

Underwood: Chapter 3: Disorders of Growth, Differentiation and Morphogenesis

The processes of *growth*, *differentiation*, and *morphogenesis* are the means by which a single cell, the fertilised ovum, develops into a large complex multicellular organism, with coordinated organ systems containing a variety of cell types, each with its own individual specialised function. Growth and differentiation continue throughout adult life, as many cells of the body undergo a constant cycle of death, replacement and growth in response to normal (physiological) or abnormal (pathological) stimuli.

Growth

Growth is the process of increase in size and mass resulting from the synthesis of specific tissue components.

Types of growth in a tissue are:

- *Multiplicative*, involving an increase in numbers of cells (or nuclei and associated cytoplasm in syncytia) by mitotic cell divisions. This type of growth is present in all tissues at some stage of development.
- *Auxetic*, resulting from increased size of individual cells, as seen in growing skeletal muscle.
- *Accretionary*, an increase in intercellular tissue components between cells, as in bone and cartilage.
- *Combined patterns* of Multiplicative, auxetic and accretionary growth as seen in embryological development, where there are differing directions and rates of growth at different sites of the developing embryo, in association with changing patterns of cellular differentiation.

Differentiation

Differentiation is the process whereby a cell develops an overt specialised function or morphology which distinguishes it from its parent cell. Thus, differentiation is the process by which genes are selectively expressed and gene products act to produce a cell with a specialised function. After fertilisation of the ovum, and up to the eight-cell stage of development, all of the embryonic cells are apparently identical. Thereafter, cells undergo several stages of differentiation in their passage to fully differentiated cells.

Morphogenesis

- Complex process of embryological development
- Responsible for formation of shape and organisation of body organs
- Involves cell growth and differentiation, and movement of cell groups
- Programmed cell death (apoptosis) removes unwanted features.

Morphogenesis is the term used to describe the highly complex process of development of structural shape and form of organs, limbs, facial features, etc. For morphogenesis to occur, primitive cell masses must undergo a coordinated process of growth and differentiation, with relative movement of some cell groups with respect to others, and focal programmed cell death to remove unwanted features.

Cell Turnover

In both fetal and adult life, tissue growth depends upon the balance between the increase in cell numbers, due to cell proliferation, and the decrease in cell numbers due to cell death.

In fetal life, growth is rapid and all cell types proliferate, but even in the fetus there is constant cell death, some of which is an important (and genetically programmed) component of morphogenesis.

Regeneration

- Process of replacing injured or dead cells
- Cell types vary in regenerative ability
- Labile cells: very high regenerative ability and rate of turnover (i.e., intestinal epithelium)
- Stable cells: good regenerative ability but low rate of turnover (i.e., hepatocytes)
- Permanent cells: no regenerative ability (i.e., neurones).

The Cell Cycle

Unlike the synthesis of most cellular constituents, which occurs throughout the interphase period between cell divisions, DNA synthesis only takes place during a limited period of the interphase; this is denoted the *S phase* of the cell cycle. A further distinct phase of the cycle is the cell-division stage or *M phase* comprising nuclear division (mitosis) and cytoplasmic division (cytokinesis). Following the M phase, the cell enters the *first gap* (G_1) phase and, via the S phase, the *second gap* G_2 phase before entering the M phase again.

Cell cycle times (generation times) range from as little as eight hours, in the case of gut epithelial cells, to 100 days or more exemplified by hepatocytes in the normal adult liver. The principal difference between rapidly dividing cells and those which divide slowly is the time spent in the G_1 phase of the cell cycle; some cells remain in that phase for days or even years. In contrast, the time taken for a cell to progress through the S, G_2 and M phases of the cell cycle is remarkably constant, and independent of the rate of cell division.

Some cells (i.e., some of the stable cells) may 'escape' from the G_1 phase of the cell cycle by temporarily entering a G_0 'resting' phase; others 'escape' permanently to G_0 by a

process of terminal differentiation, with loss of potential for further division and death at the end of the lifetime of the cell; this occurs in permanent cells, such as neurones.

Cell Death in Growth and Morphogenesis: Apoptosis

Apoptosis is a biochemically specific mode of cell death characterised by activation of non-lysosomal endogenous endonuclease which digests nuclear DNA into smaller DNA fragments. Morphologically, apoptosis is recognised as death of scattered single cells which form rounded, membrane-bound bodies; these are eventually phagocytosed (ingested) and broken down by adjacent unaffected cells.

In embryological development, there are three conceptual categories of individual cell death, although these overlap and all are mediated by apoptosis: morphogenetic, histogenetic and phylogenetic apoptosis.

Morphogenetic apoptosis is involved in alteration of tissue form. Examples include:

- the interdigital cell death responsible for separating fingers
- the cell death leading to removal of redundant epithelium following fusion of the palatine processes
- the cell death in the dorsal part of the neural tube during closure, required to achieve continuity of the epithelium, the two sides of the neural tube and the associated mesoderm.

failure of morphogenetic apoptosis in these three sites is a factor in the development of syndactyly, cleft palate and spina bifida, respectively.

Histogenetic apoptosis occurs in the differentiation of tissues and organs, as seen, for example, in the hormonally-controlled differentiation of the accessory reproductive structures from the Mullerian and Wolffian ducts. In the male, for instance, anti-Mullerian hormone produced by the Sertoli cell of the fetal testis causes regression of the Mullerian ducts (which in females form the fallopian tubes, uterus and upper vagina) by the process of apoptosis.

Phylogenetic apoptosis is involved in removing vestigial structures from the embryo; structures such as the pronephros, a remnant from a much lower evolutionary level, are removed by the process of apoptosis.

Systemic Growth and Its Disorders

The most rapid normal growth occurs during fetal life, when the embryo undergoes the equivalent of some 42 cell divisions in progressing from a fertilised ovum to term (40 weeks), with only five more cell division needed to achieve adult size. In the first 2 months of embryological life, differing rates of growth, death and migration of cells are responsible for morphogenesis within the developing fetus. Maximal growth velocity, however, does not occur until about 20 weeks' gestation (for body length) and 34 weeks (for body weight); growth velocity then slows until term, as maternal factors such as the size of the uterus confine the fetus.

In childhood, girls are typically shorter than boys, but they become temporarily taller than boys as a result of their prepubertal growth spurt (9 cm/year), which starts at around 10.5 years of age. The boys' growth spurt starts at about 12.5 years, but the higher growth velocity (10.2 cm/year) results in their overtaking the girls in height at about 14 years, and accounts for the final height advantage in boys.

