

Syllabus 2020



Basic Pathological  
Sciences

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## Table of Contents

Table of Contents.....	2
About the Basic Pathological Sciences Examination.....	3
Section 1: The cell as a unit of health and disease .....	4
Section 2: Cellular responses to stress and toxic insults .....	7
Section 3: Inflammation and repair .....	10
Section 4: Haemodynamic disorders: thromboembolic disease and shock .....	13
Section 5: Genetic disorders .....	15
Section 6: Diseases of the immune system .....	17
Section 7: Neoplasia.....	19
Section 8: Infectious diseases .....	22
Section 9: Environmental and nutritional disorders.....	25
Section 10: Diseases of infancy and childhood .....	27
Section 11: Blood vessels.....	28
Section 12: Research concepts .....	30

## About the Basic Pathological Sciences Examination

The Basic Pathological Sciences (BPS) examination is designed to ensure that all doctors undertaking the RCPA training program can demonstrate at an early stage of training that they have adequate foundation knowledge.

The BPS examination is not an entry requirement for the RCPA training program nor is it a prerequisite for sitting the Part I examination, but a pass in this examination (or exemption) must be achieved before proceeding to sit the Part II examination.

The BPS examination may be taken before commencement of training and is open to registered trainees. Prevocational doctors or medical students who have had pathology included within their studies may also attempt the examination prior to registering with the College. This helps with preparation for training and enables trainees to proceed more rapidly with specific discipline training in pathology. It also provides an opportunity to demonstrate commitment to a career in pathology.

The list of examination topics (syllabus) was approved by the RCPA Board of Education and Assessment in 2014 and reflects knowledge that appears in current, authoritative texts as well as newer knowledge that may not yet appear in textbooks.

The syllabus covers the basic mechanisms of disease that trainees need to understand so they are equipped to train in their chosen discipline and to understand pathology disciplines other their own chosen field. For example, the microbiology trainee needs to understand the mechanisms of Systemic Inflammatory Response Syndrome or what a septic infarct looks like; the chemical pathology trainee needs to know about the anatomical pathology changes seen in metabolic syndrome; the anatomical pathology trainee needs to understand why certain antibodies used in routine diagnosis are relevant and the genetic pathology trainee needs to understand how enzyme deficiencies may lead to morphological changes, etc.

The syllabus is primarily based on **the first 11 chapters** of the **Professional Edition** of Robbins and Cotran Pathologic Basis of Disease, by Vinay Kumar, Abul K. Abbas, and Jon C. Aster (editors), 9th edition, 2015, Elsevier (including the online version). Supplementary references have been included, which may either explain details more clearly than the textbook or may contain diagrams that help explain basic concepts, or that cover research design. As much as possible these references are from Open Access journals but for copyright reasons the actual articles are not able to be placed on the College website.

## Section 1: The cell as a unit of health and disease

### 1.1 The genome and epigenome

#### *Gene organisation*

- DNA variants – SNP: what they are and significance in disease, e.g. drug sensitivity
- CNV: what they are and significance in normals and disease, e.g. ERBB2, SMA
- Linkage disequilibrium
- miRNA
- siRNA

#### *Genomic and epigenomic sciences*

- Genome organization, including repetitive DNA, transposons, gene regulatory regions, pseudogenes, etc.
- Mitochondrial genome (structure and function)
- Chromatin structure and function; higher-order chromatin folding and fractal packaging

#### *Gene structure, expression and regulation*

- RNA transcription and post-transcriptional processing
- RNA-mediated regulation of cell function
- Protein translation and post-translational processing
- Epigenetic regulation: DNA methylation, histone modifications/ histone code, RNA-mediated regulation of gene expression
- Epigenome organisation

### 1.2 Control of normal cell proliferation in tissue growth

- Cell cycle diagram
- Labile and stable: which cells are labile and which are stable
- Permanent

### 1.3 Stem cells

- Definition
- Embryonic versus adult: use of Oct4 in IHC and role in carcinogenesis. Role of NANOG
- Use of ESC
- Identification of ESC
- iPS: use in disease identification and treatment

### 1.4 Adult stem cells – where located

- Bone marrow
- Liver
- Brain
- Skin
- Intestine
- Muscle
- Connective tissue

### 1.5 Cell cycle and the role of

- Rb: abnormalities associated with tumour development and progression
- Cdk; use of antibodies in diagnostic pathology and interaction with oncogenic viruses
- Cyclin: use of antibodies in diagnostic pathology and interaction with oncogenic viruses

### 1.6 Growth factors:

- EGFR: mutations in various malignancies
- TGF $\alpha$
- HGF: c-met not only involved in carcinogenesis but also in myocardial infarction
- PDGF: Role in GIST, GBM, DFSP
- VEGF: Antibody therapy and diagnosis in tumours
- FGF: Involvement in organogenesis and may also interact with CD20 affecting Rituxumab therapy
- TGF $\beta$ : A key role in neoplasia, chronic inflammation and keloids
- Ras and mutations: How mutated KRAS is permanently turned on leading to cell proliferation

