NELSON ON PATHOLOGY

BY PROFESSOR OF MEDICINE
WILLIAM NELSON

IMUNE 2007
Nelson on Pathology  
By Professor of Medicine William Nelson  
IMUNE 2007  

We open this book with a conversation of the causes the aetiology of disease, we will discuss some more modern pathways of disease such as the Psycho-Neuro-Immuno-Soma links. This will entail pathway topics. Such topics include cytokines and their role in cell regulation, immune responses, inflammation and systemic responses; genetic events, growth factors and oncogenes in neoplasia; mechanisms in immune tolerance and other advances in immunopathology; viral infection in atherosclerosis; cell adhesion and cell-matrix interactions; and many other. My dedication has been to present a thorough account of the basic mechanisms and components of disease in a comprehensive, yet concise, manner so that the medical undergraduate or the postgraduate trainee in pathology has available a compact revision guide to summarise and reinforce knowledge gained from their teachers on pathology.

Topics:
Introduction:
Causes of disease
Pathway of disease
Iatrogenic disease

1. The cell and cell injury
2. Cellular adaptation and ageing
3. Acute inflammation
4. Healing
5. Chronic inflammation
6. Immunopathology
7. Resistance to infection
8. Immune deficiency
9. Granulomatous diseases
10. The effects of infection and injury on the body
11. Fluids and ions
12. Oedema and congestion
13. Hypertension
14. Atherosclerosis and aneurysms
15. Thrombosis, embolism, and infarction
16. Congenital and inherited disorders
17. Neoplasia
18. Alimentary system
19. Liver, gall-bladder and pancreas
20. Cardiovascular system
21. Respiratory system
22. Urinary system
23. Reproductive system
24. Breast
INTRODUCTION

What’s really killing people in the world today is number one: Tobacco. This is the number one killer. David Kessler was the head of the American FDA in the 1980’s. And when I met Kessler at an FDA meeting he was going to do his job to protect the public. I met him at a meeting in Salt Lake City, Utah and he said he wanted to go after the most major risk to health, smoking. That his job was to protect the American people, included that he should go after big tobacco and to clamp down and to make sure that the people were protected. He was denied that. He was stopped from doing that. He quit the FDA, unable to do his job, as he said. Big tobacco is killing over a million people a year.

The next leading killer is factors that is related to sugar, Big Sugar for it’s corporate name. As people who get bad sugars and bad oils, trans-fatty acids and cooked oils. Factors of bad nutrition in America are making people sick, producing blood sugar problems, producing obesity, cardiovascular problems, and many, many things that the FDA could also affect. Limiting trans-fatty acids, making good sugars (Left handed Fructose), rather than bad sugars(right handed Dextrose).

The body needs right handed sugar (Blood Glucose) to enter the cell for energy. Right handed sugars such as sugar cane, beet sugar, grape sugar, corn sugar are right handed and they enter the cells too fast. This produces fat more easily, hyperglycemia (mild addiction) and then hypoglycemia (mild depression). This puts a burden on the pancreas, the eye and other organs. There is also a well documented negative effect on the immune system from dextrose. If you use chemicals to strip away vitamins and minerals to make the sugar white, and it gets even worse.

Fructose revolves to the left and needs to be converted to the right. A process that takes time and thus allows for a more smooth delivery of the glucose. Less fat, less stress on organs, less craving, less depression, less blood sugar fluctuations. More hormonal and enzyme production thus it is an anti-aging therapy. Use fresh fruits as a sweetener, it will change your life.

Crazy food additives that have not been fully tested add to the food and drug problems. The synthetic foods and drugs have failed. Our society has learned to avoid and mistrust synthetic foods. We will not order them on a menu or buy them of the shelf. We have learned to be chemi-phobic. We know that synthetic foods create cancer and disease. Our society must learn that this is true of our medicines as well.

Our body needs good fatty acids. They make up the cell membrane of all of
our cells. Stress sets them free. Cooking destroys most fatty acids. Meat and potatoes contain very little. In fact the fatty acids from an animal are saturated. Fresh and raw vegetable and unheated vegetable juice are the best source.

Bad food is a problem in degenerative disease. And this is also another industry the FDA is not attacking that the FDA is not doing their job to protect the human beings of America. Big Sugar and cholesterol are leading to diseases that are killing over a million people a year.

In the next category is allopathic doctor prescribed drugs. The medical doctor prescribed medicines are the third largest killer. Big pharmaceuticals are killing in the neighborhood of some 600 – 700 thousand people a year. By all of these statistics, big tobacco, Big Sugar, Big fast food, and Big Pharma, collectively they are in the neighborhood of directly 3 million deaths a year in America alone and possibly 10 million complicating factors creating an incredible burden on the health care system.

We need to embody a new theory of health care. The Hans Selye theory tells us that the cause of disease is a stressor.

**Major stressors include:**

**LACK OF AWARENESS OR LACK OF EDUCATION**

**STRESS**

**HEREDITY**

**MENTAL FACTORS** (GREED, ANGER, DELUSION, ARROGANCE ETC)

**ALLERGY**

**TOXICITY**

**TRAUMA** **INJURY**

**PATHOGENS** **(MICRO-ORGANISMS, WORMS, ETC.)**

**PERVERSE ENERGY** (HEAT, COLD, WIND, DRYNESS, RADIATION ETC)

**DEFICIENCY OR EXCESS OF NUTRIENTS**

**HEALTH THEN ENTER STRESSOR** (TOXIN ETC)-enters

1. **ALARM** symptoms are the alarm
   if stressor continues then
2. **ADAPTATION** symptoms go away as we adapt
   if stressor continues then
3. **EXHAUSTION** the stressors burden the organs
   if stressor continues then
   a. **FUNCTIONAL** first the stressors effect the organ function
      if stressor continues then
   b. **ORGANIC** then the organs start to swell or shrink
      if stressor continues then
4. **DEATH** cellular, organ, organ system, organism death
INTRODUCTION II-

We can see the importance of stress detection and stress reduction. This form of medicine is a more true form of health care where now a days medicine is much more positioned at the end of this scale. In other words a heroic medicine, a disease care system designed to stop you from dying. I have spent a life time trying to build an educational system and a program to make health care more available the Nelson Method of medicine is as follows.

1. Reduce the Causes of Disease
2. Repair the organs weakened by the Causes
3. Unblock the Blockages to energy, nutrition, Oxygen, waste FLOW
4. Treat the symptoms with natural means before resorting to Synthetic
5. Balance the metabolic typing or constitutional imbalances

INTRODUCTION III- iatrogenic (Medical Doctor Caused) disease

The major problem centers around the adverse effects of pharmaceutical agents, biological agents such as vaccines and blood products, and the 'side-effects' of chemotherapy and irradiation. Chemotherapy and irradiation are covered under cancer therapy.

DRUG-INDUCED DISEASE

Adverse reactions to drugs result from either a predictable toxic effect usually related to the dosage level, or an unexpected effect which may have an immunological mechanism or be described as 'idiosyncratic'. Under special circumstances drugs may be teratogenic (i.e. producing mal development in the fetus) or mutagenic.

A. Predictable toxicity is the manifestation of secondary pharmacological actions.
   Drugs injure cells either by:
   1. Direct toxicity, e.g.
      (i) Tetracycline producing fatty liver
      (ii) Oxygen in high concentration giving rise to hyaline membranes in the lung andretrolental fibroplasia in the eye
      (iii) Aspirin injury to the gastric mucosa
   2. Metabolic products
      e.g. Paracetamol metabolism following an overdose results in liver necrosis
   Certain groups of patients are at increased risk from the predictable toxic or side-effects of drugs:
1. Age - the very old and the very young are less tolerant of drugs
2. Genetically determined defects of metabolism:
   (i) Slow acetylation leads to persistence of drugs
   (ii) Pseudocholinesterase deficiency prolongs the effects of neuromuscular blockers
   (iii) Glucose-6-phosphatase deficiency can give rise to haemolytic anaemia during treatment with sulphonamides, anti-malarials
3. Impaired drug metabolism
   (i) Liver disease
   (ii) Immaturity, i.e. in the neonate
4. Reduced drug excretion
   (i) Renal failure
   (ii) In neonates

B. Immunological mechanisms
1. Hypersensitivity reactions - drugs may function as allergens but most only act as antigens after combining with a host macromolecule, usually protein, i.e. they act as hapten. All the classical hypersensitivity reactions can be provoked by drugs:
   (i) Type I
      a. Anaphylactic reactions - e.g. sudden death after parenteral injection of penicillin
      b. Atopic reactions - e.g. urticaria and bronchospasm
   (ii) Type II - most commonly seen as haemolytic reactions following attachment of the drug or a metabolite to the red cell membrane
   (iii) Type III - immune complex formation leading to serum sickness'-type reactions
   (iv) Type IV - cell-mediated reactions are frequently seen in the skin where a drug-protein complex is antigenic to T-cells, so-called 'contact dermatitis'
2. Immunosuppression - drugs which have actions on immune mediators, for example corticosteroids, azathioprine, cyclophosphamide, etc., may increase susceptibility to secondary infection and, in rare instances, predispose to neoplasia

C. Idiosyncrasy
This is an inherent qualitatively abnormal reaction to a drug. Most instances are inexplicable, but some patients are genetically predisposed to such reactions:
1. Mepacrine induced haemolytic anaemia in patients with glucose-6-phosphatase deficiency
2. Drug induced porphyria in genetically susceptible individuals

D. Teratogenesis
Congenital malformations induced by drugs taken during pregnancy, e.g. thalidomide use resulting in absence of limbs

E. Mutagenesis and carcinogenesis
As would be expected with adequate animal testing of drugs, these potential hazards are rarely encountered although it is possible for recessive point mutations to occur without these becoming clinically apparent. The role of drugs in carcinogenesis is
difficult to establish. Neoplasms should develop at the sites of maximum drug concentration, e.g. transitional cell carcinomas in the renal pelvis and bladder in patients taking excessive quantities of phenacetin-containing analgesics, liver neoplasms occurring when carcinogens are generated following hepatic metabolism. Of historical interest neoplasms have occurred at the sites of deposition of drugs or other agents, e.g. skin cancers resulting from arsenical administration, liver sarcomas resulting from thorotrast deposition (a radio-active substance used in radiology).

**ADVERSE EFFECTS OF BIOLOGICAL AGENTS**

Many reactions provoked by animal and human products are being eliminated by the use of biologically engineered compounds, e.g. interferon, insulin, growth hormone. Complications arising from the use of serum and vaccines include:

1. Human sera and blood products
   (i) Infection - HIV, viral hepatitis, cytomegalovirus
   (ii) Hypersensitivity reactions

2. Animal sera
   (i) Hypersensitivity reactions - Arthus reactions, serum sickness, anaphylaxis
   (ii) Neurological effects - encephalitis, Guillain-Barré polyneuritis

3. Live vaccines
   (i) Local or systemic spread, e.g. BCG infection, progressive or generalized vaccinia
   (ii) Neurological effects, e.g. post-vaccinial encephalitis

4. Toxoids and dead vaccines
   (i) Hypersensitivity reactions - mainly local immediate and cell-mediated types
   (ii) Neurological effects - possible role of pertussis vaccine in encephalitis

**INTRODUCTION IV-
Stress Detection and Stress Reduction as New Adjunct to Modern Medicine**

The Bible says “that as a Man thinketh, So is He” Jesus when asked about what food to eat, said it is not what goes into the mouth that defiles someone but what comes out. In fact the Bible, Koran, and all of the religious books abound with references of how the mind affects the body. Prayer and its ability to help people is a basic believe. This was all general knowledge many millennia ago. Our science has no proven these beliefs even further. But today the antiquated science of medicine and small minded doctors have a hard time accepting this fact. Physician Heal Thyself.

Mendeleev made a chart of the elements based on his observations. Then
later it would be learned that this organization of the chemical elements was because of the quantum states of the outer electrons. Quantum theory alone gave us an understanding of chemistry. But quantum theory has the observer effect where the mind of the observer can affect the outcome. Medicine seems to have an unstable phobia and an over compensative distaste for the powers of the mind.

Science has developed a basic understanding of electronics several centuries ago. Electronics made a major boom in technology. It allowed us to understand so much of the world. But modern medicine has resisted an electrical analysis of the body. Yes technology allows for tech measures of the body, but there is little analysis of the body electric. Energetic medicine of Dr. Nelson defines a process to explain the body electric. But the modern medicine fixation on the financial hold of the synthetic chemical industry has prevented a progression of medicine into the modern age.

Nearly a century ago, quantum research overturned the 17th century mechanistic paradigm of “world as a machine,” within which phenomena are to be understood by reducing them to their parts. Reductionism worked for making cars, buildings and was so valuable to our society. But reductionism fails in a complex situation.

Chaos theory gave us an enlightenment that reductionism does not work in complex systems like the human body. Fractal dynamics teach us that the reductionistic model fails in biology.

In an overly complex closed system Fractal dynamics are unpredictable. Reductionism is completely invalid.

The Rules of a Fractal System are 1. nothing ever repeats exactly as before, 2. small changes can prompt very large and dramatic effects, 3. observer effects and the mind can have effect on a complex fractal system (prayer works).

Reductionism is the process of taking a complex situation and reducing it to simple terms. We reduce the weight of a building to a simple vector to calculate the strength of a support wall. Reductionism has been responsible for allowing us to build cars, boats, machines, etc. But reductionism fails in very complex situations. The human body has over 200,000,000,000 cells. Each cell is more complex that we can presently imagine in our verbal minds. This complexity makes our bodies a fractal. Reductionism can not work for
medical analysis.

When the drug companies wanted to test a blood pressure medication they reduce the patient from the complexity of life to a simple variable, blood pressure. They test the blood pressure before, the pre test. Give an intervention, the drug. and then test the blood pressure again, the post test. They do not test the side effects, they observe them. This is important because they can only observe gross side effects and still they get by. If they would have tested the blood sugar, they would have found out that all patients taking certain blood pressure medications get some degree of diabetes every one of them. If they were to test all variables for side effects, it would cost too much to do testing. And there are not enough people to do the test for statistical satisfaction. There are not enough rats, There are not enough fruit flies. the statistics of total protection against side effects are tremendous. These side effects are killing not hundreds of people, not thousands, not tens of thousands, but millions of people every year.

Our society has rejected synthetic foods. We tried the synthetic experiment and it failed. The synthetic foods made cancers and diseases. We will not choose them from a menu, we will not buy them from the shelve. We know from the gourmet that the finest quality is always from the natural. Thus is undeniable. It is just a simple step of intellect to see that it is also true about our medicines as well.

In the IJMSH of 2009 there is an entire issue of the failure of the FDA to protect people from these side effects of synthetic drugs. I spell it SINthetic. It is a sin to kill so many in the name of profit and ignorance, selecting the benefits of natural medicine is ignorance at its ultimate ignorant best. All justified by reductionism. A science not used today by anybody but medicine. The reductionistic methods of drug testing are killing millions and wounding many, many more. But big money is hard to beat, especially when there is 30 billion spent by the drug companies on political lobbying alone in America. Fractal non-linear science has stepped forward to help us understand medicine.

When it was developed in the 1920’s, quantum mechanics was viewed primarily as a way of making sense of the host of anomalous observations at
the level of molecules, atoms, and subatomic particles that could not be explained in terms of older mechanical models. Now, in the 21st century, most physicists are confident that quantum mechanics is a fundamental and general description of the physical world. Indeed, quantum ideas are now being applied to understand the workings of consciousness, environment, electromagnetic field interactions, low-dose healing effects, non-local phenomena, and many other observable phenomena that are unexplainable with an outdated mechanistic world view.

During the last century, traditional medical and philosophical practices, such as Traditional Chinese Medicine, acupuncture, Qi Gong, Tai Chi, meditation, homeopathy, naturopathy, and mind-body techniques considered “esoteric” by the scientific establishment, have been largely ignored while the world’s attention was focused solely on drugs, surgery, radiation, genetics, and other invasive and reductionist approaches. Approaches that make money for the synthetic chemical cartel. But these synthetic therapies are failing. One by one the synthetic pharmaceuticals are being discredited.

With massive public pressure to support research of safer Complementary and Alternative Medicines (CAM), and with athletic communities seeking effective drugless performance advantages, significant funds are moving in those directions. Quantum physics and non-linear mathematics are providing scientists with better models for understanding complex systems and subtle interactions, like mental, emotional, environmental, and electro-physiological interactions in the human body. With new ways of measuring and verifying energetic and quantum events and their effects on health, disease, and performance, scientists are re-igniting interest in traditional healing techniques, and the field of subtle-energy medicine is emerging.

One of the most exciting and promising fields of CAM involves bioelectromagnetics (BEM)—the study of electromagnetic fields (EMF’s) and their biological effects. Based largely on biofeedback principles, BEM diagnostic and healing devices are well entrenched in mainstream medicine already, but scientists are really only beginning to realize the practically limitless potentials that this field offers.
The purpose of this article is to introduce modern advanced biofeedback, one of the fastest growing areas within the field of BEM, and provide supportive evidence for its use with Olympic-level athletes. Focus is given to the most advanced biofeedback technology, the SCIO (Scientific Consciousness Information Operating System), which combines mind-body training with a methodology of applying micro-currents at various frequencies to the body, measuring feedback, and utilizing the resultant information for stress reduction, education, behavioral modification, and self-adjusting cybernetic correction (an historic innovation exclusive to the SCIO).

“Conventional” biofeedback, the use of devices to monitor physiological processes and enhance mind-body interactions, has been one of the most researched branches of CAM for over 60 years, and it provides the basis for this study and for claims made in athletic sport performance. “Quantum” biofeedback is the term adopted to describe advanced Quantum Electro-Dynamic Biofeedback capabilities performed with the SCIO system, which combines the benefits of both conventional and advanced methods.

**PSYCHO-SOMATIC and SOMA-PSYCHO DISEASE**

Medicine was shocked to see that there was indeed a set of diseases that were psycho-somatic. The mind can affect the body. The largest type is the stomach ulcer or other gastric disturbance. Here stress upsets the sympathetic nervous balance versus the parasympathetic. There are also soma-psycho diseases such as when hormonal disturbances produce mental abnormalities. Medicine was shocked at the proof of this. But this threatened pharmaceutical sales.

As time goes by the list of possible involvements from psycho-somatic and soma-psycho disease grows and grows. Till now there is overwhelming evidence that there is mental involvement in over 80% of disease.

Stress detection and stress reduction then become an integral component in disease care and thus health care. There is an overwhelming evidence for a Psych-Neuro-Immuno-Soma link this is so well documented as to be an irrefutable fact. But still some over
fastidious small minded geeks will reject this truism. In the PNIS issue of the journal we see more collective evidence.

THE END OF DEGENERATIVE DISEASE

We need to bring an end to degenerative disease as a predominant killer. To do so has taken a lifetime of dedication, persecution, and violent attacks from so many places. First we must confront the failure of the FDA to protect Americans from degenerative disease. Let's review the largest killers.

What's really killing people in the world today is number one: Tobacco. This is the number one killer. David Kessler was the head of the American FDA in the 1980's. And when I met Kessler at an FDA meeting he was going to do his job to protect the public. I met him at a meeting in Salt Lake City, Utah and he said he wanted to go after the most major risk to health, smoking. That his job was to protect the American people, included that he should go after big tobacco and to clamp down and to make sure that the people were protected. He was denied that. He was stopped from doing that. He quit the FDA, unable to do his job, as he said. Big tobacco is killing over a million people a year.

The next leading killer is factors that is related to sugar, Big Sugar for it's corporate name. As people who get bad sugars and bad oils, trans-fatty acids and cooked oils. Factors of bad nutrition in America are making people sick, producing blood sugar problems, producing obesity, cardiovascular problems, and many, many things that the FDA could also affect. Limiting trans-fatty acids, making good sugars (Left handed Fructose), rather than bad sugars (right handed Dextrose).

The body needs right handed sugar (Blood Glucose) to enter the cell for energy. Right handed sugars such as sugar cane, beet sugar, grape sugar, corn sugar are right handed and they enter the cells too fast. This produces fat more easily, hyperglycemia (mild addiction) and then hypoglycemia (mild depression). This puts a burden on the pancreas, the eye and other organs. There is also a well documented negative effect on the immune system from dextrose. If you use chemicals to strip away vitamins and minerals to make the sugar white, and it gets even worse.

Fructose revolves to the left and needs to be converted to the right. A process that takes time and thus allows for a more smooth delivery of the glucose. Less fat, less stress on organs, less craving, less depression, less
blood sugar fluctuations. More hormonal and enzyme production thus it is an anti-aging therapy. Use fresh fruits as a sweetener, it will change your life.

Crazy food additives that have not been fully tested add to the food and drug problems. The synthetic foods and drugs have failed. Our society has learned to avoid and mistrust synthetic foods. We will not order them on a menu or buy them of the shelf. We have learned to be chemi-phobic. We know that synthetic foods create cancer and disease. Our society must learn that this is true of our medicines as well.

Our body needs good fatty acids. They make up the cell membrane of all of our cells. Stress sets them free. Cooking destroys most fatty acids. Meat and potatoes contain very little. In fact the fatty acids from an animal are saturated. Fresh and raw vegetable and unheated vegetable juice are the best source.

Bad food is a problem in degenerative disease. And this is also another industry the FDA is not attacking that the FDA is not doing their job to protect the human beings of America. Big Sugar and cholesterol are leading to diseases that are killing over a million people a year.

In the next category is allopathic doctor prescribed drugs. The medical doctor prescribed medicines are the third largest killer. Big pharmaceuticals are killing in the neighborhood of some 600 – 700 thousand people a year. By all of these statistics, big tobacco, Big Sugar, Big fast food, and Big Pharma, collectively they are in the neighborhood of directly 3 million deaths a year in America alone and possibly 10 million complicating factors creating an incredible burden on the health care system.
1. The cell and cell injury

STRUCTURE AND FUNCTION OF CELL COMPONENTS

**Nucleus**
The nucleus is composed principally of deoxyribonucleic acid (DNA) in combination with a protein (histone) within a ground substance. The nucleic acid material (chromatin) stains well with basic dyes such as haematoxylin and methylene blue, and DNA can be stained specifically by the Feulgen technique. Chromatin patterns vary from cell to cell. The plasma cell, for example, has a distinctive 'cartwheel' pattern. The nucleus is separated from the cytoplasm by a double membrane - the nuclear envelope - containing circular holes 50 to 70 nm in diameter - nuclear pores. The pores, which are usually crossed by a diffuse membrane, probably represent the sites of interchange between nucleus and cytoplasm.

Functions of the nucleus
1. Replication of DNA
2. Production of messenger RNA
3. Synthesis of some nuclear proteins

**Nucleolus**
The nucleus normally contains one or more small basophilic structures - nucleoli, composed of a dense network (nucleolonema) enclosing paler areas (the pars amorphha). The granules of the nucleolonema are thought to represent newly-synthesised ribosome subunits which pass out of the nucleus along with messenger RNA and direct the synthesis of specific proteins in the cytoplasm.

**Cytoplasm**
Cytosol differs from extracellular fluid in having a high concentration of potassium, magnesium and phosphate. Sodium is actively excluded by the ATP-dependent 'sodium-pump' across the cell membrane. Many functions reside in the cytosol or cytoplasmic matrix, namely:
1. Glycolysis
2. Some reactions in gluconeogenesis
3. Activation and synthesis of some amino acids
4. Fatty acid synthesis
5. Mononucleotide synthesis
6. Phosphogluconate pathway
7. Second messenger signalling pathways

**Mitochondria**
These round, ovoid, or sinuous cytoplasmic organelles possess a complete outer trilaminar membrane and an inner membrane which shows numerous infoldings termed cristae. Although all mitochondria have this basic structure there is considerable variability both in the number and length of the cristae and in the number and general outline of the mitochondria. Cells with a high metabolic activity have large mitochondria with numerous cristae, for example cardiac muscle and gastric parietal cells. In the liver, whilst the mitochondria are large, the cristae are sparse and irregular. Mitochondria contain most of the enzymes of the citric acid cycle and the energy derived from the oxidation of acetyl Co-A in the cycle is used to
convert adenosine diphosphate to triphosphate - oxidative phosphorylation.

**Endoplasmic reticulum**
All cells contain a system of complex paired membranes enclosing small vesicles or channels - the cisternae. These membranes form the endoplasmic reticulum (ER) and are either studded with ribosomes forming so-called rough ER or are devoid of granules and are termed smooth ER. The main function of the rough ER, together with free ribosomes in the cytoplasm, is protein synthesis. Protein produced by the rough ER is usually for export via the Golgi apparatus. Ribosomes are basophilic so that the cytoplasm of cells capable of rapid protein synthesis stains well with haematoxylin or pyronin. Examples of cells showing such cytoplasmic basophilia are plasma cells, exocrine cells of the pancreas, and hepatocytes. The smooth ER is concerned with synthesis of triglycerides from free fatty acids, drug metabolism and detoxification, glycogen synthesis, and the synthesis of steroid hormones. Cells rich in smooth ER (as well as mitochondria) show a greater affinity for acidic dyes such as eosin and acid fuchsin.

**The Golgi apparatus**
The Golgi apparatus is a series of membrane lamellae, membrane-bound vacuoles and small vesicles, best seen in secretory cells such as those of the exocrine pancreas, goblet cells, and the absorptive cells of the gut. The Golgi is thought to package secretions which reach it through the cisternae of the ER. The secretion granules then bud off and migrate to the apex of the cell.

**Microfilaments**
Microfilaments are thin filaments with an average diameter of 6 nm composed of polymerised actin. They are usually found in bundles within a network and are important in retaining the shape of cells and in cell motility.

**Microtubules**
Microtubules are non-contractile structures, about 25 nm in diameter, and of variable length. They are composed of subunits (dimers) of tubulin which can be rapidly re-assembled thus providing a dynamic cytoskeleton, and are found in cilia and flagella as well as forming mitotic spindles and centrioles in all types of cells. Microtubules are involved in:
1. Maintaining the cytoskeleton
2. Mitotic division
3. Transport pathways for secretions and other organelles
4. Ciliary activity
5. Phagocytosis
6. Sensory transduction, e.g. in polymorphs
7. Cell motility

**Intermediate filaments**
Intermediate filaments are tubular structures 7-11 nm in diameter composed of polymers of one or more (up to 10) polypeptides. The various polymers show a degree of tissue specificity and their detection has proved useful in the characterisation of tumour cells. Tissue specificity is as follows:
1. Vimentin - mesenchymal cells
2. Desmin - muscle cells
3. Cytokeratins - epithelial cells
4. Neurofilaments - neurones
5. Glial fibrillary acidic protein - glial cells

Lysosomes
These are rounded, membrane-bound bodies showing wide variation in their size, shape, and internal structure. They are the main components of an intracellular digestive system and contain numerous hydrolases active at acid pH, such as phosphatase, betaglucuronidase, esterases, ribonuclease and deoxyribonuclease. The digestive activity is generally contained within the lysosomes themselves. In heterophagy exogenous material enters the cell by endocytosis and the vacuole thus formed fuses with primary lysosomes, probably produced by the Golgi apparatus. In autophagy, damaged cytoplasmic components are enveloped to form an autophagic vacuole which fuses with primary lysosomes. Digestion proceeds in the secondary lysosomes so-formed and products diffuse out to be re-utilised by the cell. Undigested material can in some instances be expelled by exocytosis, otherwise it remains in the cell as a residual dense body. Examples of proteins taken into cells and digested within lysosomes are:
1. Haemoglobin
2. Native immunoglobulin and immune complexes
3. Denatured proteins
4. Protein reabsorption in renal tubules

Lysosomes are important in:
1. Polymorphs and macrophages in killing and digesting infective agents
2. Removal of unwanted cells during embryonic development
3. Disposal of excess secretary products in glandular cells
4. Osteoclastic remodelling of bone by secreted enzymes
5. Supply of nutrients, e.g. in liver

Microbodies
Microbodies or peroxisomes consist of a homogeneous matrix sometimes containing a central crystalline nucleus enclosed in a single membrane. They contain a number of enzymes, including amino-acid oxidases, urate oxidase and catalase, and are most numerous in liver and kidney cells. Their role in the cell economy is obscure but one of their functions may be the regulation of blood lipid levels.

Cell membrane
Cells are enclosed by a unit membrane composed of lipids, proteins, and oligo- and polysaccharides. The membrane is essentially a phospholipid bilayer with the hydrophobic lipid moieties internalised and the proteins (and glycoproteins) present as:
1. Integral membrane proteins - globular proteins intercalated to varying depths within the bilayer and in some instances completely spanning the membrane. Integrated glycoproteins are always arranged so that their carbohydrate moieties are exposed at the cell surface where they act as specific receptor molecules. Whilst some integral proteins are capable of lateral movement within the lipid bilayer (thus altering the molecular pattern presented at the surface) others appear to be attached to microtubules and microfilaments and mediate 'transmembrane cytoskeletal control'
2. *Peripheral* membrane proteins - are not essential to structural integrity and are bound to integral proteins or glycolipids by ionic bonds.

The cell membrane has a number of important functions:
1. Intake of exogenous material by phagocytosis, pinocytosis or micropinocytosis
2. Selective permeability
3. The ATP-associated sodium-pump which actively shifts sodium ions across the membrane out of the cytoplasm
4. Cell-to-cell contact and adhesion by means of junctional complexes - tight junction, intermediate junction, and desmosome
5. Contact inhibition - the mechanism whereby further proliferation and movement of cells is inhibited by contact with like cells
6. Antigenicity (histocompatibility)
7. Recognition - the capacity to recognise foreign antigens and altered or effete host cells, resides at the cell membrane and is mediated by cell-bound antibodies or antibody-like molecules
8. Receptor sites for stimulatory hormones, cytokines and other chemical mediators.

**PROTEOLYSIS AND PROTEIN FOLDING**

While it is self evident that rapid and efficient proteolysis is central to the proper functioning of the cell; it is only recently that the mechanisms controlling proteolysis have begun to be understood. For instance, there is a very close connection between proteolysis and control of the cell cycle. Indeed a single protein, *cyclin B*, which accumulates during the G1 and S phases must be degraded for cells to exit mitosis. One of the major factors in the regulation of such degradation is the protein *ubiquitin*. As its name implies, this protein is highly conserved throughout eukaryotes, and is unique in its ability to become reversibly cross-linked to other proteins. In doing so it is likely that ubiquitin serves as a movable binding site for proteins that do not have complementary structures and by bringing such proteins into close association is an essential component of many important proteolytic pathways.

The proper functioning of newly synthesised proteins is dependent upon them attaining the correct three dimensional configuration. The complex folding of polypeptides involved in this process is controlled by other proteins which are either enzymes promoting disulphide formation and isomerisation, or members of a family of proteins which stabilise unfolded and partially folded structures and prevent the development of inappropriate intra- and inter-chain bonds. They achieve this without themselves becoming incorporated into the structure. These proteins are termed *chaperones* and are vital to the correct translocation, assembly, disassembly and transport of polypeptides and protein oligomers. The proteins first came to notice when found in excessive amounts as part of the cellular response to high temperature, hence the name 'heat-shock' proteins. Now that it is appreciated that they are essential to normal function and increased in many forms of injury they are termed *stress* proteins and *chaperonins*.

**CELL - CELL ADHESION**

1. Junctional mechanisms
   (i) Desmosomes - intercellular junctions linked to the intermediate filaments of the cytoskeleton. They are composed of a series of transmembrane glycoproteins
and proteins termed desmogleins and desmplakins

(ii) Adherens junctions which contain different forms of transmembrane adhesion molecules, the main members being the *cadherin* family. These molecules are responsible for calcium dependent intercellular adhesion. Other junctions between cells, namely *gap and tight* junctions, are not adhesive structures. Their function is to allow the passage of small molecules into, or between, cells.

2. **Non-junctional mechanisms**

Intercellular adhesion is also facilitated by membrane-bound cell adhesion molecules (CAMs). Some CAMs are specific to certain tissues whereas others, for example so-called liver cell adhesion molecule (L-CAM), are widely distributed in epithelial and other tissues. The existence of non-specific adhesion molecules means that only a small repertoire of such molecules is required for adhesion between a multiplicity of cell types.

**CELL - MATRIX ADHESION**

1. **Junctional mechanisms**
   
   (i) Hemidesmosomes bind cells to their substratum
   
   (ii) Focal contacts

2. **Non-junctional mechanisms**

The cell surface is equipped with a variety of receptors for extracellular matrix molecules such as fibronectin and laminin. The major receptors are members of the *integrin* family. Integrins are heterodimers that recognise and bind to a specific amino-acid sequence in the matrix molecule. They are transmembrane proteins whose cytoplasmic domains interact through intermediate proteins such as *vinculin* or *talin* to bind to actin microfilaments. Thus integrins act as an important bridge between basement membrane or connective tissue matrix proteins and intra-cytoplasmic microfilaments and permit anchorage of cells to matrix components.

**THE CELL CYCLE AND CELL REPRODUCTION**

After division (mitosis) the cell enters the first resting phase - *G1* (Gap 1). This phase is variable and in some cells may be so prolonged that they are effectively out of cycle (Go). They may return to the cycle or become fully differentiated 'end-cells' incapable of division. *S*-phase is concerned with the synthesis of DNA and histones taking the cell up to a tetraploid state. At the same time there is parallel synthesis of RNA and proteins. The cell then enters a second, brief resting phase - *G2* (Gap 2) which is followed by mitosis. If both 'daughter' cells enter the replicative cycle then the total number of cells will double with each generation and the population will grow exponentially. Whilst this does occur in the early stages of embryonic life, later in development the cells do not immediately enter the cycle so that doubling times are prolonged.

Two categories of dividing cells are recognized, *stem cells* and *progeny cells*:

1. Stem cells are capable of producing different forms of progeny cell. When they divide they give rise to one replacement stem cell and one dividing progeny cell.

2. Progeny cells divide but also differentiate into one or more types of specialised cells. Thus, the progeny cell pool gradually diverges in form and function and is
only renewed by input from the stem cells.
The rate of growth of a tissue is a function of the frequency with which stem cells reproduce and supply the progeny pool and the number of 'amplifying' divisions undergone by the progeny cells during their lifetime. The number of such amplifying divisions is modified by:
1. The spatial distribution of cells within a tissue
2. Surface attachments
3. Cytokines and their receptors

**CYTOKINES**

Cytokines are a family of glycosylated or non glycosylated polypeptides and proteins secreted by cells in response to a stimulus which modulates the behaviour of target cells. They exert their effects in three ways:
(i) They act on the cell producing them - *an autocrine effect*
(ii) They act on cells in the vicinity of the producing cell - *a paracrine effect*
(iii) They act systemically on distant sites - *an endocrine effect.*

*Classes of cytokines*
1. Growth factors
2. Colony stimulating factors
3. Interleukins
4. Tumour necrosis factors
5. Interferons

Growth factors and colony stimulating factors are involved in cell proliferation and differentiation in a wide variety of tissues. The major activities of interleukins, tumour necrosis factors and interferons are concerned with the immune response and inflammation and will be considered later.

1. Growth factors (GFs)
These are small polypeptides produced by various cells. They have a number of actions, the most important of which are the control of cell proliferation and differentiation..
(i) Epidermal growth factor family
   a. Epidermal growth factor
   b. Transforming growth factor a
   c. Amphiregulin

These GFs are produced by many cell types. They interact with the erb-B family of receptors and are important in epithelial cell proliferation and differentiation
(ii) Platelet derived growth factor (PDGF)
   Dimers of two subunits PDGF-A and PDGF-B produced by platelets, endothelial cells, activated macrophages etc., important in tissue repair and chronic inflammatory processes
(iii) Transforming growth factor b family
   a. TGFb1-3 (major actions - growth regulation, connective tissue synthesis )
   b. BMP2A, 2B and 3 (bone morphogenesis)
   c. Inhibins A and B (regulation of pituitary gonad axis)
   d. Activin A and AB (antagonism of inhibins actions)
   e. Mullerian inhibitory substance (development of male reproductive system)
(iv) Fibroblast growth factor (FGF)
   a. Acidic FGF
   b. Basic FGF
   c. int 2
   d. FGF5
   e. hst
These GFs are potent stimulatory factors for neuroectodermal cells, endothelial cells, fibroblasts etc., and play a major role in embryogenesis
(v) Insulin-like growth factor
   a. Type I
   b. Type II
Mediate action of hormones such as growth hormone
(vi) Nerve growth factors
   a. Nerve growth factor
   b. Neuroleukin
Neurotropic factors for neural tissues which play a role in wound healing

2. **Colony stimulating factors**
Regulate the proliferation and differentiation of haematopoietic cells.

<table>
<thead>
<tr>
<th>CSF</th>
<th>Principal source</th>
<th>Major action</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-CSF granulocytes (granulocyte/macrophage)</td>
<td>T lymphocytes and many other cell types</td>
<td>Proliferation and activation of granulocytes and macrophages.</td>
</tr>
<tr>
<td>G-CSF (granulocyte) activation</td>
<td>Monocytes, fibroblasts and endothelium</td>
<td>Enhances granulocyte production and chemotactic activation</td>
</tr>
<tr>
<td>M-CSF macrophages and (macrophage) and erythropoietin erythroid</td>
<td>Monocytes, fibroblasts and endothelium</td>
<td>Chemotactic activation of secretion of prostaglandin E</td>
</tr>
<tr>
<td></td>
<td>Kidney and some other cell types</td>
<td>Differentiation of precursors</td>
</tr>
</tbody>
</table>
CYTOKINE RECEPTORS

Receptors consist of
(i) an external domain which is the binding site for the ligand
(ii) a transmembrane region which spans the cell membrane
(iii) an intracellular domain which delivers the signal to the cytosol

Receptors may consist of a single polypeptide chain on its own, e.g. EGF-R, a single polypeptide chain plus a second helper protein, e.g. IFN-γ receptor, or two polypeptide chains, e.g. IGF-1 receptor. Receptors can be of high or low affinity, e.g. IL-2, or they can have a different level of response to different ligands, e.g. IGF-1 receptor binding IGF-1 and insulin.

Receptor modulation is achieved by altering:
(i) the rate of synthesis and membrane insertion
(ii) receptor internalisation and recycling
(iii) receptor degradation via lysosomes

Signal transduction
Following binding of cytokine with its appropriate receptor there follows a cascade of events that eventually (after several hours) lead to stimulation of DNA synthesis and cell division or induction of mRNA and protein synthesis. The mechanisms involved in this 'signal transduction' are highly complex. Some receptors operate through activation of their internal tyrosine kinase domain, e.g. erb-B family, PDGF-r, IGF1-r; others transduce their signals via cytoplasmic tyrosine or serine/threonine kinases, e.g. src, yes, fgr; yet others operate through phospholipase-C activity, e.g. crk. These enzymes act through a series of intermediaries and protein phosphorylation to 'switch on' DNA and protein synthesis.

Generation of inositol triphosphate through phospholipase-C activity leads to mobilisation of calcium ions from internal pools and thereby modulates many calcium-dependent processes. This is an example of calcium ions acting as a 'second messenger'.