Endocrinological Growth Control and Its Disorders

Cells may be stimulated into growth by the action of both hormones and growth factors.

Individual hormones and growth factors require highly specific cellular receptors to mediate their actions on target cells. Steroid hormone receptors are intracellular, but receptors for peptide hormones and growth factors are located on the cell membrane.

Postnatal Growth

Growth hormone (GH) is central to the endocrine control of postnatal growth.

The release of GH from the pituitary is regulated by the opposing actions of hypothalamic growth hormone releasing factor (GRF) and the inhibitory hormone somatostatin. GH does not itself stimulate growth, but acts via the intermediary hormones - the somatomedins, insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II); these are predominantly (but not exclusively) synthesised in the liver. Somatomedins may also be released from the liver under the influence of insulin, sex-steroid hormones, thyroid hormone and nutritional factors. GH may have a minor direct anabolic effect on non-skeletal tissues, but here too IGH-I and IGF-II are quantitatively more important.

Reduced Growth

Reduced GH production due to hypopituitarism (of whatever pathological cause) in childhood leads to dwarfism which can be corrected by regular GH injections given before puberty arrests skeletal growth by epiphyseal fusion. It is characterised by normal body proportions in contrast to the effects of reduced thyroid hormones.

Reduced GH receptors are a feature of the rare Laron dwarfism. The liver is insensitive to GH, and circulating somatomedins are greatly reduced.

Reduced thyroid hormone secretion causes a reduction in hepatic IGF-I secretion. The head is of normal size but the limbs are stunted because bone ossification is reduced. Thyroxine administration is corrective if given before puberty.

Block between GH and IGF-I release may occur in malnutrition or emotionally-based growth retardation, although the metabolite-mobilising actions of GH are maintained. IGF-I levels correlate positively with the protein content of the diet and nitrogen balance.

Inhibition of growth by corticosteroids may occur with endogenous corticosteroids, i.e., Cushing's disease, or with exogenous corticosteroids used, for example, in the treatment of asthma or leukaemia.

Increased Growth

Increased GH secretion from a normal pituitary or a pituitary tumour results in increased IGF-I and increased growth. Before puberty this causes gigantism; after puberty, longitudinal skeletal growth cannot occur (due to maturation and ossification with resulting epiphyseal fusion), but the hands, feet and head increase in size to produce acromegaly.

Increased sex-steroid hormone secretion in childhood may lead to precocious puberty, with an initial increase in height resulting from a premature rise in pubertal IGF-I levels. However, epiphyseal fusion in long bones is advanced, and the final height may be *below* normal.

Embryo and Fetal Growth

The mechanisms of endocrinological growth control in the first few weeks of embryological life are as yet unknown, although it is likely that autocrine and paracrine actions of growth factors are involved.

The fetus is a self-contained unit with respect to growth, as maternal peptide and thyroid hormones do not cross the placenta in physiologically significant concentrations and, although sex-steroid hormones and other steroids do cross the placenta, they are generally metabolised into inactive forms.

The fetus produces its own growth hormone, but this is not used to promote growth as the GH receptor is greatly reduced in the fetus (particularly in the liver). Fetal growth does not require a pituitary, a hypothalamus or even a head, and anencephalic human fetuses often attain normal weights for gestational age.

Although fetal growth is not GH-mediated, somatomedins (particularly IGF-II in the fetus) are important, although they are not yet under GH control. Other growth factors, such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-beta) and nerve growth factor (NGF), to name but a few, are probably also involved.

The most important growth-regulating hormone in the fetus is, without doubt, insulin. As in the adult, blood insulin concentrations in the fetus are controlled by glucose concentrations, and both insulin and glucose are required for normal metabolic functions of the fetus and the placenta. In addition, however, insulin directly stimulates the production of growth factors (in particular the somatomedin, IGF-II) in cells, and these act on the IGF-II-synthesising cells and adjacent cells, by autocrine and paracrine mechanisms respectively, to stimulate growth. Additional, but relatively less important, effects on growth factor synthesis are stimulated by human placental lactogen (HPL) - a hormone which has marked structural similarity to GH, and is synthesised by the placenta - and fetal thyroid hormones.

Birthweight

Many factors may affect fetal growth rate and ultimate size. It should be noted that while insulin levels are crucial, the most common causes of low birthweight are premature delivery (before 40 weeks' gestation) and genetically controlled small size (a small baby born to small parents). It is therefore important to relate the birthweight to gestational age and parental size.

Reduced Growth

Reduced fetal insulin production may lead to a reduction in fetal size at birth, i.e., birthweight 1.2-2 kg (normal mean 3 kg). The causes are uncommon, and include:

- pancreatic agenesis (failure of development)
- fetal diabetes mellitus

Reduced fetal insulin receptors, with resultant insensitivity to circulating insulin, causes a similar growth reduction (Leprechaun syndrome).

Increased Growth

Increased growth may be seen in conditions involving increased circulating insulin levels in the fetus (hyperinsulinaemia).

Diabetic mothers may have infants of increased birthweights, although birth lengths are not usually increased. Increased glucose diffuses passively into the fetus from the mother, stimulating fetal insulin secretion. The increased weight is largely attributable to excess fat.

Infants with hyperinsulinaemia associated with the rare condition *nesidioblastosis* (an uncontrolled proliferation of pancreatic endocrine cells) or Beckwith-Weidemann syndrome are more obviously overgrown, i.e., birthweight 4.5-5.5 kg.

Genetic Factors in Growth Control

- parental height, probably mediated by multifactorial genetically controlled endocrinological factors
- the sex of the individual, mediated by sex-steroid hormones.

Proportionate Alterations of Skeletal Growth

Autosomal Chromosomes

Proportionate alterations of skeletal growth may result from abnormalities of chromosomes 1-22:

- *Pygmies*: genetically-mediated inability to make the somatomedin IGF-I (chromosome 12)

- *Down's syndrome (Mongolism)*: short stature associated with trisomy 21 (extra 21 chromosome)

- *Beckwith-Weidemann syndrome*: increased growth due to a rare duplication of the short arm of chromosome 11 (carrying the genes for insulin and the somatomedin IGF-II).

Sex Chromosomes

- *Turner's syndrome*: females have an XO rather than XX genotype. In its most extreme form, girls have no ovaries, and lack of oestrogens prevents a normal pubertal growth spurt.