### 1.7 Growth factor receptors

- Intrinsic TK activity: mechanisms of treatment
- Without intrinsic TK activity: mechanisms of treatment
- G protein receptors: mechanisms of treatment
- Steroid hormone receptors: mechanisms of treatment

### 1.8 Regeneration after liver injury

- Mediators of regeneration

### 1.9 Role of the extracellular matrix – role in inflammation and invasion for neoplasia

#### ***Fibrous structural proteins***

- Collagen
- Elastin

#### ***Cell adhesive glycoproteins***

- Integrins: Postulated role in viral infection and neoplasia
- Cadherins: Usefulness in diagnosis of neoplasia
- Catenins and Wnt pathway: Role in neoplasia and influenced by virus (e.g. KSHV)
- SPARC/osteonectin: Note its role in collagen formation
- Osteopontin: Diverse roles in cancer
- Tenascin: Involved in Ehlers-Danlos, heart remodelling

#### ***Proteoglycans and hyaluronic acid: not passive but involved in cell growth and remodelling***

- Glycosaminoglycans and their families
- Heparan sulfate: Needed to enhance binding of growth factors to receptors; role in toxic shock syndrome
- Chondroitin/dermatan sulfate: Role in osteoarthritis and nerve injury
- Keratan sulfate: Role in osteoarthritis and use as treatment
- Hyaluronan
- Low molecular weight hyaluronic acid: mechanism of action

### 1.10 Cell structure, including the cell membrane, endoplasmic reticulum and intracellular intermediate filaments (keratin, tubulin, actin, desmin) and their role in disease

## Supplementary references

### **NOTCH review**

Gude NA, Emmanuel G, Wu W, Cottage CT, Fischer K, Quijada P, Muraski JA, Alvarez R, Rubio M, Schaefer E, Sussman MA. Activation of Notch-mediated protective signaling in the myocardium. *Circ Res* 2008 May 9;102(9):1025-35.

### **Mitochondria review**

Galluzzi L, Kepp O, Kroemer G. Mitochondria: master regulators of danger signalling. *Nat Rev Mol Cell Biol*. 2012 Dec;13(12):780-8.

### **NF-KB review**

Gordon JW, Shaw JA, Kirshenbaum LA. Multiple facets of NF- $\kappa$ B in the heart: to be or not to NF- $\kappa$ B. *Circ Res*. 2011 Apr 29;108(9):1122-32.

### **RAS review**

Yutzey KE, Colbert M, Robbins J. Ras-related signaling pathways in valve development: ebb and flow. *Physiology (Bethesda)*. 2005 Dec;20:390-7.

### **RET and PTEN review**

Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. *Nat Rev Cancer*. 2007 Jan;7(1):35-45. Epub 2006 Dec 14.

### **WNT review**

Saito-Diaz K, Chen TW, Wang X, Thorne CA, Wallace HA, Page-McCaw A, Lee E. The way Wnt works: components and mechanism. *Growth Factors*. 2013 Feb;31(1):1-31.

### **TGF review**

Akhurst RJ, Hata A. Targeting the TGF $\beta$  signalling pathway in disease. *Nat Rev Drug Discov*. 2012 Oct;11(10):790-811.

## Section 2: Cellular responses to stress and toxic insults

### 2.1 How cells respond to injury

#### **Adaptation**

- Hyperplasia versus hypertrophy
- Physiological versus pathological adaptation:
  - Understanding a major mechanism of disease (myocardial hypertrophy) in the population.
  - Understand the 2 pathways involved (Ca and NO)

#### **Atrophy – Causes and effects**

#### **Reversible injury**

- Fatty change: Role of fructose in NAFLD
- Cellular swelling
- Necrosis
  - Understand the different mechanisms and how these changes can be produced by different stimuli (e.g. infection, oxygen).
  - Why different tissues have different types of necrosis
- Apoptosis (see below)
- Necroptosis: An emerging concept and proposed to be important in SIRS, AMS, ischaemia/reperfusion injury, certain pathogen infections and the importance that this can be modulated.

#### **Mechanisms of cell injury**

- ATP depletion
- Mitochondrial damage
  - How apoptotic signals cause release of cytochrome c and apoptosome formation) and inhibitory role of bcl2 (apoptosis and mitochondria)
- Ca<sup>++</sup> influx
- Oxygen radicals: Recent understanding that these may actually be anti-inflammatory rather than pro-inflammatory
- Membrane permeability
- Protein misfolding: 3 types
  - Loss of function
  - Gain of toxic function
  - Infectious misfolding
- Cellular swelling
- Proteasome-ubiquitin pathway

### 2.2 Ischaemia

- Mechanism: Why ischaemia can lead to cell death
- Reperfusion injury: Important consequence of some therapies

### 2.3 Apoptosis

- Physiological: Identify morphological changes in normal tissues
- Pathological: Identify morphological changes in abnormal tissues
- Mechanisms
  - Understand the key role of the mitochondrion in apoptosis.
  - Recognize the important work done by Australian researchers in this field

### 2.4 Necroptosis

- Mechanisms: Role in inflammation, viral infections etc (see above)

