

FRAZER'S MANUAL OF EMBRYOLOGY

The Development of the Human Body

BY

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PREFACE TO THE THIRD EDITION

IN the preparation of a third edition of this book I have been at pains to preserve the original character of it. The manual is largely a record of the personal observations of one man extending over many years and, indeed, is the only complete record of those observations that is available to us. The subject matter, then, of the second section of the book remains much as the late Professor Frazer set it down. Any alterations and revisions that have been made by me concern matters of detail only, or represent the subsequent work of others which has seemed to me worthy of incorporation. Further, the regional method of treatment of the subject as opposed to the ~~s~~systematic has been deliberately retained. It is an unusual mode of presentation of the subject of human development, but I believe that it has many advantages.

The first section of the book deals with the early stages of development. Important advances in our knowledge of this phase of the subject have taken place in the past twenty years, and I have been compelled to rewrite this section almost completely in order to bring it into line with modern thought. A number of new illustrations and photographs have been introduced, especially in this section, and I am indebted to my publishers for their benevolence in this matter. Finally, I should like to thank my secretary, Miss Nancy D. Wood, for her great kindness in preparing the index.

J. S. BAXTER.

CARDIFF,
September, 1952.

PREFACE TO THE FIRST EDITION

IN writing this book the general aim was to give the student some sort of connected mental picture of the developing embryo, rather than a patchy series of discrete descriptions of the formation of organs. It appeared more reasonable, therefore, to make use of the regional method which has been so successful in descriptive human anatomy, although the continually changing conditions make its application more difficult. This implies that there are many disadvantages in its use—such, for example, as the breaking up of the consideration of a compound formation into two or more parts—but these appear to be decidedly outweighed by its descriptive advantages.

In the second place, the opportunity has been taken of bringing together certain new descriptions. During the last twenty-five years I have devoted much time to working out on human material the processes of development of organs and regions. This work, approached with an open mind, led to results which were frequently not in accord with the usual descriptions. Some of these results were recorded from time to time in independent papers, and in many cases have found their way into English textbooks. Only certain pieces of work, however, appeared in this way, and the writing of this book afforded an opportunity for bringing forward most (if not all) of these results—in their chief contentions, at any rate.

The reason for the plan adopted in writing the book now becomes more apparent. No references (as usually understood) are given, but, where a statement is made on the authority of some other worker, the name is put in brackets. When no such interpolation is found, the statement is either one generally accepted or is made on the results of my own observations: that is to say, then, that I must be held responsible ultimately for the accuracy of a statement not supported by some other name. Thus, when a description apparently proceeding along conventional lines is found to diverge from these in some way, great or small, it should be understood that it is really following lines which have appeared to me to be correct when working it out. In

spite of its imperfections, I hope the book, with its new points of view, will be of use not only to the anatomical student, but to the senior man desiring light on some embryological question arising in his work.

In conclusion, to one who believes that organogeny has a future before it in pathology and other medical sciences, the drastic cutting down of detail is not pleasant. Embryology will be useful in these matters in proportion as detail is dealt with and understood. In a book of this sort, however, something has to be cut down, and its objects would suffer less perhaps in this than in shortening the larger topical descriptions; hence masses of detailed observations have been curtailed or suppressed *in toto*. The same reason accounts for the absence of much comparative embryological morphology.

I am indebted to the publishers for the generous spirit in which they have received my numerous illustrations; to my colleague, Dr. R. H. Robbins, for careful reading of the proofs; and not least to my wife for much trouble in preparing the index.

J. ERNEST FRAZER.

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MANUAL OF EMBRYOLOGY

PART I

CHAPTER I

DEVELOPMENT, SEX-CELLS, FERTILIZATION, SEX DETERMINATION

THE term **development**, in its true sense, includes all those changes which are of the nature of growth and tend toward the formation of the physiologically perfect body or organ. Development, in this sense, may be said to cease only at death, for cell repair and substitution are processes of growth which continue during life, and no living body can remain physiologically perfect without constant renewal of its constituent parts. It is customary, however, and more practical, to limit the idea of development to the processes which lead to this perfection, and only to include theoretically those which are employed to maintain it.

