

Human Embryology

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SECOND EDITION

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Preface to the Second Edition

For its second edition, this book has been completely revised and largely re-written. Its change in title from 'Human Embryology and Genetics' to 'Human Embryology' reflects a considerable change in emphasis. Genetics is now normally taught as a separate course in most medical schools and there are many excellent text books suitable for undergraduates. This subject has, therefore, been largely deleted from the present volume although a basic account has been given in order to make intelligible the mode of inheritance of various congenital malformations and diseases. The other major change is that the embryological basis of congenital malformations has been covered in very much more detail than in the first edition and their clinical features are described and illustrated in the hope that the book will be of help to 'clinical' as well as 'preclinical' students. To this end, a clinician (D.P. Davies) has made a substantial contribution to the new edition, not only in respect of the pathology of the newborn baby but also of normal and abnormal growth and development.

It is our hope that this book will be an aid to the preclinical student in his study of this important subject and that it will dovetail helpfully with the later study of both obstetrics and paediatrics.

Inevitably, as in all books that attempt to cover a wide multidisciplinary field, the authors are deeply indebted to a number of friends and colleagues who have given valuable advice and assistance. We should like to mention particularly Professor J. MacVicar, Dr I. Young, Professor H.C. McGregor and Dr M.A. England.

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We wish to thank Miss Margaret Reeve for typing and checking our manuscript. Her commitment has enabled us to produce this edition more quickly than we had dared to hope. We are also grateful to Miss Catherine Hemington and Mrs Angela Chorley for preparing the new illustrations included in this edition.

A number of the new illustrations are drawings from original photographs or are diagrams that have appeared in books or journals. We would like to express our thanks to the authors and editors for permission to publish the following:

Fig. 9.11 supplied by Dr. Ian Young

Figs. 10.21-10.24 from *Congenital Abnormalities of the CNS* by P.M. Davidson & D.G. Young (*British Journal of Hospital Medicine*, 1981, 26, 222)

Fig. 17.9 from *Growth at Adolescence* by J.M. Tanner (Blackwell Scientific Publications, Oxford, 1962)

Fig. 17.11 from *Revised Standards for triceps and subscapular skin folds in British children* (*Archives of the Diseases of Childhood*, 1975, 50, 12)

Figs. 17.12, 17.13, 17.16 and 17.18 from *Foetus into Man* by J.M. Tanner (Open Books Publishing Ltd) (17.12 is slightly modified)

Fig. 17.14 from *Daily velocity, weight gain in infants over the first 5 months of life* by M. Fujimura & F. Seryce (*Archives of the Diseases of Childhood*, 1977, 52, 105)

Introduction — Aids to the Study of Embryology

To the student studying embryology for the first time, the development of the various organs seems complex and sometimes difficult to follow. The latter is true even for professional embryologists and some of the processes of development are still imperfectly understood.

However, there are a number of general principles involved, knowledge of which will help greatly in the assimilation of embryological facts and figures. We suggest, therefore, that you read the following account carefully and refresh your memory from time to time as you study the development of the various organs.

(a) Cranio-caudal developmental gradient

There is frequently a cranio-caudal gradient of development, i.e. the most cranial part of the embryo, of a system, or of an organ, develops first and the process of maturation proceeds caudally, the cranial end of the system sometimes degenerating while the caudal end is still at an early stage of development. This gradient can easily be seen in the whole embryo when the mesodermal somites are developing and becoming differentiated into vertebrae, muscles etc. (Chapter 9). At the cranial end of the series the cervical somites may already be giving rise to the precursors of the vertebral bodies and early muscle cells (myoblasts) may be recognised. At the same time, the most caudal somites are still small and incompletely developed.

The aortic arches (Chapter 12) are never all present at the same time so that the 'Christmas tree' diagrams that are sometimes seen showing all five arches are misleading. The aortic arches develop sequentially but by the time the third arch is beginning to appear, the first is already breaking up. Later, the fourth arch develops but by this time the first arch has disappeared (apart from a few remnants) and the second arch is degenerating. Finally the sixth arch appears and only arches 3, 4 and 6 remain to play a major part in the development of the great arteries.

