# Paper 1 Answers

## Question 1

**A.** false **B.** true **C.** true **D.** false **E.** false

Studies in molecular genetics have shown that mutations or deletions underlie some diseases such as:

1. Some forms of Alzheimers (point mutation in the gene for the amyloid precursor protein)
2. The spongiform encephalopathies such as Creutzfeldt-Jakob disease (mutations in the prion protein gene)
3. Familial amyotrophic lateral sclerosis (abnormalities in the superoxide dismutase gene)
4. Charcot Marie Tooth disease (reduplication of the chromosome 17 gene)
5. Duchenne and Becker muscular dystrophies (deletion of the dystrophin gene)
6. Mitochondrial DNA deletions underlie Lebers optic atrophy, Leighs necrotizing encephalopathy of childhood, and the mitochondrial myopathies.
7. Abnormal amplification of particular trinucleotide repeats occurs in X linked bulbospinal muscular atrophy, fragile X syndrome, myotonic dystrophy, Huntington's Chorea, Spinocerebellar ataxia type I, and Dentatorubral pallidoluysian atrophy. They share a progressive lengthening of the trinucleotide repeat (CGG, CAG, CTG) sequence from one generation to the next and at some critical length the associated gene malfunctions.

| ***Syndrome*** | ***Linkage*** | ***Anticipation*** |
|---|---|---|
| Fragile X | X linked | Yes |
| Spinobulbar muscular atrophy | X linked | No |
| Myotonic dystrophy | Aut Dom | Yes |
| Huntingdons disease | Aut Dom | Yes |
| Spinocerebellar ataxia type I | Aut Dom | Yes |
| Fragile X | X linked | No |
| Dentatorubral pallidoluysian atrophy | Aut Dom | Yes |

Myotonic dystrophy is a good example of a disease demonstrating anticipation in which there is increased severity at an earlier age of onset with successive generations. For example the grandparent may just have cataracts and the diagnosis will not be considered until the offspring presents with classical myotonia in early adult life. (In some cases it is difficult to decide which grandparent is affected). The grandchild however may have congenital disease (especially if the transmitting parent is the mother). A correlation exists between the age of onset and the length of the CTG repeat in the untranslated 3' end of the myotonin protein kinase gene.

Causes of optic atrophy

| | |
|---|---|
| Hereditary | Lebers optic atrophy |
| | Dominant optic atrophy |
| | Retinitis pigmentosa |
| | Tay Sachs disease |
| Acquired | Trauma to optic nerve (e.g. birth hypoxia) |
| | Infections (meningitis, encephalopathies, neuropathies) |
| | Demylination disorders |
| | Pituitary tumours |
| | Meningiomas |
| | Toxins (methanol, quinine, tobacco amblyopia) |

Pembrey ME. Genetic factors in disease
Oxford Textbook of Medicine. Oxford University Press

## Question 2

**A.** false **B.** true **C.** false **D.** true **E.** true

Causes and associations of diabetes mellitus:

***Primary causes:***

| | |
|---|---|
| Type I | insulin dependent |
| II | non insulin dependent |
| III | (limited to the tropics) malnutrition related |

***Secondary***

pancreatitis (acute/chronic)
haemochromatosis
endocrine disorders producing excess levels of:
- cortisol (Cushing's syndrome)
- growth hormone (acromegaly)
- glucagon (glucagonoma)
- adrenaline (phaeochromocytoma)

Drug induced, certain genetic syndromes

Type I diabetes (IDDM), once termed juvenile type onset diabetes, is the result of an autoimmune destruction of the islets of Langerhans. It typically presents before 30 years, but it can occur at any age. It results in a very substantial destruction of the total capacity of the islet beta cells to secrete insulin. Islet cell antibodies are usually found in the plasma for a period of 1–2 years after diagnosis, but in a minority (20%) these may persist for the remainder of the patients life. Members of this subgroup, sometimes called type Ib, are particularly liable to suffer other autoimmune diseases e.g. coeliac disease or rheumatoid arthritis. In Ib there is a higher percentage of females and older age of onset. There is an association with HLA types e.g. DR3 (males) DR4 (females). Patients are mostly young and often markedly thin at diagnosis. In the early phase they retain some endogenous insulin secretion and may have a honeymoon phase; later there is no endogenous insulin. Ketoacidosis develops when insulin is withdrawn or during stress states.

Individuals at risk of developing IDDM can be identified by the presence of autoimmune serological markers, including islets cell antibodies, antibodies to insulin and glutamic acid decarboxylase (GAD) and a decline in beta cell insulin secretory capacity. GAD is an enzyme involved in the conversion of glutamate to $\gamma$-amino butyric acid, a key neuroendocrine transmitter. Antibodies to GAD are highly predictive of future IDDM and insulin dependency.