Human development can be said to begin, then, with the conception of the embryo, to include its formation and growth in the uterus, its birth, and the subsequent growth during childhood and adolescence up to the time that the full stature of man in physique and intellect has been reached. The whole field can be divided, therefore, into *intra-uterine* and *extra-uterine* development. Of the two, the last is by far the more extensive and also the less known, for the difficulties of research under this heading are great. The intra-uterine period, more dramatic in its changes if shorter in time, is better known, but it is necessary to point out that even here knowledge is very imperfect and fragmentary, and the progress of developmental change is often, as described, little more than a matter of inferences and assumptions: as detailed observations increase in number and exactitude the inferences are more controlled, and nearer approximations to the truth result. An account of the development of the body, therefore, in the nature of things, must be looked on as an attempt to make a continuous story out of an array of facts not necessarily directly connected, for the purpose of showing how the human body probably attains to its adult state.

In addition to the value of the descriptive study of development in the better understanding of the anatomy of the human body, and of some of its pathological affections, it has another aspect in which its utility increases with increasing know-

ledge. The embryological changes form a record of what the human species has gone through to reach its present state: whether the record is to be looked upon as true or as falsified in some ways depends on the bias of the observer, but it remains as the only document extant. Thus, in the study of the relation of the human species to other forms—general and special morphology—the comparison of embryonic forms and processes of the different sorts of animals concerned is a matter of prime interest, for here we have the earlier and simpler stages of the animals in question, when they were nearer to one another and not yet modified by more lately acquired characters.

The human individual, like all other animals which multiply through sexual congress, develops as a result of *impregnation of a female germ-cell by a male germ-cell*: whatever means are employed to bring the two cells together—and Nature is prodigal in arrangements to this end—the essential point in the process is the same in all cases—the **conjugation** of the nuclei of the two sex-cells. The female sex-cell is nearly always larger and passive, the male cell small and motile, and the conjugation is effected by the smaller male germ-cell entering the female cell, and thus bringing about *fusion of the nuclei* of the two cells. The sex-cells are animal cells, modified in various ways according to the sex, and contain and consist of the parts found in animal cells; they are developed from less specialized cells as results of a peculiar variety of mitotic division, but they are (when fully formed and sexually potent) **mature** cells, which do not possess the power of further division except when conjugation has been effected. The female sex-cell is termed the **ovum**, and the male cell the **spermatozoon**.

Spermatogenesis.—There are two phases in the formation of the spermatozoon. In the first, the germ cells divide repeatedly and become modified so that they contain only one-half of the amount of chromatin possessed by the ordinary somatic cells. This is called *spermatocytogenesis*. The cells arising in this manner then become transformed into spermatozoa by a series of alterations which make up the process of *spermiogenesis*. All these events take place in the walls of the convoluted tubules of the testis, and representative stages of them are shown in Fig. 1.

Spermatocytogenesis.—The primitive spermatogenic cells, the *spermatogonia*, lie next to the basement membrane of the convoluted tubules of the testis. Their cytoplasm contains numerous small, rounded mitochondria, and isolated masses of Golgi material form a cap over one pole of the nucleus. These cells undergo repeated divisions, and at each mitosis one of the daughter cells is displaced towards the tubule lumen. During mitosis the spermatogonia present forty-eight chromosomes, twenty-three pairs being autosomes and one pair (X-Y) forming the sex chromosome complex (Painter, 1923).

After a period of growth the cells become known as *primary spermatocytes*, large oval or rounded cells, which occupy much of the width of the tubule wall. The mitochondria are arranged in a zone around the nucleus, near one side of which is found an idiozome or attraction

sphere. The idiozome has a cortex of osmiophile Golgi material, and in the interior are a number of minute, pro-acrosomic granules. A centriole is found between the nucleus and the idiozome. The division of a primary spermatocyte is of a peculiar nature (*meiotic or reduction division*), since it results in the production of two *secondary spermatocytes*, each containing one-half of the number of chromosomes found in the parent cell. Briefly, the significant events in meiosis are