- *Pseudohypoparathyroidism*: a very rare X-linked dominant condition characterised by tissue insensitivity to parathyroid hormone (PTH), probably due to reduced or absent PTH-receptors.

Disproportionate Alterations of Skeletal Growth

Disproportionate shortness of stature at birth is often the result of the genetically-mediated *osteochondrodysplasias* (specific disorders of growth of bone and/or cartilage). These can be classified into two groups, depending upon whether the disproportionate shortness of limbs is, or is not, accompanied by a significantly shortened spine.

Achondroplasia

It is the most common of the osteochondrodysplasias. It is an autosomal dominant condition (although there are many sporadic cases). The genetically-mediated defect is considered to be a primary disturbance of endochondral ossification which occurs early in life and is well established by birth (although severely affected fetuses may die towards the end of pregnancy). Achondroplastics, if they survive the neonatal period, usually reach adult life but with reduced stature. Mildly affected cases are usually of normal intelligence, but this may be reduced in more severe cases.

They have variably severe shortening of the limbs (hypomelia or micromelia), with long bones as little as half the normal length. Epiphyses are greatly enlarged, and the shafts of long bones widen to surround the enlarged epiphyses at the ends of long bones. Accompanying changes in the base of the skull may cause narrowing of the foramen magnum, with spinal cord compression. The spine itself is not shortened.

Rare Osteochondrodysplasias

Many, but not all, have an autosomal recessive mode of inheritance. They include achondrogenesis, which is incompatible with life, pseudoachondroplasia, where the spine is shortened in addition to the limbs.

Nutritional Factors in Growth Control

Fetal growth. Maternal nutrition, surprisingly, has a very small influence on human fetal size, and even severe food deprivation results in little more than a 200-300 g reduction in birthweight (normal mean 3 kg).

The fetus is, however, highly susceptible to diffuse placental disorders such as infection or to partial detachment, both of which reduce both the fetal intake of nutrients and reduce gas exchange; the result, if not fatal, may be a severe reduction in birthweight.

In *postnatal life*, growth may be severely affected by low or poorly-balanced nutritional intake.

Environmental Factors in Growth Control

Fetal growth can be affected by several physiological and pathological environmental factors:

- *Uterine size.* Clinical observations of humans suggest that the uterine effect on fetal growth occurs late in gestation, and does not affect the fetus during early pregnancy.

- *Altitude.* Infants born at an altitude of 15000 feet have a birthweight 16% less than infants born at 500 feet; this is due to decreased intra-uterine oxygen availability.

- *Maternal smoking.* The effect of smoking 20 cigarettes per day is to reduce birthweight by about 200 g (about 7%), probably by reducing uterine blood flow.

- *Maternal alcohol abuse.* This retards fetal growth, and catch-up growth does not occur. Fetuses may be microcephalic, with hypotonia and mental retardation. Cardiac atrial septal defects are common, and there may be altered facies. This is the 'fetal-alcohol syndrome'.

- *Maternal drug abuse.* About half of the fetuses exposed to heroin have a low birthweight. The newborn infants often develop withdrawal symptoms.

- *Postnatal environmental growth effects* can be seen in children from unstable home backgrounds.

Effect of Intercurrent Disease on Growth

Normal and Abnormal Growth in Single Tissues

Increased Growth: Hypertrophy and Hyperplasia

- Hyperplasia and hypertrophy are common tissue responses

- May be physiological (i.e., breast enlargement in pregnancy) or pathological (i.e., prostatic enlargement in elderly men)
- Hypertrophy: increase in cell size without cell division
- Hyperplasia: increase in cell number by mitosis.

Physiological Hypertrophy and Hyperplasia

- *Muscle hypertrophy*
- *Hyperplasia of bone marrow cells.* Erythropoietin stimulates production of red blood cells at high altitude.
- *Hyperplasia of breast tissue* under the influence of oestrogens, progesterone, prolactin, GH and human placental lactogen.
- *Hypertrophy and hyperplasia of uterine smooth muscle* stimulated by oestrogens.
- *Thyroid hyperplasia.*

Repair and Regeneration

The proliferation of myofibroblasts in scar tissue and the regeneration of specialised cells within a tissue are the important components of the responses to tissue damage at various sites.

The Skin

The healing of a skin wound is a complex process involving the removal of necrotic debris from the wound and repair of the defect by hyperplasia of capillaries, myofibroblasts and epithelial cells.

When tissue injury occurs there is haemorrhage into the defect from damaged blood vessels; this is controlled by normal haemostatic mechanisms, during which platelets aggregate and thrombus forms to plug the defect in the vessel wall. Because of the interactions between the coagulation and complement systems, inflammatory cells are attracted to the site of injury by chemotactic complement fractions. In addition, platelets release two potent growth factors, platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-beta), which are powerfully chemotactic for inflammatory cells, including macrophages.

In the *epidermis*, PDGF acts synergistically with epidermal growth factor (EGF) and the somatomedins (IGF-I and IGF-II) to promote the progression of basal epithelial cells through the cycle of cell proliferation. PDGF acts as a 'competence factor' to move cells from their 'resting' phase in G_0 to G_1 . EGF and IGFs then act sequentially in cell progression from the G_1 phase to that of DNA synthesis. Thereafter, the cells is growth-factor-independent. In

the epidermis, EGF is derived from epidermal cells (autocrine and paracrine mechanisms), and is also present in high concentrations in saliva when the wound is licked. IGFs originate from the circulation (endocrine mechanisms) and from the proliferating cell and adjacent epidermal and dermal cells (autocrine and paracrine mechanisms).

In the *dermis*, myofibroblasts proliferate in response to PDGF (and TGF-beta); collagen and fibronectin secretion is stimulated by TGF-beta, and fibronectin then aids migration of epithelial and dermal cells.

Capillary budding and proliferation are probably stimulated by the presence of angiogenic growth factor. The capillaries ease the access of inflammatory cells and fibroblasts, particularly into large areas of necrotic tissue.

The presence of other hormones (i.e., insulin and thyroid hormones) and nutrients (i.e., glucose and amino acids) is also required. Lack of nutrients or vitamins, the presence of inhibitory factors such as corticosteroids or infection, or a locally poor circulation with low tissue oxygen concentrations, may all materially delay wound healing; these factors are very important in clinical practice.