## 2.5 Intracellular accumulation

- Lipids: Important clinical condition (NAFLD, NASH)
- Cholesterol: Understanding how atherosclerotic plaques develop
- Proteins
  - Clinical conditions that have increased proteins
    - A1AT
    - Diabetes mellitus
    - Neurofibrillary tangles
    - Alcoholic hyaline
- Glycogen
  - Diabetes mellitus
  - Glycogen storage diseases
- Pigments
  - Carbon
  - Lipofuscin
  - Melanin
  - Haemosiderin

## 2.6 Calcification

- Dystrophic versus metabolic: Aortic valve calcification

## 2.7 Autophagy

- Autophagy pathways
  - Autophagy in atherosclerosis
  - Autophagy in liver diseases

## 2.8 Aging

- Telomeres: Factors affecting telomere length. Australian Nobel prize winner!
- Oxidative damage
- Calorie restriction: Protective role in disease e.g. Alzheimer's. Potential role of sirtuins

## Supplementary references

### Apoptosis and Necrosis

Guicciardi ME, Malhi H, Mott JL, Gores GJ. Apoptosis and necrosis in the liver. *Compr Physiol*. 2013 Apr;3(2):977-1010.

### Autophagy

Martinet W, De Meyer GR. Autophagy in atherosclerosis: a cell survival and death phenomenon with therapeutic potential. *Circ Res*. 2009 Feb 13;104(3):304-17.

Schneider JL, Cuervo AM. Liver autophagy: much more than just taking out the trash. *Nat Rev Gastroenterol Hepatol*. 2014 Mar;11(3):187-200.

### Calcification

New SE, Aikawa E. Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification. *Circ Res*. 2011 May 27;108(11):1381-91.



**Necroptosis review**

Linkermann A, Green DR. Necroptosis. *N Engl J Med*. 2014 Jan 30;370(5):455-65. doi: 10.1056/NEJMra1310050. Review.

**Protein misfolding review**

Saibil H. Chaperone machines for protein folding, unfolding and disaggregation. *Nat Rev Mol Cell Biol*. 2013 Oct;14(10):630-42.

**Telomeres**

Fyhrquist F, Saijonmaa O, Strandberg T. The roles of senescence and telomere shortening in cardiovascular disease. *Nat Rev Cardiol*. 2013 May; 10(5):274-83.

## Section 3: Inflammation and repair

### 3.1 Stimuli for acute inflammation

### 3.2 The vascular phase

- Flow calibre: how to explain cardinal signs
- Vascular permeability

### 3.3 The cellular phase

- Getting cells to the area: Why CD31 and CD99 are useful antibodies
- Getting cells to identify microbes and dead tissues

### 3.4 Removal of the agent

- Phagocytosis: Key antibacterial mechanism
- Engulfment
- Role of NETS: Role in pathogenesis of SLE
- Getting cells to the area: Role of complement and adhesion molecules
- Getting cells to identify microbes and dead tissues: Role of pathogen recognition mechanisms
- Role of macrophage
  - One of the key cells involved in acute and chronic inflammation
  - Understand the different roles played by different types of macrophages (M1, M2)
- Leukocyte abnormalities: How these may lead to bacterial infection
- Role of the platelet in inflammation
- Termination of the acute inflammatory response
- The MPO system Understanding deficiencies and role in infections
- Role of macrophage
  - One of the key cells involved in acute and chronic inflammation
  - Understand the different roles played by different types of macrophages (M1, M2)

### 3.5 Mediators – cell derived

- Vasoactive: key mediators in the inflammatory process
  - AA, LT
  - PAF
  - ROS
  - NO
  - Cytokines
  - Chemokines

### 3.6 Mediators – plasma derived

- Complement: Use in renal biopsies (see below for abnormality)
- Coagulation and kinins: Role in DIC and Sepsis (see below)

### 3.7 Sterile inflammation and the inflammasome

- Role in NAFLD, gout, silicosis

### 3.8 Chronic inflammation

- Causes
- Features: The ability to distinguish between acute and chronic
- Role of the macrophage: Importance in innate immunity and antigen presentation
- Macrophage activation: Role in obesity and insulin resistance
- How granulomas form: The good and bad of granulomatous inflammation

### 3.9 Systemic effects

- Fever
- Acute phase reactants: Involvement in the development of amyloidosis

### 3.10 Angiogenesis

- Role of VEGF: How it works in antibody directed therapy for a number of diseases such as macular degeneration
- Role of NOTCH
- Stimulation by angiopoietin: Contrasting role of Ang1 and Ang2 and role in sepsis and endothelial dysfunction (see below). Now an antibody against this for trial in ovarian cancer

### 3.11 Wound healing

- Formation of blood clot: a key component in preventing undue haemorrhage
- Formation of granulation tissue
- Cell proliferation and collagen deposition
- Remodelling

### 3.12 Pathological aspects of repair

- Too much
- Too little

### 3.13 Fibrosis

## Supplementary references

### Endothelial cells in inflammation

Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol.* 2007 Oct;7(10):803-15.

