products from the fluids of the mother, for the placenta is no barrier to soluble substances. Thus, sheep which have been immunized to anthrax have moderately immune young. On the other hand, animals vaccinated with cowpox have not been found to have immune offspring. Antitoxins injected into the parents apparently pass the placenta, giving thus a slight transitory passive immunity. A slight immunity is also given by immune mothers through their milk, a small amount of antitoxic substance being absorbed.

William H. Park.

IMPETIGO.—This is an acute specific inflammatory affection of the skin, spontaneously and experimentally inoculable, contagious, and epidemic; characterized by the formation of superficial flaccid vesicles which soon rupture and give place to crusts formed by the drying of the effused serum. These crusts are without inflammatory areola and look as if stuck on the sound skin, the underlying epidermic erosions healing in a few days without leaving cicatrices.

Impetigo is a disease peculiar to infants and young children, not that there is with them any special underlying predisposing cause in the soil, so to speak, such as a strumous or lymphatic condition as is often alleged, but that simply their skins are more delicate, particularly that of the face, where the corneal epidermis is less thick and where impetigo occurs most frequently.

Given an erosion of the skin—and the thinner the skin the more easily does erosion occur—and the introduction of the special germ, a characteristic lesion of impetigo will result. The *accidental* causes which lead to this inoculation are those that conduce to scratching by which the skin is broken, such as phthiriasis, especially of the scalp, and scabies. Eczema may lead to impetigo. The contagiousness of impetigo was clinically established by Devergie and experimentally proven later by Tilbury Fox, of London, and others. Fox prefixed the term contagious, which would make it appear that his "contagious impetigo" was a different affection from the impetigo of the French school, which is not the case. Impetigo and "contagious impetigo" are one and the same disease and "contagious" is an entirely unnecessary and confusing qualification. Through the more or less intimate association with the greater opportunity for contagion that takes place in schools and families, impetigo may become epidemic solely through the inoculation of one by the other of the members of such bodies. The direct and efficient cause of impetigo is a microorganism—one of the streptococci.

The elementary lesion of impetigo is an erythematous spot but slightly if at all elevated, varying in size from the head of a large pin to that of a split pea. This lesion is very transitory and gives place in a few hours to a superficial flaccid vesicle containing a clear limpid serum. The thin corneal covering of this blister-like lesion is easily ruptured, spontaneously or by scratching, allowing to exude a limpid serum which quickly coagulates and forms the characteristic honey-like crusts that appear as if stuck on the sound skin. An accumulation of these friable amber-yellow crusts, without surrounding inflammatory areola, over the cheeks, forehead, and chin, and around the lips, presents a classical picture of the disease known as impetigo. It may occur on any part of the body, but the face is the familiar location. At times, after the breaking of the imperfect vesicle, little or no exudation will take place, so that no crusts are formed, there being merely a thin glaze over the underlying superficial erosion which heals quickly, leaving an erythematous spot that slowly disappears. This abortive attempt is noticed more frequently in grown persons. Ordinarily through successive reinoculations an attack of impetigo will last for from three to four weeks. The burning and itching, though slight, are sufficient in a child to cause it to scratch the lesions, thereby infecting the finger nails, and thus transference to other parts is effected with the establishment of new lesions. When uncomplicated, the lesion of impetigo never suppurates and terminates, after falling of the crust and the gradual

disappearance of the underlying reddened, area without cicatrix.

Impetigo may be diagnosed from varicella by the more widespread distribution of the latter, impetigo being essentially regional; the vesicle of varicella is smaller and more prominent, is surrounded by a wide area of erythema, and dries up into smaller and far less bulky crusts.

From ecthyma the diagnosis is made by the distribution of the lesions of the latter on the covered portions of the body, and by the greater intensity of the inflammatory process in ecthyma with accompanying indurated base, wide inflamed areola around the crust-covered pustule, and deeper erosive action upon the skin.