(b) Postnatal continuation of development

It should always be remembered that many organs are still not completely developed by full term and birth should be regarded only as an incident in the whole

developmental process. Thus the lungs (Chapter 13) continue to develop new alveoli after birth and the kidneys (Chapter 14) develop new glomeruli and nephrons. The reproductive system, of course, does not complete its full development until puberty. The clinical importance of these observations will be referred to frequently in connection with the complications of prematurity.

(c) Development of organs lined by epithelium

The development of most organs and tissues that are covered by or lined by epithelium are very similar. To take the intestine as an example, it is first formed as a tube of endodermal cells. This is surrounded by *mesenchyme* (i.e., loose mesodermal tissue — the embryonic connective tissue) and it eventually pulls away from the dorsal body wall to form a mesentery. The endoderm differentiates to form the lining epithelium of the gut, with all its glands (see section (d)) while the surrounding mesenchyme becomes condensed and forms the smooth muscle, connective tissue and blood vessels of the gut wall. The surface layer of mesenchymal cells form a thin epithelium (a *mesothelium*) which is the visceral layer of peritoneum.

The ureter begins its life as a tube derived from mesoderm which is surrounded by mesenchyme. The mesoderm forms the transitional epithelium of the ureter, while the mesenchyme around it differentiates into smooth muscle, connective tissue and blood vessels.

(d) Development of glands

When, in the adult, a gland or organ A is connected to a lumen or a surface B, A almost always develops as one or more outgrowths from B, the number of outgrowths depending on the number of connecting ducts. Thus, the liver and gall bladder are connected to the duodenum (foregut) by the common bile duct and they develop as an outgrowth from the foregut. The outgrowth divides into two, one division forming the gall bladder and the other the common hepatic ducts, the bile duct system in the liver and the liver cells themselves.

The pancreas (usually) has two ducts — one main and one accessory — which connect it to the duodenum. The pancreas thus develops as two outgrowths from the foregut. The prostate is connected to the urethra by 15–20 ducts and it develops from 15–20 outgrowths from the embryonic urethra. Section (c) should also be applied to this form of development — in the case of the gall bladder, for instance, the endodermal outgrowth forms the columnar epithelium that lines the gall bladder, while the surrounding mesenchyme becomes condensed and forms the smooth muscle, connective tissue and blood vessels of the gall bladder wall.

Note however that there are a few exceptions to this general rule, the most important being the kidney and ureter. The collecting ducts, calices, pelvis and ureter develop from an outgrowth (the *ureteric bud*) not from the bladder but from

a part of the mesonephric duct which will later form the trigone. The nephrons themselves develop from quite a different source (p.251).

(e) Migration

Be careful when describing 'migrations' of organs, which are often more apparent than real. In order to define a movement in any direction one needs a fixed point to which the movement can be related, and there are no such fixed points in a rapidly developing embryo. Thus, it is convenient sometimes to refer to the 'descent' of the diaphragm from the neck region, thus explaining the long course of the phrenic nerve from C3, 4 and 5 down to the midriff. In fact, when the diaphragm begins to develop, the embryo does not have a neck or thorax, and the descent of the diaphragm is really due mostly to growth of the thorax and neck away from it. The embryo may, in fact, be said to be 'sticking its neck out'.

The descent of the testis, too, is largely due to the growth in length of the posterior abdominal wall, the testis remaining almost stationary.

One must, therefore, be careful not to think of embryonic events in terms of adult anatomy. Students often picture the testis as developing high in the embryonic abdomen and slithering gracefully down a long slide to end up in the scrotum, so accounting for the long testicular vessels. In fact the posterior abdominal wall in the embryo is so short that the testis spends the whole of its intra-abdominal life very close to the deep inguinal ring. It is also difficult to picture the development of a horseshoe kidney (p.270) until one realises that when the metanephros first develops, it is only a fraction of a millimetre away from the metanephros of the opposite side, so that fusion can occur quite easily.

(f) Temporary embryonic structures

Remember that many structures in the embryo have only a temporary existence and soon degenerate or remain as vestigial remnants which may give rise to cysts in later life. Often such temporary structures, however, have a second-hand value and they may be used for other purposes. In the male mesonephros, for instance, there is a cranio-caudal gradient of development; the cranial mesonephric tubules functioning as excretory organs and then degenerating, their function being taken over by ever more caudal tubules until, with the development of the metanephros, the mesonephros becomes non-functional. Some of the tubules remain as remnants near the epididymis and may become cystic in later life. Others remain and take on a new lease of life to form the ductuli efferentia.