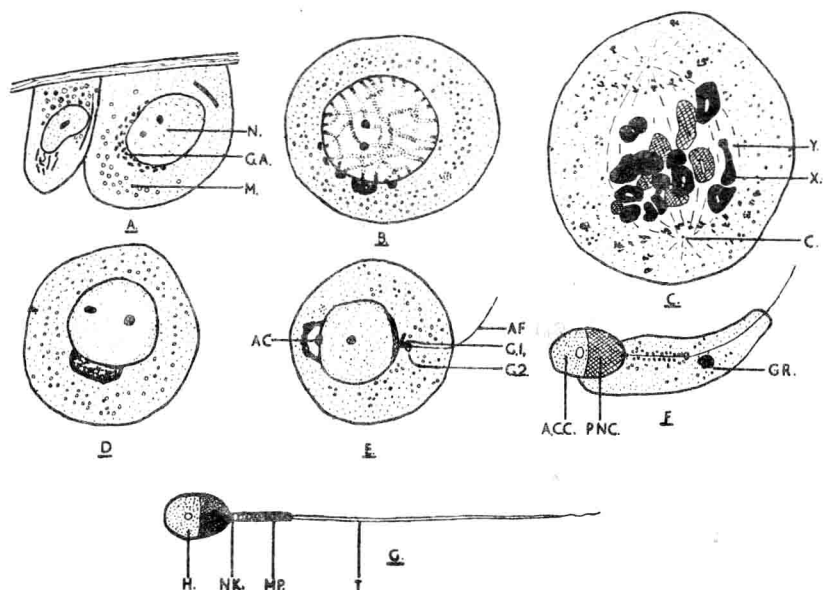


FIG. 1.—STAGES IN THE SPERMATOGENESIS OF MAN (ADAPTED FROM GATENBY AND BEAMS).

A, spermatogonium and a small Sertoli cell lying adjacent to the tubule wall. The spermatogonium contains a Lubarsch crystalloid. B, primary spermatocyte. C, primary spermatocyte in the metaphase stage of meiosis. The X-Y sex chromosome complex is shown. D, secondary spermatocyte. E, early stage of metamorphosis of the spermatid. F, late stage of the same. G, mature spermatozoon.
AC, acrosome; ACC, acrosome cap; AF, axial filament; C, centriole; C1, proximal centriole; C2, distal centriole; GA, Golgi apparatus; GR, Golgi remnant; H, sperm head; M, mitochondria; MP, middle piece of sperm; N, nucleus; NK, neck of sperm; PNC, post-nuclear cap; T, sperm tail; X, X-chromosome; Y, Y-chromosome.

these. During the preliminaries to cell division the chromosomes unite, side by side, in pairs (*synapsis*). The nucleus now contains one-half of the somatic number of chromosomes, these being *bivalent*. Each member of such a pair shows a longitudinal split, so that we are really dealing with groups of four half-chromosomes. Such groups are known as *tetrads*. During metaphase the tetrads become arranged on the equator of the spindle, and then at the anaphase they split along the line of previous fusion of the chromosome mates, single chromosomes moving to the poles of the spindle. These may show

evidence of the longitudinal splitting mentioned above and are termed *dyads*. In this division the X-chromosome passes to one daughter cell and the Y-chromosome to the other. Hence there are two varieties of secondary spermatocyte.

The *secondary spermatocyte* is a somewhat smaller cell than the primary spermatocyte. It contains the reduced, or *haploid*, number of chromosomes (twenty-four in man), and it divides giving origin to two *spermatids*. In this division the chromosomes appear to split longitudinally so that the spermatids each contain twenty-four; half the spermatids will possess an X-chromosome, the other half a Y-chromosome. Formation of the spermatids completes the process of spermatocytogenesis.