Calcium fluxes in cell regulation
Although extracellular fluid has a high Ca^{2+} concentration (10^{-3} \text{ M}), intracellular levels are several orders lower (about 10^{-5} \text{ M}). This steep electrochemical gradient is maintained by the relative impermeability of the plasma membrane to calcium ions, and by active exclusion by a calcium pump. When a cell is activated, for example by a cytokine, hormone or nerve impulse, calcium ions move into the cell cytoplasm.
The ions originate either from:
1. Extracellular calcium ions which enter through:
   (i) Receptor operated channels
   (ii) Voltage dependent channels
2. Calcium 'stores' in the smooth endoplasmic reticulum The influx of calcium ions leads to the activation of a calciumbinding protein calmodulin. The active calmodulin-calcium complex regulates a wide range of intracellular processes including:
   1. Cyclic nucleotide metabolism
   2. Microfilament polymerisation
   3. Microtubule assembly-disassembly
   4. Secretion, e.g. in enterocytes and in the exocrine pancreas
5. Glycogen metabolism

**CAUSES OF CELL INJURY**

1. **Toxic substances**
   - (i) Biochemically specific - enzyme poisons such as cyanide on cytochrome oxidase; sodium fluoracetate block of the Krebs cycle
   - (ii) Tissue specific - e.g. paracetamol (acetaminophen) producing liver necrosis; alloxan giving rise to necrosis in B-cells of the pancreatic islets
   - (iii) General - e.g. ethyl alcohol, psychotropic drugs, heavy metal poisons

2. **Physical agents**
   - (i) Trauma
   - (ii) Temperature injuries, i.e. extreme heat or cold
   - (iii) Pressure effects (blast injuries)
   - (iv) Ionising radiation
   - (v) Electrical injuries

3. **Lack of nutrients**
   - **Local**
     - (i) Failure of cellular absorption, e.g. glucose in diabetes mellitus
     - (ii) Failure of blood supply – ischaemia
   - **General**
     - (i) Hypoxia, e.g. severe anaemia, respiratory failure
     - (ii) Malnutrition resulting from dietary deficiency or malabsorption
     - (iii) Hormonal deficiency

4. **Infective agents and parasites**
   - **Injure by**
     - (i) Production of toxins, exotoxins and endotoxins (lipopolysaccharide)
     - (ii) Competition for essential nutrients
     - (iii) Provocation of an inflammatory cell or immune response
     - (iv) Intracellular multiplication

5. **Immune mechanisms**
   - (i) Autoimmune diseases
   - (ii) Hypersensitivity states, e.g. contact dermatitis

6. **Genetic defects**
   - (i) Change in chromosome make-up
     - a. Alteration in number - aneuploidy
     - b. Alteration in structure as a result of chromosomal deletion or translocation
   - (ii) Change in genetic code
     - a. Inherited, e.g. inborn errors of metabolism, thalassaemia
     - b. Acquired
       - Mutation
       - Deletion of gene
EVOLUTION OF CELL INJURY

The term 'injury' embraces a wide range of adverse events which will affect cellular homeostasis. Where an injury is mild and transient the cell may suffer limited damage to membranes and organelles which can be readily repaired and normal structure and function restored. Such injuries induce increased synthesis of specific stress proteins which could help in the dissociation and clearance of denatured proteins and protein complexes, and satisfy the greater demand for protein folding brought about by the adverse conditions. Unwanted or effete organelles and membranes are removed by autophagocytosis.

More severe and sustained injury may result in degenerative changes such as cloudy swelling and fat accumulation which, if the injurious agent is withdrawn, are also reversible and the cell recovers. If, however, the injury persists the cell may degenerate further, become irreversibly damaged, and die. In some circumstances the injury may be so catastrophic that the cell dies without showing these intermediate changes.

Alternatively, when an adverse environment persists, the cell may adapt and establish a new steady state. Only when the cell fails to establish an altered level of homeostasis in response to injury is cell death inevitable. Under some circumstances the new environment may require a heightened state of activity for homeostasis to be maintained. Increased functional activity is brought about by an increase in the number of organelles and a concomitant increase in cell size - cellular hypertrophy. An increase in cell number may be required to cope with increased demands or to compensate for a shortened life span - hyperplasia. More frequently, a cell adapts to an adverse environment by functioning at a lower level than normal. The diminution in functional organelles is paralleled by reduced cell size - atrophy. Finally tissues exposed to an adverse environment over a sustained period may adapt by altering the direction of cellular differentiation to produce cells more capable of combating the environment. Such a change is termed metaplasia.

SUBLETHAL CELL INJURY

Sublethal injury may result in long-term adaptive changes or in degenerative changes which can be reversed but might also herald the onset of cell death. The degenerative consequences of cell injury comprise:

1. Injury to cell membranes and mitochondria
   (i) Loss of microvilli and focal expansions of the plasma membrane
   (ii) Formation of vacuoles by enfolding of the plasma membrane - endocytic vacuolation
   (iii) Disruption of the RER and loss of ribosomes. This brings about the loss of cytoplasmic basophilia seen on light microscopy
   (iv) Mitochondrial swelling and loss of cristae

2. Cloudy swelling (intracellular oedema)
This results from the accumulation of watery fluid in the dilated sacs or cisternae of the endoplasmic reticulum and mitochondria.
   (i) Early stages - under the light microscope, the cytoplasm has a fine granularity like ground-glass
   (ii) Later stages - progressive dilatation of the ER leads to the appearance of clear
vacuoles visible by light microscopy - *hydropic vacuolation*

**Mechanism**
(i) Fall in oxidative phosphorylation due to  
   a. Lack of oxygen  
   b. Damage to mitochondria or its enzymatic pathways  
The diminished formation of ATP affects all the energy requiring reactions in the cell but in particular leads to failure of the sodium-pump. Sodium ions enter the cell in exchange for potassium and as the former have a larger hydration shell, there is a net influx of water.  
(ii) Increased intracellular osmotic pressure resulting from  
   a. Accumulation of lactate and pyruvate  
   b. Net catabolism of macromolecules

**3. Fatty change**  
This is the appearance of abundant spherical globules of fat (triglyceride) within the cytoplasm. It can be demonstrated using frozen sections and staining with lipid-soluble dyes such as Oil red 0 or Sudan black, and is most commonly seen in cells of the liver, kidney and myocardium. Fatty change must be distinguished from pathological adiposity where fat cells (lipocytes) infiltrate an organ or tissue. This is a feature of severe obesity. In normal cells fat is held in a dispersed state and transported out of the cell as micelles or lipoprotein complexes (triglyceride with phospholipid and/or protein). Triglycerides are synthesized from free fatty acids (FFAs) entering the cell from the blood. FFAs also undergo oxidation to CO₂ and conversion to phospholipid.

**Mechanism**  
Fatty change results from:  
A. Impaired metabolism of fat  
   (i) Reduced oxidation of FFAs with increased conversion to triglycerides  
   (ii) Reduced synthesis of phospholipid and protein. This results in:  
      a. Reduced dispersal of fat leading to globule formation  
      b. Diminished release of fat from the cell as lipoprotein  
B. Excessive entry of FFAs and triglyceride into the cell  
**Causes**  
(i) Diabetes mellitus  
(ii) Congestive cardiac failure  
(iii) Severe anaemia  
(iv) Malnutrition and wasting disease  
(v) Ischaemia, e.g. coronary insufficiency  
(vi) Infections (septicaemia)  
(vii) Chronic alcoholism (liver)  
(viii) Poisons, e.g. carbon tetrachloride, phosphorus (liver)

**4. Lysosomal damage**  
A. Lysosomal rupture is thought to be responsible for some forms of cell injury, e.g. injury to alveolar macrophages after phagocytosis of silica. In toxic injury, however, rupture is thought to be a consequence of advanced cellular damage rather than an
initiating factor.

B. **Lysosomal overloading.** Many metabolic processes depend upon the hydrolysis of intermediates by lysosomal enzymes. When a particular hydrolase is deficient or absent, all substances entering lysosomes or arising within them that require this enzyme for their further digestion, accumulate and progressively enlarge the lysosome.

Substances accumulating in this way include:

(i) *Lipofuscin* (see below)
(ii) *Glycogen* - Type 11 storage disease (Pompe)
(iii) *Protein* - forming the hyaline deposits in kidney tubule cells in the nephrotic syndrome
(iv) *Lipids* - Gaucher's disease (glucoceramide) Niemann-Pick disease (sphingomyelin)

Tay-Sachs disease (gangliosides)
(v) *Mucopolysaccharide* - Hurier's syndrome (gargoylism)
(vi) *Cystine* - cystinosis

5. **Sublethal nuclear injury**

A. Inclusions

(i) False inclusions resulting from invagination of the nuclear membrane
(ii) Abnormal deposits of glycogen, lamellar bodies, etc.
(iii) Viral inclusions, e.g. herpes

B. Abnormal DNA-dependent RNA synthesis

C. DNA damage

Ionising radiation and certain chemical compounds such as the mustards and ethylenimides exert their toxic effects principally on cell nuclei. High doses result in cell death, but smaller doses may produce:

(i) Mutations. Latent injury to DNA may result in mutation and the development of malignant cells.

(ii) Genetic abnormalities. Similar injury to germ cells may produce changes in the DNA code which result in genetic abnormalities in the offspring.

6. **Excessive or abnormal products**

(i) Excess of normal secretions, e.g. mucus
(ii) Amyloid
(iii) Basement membrane-like material
(iv) Calcification
(v) Mallory's hyaline

7. **Accumulation of lipofuscins**

These are widely distributed brown-pigments derived from the oxidation of lipids and are of heterogeneous composition. The pigment is seen in the following situations:

(i) In certain apparently normal cells
   a. Epithelial cells of the epididymis
   b. Interstitial cells of the testis
   c. Ganglion cells and neurones

(ii) In ageing cells - so-called 'wear-and-tear' pigment. This is best seen in 'permanent' tissues such as myocardium where the fibres show increasing
pigmentation with age. It is particularly evident where the heart has atrophied as a result of wasting disease -'brown atrophy'. Also seen in liver cells with increasing age and with certain drugs, e.g. phenobarbitone

(iii) As 'ceroid' pigment in the liver after liver cell necrosis and oxidation of lipid membranes, e.g. after viral hepatitis, drug hepatotoxicity

(iv) In liver cells in the Dubin-Johnson syndrome

(v) In the 'brown-bowel' syndrome. Pigmentation of smooth muscle cells accompanies various malabsorption states

LETHAL CELL INJURY

An immediate consequence of damage to the plasma membrane is altered permeability with an influx of calcium ions. The ensuing disturbance of intracellular calcium homeostasis has far-reaching effects on cellular function and sets in train (or accelerates) the metabolic changes that will lead to cell death. These include:

1. Cessation of oxidative phosphorylation in damaged mitochondria
2. Failure of ATP-dependent pumps so that more calcium and sodium ions enter the cell (together with water) and potassium ions pass out. With advancing membrane disruption, semipermeability is lost and the influx of water ceases.
3. Disordered nuclear function and a decrease in DNA-dependent RNA synthesis
4. Continuing anaerobic glycolysis leads to a fall in pH which activates hydrolytic enzymes escaping from damaged lysosomes and accelerates autolysis.

It seems likely that plasma membrane injury caused by a wide variety of agents inevitably leads to a rapid influx of calcium ions and that this influx initiates a final common pathway of metabolic disturbances leading to cell death.

Cell death is recognized by:

1. Ultrastructural changes
   (i) Margination or progressive loss of nuclear chromatin
   (ii) Focal rupture of the nuclear membrane
   (iii) Breakdown of the plasmalemma
   (iv) Development of flocculent densities in mitochondria

2. Changes in the nucleus
   (i) Swelling and clumping of chromatin
   (ii) Pyknosis - condensation of chromatin and shrinkage of the nucleus
   (iii) Karyorrhexis - fragmentation of the nucleus
   (iv) Karyolysis - dissolution of the nucleus by deoxyribonuclease

3. Changes in the cytoplasmic staining
   (i) Positive staining with vital dyes such as trypan blue, which reflects abnormal membrane permeability. Viable cells are impermeable to these dyes.
   (ii) Opacification - denaturation of proteins leads to aggregation with resultant opacification of the cytoplasm
   (iii) Eosinophilia - exposure of basic amino groups results in increased affinity for acidic dyes such as eosin

4. Biochemical changes
   (i) Release of K' by dead cells
   (ii) Release of enzymes into the blood, e.g. increased plasma levels of creatine kinases, lactic dehydrogenase and aspartate aminotransferase (formerly GOT)
(iii) Release of protein or protein breakdown products into the blood, e.g. myoglobin from injured skeletal muscle cells.

CELL DEATH AND NECROSIS

Cell death occurs at the point where injury becomes irreversible. The dead cell then enters a phase in which there is progressive degradation brought about by denaturation and hydrolysis of cell constituents - this is necrosis. The term autolysis is sometimes applied to degradation associated with somatic death but the distinction from necrosis following individual or multiple cell death is artificial.

APOPTOSIS

Apoptosis is a form of cell death in which single cells are eliminated from living tissue. In apoptosis the cell passes through the following stages:
1. Condensation of chromatin in the nucleus
2. Deep invaginations of the nuclear membrane
3. Fragmentation of the nucleus
4. Contraction of the cytosol and aggregation of cytoplasmic organelles
5. Budding and separation of membrane-bound bodies containing condensed organelles and nuclear fragments

This converts the cell into several small apoptotic bodies which are usually phagocytosed by surrounding healthy tissue cells or by macrophages. Apoptosis does not provoke an acute inflammatory response and large numbers of cells can be eliminated from tissues without disturbing the basic architecture. This is the mode of cell death seen in normal cell-turnover and in the following situations:
1. Embryological development and metamorphosis
2. Atrophy, which may be either physiological (involution) or pathological
3. Spontaneous cell-deletion in tumours
4. In certain viral infections, for example those affecting the liver, viral hepatitis, yellow fever,
5. Cells dying as a result of a cytotoxic T-lymphocyte attack, for example in chronic active hepatitis graft-versus-host reactions
6. Irradiation and chemotherapy applied at doses lower than those which cause frank necrosis
7. Clonal selection in the immune system

Apoptosis has been termed 'programmed cell death' and is brought about by a stereotyped mechanism involving calcium and magnesium-dependent endonucleases which cleave nuclear DNA and other effector molecules which require continuing synthetic activity by the cell. It is reasonable to assume that apoptosis is to some extent under genetic control and two genes claimed to be involved in programmed cell death have recently been partly characterized, but changes in the immediate environment of the cell are of crucial importance. The effect of these environmental signals will differ according to the cell type and to its stage of development or maturation. Furthermore, apoptosis may be induced by the appearance of a stimulus as when immature thymocytes are exposed to glucocorticoids, or when a stimulus is withdrawn such as removal of interleukin-2
from mature T lymphocytes.

FORMS OF NECROSIS

A. General forms
1. Coagulative necrosis
   (i) Architecture preserved, e.g. renal infarct, syphilitic gumma
   (ii) Architecture destroyed, e.g. caseous necrosis in tuberculosis
2. Colliquative necrosis - necrosis and liquefaction, e.g. cerebral infarct

B. Special forms
1. Fat necrosis
   (i) Traumatic - release of lipid from fat cells provokes a chronic inflammatory and giant cell response as seen in subcutaneous fat or the breast
   (ii) Enzymatic - as occurs in association with acute pancreatitis
2. Fibrinoid 'necrosis' - this is not a true necrosis but a strongly eosinophilic degeneration of collagen, e.g. in a rheumatoid nodule; or in polyarteritis nodosa. A similar appearance may result from:
   (i) Deposition of fibrin
   (ii) Deposition of antigen-antibody complexes
   (iii) Necrosis of smooth muscle
3. Gangrene

CONSEQUENCES OF NECROSIS

1. Acute inflammation
2. Healing by repair or regeneration
3. Chronic inflammation
4. Immunological reactions to subcellular components released by dead tissue, or to self-antigens altered by denaturation, e.g. the post-myocardial infarction syndrome
5. Calcification, e.g. in old caseous foci of tuberculosis

2. Cellular adaption and ageing

ATROPHY

Atrophy is the acquired diminution in size of an organ or tissue brought about by loss or decrease in size of its constituent cells. Loss of cells is by single-cell necrosis (apoptosis). Reduction in size of cells is a result of disturbed intermediary metabolism with decreased oxidative phosphorylation and an increase in glycolysis. There is increased focal cytoplasmic degradation and the effete intracellular components are taken into autophagic vacuoles. In some cells, e.g. liver, heart, brain, oxidised lipids derived from these membranes persist as the brown pigment
lipofuscin. Evidence of other types of sublethal injury such as cloudy swelling and fatty change may precede atrophy of cells. Atrophy must be distinguished from a failure in development of an organ or tissue.

Hypoplasia is a partial failure of development whereby an organ does not attain the normal size, e.g. hypoplasia of one or both kidneys.

Agenesis is a complete failure of development, e.g. congenital absence of one or both kidneys.

Atrophy can occur under physiological or pathological conditions:

A. Physiological atrophy
   1. In the fetus
      (i) Branchial clefts
      (ii) Thyroglossal duct
      (iii) Notochord
   2. In the neonate
      (i) Ductus arteriosus
      (ii) Umbilical vessels
      (iii) Urachus
   3. Post adolescence
      (i) Lymphoid tissue
         a. Tonsils
         b. Mesenteric lymph nodes
         c. Appendix
         d. Thymus
   4. In the adult
      (i) Post-partum involution of the uterus
      (ii) Post-lactational atrophy of the breasts
      (iii) Post-menopausal atrophy of the uterus, ovaries, and breasts

B. Pathological atrophy
   1. Localized atrophy
      (i) Ischaemia, e.g. cerebral atrophy due to atherosclerosis
      (ii) Pressure
         a. Aortic aneurysm eroding bone
         b. Meningioma causing atrophy of overlying skull
         c. Hydronephrosis producing atrophy of the kidney parenchyma
      (iii) Disuse
         a. Local osteoporosis and muscular atrophy resulting from immobilisation
         b. Obstruction of a duct draining an exocrine gland leads to atrophy of the glandular elements, e.g. salivary gland
      (iv) Autoimmune
         a. Adrenal atrophy in idiopathic Addison's disease
         b. Gastric parietal-cell atrophy in pernicious anaemia
      (v) Hormone withdrawal
a. Endometrial atrophy after oestrogen withdrawal
b. Testicular atrophy, in cirrhosis, oestrogen therapy, etc.
(vi) Neuropathic
   a. Muscle atrophy following loss of nerve supply
(vii) Idiopathic
   a. Villous atrophy in coeliac disease

2. Generalized atrophy results from:
   (i) Sustained increased catabolism in fever, following severe trauma, etc.
   (ii) Simple starvation, severe malnutrition, malabsorption and malignant cachexia
   (iii) Senility
   (iv) Hypopituitarism

Generalized atrophy is characterized by:
   (i) Muscle wasting
   (ii) Loss of adipose tissue
   (iii) ‘Brown atrophy’ of the heart
   (iv) Microsplanchnia

**HYPERTROPHY**

**Hypertrophy** is the increase in size of an organ or tissue brought about by an increase in size of its specialized cells. In a pure form, hypertrophy is found only in muscle and is usually a response to an increased demand for work. A further rare cause is the hypertrophy of the tongue and heart seen in acromegaly resulting from increased stimulation by growth hormone.

1. Cardiac muscle
   (i) Left ventricle (> 1.5 cm average thickness)
      a. Systemic hypertension
      b. Aortic valvular disease
      c. Mitral incompetence
      d. High-output states such as severe anaemia, hypercapnia, thyrotoxicosis
      e. Hypertrophic cardiomyopathy
   (ii) Right ventricle (> 0.4 cm thickness)
      a. Chronic lung disease - cor pulmonale
      b. Mitral stenosis
      c. Secondary to left ventricular failure
      d. Congenital left to right shunts
      e. Pulmonary or tricuspid valvular lesions

2. Skeletal muscle - exercise

3. Smooth muscle
   (i) Uterus - pregnancy
   (ii) Arteries - hypertension (medial hypertrophy)
   (iii) Alimentary tract (usually proximal to an obstruction), e.g.
      a. Above an oesophageal stricture
b. Proximal to an annular carcinoma of the colon
c. Idiopathic hypertrophic pyloric stenosis

(iv) Urinary bladder (obstruction to outflow)
   a. Prostatic enlargement
   b. Urethral stricture
   c. Meatal stricture
d. Severe phimosis
e. Congenital bladder neck obstruction

HYPERPLASIA

Hyperplasia is an increase in size of an organ or tissue brought about by an increase in number of its specialized cells. In many cases, hyperplasia is associated with some degree of hypertrophy of individual cells.

1. Endocrine glands
   (i) Adrenal cortex
      a. ACTH administration
      b. Basophil adenoma of the pituitary
      c. Idiopathic hyperplasia
      d. Congenital adrenal hyperplasia
   (ii) Parathyroids
      a. Primary (idiopathic) hyperplasia
      b. Secondary to chronic renal failure
   (iii) Thyroid - primary thyrotoxicosis (Graves' disease)
   (iv) Pituitary
      a. Acidophil hyperplasia is an occasional cause of acromegaly
      b. Basophil hyperplasia - Cushing's syndrome
   (v) Pancreatic islets
      Hyperplasia is seen in the babies of diabetic mothers

2. Endocrine target organs
   (i) Breasts
      a. Physiological hyperplasia in pregnancy and lactation
      b. Pathological in cystic disease of the breast
   (ii) Endometrium
      Cystic hyperplasia in response to excessive oestrogen stimulation
   (iii) Prostate - benign nodular hyperplasia

3. Skin
   (i) Prickle-cell hyperplasia (acanthosis) is seen in many skin diseases including
      a. Psoriasis (in the rete pegs)
      b. Chronic dermatitis
      c. Acanthosis nigricans
      d. Viral warts
   (ii) Pseudo-epitheliomatous hyperplasia is seen
      a. In association with chronic inflammation and granulation tissue
      b. Overlying dermal tumours such as granular-cell myoblastoma
      c. In kerato-acanthoma
4. **Lining epithelia**

   e.g. at the margins of healing ulcers in the stomach, duodenum or colon

5. **Bone marrow**

   Hyperplasia is most commonly seen where demand for red blood cells is increased by

   (i) Haemolytic states
   (ii) Hypoxia

**METAPLASIA**

Metaplasia is the conversion or replacement of one normal adult cell type by a different adult (fully-differentiated) cell type. In most instances, such conversion is achieved by a change in differentiation in the progeny pool but the term is also employed where one type of epithelium is substituted by another, for example by migration from the margins of an ulcer at a junction between two epithelia. Metaplasia is usually a response to chronic irritation or inflammation and rarely does the alteration cross histogenetic boundaries.

Altered environmental factors inhibit differentiation along the usual pathway whilst promoting differentiation via some new pathway. Such factors cause cells to stop growing at different growth-arrest points thereby altering the differentiation potential of the precursor cells. However, these cells have no intrinsic defect in their regulatory processes so that further changes in the environment are capable of reversing the metaplastic process.

The appearance of different forms of epithelia within a tissue might also be due to the development of novel cell lineages whose progeny adopt a phenotype not usually found at that site. The appearance of so-called pyloric metaplasia (ulcer associated cell lineage) in the mucosa of the intestine following ulceration might arise by this mechanism.

Metaplasia can have disadvantages in that the normal function of the original cell type is lost and this may render the parent organ vulnerable to damage, e.g. loss of the mucociliary escalator when tracheo-bronchial epithelium changes to a squamous cell type.

**FORMS OF METAPLASIA**

**A. Epithelial**

1. **Squamous metaplasia**

   (i) From pseudo-stratified columnar ciliated epithelium
      a. In the trachea and bronchi in chronic bronchitis, cigarette smokers, bronchiectasis
      b. In nasal sinuses, (occasionally) in chronic sinusitis and in hypovitaminosis A
   (ii) From simple columnar epithelium
      a. Endometrium in senility
      b. Gall-bladder in cholelithiasis
      c. Prostatic ducts in ageing and oestrogen therapy
      d. Endocervical mucosa and glands associated with cervical 'erosion'
   (iii) From transitional cell epithelium
      a. Renal pelvis with calculi
b. Urinary bladder with chronic cystitis or schistosomiasis
(iii) From mesothelium of the pleura and peritoneum

2. Columnar metaplasia
(i) 'Pink-cell' or apocrine metaplasia seen in cystic disease of the breast
(ii) Intestinal metaplasia of the gastric mucosa in chronic gastritis
(iii) In mesothelium of peritoneum, pleura and synovium

B. Connective tissue
1. Osseous metaplasia
   (i) In sites of dystrophic calcification
      a. Scars
      b. Old tuberculous lesions
      c. Medial calcification of arteries
   (ii) In muscle
      a. Localized myositis ossificans
      b. Post-traumatic
      c. After tetanus
      d. Paraplegia
   (iii) In soft tissues
      a. Tumoral calcinosis (?) 
      b. Progressive fibrodyplasia ossificans
      c. Pseudo-hypoparathyroidism
      d. Hereditary osteodystrophy (Albright's)

2. Myeloid metaplasia
   a. Development of haemopoietic tissue in the metaplastic bone
   b. Extra-medullary haemopoiesis in the liver and spleen, e.g. in myelofibrosis

AGEING

The mechanisms underlying ageing at the somatic and cellular levels remain obscure. Several factors indicate a genetic basis:
1. Each species has a characteristic mean and maximum life span
2. In the human, although life expectancy has generally increased, the maximum life span remains virtually unchanged
3. Longevity has definite familial associations
4. Certain diseases with a genetic basis are associated with accelerated ageing and a diminished life span, e.g. Werner's syndrome and progeria.

Research on cell culture lines has demonstrated that normal cells have a finite capacity for replication, the so-called Hayflick number. However, this limit is rarely, if ever, reached by cells in vivo so that senescence cannot be attributed solely to a failure of cell division. Nevertheless, it may be that following mitosis cells are produced which enter a permanent G_0 phase and are irreversibly committed to senescence and death. Such 'committed' cells may exhibit normal growth (for a time) but dilute the fraction of cycling cells to a point where the population cannot be maintained. Strong experimental evidence for a genetic control mechanism of ageing by a family of senescence genes has accumulated. Fusion of immortal cells with normal cells can lead to senescence of the hybrid, and subsequent non-random loss of chromosomes can restore immortality. Transfection of selected chromosomes back into immortal cell lines restores senescence. The function of
these genes has not yet been established.

**Theories of cellular ageing**

1. **Random**
   - (i) **Somatic mutation**
     Ageing results from random damage to DNA produced by mutagens such as radiation, viral infection, free radicals, etc., which is not adequately remedied by DNA repair. The repair mechanisms themselves may decrease in efficiency and contribute to the accumulation of mutations.
   - (ii) **'Error catastrophe'**
     Ageing is envisaged as a deterioration in the mechanisms responsible for the accuracy of transcription and translation. Minor errors in the synthesis of proteins and, in particular, enzymes, gradually accumulate to the point where the cell can no longer survive.

2. **Programmed**
   This theory implicates senescence or 'lethal' genes which slow down or stop vital processes. Selection or expression of such genes is seen as an active process brought about by evolutionary pressures which confer an advantage on the species at the expense of individual death.

These theories are not mutually exclusive. The maximum life span may be a programmed phenomenon which is shortened to the actual life span by environmental factors or random genetic events reducing the cells' capacity to survive.

**3. Acute inflammation**

'The reaction of vascularized living tissue to local injury'

**BASIC COMPONENTS**

1. Changes in the microcirculation
2. Formation of a fluid exudate
3. Formation of a cellular exudate

**1. Changes in the microcirculation**

*Changes in calibre*
   - (i) Transient arteriolar constriction as a direct response to the injurious agent
   - (ii) Persistent vasodilatation of arterioles, venules, and lymphatics, and an opening up of 'dormant' parts of the capillary network - *active hyperaemia*

*Changes in flow*
   - (i) Initially rapid as a result of vasodilatation
   - (ii) Slowing with disturbance of axial flow as a result of increased blood viscosity secondary to loss of plasma through the vessel wall

**2. Formation of a fluid exudate**

Normally the walls of small blood vessels are freely permeable to water and
crystalloids but most of the plasma proteins are retained, i.e. there is 'molecular sieving'.

Normal fluid transport may be via:
(i) Micropinocytosis - transfer of plasma across the endothelial cell within vesicles
(ii) Intermittent opening of inter-endothelial cell junctions
(iii) 'Closed' inter-endothelial junctions

The quantitative importance of these various routes is not known. Micropinocytosis and transient opening of junctions would permit the passage of plasma including high molecular weight proteins across the endothelium, so that molecular sieving would have to occur at the basement membrane. This membrane, however, is freely permeable to large molecules so these mechanisms cannot explain the low protein fluid output of normal vessels. On the other hand, normal ('closed') inter-endothelial cell junctions allow the passage of water, crystalloids and low molecular weight proteins, so that this mechanism adequately accounts for molecular sieving.

The formation of a protein-rich fluid exudate in inflammation is facilitated by separation of the intercellular junctions of the endothelium. Such separation, which is maximal in post-capillary venules, increases vascular permeability for higher molecular weight proteins such as fibrinogen and immunoglobulins. Gap formation between endothelial cells is a consequence of:
(i) Direct injury
   a. Lethal - resulting in the desquamation of dead cells and production of defects in the endothelial lining
   b. Sub-lethal - causing cells to 'round-up' and separate
(ii) Contraction of microfilaments under the influence of chemical mediators of inflammation

The fluid exudate carries into the inflamed tissue the following important constituents of the plasma:
(i) Components of the complement system
(ii) Specific antibodies which can act by coating bacteria prior to phagocytosis, or by neutralising exotoxins
(iii) Circulating cytokines e.g. interleukin-1
(iv) Acute phase proteins of which the principal member is fibrinogen. Once in the interstitium fibrinogen is converted to fibrin. Fibrin is important as a:
   a. Cement substance uniting severed tissues
   b. Scaffold for repair processes
   c. Barrier against the spread of organisms
   d. Surface against which the phagocytosis of microorganisms is enhanced - contact phagocytosis
(v) Therapeutic agents-antibiotics, anti-inflammatory drugs, etc.

In addition, the increased fluid transit through the inflamed part has a beneficial dilutional effect on toxin and metabolite accumulation.

3. Formation of a cellular exudate
Following the phase of increased vascular permeability, leucocytes migrate through the walls of venules and appear in the interstitium. It was formerly believed that the leucocytes utilised the enlarged gaps between endothelial-cells to facilitate emigration, but recent work has demonstrated that the phase of increased
permeability may be finished before migration begins. It is now thought that polymorphs (the first cells to appear) themselves open-up the gaps by inserting a cytoplasmic projection or pseudopodium into the junction. After the cell has passed through, the junction immediately closes and prevents further escape of plasma. The exudation of polymorphs is followed by monocyte emigration which may take 6-12 hrs to reach maximal levels. By this time the rate of polymorph accumulation is declining in a non-pyogenic inflammatory response.

Polymorph emigration can be divided into two main phases, adhesion and penetration:

(i) Adhesion between polymorphs and endothelial cells. The mechanisms underlying adhesion are much more related to changes in the endothelial cell than to alterations in polymorphs and this explains the localized nature of polymorph margination and adhesion. The mechanisms underlying polymorph adhesion are:
   a. Synthesis of adhesion molecules by endothelial cells which bind to specific receptors on the polymorph, e.g. ELAM-1 (endothelial leucocyte adhesion molecule), and ICAM-1 (intercellular adhesion molecule)
   b. Production of platelet activating factor (PAF) by endothelial cells may promote rapid adhesion, i.e. in the first few minutes following injury
   c. Complement activation leads to the deposition of C3b on the endothelial cell and serves as a bridge with the C3b receptor on polymorphs

Induction of adhesion molecule synthesis is brought about by:
   a. Cytokines, such as tumour necrosis factor (TNF) and interleukin 1 (IL-1)
   b. Bacterial endotoxins

(ii) Penetration of the vessel wall by polymorphs involves:
   a. Opening up of gaps between endothelial cells by insertion of a 'pseudopodium'
   b. Migration into the subendothelial space under the influence of cytokines, TNF, IL-1 and chemotactic agents
   c. Passage through the vascular basement membrane following its physical disruption. How the polymorph achieves this disruption is not known

MEDIATORS OF INFLAMMATION

The endogenous mediators of inflammation are derived either from plasma constituents or from cells.

Plasma-derived mediators
A. The complement system
B. The kinin system
C. The coagulation-fibrinolysis system

Cell-derived mediators
A. Vasoactive amines
B. Acidic lipid products
C. Lysosomal products
D. Cytokines
PLASMA-DERIVED MEDIATORS

A. The complement system

Complement is the main effector pathway of the humoral immune response and results in
(i) cytolysis
(ii) the production of biologically active products which increase vascular permeability and enhance leucocyte migration and phagocytosis
(iii) involvement of the coagulation and fibrinolytic systems

1. The classical pathway
Activation initiates a sequence of cleavage reactions each of which produces an enzyme responsible for the next step in the cascade. In this way considerable amplification of the response is achieved. The major components are identified as Cl-C9 whilst their cleavage products carry a lower case suffix. The high molecular weight products are usually designated 'b', e.g. C3b, whilst the minor fragments are designated 'a'. (C2b is an exception being of low molecular weight.) Activated components are identified by a bar over the numbers.
There are 11 proteins in the classical pathway, Cl having three main components, Clq,Clr and Cls, held together by calcium ions. Activation may be triggered by a number of agents, the most important of which are complexes of IgG and IgM with antigen. The antigen is usually a cell or bacterial wall with antibodies attached by their Fab sites. Clq combines with their Fc regions and activates Clr which cleaves a peptide from Cls. The activated Cls acts as an esterase on C4 and C2 and the major products C4b and C2a remain attached to the cell membrane where they act in combination as the classical C3 convertase. C4b2a acts on several C3 molecules releasing the anaphylatoxin C3a into the fluid phase. The major product C3b combines with C4b2a and the enlarged complex then cleaves C5 releasing a second anaphylatoxin C5a. Without further enzymatic action C5b binds C6 and C7, and this complex binds C8 and six or more C9 molecules to form the final membrane attack unit.

2. The alternate pathway
Complement can also be activated at the C3 level without prior involvement of Cl, C4 and C2. Activation of an initiating factor (IF) in conjunction with C3 triggers the alternate pathway. The most important activators are bacterial lipopolysaccharides (endotoxins) and aggregated IgA, IgE and IgG4. Activated IF binds to a site on the bacterial wall and reacts with activated Factor B (C3 activator) and native C3 to form an enzyme with limited C3 convertase activity. This acts on more C3, releasing C3a into the fluid phase and depositing C3b at further sites on the cell membrane. The C3b combines with activated B to form a complex which has labile C3 convertase activity. In this way more C3b is generated and by further combinations with B can greatly multiply the number of cell-bound C3b complexes. This is the amplification feed-back loop. These complexes bind properdin (P) to form stable C3 and C5 convertases, the latter activity initiating the final membrane-attack sequence as in the classical pathway.

Activities of the complement system
Cytolysis
The C8 component of the final membrane attack complex C5-9 is thought to be responsible for cytolysis. It may act by an enzymatic (phospholipase) action or create defects by insertion of the protein complex into the membrane.

2. Anaphylatoxins
C3a and C5a bring about histamine release from mast cells and platelets.

3. Chemotaxins
C5a and C567 have a chemotactic effect on polymorphs, eosinophils and monocytes.

4. Immune adherence
C3b molecules opsonise bacteria and cell membranes permitting adhesion to polymorphs and macrophages via their C3b receptor sites. This ligand function, referred to as immune adherence may:
(i) facilitate phagocytosis
(ii) facilitate polymorph adhesion to endothelial cells prior to expression of adhesion molecules
(iii) bring about destruction of the C3b-coated target cell by release of cytotoxic enzymes
(iv) hold antigenic material and immune complexes on antigen presenting cells
(v) increase the solubility of immune complexes by disrupting their lattice structure

5. Kinin activity
C2b displays kinin-like activity in directly increasing vascular permeability

6. Blood coagulation
Platelet aggregation by C3b and lysis of platelets, together with activation of Factor XII by C567 initiate blood coagulation

The control of complement activation
1. Spatial control by membrane binding
2. Spontaneous decay, e.g. of C3 and C5 convertase
3. Specific inhibitors exert a modifying effect at many points in the pathway. Examples are:
   (i) Cl esterase inhibitor
   (ii) C3b inactivator which is important in controlling the amplification loop
   (iii) Carboxypeptidase B which inhibits the anaphylatoxins C3a and C5a

B. The kinin system
The kinins are polypeptides composed of 8-10 amino-acids and are present in the plasma globulin fraction as inactive precursors kininogens. These precursors are activated by widely distributed plasma and tissue enzymes, kininogenases. The major plasma enzyme with this property is kallikrein which itself is generated by the action of either activated Factor XII (Hageman factor) or plasmin on prekallikrein. Factor XII is activated by:
1. Contact with negatively charged surfaces including exposed collagen
2. Antigen-antibody complexes
3. Bacterial endotoxins
4. Polymorph lysosomal enzymes
The major kinins are bradykinin (amino acids) and kallidin (10 amino acids, lysyl-bradykinin), and both cause:
1. Vasodilatation
2. Increased vascular permeability
3. Stimulation of pain receptors

C. The coagulation-fibrinolysis system
Activation of Factor XII also initiates the blood clotting cascade so that coagulation and fibrinolysis are intimately connected with the acute inflammatory response. The principal mediator is plasmin which is formed by the action of kallikrein on plasminogen. The main actions of plasmin are:
1. Breakdown of fibrin to fibrinopeptides - fibrin degradation products (FDPs).
   These products directly increase vascular permeability and are chemotactic for polymorphs
2. Converts kininogens into kinins
3. Converts prekallikrein to kallikrein
4. Acts on C3 to initiate the alternate pathway

CELL-DERIVED MEDIATORS

A. Vasoactive amines

1. Histamine
   This is the best documented of the chemical mediators and is widely distributed through the tissues. Histamine is formed by the action of the enzyme histidine decarboxylase on the amino acid histidine. The most important source of histamine is from the degradation of mast-cells.
   Degranulation is provoked by:
   (i) Antigen interaction with cell-bound IgE antibodies
   (ii) Anaphylatoxins (C3a, C5a)
   (iii) Cytolysis by the full complement pathway
   (iv) Direct injury
   Histamine release causes arteriolar dilatation, constriction of veins, and increased vascular permeability of short duration (10-15 min).

2. 5-Hydroxytryptamine (serotonin, 5HT)
   This amine is also present in mast-cells together with platelets and enterochromaffin cells. 5HT is a potent vasoconstrictor and is relatively more active on the smooth muscle of veins than of arterioles and so produces a rise in capillary pressure. However it does not increase vascular permeability and its role in the acute phase of inflammation is questionable.

B. Eicosanoids (acidic lipid products)

This group consists of long-chain fatty acid derivatives of the ubiquitous 20-carbon parent compound arachidonic acid. Arachidonic acid is a major constituent of the phospholipids of plasma membranes and is readily released for further metabolism by the enzyme phospholipase A2. The products can be allocated to two main groupings depending upon the initial enzymic pathway, the cyclo-oxygenase products are the Prostaglandins and the lipoxygenase products are the hydroperoxy fatty acids, notably the leukotrienes but also including long-chain hydroperoxides (HPETEs) and hydroxyacids (HETEs).
1. Prostaglandins
The 'classical' Prostaglandins involved in acute inflammation are E\textsubscript{2}, D\textsubscript{2} and F\textsubscript{2a}, of which E\textsubscript{2} is the most potent. They cause vasodilatation and potentiate the increase in permeability brought about by histamine and bradykinin. Prostaglandins also manifest anti-inflammatory effects, however, and may suppress the release of polymorph lysosomal enzymes and mast-cell degranulation by raising intracellular cAMP levels. Two further cyclo-oxygenase products are prostacyclin (PG\textsubscript{I}2), a potent vasodilator, and thromboxane A\textsubscript{2} (TxA\textsubscript{2}) a vasoconstrictor antagonising the effects of prostacyclin and a powerful aggregator of platelets.

2. Leukotrienes
It is now clear that the chemical mediator long known as 'slow reacting substance' (SRS) is a mixture of leukotrienes - C\textsubscript{4}, D\textsubscript{4}, and E\textsubscript{4}, and that these substances are responsible for the smooth muscle contraction and increased vascular permeability formerly attributed to SRS. Subsequently a more potent inflammatory mediator has been identified as leukotriene B\textsubscript{4} which has the following actions:
   (i) Chemotactic for polymorphs
   (ii) Enhances polymorph movement
   (iii) Causes degranulation of mast-cells
   (iv) Causes release of lysosomal enzymes
   (v) Enhances the increase in vascular permeability brought about by classical prostaglandins.
A major source of LTB\textsubscript{4} is synthesis by leucocytes including polymorphs, thereby amplifying polymorph exudation in an acute inflammatory reaction.