There are many other such embryonic remnants in the adult. The thyroglossal duct (p.179), for example, may persist and give rise to thyroglossal cysts while the allantois, which normally degenerates in part to form the urachus, may persist *in toto* to produce a channel (*fistula*) from the bladder to the umbilicus, or, locally to produce a urachal cyst. Many other examples will be given in this book.

(g) Combined deformities

Congenital abnormalities tend to occur in 'clusters' rather than singly. Many of these combinations of deformities can be explained on embryological grounds. For example, since the differentiation of the local mesoderm to form nephrons depends upon the presence of an ureteric bud (p.251) it is obvious that an absent ureter must necessarily also mean the absence of a whole kidney. If both kidneys are absent or do not secrete the normal amount of urine, there will be a deficiency in the volume of amniotic fluid which, in turn, will result in the presence of other deformities such as Potter's syndrome (p.267).

In other cases, the connecting link is not so obvious but the deformities do form a well recognised pattern (*a syndrome*) and such groups of deformities often bear the name of the person who first described them. For example the combination of a ventricular septal defect, pulmonary stenosis, an overriding aorta and an enlarged right ventricle is called the *tetralogy of Fallot* (p.229) while *Marfan's syndrome* comprises abnormally long arms and fingers, defects of the arch of the aorta and other malformations of structures of mesodermal origin.

(h) Embryonic physiology

It should always be remembered that the embryonic organs and tissues may be carrying out important functions, even while they are developing and that you have to study developmental physiology as well as developmental anatomy. The embryonic heart, even in its earliest stage of development, is solely responsible for the circulation of the blood, including the fetal side of the placental circulation. The mesonephros is actively secreting a form of urine during its existence, and this is voided, making an important contribution to the amniotic fluid. Muscle contractions after the 5th month cause movements that can be felt by the mother, and these movements play an important role in the development of the synovial joints by modifying their shape. However, some organs in the embryo have a function different to that which they acquire later. The liver, for example, is an important haemopoietic organ during intra-uterine life, although it also produces bile which is responsible for the colour of the fetal faeces (*meconium*).

(i) Developmental age and developmental stages

Some variation exists in the rate at which individual human embryos and fetuses develop *in utero*. The post-fertilization age of a conceptus is, therefore, not an entirely accurate guide to its developmental stage and this should be borne in mind when consulting the sections on developmental stages given at the end of most chapters.

Some forty years ago G.L. Streeter, working at the Department of Embryology of the Carnegie Institution of Washington, used a very comprehensive collection of human embryonic material to construct a series of 'developmental horizons'. He described successive developmental stages in detail so that it became possible to

correlate the state of individual systems with accuracy. Since then 'Streeter's Horizons' have been the most widely used system for classifying stages of human development.

Developmental horizons

Developmental Horizons in Human Embryos, description of age group XI, 13–20 somites and age group XII, 21–29 somites, G.L. Streeter, *Contr. Embryol. Carnegie Inst.* 30, 211, 1942.

Developmental Horizons in Human Embryos, description of age group XIII, embryos about 4 or 5 mm long and age group XIV period of indentation of lens vesicle, G.L. Streeter, *Contr. Embryol. Carnegie Inst.* 31, 27, (1945).

Developmental Horizons in Human Embryos, description of age groups XV. Being the 3rd issue of a survey of the Carnegie collection. XVI, XVII and XVIII, G.L. Streeter, *Contr. Embryol. Carnegie Inst.* 32, 133, (1948).

Developmental Horizons in Human Embryos, description of age groups XIX, XX, XXI, XXII and XXIII. Being the 5th issue of a survey of the Carnegie collection, G.L. Streeter, *Contr. Embryol. Carnegie Inst.* 34, 165, (1951).