The Liver

In severe autoimmune hepatitis or chronic hepatitis due to alcohol abuse or hepatitis B infection extensive hepatocyte loss is followed (if the patient survives the liver failure) by scarring, as is the case in the skin of other damaged tissues. Hepatocytes, like the skin epidermal cells, have massive regenerative potential, and surviving hepatocytes may proliferate to form nodules. Hyperplasia of hepatocytes and fibroblasts is presumably mediated by a combination of hormones and growth factors, although the mechanisms are far from clear. The combination of regenerative nodules of hyperplastic hepatocytes and scar tissue form the components of cirrhosis of the liver.

The Heart

Myocardial cells are permanent cells. Hyperplastic myofibroblast scar tissue replaces the dead myocardial tissue.

Non-Regenerative Hypertrophy and Hyperplasia

The Heart

The heart may have a hypertrophied left or right ventricle as a result of increased functional demand.

Arterial Smooth Muscle

It is hypertrophied in systemic hypertension.

Capillary Hyperplasia

This is a particular problem in the eyes of patients with diabetes mellitus, where it is a component of the relatively common proliferative retinopathy. The retina may be covered by an opaque layer of capillaries and fibrous tissue, and fragile capillaries may extend into the vitreous, where they may cause massive haemorrhage.

Bone Marrow Hyperplasia

Cytotoxic T-lymphocytes Hyperplasia

This form of hyperplasia occurs in the presence of antigens and in an important component of the cell-mediated immune reaction to antigens. In this system the earliest event is the presentation of the antigen, by an antigen-presenting cell (APC), of macrophage lineage, to cytotoxic T-cells and T-helper cells, both of which have specific receptors for the antigen. As a result of the interaction between lymphocytes, antigen and APC, the APC produces the cytokine (a leucocyte growth or differentiation factor) interleukin-1 (IL-1). The paracrine effect of IL-1 on cytotoxic T-cells and T-helper cells is different; IL-1 causes cytotoxic T-cells to produce a membrane interleukin-2 (IL-2) *receptor* whilst T-helper cells produce IL-2 itself. In the final stage, IL-2 from T-helper cells reacts with IL-2 receptor on the cytotoxic T-cell, stimulating it to divide. Thus, functionally intact antigen-presenting cells and T-helper cells are required for cytotoxic T-cell hyperplasia.

Breast Hyperplasia

In females, pathological breast hyperplasia may develop soon after puberty (or occasionally pregnancy). There is an increase in connective tissue, but no real increase in glandular tissue. Usually both breasts enlarge (although unilateral enlargement does occur), and they may weigh several kilograms. Increased circulating oestrogens or increased receptor-mediated tissue sensitivity to oestrogens are the cause.

Male breast hyperplasia (gynaecomastia) may be unilateral or bilateral, and occurs around puberty. Usually, enlargement is not great and is related to increased mucinous stromal tissue. Gynaecomastia may result from high oestrogen levels (i.e., in hepatic cirrhosis, hormone treatment of prostate cancer) or oestrogen-secreting adrenal tumours.

Prostatic Hyperplasia

This is the most common cause of urinary retention in elderly men. An age-related alteration in the ration of circulating androgens and oestrogens causes an oestrogenic stimulus to the oestrogen-sensitive central zone of the prostate.

Thyroid Gland Hyperplasia

It occurs as a result of thyroid stimulation by increased circulating thyroid-stimulating hormone (TSH), or increased TSH receptor activity. Note, however, that the thyroid may be enlarged also as a result of increased colloid storage, *without* hyperplasia. Circulating TSH levels may be elevated due to a (rare) TSH-secreting pituitary tumour, or in thyroid

dyshormonogenesis. In the latter, failure to produce thyroid hormones due to a congenital enzyme defect causes low circulating thyroid hormone concentrations, with a consequent increased pituitary secretion of TSH.

The thyroid TSH receptor may be abnormally stimulated by an antibody to the receptor which is produced in the not uncommon autoimmune condition, Graves' disease, where the thyroid gland is enlarged and hyperactive.

Adrenal Gland Hyperplasia

This may occur with stimulation by adrenocorticotrophic hormone (ACTH) produced by a pituitary ACTH-secreting tumour, or as a result of a congenital adrenal enzyme defect causing reduced circulating cortisol levels and consequent increased ACTH secretion (congenital adrenal hyperplasia). ACTH may on occasion be secreted inappropriately by tumours such as bronchogenic carcinoma.

Myointimal Cell Hyperplasia

Myointimal cell hyperplasia is an important component of the developing lesions of atheroma. As a result of platelet aggregation and degranulation, platelet-derived growth factor (PDGF) is released, and its chemotactic and mitogenic effects attract smooth muscle cells from the media into the intima and initiate cell division. Transforming growth factor beta (TGF-beta), also from platelets, probably stimulates these cells to produce collagen and fibronectin (which aids cell migration). PDGF and TGF-beta are both chemotactic for neutrophils and macrophages, and it is possible that these cells produce growth factors, such as macrophage-derived growth factors (MDGF), which may also stimulate smooth muscle cells. Little is known about possible direct effects of lipids and autocrine, paracrine or endocrine growth factors or hormone effects on smooth muscle cells; the effects of mitogenic hydrocarbons from cigarettes, or the possible loss of growth inhibitors, are similarly unclear.

Osteoclast Hyperplasia

It is seen in response to increased secretion of parathyroid hormone from, for example, a parathyroid adenoma. The increased numbers of hyperactive osteoclasts excavate bone to release calcium, occasionally seriously weakening the bone, or forming large 'tumours' of hyperplastic osteoclasts.

Apparently Autonomous Hyperplasias

In some apparently hyperplastic conditions, cells appear autonomous, and continue to proliferate rapidly despite the lack of a demonstrable stimulus or control mechanism.

Three particular conditions will be considered in this category: psoriasis, Paget's disease and the fibromatoses.

Psoriasis

It affects about 2% of the UK population. It is characterised clinically by scaly red patches, which may occasionally affect a very large area of skin. Histologically, there is marked epidermal hyperplasia, with elongation of rete ridges in addition to general epithelial thickening. Cell proliferation studies indicate a striking increase in cell turnover in psoriatic skin (3-4 days compared with 28 days in normal skin) and it has been calculated that the number of cells per unit area may be doubled. According to one (controversial) hypothesis, epidermal chalone (locally-produced substances which inhibit cell growth when the normal thickness of the epidermis is attained) are reduced or inactive, leading to a lack of growth control.