A bullous impetigo—a rare form—has at times been erroneously reported as "acute pemphigus in children."

A crusted impetigo lesion may simulate a syphilide, especially when situated around the mouth and chin in adults; if the lesion is one of syphilis the crust on being removed will be found to have surmounted a papule or a sanious ulcer.

Treatment is simple and effective. Removal of the crusts by soaking in olive oil until they are easily detached is the first step, after which an application, renewed twice daily, of a five- to ten-per-cent. ointment of ammoniated mercury will complete the healing in a few days, leaving only the after-redness which in turn gradually disappears. This treatment is all-sufficient, and while there are many other remedies that will perhaps cure as well, there is none better than this.

Charles Townshend Dade.

IMPOTENCE. See *Sexual Organs, Male, Affections of.*

IMPREGNATION is the union of two germ cells, to form a single new cell, capable of initiating by its own division a rapid succession of generations of descendent cells. This process is more frequently called *fertilization* or *fecundation*. The new cell is called the impregnated, or fertilized, ovum; also, especially in botany, it is called *oöspore* or *zygote*. The production of cells from it is called its segmentation, or cleavage. For the theory of the relation of the elements to one another and to other cells, see *Sex;* for accounts of the sexual bodies, see *Ovum* and *Spermatozoon*.

In all multicellular animals, impregnation is effected by three successive steps: 1, The bringing together of the egg and spermatozoon; 2, the entrance of the spermatozoon into the ovum, and formation of the sperm nucleus; 3, fusion of the sperm nucleus with that of the egg to form the segmentation nucleus. We proceed to consider these steps in their order.

1. The Bringing Together of the Germ Cells.—This is effected among animals in a great variety of ways, which, however, fall into two groups, according as the impregnation is effected, (*a*) outside the body of the mother, or (*b*) inside. The simplest manner is the discharge of the eggs and spermatozoa at the same time into the water, leaving their actual contact to chance, the method of the osseous fishes for the most part, and of many invertebrates. An advance is the copulation of the Anura (frogs, etc.), the male embraces the female, and as the latter discharges the ova, ejects the sperm upon them. In the higher vertebrates the seminal fluid is transferred from the male to the female passages during coitus. The physiology of this complicated function does not fall within the scope of this article.

For a long time it was not known how the semen fertilized the ova; the problem was long fruitful of fruitless speculation. The first step toward gaining actual knowledge was the discovery of the possibility of artificial fecundation by Jacobi, in 1764. Spallanzani was the first to take advantage of this, and to show that fecundation implied a material contact of the semen with the ova, and thus to set aside De Graaf's notion of the *aura seminalis*. But not until fifty years later did the memorable experiments of Prévost and Dumas (*Annales des Sciences Naturelles*, 1824) establish the fact that the spermatozoa are the essential factors of fertilization. Again, a little over fifty years later, Hertwig and Fol showed that one spermatozoon suffices to impregnate an ovum.

We have then to consider how the spermatozoa, after the semen has been transferred to the female, attain the ovum. They are found in mammals after copulation in the vagina and even in the uterus, but it is not clearly ascertained how they get beyond the vagina. It is probable that they travel through the female passages partly by the movements thereof, partly by their own locomotion, and enter the Fallopian tubes, though why or how is really unknown, and pass upward to meet the ovum. They are found in considerable numbers in the Fallopian tubes. The ovum meanwhile travels down the oviduct, it probably being impelled by peristaltic movements of the duct.

The meeting point or site of impregnation in placental mammals is about one-third, perhaps one-half way down from the fimbria to the uterus. It is remarkably constant for each species. Nothing positive is known as to the site of impregnation in man, but there is no reason to suppose, as is unfortunately often done, that the site is variable or different from that in other mammalia.

In the sexual reproduction of plants the germ cells are brought together in a great variety of ways; and in the higher forms the process is complicated by an alternation of generations. It will suffice for our present purpose to note that in many of the lower plants the male germ cell is an actively motile *spermatozoid*, homologous with the spermatozoon of animals, on the one hand, and with the germ cell of the pollen grain in higher plants, on the other hand.