Note: Developmental horizons I to X are not separately described. I = One cell egg. II = Segmenting egg. III = Free blastocyst. IV = Implanting ovum. V = Ovum implanted but still avillous. VI = Development of primitive villi and a distinct yolk-sac. VII = Branching villi, axis of germ disc defined. VIII = Development of Hensen's node and primitive groove. IX = Stage of neural folds and elongated notochord. X = Early somites present.

Recently O'Rahilly has updated the staging of human embryos and included in his work much new material derived after Streeter's original publications. The table on p.xi is taken from his important review article in *Eur. J. Obstet. Gynec. Reprod. Biol.* (1979) 9, 273–80.

(i) Developmental age and developmental stages

Some variation exists in the way in which individual human embryos and fetuses develop in utero. The post-fertilization age of a conceptus is, therefore, not an entirely accurate guide to its developmental stage and this should be borne in mind when consulting the sections on developmental stages given at the end of most chapters.

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Table I Developmental stages in human embryos. Early human development and the chief sources of information on staged human embryos. Courtesy of Professor R. O'Rahilly and the Carnegie Institution of Washington.

Carnegie stage	Pairs of somites	Length (mm)	Age (days) ¹	Age (days) ²	Features
1				1	Fertilization.
2			1.5-3	2-3	From 2 to about 16 cells.
3			4	4-5	Free blastocyst.
4			5-6	5-6	Attaching blastocyst.
5		0.1-0.2	7-12	7-12	Implanted although previllous.
5a		0.1	7-8		Solid trophoblast.
5b		0.1	9		Trophoblastic lacunae.
5c		0.15-0.2	11-12		Lacunar vascular circle.
6		0.2	13	13-15	Chorionic villi; primitive streak may appear.
6a					Chorionic villi.
6b					Primitive streak.
7		0.4	16	15-17	Notochordal process.
8		1.0-1.5	18	17-19	Primitive pit; notochordal and neurenteric canals.
9	1-3	1.5-2.5	20	19-21	Somites first appear.
10	4-12	2-3.5	22	22-23	Neural folds begin to fuse; 2 pharyngeal bars; optic sulcus.
11	13-20	2.5-4.5	24	23-26	Rostral neuropore closes; optic vesicle.
12	21-29	3-5	26	26-30	Caudal neuropore closes; 3 pharyngeal bars; upper limb buds appearing.
13	30-?	4-6	28	28-32	Four limb buds; lens disc; otic vesicle.
14		5-7	32	31-35	Lens pit and optic cup; endolymphatic appendage distinct.
15		7-9	33	35-38	Lens vesicle; nasal pit; antitragus beginning; hand plate; trunk relatively wider; cerebral vesicles distinct.
16		8-11	37	37-42	Nasal pit faces ventrally; retinal pigment visible in intact embryo; auricular hillocks beginning; foot plate.
17		11-14	41	42-44	Head relatively larger; trunk straighter; nasofrontal groove distinct; auricular hillocks distinct; finger rays.
18		13-17	44	44-48	Body more cuboidal; elbow region and toe rays appearing; eyelids beginning; tip of nose distinct; nipples appear; ossification may begin.
19		16-18	47.5	48-51	Trunk elongating and straightening.
20		18-22	50.5	51-53	Upper limbs longer and bent at elbows.
21		22-24	52	53-54	Fingers longer; hands approach each other, feet likewise.
22		23-28	54	54-56	Eyelids and external ear more developed.
23		27-31	56.5	56-60	Head more rounded; limbs longer and more developed.

¹ Olivier, G. & Pineau, H. (1962) *C.R. Ass. Anat.* 47, 573-576 for stages 11-23; miscellaneous for stages 1-10.

² Jirásek, J.E. (1971) *Development of the genital system and male pseudohermaphroditism*. Johns Hopkins Press, Baltimore.

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1

Mitosis and Meiosis

The basic concept of the cell as the fundamental unit of biological structure stems from the work of Schleiden and Schwann who, in 1838, proposed that organisms are made up entirely of smaller units or cells and their products. In just over a century this idea has become commonplace and its extraordinary impact all but forgotten. Without it we could not begin to think of development in a meaningful way, but largely as a result of it we are able to divide embryological processes into three essential and to some extent interrelated processes. The first of these is *growth* which involves cell growth, cell division and the elaboration of extra-cellular materials. Conceptually this may be separated from *morphogenesis* which includes mass cell movements, allowing new cells to inter-react with each other as well as with extra-cellular structures such as basement membranes and results in the formation of discrete organs. *Differentiation* from the single fertilized egg to a multiplicity of adult cells and tissues performing specialized functions provides the third fundamental of development. Although these ideas will be further elaborated at various points in this book they should be borne in mind wherever any ontogenic process is being considered.