### Angiogenesis

Chung AS, Lee J, Ferrara N. Targeting the tumour vasculature: insights from physiological angiogenesis. *Nat Rev Cancer.* 2010 Jul;10(7):505-14.

### Macrophage activation

Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol.* 2008 Dec;8(12):958-69. doi: 10.1038/nri2448

### Inflammasome review

Walsh JG, Muruve DA, Power C. Inflammasomes in the CNS. *Nat Rev Neurosci.* 2014 Feb;15(2):84-97

Rock KL, Kataoka H, Lai JJ. Uric acid as a danger signal in gout and its comorbidities. *Nat Rev Rheumatol.* 2013 Jan;9(1):13-23

**Neutrophil review**

Phillipson M, Kubes P. The neutrophil in vascular inflammation. *Nat Med.* 2011 Nov 7;17(11):1381-90.

**Neutrophils and innate immunity**

Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol.* 2011 Jul 25;11(8):519-31

## Section 4: Haemodynamic disorders: thromboembolic disease and shock

### 4.1 Oedema - 5 categories (2% of Australians died of heart failure)

- Increased hydrostatic
- Decreased plasma oncotic
- Na<sup>+</sup> retention
- Lymphatic obstruction
- Inflammation
- Types of exudates and effusions

### 4.2 Haemorrhage

- Haematoma formation: Correlation of clinical appearances with pathological changes
- Petechiae formation: Correlation of clinical appearances with pathological changes
- Purpura causes
  - Correlation of clinical appearances with pathological changes
  - Relation to immune dysfunction and inflammation
- Ecchymosis: Correlation of clinical appearances with pathological changes
- Breakdown of blood

### 4.3 Haemostasis

- Vasoconstriction
- Primary haemostasis
- Secondary haemostasis

### 4.4 Platelets

- Receptors
- $\alpha$  granules: components and role in inflammation and thrombosis
- $\beta$  granules: components and role in inflammation and thrombosis
- Adhesion: components and role in inflammation and thrombosis
- Secretion: components and role in inflammation and thrombosis
- Aggregations

### 4.5 Coagulation cascade

- Role of fibrin
- Role of thrombin
- Role of factor XII: inhibiting factor XII may reduce sepsis induced inflammation and injury

### 4.6 Thrombosis

#### ***Factors leading to thrombosis***

- Endothelial injury: key initiator in atherosclerosis, sepsis and DIC
- Stasis of blood
- Hypercoagulability of blood
- Primary: Leiden mutation: common mutation in Australia
  - PT gene mutation: common mutation in Australia
  - Homocysteine: role in atherosclerosis
- Secondary: Drugs
  - Cancer
  - HIT
  - Antiphospholipid: role in systemic diseases, e.g. SLE

#### ***Fate of thrombus***

#### 4.7 Fibrinolytic pathway

- Evidence of fibrinolytic dysfunction in metabolic syndrome

#### 4.8 DIC

#### 4.9 Emboli – types

- Thromboemboli: 4% of deaths in Australia
- Fat and marrow
- Air
- Amniotic fluid
- Septic
- Systemic embolism

#### 4.10 Infarct - Red and white

- Correlate gross appearances with pathology

#### 4.11 Shock – Mechanisms

- Septic: 12% of all admissions to Australian and New Zealand ICU are due to severe sepsis with a mortality of 60%
  - SIRS (pro-inflammatory)
  - CARS (anti-inflammatory)
  - MARS
  - Immunopathogenic
  - Coagulation disorders in sepsis: How sepsis is able to activate the coagulation cascade. Review of therapies attempted to try and modulate this

### Supplementary references

#### Coagulation review

Hoppe B, Dörner T. Coagulation and the fibrin network in rheumatic disease: a role beyond haemostasis. *Nat Rev Rheumatol*. 2012 Dec;8(12):738-46.

#### Coagulation and neutrophils

Ruf W, Ruggeri ZM. Neutrophils release brakes of coagulation. *Nat Med*. 2010 Aug;16(8):851-2.

#### Sepsis

Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, Remick DG. Sepsis: multiple abnormalities, heterogeneous responses and evolving understanding. *Physiol Rev*. 2013 Jul;93(3):1247-88.

M Lee WL, Liles WC. Endothelial activation, dysfunction and permeability during severe infections. *Curr Opin Hematol*. 2011 May;18(3):191-6

Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013 Dec;13(12):862-74.