2. The Entrance of the Spermatozoon into the Ovum and Formation of the Sperm Nucleus.—With our present knowledge, the assumption appears unavoidable that the ovum exerts a specific attraction upon spermatozoa of the same species. We observe, in fact, when artificial fecundation is employed, the spermatozoa swarming around the ova as if held by an irresistible impulse. This phenomenon occurs with every class of animals, even in mammals, whose freshly removed ova were examined on a warm stage under the microscope (Rein). Stassano has maintained that the eggs of echinoderms do exert such an attraction and also a similar but less strong attraction upon the spermatozoa of allied species. Since the brothers Hertwig have found by their experiments with sea urchins that hybrid impregnation takes place more readily after the ova have been kept awhile, Stassano's view involves the further assumption that the specific nature of the attraction fades away during a few hours. Very suggestive in this connection is Pfeffer's discovery that certain chemical substances may attract moving spores, etc., to definite spots. It is conceivable that the ovum may draw the spermatozoa toward itself by chemical influence, acting as an attracting stimulus. That this attraction may be exerted by the cytoplasm of the egg alone, is shown by the experiments of Boveri, Hertwig, Bresi, and Morgan, who found that spermatoza will enter enucleated fragments of eggs.

There may be mechanical devices to facilitate the entrance of the spermatozoon; this is, perhaps, generally true of all ova with micropyles serving for the passage of the spermatozoa. A careful study of such devices in the cockroach has been made by Dewitz, who found that the motions of the spermatozoa of this insect are peculiar, and adapted to increase the probability of their passing through one of the micropyles of the ovum. In ova without micropyles, among which those of mammals are included, the spermatozoa may, so far as we know, penetrate any part of the envelopes.

In the rabbit (Rein) about ten hours after coitus the ovum is found nearly half-way through the oviduct, and surrounded by many spermatozoa, perhaps a hundred, more or less. These are all, or nearly all, in active motion, for the most part pressing their heads against the zona radiata. Several of them make their way through into the interior of the zona. According to Hensen, only those spermatozoa which enter the zona along radial lines can make their way through; those which take oblique courses remain caught in the zona, and may still be seen there during segmentation. As the ovum at this time is already fully matured (see *Ovum*), there is a space between the contracted ovum and the zona. In this space, as well as in the zona itself, several spermatozoa may be observed at scattered points (Fig. 2787). The egg nucleus (see *Ovum*) is present, having been reformed since the expulsion of the second polar globule from the ovum, while in the ovary. One spermatozoon gets into the egg proper, and its entrance apparently prevents the penetration of other spermatozoa—*how* is undetermined. The tail of the spermatozoon soon disappears; while the head, which consists almost entirely of nuclear material, chromatin, enlarges, probably by the imbibition of fluid from the cytoplasm of the egg, and becomes the sperm nucleus. This was formerly called the *male pronucleus*, in distinction from the egg nucleus, which was called the *female pronucleus;* but they differ in no respect from other nuclei, except in the number of chromozomes which they contain.

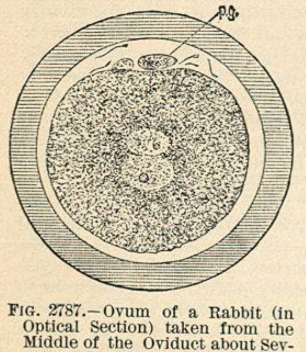

FIG. 2787.—Ovum of a Rabbit (in Optical Section) taken from the Middle of the Oviduct about Seventeen Hours after Coitus. The sperm and egg nuclei are close together at the centre of the egg; the polar globules, *p.g.*, are shown; numerous spermatozoa lie within the zona, *z*. (After Rein.)