During embryogenesis a dividing cell must pass on its total genetic potential (or *genome*) to each of its daughter cells. It is true that differentiation implies that only restricted portions of the genome are allowed to function in each cell type but the balance of evidence points to the fact that the whole of the genome is represented in each nucleated cell.

In all but the simplest cells such as bacteria, the genetic material is contained (with some exceptions not pertinent to this argument) in a specialized cell nucleus in which it is present in organized structures known as *chromosomes*. The latter contain information in the form of a code which the cellular synthetic machinery can decipher to form its specific protein constituents and secretions. Biologists call each unit of information a *gene* and biochemists prefer to use the term *cistron*. Genes are arranged in a linear fashion along the length of chromosomes. Between divisions (the so-called *interphase*) the cell is concerned with making protein under the direction of its genes and its chromosomes are extremely elongated so that no known method of staining is able to demonstrate them individually. In growing tissues a cell, when it reaches an optimal size, undergoes division during which morphologically discrete chromosomes appear and divide longitudinally so that a full complement of new chromosomes (representing the whole genome)

passes to each daughter cell. This process is known as *mitosis*.

The cell cycle

In some adult organs certain differentiated cells such as nerve cells *never* divide. Other organs in the same individual contain cells such as those of the liver parenchyma which divide only occasionally. This occurs when an extra functional load is put upon the liver so that its individual cells have either got to multiply or would have to increase their cytoplasmic mass to a point at which the nucleo-cytoplasmic ratio is such that they could not function optimally. A third category of cells continue to divide throughout life — for example, relatively undifferentiated cells in the skin, gut lining, nails, hair etc. are continually dividing to make good the mechanical wear and tear to which the structure is subject.

The interval between one cell division and the next in continually dividing cells is known as the cell cycle (Fig. 1.1). It consists of a G1 phase immediately following mitosis and characterised by active protein synthesis. This is followed by an S phase during which the DNA of the cell nucleus replicates but protein synthesis still continues; finally, another short phase of protein synthesis G2 is terminated by the onset of the next mitosis. Most adult cells, however, are not continually dividing and may remain for many weeks in interphase. Sometime during this period the cell may enter a transition phase which ends with a division signal so that after a lag period the doubling of its DNA content (at the S phase) begins. In embryonic tissues many (perhaps most) of the undifferentiated cells progress immediately from one cell cycle into the next. Sooner or later some

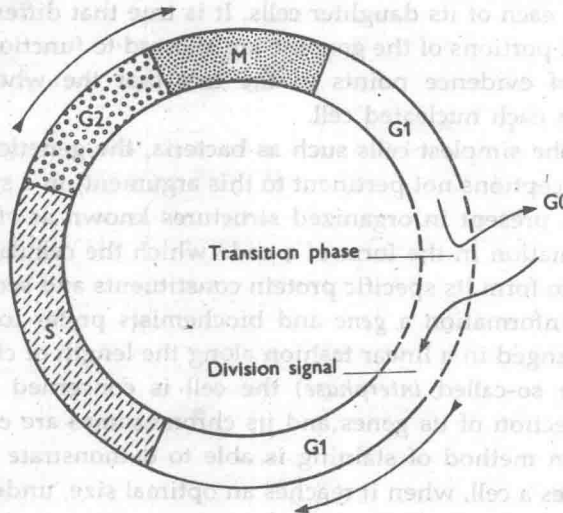


Fig. 1.1. Diagram to illustrate the cell cycle. See text for description.