Spermiogenesis.—The spermatid is a relatively small cell with a dense nucleus. The cytoplasm contains mitochondria, the idiozome with the Golgi apparatus and a pair of centrioles. All these go through a series of changes which result in the formation of the mature spermatozoon. The idiozome (now called the *acroblast*) becomes attached to the nucleus at what will be the anterior pole of the sperm. The pro-acrosomic granules run together to form an *acrosome* which fuses with the nucleus and spreads out over its anterior half as the *acrosome cap*. The remainder of the acroblast moves off into the cell cytoplasm with which it is eventually eliminated. The centrioles at first lie near the periphery of the cell at the opposite pole to the acrosome. An *axial filament* grows out through the cell surface and, with increase in length of this, the centrioles move deeply to the posterior pole of the nucleus. Some of the axial filament will thus be intra- and some extra-cellular. A *posterior nuclear cap* forms to cover the hinder part of the nucleus. Just behind this lies a *neck granule* with which the anterior centriole becomes associated. The *posterior centriole* grows larger, assumes a ring form, and moves distally along the axial filament until it comes to rest at the posterior limit of the middle piece of the spermatozoon. Most of the mitochondria arrange themselves around the axial filament of the middle piece. The remainder, along with the degenerating Golgi material and almost all the cytoplasm, are cast off from the spermatozoon and undergo dissolution. During this time the axial filament has increased in length to form the *tail of the spermatozoon*, most of which is clothed with a very delicate cytoplasmic sheath, the terminal part alone being naked.

During spermiogenesis groups of spermatids become closely associated with Sertoli cells, possibly because of special protective needs during this time. After the elimination of excess cytoplasm the maturing spermatozoa become detached into the tubule lumen.

Mature Spermatozoon.—The human spermatozoon is some 60μ in length, and consists of a *head*, a *middle piece* and a *tail*. The head and middle piece are separated by a very short *neck*.

The head is flattened and pyriform in shape, $4-5\mu$ in length by

2.5-3.5 μ in width and depth, and is essentially a condensed nucleus. The anterior part is pale and is covered by the acrosome cap; the posterior part is darker, being clothed by the post-nuclear cap. A spiral sheath of mitochondria surrounds the *middle piece*, which is about 5 μ long and has the proximal centriole and the ring centriole at its two extremities. The very short *neck* contains a dark-staining mass, the neck granule, of unknown origin. The *tail* of the spermatozoon gradually tapers down from its junction with the middle piece to the terminal naked axial filament.

In the semen the number of spermatozoa is about 60,000 per cubic millimetre, and some 200 million are present in a normal ejaculation. Spermatozoa are described to have a spiral rotatory movement—14 to 23 μ per second—which carries them in a forward direction quite rapidly for their size. They are not active when they leave the testis tubules, but mixture of the testicular output with the secretions of the prostate and other accessory glands leads to the exhibition of their full activity. They may retain their activity for a week or more in the female genital tract, but it is not considered that the power to fertilize an ovum persists for more than about forty-eight hours after ejaculation.

Oogenesis.—The female germ cells, or *ova*, are derived from the *cells* of the *germinal epithelium* covering the ovary. It is not known with certainty whether, in the human, they arise from the germinal epithelium itself, or from cells (*primordial germ cells*) which have migrated to the germinal epithelium from other regions during embryonic life and become intercalated in the epithelium, as has been described by Everett (1943) for the mouse. It was formerly held that all ova destined to become mature were formed before birth, and that only a small fraction of them ever attained to full development during the later reproductive period of life. A considerable amount of evidence has been brought forward by Allen (1923), Evans and Swezy (1941) and by others to show that these primordial ova degenerate shortly after birth, and that the definitive ova in adult life arise by cyclic proliferation from the germinal epithelium, which thus contains the oögonia.

Primary Follicle.—Whatever may be the mode of origin, young germ cells are found in the periphery of the ovarian cortex lying in the *primary follicles*. A single layer of flattened follicular cells surrounds the large ovum which may be termed a *primary oöcyte*, since it corresponds to the primary spermatocyte of the male. The oöcyte nucleus lies slightly to one side of the cell, and a number of mitochondria, a Golgi network and a cytocentrum are found in the cytoplasm near one pole. The nucleus contains the somatic number of chromosomes for the species—that is, *forty-eight in the human subject*. Forty-six of these are autosomes, two are \bar{X} or sex chromosomes.