C. Platelet Activating Factor
PAF is a potent vascular permeability factor produced by degranulating mast cells which causes aggregation of platelets and release of histamine and 5HT. Other cell types are capable of synthesising PAF including neutrophils, macrophages and endothelial cells and in addition to its permeability effects PAF increases polymorph adhesion to endothelial cells and is chemotactic for polymorphs. PAF also stimulates the production of other inflammatory mediators such as Prostaglandins and leukotrienes.

D. Lysosomal products
A wide variety of lysosomal products (mainly enzymes) are released by polymorphs, and to a lesser extent by monocytes, in acute inflammation. These include:

1. Cationic proteins capable of:
   (i) Degranulating mast-cells
   (ii) Increasing vascular permeability independent of mast-cells
   (iii) Chemotactic effects on monocytes

2. Proteases
   (i) Leukokininogenase, an acid protease which acts on plasma precursors to produce leukokinin
   (ii) C5-cleaving enzyme which releases the anaphylatoxin C5a
(iii) Plasminogen activator

E. Cytokines
Lymphocyte and macrophage products which have a role in acute inflammation include:
(i) Granulocyte-macrophage colony stimulating factor (GM-CSF) increases the production of polymorphs
(ii) Interleukin-1 promotes leucocyte-endothelial adhesion and activates eosinophils and basophils
(iii) Interleukin-8 is chemotactic for polymorphs
(iv) Tumour necrosis factor (TNF) increases expression of endothelial adhesion molecules
and enhances polymorph chemotaxis and phagocytosis

THE ROLE OF MEDIATORS IN VASCULAR PERMEABILITY
The early increase in vascular permeability is brought about by histamine released by mast-cells activated by C3a, C5a and PAF, probably aided by bradykinin. Plasma leakage may be potentiated by increased blood flow induced by vasodilator Prostaglandins. Lipo-oxygenase products are likely to be important in sustaining vascular permeability; in particular LTC₄ and D₄ are potent inducers of macromolecular leakage from post-capillary venules. Likewise, in combination with vasodilator Prostaglandins, LTB₄ potentiates plasma leakage.

ACTIVITIES OF THE NEUTROPHIL POLYMORPH
A. Movement
Polymorphs move by amoeboid motion brought about by contractile forces provided by a network of microfilaments. The network is made up of actin, actin-binding protein, and myosin. Microtubules also play some part and probably translate membrane signals into the correct locomotory response (sensory transduction). Energy for movement and ingestion is provided by ATP generated by anaerobic glycolysis.
Polymorph movement can be:
1. Enhanced by chemokinetic factors such as leukotriene B₄
2. Directed by chemotactic factors which the cell detects as a concentration gradient over its membrane

A wide variety of chemotactic factors have been described but the number of receptors on the neutrophil is likely to be small. It is possible, therefore, that many chemotaxins act on a common receptor or induce chemotaxis indirectly by stimulating cells to produce a common chemotactic factor.

Chemotactic factors
1. Plasma derived
   (i) Complement products
      a. C5a
      b. C5a des arg (C5a minus the terminal arginine) is chemotactic in the
presence of a serum 'helper factor'
c. C567
(ii) Kinin system Kallikrein
(iii) Fibrinolytic system
  Fibrin degradation products - fibrinopeptide B
  Thrombin
2. Cell derived
  (i) Leukotrienes, especially LTB₄
  (ii) Neutrophil chemotactic factor (NCF) produced by activated macrophages
  (iii) Platelet activating factor (PAF)
  (iv) Cytokines, e.g. interleukin-8, TNF
3. Bacterial factors
  (i) Soluble, low molecular weight (<3600) bacterial peptides, e.g. f-Met-Leu-Phe
  (ii) Proteases which cleave C5
4. Tissue breakdown products
  Tissue injury results in the partial digestion of collagen, elastic and other proteins. The resulting protein fragments are directly chemotactic for polymorphs

B. Phagocytosis
Polymorphs ingest bacteria or other particles by extending pseudopodia around them. Subsequent fusion of these processes encloses the bacterium in a heterophagic vacuole formed by the internalised plasmalemma. Adhesion of micro-organisms to polymorphs is facilitated by opsonisation - coating of the organism with immunoglobulin or complement products which can then attach to the Fab or C3b receptors on the polymorph surface membrane. The mode of opsonisation is related to the immune status:

1. Non-immune state The alternate pathway is activated by bacterial lipopolysaccharide and adhesion brought about by generation of C3b.

2. Normal immune state The classical pathway of complement is activated by specific antibody binding to bacterial antigen. Adherence by C3b and Fc receptors follows.

3. Hyper-immune state (that is following recent infection or immunisation). A high concentration of specific antibody (IgG and IgM) is present; the Fab portions attach to the surface antigen leaving the Fc terminals to attach to specific receptor sites on the neutrophil. This is complement independent opsonisation.
The intracellular events during phagocytosis include
  1. Rise in oxygen consumption
  2. Increased glycogenolysis
  3. Increased glucose oxidation via the hexose-monophosphate shunt
  4. Production of reactive oxygen metabolites

C. Intracellular microbial killing
Within the phagocytic vacuole, bacteria and other micro-organisms are attacked by
several agents aimed at destruction of the organism. These agents or mechanisms may or may not involve oxygenation: the oxygen dependent mechanisms are the most important in achieving bacterial killing:

1. **Oxygen dependent mechanisms**
   (i) Hydrogen peroxide (produced via the hexose-monophosphate shunt) reacts with myeloperoxidase to form a highly oxidative complex. This reacts with a co-factor such as halide ions or thiocyanates to form a strong antimicrobial agent
   (ii) Highly reactive products of oxygen reduction may contribute to bacterial killing:
       a. Superoxide anion (O$_2^-$)
       b. Singlet oxygen (O$_2^*$)
       d. Hydroxy radicals (OH$_2$)

2. **Oxygen independent mechanisms**
   (i) Low intravacuolar pH resulting from lactic or carbonic acid formation
   (ii) Lactoferrin acts by chelating the iron required for bacterial growth
   (iii) Lysozyme (muramidase)
   (iv) Granular cationic proteins

**D. Release of lysosomal products**
Release of lysosomal products into the external medium:
1. Injure tissues by proteolysis - collagenase, elastase, cathepsins, etc. These enzymes are activated by oxidants escaping from polymorph granules, and are subsequently neutralized by antiproteases such as alpha-l-antitrypsin
2. Initiate blood coagulation by activating Factor XII
3. Increase vascular permeability - leucokinins
4. Attract other leucocytes

**DISORDERS OF POLYMORPHS**

**A. Defective production (neutropenia)**
1. Drug-induced neutropenia
2. Associated with aplastic anaemia
3. Associated with acute leukaemia
4. Associated with splenomegaly
5. Immune neutropenia resulting from
   (i) Multiple blood transfusions (anti-leucocyte antibodies)
   (ii) Passive maternal antibodies in neonates
   (iii) Auto-immune reactions in SLE, rheumatoid disease, etc.
6. Chronic infantile agranulocytosis
7. Chronic idiopathic neutropenia
8. Associated with thymic aplasia or dysgammaglobulinaemia
9. Associated with exocrine pancreatic insufficiency (Schwachman's syndrome)

**B. Defective chemotaxis**
1. Abnormalities of adhesion molecules
Inherited deficiency of leucocyte adhesion proteins

2. **Abnormalities of chemotactic factors**
   (i) Decreased production, e.g. deficient complement components C3, C5
   (ii) Inhibition of chemotactic factor formation and action, e.g. in uraemia, hepatic failure
   (iii) Circulating chemotactic factor inactivator in Hodgkin's disease

3. **Cellular defects**
   (i) Abnormal polymorph adherence, e.g. in steroid therapy, diabetes and acute alcohol intoxication
   (ii) Abnormal deformability, e.g. Chediak-Higashi disease an autosomal recessive condition characterized by partial albinism and recurrent pyogenic bacterial infections, possibly resulting from abnormal cyclic GMP metabolism and faulty microtubule assembly
   (iii) Abnormal random migration -‘lazy leucocyte syndrome’ possibly related to defective polymerisation of actin in the microfilaments
   (iv) Abnormal directed migration in response to chemotaxins

C. **Defective phagocytosis**
1. Disorders of opsonisation
   (i) C3 deficiency
   (ii) Low IgM, e.g. in neonate, hypogammaglobulinaemia

2. **Diminished ingestion**
   Immaturity of neutrophils, e.g. in acute leukaemia

D. **Defects in bactericidal activity**
1. Disorders of granules
   (i) Chediak-Higashi disease, in which giant lysosomes fail to fuse with the phagosome
   (ii) Deficiency of lysozyme and secondary granules

2. **Defective microbial killing**
   (i) Chronic granulomatous disease which results from a failure to produce hydrogen peroxide, due to a deficiency of NADH oxidase
   (ii) Myeloperoxidase deficiency
      a. familial
      b. secondary to acute myeloid leukaemia
   (iii) Severe glucose-6-phosphate dehydrogenase deficiency
   (iv) Inhibition of the hexose-monophosphate shunt by a serum factor in hepatic failure

**VARIETIES OF ACUTE INFLAMMATION**

The general response to injury is modified according to the tissue and the nature of the injurious agent resulting in several descriptive types of inflammation.

1. **Serous.** formation of a protein-rich fluid exudate with minor cellular exudation, e.g.
synovitis, peritonitis

2. **Fibrinous**: exudate contains abundant fibrinogen which is precipitated as a thick fibrin coating, e.g. pericarditis

3. **Haemorrhagic**: inflammation associated with conspicuous haemorrhage as a result of vascular damage, e.g. meningococcaemia, viral pneumonia

4. **Suppurative** (or purulent) - characterized by the production of pus composed of:
   (i) Dead and dying polymorphs
   (ii) Liquefied tissue
   (iii) Pyogenic organisms

Suppuration may result in the formation of:
   (i) Abscess - a localized collection of pus in an organ or tissue
   (ii) Empyema - a collection of pus in a hollow viscus, e.g. in the gall-bladder or appendix, or a body space, e.g. empyema thoracis in the pleural space

5. **Membranous**: inflammation of a lining epithelium with a coating of fibrinous exudate, more or less intact sheets of detached epithelium, and inflammatory cells

6. **Pseudo-membranous**: the adherent coat is composed of matted fibrin and inflammatory cells and is usually associated with only focal superficial ulceration, e.g. pseudomembranous colitis

7. **Catarrhal**: inflammation of mucosal surfaces with hypersecretion of mucus, e.g. common cold

8. **Necrotising or gangrenous**: acute inflammation associated with widespread necrosis of the organ probably resulting from superimposed thrombosis or vascular occlusion due to high tissue pressure, e.g. in severe acute appendicitis

**OUTCOME OF ACUTE INFLAMMATION**

1. **Resolution**. The inflammatory exudate is reabsorbed and the tissue restored to normal, e.g. lobar pneumonia. This presumes that there has been no tissue destruction.

2. **Healing** by repair or regeneration where tissue has been destroyed.

3. **Chronic inflammation**. Continuing acute inflammation with attempts at healing.

4. **Spread**
   (i) Direct - e.g. cellulitis
   (ii) Lymphatic - lymphangitis progressing to acute lymphadenitis
   (iii) Blood vessels
      a. Pyaemia - spread of pyogenic organisms in infected micro-thrombi via the blood stream possibly giving rise to secondary (metastatic) abscesses.
      b. Septicaemia – multiplication of organisms in the blood stream in the absence of adequate host defenses
5. Death resulting from
   (i) Toxaemia, e.g. endotoxic shock and its complications
   (ii) Involvement of vital organs, e.g. encephalitis, myocarditis

4. Healing

Healing is the body's replacement of destroyed or lost tissue by viable tissue. Tissue replacement is achieved in two ways:

**Regeneration.** The proliferation and migration of specialized cells re-establishing the anatomical and functional integrity of an organ or tissue.

**Repair.** The proliferation and migration of connective tissue cells leading to fibrosis and 'scar' formation.

As cellular proliferation is an essential component of repair, there is considerable overlap between the processes of regeneration and repair.

**MAJOR CAUSES OF TISSUE DESTRUCTION**

1. Loss of blood supply - *ischaemic necrosis*, e.g. myocardial infarction
2. Inflammatory agents
   (i) By direct physical or toxic effects, e.g. an abscess
   (ii) Indirectly as a result of the host response, e.g. caseous necrosis in tuberculosis
3. Traumatic excision
   (i) Accidental
   (ii) Surgical
4. Radiotherapy

**REGENERATION**

The capacity of damaged tissue to respond by regeneration varies considerably. Tissues can be allocated to one of three categories:

1. *Labile cells* which continue to proliferate throughout life, e.g. epidermis, lining epithelia, endothelium, connective tissue, haemopoietic tissue
2. *Stable cells* which retain the capacity to regenerate and occasionally exhibit mitoses by virtue of normal cell-turnover, e.g. liver, renal tubular epithelium, smooth muscle
3. *Permanent cells* which cannot reproduce themselves after attaining maturity, e.g. neurones of the CNS, sensory organs, renal glomeruli, striated muscle, adrenal medulla

Following injury labile tissues heal by regeneration with little or no repair. Permanent tissues are incapable of regeneration and heal entirely by repair. Most organs show evidence of both processes.

**Control of regeneration**

Regeneration appears to be controlled by the balance between *stimulators and inhibitory* growth factors or hormones. Stimulation appears to be a two-stage
process:
1. **Priming.** Cells in G₁ or growth arrested cells in G₀ are primed for progression to cell division. An example of this type of factor is *platelet derived growth factor* (PDGF) which is released following activation of platelets but is also produced by endothelial cells and macrophages. PDGF initiates the proliferation of fibroblasts and smooth muscle cells.

2. **Progression.** Once primed, the cells are acted upon by other growth factors which stimulate DNA synthesis. These potentiating factors include *epidermal, fibroblast and transforming growth factors* (EGF, FGF, and TGFₐ). Cell proliferation is also under the influence of general or nonspecific stimulators like growth hormone, and insulin-like growth factor. Fibroblasts are also stimulated to divide by interleukin-1 and tumour necrosis factor which also up-regulates collagen synthesis. Inhibition of cell division is less clearly understood. TGFₐ is known to act as an inhibitor under certain circumstances, and Prostaglandins and (a-interferon are known to inhibit fibroblasts in *vitro.*

**REPAIR**

Injury to tissues is followed by extravasation of blood and a complex series of reactions embracing the coagulation, complement and kinin systems. Endothelial damage results in leakage of platelets into the interstitium where they release PDGF and other growth factors from their granules. PDGF initiates fibroblast replication which is the predominant feature of early repair. Repair involves two overlapping processes:
   1. Organisation
   2. Progressive fibrosis

1. **Organisation**
   This is the conversion of dead tissue or inert material into *granulation tissue* - immature fibrovascular tissue. Organisation is seen in:
   (i) Haematomas in wound and fracture healing
   (ii) Thrombi
   (iii) Infarcts
   (iv) Fibrinous exudates

Granulation tissue forms by:
   (i) **Demolition.** Monocytes migrate into the area, take on the properties of macrophages, and phagocytose cell debris, fibrin and red blood cells. Clearance of dead tissue is facilitated by the secretion of proteolytic enzymes by macrophages (e.g. collagenase, elastase) and other secretary products are important in promoting repair, e.g. interleukin-1
   (ii) **Fibroblast activity.** Local resting fibroblasts (fibrocytes) proliferate rapidly and migrate into the area where they continue to divide and commence synthetic activity. Initially the activated fibroblasts produce proteoglycans but as they mature switch over to collagen synthesis. At the same time, some fibroblasts develop bundles of microfilaments in their cytoplasm and acquire contractile properties. Such modified fibroblasts are termed *myofibroblasts.*
   (iii) **Ingrowth of capillaries.** Endothelial cells in the severed blood vessels of surrounding viable tissue undergo rapid proliferation and grow into the area as solid cords. Angiogenesis is stimulated by TGFα and *basic FGF which* is stored extracellularly bound to heparin sulphate on the cell surface and in the
matrix. The proliferating endothelial cells form 'buds' which:
a. Link up to form arcades
b. Canalise. This occurs within hours of formation
c. Become freely permeable to plasma, RBCS, leucocytes and platelets
d. Differentiate into arterioles, capillaries and venules

2. Progressive fibrosis
   (i) Continued accumulation of intercellular collagen
   (ii) Collagen re-orientation along lines of stress - remodelling
   (iii) Diminished cellularity
   (iv) Formation of an avascular, hypocellular 'scar'

Further changes in scars:
   (i) Cicatrizion - a late diminution in size resulting in deformity
   (ii) Calcification
   (iii) Ossification

CELL-MATRIX INTERACTIONS

The matrix of repair tissue consists predominantly of collagen and proteoglycans. The proteoglycans or 'ground substance' of connective tissues are, as their name implies, macromolecules composed of a protein core to which carbohydrate is attached. The carbohydrate moieties take the form of long linear polysaccharides which are attached radially around the protein molecule. They can be divided into sulphated and non-sulphated types:

*Sulphated:
Heparan sulphate
Keratan sulphate
Chondroitin sulphates A, B, and C

*Non-sulphated:
Hyaluronic acid
Chondroitin

The protein moiety is synthesized in the rough ER of the fibroblast and to this core the hexose sugars are sequentially added to form the polysaccharide attachments. Sulphation follows as a separate step.
Collagen is the most abundant protein in the body and forms the major structural component of many organs. Collagen molecules consist of three polypeptide chains arranged in a triple helix and whilst the basic polypeptide structure is straightforward, the molecule undergoes a complex series of post-translational modifications and interactions with proteoglycans which greatly modifies its properties. On the basis of the differing composition and combinations of its constituent chains, eleven types of collagen have been recognized thus far; Types I, II and III are fibrillar collagens while Types IV to XI are amorphous forms found in basement membranes or in the interstitium.
<table>
<thead>
<tr>
<th>Collagen type</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All connective tissues (bone, dermis, tendon, cornea)</td>
</tr>
<tr>
<td>II</td>
<td>All cartilages, nucleus pulposus, eye</td>
</tr>
<tr>
<td>III</td>
<td>Reticulin fibres, early scar tissue, fetal and infant connective tissue</td>
</tr>
<tr>
<td>IV</td>
<td>Basement membranes (epithelial and endothelial)</td>
</tr>
<tr>
<td>V-XI</td>
<td>Interstitial tissues and blood vessels</td>
</tr>
</tbody>
</table>

Whilst it has long been appreciated that certain cells require to be attached to substrate before they can proliferate normally, it has only recently been established that such attachment is brought about by a series of specific binding proteins. These proteins are particularly important in the proliferation of connective tissue cells:

1. **Fibronectin** attaches fibroblasts to collagen
2. **Chondronectin** binds chondrocytes to Type II collagen, the matrix of cartilage
3. **Laminin** binds epithelial cells to the Type IV collagen of basement membranes
   - Specific receptors (integrins) link the binding proteins to the appropriate cell type and form a molecular bridge between the cell and the matrix
4. **Osteonectin** binds hydroxy-apatite and calcium ions to Type I collagen (bone matrix) and initiates mineralization

### WOUND HEALING

In considering the healing of a skin wound two types are usually distinguished:
1. A clean wound with closely apposed margins - an incised wound
2. An open or excised wound

There are no fundamental differences between these two types, they merely differ in the degree to which the various stages apply.

#### Stages in wound healing

1. Escape of blood and exudate
2. Acute inflammatory response at the margins
3. Hardening of the surface forming a scab
4. Demolition by macrophages with phagocytosis of cellular debris and secretion of proteolytic enzymes which assist in the removal of dead tissue, for example collagenases and elastase. In addition macrophages secrete products which are important in the early stages of repair such as interleukin-1 and fibronectin.
5. Platelets escaping from the severed vessels release PDGF, EGF, TGFα and other growth factors
6. Organisation:
   - (i) PDGF initiates fibroblastic proliferation
   - (ii) Activated fibroblasts secrete proteoglycans
   - (iii) Fibroblasts produce Type III collagen (reticulin) fibres and migrate along this 'scaffold'
   - (iv) Fibronectin-mediated attachment of fibroblasts to collagen is followed by enhanced proliferation
   - (v) Simultaneous proliferation and migration of endothelial cells
7. Contraction of the wound - an early diminution in size brought about by the inward movement of the skin margins which greatly reduces the volume of repair tissue required for healing. Such contraction is attributed to the activity of
myofibroblasts and to resorption of proteoglycans

8. Epidermal proliferation. By mitotic activity and migration, epidermal cells grow in from the margins and undermine the surface scab. When they meet in the centre of the wound, mitosis and migration cease presumably as a result of some cell-to-cell signal. This phenomenon is known as 'contact inhibition'. The factors controlling epidermal proliferation are not fully understood, but the following mechanisms have been proposed:

(i) Tissue injury brings about the production and release of epidermal growth factor (EGF). EGF stimulates replication until regeneration is complete at which point synthesis is curtailed.

(ii) Injury depletes the local concentration of an inhibitory factor, possibly TGFO, which removes its negative influence on mitosis. As the wound heals, levels of such factors build up and mitotic activity subsides to the pre-injury state

9. Progressive increase in collagen fibres

10. Loss of vascularity and shrinkage of the scar

The healing of an excised wound differs from that of an incised wound in that there is:

1. Greater tissue loss
2. More inflammatory exudate and necrotic tissue to remove
3. Wound contraction is necessary
4. More granulation tissue is required, a bigger scar is formed and this may result in deformity
5. Slower process
6. Increased liability to infection

Factors influencing wound healing

1. Local factors adversely affecting healing
   (i) Type of wounding agent; blunt, crushing, tearing, etc.
   (ii) Infection
   (iii) Foreign bodies in wound
   (iv) Poor blood supply
   (v) Excessive movement
   (vi) Poor apposition of margins, e.g. large haematoma formation
   (vii) Poor wound contraction due to tissue tethering, e.g. skin over tibia
   (viii) Infiltration by tumour
   (ix) Previous irradiation
   (x) Tissue pressure
      a. External, e.g. sacral bed sores
      b. Intrinsic, e.g. lymphoedema

2. General factors adversely affecting healing
   (i) Poor nutrition
      a. Deficiency of protein. This results in a lack of the sulphur-containing amino acids methionine and cystine which are essential for the synthesis of collagen
      b. Lack of ascorbic acid (vitamin C) results in abnormal granulation tissue and deficient collagen production
      c. Zinc deficiency
(ii) Excessive glucocorticosteroid production or administration
(iii) Fall in temperature
(iv) Jaundice
(v) Old age

3. Factors accelerating wound healing
   (i) Ultraviolet light
   (ii) Administration of anabolic steroids, deoxycorticosterone acetate, and (?) growth hormone
   (iii) Rise in temperature
   (iv) Therapeutic administration of growth factors

Complications of wound healing
1. Wound rupture
2. Infection
3. Implantation of epidermal cells giving rise to keratin-filled epidermal cyst
4. Weak scars with possible development of incisional herniae
5. Cicatization and deformity
6. Keloid formation. The production of an elevated scar by excessive connective tissue proliferation and fibrosis
7. Malignant change. The development of squamous carcinoma in old healed incisions is a recognized but rare complication

HEALING OF A FRACTURE

Steps in the healing of a fractured long bone are:
1. Haemorrhage from the highly vascular severed ends producing a large haematoma
2. Inflammation - an acute inflammatory response to injury
3. Organisation - the haematoma is infiltrated by fibroblasts and endothelial cells. At the same time demolition by macrophages assists in the partial reabsorption of blood clot and cell debris.
4. Proliferation of specialized cells - cells derived from the periosteum and the severed ends of the endosteum secrete proteoglycans (like fibroblasts in general matrix special form of collagen (Type I) that provides the bone matrix - so-called osteoid. These specialised connective tissue cells are osteoblasts.
5. Mineralization - the Type I collagen fibres of the osteoid bind the attachment protein osteonectin which sequesters calcium and phosphate ions out of solution. In this way calcium phosphate precipitates on the fibres and after one or more intermediate phases, hydroxyapatite crystals are formed at discrete sites. Subsequently the secondary processes of crystal-growth and seeding of other crystals by the original deposits extend the area of mineralization over the fibres. The result of mineralization of the irregularly arranged collagen fibres of osteoid is woven bone. By this stage the fractured ends of the bone are united by a hard fusiform mass of granulation tissue and woven bone - this is fracture callus. Where there is excessive movement, e.g. in a rib fracture, or there is a relative lack of nutrients, as for example at the centre of a large haematoma, the connective tissue cells differentiate into chondroblasts. These cells produce large amounts of proteoglycans and synthesise Type II collagen fibres which in
combination make up cartilage. The cartilage also becomes calcified.

6. **Conversion to lamellar bone** - the woven bone, and any calcified cartilage present, undergoes phagocytic resorption by multinucleate osteoclasts. At the same time osteoblasts lay down regular Type I collagen plates with Haversian systems which on mineralization forms lamellar bone.

7. **Remodelling of lamellar bone** - continuing osteoclastic and osteoblastic activity over many months brings about remodelling of the bone. Remodelling is a complex process regulated by hormones and growth factors. Most of the local growth factors are common to those which regulate wound healing. Thus interleukin-1, TNFa, PDGF and lymphocyte-derived interferon-g, all play a part. There are however, additional factors derived from skeletal cells and the bone matrix; these include TGF-β, basic FGF and somatomedin C. The final contour of the bone appears to be dictated by the lines of stress set up within it on mobilisation.

**Complications of fracture healing**

1. Delayed union
2. Mal-union
   (i) Angulation
   (ii) Shortening
3. Fibrous union resulting from
   (i) Excessive movement which may lead to the development of a false joint (pseudoarthrosis)
   (ii) Infection which may also give rise to osteomyelitis
   (iii) Ischaemia
4. Non-union if soft-tissues such as muscle or fat are interposed between the severed ends

**PATHOLOGICAL FRACTURES**

These are fractures occurring spontaneously (that is with normal stresses) because of intrinsic disease of the bone.

**Causes**

1. Osteoporosis
2. Metastatic tumours
3. Primary tumours (benign and malignant)
4. Paget's disease
5. Bone lesions of hyperparathyroidism
6. Osteogenesis imperfecta

**HEALING IN OTHER SITES**

1. **Liver**
   (i) After a single, short-lived injury such as drug-induced necrosis or acute hepatitis, the liver heals completely by regeneration
   (ii) Repeated injury, as in alcoholic abuse or chronic hepatitis, leads to collapse of the reticulin framework, production of collagen by mesenchymal cells, and
irregular, nodular regeneration, resulting in cirrhosis.

2. Kidney
Regeneration is virtually confined to the tubular epithelium and is seen for example after acute tubular necrosis. Otherwise injury results in loss of glomeruli and scarring.

3. Mucosal surfaces
(i) Superficial ulceration (erosion) is followed by regeneration of the epithelium but there may be loss of specialized cells. In the stomach, for example, healed areas may be covered by intestinal-type epithelium or show pseudo-pyloric metaplasia (ulcer-associated cell lineage)

(ii) Deeper ulceration with involvement of submucosa and muscle heals by scar formation and epithelial regeneration

4. Nervous system
Adult neurones are incapable of mitotic division but limited regeneration is possible
(i) Peripheral nerve section results in distal Wallerian degeneration, growth of axon-sprouts from the cut end, and proliferation of Schwann cells, with eventual enclosure in a new myelin sheath
(ii) Central nervous system. If the involved neurone survives axons and dendrites can regrow, but most tissue loss is followed by astrocytic proliferation with the formation of a glial scar often around a fluid filled cavity

5. Muscle
(i) Cardiac muscle shows no regeneration and healing is achieved entirely by fibrous repair
(ii) Skeletal muscle shows a limited capacity to regenerate and if only part of a muscle fibre is destroyed then the fibre may regrow within the sarcolemmal sheath
(iii) Smooth muscle cells are capable of proliferation and minor tissue loss may be followed by successful regeneration

5. Chronic inflammation
A process in which there is continuing inflammation at the same time as attempts at healing resulting from persistence of the injurious agent.'

Mechanisms
The injurious agent may persist because:
1. There is a defective acute inflammatory response
   (i) Poor blood supply
   (ii) Poor general nutrition
   (iii) Abnormal neutrophil function
   (iv) Anti-inflammatory drugs, especially corticosteroids
2. The agent is resistant to phagocytosis and/or intracellular destruction
(i) Intracellular infectious agents, e.g. tuberculosis, salmonellosis, brucellosis, viral infections
Foreign-body reactions. These act as a nidus for persistent infection or as tissue irritants which directly provoke a chronic inflammatory reaction.
Such irritants can be divided into:
   a. Endogenous, e.g. necrotic adipose tissue, cholesterol crystals, uric acid crystals in gout
   b. Exogenous, e.g. suture material, metallic fragments, silica, asbestos fibres
3. The provoking agent is a body constituent as in:
   (i) Auto-immune diseases, e.g. diffuse lymphocytic thyroiditis (Hashimoto’s disease), auto-immune atrophic gastritis, adrenal atrophy, etc.
   (ii) Reactions to altered self-antigens, e.g. contact dermatitis to rubber, nickel, etc.

CLASSIFICATION

1. Clinical
   (i) Following a recognizable acute inflammation, e.g. chronic osteomyelitis
   (ii) Arising de novo, e.g. brucellosis, tuberculosis

2. Histological
   (i) Specific - having a reproducible histological pattern, e.g. tuberculosis, syphilis, leprosy
   (ii) Non-specific - showing only the general features of inflammation, e.g. chronic cholecystitis, chronic pyelonephritis

GENERAL FEATURES

1. Continuing acute inflammation
   (i) Polymorph infiltration
   (ii) Fibrinous exudation
   (iii) Increased vascularity
2. Features of healing - repair and/or regeneration
3. Infiltration by chronic inflammatory cells
   (i) Macrophages
   (ii) Lymphocytes
   (iii) Plasma cells
   (iv) Eosinophils

CELLS OF CHRONIC INFLAMMATION

A. Macrophages
Although monocyte emigration is a feature of the later stages of acute inflammation, their accumulation as macrophages in chronic inflammation is frequently conspicuous and they may constitute the predominant cell type. When macrophages are the dominant cell, and in particular when they are found in circumscribed aggregates, the inflammatory reaction is termed granulomatous. The aggregates themselves are termed granulomas.
Granulomas with a high turnover of cells recruit macrophages from the circulating
monocyte 'pool'. The demands of low-turnover granulomas can be met by proliferation of local tissue macrophages.

1. The mononuclear-phagocyte system
   A system composed of macrophages and their precursors.

2. Functions of the macrophage
   (i) Phagocytosis
      a. Ingestion and destruction of bacteria (particularly after a lymphokine response)
      b. Removal of effete cells or necrotic cell debris
      c. Storage of irritant substances, e.g. carbon particles
   (ii) Antigen handling
      a. Endocytosis and processing of antigen with production of polypeptide fragments which are expressed on the cell surface in conjunction with Class II major histocompatibility antigens
      b. Direct cell-to-cell binding with specifically sensitized lymphocytes
   (iii) Enzyme production
      a. Neutral proteases
         Collagenase
         Elastase
         Plasminogen activator
         Angiotensin convertase
      b. Acid hydrolases
         Lipases
         Acid proteases
         Ribonucleases
         Phosphatases
         Glycosidases
         Sulphatases
      c. Lysozyme (anti-bacterial activity)
   (iv) Synthesis of
      a. Complement components
      b. Arachidonic acid metabolites
         Prostaglandins
         Thromboxane
         Leukotrienes
      c. Binding proteins
         Fibronectin
         Transferrin
         Transcobalamin
      d. Enzyme inhibitors
         Plasmin inhibitors
         (a-2-macroglobulin)
   (v) Soluble mediator (cytokine) production
      a. Interleukins-1, 6 and 8
      b. Tumour necrosis factor a
      c. Interferon a
3. **Special forms of macrophage**
   (i) Epithelioid cells - enlarged macrophages with finely granular eosinophilic cytoplasm which have an increased secretory capacity and are found in tuberculosis, sarcoidosis, Crohn's granulomas, etc.
   (ii) Siderophages - macrophages laden with haemosiderin and found in:
      a. Areas of haemorrhage
      b. Chronic venous congestion of the lung ('heart failure cells')
      c. Haemosiderosis
   (iii) Melanophages - melanin-laden macrophages found in the interstices of a malignant melanoma, pigmented naevus, etc.
   (iv) Lipophages - macrophages with 'ground-glass' cytoplasm after phagocytosis of:
      a. Altered fat, e.g. in traumatic fat necrosis
      b. Cholesterol, e.g. in atherosclerosis, cholesterolosis of the gall-bladder, etc.
   (v) Muciphages - macrophages which have ingested mucin following its release from damaged epithelium, e.g. in the lamina propria of the large intestine after an episode of inflammatory bowel disease

4. **Giant cells**
   In some circumstances macrophages fuse and give rise to multinucleate giant-cells:
   (i) Specific infections
      a. Tuberculosis (Langhans giant-cells)
      b. Syphilis
      c. Fungal infections
   (ii) Foreign-body reactions
   (iii) Lipid phagocytosis (Touton giant-cells) in xanthogranuloma, fibro-histiocytoma, etc.
   (iv) 'Collagen' diseases
      a. Rheumatic fever (Aschoff giant-cells)
      b. Rheumatoid nodules
      c. Giant-cell arteritis
   (v) Granulomatous diseases of unknown aetiology
      a. Sarcoidosis
      b. Crohn's disease
      c. Wegener's granulomatosis

**B. Lymphocytes and plasma cells**
Small lymphocytes can be divided into two reactive populations
   (i) B-lymphocytes which are responsible for antibody mediated (humoral) immunity
   (ii) T-lymphocytes which are dependent upon the thymus for their proper development and are responsible for cell-mediated immune responses such as direct cytotoxicity, and also regulate antibody synthesis by B-lymphocytes

Following macrophage uptake and processing of antigens, polypeptide fragments are expressed at the cell surface and are recognized by either 'helper' T-lymphocytes or by 'cytotoxic' T-cells. The specific interaction with antigen leads to the synthesis and release of soluble growth and differentiation factors both by the antigen-presenting cells and the T-lymphocytes. The factors released by lymphocytes are termed lymphokines, and are responsible for the rapid proliferation and differentiation of the initially small population of antigen-specific lymphocytes present in the previously
unchallenged host. B-lymphocytes bear monomeric immunoglobulin (mlgM) on their surface which acts as the antigen receptor. B-cells may respond directly to some antigens, but the majority of antigen responses require the participation of helper T (T\textsubscript{H}) cells. Sensitized helper cells activate B-cells into the cell cycle and progressive multiplication ensues. At the same time genetic 'switching' leads to differentiation into a clone of plasma-cells producing an antibody identical to that present in monomeric form at the surface. At the same time a small population of primed 'memory' cells equipped with the same immunoglobulin surface receptor are generated.

A third population of lymphocytes do not give conventional results in tests of T- and B-cells and these cells have been designated 'null cells'. This population also includes cells capable of antibody-dependent cytotoxicity (K cells), natural killer cells (NK cells) which spontaneously destroy tumour cells \textit{in vitro} and lymphokine activated killer cells (LAK cells).

In the normal individual about 75% of the peripheral blood lymphocytes are T-cells. About \(\frac{2}{3}\) of these belong to the helperinducer subset (CD4\textsubscript{+}), and the other \(\frac{1}{3}\) are of the cytotoxic or suppressor type (CD8\textsubscript{+}).

C. Eosinophils

Whilst eosinophils are seen in certain acute inflammatory responses such as atopic hypersensitivity reactions, they are more characteristic of chronic inflammation. They are poorly phagocytic cells whose granules have a high content of an arginine-rich cationic protein in addition to the usual granulocyte enzymes. They possess receptors for IgG, C3b and C3d.

1. \textit{Functions} (possible)
   (i) Neutralisation of leukotrienes
   (ii) Inhibition of histamine release from mast-cells via the cyclic AMP system, probably by production of EI and E2 Prostaglandins
   (iii) Production of enzymes capable of killing helminths
   (iv) Killing of antibody-coated cells

2. \textit{Chemotaxis}

   Eosinophils respond to the same chemotactic factors as neutrophil polymorphs with the following important additions:
   (i) Eosinophil chemotactic factor of anaphylaxis (ECF-A) released from sensitized tissues on exposure to antigen
   (ii) A specific eosinophil chemotactic factor produced by sensitized T-lymphocytes on exposure to antigen
   (iii) A pre-formed factor released from mast-cell granules (ECF-M) which may be identical with ECF-A
   (iv) A complement dependent factor EF-C

\textbf{CYTOKINES IN INFLAMMATION AND IMMUNITY}

Cytokines secreted by macrophages and lymphocytes (and occasionally by other cells) play a vital role in immune and inflammatory responses. These cytokines have previously been classified into lymphocyte-derived mediators (\textit{lymphokines}) and
those of monocyte origin \textit{(monokines)} but recent changes in nomenclature have categorized them as \textit{interleukins}. Other cytokines, such as \textit{interferons and tumour necrosis factor}, continue under their original names.

1. Interleukins

Currently 12 different interleukins have been identified but the list will continue to grow and only the better characterized are listed here:

(i) Interleukin-1 exists as two species (a and b) and are produced by macrophages, lymphocytes and a wide range of non-immune cells such as endothelial, epithelial and haemopoietic cells. Its principal effects include:

a. Activation of $T_H^+$ and B-cells
b. Stimulation of thymocyte proliferation
c. Induction of synthesis of acute phase proteins by the liver
d. Activates eosinophils and basophils
e. Promotes leucocyte/endothelial adhesion
f. Increases collagenase synthesis by fibroblasts and chondrocytes
g. Acts as a pyrogen

(ii) Interleukin-2 is synthesized and secreted by T-lymphocytes following their activation by antigen and acts in an autocrine manner on the secreting cells and on other T-lymphocytes causing proliferation and expression of more IL-2 receptors. In this way the lymphocyte response is greatly amplified. IL-2 also induces T-lymphocyte cytotoxicity and stimulates natural killer cell activity. In combination with interferon, IL-2 also activates macrophages

(iii) Interleukin-3 is released by antigen activated T-lymphocytes and acts as a stimulator of haemopoietic stem cells leading to the production of many of the major cell types in the bone marrow

(iv) Interleukin-4 is produced by a subset of T helper cells which also produces IL-5 and IL-6. Its most important action is in stimulating B-cell proliferation and regulating their production of immunoglobulin isotypes

(v) Interleukin-5 has multiple effects on B-cells leading to increased immunoglobulin secretion. It may also act as a stimulator of eosinophil growth and differentiation

(vi) Interleukin-6 is produced by activated macrophages and T-cells. Although originally described as a B-cell differentiation factor which stimulated antibody formation without prior cellular proliferation, IL-6 also serves as a co-stimulator of T-lymphocytes and induces the differentiation of cytotoxic T-cells. IL-6 has a multiplicity of actions including:

a. Generates thrombopoietin to increase platelet numbers
b. Increases the proliferation of a variety of cell types including keratinocytes, mesangial cells, and nerve fibres
c. Has procoagulant properties
d. Releases corticotrophin from the anterior hypothalamus
e. In conjunction with IL-1 it stimulates acute phase protein production

(vii) Interleukin-7 is produced by stromal cells in the bone marrow and induces the proliferation and differentiation of B-cell precursors

(viii) Interleukin-8 is produced by T-cells and activated macrophages and is a potent chemotaxin for polymorphs
2. Interferons
Three classes of interferon (a, b and c) are recognized. IFN-a and IFN-b are important for their antiviral effects, but IFN-c has a wide range of activities and has a key role in immunoregulation. IFN-c is produced by antigen-specific T-cells and NK cells recruited by IL-2. Its activities include:
(i) Activation of macrophages, which show enhanced phagocytosis and tumour killing capacity
(ii) Activation and growth enhancement of cytotoxic T-cells and NK cells
(iii) Induction of class 11 MHC expression on macrophages and many other types of cells
(iv) Induces immunoglobulin secretion in B-cells primed by IL-2
(v) Potentiates B-cell proliferation induced by IL-4

3. Tumour necrosis factors
TNF is found in two main forms (a and b). TNF-a (also known as cachectin) has many actions in common with IL-1 and is released by macrophages, T-lymphocytes, NK cells, astrocytes and microglia, and Kupffer cells in response to inflammation and infection. The effects of TNFa depend upon its concentration and duration of production, so that small amounts produce beneficial effects in inflammation and tissue repair, whereas sudden systemic release leads to shock and tissue injury and chronic over-production results in cachexia.
(i) Inflammation TNF-a acts as an inflammatory mediator by:
   a. increasing expression of ICAMs and ELAMs and improves leucocyte adhesion
   b. enhancing chemotaxis of macrophages and polymorphs
   c. increasing phagocytosis and cytotoxic activity
   
   TNF-a also acts as a pyrogen by
   a. a direct effect on the hypothalamus
   b. inducing IL-1 synthesis
(ii) Tissue repair.
   TNF-a has an important role in tissue remodelling by virtue of its proliferative and destructive properties. On the one hand it can stimulate fibroblasts, osteoblasts, chondrocytes and endothelial cells to proliferate, and induce the synthesis of other growth factors, while on the other hand TNF-a can be directly cytotoxic to endothelial cells and promote the synthesis of proteases active against connective tissue matrix.
(iii) Septic shock.
   TNF-a is now regarded as the central mediator of the pathophysiological changes consequent upon the release of lipopolysaccharide (LPS) from bacterial cell walls. Its effects include:
   a. Fever
   b. Respiratory arrest
   C. Capillary leak syndrome
   d. Haemorrhagic necrosis
   e. Lactic acidosis
   f. Release of ‘stress’ hormones
   g. Biosynthesis and release of reactive oxygen intermediates and arachidonic acid metabolites

(iv) Cachexia.
   Long term over-production of TNF-U, results in:
a. Loss of fat and protein  
b. Anorexia  
c. Anaemia  
d. Fever  
e. Hypertriglyceridaemia  
f. Increased acute phase protein synthesis

TNF-β (also known as lymphotoxin) shares some of the biological activity of TNF-α and basic fibroblast growth factor. It is responsible for some lymphocyte mediated tissue destruction.