## Section 5: Genetic disorders

### 5.1 Mutation

- Point mutation in coding sequence
- Missense versus nonsense, e.g. HbA to HbS
- Mutation within non-coding
- Deletions
- Trinucleotide repeats

### 5.2 Single gene

- Types
  - Autosomal dominant – loss of function
  - Gain of function
  - Autosomal recessive
  - X-linked
- Result in
  - Enzyme defects
    - Increased substrate
    - Decreased end product
    - Decreased inactivation of tissue damage
  - Defects in receptors
  - Alteration in structure/function
  - Adverse reaction to drugs

### 5.3 Structural abnormalities

- Number
  - Aneuploidy
  - Trisomy: common congenital pathology (T21, 18, 13)
  - Mosaicism
- Structure
  - Deletions
  - Ring
  - Inversion
  - Isochromosome
  - Translocation

### 5.4 Non-classical inheritance

- Trinucleotide
- Mitochondrial
- Genomic imprinting
- Gonadal disorders

### 5.5 Methodology

- Advantages and disadvantages of each methodology
  - PCR and detection of DNA sequence
  - Polymorphic markers
  - Southern blotting
  - FISH
  - CGH
  - Immunohistochemistry

## **Supplementary reference**

### **Molecular genetics and genomics**

Coleman WB, Tsongalis GJ (Eds). Diagnostic molecular pathology: a guide to applied molecular testing. London, UK: Academic Press, Elsevier, 2017.



## Section 6: Diseases of the immune system

### 6.1 Innate immunity

- Epithelial barrier – skin, GI, respiratory
- Neutrophils and macrophages
- Dendritic cells
  - Peripheral
  - Follicular
- NK cells
- Complement
  - Understand how complement deficiency may lead to bacterial infections or associated conditions
  - Understanding downstream effects of complement
  - Understand the role of complement in development of atherosclerosis
- PAMP: role in infection and autoimmunity
- DAMP: role in infection and autoimmunity
- TLR: role in infection and autoimmunity

### 6.2 Adaptive

- Humoral: B-cells and Ig
- Structure of lymph nodes and spleen
- Cellular: T-cells (CD4 and CD8)
  - TCR: structure and use of antibodies to detect components
  - Rearrangement: role in assessment of T-cell neoplasia

### 6.3 MHC

- Class I versus Class II: How one triggers CD4 and the other CD8.
- Role of HLA

### 6.4 T-cell subsets

- Th1
- Th2
- Th17
  - IL-17 functions in inflammation, a host defence and autoimmunity.
  - How IL-17 stimulates cytokines and chemokines and functions as antimicrobial.
- Tgamma-delta: allows a quick triggering of the immune response system
- Treg

### 6.5 Hypersensitivity reactions

- Type I – Immediate: A (Atopy/Anaphylaxis)
- Type II – Antibody-mediated: C (Complement/Cytotoxic)
- Type III – Immune complex: I (Immune complex)
- Type IV – T-cell mediated: D (Delayed Type – PPD)

### 6.6 Tolerance

- Central: how escape may lead to auto-immune disease
- Peripheral: role of co-stimulatory molecules such as CD28 and CTLA-4, and development of anergy, apoptosis or suppression

### 6.7 Autoimmunity with

- SLE as example
- RA
- Scleroderma
- IgG4 related disease

### 6.8 Transplant rejection

### 6.9 HIV pathogenesis

- PTLD

### 6.10 Amyloidosis – types

- Mechanism of development
- Why patients with RA can develop Aa

## Supplementary references

### Dendritic cells

van Vliet SJ, García-Vallejo JJ, van Kooyk Y. Dendritic cells and C-type lectin receptors: coupling innate to adaptive immune responses. *Immunol Cell Biol.* 2008 Oct;86(7):580-7.

### Innate immunity

Geijtenbeek TB, Gringhuis SI. Signalling through C-type lectin receptors: shaping immune responses. *Nat Rev Immunol.* 2009 Jul;9(7):465-79.

Hajishengallis G, Lambris JD. Microbial manipulation of receptor crosstalk in innate immunity. *Nat Rev Immunol.* 2011 Mar;11(3):187-200.

### PD-1

Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. *Nat Immunol.* 2013 Dec;14(12):1212-8.

### Toxic shock

Low DE. Toxic shock syndrome: major advances in pathogenesis, but not treatment. *Crit Care Clin.* 2013 Jul;29(3):651-75.

### Tolerance

Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nat Rev Immunol.* 2014 Jun;14(6):377-91.

## Section 7: Neoplasia

### 7.1 Nomenclature

- Benign versus malignant
- Hamartoma: understanding of terminology
- Choristoma: understanding of terminology
- Dysplasia: understanding of terminology

### 7.2 Determination of rates of growth

### 7.3 Cancer stem cells and tumour initiating cells (see above on stem cells)

### 7.4 Metastasis

- Seeding of body cavities
- Lymphatic spread
- Haematogenous

### 7.5 Geographic and environmental factors

- Mechanism of cell induced damage by occupational factors such as:
  - Arsenic
  - Asbestos
  - Benzene
  - Cadmium
  - Chromium
  - Nickel
  - Radon
  - Vinyl chloride

### 7.6 Genetic predisposition

- AD inherited
- Defective DNA repair

### 7.7 Non-hereditary

- Chronic inflammation:
- Viral hepatitis
- Chronic gastritis
- COX-2
- Pre-cancerous conditions e.g. adenoma

### 7.8 Molecular basis:

#### *Self-sufficiency that drives proliferation:*

- Proto-oncogenes and oncogenes
- Growth factors
- Signal transducers
- Alterations in non-receptors e.g. Tyrosine kinase, nMYC
- Transcription factors
- BRAF: Presence in some tumours and use of monoclonal therapy (BRAF monoclonal) as well as diagnosis in histopathology