Paget's Disease of the Bone

It affects many elderly people. There is a marked increase in bone turnover and a net increase in bone mass; both osteoclasts and osteoblasts are hyperplastic. Although the bone is thickened, it is weaker and considerably more susceptible to fracture and severe deformity.

The Fibromatoses

A fibromatosis is an apparently autonomous proliferation of myofibroblasts, occasionally forming tumour-like masses. The myofibroblasts are locally infiltrative, and may mature into dense collagenous scar-like tissue. Occasionally, spontaneous 'cure' occurs. The commonest of this group of diseases, palmar fibromatosis, causes a flexion contracture of the fingers and palm, starting with the little finger (Dupuytren's contracture). Other sites for fibromatoses include muscle (desmoid tumour), the retroperitoneum (retroperitoneal fibrosis) and the penis (Peyronie's disease).

Decreased Growth: Atrophy

- Atrophy: decrease in size of an organ or cell
- Organ atrophy may be due to reduction in cell size or number or both
- May be mediated by apoptosis
- Atrophy may be physiological (i.e., post-menopausal atrophy of uterus)
- Pathological atrophy may be due to decreased function (i.e., an immobilised limb), loss of innervation, reduced blood or oxygen supply, nutritional impairment or hormonal insufficiency.

Atrophy is the decrease in size of an organ or cell by reduction in cell size and/or reduction in cell numbers. It is important to appreciate that for atrophy to occur there must be not only a cessation of growth but also an active reduction in cell numbers, mediated by apoptosis.

Physiological Atrophy

Embryo and fetus. Branchial clefts. Notocord. Thyroglossal duct. Mullerian duct in males and Wolffian ducts in females.

Neonate. Umbilical vessels. Ductus arteriosus. Fetal layer adrenal cortex.

Early adult. Thymus.

Late adult and old age. Uterus, endometrium, testes. Bone. Gums. Mandible. Cerebrum. Lymphoid tissue.

Pathological Atrophy

There are seven categories of pathological condition in which atrophy may occur.

Decreased Function

Loss of Innervation

Loss of Blood Supply

'Pressure' Atrophy

Lack of Nutrition

Loss of Endocrine Stimulation

Hormone-Induced Atrophy

Decreased Growth: Hypoplasia

- Hypoplasia: failure of development of an organ
- Process is related to atrophy
- Failure of morphogenesis

Hypoplasia is a failure in morphogenesis.

Differentiation and Morphogenesis in Human Development

Differentiation is the process whereby a cell develops an overt specialised function which was not present in the parent cell.

Normal embryological development requires highly coordinated processes of differentiation, growth and cell migration which together comprise morphogenesis.

Control of Normal Differentiation

- Embryonic differentiation of cells is controlled by genes, systemic hormones, position within the fetus, local growth factors and matrix proteins.
- Maintenance of differentiated state is dependent upon persistence of some of these factors
- Differentiation and morphogenesis may be disturbed by environmental factors (i.e., teratogens).

There are very few exceptions to the rule that differentiated cells contain an identical genome to that of the fertilised ovum.

Transcriptional Control

As most differentiated cells have an identical genome, differences between them cannot be due to amplification or deletion of genes. The cells of the body differ because they *express* different genes; genes are switched on or off to control the synthesis of gene products.

The synthesis of a gene product can in theory be controlled at several levels:

- *transcription*: controlling the formation of mRNA
- *transport*: controlling the export of mRNA from the nucleus to the ribosomes in the cytoplasm
- *translation*: controlling the formation of gene product within the ribosomes.

In fact, many of the important 'decision' stages of differentiation in embryogenesis are under Transcriptional control, and the manufacture of gene product is proportional to the activity of the gene.

There is now ample evidence to suggest that the regulation of transcription of several (or many) individuals within a group of genes is mediated by the gene products of a small number of 'control' genes, which may themselves be regulated by the product of a single 'master' gene.

Positional Control in Early Embryogenesis

Disturbances of single 'master' genes in *Drosophila* have been shown to result in major malformations. Such a *homeotic* mutation (the transformation of one body part into another part which is usually found on a different body segment) highlights the importance of another factor in the control of differentiation and morphogenesis, namely the three-dimensional spatial coordinates (position) of a cell within an embryo at a given time.

Homeobox-containing genes are transcriptional regulators influencing morphogenesis.

Cell Determination

The homeobox-containing genes, and other genes which regulate embryogenesis, act on the embryo at a very early stage, before structures such as limbs have begun to differentiate or undergo morphogenesis.

Cell Position and Inductive Phenomena

Simple changes may occur in response to a diffusible substance (such as vitamin A in the developing limb bud), and serve to control local cell growth and/or differentiation according to the distance from the source.

The pattern of differentiation in one cell type may be controlled by another, a phenomenon known as *induction*:

- the action of mesoderm on ectoderm at different sites to form the various parts of the neural tube
- the action of mesoderm on the skin at different sites to form epithelium of differing thickness and accessory gland content
- the action of mesoderm on developing epithelial cells to form branching tubular glands
- the action of the ureteric bud (from the mesonephric duct) to induce the metanephric blastema in kidney formation.

Maintenance and Modulation of an Attained Differentiated State

Once a differentiated state has been attained by a cell, it must be maintained. This is achieved by a combination of factors:

- 'cell memory' inherent in the genome, with inherited transcriptional changes
- interactions with adjacent cells, through secreted paracrine factors
- secreted factors (autocrine factors) including growth factors and extracellular matrix.

Even in the adult, minor changes to the differentiated state may occur if the local environment changes. These alterations to the differentiated state are rarely great, and most can be termed *modulations*, i.e., reversible interconversions between closely related cell phenotypes. An example of a modulation is the alteration in synthesis of certain liver enzymes in response to circulating corticosteroids.

In the neonatal stage of development, cell *maturation* may involve modulations of the differentiated state:

- the production of surfactant by type II pneumocytes under the influence of corticosteroids
- the synthesis of vitamin K-dependent blood-clotting factors by the hepatocyte
- gut maturation affected by epidermal growth factor (EGF) in milk.

Normal Differentiation and Morphogenesis: Summary

Differentiation

During development of an embryo, determination and differentiation occur in a cell by transcriptional modifications to the expression of the genome, without an increase or decrease in numbers of genes present. Expression of individual genes within the genome are *modified* during development by:

- positional information carried by a small number of 'control' gene products, causing local alterations in growth and differentiation
- migrations of cells and modifications mediated by adjacent cells (paracrine factors) or endocrine factors.