The passage of the spermatozoa through the zona was first discovered by Martin Barry, in 1843, and although his statement was received with considerable hesitation by his contemporaries, it has since had competent confirmation repeatedly. Warneck is said to have been the first (1850) to see the *two* pronuclei, but their significance was not perceived. The nature of the male pronucleus was first recognized by Oscar Hertwig, who traced its genesis in the ova of echinoderms from the spermatozoon. The fact that the male pronucleus is the metamorphosed head of the spermatozoon has since been confirmed by Selenka, Ed. van Beneden, Nussbaum, Eberth, Platner, and others.

Although a number of the spermatozoa make their way into the perivitelline space, probably always one alone normally enters the ovum there to form a pronucleus. The best observers are agreed upon this point, and in all species, the observations upon which have covered the whole series of steps in the impregnation, there has been found in normal cases always a single sperm nucleus. Schneider's statements to the contrary have been definitely corrected. Bambeke, Kupffer, and Kupffer and Benecke have observed that several spermatozoa actually enter the yolk in batrachians and Petromyzon. Hertwig, however, found only one sperm nucleus in the frog, and there has as yet been no evidence adduced that several spermatozoa are concerned in the final phases of impregnation. Fol observed that star-fish eggs are normally impregnated by one spermatozoon; but if they are exposed to the action of carbonic acid they may, while so poisoned, be impregnated by several spermatozoa, but the subsequent development in this case is abnormal.

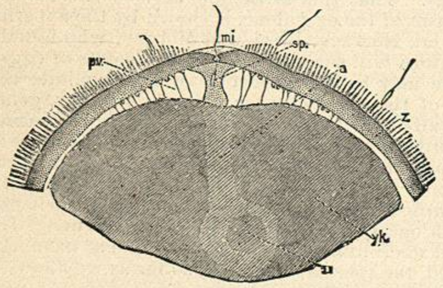

FIG. 2788.—Anterior Pole of the Ovum of Petromyzon, with a Spermatozoon (*sp*)., entering the Micropyle (*mi*). (After Calberla.) *p.v.*, Perivitelline space; *z*, zona pellucida; *a*, pathway to egg nucleus, *n*; *yk*, yolk.

The term micropyle is applied to various structures, and does not in all cases designate a passage through which spermatozoa enter—thus the micropyle of holothurians is merely a structure left in the envelopes in consequence of the way the egg is developed. A micropyle has been observed in the ova of teleosts and the lamprey, but it is doubtful whether it is, like the micropyles in the hard-shelled eggs of insects, intended for the passage of spermatozoa. Calberla saw the micropyle thus used in the lamprey, and it is possible that the fructifying spermatozoon enters that way, although Kupffer and Benecke state that spermatozoa may also pass directly through the zona. A good synopsis of the observations on the lamprey is given by Hensen (Hermann's "Handbuch," vi., ii., 120). We have only to notice that there is a special band of non-granular protoplasm leading from the micropyle to the egg nucleus (Fig. 2788), and serving as a path for the spermatozoon; a similar band has been observed in amphibian eggs by Hertwig and Bambeke; it serves perhaps as a mechanism to guide the sperm nucleus to the egg nucleus.

The manner in which additional spermatozoa are excluded, after the first has entered, is still under discussion. In cases in which there is a single micropyle, which is used for entry, it is possible that a portion of the first spermatozoon may remain to close the passage, or that in going through it sets in action some mechanism by which the opening is automatically shut. Where there are several or many micropyles, as in some insects, or where the envelopes may be pierced at any point, as in mammals, there must of course be some other device. Fol has maintained that this is found in the starfish in the rapid formation of a membrane around the yolk, immediately after the entrance of the first spermatoon. This is confirmed by the observations of Wilson and others on other echinoderm eggs. The egg is at first perfectly naked and the membrane is formed very quickly after the entrance of the head and middle piece, leaving the tail outside. Selenka (*Biolog. Centralbl.*, v., 8) describes the fertilization of the ovum of a nemertean worm—several spermatozoa enter within the vitelline membrane; the yolk contracts slowly; after a time the two polar globules are expelled, and before they separate from the yolk one spermatozoon passes into the yolk between them; the globules then break off and are knocked about by the spermatozoa in the perivitelline space. In this case there seems to be a portal opened just long enough for one spermatozoon to enter. As the phenomenon to be explained is common to all ova, its causation is presumably fundamentally identical in all cases. Beyond this surmise our present knowledge does not permit us to go. The hypothesis may be suggested that the attractive power of the ovum is annulled or weakened by the entrance of the first spermatozoon.