**Lymphocyte adhesion**
Just as neutrophils attach to adhesion molecules on endothelial cells in an acute inflammatory response, lymphocytes possess integrins - *lymphocyte function associated antigen 1* (LFA-1) and *very late activation antigen 4* (VLA-4) which enable them to bind to adhesion molecules - intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM) expressed on endothelium in chronic inflammatory reactions. Such expression is induced by cytokines and interferons. This mechanism may direct the 'homing' of memory lymphocytes into an inflammatory response and also facilitate adhesion between lymphocytes and antigen-presenting cells.

**Role of antibodies in chronic inflammation**
(i) Antigen binding followed by complement activation. Complement products facilitate phagocytosis or bring about cytolysis  
(ii) Bacterial agglutination  
(iii) Opsonisation of bacteria or foreign cells via Fc binding of phagocytic cells  
(iv) Neutralisation of toxins and virus infectivity

**Inflammatory mediators and the immune response**
Inflammatory mediators such as histamine, Prostaglandins, and beta-mimetic catecholamines (collectively termed 'autocoids') are capable of moderating a number of immune functions, usually by inhibition.
Receptors for autocoids on lymphocytes are non-randomly distributed. A proportion of suppressor T-cells always have receptors, but precursor B-cells and precursors of helper and cytotoxic T-cells do not. The inhibitory modulating effect is mediated by and directly proportional to the intracellular concentrations of cyclic AMP generated by the autocoid. Thus autocoids generated in acute and chronic inflammation, or during an immunological reaction, not only mediate the inflammatory response but act as a feed-back mechanism modifying the immune response.
Autocoids have the following actions on lymphocyte responses:  
(i) After B-cells have been specifically stimulated to respond to an antigen, autocoids can inhibit the release of antibody  
(ii) T-cell cytolysis is inhibited by autocoids  
(iii) Histamine can induce a sub-set of T-suppressor cells to produce a suppressive factor which regulates the ability of another activated lymphocyte to pass through the cell cycle.
(iv)
LEUCOCYTOSIS IN ACUTE AND CHRONIC INFLAMMATION

1. *Neutrophilia in*
   (i) Pyogenic infections
   (ii) Tissue breakdown - myocardial infarction, mesenteric infarction

2. *Eosinophilia in*
   (i) Allergic disorders - hay fever, drug allergy
   (ii) Parasitic infestation - trichinosis, schistosomiasis, filariasis, hydatid disease, strongyloides
   (iii) Skin diseases - some cases of exfoliative dermatitis, dermatitis herpetiformis, pemphigus, eczema, psoriasis, scabies
   (iv) Pulmonary eosinophilia - Loeffler's syndrome (simple pulmonary eosinophilia), prolonged pulmonary eosinophilia, tropical eosinophilia
   (v) Polyarteritis nodosa

3. *Lymphocytosis in*
   (i) Chronic infection - tuberculosis, secondary syphilis, brucellosis, typhoid fever
   (ii) Viral infection - influenza, rubella, mumps, measles, chicken-pox, infectious mononucleosis
   (iii) Whooping-cough
   (iv) Acute infectious lymphocytosis

4. *Monocytosis in some cases of*
   (i) Bacterial infections - tuberculosis, typhoid fever, brucellosis, subacute bacterial endocarditis
   (ii) Protozoal and rickettsial infections - malaria, leishmaniasis, trypanosomiasis, Rocky Mountain spotted fever

6. Immunopathology

The immune system is concerned with the recognition of foreign materials (*antigens*) and through a variety of reactions rejecting or nullifying them. In carrying out these functions the system must be capable of distinguishing foreign, that is "non-self", from "self". In the fetus the developing lymphoid system is exposed to body constituents and is rendered unresponsive (*tolerant*) to these self proteins. When immunological maturity is established after the neonatal period, a non-self protein is recognized as foreign and a specific immunological reaction follows. There are two basic types of response.

1. The formation of immunoglobulins which are released into the blood and other body fluids following a B-lymphocyte response - humoral antibodies
2. The production of specifically sensitized small lymphocytes which possess antibody-like molecules on their surface (the T-cell antigen receptor - TCR) and by virtue of cytokine production or direct cytotoxicity are the effectors of cell mediated immunity

In the majority of cases both types of response depend upon the initial recognition of
a foreign antigen by T-lymphocytes. The ability of these cells to respond rests on their possession of a specific antigen receptor and correct presentation of the antigen by an appropriate major histocompatibility molecule on the antigen presenting cell. The T-cell receptor is made up of two glycoprotein chains of differing composition (i.e. heterodimers) non-covalently linked to the T-cell surface antigen T3 (CD3). The majority of T-lymphocytes have an a/b heterodimer receptor but a small proportion (around 10%) have a c/d receptor.

The specificity of individual T-cells is determined during their development in the thymus. As the cells mature random rearrangement of the variable (V), diversity (D) and joining (J) gene segments at a the and b loci (or in another lineage at the c/d loci) leads via a multitude of combinations to the potential expression of millions of different TCR specificities. Not all specificities, however, are expressed following fetal development because of selection events in the thymus that restrict the T-cell repertoire to cells capable of recognizing foreign antigens in the context of self MHC molecules. Thus positive selection allows the maturation of T-cells bearing receptors that bind self MHC in the thymus, whereas negative selection eliminates or nullifies those T-cells capable of reacting against self antigens thereby producing a state of tolerance.

THE HLA SYSTEM AND THE MAJOR HISTOCOMPATABILITY ANTIGENS

The search for factors controlling the acceptance or rejection of tissues following transplantation, led to the identification of a complex series of histocompatibility antigens present on cell surfaces. The antigens were first identified on the surface of blood leucocytes and were therefore referred to as human leucocyte antigens (HLA).

The antigens comprising the HLA system are determined by genes situated on the short arm of the sixth chromosome, and the major loci have been designated A,B,C (Class I major histocompatibility antigens) and DR (Class II MHC antigens). In normal tissues expression of Class II antigens is confined to B-cells, monocytes/macrophages, dendritic cells, and vascular endothelium, whereas Class I antigens are expressed on all nucleated cells. Each locus possesses many different alleles which have been numbered, e.g. HLA-A8, HLA-B27, etc. Certain specific alleles of the various loci tend to be found together (as a 'haplotype') more frequently than would be expected by chance. This 'linkage disequilibrium' of alleles may exert a governing effect on general immune responsiveness.

Immune reactions might, however, be controlled by specific genes. Based on animal studies, immune responsive (1r) and suppressive (is) genes have been postulated which are either controlled by genes of the HLA system or are themselves linked to the HLA loci. Thus it has been shown, for example, that immune hyper-responsiveness toward many different antigens is associated with two HLA haplotypes, AI,B8,Dw3 and A3, B7,Dw2.

TOLERANCE

Three main mechanisms have been proposed for the induction of self-tolerance in T- and B-lymphocytes, these are:

1. **Clonal deletion**
   
   Engagement between the developing T-lymphocytes and selfantigens expressed on bone-marrow derived dendritic cells in the thymus leads to cell
death by apoptosis and elimination of the auto-reactive T-cells.

2. **Induction of clonal anergy**

   This mechanism assumes the survival of some self-reactive lymphocytes which have been rendered functionally inactive following interaction with thymic epithelium. This creates clones of T-cells anergic to epithelial-specific peptides. Such cells retain the capacity to bind to antigens but fail to produce lymphokines and do not proliferate.

3. **Suppression**

   This mechanism assumes survival of auto-reactive lymphocytes which retain the ability to respond to self-antigens but are held in check by T-suppressor cells or their products.

When self-tolerance breaks down, the immune system may mount a cell-mediated attack or produce antibodies directed against the body's constituents - auto-immunity.

**THE IMMUNE RESPONSE**

**A. Primary response**

When foreign antigen is first introduced into the body it undergoes processing in antigen-presenting cells and the resulting peptide in combination with the appropriate MHC molecule is recognized by one or more specifically responsive small lymphocytes. B-lymphocytes may be activated directly by some antigens but most responses depend upon initial T-cell recognition.

(i) **Cytotoxic T-lymphocytes** are involved in the recognition and destruction of virally infected cells or rejection of foreign cells. These CD8+ lymphocytes recognize either foreign Class I MHC molecules on 'non self' cells, or react to viral antigens expressed at the surface of host cells in combination with Class I MHC antigens. Thus cytotoxic lymphocytes are generated that will react to a certain haplotype of MHC together with viral antigen but they will not kill cells of a different haplotype infected by the same virus. This mechanism, termed 'haplotype restriction' has probably evolved so that antigen receptors on T-cells do not become saturated with free virus and block their cytotoxicity.

(ii) **Helper T-lymphocytes.** These CD4+ cells co-operate with macrophages and assist B-cells to respond to certain (T-dependent) antigens. Helper T-cells only respond to antigen which following processing is presented in peptide form in association with major histocompatibility antigens of the Class II type (HLA- DR) on the surface of the individual's own monocytes, macrophages, dendritic or B-cells all of which act as antigen-presenting cells. However, under certain circumstances tissue cells may acquire Class II antigens (for example in rejection and after interferon stimulation) and this renders them capable of presenting antigens to helper/inducer cells.

Depending on their lineage the lymphocytes will react in different ways:

1. B-lymphocytes may react:
   (i) Directly to a T-independent antigen, or
   (ii) Only after interaction with a T-helper cell with the majority of antigens.

Following blast cell transformation the cell will either:

(i) Develop rough endoplasmic reticulum and differentiate into a plasma-cell capable of manufacturing a specific immunoglobulin (in the first instance) of the IgM
2. T-lymphocytes will undergo blast transformation and either:
   (i) Proliferate to form a population (clone) of cells capable of acting as effector cells in a specific cell-mediated response. Such activated T-lymphocytes will act either as cytotoxic cells or secrete cytokines which will stimulate macrophages and enhance bacterial killing or recruit other lymphocytes and further amplify the response, or
   (ii) Revert to a small (T) lymphocyte and act as a primed cell

B. Secondary response
On subsequent exposure to the same antigen, there is some interaction with pre-formed humoral antibody and with an enlarged population of responsive lymphocytes. There is therefore a greatly amplified humoral antibody response and a more rapid recruitment of sensitized cells. Memory B-cells are capable of secreting IgG and IgA immunoglobulins following appropriate antigenic stimulation (see below).

IMMUNOGLOBULINS

Immunoglobulins share a similar basic structure. They consist of two heavy and two light polypeptide chains linked by disulphide bonds. Splitting by papain produces two univalent fragments capable of binding antigen (Fab) and a third fragment without this capacity (Fc fragment). The light chains are of two types, kappa (K) and lambda (L) and each immunoglobulin molecule has either two K or two L chains but never one of each. The heavy chains are of five major types and each molecule has a pair of identical type. Thus five distinct immunoglobulin classes are recognized on the basis of their heavy chains: IgG, IgA, IgM, IgD and IgE which have two c, a, m, d or e heavy chains respectively. Half of each light chain and a quarter of each heavy chain consists of a variable (v) region. The initial germ line DNA contains genes which code for different variable and constant (c) regions as well as different 'joining' genes which code for the amino acids of the region (j) joining constant and variable segments. The joining of v to j regions is imprecise so this adds further diversity to antibody structure. In the production of heavy chains additional variability is introduced by differences in the 'diversity' chain of DNA. Variation in all these components leads to the production of millions of different antibodies each of which is expressed on individual lymphocytes. Just as with T-lymphocytes, those B-cells bearing anti-self antibodies must be eliminated or nullified.

1. IgG is the major serum immunoglobulin accounting for about 70% of the total immunoglobulin pool. The heavy chains of IgG exist in four different forms so that four sub-classes can be distinguished (IgGl-G4)
   Molecular weight = 150 000 Properties:
   (i) Crosses the placental barrier and is therefore the major protective immunoglobulin in the neonate
   (ii) Diffuses easily into all extracellular fluids
   (iii) Acts as an antitoxin (neutralising antibody)
   (iv) Responsible for opsonic binding of bacteria
(v) Coats cells prior to killing by K-cells (macrophages and T-lymphocytes with specific cytotoxic activity related to their surface receptors for Fc)
(vi) Complement activation by two or more molecules through their Fc portions

2. **IgA** represents 15-20% of the immunoglobulin pool. It exists as a monomer, dimers, trimers and polymers. It polymerises by spontaneous binding through a cysteine-rich polypeptide joining (J) chain (J-chain). It is secreted through epithelia as the dimer bound to a third polypeptide, the secretary or transport piece, which stabilizes the molecule against proteolysis. IgA is therefore the major factor in 'secretory immunity'
Molecular weight = 160 000+
Properties:
(i) Principal immunoglobulin in secretions such as those of the respiratory and gastrointestinal tracts and in sweat, saliva, tears and colostrum
(ii) Prevents infection of mucous membranes by inhibiting adhesion of organisms to the epithelium
(iii) When aggregated will bind polymorphs and activate complement by the alternate pathway

3. **IgM** accounts for about 10% of the immunoglobulin pool. This is usually a polymeric pentamer linked by J-chain, however a monomeric form is present on the surface of B-lymphocytes and acts as the antigen receptor
Molecular weight = 900 000
Properties:
(i) Produced early in response to infection
(ii) Largely restricted to plasma
(iii) Act as agglutinating and opsonising antibodies

4. **IgD** accounts for less than 1% of the Ig pool
Molecular weight = 185 000
Properties:
Acts as a cytophilic antibody on B-lymphocytes and may play a role in antigen-induced lymphocyte differentiation

5. **IgE**
This is only present in trace amounts in the immunoglobulin pool
Molecular weight = 200 000
Properties:
(i) Becomes firmly fixed via its Fc fragment to mast cells and basophils. These coated cells degranulate when exposed to the appropriate antigen and release histamine and other agents
(ii) May play a role in immunity to helminthic parasites

**HYPERSENSITIVITY**

Excessive or altered reactions to an antigen producing adverse effects are termed hypersensitivity or allergy. These reactions have been classified into five groups:
Type I - Immediate (anaphylactic-type) hypersensitivity
Type II - Cytotoxic type hypersensitivity
Type III - Complex-mediated hypersensitivity
Type IV - Cell-mediated (delayed-type) hypersensitivity
Type V - Stimulatory hypersensitivity
Type I - Anaphylactic

A. Systemic anaphylaxis
Anaphylactic shock is characterized by intense bronchospasm, laryngeal oedema and a fall in blood pressure, and occasionally results in death. It can be provoked by injecting a large dose of an antigen some time after one or more smaller sensitizing doses of the same antigen. The principal pathogenetic type is cytotoxic anaphylaxis where antigen reacts with antibodies (usually of the IgE class) bound to mast-cells or basophils by their Fc portions and results in the release of histamine and other mediators such as leukotrienes and platelet activating factor. Anaphylaxis can also result from Type III reactions (see below)

B. Local anaphylaxis (atopic allergy)
Local reactions result from the exposure of tissue mast-cells in sensitized individuals to specific antigens and are seen in three main situations:
1. Respiratory tract
   (i) Allergic rhinitis (hay fever)
   (ii) Extrinsic asthma
2. Intestine: Food allergy - shellfish, strawberries, etc.
3. Skin: Urticarial reactions to drugs, chemicals, injected antigens, etc.
In highly sensitized individuals provocation with the appropriate antigen may result in systemic anaphylaxis.

Type II - Cytotoxic
Reactions of this type occur when an antibody combines with an antigen on the surface of a cell and results in cell-death by:
(i) Complement-mediated cytolysis (C89)
(ii) Phagocytosis of the cell in response to an opsonic antibody effect or by immune adherence (C3b)
(iii) Promotion of cytotoxicity by cells activated through their Fc receptors. Such antibody-dependent cell-mediated cytotoxicity (ADCC) can be effected by monocytes, polymorphs and NK cells.
Examples:
(i) Haemolysis resulting from antibodies directed against red-cell antigens or antigens attached to the surface
   a. Transfusion reactions
   b. Rhesus incompatibility
   c. Auto-immune haemolytic anaemia
   d. Drug-induced haemolysis, e.g. a-methyldopa, chlorpromazine, phenacetin
   e. Associated infections, e.g. salmonellosis
(ii) Thrombocytopenia following treatment with Sedormid (now withdrawn) and occasionally aspirin, tetracyclines, PAS, oestrogen and other drugs
(iii) Agranulocytosis associated with amidopyrine, quinine, PAS, thiouracil, colchicine, phenothiazines, etc.
(iv) Anti-glomerular basement membrane antibodies in Goodpasture's syndrome activate complement and provoke an acute inflammatory response in the glomerulus and lung
(v) Hashimoto's thyroiditis
Type III - Complex-mediated

When large amounts of a soluble antigen are introduced into the circulation and an antibody reaction commences, immune complexes are formed in extreme antigen excess. These complexes (e.g. Ag2Ab, when antibody binds two antigen molecules) do not fix complement but can be cleared through Fc mediated phagocytosis by polymorphs and macrophages. When complexes are formed in the presence of higher concentrations of antibody (e.g. Ag3Ab2, Ag2Ab3) complement is activated and phagocytosis by the more efficient C3b mechanism follows. Accumulation of complexes in the circulation may result from defective phagocytosis or from excessive production in response to a large antigenic challenge. Small complexes are deposited in glomeruli whereas larger complexes by activating complement increase vascular permeability and may be found in the skin, the intestine, in synovial membranes, etc. When complexes are formed in antibody excess they tend to be insoluble and remain localized to the site of formation. Complexes of this type entering the circulation are cleared rapidly by macrophages of the RES.

Antigen-antibody complexes will initiate an acute inflammatory reaction by the activation of complement and subsequent formation of anaphylatoxins, leucotaxins, and aggregation of platelets. Tissue destruction may result from complement-mediated cytolysis or by release of lysosomal enzymes from polymorphs which will also activate Factor XII and promote coagulation.

A. Antibody excess
   (i) Arthus reaction - an acute vasculitis produced by the introduction of antigen into the skin in the presence of high levels of precipitating antibody (IgG), e.g.
      a. Reaction to insulin injection in sensitized diabetics
      b. Erythema nodosum leprosum
   (ii) In the lung - extrinsic allergic alveolitis
      Type III reactions to inhaled organic materials or microorganisms which lead to inflammation and fibrosis producing progressive restrictive lung disease

B. Antigen excess
   (i) Serum sickness - a syndrome characterized by pyrexia, urticaria, joint pains, generalized lymphadenopathy and albuminuria, which is occasionally seen following large injections of foreign protein
   (ii) Glomerulonephritis
      a. Post-streptococcal and other infections
      b. Systemic lupus erythematosus (SLE)
      c. Quartan malaria
      d. Drug-induced, e.g. penicillamine in rheumatoid arthritis
   (iii) Skin lesions
      a. Erythema multiforme
      b. Secondary syphilis
   (iv) 'Vasculitides'
      a. Polyarteritis nodosa
      b. Henoch-Schönlein disease
      c. Drug-induced vasculitis
      d. Wegener's granulomatosis (?)
   (v) Lung lesions due to such complexes occur in
      a. Respiratory syncytial virus infection
      b. Measles in an 'immunized' individual
   (vi) Central nervous system SLE
(vii) Arthritis (associated with various viral infections)
(viii) Rheumatic fever (complexes with streptococcal antigen deposited in small blood vessels in a wide variety of tissues)

Type IV - Cell-mediated (delayed-type) hypersensitivity
When a specifically sensitized T-lymphocyte (T-memory cell) comes into contact with the appropriate antigen it undergoes blast-cell transformation and cell division. Simultaneously, the cell produces numerous cytokines which promote a mixed inflammatory reaction.

T-lymphocyte responses are usually beneficial and underlie a number of important defense mechanisms against certain bacterial, viral and fungal infections (cell-mediated immunity). In some circumstances however they may have a deleterious effect and constitute a hypersensitivity reaction Examples:
(i) Cell-mediated hypersensitivity to bacterial antigens (bacterial allergy) is responsible for:
   a. The Mantoux reaction to an intradermal injection of tuberculin
   b. Caseation in tuberculosis
   c. The tuberculoid form of leprosy
(ii) Contact hypersensitivity in the skin: simple chemicals acting as hastens attach to skin proteins and render them antigenic. The resulting cell-mediated response produces erythema, oedema and often vesiculation - contact dermatitis.
   Common skin sensitizers are:
   a. Nickel
   b. Rubber
   c. Poison-ivy and primulus
   d. Topical medicaments - neomycin, lanolin, penicillin
   e. Iodine
   f. Dinitrochlorobenzene (DNCB)
(iii) Graft rejection
(iv) Some auto-immune diseases

Type V - Stimulatory hypersensitivity
Thus far only one example of this form of hypersensitivity has been defined and that is the stimulatory auto-antibody responsible for a type of thyrotoxicosis (Graves' disease). The auto-antibody, long-acting thyroid stimulator (LATS), is directed at the same surface receptor as is activated by TSH, and results in prolonged hypersecretion of thyroxine and triiodothyronine by the cell.

TISSUE TRANSPLANTATION

Nomenclature
Autograft - transplantation within the same individual Isograft or syngeneic graft - between identical twins or in-bred animals
Allograft - between individuals of the same species but of different genetic make-up (formerly homograft)
Xenograft - between different species

Transplantation antigens
All nucleated cells possess surface histocompatibility antigens determined by
separate gene loci. Tests for histocompatibility employ leucocytes and specific antisera. Although an individual's tissues are antigenically similar, the concentration of antigens varies from tissue to tissue, for example skin has a high concentration, whilst placenta, muscle, aortic wall, have low levels.

**Rejection**

Three patterns are described.

(i) Hyperacute rejection occurs where there is major incompatibility with high levels of humoral antibodies resulting in an Arthus-type reaction

(ii) Acute rejection occurs 2 to 3 weeks after grafting and results from antibody- and cell-mediated hypersensitivity. Destruction of the graft is brought about by:

a. The direct action of sensitized cytotoxic (CD8+) T-lymphocytes
b. Phagocytosis of graft cells by macrophages activated by cytokines or following C3b opsonisation
c. Attack by K-cells on IgG-coated graft cells

(iii) Chronic rejection consequent upon gradual vascular obliteration, probably due to deposition of immune complexes and activation of complement and blood coagulation

**Prevention of rejection**

(i) Favorable sites for transplantation

a. Cornea and anterior chamber of the eye
b. Meninges
c. Testis

These sites may be protected by virtue of unusual vascularity or lymphatic drainage

(ii) Accurate tissue matching

(iii) Immune deficiency states, pregnancy, and uraemia

(iv) Immunosuppression

a. Corticosteroids
b. Azathioprine
c. Antilymphocyte serum
d. Whole-body irradiation
e. Induction of immune tolerance

**AUTO-IMMUNITY**

**Mechanisms**

The formation of antibodies or cell-mediated reactions directed against 'self' constituents may result from:

1. **Alteration of self-proteins**
   
   (i) Combination with haptens, as in contact dermatitis and a-methyldopa-induced haemolysis
   
   (ii) Modification by degenerative or infective conditions, e.g. to skin proteins following burns, red cells in mycoplasma infection, or to enzymically altered thyroglobulin or gammaglobulin.
2. **Exposure of hidden antigens**
Some antigens remain hidden or sequestered from the immune system and tolerance does not develop. On subsequent exposure in the mature animal they will be treated as non-self.
   (i) Spermatozoa. Orchitis may be followed by production of antisperm antibodies and lead to sterility
   (ii) Lens protein. Degeneration and/or removal of a cataract may result in auto-antibodies and damage to the contralateral lens
   (iii) Sympathetic iritis following damage to the contralateral iris
   (iv) Release of myelin basic protein from the brain and the subsequent immune response may have a role in multiple sclerosis

3. **Cross-reactions**
Immune reactions to exogenous antigen may cross-react with self-proteins
   (i) T-lymphocyte responses induced by bacterial or parasitic heat-shock (stress) proteins may cross-react with self stress proteins with which there is considerable homology, e.g. T-lymphocyte responsive to mycobacterial stress proteins in rheumatoid arthritis
   (ii) Antibodies to streptococcal antigens may react with constituents of cardiac muscle or connective tissue in rheumatic fever
   (iii) An immune response to heterologous brain tissue in rabies vaccine may give rise to encephalitis

4. **Breakdown of tolerance**
   (i) Genetic. An inherited defect or lack of efficiency in antibody production may lead to the formation of damaging antigen-excess complexes
   (ii) Direct disturbance of the immune system by drugs, chemicals, infective agents, and neoplasia. Examples:
   a. Hydralazine precipitating SLE
   b. Virus infection of NZB mice appears to underlie the development of auto-immune haemolytic anaemia and complex-mediated glomerulonephritis
   c. Chronic lymphocytic leukaemia and malignant lymphomas may be associated with auto-immune haemolytic anaemia
   (iii) Stimulation of pre-existing clones of T- and B-cells capable of self-reactivity by infectious agents or adjuvants, either directly or by eliminating the appropriate suppressor T-lymphocytes.

**HLA AND AUTO-IMMUNE DISEASE**

As outlined above there are strong links between the HLA system and normal immune reactivity. It is not surprising, therefore, that there exists a close association between certain HLA antigen types and auto-immune disease.
The basis for the relationship between auto-immunity and the HLA system rests on:
1. Communication between antigen-presenting cells and abnormal T- and B-subsets, namely:
   (i) Increased numbers of activated T-helper cells
   (ii) Decreased numbers of T-suppressor cells
2. Participation of complement
   The link between auto-immunity and complement (which is genetically
encoded in the HLA region) is exemplified by the finding that most patients with SLE carry at least one null allele for C4 and C2, suggesting that people with only one gene dose for these components are genetically susceptible to the disease.

Examples of the association between HLA status and auto-immune disease include:

1. HLA-A3 Haemochromatosis
2. HLA-B8 with
   (i) Coeliac disease
   (ii) Dermatitis herpetiformis
   (iii) Addison's disease
   (iv) Graves' disease
   (v) Chronic active hepatitis (auto-immune type)
3. HLA-B27 with
   (i) Ankylosing spondylitis
   (ii) Post-infective (e.g. gonococcal) arthritis
   (iii) Acute anterior uveitis
4. HLA-DR2 with Multiple sclerosis
5. HLA-DR3 with
   (i) Chronic active hepatitis
   (ii) Sjögren's syndrome
6. HLA-DR3/DR4 Insulin dependent diabetes
7. HLA-DR4 with Rheumatoid arthritis

**Pathogenesis of auto-immune disease**

Auto-antibodies can be found in the sera of apparently healthy individuals and increase in incidence with age. In most cases no harmful effects can be attributed to the antibodies. Auto-immune reactions having a primary role in disease operate through:

1. Humoral antibodies in
   (i) Auto-immune haemolytic anaemia (anti-RBC antibodies)
   (ii) Idiopathic thrombocytopenia (anti-platelet)
   (iii) Some cases of lymphopenia (anti-lymphocyte)
   (iv) Some cases of agranulocytosis (anti-neutrophil)
   (v) Hashimoto's thyroiditis (anti-thyroglobulin, antimicrosomal)
   (vi) Pernicious anaemia (anti-intrinsic factor, anti-parietal cell)
   (vii) Some cases of male infertility (anti-spermatozoa)
   (viii) Goodpasture's syndrome (anti-basement membrane)
   (ix) Lens-induced endophthalmitis
   (x) Thyrotoxicosis (stimulatory or anti-TSH receptor antibody)

2. Immune complexes in
   (i) SLE (anti-DNA)
   (ii) NZB mice infected with leukaemia virus
   (iii) Aleutian mink disease

3. Cell-mediated reactions in
   (i) Experimental allergic encephalomyelitis and in association with auto-antibodies in
   (ii) Atrophic gastritis
   (iii) Hashimoto's disease
   (iv) Auto-immune orchitis

Diseases in which auto-antibodies are found but a primary role in producing the
disease has not been established include:

1. Connective tissue disorders
   (i) Rheumatoid disease - anti-IgG, anti-IgM antibody
   (ii) Scleroderma - anti-IgG/antinuclear
   (iii) Dermatomyositis - anti-IgG/antinuclear
   (iv) SLE - lymphocytotoxic antibodies

2. Skin diseases
   (i) Discoid lupus erythematosus - antinuclear/anti-IgG
   (ii) Pemphigus - anti-intercellular cement substance
   (iii) Pemphigoid - anti-basement membrane
   (iv) Dermatitis herpetiformis - anti-reticulin

3. Alimentary system
   (i) Ulcerative colitis/Crohn's disease - lymphocytotoxic
   (ii) Primary biliary cirrhosis - anti-mitochondrial
   (iii) Chronic active hepatitis - anti-smooth muscle
   (iv) Some cases of 'cryptogenic' cirrhosis

4. Others
   (i) Idiopathic adrenal cortical atrophy (Addison's disease)
   (ii) Sjögren's syndrome
   (iii) Multiple sclerosis
   (iv) Myasthenia gravis - anti-end-plate
   (v) Juvenile diabetes mellitus

Meditation has been getting more attention in recent years as the understanding of the link between mind and body grows. Indeed the medical field of psychoneuroimmunology demonstrates the acceptance of the power the mind has over the body. Sadly the epidemic levels of depression and chronic stress is taking its toll on people's health. Although stress has a biological purpose the human body was never meant to be subjected to it constantly. Stress hormones are meant to aid the body in the fight or flight response and then the body is supposed to break them down and dispose of them. With the case of depression there is the poor nutrition that most people get as well as the dissatisfaction with their personal and professional lives. Keep in mind that the brain utilizes one fourth of available blood sugar as well as tremendous amounts of nutrients.

Meditation involves slowing down the constant chatter inside of a person’s mind and with it eliminates the physiological responses to the emotions evoked by said chatter. The word emotion can be considered a contraction of the words “energy in motion”. Emotions generate energy and that energy affects the body. Traditional Chinese Medicine recognizes the energy generated by emotions as well as the organs that produce or are affected by this energy. The meridians that run through the body direct the flow of energy into and out of the organs. Through various forms of meditation this energy can be controlled.

Any form of contemplative meditation teaches how to control the mind by letting discursive thoughts fade to the point of no longer disrupting conscious brain function. When the level of agitation of the mind by these thoughts diminishes a person becomes less distracted and functions more efficiently. Shamatha meditation or “peaceful abiding” of the Tibetan Buddhist tradition is one method of meditation that accomplishes this.

Chi Kung is a form of meditation that takes this a step further and teaches the control
of the energies in our body that affect the body to improve health. This form of meditation uses visualization to direct the flow of energy along the meridians. By directing the flow of energy one can not only reduce the negative effects on health caused by out of control emotions but actually harness this power to improve health. The human energy system is a concept that sadly many Western physicians are reluctant to accept. Ironically quantum physics has demonstrated that many alternative medical theories are not so farfetched. As interest in things such as yoga, t'ai chi cha'un, chi kung and other meditative arts grows so will research into the medical applications of meditation. Perhaps this will help other fields of alternative medicine become more accepted.

7. Resistance to infection

Resistance to infection is dependent upon:
A. The general body defense mechanisms
B. Innate non-specific immunity
C. Acquired specific immunity

A. BODY DEFENSES

1. Physical barriers
   (i) Skin
   (ii) Urothelium
   (iii) Mucous membranes of alimentary and respiratory tract
2. Mechanical decontamination
   (i) Desquamation of surface cells together with adherent organisms
   (ii) Flushing of the urinary tract
   (iii) Anatomical trapping, e.g. nasal turbinates
   (iv) Mucus trapping and expulsion
   (v) Dysfunction of cilia resulting from structural defects or an abnormal response to ATP may underlie some cases of: sinusitis and bronchitis
3. Antimicrobial secretions
   (i) Lysozyme (muramidase) in sweat, tears, saliva and tissue fluids
   (ii) Acidity of sweat, gastric juice and vaginal secretion
   (iii) Unsaturated fatty acids in sebum and sweat
   (iv) Immunoglobulins, e.g. IgA in intestinal secretions
   (v) Basic polypeptides
4. Growth factor secretion
   (i) EGF by Brunner's glands and salivary glands facilitates epithelial regeneration
   (ii) TGFα by sweat glands
5. Surface phagocytosis by:
   (i) Macrophages, e.g. alveolar macrophages
   (ii) Epithelial cells, e.g. in the bladder
6. Competition by commensal organisms in:
   (i) Upper respiratory tract
   (ii) Mouth
   (iii) Lower ileum and colon
   (iv) Vagina
(v) Skin

B. INNATE IMMUNE MECHANISMS

1. Genetic factors
   (i) Species, e.g. animals are generally resistant to syphilis, poliomyelitis, meningococcal meningitis whereas humans are immune to myxomatosis, foot and mouth disease, etc.
   (ii) Race, e.g. Negroes and American Indians are more susceptible to tuberculosis than Caucasians
   (iii) Individual (hereditary factors)
   (iv) Sex. The male is more prone to fatal infectious disease than the female
   (v) Age. The very young and the elderly are more susceptible to infection
   (vi) Hormonal status, e.g. infections are more common in diabetes mellitus, steroid therapy, hypothyroidism

2. Cellular factors
   (i) Phagocytosis by macrophages and polymorphs
   (ii) Cytotoxicity by NK cells, usually large granular lymphocytes

3. Humoral factors
   (i) Lysozyme is an enzyme which acts on the muramic acid present in bacterial cell walls
   (ii) Complement. Activation of the alternate pathway by endotoxin may bring about several antimicrobial effects:
      a. Bacteriolysis
      b. Opsonisation
      c. Immune adherence
      d. Leucotaxis
   (iii) Interferon, a non-specific anti-viral agent produced by a wide variety of cells but particularly by cells of the RES in response to an inducer which is probably the nucleoprotein component of the virion. Interferon is more important in the elimination of viruses in non-immune individuals than in preventing infection
   (iv) Acute phase proteins, e.g. C reactive protein acts as a natural opsonin by binding to the C protein of pneumococci

C. ACQUIRED IMMUNITY

Acquired immunity implies the generation of a specific cellular or humoral response to the infective agent. Immunity is active where an individual mounts a cellular immune response or manufactures antibodies in response to an antigen, or passive where temporary protection is afforded by giving pre-formed antibodies.

1. Active immunity
   (i) Natural, following previous infection
   (ii) Artificial, by administering toxoid, killed or attenuated organisms
      a. Toxoid, e.g. formaldehyde-treated exotoxin of diphtheria bacilli
      b. Killed organisms, e.g. typhoid vaccine, poliomyelitis (Salk) vaccine
      c. Attenuated organisms, e.g. Bacille-Calmette-Guerin vaccine is a live attenuated strain of Mycobacterium tuberculosis

2. Passive immunity
   (i) Natural, transfer of antibodies of maternal origin
a. Trans-placental (IgG)
b. Intestinal absorption from colostrum and milk (IgA)

(ii) Artificial, by the administration of immunoglobulins
a. Homologous, e.g. pooled human gammaglobulin used in treatment of measles, hypogammaglobulinaemia, etc.
b. Heterologous, e.g. tetanus anti-toxin prepared in the horse

IMMUNITY TO BACTERIAL INFECTION

1. Humoral factors
   (i) Secretory IgA antibodies may prevent attachment of bacteria to host cells
   (ii) Antibodies to M proteins and capsules promote opsonization and phagocytosis by
      a. Fc receptors
      b. Complement activation and C3b adherence
   (iii) Complement activation via the alternate pathway by endotoxin (LPS)
   (iv) Neutralising antibodies (anti-toxins) directed against bacterial exotoxins, e.g. antibodies against the erythrogenic exotoxin of *Streptococcus pyogenes* which gives rise to the skin changes of scarlet fever
   (v) Antibodies directed against bacterial stress proteins
   (vi) Serum lysozyme

2. Cellular factors
   (i) Phagocytosis by polymorphs and macrophages
   (ii) Killing mechanisms
       These are enhanced by
       a. activation by bacterial products such as LPS, formyl-methionyl-leucyl-phenylalanine and related peptides
       b. activation by cytokines such as interferon-y and TNF
   (iii) T-lymphocyte response directed at bacterial stress proteins

IMMUNITY TO VIRAL INFECTION

1. Humoral factors
   (i) Neutralising antibodies in plasma are particularly important where there is a blood-borne phase before the virus reaches its target, e.g. poliomyelitis
   (ii) Neutralising IgA antibodies in secretions from mucous membranes are important in preventing local infection, e.g. against influenzal attack on the respiratory mucosa
   (iii) Interferons. The anti-viral effects of interferons are mediated via
       a. Direct inhibition of viral replication
       b. Activation of NK cells and macrophages capable of destroying virus-infected cells
       c. Increased expression of Class I and II MHC antigens which facilitates recognition of virus infected cells by T-lymphocytes
   (iv) Tumour necrosis factor has anti-viral effects similar to the interferons

2. Cellular factors
   (i) T-lymphocyte response with
       a. Destruction of virus infected cells by cytotoxic T-cells
       b. Cytokine stimulation of B-lymphocytes and macrophages
(ii) Phagocytosis of virus by macrophages with subsequent interferon production, or transfer of the inducer to other interferon-producing cells
(iii) Antibody dependent cell mediated cytotoxicity by K cells (large granular lymphocytes)

IMMUNITY TO PROTOZOA AND HELMINTHS

1. *Humoral factors*
Antibodies directed against surface antigens and stress proteins
   (i) Lead to complement activation and lysis
   (ii) Block invasion of host cells by blood-borne parasites
   (iii) Enhance phagocytosis by Fc and C3b mechanisms
   (iv) Facilitate antibody-dependent cell cytotoxicity (ADCC) by macrophages, neutrophils and eosinophils

2. *Cellular factors*
   (i) T-cell production of cytokines such as IFNg
   (ii) Macrophage proliferation leading to granuloma formation. This may 'wall off' the parasites
   (iii) Secretion of soluble 'killing' factors by macrophages
   (iv) Killing by polymorphs and eosinophils. (The latter are recruited by a specific eosinophil stimulation promotor secreted by T-lymphocytes)

OPPORTUNISTIC INFECTION

Opportunistic infections are usually found in patients whose body defenses or immune reactivity are impaired. The infective agents may be recognized pathogens, or increasingly, may be organisms of low pathogenicity often derived from the host flora.
Organisms of low pathogenicity or uncommon pathogens which are found in opportunistic infections include:

1. Fungi
   *Candida albicans*
   *Cryptococcus neoformans*
   *Histoplasma capsulatum*
   *Aspergillus fumigatus*
   Phycomycetes
   Mucor
   Rhizopus
   Absidia

2. Bacteria
   *Nocardia asteroides*
   Atypical mycobacteria

2. Viruses
   *Cytomegalovirus*
   *Varicella - herpes zoster*     Disseminated infection
Measles
Vaccinia

4. *Pneumocystis carinii*

Predisposing factors are:

1. **Disturbance of physical body defenses**
   (i) Surgery, e.g. infection by bacteroides, staphylococci
   (ii) Trauma, e.g. staphylococci
   (iii) Foreign bodies including urinary and intravascular catheters - Gram-negative bacilli, fungi
   (iv) Burns - *Pseudomonas*

2. **Alteration of flora** by antimicrobial drugs, especially of the vagina and alimentary tract, e.g. Candidiasis, *Clostridium difficile*

3. **Immunosuppressive treatment**
   (i) Corticosteroids
   (ii) Irradiation
   (iii) Chemotherapy various organisms, especially Gram-negative bacilli

4. **Disorders of neutrophils**
   Staphylococci, streptococci, Gram-negative bacilli, fungi

5. **Deficient humoral immunity**, as in chronic lymphatic leukaemia or multiple myeloma: pyogenic cocci, Gram-negative bacilli, *Listeria monocytogenes, Pneumocystis carinii*


7. **Immunodeficiency of mixed type** - viral infections, *Pneumocystis carinii, Candida albicans*

8. **Post-splenectomy** - Streptococcus pneumoniae, Neisseria meningitides, *Haemophilus influenzae*

Psychoneuroimmunology

In the 6th Century B.C. Hippocrates wrote that "For this is the great error of our day that the physicians separate the soul from the body." Today, despite scientific advances showing how our emotions and spirit affect our health, some physicians refuse to make the connection. This despite the fact that in 1975, Dr. Robert Ader, Director of the Division of Behavioral and Psychosocial Medicine at the University of Rochester in New York, first reported that our immune system, nervous system, and endocrine system work together, each system influencing the other systems. The study of these complex interactions was originally termed psychoneuroimmunology or PNI although today it is more commonly referred to as the mind-body connection. By 1980, the early studies of Ader were reproduced and confirmed by researchers at Harvard University, and today PNI is taught at most leading medical schools.