### ***Insensitivity to growth-inhibition***

- Can't apply the brakes
- P53: use in diagnostic pathology and interaction with oncogenic viruses
- Rb: role in development of some tumours
- APC/ $\beta$  catenin: role in development of some tumours
- Cyclins: diagnostic role in some lesions such as mantle cell lymphoma
- INK4: role in HPV associated disorders and diagnosis
- TGF $\beta$ : role in development of some tumours
- PTEN: may be lost in some tumours
- NF1 and NF2: role in development of tumours in neurofibromatosis (NF) syndromes
- VHL

### ***Evasion of apoptosis***

- bcl-2
  - Viruses such as EBV have bcl-2 homologues
  - Use of Bcl-2 in immunohistochemistry.
- Death pathway (CD95)

### ***Limitless replication***

- Telomeres: Mechanism of action of telomeres in development of cell proliferation

### ***Sustained angiogenesis and vascular changes:***

- VEGF: Use of monoclonal therapy for these tumours
- Hypoxia
- P53
- bFGF: see above for FGF

### ***Ability to invade***

- Invasion of ECM
- Cell dissociation
- Degradation of basement membrane
- Change in attachment to ECM

### ***Defects in repair:***

- ATM: how mutation prevents cell arrest
- BRCA1: involvement in different cancers

## **7.9 Dysregulation of cancer associated genes:**

- Chromosomal changes
- Gene amplification
- Epigenetics

## **7.10 Microbial carcinogenesis:**

- HTLV1
- HBV: the many pathways in which HBV and HCV are involved in carcinogenesis
- HCV
- H pylori
- EBV: how LMP1 of EBV is able to stimulate cell proliferation and survival

## **7.11 Host defences:**

- Changes in tumour antigens

- Tumour immunity including CTLA-4 and PD-1
- Product of mutated genes that are recognized by Class I MHC and Class II
- Overexpressed cellular proteins (i.e. structurally normal)
  - Tyrosinase and melanin
  - Cancer-testis antigen: use in diagnosis and immunotherapy
  - Antigens produced by oncogenic viruses
  - Oncofetal antigens
  - Altered cell-surface glycolipids/glycoproteins: the concept of post-translational modification e.g. sialylation in development of malignancies
  - Ganglioside GD1, GD2: used in monoclonal therapy
  - Mucins – Ca125, CA19-9, MUC1: diagnostic role in neoplasia

### 7.12 Clinical aspects

- Local and humoral
- Cancer cachexia including Warburg effect
- Paraneoplastic:
  - Hypercalcaemia
  - Neuromyopathic
  - Hypertrophic osteoarthropathy: understand some of the proposed mechanisms
  - Migratory thrombophlebitis: activation of Factor X by mucin from tumours increased TF

### 7.13 Laboratory diagnosis

- Histology
- IHC
- Flow
- Molecular profiling
- Tumour markers

## Supplementary references

### ABL pathway

Greuber EK, Smith-Pearson P, Wang J, Pendergast AM. Role of ABL family kinases in cancer: from leukaemia to solid tumours. *Nat Rev Cancer*. 2013 Aug;13(8):559-71

### STAT pathway

Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer*. 2009 Nov;9(11):798-809

### BRAF review

Lavoie H, Therrien M. Cancer: A drug-resistant duo. *Nature*. 2011 Dec 14;480(7377):329-30.

### Micro-RNA review

Nana-Sinkam SP, Croce CM. Clinical applications for microRNAs in cancer. *Clin Pharmacol Ther*. 2013 Jan;93(1):98-104.

### Neoplasia review

Harris TJ, McCormick F. The molecular pathology of cancer. *Nat Rev Clin Oncol*. 2010 May;7(5):251-65.

### P21 review

Rowland BD, Peeper DS. KLF4, p21 and context-dependent opposing forces in cancer. *Nat Rev Cancer*. 2006 Jan;6(1):11-23.

## Section 8: Infectious diseases

### 8.1 Categories of infectious agents

- Prions
- Viruses
- Bacteria: difference between Gram +ve and -ve
- Fungi and cell wall component
- Protozoa
  - Intracellular
  - Extracellular

### 8.2 Route of entry and protective mechanisms

- Skin
  - Breaks in skin – burns, diabetes, trauma
  - Enzymes released by organism e.g. schistosomiasis
- GIT defences
  - Mucus in stomach: how overcome by organisms such as Giardia attach to epithelium
  - Pancreatic enzymes: overcome by Cryptosporidia taken up by enterocyte
  - Defensins: overcome by pore formation by *E histolytica*
  - Normal flora
  - IgA
- Respiratory pathogen strategies:
  - Overcome mucociliary: Influenza cleaves SP
  - Avoid detection by alveolar macrophages
    - Paralyse cilia: H inf, B. pertussis
    - Ciliostasis: Pseudomonas
    - Invade after epithelium lost: Strep/Staph
- Urogenital
  - *N gonorrhoeae* and *E coli* have adherence
- Protective role of mucosa in viral infection: how viruses evade these mechanism