Growth of the Follicle.—The primary follicle now enters upon a

period of growth during which striking changes occur. The oöcyte and its nucleus enlarge. The mitochondria become dispersed throughout the cytoplasm in which yolk granules appear. A refractile membrane, the *zona pellucida*, is laid down around the ovum and increases in thickness. The follicle cells outside the zona become columnar,

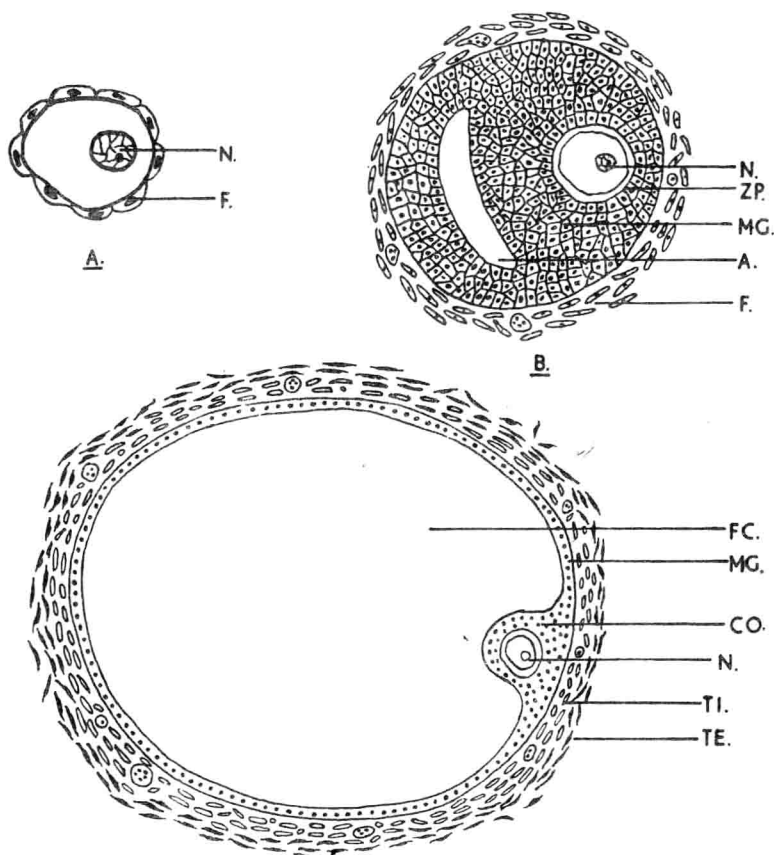


FIG. 2.—DIAGRAMS TO ILLUSTRATE FOLLICULAR GROWTH.

A, primary follicle. B, growing follicle with small antrum. C, follicle nearly mature. A, antrum; CO, cumulus oöphorus; F, follicle cells; FC, follicle cavity; MG, membrana granulosa; N, nucleus of ovum; TE, theca externa; TI, theca interna; ZP, zona pellucida.

multiply and arrange themselves in stratified form as the *membrana granulosa*. During this time the growing follicle appears to migrate towards the medulla of the ovary.

The next stage of development is seen with the appearance of spaces filled with clear fluid between the cells of the *membrana granulosa*. By their coalescence an *antrum* containing *liquor folliculi* is

formed towards one side of the follicle. This cavity enlarges very considerably and the ovum comes to be attached to the inner wall at one pole by a little mass of granulosa cells, the *cumulus oöphorus*. The large follicle (5-10 mm. in diameter) bulges towards the free surface of the ovary, and the cortical tissue overlying it becomes increasingly thinned out. The connective tissue surrounding the follicle has meanwhile become differentiated into two layers: an inner, *theca interna*, is characterized by the presence of many capillaries and large epithelioid cells; an outer, *theca externa*, is formed of dense fibrous tissue and smooth muscle.

Maturation of the Ovum.—The ovum now enters upon the process known as *maturation*. The nuclear chromatin of the primary oöcyte