Once attained, the differentiated state is *maintained* or *modulated* by:

- paracrine factors (interactions with adjacent cells)
- autocrine factors, such as growth factors and the extracellular matrix secreted by the cell.

External factors may cause alterations to the differentiated state of the cell, either during development or at any stage of adult life.

Morphogenesis

Congenital Disorders of Differentiation and Morphogenesis

The usual outcome of human conception is abortion. 70-80% of all human conceptions are lost, largely as a consequence of chromosomal abnormalities. The majority of these abortions occur spontaneously in the first 6-8 weeks of pregnancy, and in most cases the menstrual cycle might appear normal, or the slight delay in menstruation causes little concern. Chromosomal abnormalities are present in 3-5% of live-born infants, and a further 2% have serious malformations which are not associated with chromosomal aberrations.

Chromosomal Abnormalities Affecting Whole Chromosomes

Autosomal Chromosomes

The three most common autosomal chromosome defects involve the presence of additional whole chromosomes (trisomy).

Trisomy 21 (Down's syndrome) affects approximately 1 in 1000 births, and is associated with mental retardation, a flattened facial profile, slanting eyes (producing a 'mongoloid' appearance) and prominent epicanthal folds. The hands are short, with a transverse 'simian' (i.e., monkey-like) palmar crease. There are also abnormalities of the ears, trunk, pelvis and phalanges. The incidence increases with maternal age.

Trisomy 18 (Edward's syndrome) affects 1 in 5000 births. It is associated with ear and jaw, cardiac, renal, intestinal and skeletal abnormalities.

Trisomy 13 (Patau's syndrome) affects 1 in 6000 births, with microcephaly and microphthalmia, hare lip and cleft palate, polydactyly, abnormal ears, 'rocker-bottom' feet, and cardiac and visceral defects.

Sex Chromosomes

In general, variations in X chromosome numbers cause greater mental retardation.

Klinefelter's syndrome (47XXY) affects 1 in 850 male births. There is testicular atrophy and absent spermatogenesis, eunuchoid bodily habitus, gynaecomastia, female distribution of body hair and mental retardation. Variants of Klinefelter's syndrome (48XXXXY, 49 XXXXY, 48XXYY) are rare, and have cryptorchidism and hypospadias, in addition to more severe mental retardation and radio-ulnar synostosis.

Double Y males (47XYY) form 1 in 1000 male births; they are phenotypically normal, although most are over six feet tall. Some are said to have increased aggressive or criminal behaviour.

Turner's syndrome (gonadal dysgenesis; 45X) occurs in 1 in 3000 female births. About one-half are mosaics (45X/46XX) and some have 46 chromosomes and two X chromosomes, one of which is defective. Turner's syndrome female may have short stature, primary amenorrhoea and infertility, webbing of the neck, broad chest and widely spaced nipples, cubitus valgus, low posterior hairline and coarctation of the aorta.

Multiple X females (47XXX, 48XXXX) comprise 1 in 1200 female births. They may be mentally retarded, and have menstrual disturbances, although many are normal and fertile.

True hermaphrodites (most 46XX, some 46XX/47XXY mosaics) have both testicular and ovarian tissue, with varying genital tract abnormalities.

Parts of Chromosomes

Cri-du-chat syndrome (46XX, 5p- or 46XY, 5p-). This rare condition (1 in 50.000 births) is associated with deletion of the short arm of chromosome 5 (5-), and was so named because infants have a characteristic cry like the miaow of a cat. There is microcephaly and severe mental retardation; the face is round, there is gross hypertelorism and epicanthic folds.

Single Gene Alterations

All of the inherited disorders of single genes are transmitted by autosomal dominant, autosomal recessive or X-linked modes of inheritance. There are more than 2700 known Mendelian disorders; 80-85% of these are familial, and the remainder are the result of new mutations. The alteration of expression of gene product constitutes at least a modulation of cell differentiation, and some have important effects on growth and morphogenesis.

Enzyme Defects

- accumulation of galactose and consequent tissue damage in galactose-1-phosphate uridyl transferase deficiency
- accumulation of phenylalanine, causing mental abnormality, in phenylalanine hydroxylase deficiency
- accumulation of glycogen, mucopolysaccharides, etc. in lysosomes in the enzyme deficiency states of the lysosomal storage diseases.

Defects in Receptors or Cellular Transport

In one form of male pseudohermaphroditism, for example, insensitivity of tissues to androgens, caused by lack of androgen receptor, prevents the development of male characteristics during fetal development.

Cellular transport deficiencies may lead to conditions such as cystic fibrosis, a condition in which there is a defective cell membrane transport system across exocrine secretory cells.

Non-Enzyme Protein Defects

Sickle-cell anaemia is caused by the production of abnormal haemoglobin, and Marfan's syndrome and Ehlers-Danlos syndrome are the result of defective collagen production.

Adverse Reactions to Drugs

The apparently innocuous condition of glucose-6-phosphate dehydrogenase (G6PD) deficiency does not result in disease until the antimalarial drug, primaquine, is administered; severe haemolytic anaemia then results. The prevalence of G6PD deficiency in the tropics

may reflect evolutionary selective pressure, as the deficiency may confer a degree of protection against malarial parasitation of red blood cells.

Functional Aspects of Developmental Disorders

In most cases the genetic defect is unknown, although the majority are almost certainly the result of transcriptional alterations to an intact genome.

Embryo Division Abnormalities

Monozygotic twins (or multiple births) result from the separation of groups of cells in the early embryo, well before the formation of the primitive streak. On occasion, there is a defect of embryo division, resulting in:

- *Siamese twins*: the result of incomplete separation of the embryo, with fusion of considerable portions of the body (or minor fusion which are easily separated).

- *Fetus in fetu*: one of the fused twins develops imperfectly and grows on the other either externally or within the abdominal cavity. It is possible that some extragonadal 'teratomas' in neonates belong to this group.

Teratogen Exposure

If exposure occurs at the stage of early organogenesis (4-5 weeks' gestation) then the effects on developing organs or limbs are severe.

Clinical examples include the severe and extensive malformations associated with use of the drug thalidomide and the effects of rubella (German measles) on the fetus (cataracts, microcephaly, heart defects, etc.).