### 8.3 How infectious agents cause disease

- Directly
- Release toxin
- Induce host immune response

### 8.4 Viral pathogenicity:

- HIV: gp 120 binds CD4, CXCR4(T-cell)
- EBV: gp350 – binds CR2 on B cells and integrins
- JCV: Cell type restricted. Only replicates in oligodendrocytes
- Rhinovirus: Temperature sensitive

### 8.5 How viruses kill:

#### *Cytopathic*

- Prevent DNA/RNA replication: Polio
- Inhibit DNA, degrade RNA: HSV
- Increased apoptosis: HIV
- Increased caspases
  - Antiviral immune response: Hepatitis B

- Transformation of infected cells: See neoplasia.

### 8.6 How bacteria and fungi kill

- Biofilms: important aspect of bacterial endocarditis, artificial joint infection and cystic fibrosis
- Adherence to host cells
  - *Strep pyogenes*: (Adhesins) Protein F binds to surface of host cells via fibronectin
  - *E. coli*: cause UTI by binding to urothelial cells (see above)
  - *N. gonorrhoeae*: pili mediate attachment
- Intracellular inhibition of host proteins: *Shigella* and *E. coli*
- Mechanism of cell damage in anthrax
- Mechanism of disease formation in syphilis
- Blocks fusion of lysosome with phagosome: *M tuberculosis*
- Escape from phagolysosome and actin polymerization: *Listeria monocytogenes*
- Capsule and enzyme properties and switching by fungi
- Distinction between yeasts and moulds
- Toxin
  - Exotoxin
    - LPS induces cytokines and chemokines
    - Binds to CD14 and TLR4
    - If excessive may lead to DIC
  - Endotoxin
  - Enzymes: *S. aureus* destroys keratinocytes
  - Alter intercellular signalling: *B. anthrax* and *V. cholera*
  - Neurotoxin: *C. botulism*, *C. tetani*
  - Superantigens stimulate T cells polyclonally: *S. aureus*, *S. pyogenes* toxic shock syndrome

### 8.7 Specific viral pathogens

- Measles
  - Receptor CD46
  - Hallmarks: Lung giant cells
- Mumps
  - Site of replication (lymph node and salivary gland): to explain clinical symptoms
- Polio
  - Receptor unique to humans CD155
  - Percentage that develop symptoms
- WNV/JE/D
  - Replication sites and spread Pathogenesis of a vector disease
  - Role of CCR5
- Dengue
  - Mechanism of infection and reaction: emerging pathogen in Australasian region
- HSV
  - Replication sites
  - How evade CTL (inhibit MHC1): mechanism of immune evasion
- VZV
  - Similar to HSV in mucus membranes
  - Morphology of infection
- CMV
  - Latent infection of monocytes
  - Mechanism of immune evasion: decreases MHC I and II, evade NK cells

- EBV
  - Role of EBNA1, 2
  - Role of LMP1
  - Role of LMP2
  - Morphology of IM

### **8.8 Malaria**

Important infectious agent in Asia Pacific Region; Australia's leading role in development of a vaccine

- Mechanism of replication
- Role of glycoporphin
- Role of thrombospondin

### **Supplementary references**

#### **H pylori update**

Franceschi F, Zuccalà G, Roccarina D, Gasbarrini A. Clinical effects of Helicobacter pylori outside the stomach. *Nat Rev Gastroenterol Hepatol*. 2014 Apr;11(4):234-42

#### **Viral entry review**

Grove J, Marsh M. The cell biology of receptor-mediated virus entry. *J Cell Biol*. 2011 Dec 26;195(7):1071-82.



## Section 9: Environmental and nutritional disorders

### 9.1 Xenobiotic metabolism

### 9.2 Phase I and II reactions and CYP

- Phase I reactions and CYP induction: understand difference between the two
- Phase II reactions

### 9.3 Environmental pollution

- Ozone
- Particulate matter
- Carbon monoxide: a common cause of disease in humans
- Formaldehyde: a common laboratory agent

### 9.4 Metals

- Lead: mechanism of cell damage
- Mercury
- Arsenic
- Cadmium

### 9.5 Occupational health risk

- Chloroform: conversion to phosgene and toxicity
- Polycyclic hydrocarbon: presence in PM2.5 and interaction with DNA
- Organochloride
- Dioxin

### 9.6 Tobacco and role in

- Lung carcinoma
- Atherosclerosis: see atherosclerosis

### 9.7 Alcohol and other medications

- Alcohol
  - Metabolism
  - MEOS
  - Catalase
  - CYP2E1
- Acetaminophen: mechanism of cell damage. A common cause of poisoning in Australia
- Cocaine: mechanism of action
- Heroin: mechanism of action
- Amphetamine
- Morphological changes to pharmaceutical medications