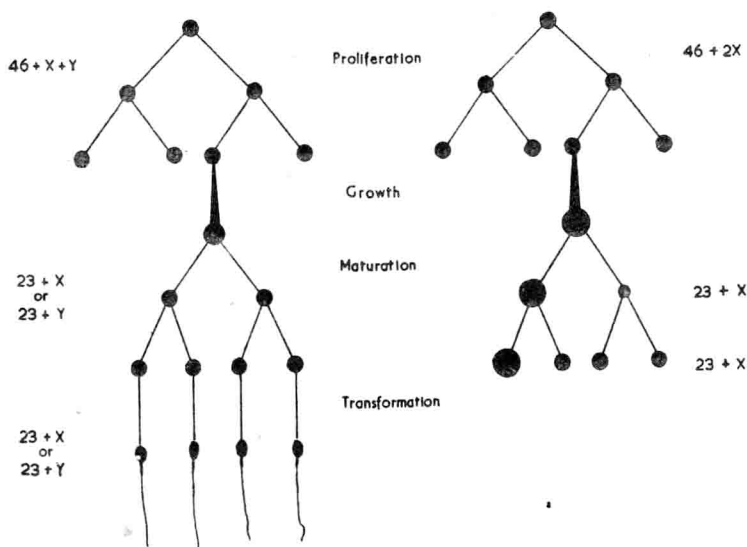


FIG. 3.—DIAGRAMS CONTRASTING SPERMATOGENESIS AND OOGENESIS.

becomes arranged as *tetrads* on the equator of an achromatic spindle. The number of tetrads will be one-half of the somatic number—that is, twenty-four in man. The spindle lies near the surface of the ovum and, when splitting of the tetrads takes place, twenty-four dyads are cast off surrounded by a very small amount of cytoplasm. This is a *first polar body*, and it lies between the ovum and the zona pellucida. It may attempt to divide again, but more usually degenerates. The other twenty-four dyads remain in the ovum (now properly called the *secondary oöcyte*), and the chromatin in these immediately becomes arranged on the second maturation spindle. It is in this condition that the ovum is extruded from the follicle in the act of ovulation (see below). The secondary oöcyte eliminates a *second polar body*, the

elements of the dyads separating, and the ovum is now mature. Its nucleus contains twenty-four chromosomes, one of which is an X-chromosome.

During the maturation divisions of the female germ cell two significant processes are to be recognized. One is the production of the reduced, or haploid, number of chromosomes, and since the sex chromosome pair in the female is of the X-X type, all mature ova must contain twenty-three autosomes and an X-chromosome. The second is the conservation of cytoplasm and yolk for the production of one large, mature ovum at the expense of two (or possibly three) polar bodies which degenerate. In this, the large passive ovum contrasts markedly with the small motile spermatozoon, in whose genesis cytoplasmic elimination is a striking feature.

Ovulation.—The actual expulsion of the ovum from the ovarian follicle (*ovulation*) has not been observed directly in the human subject. There is no reason, however, to suppose that it differs essentially from the process in lower forms, such as the rabbit, for which records are available (Hill *et al.*, 1935; Markee and Hinsey, 1936). As the time of ovulation approaches an avascular spot surrounded by dilated vessels appears on the surface of the ripe follicle. This avascular spot then bulges outwards as a little papilla (the *stigma*), an opening forms at the tip of it and the follicular fluid wells out, carrying with it the ovum detached from the inner wall of the follicle. Some of the cells of the cumulus oöphorus remain attached to the zona pellucida and so form a *corona radiata* around the ovum. After ovulation the ovarian follicle collapses and becomes transformed into a *corpus luteum* (p. 13).

Mature Unfertilized Ovum.—Evidence gathered from the study of living human ova recovered from the uterine tubes (see Hamilton, 1944, for review) indicates that ovulation takes place when the ovum is at the stage of the secondary oöcyte. It is a large cell, the average diameter, including the zona pellucida, being about 144μ . At first it is surrounded by a variable number of corona radiata cells, but these soon degenerate. The translucent zona pellucida closely surrounds the *vitellus*, or ovum proper. It is doubtful if a perivitelline space between the ovum and the zona is to be regarded as normal. The first polar body lies just beneath the zona. The nuclear chromatin of the ovum is arranged on the spindle preparatory to the second maturation division. This point, however, can only be appreciated in fixed and sectioned material, since the vitellus in the living state is highly refractile and so obscures view of the deeper structures.