50% of all cases are diagnosed before 20 years of age. In adults the onset may be much slower and the disorder may mimic NIDDM. The risk that IDDM will develop before the age of 20 years is about 6% for a sibling of a patient with IDDM and 5% for a child whose father has IDDM. The risk for the child of a mother with IDDM is 2–3% (if she was diagnosed after the age of 8) but up to 22% if she was diagnosed before 8. The major locus is in the short arm of chromosome 6. 90% of Caucasians with IDDM have DR3 or DR4; DR2 is protective. HLA-DQ alleles are even more closely associated with IDDM:

HLA DR4-DQA*0301 DQB1*0302 and

HLA DR4 DQA1*0102 DQB1*0201 predispose to IDDM.

There is relative concordance in monozygotic twins in contrast to Type II diabetics where there is a strong concordance with identical twins in studies (>90%). IgM antibodies against coxsackie virus have been found in 25–30% of new cases, suggesting recent infection. Coxsackie virus B RNA has been detected in 65% of children under

the age of 7 years with newly diagnosed IDDM, compared with 4% of controls, consistent with recent or persistent infection. Cytomegalovirus DNA sequences are incorporated into the genome in 22% of newly diagnosed diabetes, compared with 26% of controls.

Bell JI, Hockday TDR. Diabetes Mellitus
Oxford Textbook of Medicine. Oxford University Press.

## Question 3

**A.** true **B.** true **C.** true **D.** false **E.** true

As suggested from the stem there is a missing chromosome in Turner's syndrome.

The incidence is around 1 in 2500–3500 of female births and presents either at birth or infancy or in mid childhood. Turner's syndrome is probably the most common chromosomal cause of osteoporosis and the commonest cause of ovarian dysgenesis.

***Recognized features of Turner's syndrome:***
Slight reduction in expected IQ range but great majority in the normal range
Osteoporosis
Hirsutism
Primary ovarian failure
Pubertal delay
Renal anomalies
Eye findings: epicanthus/ptosis
Short stature
Webbed neck
Shield chest with wide spaced nipples
Wide carrying angle of the arms
Congenital heart defect (esp. coarctation)
Café au lait spots
Black freckles/low hairline
Double layered eye lashes
Characteristically they have XO karyotype with reduced numbers of Barr bodies in the buccal smears
Hearing loss

It is now possible to provide women with Turner's syndrome with fertility through ovum donation, although the shortage of oocytes remains an important and usually critically limiting factor. Treatment for short stature involves a slow introduction of ethinyl oestradiol at the age of 12 to 13 for 2 years (omitting the dose 1 week in every 4 once adult doses are reached) with progesterone in

the final week. For the lack of puberty recombinant human growth hormone and the mild anabolic steroid oxandrolone have been of benefit.

***Causes of Primary ovarian failure:***

Idiopathic
Turner's
Autoimmune disease (hypothyroidism, Addison's disease, IDDM)
Anticancer therapy
Resistant ovaries
Surgery
Radiotherapy
Galactosaemia
Familial
Miscellaneous

***Causes of short stature:***

| **Proportionate** | |
|---|---|
| Genetic | familial |
| Endocrine | lack of growth hormone, hypothyroidism |
| Metabolic | lysosomal storage diseases |
| | renal glomerular failure, cystic fibrosis |
| Nutritional | coeliac disease, starvation |
| Chronic disease | cyanotic heart disease |
| Intrauterine | low birth weight dwarfism |
| Chromosomal | Turner's |
| Social | emotional deprivation |

| **Disproportionate** | |
|---|---|
| Short limbs | |
| Lethal | type II osteogenesis imperfecta |
| | thanatophoric dwarfism |
| | achondrogenesis |
| Non-lethal | achondroplasia |
| | inherited hypophosphataemia |
| | metaphyseal dystosis |
| Short spine | spondyloepiphyseal dysplasia |

Preece MA. Normal growth and its disorders
Oxford Textbook of Medicine. Oxford University Press.

## Question 4

**A.** true **B.** true **C.** false **D.** false **E.** false

Down's syndrome is characterised by an extra chromosome where the karyotype is written 47,XX+21, or 47,XY+21 if male. 96% are due to primary non-dysjunction, 95% of these involve errors in the

formation of the ovum rather that the sperm. Down's syndrome has an incidence of 1 in 1,200 mothers less than 30 years to about 1 in 100 at the age of 39 years. If a couple have 1 child with Down's there is a 1 in 100 chance of another trisomy, usually Down's. Other examples of trisomies include: Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome).

In 2–3% of cases there is a chromosome translocation (usually a Robertsonian translocation); this is an indication to screen each parent to see if they carry a balanced translocation.