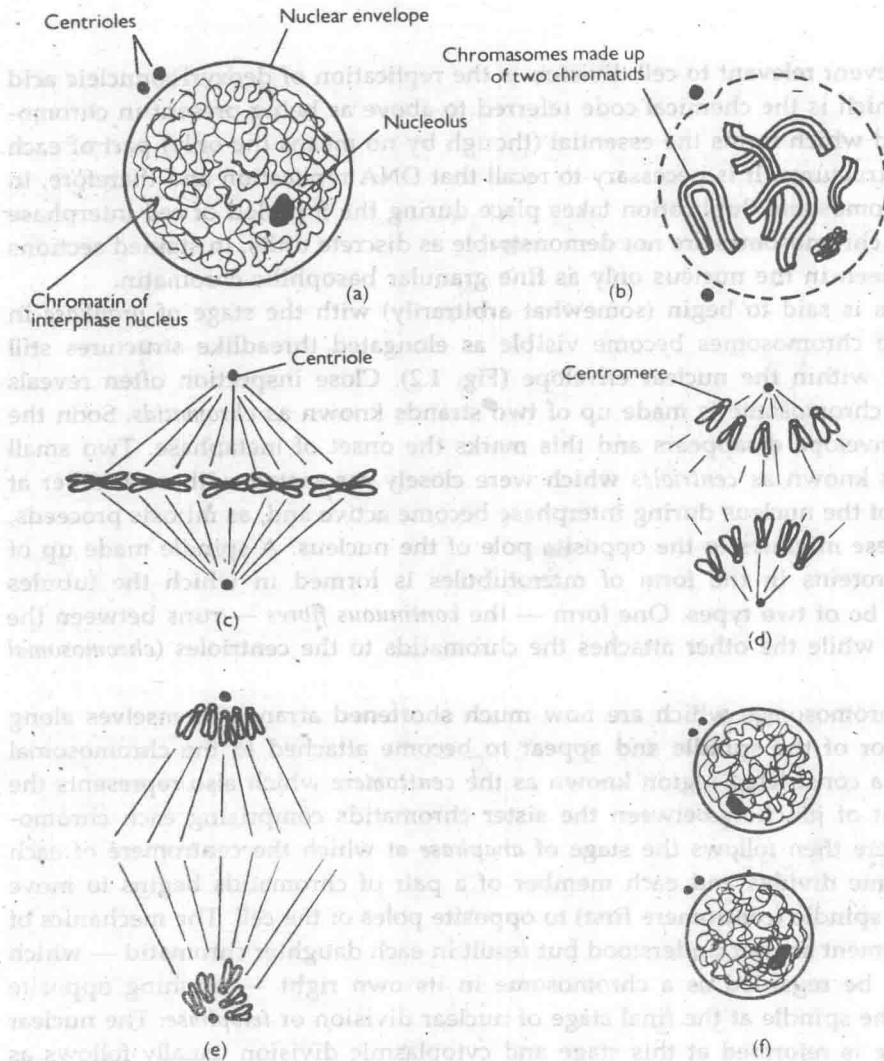


Fig. 1.2. The nucleus in mitosis:

- (a) Interphase.
- (b) Prophase.
- (c) Metaphase.

- (d) Anaphase.
- (e) Telophase.
- (f) Reconstitution of interphase nuclei.

of their progeny will cease to divide continually. At this stage they gradually take on specific tissue characteristics and are said to *differentiate* (Chapter 19). Some authors describe these cells as having passed into a so-called 'G0' stage of interphase. It should be remembered, however, that they can — as in the case of the adult liver — re-enter the division cycle if subjected to the appropriate division signal.

Mitosis

The first event relevant to cell division is the replication of deoxyribonucleic acid (DNA) which is the chemical code referred to above as being present in chromosomes and which forms the essential (though by no means the only) part of each of these structures. It is necessary to recall that DNA replication and therefore, in effect, chromosome duplication takes place during the S period of cell interphase when the chromosomes are not demonstrable as discrete units. In stained sections they are seen in the nucleus only as fine granular basophilic chromatin.

Mitosis is said to begin (somewhat arbitrarily) with the stage of *prophase* in which the chromosomes become visible as elongated threadlike structures still contained within the nuclear envelope (Fig. 1.2). Close inspection often reveals that each chromosome is made up of two strands known as *chromatids*. Soon the nuclear envelope disappears and this marks the onset of metaphase. Two small organelles known as *centrioles* which were closely associated with each other at one side of the nucleus during interphase become active and, as mitosis proceeds, one of these migrates to the opposite pole of the nucleus. A spindle made up of fibrous proteins in the form of microtubules is formed in which the tubules appear to be of two types. One form — the *continuous fibres* — runs between the centrioles while the other attaches the chromatids to the centrioles (*chromosomal fibres*).