Failure of Cell and Organ Migration

Kartagener's syndrome. In this rare condition there is a defect in ciliary motility, due to absent or abnormal dynein arms, the structures on the outer doublets of cilia which are responsible for ciliary movement. This affects cell motility during embryogenesis, which often results in situs inversus. Complications in later life include bronchiectasis and infertility due to sperm immobility.

Hirschprung's disease is a condition leading to marked dilatation of the colon and failure of colonic motility in the neonatal period, due to absence of Meissner's and Auerbach's plexuses. It results from a selective failure of craniocaudal migration of neuroblasts in weeks 5-12 of gestation. It is ten times more frequent in trisomy 21 and is often associated with other congenital anomalies.

Undescended testis (cryptorchidism) is the result of failure of the testis to migrate to its normal position in the scrotum. It may be associated with severe forms of Klinefelter's syndrome it is often an isolated anomaly in an otherwise normal male. There is an increased risk of neoplasia in undescended testes.

Anomalies of Organogenesis

- Agenesis (aplasia): failure of development of an organ or structure within it
- Atresia: failure of the development of a lumen in a normally tubular structure
- Hypoplasia: failure of an organ to attain its normal size
- Maldifferentiation (dysgenesis): failure of normal organ differentiation or persistence of primitive embryological structures
- Ectopia (heterotopia): development of mature tissue in an inappropriate site.

Agenesis (Aplasia)

The failure of development of an organ or structure is known as agenesis (aplasia).

- *Renal agenesis*. This may be unilateral or bilateral. It results from a failure of the mesonephric duct to give rise to the ureteric bud, and consequent failure of metanephric blastema induction.

- *Thymic agenesis* is seen in Di George syndrome, where there is failure of development of T-lymphocytes, and consequent severe deficiency of cell-mediated immunity. Recent evidence suggests that there is failure of processing stem cells to T-cells as a result of a defect in the thymus anlage.

- *Anencephaly* is a severe neural tube defect in which the cerebrum, and often the cerebellum, are absent. The condition is lethal.

Atresia

Atresia is the failure of development of a lumen in a normally tubular epithelial structure.

- *oesophageal atresia*, which may be seen in association with tracheo-oesophageal fistulae, as a result of anomalies of development of the two structures from the primitive foregut

- *biliary atresia*, which is an uncommon cause of obstructive jaundice in early childhood

- *urethral atresia*, a very rare anomaly, which may be associated with recto-urethral or urachal fistula, or congenital absence of the anterior abdominal wall muscles ('prune belly' syndrome).

Hypoplasia

A failure in development of the normal size of an organ is termed hypoplasia. A relatively common example of hypoplasia affects the osseous nuclei of the acetabulum causing dislocation of the hip, due to a flattened roof to the acetabulum.

Maldifferentiation (dysgenesis, dysplasia)

It is the failure of normal differentiation of an organ, which often retains primitive embryological structures.

'Renal dysplasia' is a result of anomalous metanephritic differentiation. Here, primitive tubular structures may be admixed with cellular mesenchyme and, occasionally, smooth muscle.

Ectopia and Heterotopia

Ectopic and heterotopic tissues are usually small areas of mature tissue from one organ (i.e., gastric mucosa) which are present within another tissue (i.e., Meckel's diverticulum) as a result of a developmental anomaly. Another clinically important example is endometriosis.

Complex Disorders of Growth and Morphogenesis

Three examples of complex, multifactorial defects of growth and morphogenesis will be discussed: neural tube defects, disorders of sexual differentiation, and cleft palate and related disorders.

Neural Tube Defects

Neural tube malformations are relatively common in the UK and are found in about 1.3% of aborted fetuses, and 0.1% of live births. The pathogenesis of these conditions - anencephaly, hydrocephalus and spina bifida - is uncertain, and probably multifactorial.

Disorders of Sexual Differentiation

Chromosomal abnormalities. Have been discussed already.

Female pseudohermaphroditism, in which the genetic sex is always female (XX), may be due to exposure of the developing fetus to the masculinising effects of excess testosterone or progestagens, causing abnormal differentiation of the external genitalia. The causes include:

- an enzyme defect in the fetal adrenal gland, leading to excessive androgen production at the expense of cortisol synthesis (with consequent adrenal hyperplasia due to feedback mechanisms which increase ACTH secretion)

- exogenous androgenic steroids from a maternal androgen-secreting tumour, or administration of androgens (or progestagens) during pregnancy.

Male pseudohermaphroditism, in which the genetic sex is male (XY), may be the result of several rare defects:

- testicular unresponsiveness to human chorionic gonadotrophin (hCG) or luteinising hormone (LH), by virtue of reduction in receptors to these hormones; this causes failure of testosterone secretion
- errors of testosterone biosynthesis in the fetus, due to enzyme defects (may be associated with cortisol deficiency and congenital adrenal hyperplasia)
- tissue insensitivity to androgens (androgen receptor deficiency)
- abnormality in testosterone metabolism by peripheral tissues, in 5 alpha-reductase deficiency
- defects in synthesis, secretion and response to Mullerian duct inhibitory factor
- maternal ingestion of oestrogens and progestins.

These defects result in the presence of a testis which is small and atrophic, and a female phenotype.

Cleft Palate and Related Disorders

Cleft palate, and the related cleft (or hare) lip, are relatively common (about 1 per 1000 births). Approximately 20% of children with these disorders have associated major malformations. The important stages of development of the lips, palate, nose and jaws occur in the first nine weeks of embryonic life. From about five weeks' gestational age the maxillary processes grow anteriorly and medially, and fuse with the developing fronto-nasal process at two points just below nostrils, forming the upper lip. Meanwhile, the palate develops from the palatal processes of the maxillary processes, which grow medially to fuse with the nasal septum in the midline at about nine weeks.

A cleft lip is commonly unilateral; it may involve the lip alone, or extend into the nostril or involve the bone of the maxilla and the teeth.

It appears from the relatively high incidence of these malformations that the control of palatal morphogenesis is particularly sensitive to both genetic and environmental disturbances:

- Genetic: i.e., Patau's syndrome (trisomy 13) is associated with severe clefting of the lip and palate.
- Environmental: i.e., the effects of specific teratogens such as folic acid antagonists or anticonvulsants, causing cleft lip and/or palate.