Phenotypic features: foreshortened head (brachycephaly), three fontanelles. The eyes have an upward slant and crescents of skin cover the inner canthi (epicanthic folds); small white spots are situated around the outer third of the iris (Brushfield spots). The nasal bridge is flat and the tongue protuberant and deeply furrowed. A single transverse palmar crease is present on the hand, together with a short, incurved, fifth finger (clinodactyly). A wide gap is present between the first and second toes, often with a longitudinal plantar crease. Hypotonia and delayed development are universal.

Bemberg ME. Genetic factors in disease.
Oxford Textbook of Medicine. Oxford University Press.

## Question 5

**A.** true **B.** false **C.** true **D.** true **E.** true

Apoptosis is a common process during development, adult growth, disease and tissue healing. For example it occurs in the remodelling of neurons during the development of the brain, and in adulthood the cyclic breakdown of the endometrium during menstruation, the death of enterocytes sloughed off the tip of villi during replacement of fresh tissue in the small intestine, and also occurs in pathological processes such as autoimmune disease and cancer.

During apoptosis or programmed cell death, the cell shrinks and becomes denser. There is little or no organelle swelling such as involving mitochondria which can distinguish this process of cell death from ischaemic necrosis where essentially ion-pump failure occurs leading to swelling of the cell prior to rupture. Biochemically, the DNA is broken down into segments that are multiples of around 185 base pairs, due to specific cleavage between nucleosomes. Apoptosis appears to be under genetic control and can be initiated by an internal clock and by external agents in the

extracellular compartment such as hormones, cytokines, killer cells and a variety of chemical, physical and viral agents. The time from initiation to final cell destruction is short, of the order of 30 minutes in some cell types. It may be this latter phenomenon that has led to apoptosis becoming recognized only in recent times despite clear histological descriptions even in the nineteenth century. It is important to note that cell suicide may not always occur by apoptosis, cytokine induced cell death may be via apoptosis, that there are several varieties of apoptosis and finally that different cell types may follow different rules. Two of the most prominent extracelular factors activating the process of apoptosis are Fas and Tissue Necrosis Factor (TNF). When Fas binds to its receptor on the cell membrane, a cascade of reactions is triggered by a collection of intracellular cysteine proteases originally called ICE-link enzymes (interleukin 1 beta converting enzyme) which switch on genes that initiate the process of programmed cell death. TNF acts in a similar fashion after interacting with the TNF-1 receptor. The activated apoptotic genes cause the cell to undergo DNA fragmentation, cytoplasmic and chromatin condensation, and eventually membrane bleb formation, with cell breakup and removal of the debris by phagocytes.

Just as proto-oncogenes exist that are responsible for mutations giving rise to oncogenes that have malignant properties, some genes exist that suppress tumour growth the so-called tumour suppressor genes. The most studied of these is the p53 gene on chromosome 17 which triggers apoptosis in normal physiological circumstances. In human cancer p53 genes undergo mutations and the resulting products are unable to slow the cell cycle and thus permit other mutations to DNA to occur. The accumulated mutations eventually cause malignant growth.

Ganong WF. Review of Medical Physiology 1999
19th Edition Appleton and Lange Publishers, Connecticut

## Question 6

**A.** false **B.** true **C.** true **D.** false **E.** true

Tumour necrosis factor (TNF) comprises just one of a long list of important cytokines – some of which are listed below:

Interleukins 1, 2, 4, 6, 10 and 13.
TNF alpha and beta
Interferons (IFN) alpha, beta, and gamma
Colony stimulating factor (IL-3, IL-5)

Chemokines (IL-8), monocyte chemotactic peptide, macrophage inflammatory protein

TNF alpha and beta are involved in cell activation and apoptosis. There are two types: TNF alpha is principally produced by macrophages, TNF beta is secreted mainly by T lymphocytes. TNF is around 17kDa in size; most cells have receptors for it. Whilst not produced in the necrotic centre of tumours it derives its name from its ability to induce haemorrhagic necrosis in experimental tumours. TNF alpha and beta cause fever, hypotension, hypercoagulability and cardiovascular collapse when injected intravenously. They stimulate leucocyte microbiocidal activity, induce adhesion receptors on endothelial cells, and appear to regulate cell growth and apoptosis. TNF alpha may be responsible for the shock syndrome following Gram-negative septicaemia or release of bacterial endotoxin. A low controlled concentration of TNF may be necessary for resistance to infection.