Immune System Influences
The early studies of Dr. Ader showed that the immune system can be conditioned. In one early experiment consisted of feeding mice with saccharin while simultaneously injecting a second drug that caused upset stomach. By association, the mice learned to avoid the saccharin. An additional side effect of the drug used was that it suppressed the immune system. When the experiment was repeated without the drug to reverse the aversion Dr. Ader found a high proportion of the mice formally injected died when receiving saccharin alone because of immune suppression.

Dr. Ader hypothesized that the conditioning had been so successful that saccharin alone suppressed the immune system enough to kill the mice. It is possible then, that when there is stress on the organism, mental or physical, that there is a corresponding link between the two systems. That is, if a person is depressed, this state can be interpreted by the body, and, in response, the person experiences lethargy and other corresponding ailments. Conversely, if the body is diagnosed as ailing from a serious disease, for instance multiple sclerosis, a negative mental state may ensue. By conditioning the immune system behaves accordingly. Providing the patient with some feeling of control over their circumstances may create a positive outlook and attitude.

Psychoneuroimmunology then is the scientific field of study investigating the link between bi-directional communications among the nervous system, the endocrine (hormone) system, and the immune system and the implications of these linkages for physical health.

In similar studies at Harvard University, Dr. Joan Borysenko described a study on rabbits that were treated with a potent cancer-inducing agent. Although all of the rabbits in the upper cages developed the expected cancer, the rabbits in the lower cages remained free of cancer. Upon investigating, the researchers learned that the laboratory assistant who administered the medications consistently petted the rabbits in the lower cages since they were easier to reach. Their emotional well being caused their immune system to fight the effects of the administered medication, and they remained healthy.

Stress and Emotions in Autoimmune Disease

Stress is a well-known trigger of autoimmune disease. The flares and exacerbations that are characteristic of autoimmune disorders correspond to periods of heightened stress. In studies of patients with Graves' disease, the stress associated with bereavement is a significant disease trigger.

Candace Pert, in her book on the mind-body connection explains how hormones produced during times of stress affect our emotions, and both hormonal and emotional changes produce peptides that influence immune function. In her work on Metaphysics, Louise Hay explained how specific emotions induce specific disease states and how disease states can be reversed through changes in attitude that influence emotions.
8. Immune deficiency

The proper functioning of the immune system depends upon the integrity of the thymus, the bone marrow, and the lymphoid tissues, together with normal function of polymorphs, monocytes, and the complement system. Immune deficiencies can result from a congenital defect in any of these components (primary immunodeficiency) or may arise as a consequence of some other disease.

PRIMARY IMMUNODEFICIENCY

In view of the complex interactions between T- and B-lymphocytes, division of immunodeficiency into 'pure T-cell' and 'pure immunoglobulin' deficiencies is artificial.

1. Congenital sex-linked (Bruton’s agammaglobulinaemia). This is an X-linked disease confined to males and is characterized by an almost complete absence of immunoglobulins from the serum. Affected individuals are particularly prone to bacterial infections and suffer from recurrent bronchitis, pneumonia, otitis media and skin infections.

2. Dysgammaglobulinaemia
   (i) Selective IgA deficiency
       Patients exhibit a wide range of clinical manifestations. Some are asymptomatic whilst others suffer repeated respiratory and intestinal infections, being particularly prone to intestinal giardiasis
       Associations with IgA deficiency include:
       a. Atopic reactions
       b. Malabsorption syndrome
       c. Intestinal nodular lymphoid hyperplasia
       d. Auto-immune haemolytic anaemia
   (ii) Wiskott-Aldrich syndrome
       An X-linked or sporadic disorder characterized by low IgM levels associated with:
       a. Recurrent infections especially with Streptococcus pneumoniae and H. influenzae
       b. Atopic eczema
       c. Thrombocytopenia
   (iii) Ataxia-telangiectasia syndrome
       A sex-linked disorder in which there is extremely low or absent IgA and occasional reduction in IgE or IgG. Patients exhibit:
       a. Recurrent respiratory tract infections
       b. Cerebellar ataxia
       c. Oculo-cutaneous telangiectasia
   (iv) Common variable hypogammaglobulinaemia (CVH) Probably represents several different disease entities in that varying patterns of immunoglobulin deficiency are encountered. Most patients have low IgG and variable degrees of IgA and IgM deficiency. About $\frac{1}{3}$ have reduced T-cells and show diminished delayed hypersensitivity skin-tests. The most common clinical manifestations are recurrent sinusitis, bronchiectasis, and pneumonias. These patients also have a high prevalence of autoimmune diseases, notably pernicious anaemia, haemolytic anaemia, and rheumatoid arthritis.
3. Defects in thymic development
   (i) Cellular immunodeficiency with immunoglobulins (Nezeloff syndrome) - results from isolated thymic aplasia (agenesis)
   (ii) DiGeorge's syndrome
      a. Complete
         Maldevelopment of the 3rd and 4th bronchial arches leads to thymic aplasia, absence of the parathyroids, and abnormalities of the aortic arch.
         There is a marked reduction in T-cell numbers
      b. Partial
         Thymic hypoplasia (under-development) leads to varying degrees of T-cell deficiency
   (iii) Severe combined immunodeficiency disease (SCID) The thymic and lymphoid tissues are under-developed and there is a marked reduction in T- and B-cell numbers. SCID is thought to be due to enzyme defects in purine metabolism which are inherited as autosomal recessives.

4. Chronic muco-cutaneous candidiasis
   In addition to repeated candida (and other) infections, patients frequently have an associated endocrine disorder such as
   (i) Diabetes mellitus
   (ii) Pernicious anaemia
   (iii) Addison's disease
   (iv) Gonadal dysgenesis
   There are defects in T-lymphocyte, polymorph, and monocyte function.

Limited immunodeficiency
This implies susceptibility to only a single pathogen or only a narrow range of pathogens.
   (i) Fatal infectious mononucleosis (Duncan disease)
   (ii) Unusual susceptibility to *H. influenzae* epiglottitis

Complement deficiency
Genetic deficiencies of virtually all the complement components have been described. Those associated with systemic disease include:
   (i) C1, C2 and C4 defects
      Abnormalities in the initial stages of the complement cascade are associated with an SLE-like syndrome with facial rashes, nephritis and arthritis. HLA control of immune responses and complement synthesis probably underlies this association
   (ii) C3 and C5 defects
      As the cleavage products from these components are of fundamental importance in polymorph and monocyte chemotaxis (C3a, C5a) and in immune adherence (C3b), it is to be expected that deficiencies lead to recurrent bacterial infections. Depletion of C3 could also stem from a deficiency in C3 inactivator, as the latter deficiency results in continuous fluid-phase activation of C3 rendering it unavailable for the normal complement pathway
   (iii) C6, C7 and C8 defects
      The final components of the complement pathway appear to be of particular importance in the clearance of Neisseria. Deficiency of these factors
predisposes to disseminated infection with *N. gonorrhoea* and *N. meningitides*

(iv) Alternate pathway defects
Recurrent infections may arise from a failure to generate opsonins through the alternate pathway. This is usually a result of Factor B deficiency

**Defects in polymorph and monocyte function**
1. Polymorph defects
2. Monocyte defects
Many diseases causing abnormal polymorph function also affect monocytes. Defective monocyte chemotaxis is also a feature of:
   (i) Chronic muco-cutaneous candidiasis
   (ii) Hyper-IgE syndrome
   (iii) Associated with various malignancies

**SECONDARY IMMUNODEFICIENCY**

The most notable example of secondary immunodeficiency is the acquired immunodeficiency syndrome (AIDS)

**AIDS**
AIDS results from infection by the human immunodeficiency virus (HIV), a retrovirus which binds to CD4+ (helper) T-lymphocytes and exerts cytopathic effects on them leading to profound depletion. The disease is of world-wide distribution and in the US and Europe is seen in the following groups:
1. Homosexual or bisexual males
2. Intravenous drug abusers
3. Blood and blood component recipients, e.g. haemophiliacs
4. Heterosexual contacts of infected individuals
In Africa heterosexual spread is paramount. As implied by the above high-risk groups, transmission of HIV is by sexual contact, parenteral administration or vertically from infected mothers to their offspring. The striking depletion of T-helper lymphocytes seen in AIDS means that patients are unable to mount antibody responses to new antigens and exhibit a marked reduction in cytokine synthesis which in turn affects macrophage function and haemopoietic growth and differentiation. The major disturbances of immune function are:
1. Lymphopenia
2. Decreased T-cell function results in opportunistic infection and increases susceptibility to neoplasms
3. Polyclonal B-cell activation gives rise to hypergammaglobulinaemia and circulating immune complexes
4. Impaired macrophage function
These defects in immune reactivity give rise to the following opportunistic infections:
   1. Bacterial
      (i) Mycobacterial
         a. Atypical e.g. *M. avium-intracellulare*
         b. Disseminated *M. tuberculosis*
      (ii) Salmonellosis
   2. Viral
      (i) Cytomegalovirus
(ii) Herpes simplex virus  
(iii) Varicella zoster virus

3. Fungal  
(i) Candidiasis  
(ii) Cryptococcosis  
(iii) Histoplasmosis

4. Protozoal and helminthic  
(i) Cryptosporidiosis  
(ii) *Pneumocystis carinii*  
(iii) Toxoplasmosis  
(iv) Strongyloidosis

AIDS patients also develop an unusual pattern of malignant disease.  
1. Kaposi's sarcoma - a multicentric neoplasm of vasoformative cells which follows an aggressive clinical course.  
4. CNS lymphomas.  

Other causes of secondary immunodeficiency are:  
1. Excessive loss of immunoglobulins  
   (i) Protein losing enteropathy  
   (ii) Nephrotic syndrome  
2. Depression of the immune system by  
   (i) Old age  
   (ii) Malnutrition  
   (iii) Virus infections such as measles  
   (iv) Leprosy  
   (v) Malaria  
   (vi) Sarcoidosis  
   (vii) Surgery  
   (viii) Endotoxaemia  
   (ix) Uraemia  
3. Immunosuppression by  
   (i) Radiotherapy  
   (ii) Corticosteroids  
   (iii) Cytotoxic drugs  
   (iv) Antimetabolites

4. Neoplasia  
Predominantly T-cell deficiency in:  
   (i) Hodgkin's disease  
Deficiency of normal immunoglobulins in:  
   (ii) Multiple myeloma  
   (iii) Waldenström's macroglobulinaemia  
Mixed deficiency in:  
   (iv) Non-Hodgkin's lymphoma  
   (v) Chronic lymphocytic leukaemia

5. Loss of splenic function  
Results in diminished clearance of particulate antigens and impaired production of IgM antibodies  
   (i) Splenectomy
(ii) Splenic atrophy
   a. Coeliac disease
   b. 'Idiopathic'

**Psychoneuroimmunology** is defined as the study of behaviorally associated changes in immunity and immunologically associated changes in behavior that result from the interaction among the nervous, endocrine, and immune systems (1, 2). The charge to this working group was to develop experimental protocols with which to investigate multiple chemical sensitivity (MCS) from the heretofore unconsidered perspective of psychoneuroimmunology. Given that the involvement of the immune system in MCS is still an area of some controversy, the impact of psychoneuroimmunological processes on the onset, development, and clinical course of MCS is problematic. Thus, the group also considered a reasonable area of scientific inquiry to be the possible influences on immunity of the stress associated with MCS as a chronic disability (3).

**Questions Relevant to the Relationship between Exposure and Symptoms in Chemical Sensitivities**

During its deliberations, the group raised the following six related sets of questions whose answers could reveal a relationship among behavioral stimuli, neural-immune system interactions, and MCS.

- In situations in which a sensitizing chemical may be immunomodulatory, do environmental cues temporally associated with the sensitizing exposure serve as conditioned stimuli (4)? If so, can such cues, with or without subthreshold amounts of the chemical, elicit a chemical sensitivity response? Can the chemical sensitizer itself, provide both unconditioned and conditioned stimuli?

- Are there significant immunological, neuroendocrine, and psychosocial deviations from normalcy shortly before, at the time of, or consequent to, the development of MCS symptomatology? If physiological changes are noted consequent to psychosocial changes, are those psychosocial changes implicated in the development of MCS? If so, could psychological/behavioral intervention be of therapeutic value, at least in some subset of patients (3)?

- What is the interval between the initiating event and the development of early symptoms of MCS? What is the interval between the initial trigger and the so-called increase in sensitivities to diverse stimulants?

- Is the duration of these intervals related to psychosocial factors (e.g., stress) or to personality/sex/health status (e.g., allergic status, autoimmunity or autoimmune predisposition) of the subject, or the chemical nature of the initiator? Do events perceived as stressful in the recent or past history of the individual play roles in the onset and/or progression of MCS?

- What do chemical initiators of MCS and initiators of MCS such as a car accident or childbirth have in common? Which factor is more important in the traumatic initiation: the exposure to chemicals associated with the traumatic event, and/or the stressful experience associated with the event? Can a stressor precipitate MCS in a chemically sensitized individual who is not
displaying overt symptoms of MCS at the time of stressor exposure?

Why is there variability in the development and severity of MCS? Is there any relationship between major histocompatibility complex phenotype and MCS? Is there a detectable humoral or cellular immune response to the initiating chemical? Is an immune response causal or the result of the MCS process(es)?

9. Granulomatous diseases

Chronic inflammatory conditions characterized by the finding of granulomas composed of circumscribed collections of modified (epithelioid) macrophages, unaltered macrophages and lymphocytes. Epithelioid cells show reduced phagocytosis but exhibit a prominent endoplasmic reticulum and Golgi apparatus in keeping with enhanced secretary activity. The presence of non-degradable material and/or a T-cell response involving the production of INF-g, interleukin-1 and interleukin-4 is thought to be essential for granuloma formation.

**MAJOR CAUSES OF GRANULOMAS**

Diseases characterized by granuloma formation include:

1. Bacterial
   - (i) Tuberculosis
   - (ii) Leprosy
   - (iii) Atypical mycobacterial infection
   - (iv) Syphilis
   - (v) Cat scratch disease
   - (vi) Yersiniosis

2. Fungal
   - (i) Histoplasmosis
   - (ii) Cryptococcosis
   - (iii) Coccidioidomycosis
   - (iv) Blastomycosis

3. Helminthic
   - (i) Schistosomiasis

4. Protozoal
   - (i) Leishmaniasis
   - (ii) Toxoplasmosis

5. Chlamydia - lymphogranuloma venereum

6. Inorganic material
   - (i) Silicosis
   - (ii) Berylliosis

7. Idiopathic
   - (i) Sarcoïdosis
   - (ii) Crohn's disease
   - (iii) Primary biliary cirrhosis
TUBERCULOSIS

An infective condition caused by *Mycobacterium tuberculosis*. Five varieties are recognized:

1. Human, 'classical'type
2. Bovine
3. Asian
4. African I (West Africa)
5. African II (East Africa)

Other potentially pathogenic mycobacteria include:

1. *M. man .num*
2. *M. ulcerans I*
3. *M. kansasii*
4. *M. scrofulaceum*
5. M. xenopi
6. M. avium-intracellulare
7. M. paratuberculosis

These are referred to as atypical, anonymous or opportunistic mycobacteria.

Routes of infection

1. Inhalation - pulmonary infection, the most common route
2. Ingestion - tonsillar or small intestinal infection (now uncommon as bovine tuberculosis is eradicated in developed countries)
3. Congenital (rare)
   (i) Blood spread via the placenta
   (ii) Ingestion of infected amniotic fluid
4. Skin inoculation (very rare)

Primary infection

Initial infection leads in most cases to the formation of a circumscribed cellular reaction (the primary focus) and lymphatic spread of organisms to the regional lymph glands where a similar response develops. The primary focus and the involved regional glands are referred to as the primary complex.

In the majority of cases, infection is by inhalation and the Primary focus is usually found in a mid-zonal, sub-pleural situation (Ghon focus) with associated involvement of hilar lymph glands.

The fully-developed lesion has a characteristic microscopic appearance and is termed a 'tubercle' or tuberculous follicle.

Development of the tubercle

The body's response to *M. tuberculosis* passes through the following stages:

1. A short-lived acute inflammatory response with exudation of polymorphs
2. Accumulation of macrophages
3. Infiltration of surrounding tissue by specifically sensitized T-lymphocytes which secrete lymphokines including macrophage activating and cytotoxic factors
4. Phagocytosis of tubercle bacilli followed by development of lepithelioid' features to form a granuloma
5. Some macrophages fuse to form Langhans giant cells characterized by a peripheral 'horse-shoe' arrangement of nuclei
6. Necrosis of the central zone with formation of structureless, finely-granular, eosinophilic material - caseous necrosis
7. Fibroblastic proliferation around the periphery with increasing collagenisation

**The host response to tuberculosis**
Resistance to tuberculosis varies between races and is modified by age, sex, hereditary and environmental factors. Cell-mediated immunity is of far greater importance than humoral immunity in protection and takes the form of a hypersensitivity response to tuberculoproteins derived from the bacillus, a form of bacterial anergy.

**Immune responses**
1. Macrophage phagocytosis and 'processing'
2. Accumulation of sensitized T-lymphocytes and cytokine synthesis. The cytokines include:
   (i) Mediators of acute inflammation, as seen at the site of tuberculin injection in a positive Mantoux test
   (ii) Interleukins, interferon-γ and TNF which draw monocytes (macrophages) into the infected area and inhibit their further migration, activate the macrophages and enhance intracellular killing of mycobacteria
   (iii) Cytotoxic factors which bring about destruction of macrophages and host tissue (caseous necrosis). Necrosis may be increased by ischaemia towards the centre of the tubercle
3. Fibroblastic proliferation is probably enhanced in immune patients by virtue of increased interleukin-1 production by activated macrophages

**The course of the disease**
This is dictated by:
1. Degree of resistance of the host
2. Virulence of the organism
3. Infecting dose

**Effects of the primary complex**
1. Systemic features
   In most cases there are no signs of ill-health; a few patients have:
   (i) Malaise
   (ii) Fever
   (iii) Erythema nodosum
   (iv) Raised ESR
   (v) Lymphocytosis
2. Local effects resulting from lymph gland enlargement
   (i) Peribronchial glands - lymph node compression syndrome
      a. Lung collapse
      b. Obstructive emphysema
      c. Bronchiectasis
   (ii) Cervical glands - disfiguring swelling in the neck

**The fate of the primary complex**
With most primary infections the development of specific cellular immunity is followed by progressive healing of the lesion.
1. Gradual destruction of the bacilli (this may never be completed)
2. Progressive fibrosis and slow removal of caseous material by macrophage activity
3. Calcification of persistent caseous debris or of the heavily collagenised scar tissue. Where the level of innate, and later specific, immunity is poor the lesion may spread directly, or through lymphatics, or through the blood stream.

**Post-primary (adult or re-infection) tuberculosis**

*Pathogenesis*

1. Activation of endogenous bacilli from a dormant primary lesion. The bacilli multiply when host general or local immunity deteriorates as a result of:
   (i) Old age
   (ii) Malnutrition
   (iii) Immuno-suppressive treatment
   (iv) Diabetes mellitus
   (v) Coincidental fibrosing lung diseases such as silicosis

2. Re-infection by exogenous bacilli in a patient rendered hypersensitive by previous infection but whose overall level of immunity is inadequate

Post-primary, like primary, infection is usually seen in the lung but the lesion is typically apical (Assmann focus). There is early caseation and liquefaction because of previous sensitisation and the lesion may produce a large cavity, erode into a bronchus, and discharge infected necrotic material. Tuberculous bronchopneumonia may ensue, but progressive fibrocaseous destruction is more usual.

**Spread of tuberculosis**

1. Direct
   (i) Lung
      a. Acute tuberculous bronchopneumonia
      b. Fibrocaseous pulmonary tuberculosis
      c. Tuberculous empyema
   (ii) Elsewhere
       Coalescence of caseous foci and liquefaction gives rise to a so-called 'cold-abscess'

2. Lymphatic spread to regional lymph glands is invariable in primary infection, uncommon in post-primary

3. Blood spread
   Organisms gain access to the circulation by:
   (i) Lymphatic connections, e.g. thoracic duct
   (ii) Rupture of a primary or post-primary focus into a vein
   (iii) Erosion of a blood vessel in an involved lymph gland

Two main patterns of blood spread are seen:
   (i) Widespread dissemination - *miliary tuberculosis*, to liver, spleen, kidneys, lungs, bone-marrow, adrenals, prostate, seminal vesicles, endometrium, fallopian tubes and meninges
   (ii) Single-organ involvement - implies that organisms carried to other sites are destroyed and infection progresses in an isolated organ. This may take many years to become clinically apparent by which time the pulmonary (or other) source of infection may have undergone healing by fibrosis and be difficult to identify. Common sites are meninges, kidneys, bone, fallopian tubes and epididymes

4. Infected sputum
   (i) Tuberculous ulcers in the larynx
(ii) Ulcers in the small intestine (tuberculous enteritis) resulting from the swallowing of infected sputum

**Organ involvement in tuberculosis**

1. **Lungs**
   - (i) Primary (Ghon) focus
   - (ii) Post-primary (Assmann) focus
   - (iii) Tuberculous bronchopneumonia
   - (iv) Fibrocaseous pulmonary tuberculosis
   - (v) Cavitation (may become super-infected by moulds such as Aspergillus species)
   - (vi) Miliary lesions

2. **Alimentary tract**
   - (i) Primary focus (rare)
   - (ii) Post-primary focus tuberculous enteritis

3. **Central nervous system**
   - (i) Small cortical lesion (Rich's focus)
   - (ii) Leptomeningitis arising from
     - a. Direct haematogenous involvement of the choroid plexus
     - b. Rupture of a Rich's focus
   
   Healed meningitis may give rise to hydrocephalus as a result of blockage of foramina by organised exudate.
   
   Pachymeningitis around the cord may arise by extension of vertebral infection.
   - (iii) Ischaemic lesions resulting from endarteritis obliterans
   - (iv) Tuberculous abscess (tuberculoma) which may develop in areas of cortical ischaemic necrosis

4. **Urinary system**
   - (i) Cortical lesions (appear first)
   - (ii) Tubular spread to involve pyramids and calyces - tuberculous pyelonephritis
   - (iii) Strictures at uretero-pelvic and uretero-vesical junctions
   - (iv) Tuberculous 'pyonephrosis'
   - (v) Spread to ureters, bladder, prostate and epididymis

5. **Genital tract**
   - (i) Tuberculous salpingitis
   - (ii) Tuberculous endometritis
   - (iii) Tuberculous prostatitis
   - (iv) Tuberculous epididymitis

6. **Skeletal system**
   - (i) Early lesions near the epiphyseal line
   - (ii) Destruction of cartilage and disc erosion
   - (iii) Synovitis and arthritis
   - (iv) Destruction of bone leads to pathological fractures and vertebral collapse
     - (Pott's disease of the spine)
   - (v) Spread along fascial planes (psoas abscess)

7. **Skin**
   - (i) Primary lesion (very rare)
   - (ii) Lupus vulgaris Most common on the face and neck, and may result in extensive tissue destruction and scarring. It is occasionally complicated by the development of squamous carcinoma
(iii) Scrofuloderma. Involvement of the skin by direct extension from an underlying lymph gland
(iv) Papulo-necrotic tuberculide - probably represents an extreme hypersensitivity reaction to infection elsewhere in the body
(v) Erythema nodosum
(vi) Erythema induratum I hypersensitivity reaction

8. Serous cavities
Tuberculosis of serous linings produces an exudative response characterized by an outpouring of protein-rich fluid containing large numbers of lymphocytes.
(i) Tuberculous pleurisy which may become an empyema
(ii) Tuberculous pericarditis may be followed by marked fibrosis and calcification producing constrictive pericarditis and cardiac failure
(iii) Tuberculous peritonitis may be a localized involvement associated with intestinal tuberculosis or salpingitis, or be generalized. This is a possible complication of laparotomy

9. Endocrine glands
(i) Tuberculosis of the adrenals (Addison's disease)
(ii) Tuberculous abscesses in the thyroid (rare)

10. Eyes
(i) Tubercles of the choroid in miliary spread
(ii) Phlyctenular conjunctivitis
(iii) Iridocyclitis

LEPROSY

A chronic inflammatory disease of low infectivity caused by Mycobacterium leprae.

Route of infection
1. By inhalation of droplet infection
2. Through intact skin by direct contact
When infection develops in the skin, the initial lesion is the indeterminate macule. Thereafter two major clinical forms may develop.

A. Lepromatous leprosy
This occurs in patients who have low cell-mediated immunity because of an increased proportion of suppressor T-cells. Widespread infection ensues:

1. Skin involvement
   (i) Papules
   (ii) Nodules covered by greasy skin
   (iii) Diffuse thickening, e.g. leonine facies
   (iv) Loss of hair
On histology the skin shows
   (i) Dermal infiltrates rich in histiocytes
   (ii) Clear area between epidermis and affected dermis
   (iii) M. leprae in large numbers within histiocytes. These can be demonstrated using the Ziehl-Neelsen method without acid differentiation
   (iv) Globi-enlarged, fat-laden histiocytes containing clumped degenerate bacilli

2. Nerve involvement
   (i) Oedema and ischaemic necrosis
   (ii) Progressive fibrosis
(iii) Peripheral neuritis which is symmetrical
(iv) Anaesthesia may lead to neuropathic arthropathy (Charcot's joints) and trophic ulcers

3. Mucous membranes
   (i) Nasal blockages and epistaxis
   (ii) Ulceration of the nasal septum
   (iii) Ulceration and stenosis of the larynx

4. Mouth - loss of upper incisors

5. Eyes
   (i) Punctate keratitis
   (ii) Iritis
   (iii) Corneal ulceration

6. Testes
   Testicular atrophy leading to sterility and gynaecomastia

7. Death may result from
   (i) Respiratory infection; pneumonia, tuberculosis
   (ii) Septicaemia from chronic osteomyelitis following infection of bone marrow
   (iii) Renal failure due to chronic glomerulonephritis or amyloidosis

B. Tuberculoid leprosy
This develops when there is a high cell-mediated immunity because of increased numbers of helper T-cells. The infection is limited to skin and nerves.
   1. Skin lesions
      Scattered hypopigmented, anaesthetic areas showing anhidrosis
   2. Nerve involvement
      (i) Destruction by granulomas
      (ii) Repair by fibrosis with consequent thickening
      (iii) Anaesthesia, muscle wasting

On histology these lesions show
   (i) A mass of lymphocytes and epithelioid cells
   (ii) Langhans-type giant cells
   (iii) Very few organisms
   (iv) Skin involvement extending through the dermis and epidermis in continuity
   (v) Caseous necrosis, sometimes within nerve lesions but not in the skin

Many of these features resemble those found in tuberculosis.

SARCOIDOSIS

This is a generalized disease of unknown aetiology characterized by widespread granuloma formation and protean clinical manifestations. It appears to be more common in communities which have recently eradicated tuberculosis and leprosy, but no definite link with these diseases has been established. Sarcoidosis may result from simultaneous viral and mycobacterial infection in which case viral infection is responsible for the observed T-cell depression and mycobacteria exert a stimulant effect on B-lymphocyte function, but this is speculation.
Immunological findings
The granulomas contain variable proportions of CD4+ helper cells and CD8+ cytotoxic-suppressor T-lymphocytes. Generalized immunological abnormalities include:
1. Depressed T-cell functions as shown by
   (i) Cutaneous anergy (as manifest by a negative Mantoux)
   (ii) Diminished response to non-specific mitogens
2. Exaggerated B-cell function as evidenced by increased circulating antibodies to a wide variety of antigens included EB virus, herpes simplex, rubella, measles, and parainfluenzae

The sarcoid granuloma
This consists of:
1. A well circumscribed collection of epithelioid macrophages
2. Giant-cells, mainly Langhans but also from foreign-body type
3. Inclusion bodies found in giant-cells (and occasionally in epithelioid cells)
   (i) Residual bodies about 1 Jim in diameter which are end-stage phagosomes
   (ii) Schaumann bodies - laminated, basophilic conchoidal bodies which when large become extracellular
   (iii) Asteroid bodies - small star-shaped retractive inclusions
4. An outer narrow zone of lymphocytes
5. A collar of fibrous tissue
6. Central necrosis is uncommon and mild in degree. The reticulin framework is preserved whereas in caseation it is usually destroyed
These appearances although suggestive of sarcoidosis are not specific and may be found in many other conditions.

Sarcoid-like granulomata may be found in all granulomatous diseases (see p. 100) together with:
1. Foreign-body reactions
   (i) Corn-starch grains (used in surgical glove powder)
   (ii) Talc
   (iii) Silica
   (iv) Beryllium (formerly used in fluorescent tubes)
   (v) Zirconium (used in deodorants)
2. Hypersensitivity reactions
   (i) Allergic alveolitis
   (ii) Arteritis
3. Hodgkin's disease in tissues not directly involved by neoplasm (e.g. liver/spleen)
4. 'Local' sarcoideal reactions in lymph glands
   (i) Draining a wide variety of tumours
   (ii) In association with chronic cholecystitis (Cholegranulomatous lymphadenitis)
5. Drug reactions, e.g. liver granulomata with phenylbutazone

Organ involvement in sarcoidosis
1. Lungs
   (i) Widespread 'miliary' lesions
   (ii) Linear fibrosis radiating from the hilum
   (iii) Diffuse fibrosis which may progress to 'honeycomb lung'
(iv) Collapse secondary to bronchial obstruction (rare)

2. **Lymph glands.** Hilar gland involvement is common

3. **Skin**
   - (i) Erythema nodosum is common
   - (ii) Boeck's sarcoid - purple/red papules, nodules or plaques found principally on the face, as well as on the extensor surfaces of the arms and upper back
   - (iii) Darier-Roussy sarcoid - where the lesions are subcutaneous rather than intracutaneous and are found on the trunk
   - (iv) Lupus pernio - characterized by indurated, erythematous bluish-red macules and plaques found on the face, ears and fingers

4. **Eyes**
   - (i) Uveitis - inflammation of the iris and ciliary body
   - (ii) Conjunctivitis
   - (iii) Retinal lesions
   - (iv) Keratoconjunctivitis sicca

5. **Salivary glands** resulting in enlargement and loss of secretion. Sarcoidosis is one of the many causes of Mikulicz's syndrome (bilateral enlargement and loss of secretion in salivary and lacrimal glands). Involvement is sometimes accompanied by uveitis and pyrexia - uveoparotid fever (Heerfordt's syndrome)

6. Liver involvement, whilst common, is rarely of clinical significance

7. **Spleen.** Sarcoidosis is a rare cause of mild to moderate splenomegaly

8. **Bone.** Small cystic lesions in the phalanges of the feet and hands

9. **Heart.** Myocardial granulomata and fibre atrophy may lead to heart failure or conduction defects

10. **Pituitary and hypothalamus.** Sarcoidosis is a rare cause of diabetes insipidus

11. **Central nervous system** (uncommon)
   - (i) Meningoencephalitis
   - (ii) Peripheral neuropathy
   - (iii) Transverse myelitis
   - (iv) Multifocal leucoencephalopathy

12. **Kidneys** mainly involved by nephrocalcinosis consequent upon hypercalcaemia and hypercalciuria which result from vitamin D sensitivity with increased uptake of calcium from the gut

13. **Skeletal muscle** - sarcoid myopathy.

**Histological diagnosis**

1. Kveim test. This consists of an intradermal injection of saline suspension of a sarcoid lymph gland or spleen. A positive reaction, which takes about 6 weeks to develop, appears as a firm nodule with the features of a sarcoid granuloma on histology

2. Biopsy of lymph gland, liver, skeletal muscle, labial salivary glands, skin or even lung may reveal the characteristic granulomas.

**SYPHILIS**

Syphilis is an infective disease which can spread to the fetus to give rise to congenital syphilis or acquired through sexual contact. The agent responsible is the spirochaete *Treponema pallidum.*
Natural history of acquired syphilis
1. Inoculation followed by an incubation period of 2-4 weeks but possibly 10-90 days
2. The primary lesion which is usually present for 6-8 weeks
3. Involvement of regional lymph nodes and spread into the blood stream
4. The secondary stage may take up to 9 months to disappear
5. The latent stage where there are no signs and symptoms but the infection is still present and active. The disease may then undergo spontaneous cure
6. The tertiary stage becomes clinically apparent 3-10 years after infection
7. Later involvement of the cardiovascular and nervous systems. This may take up to 20-40 years to present clinically. The late nervous system involvement is sometimes referred to as quaternary syphilis

Primary syphilis
The primary lesion is the chancre, which when fully developed is a hard, painless, indurated ulcer with regular, well-demarcated margins. Histologically there is:
1. Ulceration
2. Underlying granulation tissue
3. Endothelial proliferation in small blood vessels
4. Heavy plasma-cell and lymphocytic infiltration
5. Healing by fibrosis producing a small scar. Spirochaetes may be demonstrable by a silver impregnation method such as the Levaditi stain

Secondary syphilis
The lesions are very variable:
1. Skin rashes (syphilides)
2. Mucous membranes
3. Lymphadenitis
4. Hepatitis
5. Iritis
6. Arthritis, bursitis and periosteitis
7. Meningitis (rare)

Tertiary syphilis
The characteristic lesion is the gumma. This comprises:
1. A central zone of structured necrosis in which the original architecture can usually be distinguished
2. A surrounding zone of epithelioid cells and occasional giant cells
3. Granulation tissue heavily infiltrated by plasma cells and lymphocytes
4. Fibrosis
5. Endarteritis obliterans
Lesions are found in:
1. Skin and subcutaneous tissue
2. Mucous membranes
3. Bones, e.g. 'worm-eaten' skull
4. Liver
5. Testis
6. Rare sites - muscles and joints, gastrointestinal tract, lung, spleen, urinary tract

Cardiovascular syphilis (tertiary)
1. Aorta - syphilitic mesoaortitis
This is the commonest manifestation of tertiary syphilis and is an important cause of death.

**Pathogenesis**

(i) Infection around adventitial vessels spreads into the wall along vasa vasorum
(ii) Endarteritis obliterans develops in these small nutrient vessels
(iii) Ischaemia leads to necrosis of the media with destruction of elastic lamina

These changes are most marked in the proximal part of the thoracic aorta.

**Effects**

(i) Aneurysm formation (saccular or dissecting)
(ii) Aortic incompetence
(iii) Coronary ostial stenosis leading to myocardial ischaemia

2. **Small arteries**

(i) Intimal proliferation
(ii) Adventitial fibrosis
produce endarteritis obliterans which may lead to ischaemic damage

3. **Heart**

Gumma (very rare).

---

**Neurosyphilis (Quaternary)**

Treponema invade the CNS in up to 20% of cases during the early stages of syphilitic infection. In the absence of treatment approximately half of these patients will develop signs of neurosyphilis after a lapse of many years.

1. **Connective tissues and blood vessels (meningo-vascular)**

   (i) Leptomeningitis which may be complicated by cranial nerve palsies and internal hydrocephalus
   (ii) Pachymeningitis
   (iii) Gummata in the meninges
   (iv) Endarteritis obliterans leading to cerebral infarcts

2. **Parenchymal involvement**

   (i) General paralysis of the insane (GPI)

       A chronic syphilitic encephalitis with widespread lesions and diverse motor, sensory, and psychiatric symptoms. The main **pathological features are**:

       a. Degeneration of nerve cells and fibres with cerebral atrophy
       b. Proliferation and hyperplasia of microglia forming I rod-cells'
       c. Reactive proliferation of astrocytes - gliosis
       d. Thickening of leptomeninges
       e. Perivascular infiltration by lymphocytes and plasma cells

   (ii) Tabes dorsalis

       This is the equivalent lesion in the spinal cord and involves lower sensory neurones.

       **Pathological features**:

       a. Wasting of the posterior roots
       b. Thickening of the pia-arachnoid
       c. Gross demyelination of the dorsal columns
**Effects:**

a. Loss of coordination with ataxia
b. Deep anaesthesia resulting in Charcot's joints and penetrating ulcers

**Congenital syphilis**

The fetus may be overwhelmed by infection and die. In those that survive, the lesions found during the first 2 years are similar to those of the secondary stage. Many of the lesions appearing in the third year and after are of the gummatous type. The scars of deformities resulting from early or late lesions which have healed are termed stigmata.

**10. The effects of infection and injury on the body**

Inflammatory conditions and major tissue injury are frequently associated with a wide range of systemic responses which embrace vascular, metabolic, endocrine, neurological and immunological functions. Those occurring soon after the onset of infection or injury are called the acute phase response. The acute phase response has the outstanding characteristic of being a generalized host reaction irrespective of the localized or systemic nature of the initiating disease, and several components of the response are remarkably constant despite the considerable variety of pathological processes that induce it. This uniformity of reaction points to the involvement of relatively few mediators in the overall 'orchestration' of the acute phase response. The major mediator coordinating the response is interleukin-1, aided and abetted by tumour necrosis factor (TNFa). Thus the mononuclear phagocyte system, which serves as the major source of these cytokines, plays a pivotal role.

Mononuclear cells are stimulated to produce IL-1 and TNFa by:

1. Bacterial endotoxin - lipopolysaccharide (LPS), especially when complexed with LPS-binding protein.
2. Antigen-antibody complexes.
3. Intact micro-organisms following phagocytosis.
4. Other cytokines produced by activated lymphocytes and macrophages.