Several cellular factors are involved in the fusion of the fronto-nasal and maxillary processes. The differentiation of epithelial cells of the palatal processes is of paramount

importance in fusion of the processes. The most important mechanism is mediated by mesenchymal cells of the palatal processes, which induce differentiation of the epithelial cells, to form either ciliated nasal epithelial cells or squamous buccal epithelial cells, or to undergo programmed cell death by apoptosis to allow fusion of underlying mesenchymal cells. Positional information of genetic and chemical (paracrine) nature is important in this differentiation, and is mediated via mesenchymal cells (and possibly epithelial cells). In addition, the events may be modified by the actions of epidermal growth factor (EGF) and other growth factors through autocrine or paracrine mechanisms, and the endocrine actions of glucocorticoids and their intercellular receptors.

In the mouse, it is known that physiological concentrations of glucocorticoids, their receptors and EGF are required for normal development, but that altered concentrations may precipitate cleft palate.

Acquired Disorders of Differentiation and Growth

Metaplasia

- Metaplasia is an acquired form of altered differentiation
- Transformation of one mature differentiated cell type into another
- Reversible response to altered cellular environment
- Affects epithelial or mesenchymal cells
- May undergo further indirect transformation to neoplasia via dysplasia (i.e., squamous cell carcinoma associated with squamous metaplasia in bronchi).

Metaplasia (transdifferentiation) is the reversible transformation of one type of terminally differentiated (epithelial or mesenchymal) cell into another fully differentiated cell type. Metaplasia often represents an adaptive response of a tissue to environmental stress, and is presumed to be due to the activation and/or repression of groups of genes involved in the maintenance of cellular differentiation. The metaplastic tissue is better able to withstand the adverse environmental changes.

Examples of metaplasia in *epithelial tissues* include a change to squamous epithelium (squamous metaplasia) in:

- ciliated respiratory epithelium of the trachea and bronchi in smokers
- ducts of the salivary glands and pancreas, and bile ducts in the presence of stones
- transitional bladder epithelium in the presence of stone, and in the presence of ova of the trematode *Schistosoma haematobium*
- transitional and columnar nasal epithelium in vitamin A deficiency (for reasons which are not clear).

Another example is the replacement of normal squamous epithelium of the oesophagus by gastric-type epithelium (glandular or gastric metaplasia) in patients with reflux of gastric acid into the oesophagus (in, for example, hiatus hernia).

Examples of metaplasia in *mesenchymal tissues* are bone formation (osseous metaplasia):

- following calcium deposition in atheromatous arterial walls
- in bronchial cartilage
- following longstanding disease of the uveal tract of the eye.

Metaplasia does not itself necessarily progress to malignancy, although the environmental changes which initially caused the metaplasia may also induce dysplasia and, if persistent, progression to tumour formation.

Metaplasia is sometimes said to occur in tumours as, for example, in squamous or glandular "metaplasia" which may occur in transitional carcinomas of the bladder. These examples of transdifferentiation certainly do occur in tumours, but use of the term 'metaplasia' is, for reasons of clarity, better confined to changes occurring in non-neoplastic tissues.

Dysplasia

- Dysplasia is characterised by increased cell growth (i.e., more mitoses visible than normal), presence of atypical morphology (i.e., abnormally large nuclei), and altered differentiation (i.e., cellular immaturity)

- May be caused by chronic physical or chemical injury
- May be reversible only in early stages
- Dysplastic lesions are often pre-neoplastic.

Dysplasia (sometimes referred to as atypical hyperplasia) is a *pre-malignant* condition characterised by increased cell growth, the presence of cellular atypia, and altered differentiation. Early mild forms of dysplasia may be reversible if the initial stimulus is removed, but severe dysplasia will progress to development of a malignant neoplasm unless it is adequately treated.

Dysplasia may be caused by longstanding irritation of a tissue, with long-term chronic inflammation, or an exposure to carcinogenic substances.

In affected tissues, dysplasia may be recognised by:

- evidence of increased growth, such as increased tissue bulk (i.e., increased epithelial thickness), and increased numbers of mitoses

- presence of cellular atypia, with pleomorphism (variation in the size and shape of cells and their nuclei), a high nuclear/cytoplasmic ratio and increased nuclear DNA (recognised by hyperchromatism, i.e., more darkly stained nuclei)

- altered differentiation, as the cells often appear more primitive than normal. For example, dysplastic squamous epithelium may not show the normal differentiation from basal cells to flattened surface cells of the skin; this appearance is described as showing 'loss of epithelial polarity'.

Dysplasia may occur in tissue which has coincident metaplasia (i.e., dysplasia developing in metaplastic squamous epithelium from the bronchus of smokers). Dysplasia may also develop without coexisting metaplasia, for example in squamous epithelium of the uterine cervix, glandular epithelium of the stomach, or the liver.

Neoplasia

- Neoplasia is characterised by abnormal, uncoordinated and excessive cell growth
- Persists after initiating stimulus has been withdrawn
- Associated with genetic alterations
- Neoplastic cells influence behaviour of normal cells by the production of hormones and growth factors.

The word 'neoplasia' literally means 'new growth', and the lesion so produced is termed a *neoplasm*. A neoplasm is defined as an abnormal tissue mass, the excessive growth of which is uncoordinated with that of normal tissues, and which persists after the removal of the neoplasm-inducing stimulus. The term *tumour* is often used to denote a neoplasm, although a tumour was originally defined as being a swelling associated with inflammation, and is therefore less precise. Malignant neoplasms are popularly known as 'cancer'.

Differentiation in Neoplasia

In many tissues, neoplastic cells appear to become more primitive as tumours become more malignant, and fetal proteins such as carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP), or fetal isoenzyme types, may be expressed in malignant neoplasms. This altered differentiation is sometimes termed *fetal dedifferentiation*.

It is noteworthy, however, that neoplasms may be *more* differentiated than their putative cell of origin. Teratomas of the testis or ovary derived from primitive germ cells (cells from which the oocytes in females and spermatozoa in males are derived) may contain mature squamous or respiratory epithelium, muscle, teeth or cartilage, in addition to trophoblastic or yolk sac tissues and highly malignant poorly differentiated cells.

Cellular Anarchy in Neoplasia

Some tumours, however, express proteins which are not appropriate to the cell of origin. This occurs, for example, in the *inappropriate expression* of adrenocorticotrophic hormone or parathyroid hormone by bronchogenic carcinomas - *ectopic hormone* production.

In addition, some malignant neoplasms may secrete growth factors or cytokines which mediate some of the secondary effects of cancer, such as cachexia (partially mediated by tumour necrosis factor).