Actions of TNF

1. Treatment of melanoma by limb perfusion (targeting the tumour vasculature).
2. Structurally identical to cachectin previously described as a substance inducing weight loss in animals transplanted with human tumours. The secretion of TNF by macrophages may lead to tuberculomas in post primary TB and the subsequent wasting disease (formerly known as consumption) – characteristic of advanced untreated tuberculosis.
3. TNF and IL-2 produces fever and both may be produced in cancer patients.
4. Cytokines play a major role in the acute phase response. TNF appears to rise before IL-1 and IL-6 and in experimental animals septic shock may be prevented by prior administration of anti-TNF monoclonal or polyclonal antibodies. The characteristic intermittent fever of malaria is associated with the cyclical production of TNF that occurs at schizogony.
5. In studies of the pathogenesis of meningitis TNF induces endothelial cells to secrete nitric oxide, which is a powerful vasodilator – and this may play a role in producing meningococcal shock.
6. In patients with Louse-borne fever treatment with penicillin causes a severe Jarisch-Herxheimer reaction – associated with elevated TNF levels. Treatment with anti-TNF antibodies prior to penicillin prevents this.

Keshav S. Cytokines
Oxford Textbook of Medicine. Oxford University Press.

## Question 7

**A.** false **B.** true **C.** true **D.** false **E.** true

Anatomy of the sympathetic system: the cell bodies of the preganglionic neurons unlike those of the parasympathetic system lie within the spinal cord and exit via the thoracic and upper lumbar nerves to synapse in the peripheral sympathetic ganglia running in the paraspinal chain. The exception to the rule is the adrenal medulla, which is innervated directly by preganglionic fibres passing through the splanchnic nerves to synapse directly with secretory cells that secret catecholamines (mainly adrenaline). Sympathetic fibres from the right stellate ganglion are distributed mainly to the sinus node and the right atrium and ventricle whilst in the left, the ventrolateral cardiac nerve provides a major sympathetic supply to the left atrium and posterior and lateral surfaces of the left ventricle.

Noradrenaline (NAd) is the natural transmitter that is stored in neurosecretory granules in sympathetic nerve terminals. Depolarisation causes release of intraneuronal calcium, migration of the granules to the neuronal membrane, release of NAd into the synaptic cleft and activation of postsynaptic receptors. NAds action is controlled by neuronal uptake, on the presynaptic terminal (re-uptake), broken down by catechol-O-methyl-transferase or diffuses away into the circulation. Many adrenergic receptors exist.

| ***Receptor*** | ***Action on circulation*** |
|---|---|
| Alpha -1 | vasoconstriction (increase in contractility) |
| Alpha -2 | vasoconstriction presynaptic sympathetic inhibition |
| Beta -1 | increase in heart rate (sinus node)<br>increase in contractility (atrium, ventricle)<br>increase in conduction (AV node) |
| Beta -2 | vasodilatation (bronchodilation) |
| Dopaminergic-1 | renal and mesenteric vasodilatation |
| Dopaminergic-2 | vasodilatation |

Adrenergic receptor activity of endogenous and synthetic catecholamines

| ***Catecholamines*** | ***Receptor subtype*** | | | | | |
|---|---|---|---|---|---|---|
| | alpha-1 | –2 | beta-1 | –2 | DA-1 | DA-2 |
| Dopamine | ++ | + | ++ | 0 | +++ | ++ |
| NAd | +++ | ++ | +++ | +/– | 0 | 0 |
| Ad | ++ | ++ | +++ | +++ | 0 | 0 |
| Isoprenaline | 0 | 0 | +++ | ++ | 0 | 0 |
| Dobutamine | + | +/– | +++ | ++ | 0 | 0 |
| Salbutamol | 0 | 0 | + | +++ | 0 | 0 |
| Dopexamine | 0 | 0 | + | ++ | ++ | + |

Interaction with alpha receptors appears to increase cytoplasmic calcium whereas stimulation of the beta receptor stimulates a rise in intracellular cAMP.

Forfar JC. Catecholamines and the sympathetic nervous system. Oxford Textbook of Medicine. Oxford University Press.

## Question 8

**A.** false **B.** true **C.** false **D.** false **E.** true

Afferent pathways to the brainstem for the pupillary light reflex are as follows:

1. light impinges on the back of the retina
2. impulses are carried from the optic nerve through the optic chiasm to the lateral geniculate nucleus
3. these fibres pass to the pretectal nucleus in the midbrain
4. synaptic fibres then pass to the ipsilateral and contralateral Edinger Westphal nucleus
5. from here fibres travel in the third nerve from the midbrain to the ciliary ganglion
6. and postganglionic fibres pass from here to innervate the iris and ciliary muscles

The light reflex will be diminished if:

corneal opacities /cataracts are present
lesions of optic nerve, chiasm or optic tract exist
local disease of the eye e.g. iridocyclitis may cause adhesions preventing pupillary constriction
lesion of IIIrd nerve nucleus, IIIrd nerve, the ciliary ganglion or short ciliary nerves

***Causes of a small pupil:***
Horner's
Argyll Robertson pupil
Myotonic dystrophy
Pontine lesions
Acute iritis
Opiates
Organophosphate poisoning