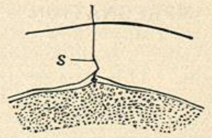

FIG. 2789.—Egg of Toxopneustes, with entering Spermatozoon (*s*), and a Protuberance of the Cytoplasm rising toward it. (After Selenka.)

The fate of the tail of the spermatozoon differs in different species. In some the whole spermatozoon enters the egg, while in others, as the echinoderms, only the head and the middle piece enter. In either case it is a well-established fact that the tail is simply a locomotor organ and takes no part in fertilization proper.

While the spermatozoon is passing through the ovic envelopes active changes occur in the cytoplasm. Of these, the most constant, as well as the most obvious, is the formation of a slight protuberance on the surface of the cytoplasm of the egg, rising up toward the spermatozoon. This protuberance (Fig. 2789) may remain, as in

echinoderms, until the spermatozoon meets it, and by penetrating it enters the ovum; or it may retract before the spermatozoon passes through the envelopes, and even withdraw, as in Petromyzon, so far from the advancing spermatozoon as to change into a depression (Fig. 2788). The protuberance lasts only a few minutes. In Bufo, according to Kupffer, several spermatozoa enter the egg and a protuberance rises toward each one, as if the cytoplasm were actively striving to reach the male element.

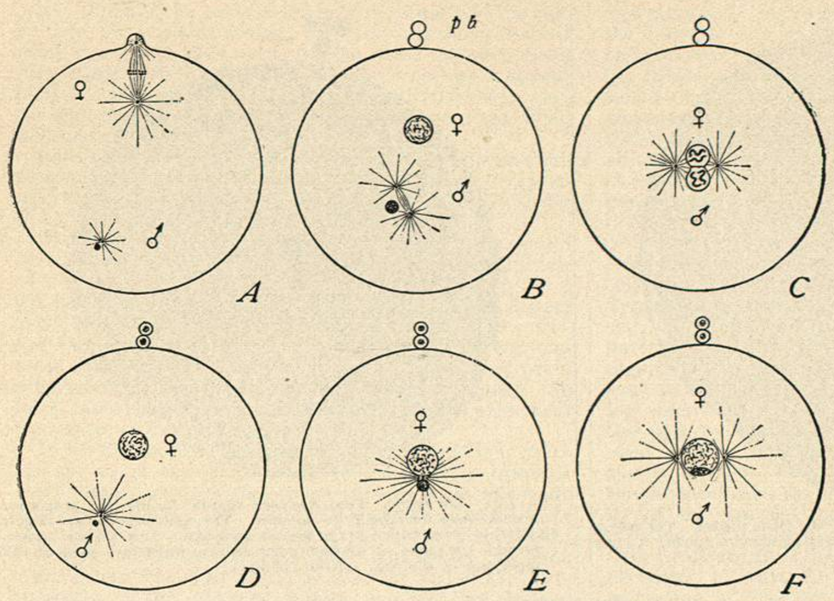

FIG. 2790.—Diagrams of Two Principal Types of Fertilization. *A*, *B*, and *C*, Polar bodies formed after the entrance of the spermatozoon, as in Nematodes, Annelids, and Mollusks; *D*, *E*, and *F*, polar bodies formed before entrance of spermatozoon, as in Echinoderms. Egg nucleus at ♀, sperm-nucleus at ♂. (From Wilson.)