The chromosomes which are now much shortened arrange themselves along the equator of the spindle and appear to become attached to the chromosomal fibres by a constricted region known as the *centromere* which also represents the only point of junction between the sister chromatids comprising each chromosome. There then follows the stage of *anaphase* at which the centromere of each chromosome divides and each member of a pair of chromatids begins to move along the spindle (centromere first) to opposite poles of the cell. The mechanics of this movement are not understood but result in each daughter chromatid — which may now be regarded as a chromosome in its own right — reaching opposite poles of the spindle at the final stage of nuclear division or *telophase*. The nuclear membrane is reformed at this stage and cytoplasmic division usually follows as the result (in animal cells) of a constriction of the cell membrane. The centriole associated with each of the two new nuclei now divides and the condensed chromosomes once again become the attenuated structures characteristic of interphase. Mitosis is diagrammatically represented in Fig. 1.2.

The normal human karyotype

Until 1956 it was believed that man had 48 chromosomes but in that year Tjio and Levan, using improved techniques, were able to demonstrate conclusively that the true number was 46. A variety of methods is now available for studying the human chromosome constitution of *karyotype* (*vide infra*) but all of these rely

upon a number of common principles. First of all it is necessary to study a tissue in which a large number of cells are in mitosis and to this end the drugs colchicine or colcemid are usually added to cell cultures of the tissue because of their ability to arrest cell division at metaphase. It is thus possible to make preparations of a variety of tissues in which mitotic figures are very numerous. Secondly, the introduction of a chemical known as phytohaemagglutinin (and more recently a number of related compounds) has made it possible to perform much of this work on blood cultures. Phytohaemagglutinin has the dual effect of agglutinating red blood cells and stimulating cell division in the lymphocyte series of white cells; it is thus possible to karyotype individuals without resorting to cultures of red marrow obtained from sternal puncture, or of biopsies of skin unless the particular cells in these body regions are of interest.

Finally, treatment of cells in metaphase arrest with hypotonic solutions causes them to swell and by dropping them onto a wet slide followed by air drying, the chromosomes are spread by a quasi-explosive action, their resulting separation allowing individual morphological assessment. The usual practice is to photograph such a preparation (*the metaphase plate*) stained with a specific chromosome stain (Fig. 1.3) under oil immersion, to prepare a montage of the individual chromosomes by placing them in homologous pairs according to their morphological characteristics and to assign each pair a number; this arrangement is called the karyotype. A widely accepted grouping of the chromosome pairs into seven groups A–G (each member of which, it will be remembered, is seen at metaphase as two chromatids joined by the primary constriction or centromere) now exists (Table 1.1). The groups of chromosomes are distinguished depending upon the position of the centromere which may be *median* (*metacentric*), *submedian* (*submetacentric*) or *subterminal* (*acrocentric*); chromosome size is also taken into

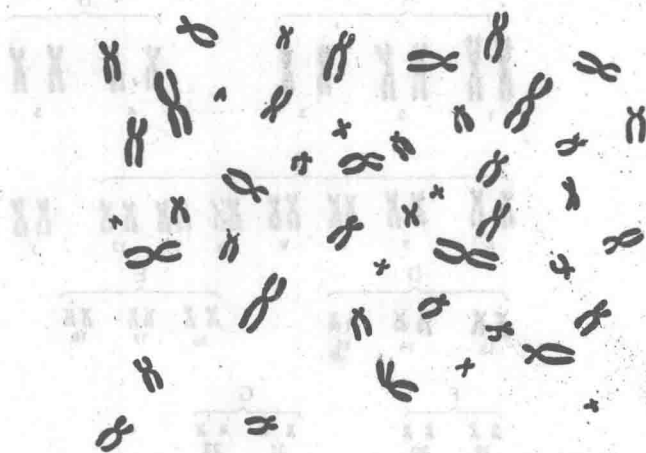


Fig. 1.3. The cell chromosomes prepared for karyotyping (a so-called *metaphase plate* preparation).