There is no direct evidence as to the length of time during which the human ovum remains capable of fertilization. Many tubal ova have shown signs of degeneration when recovered, and this would point to the period being a short one. In lower mammals the period when an ovum is fertilizable is a fairly short one, varying from about twelve hours in the rabbit to some thirty hours in the ferret (Hammond,

1941). *There is no valid reason to assume that the human ovum forms an exception to this general rule.*

Fertilization.—The meeting of the sex-cells and their conjugation occurs in all probability most frequently *in the outer part of the uterine tube*. This statement cannot, of course, be expected to rest on direct observation in the human subject, but is considered probable because the corresponding situation is known to be the site of fertilization in other animals; moreover, it is not very uncommon to find an ovum developing here instead of in the uterus, and the time that elapses between early uterine implantation and coitus, when the date of this is known, is in agreement with the view. Active spermatozoa have been found in the tube, and even round the ovary. If the fertilized ovum fails to pass into the uterus it may develop in the tube, forming what is known as a tubal pregnancy: in rare cases such development may take place altogether outside the tube, or even in the ovary, the ovum not having left the ruptured ovarian follicle: these varieties are known as abdominal and ovarian pregnancies respectively. All these abnormal developments are examples of *extra-uterine pregnancies*.

The details of the process of fertilization are quite unknown for the human, but, in all probability they resemble the events in other forms. A single spermatozoon pierces the zona pellucida and enters the cytoplasmic body of the ovum. This causes some change in the zona pellucida that prevents entry of any further spermatozoa. The *second polar body* is now extruded and the chromatin remaining in the ovum forms itself into the *female pronucleus*. The tail of the spermatozoon separates from the head and neck, lies quiescent and is ultimately broken up and destroyed. The head moves towards the female pronucleus, becoming enlarged and vesicular to form the *male pronucleus*. A centrosome, probably derived from the anterior centriole of the spermatozoon, appears between the two pronuclei, each of which is resolving into a group of chromosomes. The centrosome divides into two. These move apart, a spindle is formed between them, and the male and female chromosomes arrange themselves in pairs on its equator. It is at this stage that we may speak of union of the two pronuclei, and thus of the cell as a **fertilized ovum**. Each chromosome now splits lengthwise and the halves move apart, a mitotic division of the ovum taking place to initiate the process of *cleavage* or *segmentation*.

Two evident results are obtained by the process: the activation of the ovum and the restoration of the proper diploid state to the nucleus. To take the last point first, it is evident that the specific diploid number must be restored, and it is also evident now that the preliminary reduction was a necessary preparation for conjugation, for the addition at each generation of fresh nuclear material would, without corresponding reduction, soon make the nuclear constitution impossible. Reduction need not necessarily have been to the same amount in both sexes, but as it is the same it must be to the extent of 50 per cent. in each. The question then arises—why should there be sexual reproduction at all? It is well known that

penetration by a sperm is not necessary for the activation of the ova of many animal forms. Parthenogenesis, as it is called, is normal for some forms, and may be artificially induced by chemical or mechanical means in others. But the wide distribution of sexual reproduction is, in all probability, due to its value from the standpoint of variation and heredity. It is generally accepted that the hereditary characters of a cell are carried in the nucleus, and it is evident that the introduction of new character groups at each generation, by sexual congregation, is the most efficient way of bringing about the possible variations on which the environmental powers can act. For the same reason the half-and-half division is the most efficient division possible.

The human ovum is supposed, on very good grounds, to be fertilized by one spermatozoon only. This seems to be the rule, except among urodeles, reptiles, and birds with heavily yolked eggs, where a normal condition of polyspermy exists. Entry of the male cell leads to a rearrangement within the ovum, or the formation of a 'fertilization' membrane round the cell, which prevents the entry of another sperm: in the large polyspermic eggs the changes in the egg extend too slowly to inhibit the other sperms, but their presence does not appear to interfere with the influence of the chief activating one. In eggs normally monospermic the experimental production of polyspermy may lead to abnormal fertilization and death.