3. FUSION OF THE GERM NUCLEI, FERTILIZATION PROPER.—For many centuries the process of fecundation was wrapped in the deepest mystery, and while the keen observers of the latter half of the eighteenth century and the first half of the nineteenth did much necessary preliminary work in this direction, they so far failed to clear up the mystery that, although spermatozoa had been discovered by Hamm and Leeuwenhoek in 1677, and Spallanzani had shown in 1786 that spermatic fluid deprived of spermatozoa by filtration is sterile, Johannes Müller wrote in his "Physiology" in 1840 that it was uncertain whether the spermatozoa were parasites or not; and, although Schwann had declared the egg to be a cell as early as 1838, it was still possible in 1875 for a distinguished zoologist, Alexander Goette, to write "that the egg was a mass of non-living yolk which, under the influence of the spermatozoon, gradually came into a living condition." While the process is still sufficiently wonderful and mysterious, a great deal has been done during the past twenty-five years to render it intelligible.

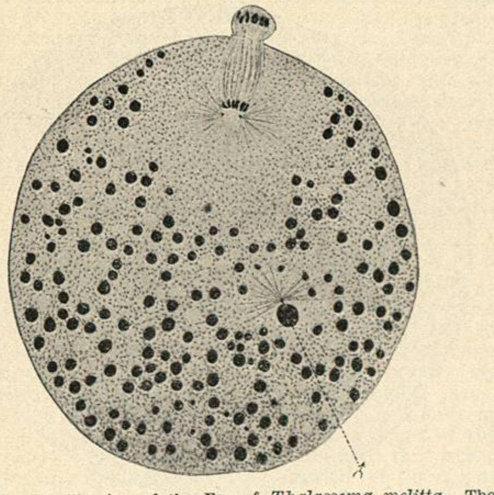

FIG. 2791.—Fertilization of the Egg of *Thalassema melitta*. The head of the spermatozoon preceded by the sperm aster is shown at ♂. The formation of the first polar body is nearly completed and the inner centrosome of the polar spindle has divided preparatory to the formation of the second polar amphiaster. Highly magnified. (After Griffin.)

The first great discovery was made by Oscar Hertwig, who observed in 1875 that the egg of a sea-urchin, *Toxopneustes lividus*, is normally fertilized by the entrance of a single spermatozoon, and that the spermatozoon gives rise to a nucleus which unites with the nucleus of the egg, forming by this union the segmentation, or cleavage, nucleus. We know now, as the result of numerous observations, that both the egg and the spermatozoon are living cells, and that they are morphologically equivalent, except in so far as they are altered in form in adaptation to a physiological division of labor, the principal difference being that the egg is provided with a large amount of cytoplasm, often heavily laden with food yolk for the nourishment of the embryo, and has no power of locomotion; while the spermatozoon is totally devoid of

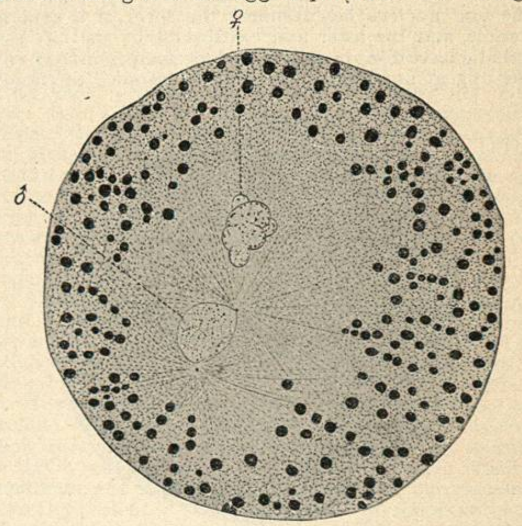

FIG. 2792.—Later Stage of the Same. The egg nucleus is shown at ♀ and the sperm nucleus at ♂. The two nuclei are approaching one another. The egg centrosome has vanished, while the persistant sperm centrosome has divided forming two centrosomes with asters. (After Griffin.)