Interleukin-1 and TNFa have a multiplicity of biological activities at the following sites:

1. Hypothalamus - fever
2. Bone marrow - neutrophilia
3. Neutrophils - activation
4. B-lymphocytes - antibody production
5. T-lymphocytes - IL-2 production
6. Liver - acute phase proteins
7. Fibroblasts - proliferation and collagen synthesis
8. Muscle - protein catabolism with amino-acid release
COMPONENTS OF THE ACUTE PHASE RESPONSE

A. Fever
Body temperature is controlled partly by reflexes initiated by the thermosensory nerve endings in the skin, but principally by a central control mechanism in the hypothalamus. The central mechanism can be likened to a thermostat, and this thermosensory centre (shown in animals to be in the anterior hypothalamus) responds to variations in the temperature of blood flowing through it. Signals from the thermosensory centre influence the activity of other hypothalamic centers which regulate the physiological processes responsible for heat production and heat loss, thus controlling the core temperature. In fever the thermostat is set high and a rise in temperature is achieved by increasing heat production and inhibiting heat loss by:

1. Cutaneous vasoconstriction:
   (i) Coldness and pallor of the skin at the onset of fever
   (ii) Contraction of the erector pili muscles ('gooseflesh') maintains an insulating layer of air next to the skin
2. Higher metabolic activity particularly in skeletal muscles and in the liver
3. Shivering - associated with increased catabolic activity and heat production in skeletal muscles.

Fever is accompanied by general malaise and anorexia. If the temperature rises to 41.6 °C (107 °F) there is a danger of direct thermal injury to various tissues, and particularly to cerebral neurones. However, a potentially beneficial effect of hyperthermia is augmentation of the immune response by T-helper cells. The high setting of the thermosensory centre in fever is brought about by interleukin-1. The effect of interleukin-1 on thermoregulation is mediated by Prostaglandins, in particular by PGE2. This mechanism underlies the value of drugs like aspirin, an inhibitor of prostaglandin synthesis, in reducing fever.

B. Neutrophil leucocytosis
Normally the neutrophil count is between 2.5-7.5 x10^9/litre. In infections this rises to 10-20 x 10^9/litre - particularly with pyogenic bacteria.
Lesser degrees of neutrophil leucocytosis occur in:
   (i) Pregnancy
   (ii) Strenuous exercise
   (iii) Severe mental stress
   (iv) Injection of glucocorticoids or adrenaline
   (v) Following necrosis of tissue, e.g. myocardial infarction

Leucocytosis may develop within a few hours of the onset of a bacterial infection and is of diagnostic value. This early rise is due partly to release of many polymorphs which normally lie marginated in the venules of the lungs and elsewhere, and partly due to release of immature polymorphs lying in the sinusoids of the red marrow. The leucocytosis is maintained, however, by an increased rate of formation in the marrow. As polymorphs have a life span of about 12 hours, death and loss of polymorphs in exudation, for example in a suppurating infection requires a large output requiring hyperplasia of the myeloid or granulocyte series in the bone marrow.
Interleukin-1 has a central role in neutrophil leucocytosis. It promotes:

(i) Release of neutrophils from their marginated state
(ii) Increases granulopoiesis

Actions on neutrophils themselves include:

(i) Release of granules
   Lactoferrin - Iron-chelation
   Lysozyme - Antibacterial properties
(ii) Increases oxidative activity
(iii) Increased hexose mono-phosphate shunt activity

C. Acute phase and stress proteins

In febrile conditions or following injections of endotoxin or interleukin-1 there is a dramatic increase in the synthesis of intracellular stress (heat shock) proteins and some proteins by the liver. These latter proteins enter the circulation and can be detected within a few hours of the onset of fever which is why they are labeled acute phase proteins.

1. Acute phase proteins These include:
   (i) C-reactive protein
   (ii) Fibrinogen
   (iii) Haptoglobin
   (iv) Ceruloplasmin
   (v) Amyloid A and P proteins

Interleukin-1 promotes protein catabolism in skeletal muscle and a flux of amino acids into the liver where protein synthesis is substantially increased. There is evidence of independent regulation of each of the acute-phase proteins. Some of these proteins, for example haptoglobin (an $a_2$ globulin capable of binding free haemoglobin) and fibrinogen are normally present in substantial levels in plasma but increase 2 or 3 fold after interleukin-1 injection. Others which normally occur at low levels, e.g. C-reactive protein, increase several hundred fold. Likewise some appear rapidly, but others require several days to reach maximum levels. C-reactive protein is capable of binding in a non-immunological way to 'foreign' antigens and activating the classical complement pathway. It thus acts as an opsonin and prepares material for phagocytosis.

2. Stress proteins

Stress (or heat shock, HSP) proteins are present in all living systems and are among the most highly conserved in nature. Their intracellular production is induced by rises in temperature and synthesis commences rapidly (within 5-15 minutes) after the onset of 'heat shock'. Other stimuli which induce the synthesis of stress proteins include:

   (i) Cytotoxic agents
   (ii) Free radicals, e.g. in reperfusion injury
   (iii) Cellular poisons, like alcohol and heavy metals
   (iv) Certain viral infections

Stress proteins together with ubiquitin are involved in the transport and degradation of proteins denatured by cell injury so that, for example, proteins 'tagged' with ubiquitin can undergo proteolysis and be recycled into the cell's economy, while HSPs and other chaperones regulate the assembly and disassembly of proteins and provide a means of shuttling polypeptides between molecular structures.
D. Nutritional responses
Following major infection or injury the body goes into substantial negative nitrogen balance, part of which meets the increased caloric needs of fever. Accelerated muscle protein degradation leads to myalgia and reduced physical performance. Interleukin-1 acts directly on skeletal muscle to promote protein catabolism, an effect mediated by an accumulation in the muscle of PGE2 which ultimately activates proteolysis in the lysosomes. This brings about amino-acid release from muscle which helps to satisfy the increased energy requirements via gluconeogenesis, but also contributes to the synthesis of proteins in proliferating immunological cells and the synthesis of acute phase reactants released from the liver.

Changes in trace metals
The serum levels of iron and zinc are depressed in the acute phase of bacterial infection. There is evidence that the decrease in serum iron is probably important in protecting the host against various bacteria as a reduction in iron suppresses the growth rate of various micro-organisms. Iron appears to be sequestered by the binding substance lactoferrin, and lactoferrin/iron complexes are deposited in the tissues. Interleukin-1 has been shown to activate lactoferrin release from neutrophils. There is also an increase in serum copper levels in keeping with the increase in the coppertransport protein ceruloplasmin. Copper is involved in enzyme and transport mechanisms but its role in fever is unknown.

E. Vascular responses and shock
Selective arterial constriction increases peripheral resistance and tends to compensate for diminished cardiac output. The main vessels involved are those of the skin and splanchnic circulation, whilst blood flow to the heart, brain and skeletal muscle is maintained at normal levels. When vasoconstriction fails to maintain normal blood pressure the clinical picture of shock develops. Underperfusion of tissues leads to accumulation of acid metabolites and vessels may cease to respond to normal constrictor stimuli. Progressive and irreversible arteriolar dilatation occurs and blood is 'sequestered' in the greatly enlarged capillary reservoir. Intractable hypotension results and this constitutes a lethal condition sometimes termed 'irreversible shock'.

Main types and causes of shock
1. Hypovolaemic
   (i) Haemorrhage
   (ii) Loss of plasma, e.g. burns
   (iii) Loss of fluid and electrolytes, e.g. severe diarrhoea
2. Cardiogenic
   (i) Myocardial infarction
   (ii) Major pulmonary embolism
   (iii) Following cardiac surgery
   (iv) Myocarditis and other causes of acute cardiac failure
3. "Septic"
   (i) Endotoxic, mediated by bacterial lipopolysaccharide e.g. endotoxin
      A from Pseudomonas aeruginosa
   (ii) Exotoxic, e.g. exotoxin from Staphylococcus aureus (toxic shock syndrome)
4. "Vascular"
(i) Anaphylactic
(ii) Neurogenic, e.g. spinal injuries

Pathogenesis
1. Hypovolaemia - a fall in cardiac output resulting from reduced blood volume
2. Cardiogenic - a fall in output resulting from inadequate heart function (‘pump failure’)
3. Septic shock
   (i) Release of TNFa and IL-1 in high concentration
   (ii) Induction of nitric oxide synthetase in endothelial and vascular smooth muscle cells leads to a buildup of nitric oxide (NO) which is responsible for sustained vasodilation and hypotension
   (iii) Activation of complement with release of anaphylatoxins C3a/C5a
   (iv) Activation of neutrophils leads to endothelial damage resulting in capillary leakage
   (v) Activation of Factor XII initiates coagulation and bradykinin formation. The former may lead to disseminated intravascular coagulation
4. Vascular mechanisms
   (i) Pooling of blood in
      a. Large peripheral vessels due to loss of vasomotor tone
      b. Capillaries resulting from persistent venular constriction
   (ii) Increased vascular permeability
   (iii) Slowing of blood flow resulting from 'sludging' of red cells

Disseminated intravascular coagulation (DIC)
This is a condition in which the activation of coagulation factors leads to deposition of platelet-fibrin thrombi in small vessels throughout the body. The consumption of coagulation factors and activation of fibrinolysis frequently leads to life-threatening haemorrhage.

F Metabolic reactions
Features of the early metabolic reaction are:
1. Hyperglycaemia
2. Fall in body temperature
3. Decreased oxygen consumption
4. Alteration of intracellular oxidative mechanisms
5. Loss of albumin from plasma due to transcapillary escape

Irreversible shock
Features include:
1. Reduced oxygen consumption
2. Diminished heat production
3. Increasing hypoxia
4. Metabolic acidosis
5. Hypotension
6. Hypoglycaemia

G. Hormonal reactions
Increased production of:
1. Catecholamines which
(i) Increase cardiac output
(ii) Constrict arterioles
(iii) Increase gluconeogenesis
2. Corticosteroids which bring about
   (i) Retention of Na$^+$
   (ii) Excretion of K$^+$
   (iii) Catabolism of proteins
3. Aldosterone
   Potassium deficiency
4. ADH
   Water retention

PATHOLOGICAL LESIONS IN SHOCK

1. Kidneys
   (i) Acute tubular necrosis
   (ii) Glomerular microthrombosis
   (iii) Acute cortical necrosis (rare)
2. Lungs - 'shock lung' or adult respiratory distress syndrome Features
   (i) Congestion and intraseptal oedema
   (ii) Microthrombi
   (iii) Hyaline-membrane formation
   (iv) Atelectasis
   (v) Interstitial pneumonia
3. Liver
   (i) Centrilobular ischaemic necrosis
   (ii) Fatty change
4. Adrenals
   (i) Lipid depletion (compact-cell change) in cortex
   (ii) Focal necrosis of cortical cells
   (iii) Massive haemorrhage (Waterhouse-Friderichsen syndrome)
5. Heart
   (i) Subendocardial haemorrhage
   (ii) Contraction bands within myocytes
6. Gastrointestinal tract
   (i) Acute ulceration of the stomach and duodenum (Curling's ulcers)
   (ii) Haemorrhagic gastroenteropathy
     Focal or more extensive haemorrhage into the stomach or intestinal
     mucosa associated with local superficial ulceration, probably resulting from
     hypoxia
7. Brain
   Anoxic or hypoxic encephalopathy (see p. 338)
8. Pituitary
   Necrosis following hypovolaemia (most commonly due to postpartum
   haemorrhage) giving rise to:
   (i) Acute insufficiency - Sheehan's syndrome
   (ii) Chronic insufficiency - Simmond's disease
LATE REACTIONS TO INJURY AND INFLAMMATION

A. Metabolic reactions

*Catabolic phase*
1. Rise in oxygen consumption
2. Rise in body temperature
3. Catabolism of protein increased
4. Increased mobilisation of fatty acids
5. Increased gluconeogenesis from amino acids derived from muscle

*Anabolic phase*
1. Positive nitrogen balance restored
2. Electrolyte equilibrium regained

B. Haematological reactions
1. Increased formation of platelets
2. Increased fibrinogen production
3. Decreased plasminogen
4. Anaemia
5. Lymphopenia

C. Hormonal reactions
Increased production of
1. Insulin which stimulates glucose uptake, and glycogen, fat and protein synthesis
2. Growth hormone - possibly involved in the mobilisation of adipose tissue
3. Thyroxine

D. Immunological reactions
1. Reactive changes in lymphoid tissues, e.g. hyperplasia in lymph nodes, splenomegaly
2. Production of IgM antibodies directed at various components of the injured tissues

E. Amyloidosis
Although the synthesis of amyloid precursor proteins is part of the acute phase response to inflammation, when inflammation is prolonged the sustained increase in the serum concentrations of these proteins leads to the appearance of fibrillar material (amyloid) in many different tissues. However, amyloid is not a specific protein. It can be composed of one or more proteins or glycoproteins all having a characteristic b-pleated fibrillar appearance on electron microscopy. Thus, amyloid complicating long-standing inflammation is made up of amyloid A (AA) and P (AP) proteins derived from partial degradation by macrophages of SAA and SAP proteins. Another major form of amyloid is composed of AL protein which is derived from immunoglobulin light chains, mainly of lambda type. In addition, a heterogeneous collection of amyloid types (some of which have not been characterized) are found in certain hereditary or familial conditions and as localized deposits.

*Diseases associated with amyloid deposition*
1. AA/AP amyloid
   (i) Chronic infections (of long standing)
      a. Tuberculosis
      b. Bronchiectasis
c. Osteomyelitis
d. Pyelonephritis
e. Leprosy
f. Syphilis

(ii) Chronic inflammatory disorders
   a. Rheumatoid disease
   b. Crohn's disease
   c. Systemic lupus erythematosus
d. Pustular psoriasis

(iii) Malignant states
   a. Hodgkin's disease
   b. Carcinomas of bladder, kidney, stomach, bronchus, ovary

2. AL amyloid
   (i) Multiple myeloma
   (ii) Waldenström's macroglobulinaemia
   (iii) Solitary plasmacytoma (localized)

3. Hereditary/familial types
   (i) Amyloid polyneuropathy
   (ii) Amyloid cardiomyopathy
   (iii) Amyloidosis associated with Mediterranean fever
   (iv) Familial amyloid nephropathy, urticaria, and deafness
   (v) Familial cutaneous amyloid

4. Localized amyloid deposition
   (i) Senility
      a. Heart
      b. Brain - also in Alzheimer's disease
      c. Islets of Langerhans
      d. Seminal vesicles
   (ii) Endocrine tumours
      a. Medullary carcinoma of the thyroid (AMCT)
      b. Pituitary adenoma
      c. Islet-cell tumours of the pancreas
   (iii) Non-endocrine tumours
      a. Naso-pharyngeal carcinoma
      b. Basal cell carcinoma
   (iv) In the islets of Langerhans in diabetes mellitus
   (v) Tumour-like deposits in:
      a. Larynx, trachea, bronchi, and lung
      b. Genito-urinary tract
      c. Eye
      d. Tongue
      e. Heart
      f. Skin

Pathogenesis
It is believed that amyloids are produced by partial degradation of precursor proteins. Degradation of AA protein takes place either in endothelial cells or in fixed macrophages of the RES, particularly in sinusoid lining cells, and this may explain the tendency for amyloid to be deposited in relation to vascular basement membranes. The abnormal, or incomplete, degradation of the precursor proteins may be under the
influence of a further protein synthesised by the liver which has been termed amyloid enhancing factor (AEF). AL amyloid is thought to arise by partial degradation of immunoglobulin light chains produced in excess by abnormal populations of plasma cells.

Detection of amyloid
1. Of his sulphuric acid produce blue coloration similar to that obtained with starch (Latin-amylum)
2. Congo-red and Sirius-red stain amyloid orange/red and when viewed under polarised light gives apple-green birefringence
3. Thioflavine-T staining gives rise to yellow fluorescence in ultraviolet light
4. Amyloid has a characteristic ultrastructural appearance being composed of parallel arrays of fibres 7 to 10 nm diameter
5. Potassium permanganate staining reveals different structural forms

Organ involvement in amyloidosis
1. Kidney
   Amyloid is deposited in:
   (i) Glomeruli (mesangium and basement membrane)
   (ii) Tubular basement membranes
   (iii) Blood vessel walls
   Results in:
   (i) Nephrotic syndrome
   (ii) Renal vein thrombosis
   (iii) Haematuria
   (iv) Nephrogenic diabetes insipidus
2. Spleen Deposited in:
   (i) Malpighian bodies (sago spleen)
   (ii) Diffusely in the walls of sinusoids
   Results in:
   No significant disturbance of function
3. Liver
   Deposited in:
   (i) The space of Disse between the sinusoid lining cells and the hepatocytes
   (ii) Blood vessel walls
   Results in:
   (i) Pressure atrophy of hepatocytes. In extreme cases this may lead to liver failure
   (ii) Portal hypertension if involvement of the central veins leads to outflow obstruction
4. Heart
   Deposited in:
   (i) Subendocardial zone
   (ii) Interstitial connective tissue
   Results in:
   (i) Cardiomegaly and cardiac failure
   (ii) Disturbances of rhythm
5. Adrenal glands
   Deposited in the zona glomerulosa and then advances throughout the cortex
Results in Addison's disease (rarely)

6. Gastrointestinal tract
   Deposited in:
   (i) The vicinity of epithelial basement membranes
   (ii) Walls of small blood vessels
   (iii) As plaques in the submucosa

   Results in:
   (i) Macroglossia
   (ii) Dysphagia (oesophageal rigidity)
   (iii) Malabsorption syndrome
   (iv) Diarrhoea
   (v) Protein-losing enteropathy
   (vi) Pseudo-obstruction
   (vii) Ulceration of plaques

7. Skin
   Forms:
   (i) Lichen amyloidosis
   (ii) Localized nodular amyloidosis

F Calcification
Calcification other than that normally occurring in the teeth and skeletal system (heterotopic calcification) is seen in the following circumstances:

1. Associated with advancing age Deposits are found in:
   (i) Pineal gland
   (ii) Tracheal and laryngeal cartilages
   (iii) Costal cartilages
   (iv) Dura mater

2. In dead or degenerate tissue (dystrophic calcification) Examples
   (i) In old tuberculous lesions
   (ii) In scars
   (iii) In dead parasites
   (iv) In degenerate tumours, especially uterine leiomyomata (fibroids)
   (v) In atheromatous plaques

3. In association with increased levels of calcium (or occasionally with increased phosphate) in the blood and tissues, usually derived from the skeleton but also involving increased absorption from the intestine and decreased loss through the kidneys. Such calcification occurs in previously normal tissues and is referred to as metastatic.
   It is found in:
   (i) Hyperparathyroidism
      
      Primary, due to:
      a. Adenoma
      b. Hyperplasia
      c. Carcinoma (very rarely)
      
      Secondary, due to:
      a. Chronic renal failure
      b. Renal tubular acidosis
      c. Malabsorption states
      d. Pregnancy and lactation
   (ii) Carcinomatosis with or without skeletal involvement, especially with
bronchial and breast cancer. 
(iii) Myelomatosis 
(iv) Vitamin D sensitivity, as in sarcoidosis and infantile hypercalcaemia 
(v) Excessive administration of vitamin D 
(vi) Paget's disease of bone (when immobilised) 
(vii) Hypophosphatasia 
(viii) Milk-alkali syndrome 
(ix) Hypoparathyroidism (deposits in the basal ganglia)

Sites of metastatic calcification
(i) Kidneys, producing nephrocalcinosis which may lead to renal failure 
(ii) Stomach 
(iii) Lungs, on the elastic fibres of the alveolar septa 
(iv) Blood vessels 
(v) Cornea

4. In calculi (stones) 
Many calculi include calcium salts among their constituents. 
Calculi are found in: 
(i) Urinary tract  
   a. calcium phosphate 
   b. calcium oxalate 
   c. calcium carbonate 
(ii) Biliary system 
   a. calcium bilirubinate 
(iii) Salivary glands 
(iv) Pancreas 
(v) Prostate

5. In neoplasia 
Microscopic laminated calcified bodies - calciospherites are found in association with: 
   a. Adenocarcinoma of the ovary 
   b. Papillary carcinoma of the thyroid 
   c. Meningioma (psammoma bodies) 
   d. Benign and malignant breast lesions 
   e. Oligodendroglioma

11. Fluids and ions

COMPOSITION

Osmolality (solute concentration per kg water) is the same in all compartments.

1. Extracellular fluid (ECF) is similar in composition to plasma but has a low protein content. The principal cation is sodium, and the major anions are chloride and bicarbonate.
2. **Intracellular fluid** (ICF) has a high protein content. The principal cations are potassium and magnesium, and the main anions are phosphate and proteins. The difference between the sum of the concentrations (in mEq per litre) of the major plasma cations and anions is known as the 'anion gap'.

\[
\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)
\]

The anion gap is increased when there are raised levels of acidic ions which are not included in the calculation, e.g. lactate, acetoacetate, phosphate, hydroxybutyrate, etc.

**CONTROL**

Plasma volume can only be maintained if the hydrostatic pressure in the vascular compartments is balanced by equal and opposite effects. The relative distribution between extra- and intracellular compartments is determined by the osmolar contents of each compartment as osmolality is equal in the two compartments. Control of the extracellular compartment is primarily by:

1. **Volume control**
   - This is primarily by regulation of the renal re-absorption of Na\(^+\) Cl\(^-\), and water
2. **Osmoiality control**
   - This is regulated by water intake and excretion modified by
     (i) Thirst
     (ii) Anti-diuretic hormone secreted by the posterior pituitary in response to stimulation by
       a. Osmoreceptors in the hypothalamus
       b. Baroreceptors sensitive to blood volume changes
3. **pH control**
   - This is regulated by
     (i) Buffers; bicarbonate ions, phosphate ions and protein
     (ii) Respiratory control of bicarbonate
     (iii) Renal excretion of acidic groups

**DISTURBANCE OF WATER BALANCE**

A. 'Pure'water depletion (i.e. in excess of sodium deficit)

*Causes:*
1. Decreased intake
2. Increased loss
   (i) Lack of ADH (diabetes insipidus)
   (ii) Unresponsiveness of the renal tubules to ADH
      a. Nephrogenic diabetes insipidus
      b. Hypercalcaemia
      c. Hypokalaemia
   (iii) Failure of tubular water re-absorption (despite cellular response to ADH)

*Effects:*
1. Increased osmolality of extracellular fluid
2. Transfer of water from intracellular compartment to equilibrate osmoiality
3. Cellular dehydration which may lead to hypotension and coma
B. 'Pure' water excess

*Causes:*
1. Excessive intake
   (i) Large infusions of glucose solution in post-operative patients
   (ii) Administration of water to patients who are sodium depleted
2. Diminished excretion
   (i) Poor renal function
   (ii) Diminished fluid delivery to the distal tubule usually resulting from increased reabsorption of Na⁺ and water in the proximal tubule, e.g. in cardiac failure
   (iii) Continued secretion of ADH despite lowered plasma osmolality
      a. In response to volume depletion, e.g. following blood loss
      b. Secretion of ADH by oat-cell carcinoma of the bronchus

*Effects:*
1. Decreased osmolality of the extracellular fluid
2. Transfer of water into cells causing intracellular oedema which may lead to disturbances in CNS and renal function

**DISTURBANCES OF SODIUM BALANCE**

A. Sodium (and water) deficiency -'dehydration'

*Causes:*
1. Severe vomiting or diarrhoea
2. Excessive sweating ('heat exhaustion')
3. Diuretic treatment

*Effects:*
1. Transfer of water into cells
2. Diminished extracellular volume - haemoconcentration
3. Low renal blood flow causes rise in plasma urea
4. Low urine output
5. Clinically:
   (i) Dehydration
   (ii) Muscular irritability - cramps
   (iii) Hypotension with shock in severe cases

B. Sodium (and water) excess

*Causes:*
1. Excessive salt consumption, especially in infants
2. Excessive administration of saline solutions to patients in acute renal failure or post-operative patients

*Effects:*
Expansion of the extracellular compartment may lead to generalized oedema
DISTURBANCE OF POTASSIUM BALANCE

A. Potassium depletion (hypokalaemia)

Causes:
1. Low intake - this is an unusual cause but can be a contributory factor in the elderly
2. Increased loss in the urine
   (i) Diuretic treatment
   (ii) Primary hyperaldosteronism
   (iii) Cushing's syndrome
   (iv) Secretion of ACTH by oat-cell carcinoma
   (v) Renal tubular disorders with failure of urinary acidification
3. Increased loss from the gut
   (i) Diarrhoea (including purgative abuse)
   (ii) Excessive mucus secretion by a colo-rectal villous adenoma
   (iii) Watery diarrhoea, achlorhydria, hypokalaemic syndrome (Werner-Morrison syndrome) due to VIP secreting tumour

Effects.
1. Cardiac
   (i) Increased sensitivity to digoxin
   (ii) Ectopic beats, paroxysmal atrial tachycardia
   (iii) Dilatation
2. Muscle weakness involving
   (i) Skeletal muscle
   (ii) Smooth muscle of the gut
   (iii) Vascular smooth muscle leading to hypotension
3. Renal
   (i) Polyuria (diminished response to ADH)
   (ii) Diminished reabsorption of Cl⁻ and increased reabsorption of bicarbonate, leads to high HCO₃⁻ and low Cl⁻ in the plasma (hypokalaemic alkalosis)
   (iii) Vacuolation of tubule-lining cells (vacuolar nephropathy)
   (iv) Pyelonephritis

B. Potassium excess (hyperkalaemia)

Causes:
An increased load in the presence of diminished renal function
(i) Acute renal failure with anuria
(ii) Chronic renal failure
(iii) Excessive potassium administration in the elderly, or in saline-depleted patients, with poor renal function

Effects:
1. Cardiac arrhythmias
2. Muscular weakness
3. Paraesthesiae
4. Confusion
DISTURBANCES OF ACID-BASE BALANCE

A. Respiratory acidosis
Inadequate ventilation leads to retention of CO₂ with formation of carbonic acid. Although the level of HCO₃⁻ also rises, it does so to a much lesser degree, so that according to the equation:

\[ \text{pH} = \text{pK} + \log \frac{\text{HCO}_3^-}{a[pCO_2]} \]

(where pK = 'dissociation constant' and a = 'solubility coefficient') the rise in the partial pressure of CO₂ leads to a fall in pH.

Respiratory acidosis leads to:
1. Increased renal excretion of H⁺ and ammonia
2. Lowering of plasma Cl⁻ level

B. Respiratory alkalosis
Hyperventilation results in excessive 'blowing off' of CO₂. The fall in pCO₂ is associated with a rise in blood pH. The kidneys attempt to compensate by increasing excretion of bicarbonate ions and reduced secretion of H⁺ ions.

C. Metabolic acidosis
The fundamental change is a primary reduction in [HCO₃⁻] followed by a fall in pH. Metabolic acidosis is usually due to increased production or ingestion of acid substances which result in a high anion gap.

However, in other circumstances there may be loss of bicarbonate ions and a relative increase in chloride ions so that there is 'hyperchloraemic acidosis' with a normal anion gap.

1. Acidosis with a high anion gap
   Causes:
   (i) Lactic acidosis
       a. Increased production of lactic acid in hypoxic tissues
       b. Failure to metabolise lactic acid in liver and renal diseases, and in patients receiving phenformin
   (ii) Chronic renal failure as there is diminished excretion of phosphate and sulphate ions
   (iii) Ketosis in:
       a. Diabetes mellitus
       b. Starvation

2. Hyperchloraemic acidosis
   Causes:
   (i) Excessive loss of bicarbonate ions from gastrointestinal secretions
       a. Diarrhoea
       b. Pancreatic fistula
   (ii) Renal tubular acidosis
       a. Failure of acidification in the distal tubule
b. Failure of HCO\textsubscript{3} reabsorption in the proximal tubule
(iii) Uretero-colic anastomosis (after removal of the bladder) leads to increased absorption of Cl\textsuperscript{-} from the colon in exchange for HCO\textsubscript{3}.

Effects of acidosis
1. Deep, rapid respirations ('air-hunger')
2. Poor cardiac function
3. Neurological disturbances
4. Shock, coma, and death

D. Metabolic alkalosis

 Causes:
1. Excessive loss of gastric acid
   (i) Persistent vomiting
   (ii) Continuous suction
2. Excessive intake of alkali - e.g. sodium bicarbonate in large quantities for 'indigestion'
3. Severe hypokalaemia

Effects:
1. Respiratory depression
2. Neurological disturbances
3. Tetany

12. Oedema and congestion

OEDEMA

Oedema is an excessive accumulation of fluid in the interstitial tissues. Accumulations in the body cavities are termed ascites (peritoneum), hydrothorax or pleural effusion, and pericardial effusion. The fluid may be either an exudate or a transudate.

Exudate. High specific gravity (>1.020) fluid containing all the plasma proteins including fibrinogen and numerous inflammatory cells, and resulting from increased vascular permeability.

Transudate. Low specific gravity (< 1.012) fluid containing small amounts of albumin and few cells. It arises from an imbalance in those forces tending to move fluid out of the vessels and those tending to retain it within them.

Even when excessive quantities of fluid are passing out of vessels, increased lymphatic drainage may prevent the appearance of oedema. Conversely, lymphatic obstruction may itself produce oedema when the other factors are at normal levels. Oedema may be generalized or localized.
A. Generalized oedema

1. Increased hydrostatic pressure of the blood
   (i) Cardiac failure

2. Decreased osmotic pressure of the blood
   (i) Excessive loss of protein
      a. Proteinuria, e.g. nephrotic syndrome
      b. Protein-losing enteropathy
   (ii) Inadequate synthesis of protein
      a. Hepatic cirrhosis
   (iii) Inadequate intake of protein
      a. Malnutrition (Kwashiorkor)
      b. Prolonged starvation
      c. Malabsorption syndrome

3. Sodium retention with expansion of the extracellular fluid compartment
   (i) Renal vasoconstriction and/or diminished glomerular filtration rate
      a. Cardiac failure
      b. Nephrotic syndrome
      c. Acute glomerulonephritis
   (ii) Increased levels of aldosterone secondary to:
      a. Cardiac failure
      b. Nephrotic syndrome
      c. Hepatic cirrhosis (failure of inactivation)
   (iii) Excess ACTH or cortisone
      a. Therapeutic
      b. Cushing's syndrome

4. Generalized increase in vascular permeability
   (i) Hypoxia
   (ii) Bacterial toxins
   (iii) Chemicals

5. Diminished tissue tension
   (i) Loss of elasticity with age
   (ii) Change in the ground substance, e.g. rendered more soluble by corticosteroids in Cushing's syndrome

B. Localized oedema

1. Increased hydrostatic pressure of the blood due to:
   (i) Venous obstruction
      a. Venous thrombosis
      b. Strangulation of vessels
      c. External pressure on veins
         Gravid uterus
         Ligatures/tourniquets
         Tumour
      d. Hepatic cirrhosis (portal hypertension)
   (ii) Gravity, e.g. ankle oedema after prolonged standing

2. Increased vascular permeability
   (i) Chemical irritants giving rise to
      a. Urticarial reactions in skin
      b. Pulmonary oedema
(ii) Immunological reactions resulting in complement activation with release of anaphylatoxins. Angioneurotic oedema is included in this category and results from genetically determined absence or deficiency of Cl esterase inhibitor
(iii) Other causes of acute inflammation

3. Lymphatic abnormalities
   (i) Congenital malformation, e.g. Milroy's disease
   (ii) Obstruction secondary to:
        a. Carcinoma
        b. Irradiation
        c. Filariasis
        d. Recurrent bacterial lymphangitis

PULMONARY OEDEMA

Causes
1. Raised left atrial pressure
   (i) LVF
   (ii) Mitral stenosis
2. Raised pulmonary capillary pressure
   (i) Over infusion
   (ii) Acute renal failure
   (iii) Veno-occlusive disease
3. Increased capillary permeability
   (i) Infection
      Bacterial/viral pneumonias
   (ii) Drug reactions
      Iodine, nitrofurantoin, busulphan, hexamethonium, methotrexate
   (iii) Irritant fumes
      Smoke, ammonia, sulphur dioxide
   (iv) Uraemia
   (v) Radiation
4. Raised intracranial pressure
5. Trauma
   (i) Direct injury to the chest
   (ii) Blast injury
   (iii) Thoracic surgery
6. Hypoxia - acute high-altitude oedema
7. Lymphatic obstruction - mainly carcinomatous
8. Hypoproteinaemia - rarely in:
   (i) Nephrotic syndrome
   (ii) Hepatic failure
   (iii) Malabsorption

CONGESTION AND CARDIAC FAILURE

An increased content of blood in an organ or tissue may be an active hyperaemia in response to increased metabolic activity, for example in skeletal muscle, or passive congestion. Passive congestion may result from local venous obstruction and parallels the formation of a transudate, or more frequently it is a consequence of
Cardiac failure can predominantly involve the right ventricle giving rise to congestion of the abdominal organs together with ascites and peripheral oedema, or involve the left ventricle producing pulmonary congestion and under-perfusion of the systemic circulation. Frequently, both ventricles are involved and a state of congestive cardiac failure results.

**Right ventricular failure (RVF)**

*Causes*
1. Secondary to left ventricular failure
2. Pulmonary hypertension
3. Pulmonary embolism
4. Congenital heart disease
   (i) Atrial septal defect
   (ii) Pulmonary stenosis
   (iii) Tricuspid anomalies
5. Myocarditis
   (ii) Myocardial infarction (rare in RVF)

*Effects of RVF*

1. **Liver**
   (i) Hepatomegaly
   (ii) 'Nutmeg' appearance due to hepatic congestion
   a. Centrilobular congestion and atrophy of liver cells
   b. Peripheral fatty change resulting from hypoxia
   (iii) Centrilobular necrosis in severe, acute congestion
   (iv) Centrilobular fibrosis in prolonged (chronic venous) congestion which may link up and give a false impression of cirrhosis. A true 'cardiac' cirrhosis, with regenerative nodules, is rare

2. **Spleen**
   (i) Mild to moderate spienomegaly
   (ii) Fibrosis of sinusoidal walls
   (iii) Haemosiderin deposition

3. **Kidneys**
   (i) Congestion
   (ii) Fatty change and/or cloudy swelling due to hypoxia
   (iii) Redistribution of blood flow with a relative increase to the medulla leading to sodium retention

4. **Oedema of the subcutaneous tissues**-mainly in the dependent parts of the body

5. **Brain**
   (i) Congestion
   (ii) Hypoxia

6. **Ascites due to portal congestion**

**Left ventricular failure (LVF)**

*Causes*
1. Systemic hypertension
2. Myocardial ischaemia (with or without infarction)
3. Rheumatic heart disease
   (i) Mitral incompetence
   (ii) Aortic stenosis or incompetence
4. Calcific aortic stenosis
5. Coarctation of the aorta
6. Congenital heart disease
7. Cardiomyopathy
8. Myocarditis
9. High output states
   (i) Pregnancy
   (ii) Severe anaemia
   (iii) Hypoxia and hypercapnia
   (iv) Pyrexia
   (v) Thyrotoxicosis
   (vi) Hepatic failure
   (vii) AV aneurysm
   (viii) Paget's disease
   (ix) Beri-beri

Effects of LVF

1. Congestive effects in the lungs
   (i) Pulmonary oedema
   (ii) Chronic venous congestion
      a. Capillary congestion
      b. Mild interstitial fibrosis mainly involving interlobular septa
      c. Intra-alveolar haemorrhage
      d. Haemosiderin-laden macrophages (‘heart-failure cells’)
   (iii) Pulmonary infarcts (especially in mitral stenosis)
   (iv) Hydrothorax
2. Effects of hypoperfusion
   (i) Acute LVF may give rise to infarcts in organs where the blood supply is already compromised by atherosclerosis. They may be found in
      a. Kidneys
      b. Brain, particularly in 'watershed' areas
      c. Large intestine (ischaemic colitis/strictures)
   (ii) Kidney Decreased blood flow leads to:
      a. Hypoxia - hydropic vacuolation in tubular epithelium
      b. Diminished glomerular filtration rate resulting in salt and water retention
   (iii) Liver
      a. Centrilobular necrosis
      b. Fatty change
   (iv) Brain
      Individual cell necrosis in susceptible areas - the cornu ammonis and the Purkinje cell layer in the cerebellum
13. Hypertension

CONTROL OF BLOOD PRESSURE
The general level of the systemic arterial blood pressure is maintained by three mechanisms:
1. Catecholamine production
2. Renin-angiotensin system
3. Aldosterone production - sodium retention

Regulation of the blood pressure against this background of endocrine control is achieved by the baro-receptor mechanism and autonomic nervous system.

1. Catecholamine production
Catecholamines are produced principally by the chromatin cells of the adrenal medulla.
Adrenaline increases:
(i) Heart rate
(ii) Cardiac output
(iii) Systolic blood pressure
Noradrenaline increases:
(i) Peripheral resistance
(ii) Both systolic and diastolic pressure

2. Renin-angiotensin system
Renin is an enzyme produced by the juxta-glomerular apparatus (JGA) in the kidney. It acts on a substrate (angiotensinogen) found in the u.-2 globulin fraction of plasma to form a decapeptide angiotensin I which in turn is hydrolysed by a converting enzyme to the more powerful octapeptide angiotensin II.
Release of renin is stimulated by:
(i) Reduction in renal perfusion pressure and low glomerular filtration rate
(ii) Hyponatraemia
(iii) b-adrenergic stimulation
(iv) Hyperkalaemia

Angiotensin II has the following effects:
(i) Contracts smooth muscle
(ii) Stimulates aldosterone secretion
(iii) Increases blood pressure by stimulating medullary vasomotor and cardiac centres and facilitates the release of adrenaline and noradrenaline
(iv) Modifies the excretion of water and electrolytes by a direct action on the kidney
(v) Stimulates thirst by an action on the central nervous system
This system may be opposed by vasodilators generated in a kallikrein-kinin system.

3. Aldosterone production - sodium retention
Aldosterone is produced by the zona glomerulosa cells of the adrenal cortex, its main actions are:
(i) Increases potassium excretion
(ii) Increases sodium reabsorption, mainly in the distal tubules
(iii) Produces a metabolic alkalosis by interfering with urinary acidification
Excessive production of aldosterone leads to hypokalaemia and hypernatraemia, with an associated moderate rise in blood pressure. Excessive production can be either primary, or secondary to an increase in renin/angiotensin formation.

Causes
(i) Primary aldosteronism
   a. Adrenocortical adenoma with suppression of renin and angiotensin as a consequence of sodium retention (Conn's syndrome)
   b. Adrenocortical micronodular hyperplasia
   c. Aldosterone-secreting carcinoma of the adrenal or ovary (very rare)
(ii) Secondary aldosteronism
   a. Diuretic therapy with increased Na' loss
   b. Na' losing renal disease, e.g. chronic pyelonephritis
   c. Cardiac failure
   d. Cirrhosis of the liver
   e. Nephrotic syndrome
   f. Malignant hypertension
   g. 'Toxaemia' of pregnancy
   h. Combination-type contraceptive pill
   i. Renal artery stenosis
   j. Renin-secreting tumours of the kidney
   k. Bartter's syndrome (hypertrophy of the JGA)

The key role of sodium in hypertension may ultimately be explained by cell membrane alterations leading to changes in ionic fluxes and intracellular sodium concentrations. Such changes have been demonstrated in red blood cells and leucocytes of hypertensive patients and in the vascular smooth muscle cells of hypertensive experimental animals.