A very large amount of experimental work has been and is being done on the conditions of fertilization, but it must be remembered that these experiments are practically exclusively carried out on the eggs of sea-urchins, starfish, and the like, so that their applicability to the human ovum is at least open to reasonable question. It has been shown that the older idea of *chemotaxis*, an attraction exerted by the ovum on the sperm, has no existence in fact, except perhaps among some plants (Pfeffer, Buller, Lidforss, Bruchmann); although there may be some response to light (Mast), there seems none to different concentrations of fluid (Buller). *Fertilizin* is the name given to a substance emitted by mature eggs (Lillie and others) which, if dilute, increases the activity of spermatozoa, but if strongly present, causes agglutination of their heads. It is no longer produced when the egg is fertilized. Complicated interactions between this and other products of egg and sperm have been described, and hypotheses concerning 'receptors' and 'antibodies' have been built up (Godlewski), but the possible bearing of these matters on the subject of the present work is so nebulous that they do not call for further notice here.

'Partial fertilization' is the name given by Boveri to cases in which the female pronucleus begins to divide before the male pronucleus joins with it, possibly owing to the aster reaching it before the chromatic substance. Division, necessarily with the haploid chromosome-number, may progress through two or three stages before the male pronucleus effects a junction with one of these blastomeres. There is no reason to suppose that this (seen in certain invertebrate eggs) may occur in human fertilization, but the bare possibility may turn out to have some theoretical pathological value.

Sex of the Embryo.—A third result of the act of fertilization is determination of the sex of the embryo. The nucleus of both the male and female germ cells carries, in addition to the ordinary chromosomes (autosomes), certain specialized, or sex, chromosomes. The female diploid number in the human is agreed to be forty-eight, and two of these are the X or sex chromosomes. When reduction occurs all ova will therefore have the haploid chromosome number of $23+X$. The diploid number for the male has been a matter of some dispute. According to von Winiwarter and Oguma (1930) it is forty-seven—that is, forty-six autosomes and one X-chromosome. The X-chromosome passes undivided to one of the daughter cells at reduction, with the

production therefore of two kinds of spermatozoa, the one carrying twenty-three and the other $23+X$ chromosomes. Now, when an ovum is fertilized by a spermatozoon carrying $23+X$ chromosomes the nuclear number becomes $46+2X$, and a female results. Fertilization by the other type of sperm gives a nuclear number of $46+X$, and the sex of the future individual is determined as male. However, as was indicated earlier in this chapter (p. 2), the male germ-cell more probably has a diploid number of forty-eight chromosomes, a small additional sex chromosome (the Y element) being found along with the X (Painter, 1923; Evans and Swezy, 1929). In this interpretation, half the spermatozoa produced will contain $23+X$ chromosomes, and if such a one fertilizes an ovum a female results. The remainder of the spermatozoa will contain $23+Y$ chromosomes, and union of one of these with an ovum gives a chromosome number of $46+X+Y$, and a male individual will develop. *The essential point in the matter is that the female always carries two X elements on the nucleus.*

The bias of prospective sex is therefore bestowed at fertilization, but there remain the questions of the action of *environment* and of *hormonal factors*. Experiments on certain animals have shown that the conditions of environment (temperature, moisture, nutrition, age of sex cells, etc.) exercise a decided influence on the sex of the individual. These experiments and observations have all been made, however, on lowly forms, or forms in which such factors might come more or less easily into operation in nature, but the environment of the human embryo in the uterus is so very much more fixed and constant that it is not considered to be significant in sex determination.

The influence of hormones upon sex determination would seem, however, to be of much greater importance. Their effects have been studied under both natural and experimental conditions. The best example of the former is the case of the freemartin, which is the sterile cow born with a normal bull fellow-twin. Lillie (1917) has shown that, in this condition, secondary anastomoses form in the uterus between the chorionic vessels of originally separate individuals, and the female comes under the influence of embryonic sex hormones elaborated by the earlier developed testis of the male twin. As a result, the ovaries are inhibited in their normal direction of growth and induced to form testis-like structures. Male sex ducts also develop, while the female internal genitalia are suppressed; the external genitalia are, however, of the female type. Thus the structure of a genetically female individual comes to resemble, in some particulars, that of the male, but the sex reversal is an incomplete one.

Hormonic influence has been investigated experimentally by applying sex hormones to the developing embryo. In the case of mammals effects have been produced on the secondary sex structures. Androgens given to female embryos have resulted in the development of male sex organs side by side with female ones, while oestrogens caused,