### 9.8 Burns

- Shock: mechanism
- Sepsis: mechanism
- Respiratory insufficiency: mechanism

### 9.9 Ionizing radiation:

- Direct and indirect effects of DNA damage
  - Cell death
  - Teratogenesis

- Carcinogenesis

**9.10 Protein energy malnutrition**

- Dietary
- Cachexia
- Kwashiorkor vs marasmus

**9.11 Vitamin A and role in:**

- Infection: stimulation of RIG-I
- RAR $\alpha$ : immune modulation

**9.12 Vitamin D and role in**

- Infection: understand role of vitamin D as an antibacterial
- Neoplasia: new information on role of vitamin D in tumour prevention and in immunity

**9.13 Vitamin C**

- Results of deficiency: antioxidant mechanism

**9.14 Obesity**

- Leptin versus ghrelin: role in metabolic syndrome

**Supplementary references**

**Sirtuin review**

Oellerich MF, Potente M. FOXOs and sirtuins in vascular growth, maintenance, and aging. *Circ Res.* 2012 Apr 27;110(9):1238-51.

**Vitamin D review**

Hewison M. Antibacterial effects of vitamin D. *Nat Rev Endocrinol.* 2011 Jun;7(6):337-45

## **Section 10: Diseases of infancy and childhood**

### **10.1 Definitions of congenital anomalies**

- Malformations
- Disruptions
- Deformations
- Malformation syndrome
- Sequence
- Agenesis, hypoplasia

### **10.2 Causes of anomalies**

- Genetic
- Environmental
- Pathogenesis regarding to timing

### **10.3 Specific abnormalities**

- Prematurity with NEC
- Fetal hydrops
- SIDS

### **10.4 Inborn errors of metabolism**

- PKU
- Galactosemia
- Cystic fibrosis

### **10.5 Paediatric neoplasms – an overview**

## Section 11: Blood vessels

### 11.1 Endothelial cells

- Contents: use of vWF antibodies and CD31 antibodies
  - Endothelial activation: beneficial but danger in sepsis (too much of a good thing)
- Expressing new inducible properties
- Endothelial dysfunction
- Impairment of vasoactivity
- Thrombogenic
  - Vascular smooth muscle
- Ability to proliferate
- Ability to produce ECM
- Ability of migrate under influence of certain factors such as PDGF, FGF, NO and IFN.

### 11.2 Response to injury

- Intimal thickening
  - Smooth muscle growth
  - Increased matrix

### 11.3 Hypertension:

- Essential
  - Multifactorial
  - Genetic
  - Decreased Na excretion
- Secondary
  - Renovascular
  - Hyperaldosteronism

### 11.4 Atherosclerosis

- Constitutional risk factors
  - Age
  - Gender
  - Genetics
- Modifiable
  - HT
  - DM
  - Inflammation
  - Hypercholesterolaemia
  - Metabolic
  - Lipoprotein a
  - Factors affecting haemostasis

### 11.5 Pathogenesis of atherosclerosis

- Endothelial injury
  - HT, hyperlipidaemia, nicotine, homocysteine, infection, haemodynamic
- Lipids
  - Increased oxygen free radicals
  - Increased nitric oxide
  - Oxidized LDL
    - Ingested by macrophages
    - Release of growth factors by endothelial cells

- Toxic to endothelials -> dysfunction
- Inflammation
  - Macrophages activated increase wbc adhesion
  - Increased T-lymphocyte
  - Increased cytokines
  - Increased complement activation

### **11.6 Consequences**

- Stenosis
- Thrombus etc
- Infarction
- Acute plaque changes
  - Rupture
  - Erosion
  - Haemorrhage
  - Aneurysm

### **Supplementary references**

#### **Atherosclerosis review**

Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nat Med. 2011 Nov 7;17(11):1410-22.

#### **Oxidative stress and vascular disease**

Kim YW, Byzova TV. Oxidative stress in angiogenesis and vascular disease. Blood. 2014 Jan 0;123(5):625-31.

## Section 12: Research concepts

### 12.1 Research

- Definition
- Research vs audit
- Planning
  - Null hypothesis
  - Literature review
  - Ethics approval
- Evidence based medicine: levels of evidence

### 12.2 Research designs

- Naturalistic
- Observational
- Case control
- Cohort
- Cross sectional/prevalence
- Experimental
- Intervention
- Randomized control trial
- Meta-analysis
- Systematic review

### 12.3 Research methods

- Quantitative
- Qualitative
- Mixed methods
- Single/double blind

### 12.4 Data

- Variables: dependent and independent
- Categorical (nominal), ordinal, ratio (interval, continuous)
- Control
- Bias and confounding
- Error – random, systematic
- Type 1 error
- Type 2 error
- P value
- Validity
- Reliability

### 12.5 Measurement

- Accuracy
- Precision
- Frequency distribution (polygon)
- Central tendency: mean, median, mode
- Dispersion: range, standard deviation
- Confidence interval
- Standard error of the mean
- Z-score

## 12.6 Tests

- Sensitivity
- Specificity
- True/false positive/negative

## References

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Schulz KF and Grimes DA. Essential Concepts in Clinical Research: Randomised Controlled Trials and Observational Epidemiology (2<sup>nd</sup> edition). Elsevier, 2019.