Investigation of the majority of patients with hypertension (BP>160/95 mmHg) reveals no underlying primary disease and the condition is termed essential hypertension. It has been proposed that essential hypertension is an exaggeration of the tendency for blood pressure to rise with age, and that it results from a repeated sequence in which autonomic nervous overactivity results in a small rise in blood pressure and produces changes in the kidney which maintain the raised level and becomes the basis for a further incremental rise.
In about 10% of patients an underlying cause is found and these cases are termed secondary. When the diastolic pressure is in excess of 120 mmHg and there is papilloedema, the hypertension may be designated 'malignant' in type as it carries a poor prognosis. The malignant phase of hypertension is associated with characteristic pathologic attributes.
Possible causes of secondary hypertension are:

A. Renal diseases
   1. Parenchymal
      (i) Chronic pyelonephritis
      (ii) Acute or chronic glomerulonephritis
      (iii) Polycystic disease
      (iv) Amyloidosis
      (v) Tumours
(vi) Hydronephrosis

2. Renal artery stenosis/obstruction
   (i) Atheroma
   (ii) Thrombosis/embolism
   (iii) Fibromuscular dysplasia
   (iv) Ligatures
   (v) Pressure from tumours
   (vi) Dissecting aneurysm

3. Microvascular disease
   (i) Diabetic nephropathy
   (ii) Polyarteritis nodosa
   (iii) Systemic lupus erythematosus
   (iv) Henoch-Schönlein syndrome

B. Endocrine
1. Excess corticosteroids
   (i) Cushing's syndrome
     a. Corticosteroid therapy
     b. ACTH therapy
   c. Cortical adenoma
   d. Cortical hyperplasia
   e. Adrenal carcinoma
   f. Basophil adenoma of the pituitary

(ii) Primary and secondary hyperaldosteronism (see p. 305)
(iii) Deoxycorticosterone excess due to a defect in 17-hydroxylation
(iv) Adrenogenital syndrome resulting from absence of 1 1-0-hydroxylase. This leads to excessive production of 1 1-deoxycorticosterone and 1 1-deoxycortisol which exert mineralocorticoid effects

2. Excess catecholamines
   (i) Phaeochromocytoma - a tumour of chromatin cells. 90% are found in the adrenal medulla: rare sites include sympathetic ganglia around the aorta and inferior vena cava and in the wall of the bladder. These tumours secrete large quantities of noradrenaline/adrenaline
   (ii) Treatment with indirect sympathomimetics (amphetamine, tyramine) in combination with monoamine oxidase inhibitors

3. Pituitary causes
   (i) Acidophil adenoma giving rise to acromegaly
   (ii) Basophil adenoma with excessive ACTH production

4. Renin-producing tumours of the kidney (very rare)

C. Cardiovascular causes
1. Coarctation of the aorta
2. High cardiac output states produce a rise in blood pressure but do not result in the systemic pathological lesions of hypertension (see p. 139)

D. Neurological causes (usually giving a transient or terminal elevation)
1. Raised intracranial pressure
   (i) Trauma
   (ii) Tumour
   (iii) Abscess
2. Lesions of hypothalamus and brain-stem

PATHOLOGICAL EFFECTS OF 'BENIGN' HYPERTENSION

A. Blood vessels

1. Arterioles
   (i) Hyalinisation: this is seen in ageing but is accentuated by hypertension. It consists of the accumulation of homogeneous eosinophilic material initially under the endothelium but later replacing the entire wall and occurs in many organs. It is seen most frequently in the kidney (afferent arterioles), spleen, pancreas, and adrenals. The hyaline deposit contains some fibrin, lipid and cholesterol and is presumed to originate from the plasma
   (ii) Medial muscular hypertrophy and later fibrosis
   (iii) Duplication of the elastic lamina
   (iv) Micro-aneurysm formation in the small perforating arteries (less than 1 mm diameter) of the brain, especially in the basal ganglia and subcortical areas. Such aneurysms are found with increasing age, but they are found earlier and in greater numbers in hypertensive patients. There is loss of the muscular media and the wall consists of dilated intima and adventitia. Some micro-aneurysms contain subintimal hyaline deposits which stain for fibrin and fat (lipohyalinosis) and these lesions are particularly prone to rupture

2. Small and medium-sized arteries
   (i) Medial muscular hypertrophy and later fibrosis
   (ii) Duplication of the elastic lamina
   (iii) Intimal proliferation

3. Large arteries
   Increase in severity of atherosclerosis and its results

Good Coping Skills May Raise 'Good' Cholesterol Levels

By Kathleen Doheny
WebMD Medical News

Reviewed by Louise Chang, MD

Aug. 20, 2007 -- The better you cope with stress, the better your "good" cholesterol level is likely to be, according to a new study.

"We know that stress and hostility affect cholesterol," says researcher Carolyn M. Aldwin, PhD, professor and chairwoman of the department of human development and family sciences at Oregon State University in Corvallis. There has been less research, however, on how coping skills can counteract the effects of stress, she says.

Good coping skills were associated with better levels of the so-called "good" cholesterol or high-density lipoprotein (HDL) in her study.

The study was released at the 115th annual convention of the American
Psychological Association in San Francisco.

**Stress and Cholesterol**

Aldwin and her colleagues evaluated data from 716 men who participated in the Normative Aging Study. The researchers looked at the interplay of hostility, stress, coping, and the participants' cholesterol levels.

The average age of the participants was 65; most were white. They were evenly split between white-collar and blue-collar occupations.

The researchers assessed the men’s hostility and asked them to describe their most stressful problem in the past week.

The men also completed a questionnaire that asked them to rate how often they used 26 different coping strategies when dealing with a stressful problem in the past month. Some were unhealthy strategies, such as socially isolating themselves when under stress or blaming themselves for the stress. Other strategies were healthy, such as making a plan of action to deal with the problem causing the stress.

The more hostile the men were, the more likely they were to look at problems as stressful. They were also more apt to use unhealthy coping skills to deal with that stress.

After fasting overnight, the men’s blood was tested for HDL cholesterol, low-density lipoprotein (LDL) or "bad" cholesterol, and triglycerides.

**Coping Skills Aid HDL Cholesterol**

The results were a surprise, Aldwin tells WebMD. "What we were really expecting is that coping would mitigate the effects of stress on LDL," she says. But the researchers found that the good coping skills only helped the protective effect of the "good" HDL cholesterol.

"People who coped well had higher levels of HDL than people who didn't cope well," she says.

She cannot cite an exact improvement in HDL or an average HDL level among those who coped well. "This is simply a correlational study," she says, finding an association between good coping skills and better HDL levels.

The amount of stress you deal with isn't as important, they also found, as how you deal with it. "Stress doesn't matter nearly as much as how you cope with it," she says.

The more hostile the men were, the worse the LDL and triglyceride levels, the researchers also found.

While the study included only men, Aldwin says she would think the same findings would apply to women.

It’s been known for years, Aldwin says, that stress affects LDL and makes it rise.

"Stress raises total cholesterol levels in general and it raises LDL levels," she says.
The results "are consistent" with research by Peter Vitaliano, PhD, professor of psychiatry and behavioral sciences, psychology, and health services at the University of Washington in Seattle. The new study, Vitaliano says, "adds to the body of research on how hostility relates to health, in particular heart disease."

Other research, he says, also found that "avoidance" coping, such as blaming oneself, is unhealthy and related to hostility and anger. "Both of those are related to blood pressure elevation and lower HDL," he says.

"Hostility is also associated with higher blood glucose levels in healthy people and in diabetics," he says, "and that raises the risk of heart disease."

Hostile people, he says, "often use emotion-focused coping," he says. "They use emotions like anger and avoidance instead of problem solving."

Ideally, total cholesterol levels should be below 200 mg/dL, according to the American Heart Association. HDL levels 60 mg/dL and above are heart-protective, while levels below 40 in men and below 50 in women are considered low and a risk factor for heart disease. LDL below 100 mg/dL is optimal, and below 130 is "near or above optimal." Triglycerides should be below 150 mg/dL.

B. Kidneys (hypertensive nephrosclerosis)
   1. Gross appearances
      (i) Normal or reduced size
      (ii) Granular surface
   2. Glomeruli
      (i) Thickening of basement membrane
      (ii) Loss of cellularity
      (iii) Hyalinisation
   3. Bowman's capsule
      (i) Deposition of collagen on inside of capsule
      (ii) Less frequently, dilatation of Bowman's space and collapse of the glomerulus
   4. Tubules
      Variable atrophy, with occasional casts.
      Most of these changes probably result from ischaemia

C. Heart
   1. Left ventricular hypertrophy
   2. Increased coronary atherosclerosis
   3. Focal myocardial fibrosis

D. Brain
   1. Massive intracerebral haemorrhage
   2. Perivascular ischaemic atrophy maximal in the globus pallidus
   3. Multiple small infarcts
   4. Multiple small haemorrhages
   5. Microaneurysms
PATHOLOGICAL EFFECTS OF MALIGNANT HYPERTENSION

A. Blood vessels

1. Arterioles
Fibrinoid 'necrosis' of the arteriolar wall in which pyknotic nuclear fragments and red blood cells may be seen. Found in the kidney, pancreas, adrenal, mesentery, brain, eye, heart and liver. Such arteriolar necrosis is also a feature of:
   (i) Systemic lupus erythematosus
   (ii) Polyarteritis nodosa
   (iii) Haemolytic-uraemic syndrome
   (iv) Irradiation

2. Arteries
Endarteritis fibrosa: concentric lamellar connective tissue and mucinous thickening of the intima ('onion-skin' thickening) which narrows the lumen. Also seen in:
   (i) Progressive systemic sclerosis
   (ii) Post-partum acute renal failure
   (iii) Haemolytic-uraemic syndrome
   (iv) Rejection after transplantation

B. Kidney

1. Gross appearances
   (i) Size is variable
   (ii) Smooth surface
   (iii) Subcapsular petechial haemorrhages

2. Glomeruli
   (i) Patchy fibrinoid necrosis of tufts
   (ii) Occasionally complete infarction tufts

3. Bowman's capsule
   (i) Deposition of fibrin in the capsular space
   (ii) Occasional epithelial 'crescent' formation

C. Brain (hypertensive vascular crisis)

1. Gross appearances
   (i) Oedema
   (ii) Petechial haemorrhages

2. Microscopic appearances
   (i) Fibrinoid necrosis of arterioles and small arteries
   (ii) Perivascular cuffing by lymphocytes

Cortisol, Stress, and Health

Today, we are more stressed than ever before. Men and women are working more hours, teens are committing suicide at high rates, and physicians cannot write enough prescriptions for antidepressant and anti-anxiety medications.

Although modern technology is light years ahead of that of our primitive forebears, our biological make-up has not changed appreciably for many thousands of years. Because of this, understanding how our bodies react to external and internal stressors is vitally important to the quest for optimal health and well-being.
While questions remain as to precisely how stress contributes to the disease process, research has shown that chronic stress causes a significant dysfunction of one of the most vital systems of our body—the neuroendocrine system.1-4

**The Mind-Body Connection**

The study of brain-body interaction, or psychoneuroimmunology, is one of the most contentious fields in medicine today. While more researchers and physicians believe that the mind and body are one, a significant number of doctors still insist that the mind and body are separate entities that have only minimal interaction.

Of course, this stubbornness is not surprising, as Western medicine has long held as one of its major axioms that the mind and body are separate entities. By contrast, Chinese and other traditional medicines have always recognized the interconnectedness of the body and mind. For those who still doubt this interplay, recent scientific research proves that what happens in the mind can profoundly influence the body.

**The Neuroendocrine Connection**

Scientists are just now beginning to unravel the ways in which in the mind influences the body, and vice versa. The hypothalamic-pituitary-adrenal (HPA) axis plays a major role in both mind and body health. The intricate connection between the brain and endocrine system broadly influences our health, and many researchers suggest that our stressful, modern lifestyles are overtaxing the HPA axis.

Before we explore how aberrations of the HPA axis can contribute to many chronic disease states, it is important to understand how the HPA axis works. It starts with the hypothalamus, a specialized glandular area of the brain that some consider the “master gland” of the neuroendocrine system. The hypothalamus has many functions, such as controlling the body’s temperature, water balance, thirst, and hunger. It also acts as a controller of the pituitary gland, a small, bean-sized structure that sits just below the hypothalamus. During times of stress, the hypothalamus releases corticotropin-releasing factor, which in turn signals the pituitary gland to release adrenocorticotropic hormone, or ACTH. This hormone then travels through the bloodstream to the adrenals, two small, triangle-shaped glands located on the top of the kidneys. When ACTH reaches the adrenals, it causes them to release a biochemical known as cortisol.

**Cortisol: the Stress Hormone**

Cortisol is, in many ways, a paradoxical hormone. A certain amount of cortisol is needed to maintain optimal health, but too much or too little can be deadly. Cortisol is involved in multiple bodily functions, including blood pressure regulation, cardiovascular and immunological function, and the metabolism of fats, proteins, and carbohydrates. In stressful situations, the body secretes cortisol at higher-than-normal rates to help break down and use fatty acids and proteins for energy production, which is especially important for optimal brain function. Unlike levels of other hormones such as testosterone and DHEA, cortisol levels generally do not decrease as we get older. In fact, some researchers now believe that many age-related problems may result from a ratio of increased cortisol and lowered DHEA.
How Stress Kills

In the 1930s, the renowned endocrinologist Hans Selye discovered that both psychological and biological stress can adversely affect human health through interactions between the mind and the adrenal glands. Following his landmark work on the crucial link between stress and the HPA axis, in 1946 Selye published his now-classic work on the relationship between chronic stress and disease. Selye reasoned that living organisms, including humans, react in physiologically predictable ways to both physical and psychological stressors, seeking to maintain homeostasis, or a constant, dynamic metabolic equilibrium wherein all organ systems function to maintain optimal health. He termed these often-complex physiological and behavioral responses to stress the “general adaptation syndrome,” or GAS. Selye also observed that if the stressors were continuous, the organism would ultimately “burn out” and die. He devised the following three-step model to describe the process:

- **Step 1**: alarm reaction. Faced with an immediate stressor (either physical or psychological), there is activation of both the “flight or fight” response and the HPA axis, leading to secretion of greater amounts of hormones such as cortisol.

- **Step 2**: resistance phase. If the perceived stressors are not countered in a timely fashion and the HPA axis is in a continual “on” mode in an attempt to maintain homeostasis, adrenal hypertrophy and numerous other deleterious health effects begin to occur.

- **Step 3**: exhaustion phase. If the perceived stress is prolonged, the adrenal glands and other organ systems begin to “burn out” and experience a precipitous decline in function. If the exhaustion phase continues long enough, the organism will die.

Stress, Cortisol, and Illness

Taking their lead from Selye’s original work, scientists have demonstrated that both acute and chronic levels of stress contribute to elevated levels of cortisol. In addition, high levels of stress are now known to be significantly linked to various illnesses, including upper respiratory infections, exacerbation of multiple sclerosis, and gastrointestinal disorders such as irritable bowel syndrome.

Since the mid-1990s, scientists have presented provocative evidence linking cancer, stress, and elevated cortisol levels. In a 1996 case-controlled study, scientists examined hormone levels of the hypothalamic-pituitary-adrenal system in women with both early-stage and metastatic breast cancer. Both groups had statistically higher levels of cortisol compared to women without breast cancer. Furthermore, those with metastatic breast cancer had higher cortisol levels than women with early-stage breast cancer. The authors noted, “these data provide evidence that breast cancer is associated with a hyperactive adrenal gland.”

A more recent report in the journal *Lancet Oncology* summarized what is currently known about the complex interactions between the HPA system, stress, and cancer. According to the authors, “Evidence mainly from animal models and human studies.
suggests that stress and depression result in an impairment of the immune system and might promote the initiation and progression of some types of cancer...Through HPA activation, the mediators released during chronic stress suppress some non-specific and specific parts of the immune response...compromising the most important effectors of the immune response against tumors.”

While cancer is probably the most widely feared chronic disease, heart disease remains the number-one killer of Americans. Mayo Clinic researchers examined the medical and economic costs of stress in heart disease patients.19 In a study of 311 men and 70 women, the authors found that patients with the highest stress levels had markedly higher rates of rehospitalization and reoccurrence of further heart disease-related problems, including heart attacks and cardiac arrest. Concluding that psychological distress may adversely affect prognosis in heart disease patients, the authors suggested that identifying and treating psychological distress could improve outcomes in these patients.

A more recent report in the *European Heart Journal* supports the theory that stress can literally be a killer.20 In this 21-year prospective study of nearly 14,000 men and women, researchers concluded, “chronic stress is an independent risk factor for [cardiovascular disease], particularly fatal stroke.” Other scientists, however, have criticized these data, indicating the need for further investigation.

Alzheimer’s disease, the most common cause of dementia in those aged 65 or older, is characterized by a progressive decline in cognition and memory. This debilitating condition currently affects over 15 million people worldwide. With the rapidly aging US population—an estimated 30% of all Americans will be 65 or older by the year 2050—projections are that 14 million people in the US alone will be affected by Alzheimer’s in the next few decades.21,22 This represents a quadrupling over the current prevalence of Alzheimer’s in the US.

Although scientists continue to search for the root cause of this devastating illness, new evidence suggests that increased levels of stress, along with high levels of cortisol, may play a significant role. Research indicates that high cortisol levels may promote degeneration and death of neurons,23-25 along with decreased memory function in otherwise healthy elderly men and women.26 Furthermore, a recent report in the journal Neurology showed that chronic stress is associated with the risk of developing Alzheimer’s disease.27 In this study, researchers found that people who were prone to experiencing high levels of stress had twice the risk of developing Alzheimer’s as those who were not prone to stress. The authors concluded, “proneness to experience psychological stress is a risk factor for [Alzheimer’s disease].”

While mainstream medicine offers little in the way of reducing chronic stress or high cortisol levels, making behavioral changes and using certain supplements can help you bring your stress load and high cortisol levels safely under control.

**Exercise Counters Stress**

Humans are designed to be physically active. However, our typical twenty-first century lifestyle—sitting in front of a computer all day—is a far cry from the daily hunting and gathering activities of our ancestors. While it is common knowledge that exercise can keep our muscles and bones strong and healthy, less often recognized
is that moderate exercise can also decrease stress and high cortisol levels.

A newly published study in the journal *Psychoneuroendocrinology* examined the effects of aging and fitness on the HPA axis response to stress. The study authors hypothesized that aging is associated with a greater HPA axis reactivity to psychological stress leading to higher cortisol levels, and that exercise could ameliorate this reactivity. The researchers subjected three groups of women—categorized as "young-unfit" (aged 25-30), "older-unfit" (aged 64-67), and "older-fit" (aged 64-68)—to a battery of psychological and physical tests meant to induce stress. These tests included an EKG-monitored treadmill test, a mental arithmetic test, an anagram test, and a cold pressor test, where subjects placed their hands in a bucket of ice water for as long as they could tolerate. While cortisol levels rose in all three groups of women, those in the older-unfit group had the most significant increase. The authors concluded that "aging is associated with greater HPA axis reactivity to psychological stress, and that higher aerobic fitness among older women can attenuate these age-related changes as indicated by a blunted cortisol response to psychological stress. These findings suggest that exercise training may be an effective way of modifying some of the neuroendocrine changes associated with aging."28

**Relaxation and Meditation**

If you want to decrease stress and lower your cortisol, then taking time out each day to relax and meditate may be just the solution. Considerable scientific evidence has established that relaxation and meditation techniques are valuable therapeutics for optimal health.

An article in *Psychoneuroendocrinology* highlighted meditation’s effects on levels of various hormones, including cortisol, in otherwise healthy male subjects who were subjected to mental and physical stressors. In this prospective, randomized study, blood samples were taken and hormone levels analyzed at the study’s onset and again four months later after the subjects had learned and practiced a meditation technique. Those who had practiced meditation had lower average cortisol levels compared to subjects who had not meditated, suggesting that meditation may help reverse the effects of chronic stress. A paper in the journal *Psychosomatic Medicine* described how women with stage I or II breast cancer could decrease their perceived levels of stress, as well as their cortisol levels, by simple cognitive-behavioral stress-management techniques.

**Supplements to Combat Cortisol**

Exercise and meditation are two important modalities that may help many individuals manage stress-filled lives. In addition, studies suggest that effective natural supplements, such as vitamin C, fish oil, phosphatidylserine, and herbal adaptogens, may help keep the HPA axis in equilibrium, reduce elevated cortisol levels, and help optimize health.

**Vitamin C**

Besides its beneficial effects in maintaining proper immune system function, vitamin C has been shown to help modulate high levels of cortisol brought about by stress. A
In a study conducted in 2001, researchers examined the effects of supplemental vitamin C on high cortisol levels brought about by physical stress in marathon runners. In a randomized, placebo-controlled study, ultramarathon runners were given 500 mg a day of vitamin C, 1500 mg a day of vitamin C, or a placebo seven days before a marathon, the day of the race, and two days after the race. Researchers found that athletes who took 1500 mg per day of vitamin C had significantly lower post-race cortisol levels than those taking either 500 mg a day or placebo.

Another study published in the journal *Psychopharmacology* reviewed evidence showing that vitamin C can reduce high cortisol levels brought about by psychologically induced stress. In a randomized, double-blind, placebo-controlled trial, researchers gave 3000 mg per day of vitamin C or a placebo to 120 volunteers who were subjected to psychological stress through the Trier Social Stress Test (TSST), a commonly used assessment tool in psychological research that simulates public speaking and arithmetic tests to induce stress and raise cortisol levels. Subjects who took vitamin C had lower blood pressure, subjective stress, and cortisol measures compared to those who were given placebo.

**Fish Oil**

In a number of clinical tests, fish oil has been shown to reduce cardiovascular risk in women and men. Preliminary research has shown that fish oil may help individuals cope with psychological stress and lower their cortisol levels. In a study published in 2003, researchers gave seven study volunteers 7.2 grams per day of fish oil for three weeks and then subjected them to a battery of mental stress tests. Blood tests showed that these psychological stressors elicited changes in the subjects' heart rate, blood pressure, and cortisol levels. After three weeks of fish oil supplementation, however, the rise in cortisol levels secondary to stress testing was significantly blunted, leading the authors to conclude that supplementation with omega-3 fatty acids from fish oil “inhibits the adrenal activation elicited by a mental stress, presumably through effects exerted at the level of the central nervous system.”

**Phosphatidylserine**

Another supplement that has been shown to be useful in combating the deleterious effects of stress is phosphatidylserine. This phospholipid constitutes an essential part of biological cellular membranes. For more than 10 years, studies have shown that phosphatidylserine is able to cut elevated cortisol levels induced by mental and physical stress. In one early study, 800 mg per day given to healthy men significantly blunted the rise in cortisol caused by physical stress. Another paper reported that even small amounts of supplemental phosphatidylserine (50-75 mg administered intravenously) could blunt cortisol increases secondary to physical stressors. In this study, eight healthy men had their blood drawn before and after physical stress induced by riding a bicycle ergometer. While all subjects showed increased cortisol levels, pretreatment with the 50- or 75-mg dose of phosphatidylserine significantly blunted cortisol response to the physical stressor.

Finally, a study published in 2004 examined phosphatidylserine’s effects on endocrine and psychological responses to mental stress. The stressor used was the Trier Social Stress Test (TSST), which consists of 15 minutes of psychological stress induced via a mock job interview, followed by a mental arithmetic challenge.
This double-blind study followed 40 men and 40 women, aged 20-45, for three weeks. The subjects were given either phosphatidylserine (either 400 or 600 mg daily) or a placebo before taking the TSST. Phosphatidylserine was effective in blunting the cortisol response to stressors, with those taking 400 mg daily (but not, surprisingly, 600 mg) of phosphatidylserine showing a significantly decreased cortisol response. The authors concluded that phosphatidylserine helped dampen the effects of stress on the pituitary-adrenal axis, and may have a role in managing stress-related disorders.36

Herbal Adaptogens

Plant-derived adaptogens can be a very useful in combating the mental and physical rigors of our modern lifestyle. Adaptogens work by modulating the levels and activity of hormones and brain neurochemicals that affect everything from cardiac activity to pain perception. For any herb or substance to be properly classified as an adaptogen, it should:

- produce a non-specific response and increase an individual's resistance to a wide range of deleterious stimuli
- produce a normalizing response in an individual when subjected to physiological, emotional, or mental stressors
- be non-toxic and not induce changes in the physiological, emotional, or mental state of a non-stressed individual.

One such herbal adaptogen is Rhodiola rosea, or rhodiola. In traditional Asian and European medicine, this herb has been used for centuries to increase physical endurance and longevity, as well as to manage fatigue, depression, and impotence. Rhodiola’s positive effects are thought to be mediated through the actions of rosavins and salidrosides, chemical compounds found in the plant’s roots. Multiple studies from the former Soviet Union have demonstrated rhodiola’s effectiveness in combating both physically and psychologically stressful conditions.37

Another herb that serves as an adaptogen is ginseng, which has been used throughout Asia since antiquity. It is important to note that ginseng is the name given to three different plants used as adaptogens. The most widely used ginseng is Panax ginseng, also known as Korean, Chinese, or Asian ginseng. Panax quinquefolium—or American ginseng—is also considered a “true” ginseng. However, Siberian ginseng (Eleutherococcus senticosus), while commonly referred to as ginseng, is not a true ginseng but a closely related plant. Yet no matter what the genus or species, all three of these plants have experimental evidence backing their adaptogenic claims. Animal studies have shown that ginsenosides, bioactive compounds in ginsengs, improve the sensitivity of the HPA axis to cortisol.38,39 In addition, studies suggest that all three plants provide protection against both physical and psychological stresses.38,39

Finally, another plant that deserves mention as an adaptogen is ginkgo biloba. For the last 5,000 years, leaves of the ginkgo tree have been used to treat various medical conditions. While ginkgo is currently used to help combat the debilitating effects of memory decline and dementia,40-42 emerging evidence suggests that it may be useful in treating the impact of stress and elevated cortisol levels. A recent
double-blind, placebo-controlled study published in the *Journal of Physiology and Pharmacology* examined ginkgo’s effects in modulating cortisol and blood pressure levels in 70 healthy male and female subjects.43 When subjected to physical and mental stressors, subjects who were given 120 mg per day of a standardized ginkgo extract saw smaller increases in their cortisol levels and blood pressure than did their counterparts who were given a placebo.

**Raising DHEA Levels**

While cortisol levels stay the same or even increase as we age, levels of another vitally important hormone, DHEA, decrease with each passing year. This relationship between cortisol and DHEA has led some to suggest that these adrenal hormones may play a significant role in the aging process and its associated negative health effects. A recent paper in the European Journal of Endocrinology examined the pathophysiological correlates of age-related changes in the HPA axis.44 The authors showed that the cortisol/DHEA ratio increases significantly as one ages, and is even higher in elderly patients who suffer from dementia. Supplemental DHEA, however, enhances the brain’s resistance to stress-mediated changes, maintains functional abilities, and protects against age-related diseases. The authors concluded, “the changes of the hormonal balance [between cortisol and DHEA] occurring in aging may contribute to the onset and progression of the aging-associated neurogenerative diseases.”44

**Conclusion**

Exercise, stress management techniques such as relaxation and meditation, and nutritional supplements can help you manage stress and lower cortisol to promote optimal health and longevity. The following are scientifically supported techniques that can help support a healthy response to stress.

1. Behavioral techniques to lower stress and manage high cortisol levels
   - Exercise: 30-45 minutes of both anaerobic (resistance training) and aerobic (jogging, cycling) every other day.
   - Meditation/relaxation: 15-30 minutes daily.

2. Supplements to reduce high cortisol levels secondary to stress
   - Vitamin C: 1000-3000 mg/day.
   - Fish oil (omega-3 fatty acids): 1-4 gm/day.
   - Phosphatidylserine: 300-800 mg/day.
   - Rhodiola rosea: 100-200 mg/day, standardized extract.
   - Ginseng: 100-300 mg/day, standardized extract.
   - Ginkgo biloba: 100-200 mg/day, standardized extract.
   - DHEA: 25-50 mg/day (any hormone supplementation should be monitored by your physician).
**PULMONARY HYPERTENSION**

The normal pressure in the pulmonary artery is about 15 mmHg. Pulmonary hypertension is characterized by pressures in excess of 30 mmHg.

**Causes of pulmonary hypertension**

1. Increased pulmonary venous pressure
   (i) Chronic left ventricular failure
   (ii) Mitral stenosis

**Rare causes:**
   (iii) Left atrial myxoma
   (iv) Cor triatriatum
   (v) Idiopathic thrombosis of pulmonary veins
   (vi) Compression of veins by mediastinal neoplasm
   (vii) Veno-occlusive disease

2. Increased pulmonary vascular resistance

**Obstruction to pulmonary arteries/arterioles**

Psychoneuroimmunology is defined as the study of behaviorally associated changes in immunity and immunologically associated changes in behavior that result from the interaction among the nervous, endocrine, and immune systems (1,2). The charge to this working group was to develop experimental protocols with which to investigate multiple chemical sensitivity (MCS) from the heretofore unconsidered perspective of psychoneuroimmunology. Given that the involvement of the immune system in MCS is still an area of some controversy, the impact of psychoneuroimmunological processes on the onset, development, and clinical course of MCS is problematic. Thus, the group also considered a reasonable area of scientific inquiry to be the possible influences on immunity of the stress associated with MCS as a chronic disability (3).

**Experimental Questions Relevant to the Relationship between Exposure and Symptoms in Chemical Sensitivities**

During its deliberations, the group raised the following six related sets of questions whose answers could reveal a relationship among behavioral stimuli, neural-immune system interactions, and MCS.

- In situations in which a sensitizing chemical may be immunomodulatory, do environmental cues temporally associated with the sensitizing exposure serve as conditioned stimuli (4)? If so, can such cues, with or without subthreshold amounts of the chemical, elicit a chemical sensitivity response? Can the chemical sensitizer itself, provide both unconditioned and conditioned stimuli?

- Are there significant immunological, neuroendocrine, and psychosocial deviations from normalcy shortly before, at the time of, or consequent to, the development of MCS symptomatology? If physiological changes are noted consequent to psychosocial changes, are those psychosocial changes implicated in the development of MCS? If so, could psychological/behavioral intervention be of therapeutic value, at least in some subset of patients (3)?
• What is the interval between the initiating event and the development of early symptoms of MCS? What is the interval between the initial trigger and the so-called increase in sensitivities to diverse stimulants?

• Is the duration of these intervals related to psychosocial factors (e.g., stress) or to personality/sex/health status (e.g., allergic status, autoimmunity or autoimmune predisposition) of the subject, or the chemical nature of the initiator? Do events perceived as stressful in the recent or past history of the individual play roles in the onset and/or progression of MCS?

• What do chemical initiators of MCS and initiators of MCS such as a car accident or childbirth have in common? Which factor is more important in the traumatic initiation: the exposure to chemicals associated with the traumatic event, and/or the stressful experience associated with the event? Can a stressor precipitate MCS in a chemically sensitized individual who is not displaying overt symptoms of MCS at the time of stressor exposure?

Why is there variability in the development and severity of MCS? Is there any relationship between major histocompatibility complex phenotype and MCS? Is there a detectable humoral or cellular immune response to the initiating chemical? Is an immune response causal or the result of the MCS process(es)?

14. Atherosclerosis and aneurysms

Atherosclerosis is a disease which affects the intima of arteries. It appears as focal thickening or plaques composed of fibrous tissue and lipid deposits. Atherosclerosis is not synonymous with arteriosclerosis. The latter term includes a number of diseases characterized by thickening of arterial vessels:

*Classification of arteriosclerosis*

1. Intimal thickening with lipid deposition - atherosclerosis
2. Hyaline thickening -- Ageing, diabetes and hypertension
3. Medial fibrosis -- Ageing, diabetes and hypertension
4. Fibrous intimal proliferation
   (atheriosclerosis obliterans) -- Hypertension
5. Medial hypertrophy -- Hypertension
6. Medial calcification

*PATHOLOGY OF ATHEROSCLEROSIS*

This disease is generally considered to pass through three stages, the fatty streak, the fibro-fatty plaque, and the complicated lesion.

1. *Fatty streaks* in the aortic intima can be found even in the first two decades of life, especially in the aortic valve region, around the ductus scar, and below the intercostal ostia. Some of the lipid is found in endothelial cells overlying the streaks, but the majority is found within *foam-cells* in the intima. These foam-cells arise from two sources: some are lipid-containing smooth muscle cells -'myogenic'foam-cells, while others are macrophages derived from circulating
monocytes. Most of the lipid in these lesions is intracellular and can therefore be mobilised and resorbed under certain circumstances, e.g. a low-lipid diet.

2. **Fibro-fatty plaques** represent the typical lesion seen in middle and old age. They consist of lipid accumulations, fibro-elastic tissue, and proliferated smooth-muscle cells in the intima.

Earlier lesions contain myogenic foam-cells and a few macrophages in the subendothelial region, but in the later free fat or cholesterol crystals in a central mass of necrotic material. New vessels develop from the vasa vasorum and adventitia and infiltrate the base of the plaque.

3. **Complicated lesions.** The fibro-fatty plaques can be complicated by:
   (i) Superimposed thrombosis
   (ii) Haemorrhage into the plaque from the vasa vasorum
   (iii) Rupture and ulceration with discharge of necrotic debris
   (iv) Calcification

**Arterial structure**

In order to understand the various theories of pathogenesis, the normal structure and the physiological pressure effects acting on large arteries must be understood.

1. **Structure of a large artery**
   (i) **Endothelium** has a structure similar to that found in capillaries and is freely permeable to fluid and electrolytes. It also allows slow leakage of large molecules, e.g. protein and lipoproteins, from the plasma into the intima
   (ii) A thin layer of loose fibro-elastic tissue lies between the endothelium and internal elastic lamina. It becomes thicker with age and shows a gradual increase in its content of smooth muscle cells. This layer together with the endothelium constitute the **intima** of the vessel.
   (iii) **The media** is composed of collagen fibres, elastic tissue and smooth muscle cells. Its main function is to resist the expansive force of the blood pressure, and convert a pulsatile to a continuous flow
   (iv) The outermost layer consists of loose fibrocellular tissue - the **adventitia**. It contains nerve fibres, lymphatics and small nutrient arteries associated with the vessel wall
   (v) **Extracellular matrix** (ground substance) fills the interstices of the wall and is most abundant in the intima. It binds or retards larger molecules passing through the wall, thus acting as a fine pored filter, and is composed of glycosaminoglycans, glycoproteins and proteoglycans
   (vi) **The vasa vasorum** are the small blood vessels which enter from the adventitia and supply the outer 2/3 of the wall

2. **Pressure effects on the wall**

Blood flow exerts shearing stresses on the wall which tend to displace the endothelium and the inner layers of the wall in the direction of flow. In addition arterial walls are subjected to a considerable compressive force amounting, for example, to about 50 kg/cm² in the aorta. This compressive force is gradually converted into a tangential force (tensile stress) by the elastic laminae and muscle fibres of the media. The vasa vasorum can only nourish those parts of the wall where the intramural compressive force is equal to or less than the capillary blood pressure, and such conditions are found only in the outer 2/3 of the wall. The intima
and inner part of the media are nourished entirely by diffusion of plasma from the lumen. There is a considerable flow of plasma into the wall and this leaves via the lymphatics and veins of the vasa vasorum.

LIPOPROTEINS

The plasma lipids are almost entirely bound to certain proteins within composite molecules known as lipoproteins.

Each can be considered as a protein fraction - the apoprotein, bound to a variety of different lipids - cholesterol, cholesterol esters, phospholipids, and triglycerides (TG). Lipoproteins are generally classified according to their ultracentrifugation properties and have been divided into high-density (HDL), low-density (LDL) and very low-density (VLDL) lipoproteins. These categories correspond to the (a, b, and pre-b) lipoproteins recognized electrophoretically. In addition triglyceride-rich lipoproteins are formed and packaged within intestinal mucosal cells and enter the circulation as chylomicrons. More recently other transport forms, chylomicron remnants, and VLDL remnants (termed intermediate density lipoproteins - IDLS), have been described.

Composition of plasma lipoproteins:
1. Chylomicrons - triglyceride and apoA-I, II, IV and apoB-48
2. VLDL - triglyceride, phospholipid and apoB-100, apoC-I, II, III and apoE
3. IDL - esterified cholesterol, phospholipid, apoB-100 and apoE
4. LDL - triglyceride, esterified cholesterol and apoB-100
5. HDL - phospholipid, cholesterol, apoA-I, II, apoC-II and apoE

Chylomicrons carry dietary TG to adipose and muscle cells where they become attached to a membrane-bound enzyme, lipoprotein lipase, on the surface of endothelial cells. The lipase liberates FFAs and monoglycerides from the triglyceride core and the chylomicron remnants re-enter the circulation, attach to receptors on liver cells, and following endocytosis are broken down by lysosomal action. In a similar fashion, VLDL manufactured by the liver from newly synthesised TG, proteins, and cholesterol (which has usually been recycled), are acted upon by lipoprotein lipase and liberate VLDL remnants which are termed intermediate density lipoproteins. IDL acquire more cholesterol esters derived from the action of plasma lecithin-cholesterol acyltransferase (LCAT) on the circulating HDL pool, and are thereby converted into particles made up almost entirely of a cholesterol ester core and an apoprotein coat. These particles constitute the LDLs which, in normal subjects, account for about two-thirds of the total plasma cholesterol.

LDLs are disposed of in two ways:
1. via high-affinity specific receptors
2. via non-specific macrophage activity

1. Receptor-mediated disposal

LDL receptors are present on liver and extra-hepatic cells. Once bound to the cell surface, the lipoprotein is internalised and undergoes lysosomal degradation. Liberated cholesterol is utilised for membrane building or steroid synthesis, or is passed back to the HDL pool. Plasma LDL concentration increases with age, probably as a result of an acquired defect in LDL receptor function.

2. Macrophage activity

Where there is a high plasma level of LDL, or some local build-up, macrophages
will absorb and degrade lipoprotein and accumulate cholesterol esters in their cytoplasm.

The major ligand for the LDL receptor and the chylomicron remnant receptor is apoprotein E. This arginine-rich protein is also associated with VLDLs and is the ligand that promotes their interaction with macrophages leading to cholesterol ester storage. Apoprotein E is involved in the transformation of VLDLs to particles of LDL size and density, and the removal of VLDLs from the circulation.

SMOOTH MUSCLE CELLS

Arterial smooth muscle cells are largely responsible for the tensile strength and the structural integrity of the wall by the synthesis of extracellular matrix and the cells vary considerably in the degree to which they manifest these 'contractile' or 'synthetic' activities. Thus, during development arterial smooth muscle cells switch from a predominantly synthetic role in the fetus to a contractile state in the adult but can readily reverse this pattern following damage to the arterial wall. The synthetic phenotype has several noteworthy differences to the contractile phenotype.

Synthetic cells:
(i) Do not contract
(ii) Migrate and proliferate following stimulation by macrophage-derived growth factors
(iii) Synthesise and secrete PDGF which acts in an autocrine fashion to further stimulate proliferation
(iv) Show increased:
   a. Collagen synthesis
   b. Degradation of VLDL
   c. Lysosomal enzyme activity, except cholesterol esterase
(v) Show diminished:
   a. Degradation of LDL
   b. Acid cholesterol esterase activity
(vi) Accumulate cholesterol

MACROPHAGES AND ATHEROSCLEROSIS

Macrophages are not normally present within the arterial wall but are a prominent feature of atherosclerosis. Just as in the inflammatory response monocytes attach to endothelial cells expressing adhesion molecules. Endothelial expression of ICAM-1 occurs in atherosclerosis and monocytes adhere via their b-2 integrin receptor and penetrate the endothelium. Once in the intima, monocytes transform into functional macrophages and by producing TNF and IL-1 increase endothelial synthesis of adhesion molecules and encourage more monocyte emigration. Such emigration is further stimulated by the production of cytokines with monocyte chemotactic properties by intimal macrophages in a positive feedback loop. Macrophages produce PDGF and other cytokines which promote the proliferation of smooth muscle cells. They also ingest oxidised LDLs present in the intima and are
converted into foam cells. Thus, both macrophages and smooth muscle cells accumulate lipid in atherosclerosis and can appear as foam cells.

RISK FACTORS IN ATHEROGENESIS

On the basis of epidemiological studies the following major risk factors have been identified:
1. Age
2. Sex
3. Obesity
4. High dietary cholesterol intake
5. Cigarette smoking
6. Hypertension
7. Diabetes mellitus
8. Hyperlipidaemia
9. Low HDL level

PATHOGENESIS OF ATHEROSCLEROSIS

The following factors have been claimed to be responsible in some measure for the development of atherosclerosis:

A. Lipid accumulation

Supporting evidence
1. Increased atherosclerosis in hyperlipidaemia states. The more common types associated with an increased risk are:
   (i) Type IIA - Familial hyper-b-lipoproteinaemia (high LDL)
   (ii) Type IIB - Over-indulgence hyperlipidaemia
   (iii) Type IV - Endogenous hypertriglyceridaemia (raised VLDL)
2. Increased atherosclerosis in hypercholesterolaemia resulting from primary (familial) or secondary deficiency of LCAT
3. Increased atherosclerosis where there is a high level of lipoprotein-A, a distinct member of the LDLs which may prevent normal uptake and disposal of other LDLs. This lipoprotein also has plasminogen-like effects and may compete for plasminogen binding sites and inhibit fibrinolysis
4. Production of fatty plaques in experimental animals by feeding with a high cholesterol diet
5. Analysis of atheromatous plaques reveals 10 or more times the normal lipid content of the intima. The increase is made up predominantly of cholesterol linoleate derived from LDLs.
6. High HDL levels protect against coronary atherosclerosis probably by inhibiting macrophage production of monocyte chemoattractants.

Possible mechanisms
1. Excess low density lipoproteins (especially lipoprotein-A) in the plasma
2. Altered permeability of the endothelium allows more plasma lipids to enter the wall
3. Retention of lipoproteins in the intima resulting from altered filtration characteristics of the ground substance
4. Defective metabolism of the smooth muscle cells leads to saturation of the
lysosomal lipoprotein disposal system. This may result from:

(i) congenital hydrolytic enzyme deficiency
(ii) acquired relative deficiency as in diabetes mellitus
(iii) effects of viral infection (see below)

5. Leakage from newly-formed vasa vasorum in fibro-fatty plaques

Effects
1. Alteration in the ground substance
2. Proliferation of smooth muscle cells - frequently monoclonal
3. Accumulation of 'foam-cells'
4. Increase in connective tissue fibres
5. Necrosis and inflammation in advanced lesions - the necrogenic effect of lipids

B. Haemodynamic stress
Supporting evidence
1. Association with systemic hypertension
2. Increased severity in coronary arteries where there is cyclical reversal of flow
3. increased incidence and severity at sites of branching where there is a relatively low flow velocity and oscillating wall shear stress
4. Absence from veins and minimal involvement of the pulmonary circulation (except where there is pulmonary hypertension)

Effects of stress
1. Low and oscillating shear stresses may weaken interendothelial cell junctions so that there is greater ingress of lipids into the intima
2. Low shear stresses encourage the attachment of platelets, monocytes and polymorphs to endothelial cells. The former may initiate surface micro-thrombosis while the latter may alter vascular permeability or increase the rate of monocyte entry into the intima.
3. Polymerisation of the ground substance which alters its filtration characteristics
4. Formation of new collagen and elastin fibres
5. Intimal thickening resulting from the connective tissue and smooth muscle cell proliferation
6. Rupture of the elastic lamina

C. Organisation of surface thrombosis
Supporting evidence
1. The microscopic appearances of an organised mural thrombus and an atheromatous plaque can be identical
2. Deposition of fibrin and platelets on vascular endothelium is a frequent event
3. Atheromatous plaques contain large quantities of fibrinogen, fibrin, and platelets
4. Hyperlipidaemic states are associated with a decreased clotting time and impaired fibrinolysis

Probable mechanisms
1. Endothelial injury results in surface microthrombosis
2. Lipoproteins may prevent initial access and binding of plasminogen to the deposited fibrin thereby blocking lysis
3. Re-endothelialisation increases the rate of entry of LDLs into the organising thrombus by micropinocytosis
4. Fibrin degradation products stimulate smooth muscle cell proliferation in the intima

D. Viral infection

**supporting evidence**
1. Herpes viruses can be found in the arterial wall
2. Atherosclerosis can be induced in normocholesterolaemic animals by herpes viruses
3. Herpes virus infection of smooth muscle cells *in vitro* leads to inactivation of cholesterol ester hydrolase and accumulation of free and esterified cholesterol
4. Endothelial infection by herpes simplex virus leads to increased synthesis and expression of glycoprotein C which can act as a binding site for Factor X and initiate blood coagulation
5. Herpes viruses can induce the synthesis of cytokines which act as growth promoters for cells within the vessel wall
6. Cytomegalovirus infection following cardiac transplantation can lead to accelerated atherogenesis

**Probable mechanisms**
1. Initial binding of herpes simplex virus to heparan sulphate is followed by attachment to endothelial and smooth muscle cells via their FGF receptors
2. Entry of virus into endothelial cells is followed by lethal injury and cellular desquamation or sublethal cytopathic effects
3. Desquamation results in exposure of collagen which leads to platelet aggregation
4. Sublethal injury leads to enhanced platelet binding to endothelium, diminished PGJ₂ production and reduced synthesis of heparan sulphate which normally acts as a surface anticoagulant. These effects promote thrombosis in the area of endothelial infection
5. The damaged endothelium also releases growth factors and cytokines which stimulate smooth muscle proliferation
6. Infection of smooth muscle cells leads to altered metabolic activity in which there is increased binding of LDL cholesterol esters coupled with decreased cholesterol ester (CE) hydrolysis resulting in accumulation of CE-enriched lipid droplets

**Multifactorial causation**
1. Endothelial injury is likely to be the initial event
2. Injury probably results from haemodynamic stress but may also be related to toxins (e.g., nicotine, carbon monoxide), metabolites, or viral infection
3. Endothelial injury or inflammation promotes Polymorph, monocyte and platelet adhesion. Increased numbers of monocytes may enter the intima where they produce cytokines that amplify cellular emigration
4. Dietary fatty acids may influence platelet-vessel wall interactions by modulating the balance between prostacyclin and thromboxane synthesis. Platelet aggregation then leads to surface thrombosis
5. Smooth muscle cells are stimulated by macrophage-derived growth factors including PDGF and switch to a synthetic phenotype. The cells proliferate and
secrete increased amounts of proteoglycans and collagen
6. The proteoglycans in the matrix favour the entrapment of apo B containing lipoproteins and the resulting lipid-rich complexes and oxidised LDLs are taken up by macrophages
7. Altered endothelial permeability, matrix trapping and defective lysosomal disposal lead to an accumulation of LDLs in the intima
8. The rate and extent of LDL accumulation is modified by the plasma lipoprotein levels

EFFECTS OF ATHEROSCLEROSIS

1. Progressive occlusion leading to ischaemia
2. Infarction resulting from sudden occlusion due to
   (i) Superimposed thrombosis
   (ii) Haemorrhage into plaque
3. Rupture of a plaque leading to micro-embolisation by atheromatous debris
4. Aneurysm formation

ANEURYSMS

An aneurysm is a localized dilatation of an artery or part of the heart consequent upon weakening of its wall.
1. Large and medium-sized arteries. Aneurysms may result from:
   (i) Atherosclerosis. This is the commonest cause. Secondary weakening of the media gives rise to fusiform or saccular dilatations usually in the abdominal portion of the aorta
   (ii) Congenital defects. A congenital deficiency of the media and elastica in cerebral arteries leads to 'berry' aneurysm formation
   (iii) Cystic medionecrosis. In this disorder there is focal loss of elastin and accumulation of acid glycoproteins in the media with subsequent cystic degeneration and splitting of the vessel giving rise to a 'dissecting aneurysm'. Dissecting aneurysms also occur in Marfan's syndrome.
   (iv) Trauma, especially in arteries of the legs
   (v) Syphilis. The mesoaortitis of tertiary syphilis can lead to aneurysms in the thoracic aorta
   (vi) Polyarteritis nodosa
   (vii) Infection of the vessel wall by bacteria brought there by infected emboli giving rise to 'mycotic' aneurysms, e.g. in bacterial endocarditis
2. Small arteries. Microscopic dilatations of small arteries (microaneurysms) which predispose to rupture are found in:
   (i) Systemic hypertension, in small intracerebral arteries
   (ii) Pulmonary hypertension, as dilatation lesions in muscular arteries
   (iii) Diabetic retinopathy
3. Heart. Ventricular aneurysms may complicate myocardial infarction
15. Thrombosis, embolism, and infarction

Thrombosis is the formation of a solid mass from the constituents of the blood within the vascular system during life. The solid (or semi-solid) mass is called a thrombus.

CAUSES OF THROMBOSIS

These are best considered under the three headings originally proposed by Virchow in 1856:
A. Changes in the vessel wall
B. Changes in blood flow
C. Changes in the constitution of the blood

A. Changes in the vessel wall
   1. Arteries
      (i) Atherosclerosis
      (ii) Inflammation
         a. Direct involvement in wall of an abscess, ulcer, etc.
         b. Auto-immune or drug induced
         c. Polyarteritis nodosa
         d. Giant-cell arteritis
         e. Thromboangiitis obliterans
   2. Veins
      (i) Inflammation (thrombophlebitis) resulting from
         a. Trauma - fractures, tourniquets, i.v. catheters
         b. Chemical injury - e.g. sclerosing fluids for treatment of varicose veins and haemorrhoids, irritant fluids administered intravenously
         c. Bacterial infection, e.g. thrombophlebitis of venous sinuses complicating acute suppurative otitis media or mastoiditis

B. Changes in blood flow
   1. Arteries
      Stasis and/or turbulence related to
      (i) Aneurysms
      (ii) Atherosclerotic plaques
      (iii) Spasm
   2. Veins
      (i) Local causes
         a. Inactivity. Lack of muscular ‘pumping’ action greatly reduces venous flow
         b. Pressure on veins by ill-fitting plasters, bandages, gravid uterus, tumours, etc.
         c. Dilatation and valvular incompetence, e.g. in varicose veins
      (ii) General factors
         a. Congestive cardiac failure
         b. Circulatory collapse following severe trauma, burns, etc.
C. Changes in the constitution of the blood

1. Increased viscosity associated with erythraemia (or polycythaemia) promotes thrombosis in arteries and veins.

Causes:
   (i) Dehydration, particularly in infancy leading to renal and cortical vein thrombosis
   (ii) Chronic hypoxic states, e.g. respiratory failure, cyanotic congenital heart disease
   (iii) Polycythaemia rubra vera

2. Increased viscosity resulting from high plasma protein content, e.g. multiple myeloma

3. Hypercoaguable states found
   (i) Following major surgery or trauma
   (ii) In pregnancy and parturition
   (iii) In some users of the oral contraceptive pill
   (iv) In some cases of leukaemia and polycythaemia rubra vera due to thrombocytosis
   (v) After splenectomy
   (vi) In endotoxaemia, shock, hypersensitivity reactions
   (vii) In association with some tumours, e.g. carcinoma of the pancreas

**STEPS IN THE FORMATION OF A THROMBUS**

1. Adhesion of platelets to exposed collagen at the site of endothelial damage. Adhesion is mediated by fibronectin on the surface of platelets and is stimulated more by Type III collagen than basement-membrane collagen
2. Secretion of adenosine diphosphate (ADP) and thromboxane A2 by the adherent platelets
3. ADP and thromboxane induces platelet aggregation
4. Activation of blood coagulation by:
   (i) **The intrinsic pathway** (‘intrinsic’ because all the necessary factors are already present in the blood) is initiated by collagen activation of Factor XII and facilitated by platelet phospholipid (Factor III) which is present on the surface of the aggregates
   (ii) **The extrinsic pathway** initiated by tissue thromboplastins derived from damaged endothelial cells, etc. The final common pathway leads to thrombin formation which in addition to converting fibrinogen to fibrin causes further ADP and thromboxane release from platelets thus promoting aggregation. The aggregates are stabilised by the deposited fibrin
5. The rough surface of the developing thrombus acts as a stimulus for further platelet adhesion which is followed by deposition of another layer of fibrin and entrapped red blood cells

In this way, a laminated mass composed of alternating layers of platelet (pale) thrombus, and fibrin with enmeshed red blood cells (red thrombus) is built up. The irregular pale laminae are sometimes visible to the naked eye and are termed **lines of Zahn**. Once complete occlusion of the vessel has occurred, the static blood beyond the thrombus may undergo coagulation. Here coagulation is not occurring in circulating blood, and a homogeneous red **clot** is produced. In veins, the tail of this clot may reach a tributary vessel in which there is flowing blood and initiate a fresh thrombus. In this way, occlusion of small veins by thrombus and blood clot may
extend proximally into major veins, a process termed *propagation*.

**VENOUS THROMBOSIS**

Venous thrombosis is much more common than thrombosis in arteries. It is increasing in frequency and is apparently related to the general prosperity of the population, being much less common in underdeveloped countries. The explanation for this might lie in differences in diet, in levels of activity, in longevity and in the number of surgical operations performed. Many thrombi are clinically 'silent'.

**Factors implicated in venous thrombosis (phlebothrombosis)**

1. Surgical operations. Thrombosis is common after operations.
   - (i) General effects, e.g. splenectomy
   - (ii) Local effects, e.g. gynaecological and hip operations
   - (iii) Loss of muscle 'pump' and direct pressure on veins during anaesthesia
   - (iv) Immobilisation, especially in orthopaedic cases
2. Congestive cardiac failure and myocardial infarction. These are associated with venous stasis and immobilisation
3. Age. Thrombosis increases with age
4. Pregnancy
   - (i) Hypercoaguable state
   - (ii) Pressure on pelvic veins by gravid uterus
5. Oral contraceptive pill - high oestrogen type
6. Obesity
7. Malignancy, e.g. carcinoma of pancreas, possibly related to production of thromboplastins by the tumour cells

**Location**

1. Deep veins of the calf
2. Iliofemoral segment by propagation from the calf or arising de novo
3. Multiple sites simultaneously
   - Most venous thrombi are thought to originate in or close to a valve pocket.

**Special varieties of venous thrombosis**

1. Thrombophlebitis - thrombosis secondary to inflammation of the vein wall
2. Thrombophlebitis migrans
   - (i) Recurrent thrombosis at different sites
   - (ii) Typically involves limb veins
   - (iii) Often associated with visceral malignancy (Trousseau's sign)
3. Phlegmasia alba dolens - 'painful white leg of pregnancy' thrombosis of the femoral and external iliac veins together with arterial spasm
4. Mondor's disease - localized phlebitis affecting subcutaneous veins of the abdominal or thoracic wall, especially around the breast

**ARTERIAL THROMBOSIS**

**Factors implicated in arterial thrombosis**

1. Damage to the endothelial lining, e.g. atherosclerosis, trauma
2. Micro-turbulence around irregular atheromatous plaques
3. Major disturbances of flow in aneurysms or due to sustained spasm
Types of thrombus
1. Occluding thrombus in medium and small arteries frequently in association with concentric atherosclerosis
2. Thrombosis occurring over part of the wall of a large artery or the aorta - mural thrombosis

CARDIAC THROMBOSIS
Factors implicated in intracardiac thrombosis
1. Endocardial damage resulting from
   (i) Underlying myocardial damage as in myocardial infarction
   (ii) Primary endocardial inflammation as in acute rheumatic fever
   (iii) Haemodynamic factors in chronic valvular disease with resultant mechanical injury
2. Disordered myocardial contraction, e.g. intra-atrial thrombosis resulting from atrial fibrillation
3. Turbulence, as in a ventricular aneurysm following myocardial infarction

Types of cardiac thrombosis
1. Valvular thrombosis

Thrombi composed of platelets, fibrin and variable numbers of red blood cells formed on the valve cusps are termed vegetations. They are found in:
   (i) Acute rheumatic fever. The vegetations (which are composed almost entirely of platelets) are small, compact, firm and rubbery
   (ii) Infective endocarditis. This condition affects valves previously damaged by rheumatic fever or congenitally abnormal valves, e.g. bicuspid aortic valve. The vegetations are large, friable, and contain the infective agent, e.g. bacterial 'colonies' or more rarely, rickettsia, fungi and yeasts
   (iii) Non-infective ('abacterial') thrombotic endocarditis. Known for many years as Lambi's excrescences, these sterile vegetations are found with increased frequency in patients with wasting diseases, particularly carcinomatosis. They are of variable size and may break off giving rise to cerebral infarction
   (iv) Verrucous endocarditis (Libman-Sacks) found in some cases of systemic lupus erythematosus

2. Mural thrombosis
Thrombosis adherent to part of the endocardial lining is found in:
   (i) Myocardial infarction which can result in inflammation of the endocardium and subsequent thrombosis
   (ii) Rheumatic fever, MacCallum's patch in the left atrium resulting from mitral regurgitation
   (iii) Acute myocarditis

3. Ball thrombus
A detached, ovoid or spherical thrombus may be formed in the atria in atrial fibrillation. This can impact in the mitral ring and produce a syncopel attack or even sudden death. More commonly, atrial fibrillation is associated with thrombosis in the atrial appendage or a polypoid thrombus attached to the wall.
1. Resolution
The thrombus may be completely removed by a combination of
(i) Shrinkage by a process analogous to clot-retraction in vitro
(ii) Platelet autolysis
(iii) Fibrinolysis brought about by:
   a. Binding of the circulating proenzyme plasminogen and plasminogen activator (released by vascular endothelium) to fibrin
   b. Generation of plasmin, a powerful proteolytic enzyme which if not bound to fibrin is inactivated by plasma (α-2-antiplasmin
   c. Degradation of fibrin by plasmin with release of fibrinopeptides (fibrin degradation products) into the circulation
(iv) Phagocytosis by macrophages which infiltrate the thrombus

2. Organisation
   Ingrowth of endothelial cells, fibroblasts and smooth muscle cells convert the thrombus into fibrovascular tissue rich in collagen and elastin fibres.
   (i) In occluding thrombi continuity of newly-formed vascular channels may be established and their subsequent dilatation lead to partial restoration of blood flow - a process known as re-canalisation
   (ii) In mural thrombi the surface becomes re-endothelialised and the organised thrombus eventually becomes a fibrous plaque which may be indistinguishable from an atherosclerotic lesion

3. Detachment
   A portion of a friable or loosely attached thrombus may break off into the circulation forming an embolus.

EMBOLISM

Embolism is the impaction in part of the vascular system of any abnormal undissolved material carried there by the blood stream. The recognized types are:
1. Thrombi
2. Fat emboli
3. Gaseous embolism
4. Tumour fragments
5. Infective agents
6. Atheromatous material
7. Amniotic fluid
8. Foreign bodies

1. Thrombi
   These are by far the commonest type. The detached thrombus may be of venous, arterial, or cardiac origin.
   Venous thrombosis in the leg or pelvic veins may lead to embolism to the pulmonary arteries. The possible results are:
   (i) Sudden death after obstruction by major embolism. Death results from
      a. Systemic anoxia
      b. Acute right ventricular failure
      c. ? Liberation of 5-HT causing spasm of the pulmonary arterial system
      d. ? Reflex vagal inhibition
   (ii) Ischaemic necrosis of lung tissue - infarction. In the lung, infarcts are
haemorrhagic because of the dual blood supply (via pulmonary and bronchial arteries)

(iii) Progressive obliterative pulmonary hypertension from multiple microemboli
(iv) Splits in the wall and aneurysms in the proximal pulmonary artery following acute stretching

Arterial and cardiac thrombosis The main sites are:
(i) Mural thrombus in the left ventricle
(ii) Thrombus on atheromatous lesions in the aorta and major branches
(iii) Vegetations on valves
(iv) Atrial thrombus Detachment results in:
(i) Lodgement in end-arteries, e.g. in brain, kidneys, spleen, retina, etc.
(ii) Arterial occlusion leading to gangrene of the intestine or limbs
(iii) Large embolism lodging across the aortic bifurcation I saddle' embolus, producing ischaemic changes in the lower limbs

2. Fat embolism
Is the impaction of large fat globules in small arteries and capillaries. It differs from thromboembolism in that the globules are fluid and deformable and so occlusion may be temporary or incomplete.

Causes of fat embolism
(i) Fracture of long bones is the major cause
(ii) Operative manipulation of fractures, e.g. in arthroplasty
(iii) Trauma to adipose tissue (rare)
(iv) Trauma to a fatty liver (very rare)

Sites and effects
(i) Pulmonary fat embolism
   a. Minor degrees probably have little significance
   b. More marked embolism is associated with hypoxaemia which may result from shunting of blood through pre-capillary anastomoses. Such shunting can also give rise to systemic embolism
(ii) Systemic fat embolism is never found in the absence of pulmonary embolism. The most important site for impaction is the cerebral vasculature. This produces multiple small haemorrhagic and ischaemic lesions particularly in the white matter which may lead to coma and death. Multiple petechiae may be found in the skin.

Origin of fat emboli
(i) Disruption of fat cells releases globules of fat into the marrow veins, which then pass to the lungs
(ii) Large fat globules form by fusion of chylomicrons under the influence of platelet factors released following trauma

3. Gaseous embolism Causes
(i) Mismanaged intravenous infusions, especially with infusion pumps
(ii) Operations in which large veins are opened
(iii) Air injections for radiological techniques
(iv) Insufflation of the Fallopian tubes
(v) Criminal abortion
(vi) Caisson disease or decompression sickness (nitrogen bubbles forming as a consequence of rapid decompression)

Effects
(i) Sudden death as a result of a large volume of air reaching the right ventricle and preventing the propulsion of blood into the pulmonary artery
(ii) Sudden decompression leads to tissue damage by bubble formation especially in the CNS ('divers's bends') and aseptic necrosis of bone resulting in osteoarthrosis

4. Tumour fragments
Vascular invasion is a common finding in malignant neoplasms, and clumps of tumour cells may detach and impact at some distant site. Whilst this may be a source of secondary tumours such embolism is rarely large enough to produce ischaemic damage. An exception is renal carcinoma where growth into the renal vein may give rise to relatively large tumour emboli.

5. Infective agents
(i) Bacterial clusters, e.g. from infective endocarditis giving rise to pyaemic abscesses or 'mycotic' aneurysms
(ii) Parasites, e.g. clumps of plasmodia in cerebral malaria

6. Cholesterol embolism
Rupture of the thin fibrous cap over a soft atherosclerotic plaque may lead to release of granular lipidic debris into the artery. Many cases arise following medical interventions, such as aortic surgery, aortography, cardiac catheterisation and angioplasty, but spontaneous emboli can occur in patients with severe aortic atheroma. Depending upon the site of origin and size, such embolism can give rise to:
(i) Myocardial infarction or multifocal necrosis (coronary arteries)
(ii) Livedo reticularis in skin of the lower limbs
(iii) Splinter haemorrhages of the nails
(iv) Cerebral or spinal cord infarction
(v) Multifocal renal infarction
(vi) Acute pancreatitis
(vii) Intestinal infarcts or strictures

7. Amniotic fluid
Fluid may be driven through the placental bed into the maternal circulation during labour, particularly where there is obstruction.

Effects
(i) Acute respiratory distress and shock which may be fatal
(ii) Disseminated intravascular coagulation produced by thromboplastins in the fluid
(iii) Afibrinogenaeemia following plasmin activation
8. Foreign bodies

This is rare, but an important example is embolism of Polythene catheters used in intravenous infusions which may break off and lodge in the heart.

Paradoxical embolism

Is defined as the passage of an embolism from the right to the left side of the heart through a septal defect (with a right to left shunt) resulting in systemic arterial embolism from a venous source.

INfarction

An infarct is an area of tissue necrosis resulting from ischaemia (deprivation of blood supply). Infarcts therefore arise from arterial occlusion by either thrombosis, embolism, or as a complication of atherosclerosis. Whether or not an infarct follows arterial blockage depends upon:

1. The size of artery occluded - occlusion of a single small vessel may not give rise to tissue necrosis
2. The collateral circulation - organs with a dual blood supply (e.g. liver) rarely suffer infarction
3. The general state of the circulation - when the circulation is already impaired as a result of congestive cardiac failure, the effects of arterial occlusion may be exacerbated. For example, although the lungs have a dual blood supply (pulmonary and bronchial arteries), occlusion of a pulmonary artery in a patient with chronic venous congestion will lead to infarction.

Major sites

The major sites of infarction are:

1. Myocardium - resulting from atherosclerosis and its complications in the coronary arteries
2. Brain - resulting from
   (i) Systemic embolism by
      a. Detached thrombus from the left side of the heart
      b. Vegetations from the aortic or mitral valves
   (ii) In situ thrombosis Of a cerebral artery
3. Lungs - resulting from impaction in the pulmonary arterial tree of a thrombo-embolus formed in the leg or pelvic veins
4. Kidneys, spleen, or intestines - resulting from systemic thromboembolism or from atherosclerosis and its complications in the supplying arteries

Events in an infarct

1. Necrosis, which may be:
   (i) Coagulative in a solid organ such as the heart, kidney, or spleen
   (ii) Colliquative in the brain
   (iii) Haemorrhagic in the lung
2. An inflammatory response provoked by tissue breakdown products such as membrane fragments, denatured proteins, released enzymes, etc. This is manifest as a surrounding rim of hyperaemia and neutrophil polymorph infiltration
3. Demolition of dead tissue by macrophages
4. Organisation - ingrowth of fibroblasts and endothelial cells
5. Scar formation. Even in organs capable of regeneration, this is always very limited after infarction, and a fibrous scar is the usual end result.

Gangrene
This is a special form of infarction where the dead tissue is infected with putrefactive organisms.

Varieties:
1. 'Dry gangrene' - a term usually applied to ischaemic necrosis in a limb. To be precise, this should not be referred to as gangrene as it is not super-infected with putrefactive organisms; the proper term is 'mummification' but this is rarely used.
2. 'Wet' gangrene - this is where there is super-infection, e.g. in infarcts of the intestine.
3. Gas-gangrene - where the putrefactive organisms produce gas which collects as 'bubbles' in the affected tissues. The organisms are almost always of a clostridia species.

16. Congenital and inherited disorders

DEFINITIONS

A *congenital* disease or abnormality is one present from birth which may or may not be genetic.

An *inherited* disease results from genetic factors but may not become apparent until adulthood.

A *genetic disorder* can be either inherited or mutational.

*Congenital malformations* are primary defects in body structure resulting from an error in morphogenesis. They are to be distinguished from *deformations* which are alterations in shape and/or structure of a previously normally formed part, e.g. congenital torticollis, congenital postural scoliosis, talipes (deformities of the feet), etc.

GENETIC DISORDERS

A. Chromosome abnormalities

1. *Non-disjunction* - failure of a chromosome pair to separate during the formation of gametes by meiosis means that one gamete receives both chromosomes and the other none
2. *Translocation* - also occurs during meiosis when one of a chromosome pair (or part of a chromosome) fuses to another to form a large composite chromosome
3. *Deletion* - loss of the whole, or part, of a chromosome during meiosis

In addition, non-disjunction and deletion can occur during the early mitotic divisions after fertilisation and give rise to *mosaics*, individuals possessing two or more
populations of cells having a different chromosomal make-up. Chromosome abnormalities may affect both the sex chromosomes and the *autosomes*, although absence of an autosome is almost always lethal.

**Sex chromosome abnormalities**

These are almost invariably the result of non-disjunction and include:

1. Klinefelter's syndrome - XXY
   (i) Testicular hypoplasia
   (ii) Sterility
   (iii) Mental subnormality

   There are clinically similar cases who prove to be 46XY. Here the abnormalities result from a primary failure of germ-cell development.

2. 'Super-male'- XYY Tall, aggressive males who may show:
   (i) Sexual maldevelopment
   (ii) Skeletal disorders
   (iii) Myopia
   (iv) Marfan's syndrome

3. 'Super-female'- XXX Females showing some loss of intelligence and infertility.

4. Turner's syndrome - XO
   (i) Dwarfism
   (ii) Sexual infantism
   (iii) Increased carrying angle of lower arms
   (iv) Webbed neck
   (v) Broad chest with widely spaced nipples
   (vi) Streaked gonads in position of ovaries
   (vii) Coarctation of the aorta

**B. Gene abnormalities**

   (i) Multigene deletion
   (ii) Single gene deletion
   (iii) Exon deletion
   (iv) Within exon deletion
   (v) Frame shift deletion (i.e. 3 base deletion)
   (vi) Base pair mutation
   (vii) Splice site mutation/deletion
   (viii) Promotor mutation/deletion
   (ix) Termination codon mutation/deletion
   (x) Poly A signal mutation/deletion
   (xi) Expansion of a tandem short repetitive sequence (e.g. trinucleotides)

Altered genes can be transmitted through families according to Mendelian laws. Three main patterns of inheritance are recognized:

1. Dominant
2. Recessive
3. Intermediate

In addition the mutant gene may be sited on the X or Y chromosome in which case its inheritance is sex-linked.

**Dominant inheritance**

Every individual who carries a dominant abnormal gene will suffer from the disease. Nearly all affected individuals are heterozygous.
Examples include:
1. Achondroplasia
2. Brachydactyly
3. Hyperelastosis cutis (Ehlers-Danlos syndrome)
4. Marfan's syndrome
5. Familial adenomatous polyposis
6. Spherocytosis
7. Huntington's chorea

*Recessive inheritance*
Here the genetic abnormality is only expressed when the individual is homozygous (that is both alleles are affected). Autosomal recessive diseases are usually caused by abnormalities in genes coding for enzymes or tumour suppressor genes. The presence of abnormal enzymes, or deficiencies of normal enzymes, gives rise to the so-called 'inborn errors of metabolism'. Recessive diseases include:
1. Cystic fibrosis
2. Wilson's disease (hepato-lenticular degeneration)
3. Retinitis pigmentosa
4. Werdnig-Hoffmann disease (progressive spinal muscular atrophy of infants)

*Intermediate inheritance*
In this situation the possession of a single recessive mutant gene leads to detectable abnormalities but less severe than in homozygotes.
Examples include:
1. Sickle-cell trait
2. Thalassaemia minor
3. Carriers of the phenylketonuria gene

*Sex-linked inheritance*
This can be either dominant or recessive

1. X chromosome
   (i) Haemophilia
   (ii) Christmas disease
   (iii) Colour blindness
   (iv) Chronic granulomatous disease
   (v) Muscular dystrophy (Duchenne type)
   (vi) Glucose-6-phosphate deficiency
2. Y chromosome, e.g hairy ears

Examples of inherited conditions where the type of genetic lesion is known:
1. Point mutation
   (i) Cystic fibrosis (CFTR)
   (ii) Glucose-6-phosphate dehydrogenase deficiency (G-6-P D)
   (iii) Alpha-l-antitrypsin deficiency (alpha-l-antitrypsin)
   (iv) Marfan syndrome (fibrillin)
   (v) Beta thalassaemia (beta globin)
   (vi) Retinitis pigmentosa (rhodopsin)
   (vii) Familial adenomatous polyposis (apc)
2. Frame shift deletion
   (i) delta 508 deletion in cystic fibrosis (CFTR)
(ii) Beta thalassaemia (beta globin)
(iii) Haemophilia A and B (factor VIII and IX deficiency)

3. Exon or gene deletions
(i) Duchenne muscular dystrophy (dystrophin)
(ii) Lesch-Nyhan syndrome (HGPT)
(iii) Retinoblastoma (rb)
(iv) Wilm's tumour (Wt)
(v) beta thalassaemia (beta globin)
(vi) Haemophilia A and B (factor VIII and IX)

4. Expansion of a short tandem repetitive sequence
(i) Myotonic dystrophy
(ii) Fragile X syndrome
(iii) X linked spinal bulbar atrophy

C. Polygenic abnormalities
Many congenital abnormalities and major diseases such as cardiovascular disease cannot be explained on the basis of single gene inheritance. It is assumed that these defects and diseases arise by virtue of the additive effect of multiple genes. For example genes that have been implicated in atherosclerosis:

1. Low density lipoprotein gene (mutated in familial hypercholesterolemia)
2. Apoprotein B-100 (mutated in familial defective apolipoprotein B-100)
3. Apoprotein C11 lipoprotein lipase (defective in lipoprotein lipase deficiency)
4. Apoprotein's A1, CIII and AIV (increased allele frequency in cardiovascular disease)
5. Fibrinogen (increased frequency of the beta allele)
6. Other genetic defects might be found in:
   (i) Lipoprotein or cholesterol metabolism
   (ii) Blood clotting and fibrinolysis
   (iii) Macrophage function
   (iv) Smooth muscle cell proliferation

ENVIRONMENTAL FACTORS IN CONGENITAL DISEASE

1. Nutritional disturbances
Experimental studies have demonstrated the importance of essential vitamins (vitamin A, riboflavin, folic acid) but clinical proof is lacking
2. Maternal infection
   (i) Rubella
   (ii) Cytomegalovirus
   (iii) Toxoplasmosis
      Malformations have also been described after influenza, measles, mumps, polio, echo and coxsackie infections. These are all rare associations and a causal relationship has not been proven.
3. Hormonal agents
   (i) Masculinisation of females has resulted from administration of androgens or progesterone in early pregnancy, or as a result of congenital adrenal hyperplasia
   (ii) Insulin used in treatment of maternal diabetes may lead to malformation (?)
   (iii) Hypoplasia of the adrenals results from pituitary deficiency in anencephaly
4. Drugs
(i) Thalidomide (limb defects)
(ii) Anti-metabolites
(iii) Other commonly used drugs, e.g. salicylates, sulphonamides, and streptomycin, have had teratogenic effects in animals, but evidence in humans is lacking

5. Mechanical factors
Compression of the fetus is important in producing deformations, and may exaggerate deformities associated with malformations, e.g. in congenital dislocation of the hip

6. Irradiation
7. Hypoxia - may lead to cardiac malformations in children born at high altitudes
8. Disordered circulation in the embryo

9. Maternal age and birth rank
(i) Mongolism
(ii) Hydrocephalus
(iii) Achondroplasia
(iv) Anencephaly
Are more frequent with increasing maternal age

10. Paternal age has an effect on some dominant mutations, e.g. achondroplasia
11. Multiple births

CONGENITAL MALFORMATIONS

Major congenital malformations are found in about 2.5% of total births, and of these neural tube defects such as spina bifida and anencephaly, and congenital heart disease account for about two-thirds. The most important malformations are:

1. Limbs
   (i) Congenital dislocation of the hip
   (ii) Bowing of the tibia
   (iii) Talipes equinovarus (club foot)
   (iv) Congenital elevation of the shoulder (Sprengel's shoulder)
   (v) Radio-ulnar synostosis
   (vi) Syndactyly/brachydactyly

2. Alimentary tract
   (i) Cleft lip and palate
   (ii) Microstomia and macrostomia
   (iii) Atresia of the oesophagus
   (iv) Diaphragmatic hernia
   (v) Congenital pyloric stenosis
   (vi) Atresia of the intestine
   (vii) Duplication
   (viii) Hirschsprung's disease
   (ix) Imperforate anus

3. Cardiovascular system
   (i) Septal defects
      a. Atrial
      b. Ventricular
(ii) Stenosis
   a. Aortic
   b. Pulmonary
   c. Infundibular (RV)
(iii) Coarctation of the aorta
(iv) Persistent ductus arteriosus
(v) Fallot's tetralogy
(vi) Transposition of the great vessels

4. **Central nervous system**
   (i) Hydrocephalus
   (ii) Anencephalus
   (iii) Meningocele/myelocele

5. **Genito-Urinary system**
   (i) Kidneys
      a. Agenesis
      b. Hypoplasia
      c. Cystic diseases
   (ii) Bladder
      a. Ectopia vesicae
      b. Persistent urachus
   (iii) Testes
      a. Absence
      b. Undescended
   (iv) Penis Hypospadias
   (v) Uterus
      a. Double
      b. Septate
      c. Bicornuate

**INBORN ERRORS OF METABOLISM**

When a genetic error results in the formation of an abnormal protein, and this protein is an enzyme, the resultant biochemical defect may become manifest through the accumulation of some precursor or substrate which brings about a disease syndrome. Such diseases, usually inherited as Mendelian recessives, are termed inborn errors of metabolism. They can be grouped into four main categories involving:

A. Errors of carbohydrate metabolism
B. Errors of amino-acid metabolism
C. Errors of lysosomal function
D. Errors of steroid metabolism
E. Errors of porphyria metabolism
F. 

A. **Errors of carbohydrate metabolism**
   1. Galactosaemia (deficiency of galactose-1-phosphate uridyl transferase)
   2. Glycogen storage diseases include:
      (i) von Gierke's (glucose-6-phosphatase)
      (ii) Pompe's (a-1,4,6 glucosidase)
      (iii) Limit dextrinosis (amylo-1, 6-glucosidase (debrancher))
      (iv) IV (amylo-1, 4-1, 6-transgiucosidase [brancher])
(v) V McArdle's (muscle phosphorylase)  
(vi) VI (liver phosphorylase)  
(vii) VII (glycogen synthetase)  
3. Fructose intolerance (fructose-l-phosphate aldolase)

B. Errors of amino-acid metabolism
1. Phenylketonuria (phenylalanine hydroxylase deficiency resulting in accumulation of phenylalanine)  
2. Tyrosinosis (p-hydroxyphenylpyruvic acid oxidase deficiency resulting in accumulation of phenylalanine and tyrosine).  
3. Alkaptonuria (homogentisic acid oxidase deficiency)  
4. Maple syrup urine disease (branched-chain ketoacid decarboxylase deficiency resulting in accumulation of a-ketoacids)  
5. Homocystinuria (cystathione synthetase)

C. Errors of lysosomal function
1. Accumulation of sphingolipids  
   (i) Tay Sachs' (hexosaminidase A)  
   (ii) Generalized gangliosidosis (b-galactosidase)  
   (iii) Krabbe's (b-galactosidase)  
   (iv) Gaucher's (b-glucosidase)  
   (v) Niemann-Pick's ( sphingomyelinase)  
   (vi) Metachromatic leucodystrophy (sulphatidase)  
   (vii) Anderson-Fabry's (ceramide trihexosidase)  
2. Accumulation of neutral lipids  
   (i) Wolman's (acid esterase)  
   (ii) Cholesterol ester (?)  
   (iii) Cerebro-tendinous xanthomatosis  
3. Accumulation of glycosaminoglycans (mucopolysaccharidoses)  
   (i) IH - Hurler (a-L-iduronidase)  
   (ii) IS - Scheie ((a-L-iduronidase)  
   (iii) II - Hunter (L-iduronosulphate sulphatase)  
   (iv) IIIA - Sanfilippo (heparan sulphate sulphamidase)  
   (v) IIIB - Sanfilippo (a-N-acetylglucosaminidase)  
   (vi) IV - Morquio (N-acetyl hexosamine)  
   (vii) VI - Maroteaux-Lamy (aryl sulphatase-B)  
4. Accumulation of mucolipids  
   (i) Mucolipidosis types I-IV  
   (ii) Fucosidosis  
   (iii) Mannosidosis  
5. Accumulation of other compounds  
   (i) Refsum's disease (phytanic acid)  
   (ii) Cystinosis - Lignac-Fanconi (?)  
   (iii) Pompe's disease (lysosomal-a-glucosidase)
6. Other lysosomal enzyme disorders
   (i) Hyperphosphatasia
   (ii) Hypophosphatasia
   (iii) Acid phosphatase deficiency
   (iv) Ceroid-lipofuscinosis

D. Errors of steroid metabolism
Resulting in congenital adrenal hyperplasia
The principal defects are:
   1. 21-Hydroxylase deficiency
   2. 11-Hydroxylase deficiency
Other enzymes may be involved, these are:
   3. 17-Hydroxylase
   4. 3-b-Hydroxysteroid dehydrogenase
   5. Desmolase

17. Neoplasia

Neoplasia means 'new growth'.

Psychoneuroimmunology: Stress Reduction To Prevent Cancer Recurrence

After the surgical removal of a malignant tumor, the chance that cancer will re-appear in a different location of the body remains high. But new research from Tel Aviv University, in a bold new field called Psychoneuroimmunology, may prevent those cancer cells from taking root again - and the key to the treatment is stress reduction.

A new study led by Prof. Shamgar Ben-Eliyahu, from Tel Aviv University's Department of Psychology, has shown scientifically that psychological and physiological stress prior to, during and after surgery has a biological impact that impairs immune system functioning. This impairment bears down on disease progression, he says, especially at the critical point during oncological surgery when a primary tumor is being removed.

The study was published in the journal Brain, Behaviour, and Immunity (2007). The results are expected to influence cancer intervention programs in the future.

Effects of Fear

"The psychological stressors of surgery deal a blow to the immune system, but this is hardly discussed in the medical community," says Prof. Ben-Eliyahu. "Ours is among the first studies to show that psychological fear may be no less important than real physiological tissue damage in suppressing immune competence."

The surprising part of Prof. Ben-Eliyahu's studies is that stress hormones such as adrenaline, which are released before and during surgery, "underlie much of the devastating effects of surgery on immune competence," says Prof. Ben-Eliyahu.
Until now, doctors assumed that the immune system was weakened due to tissue damage and the body’s responses to it. A weak immune system is one of the major factors that promotes cancer metastases after an operation, explains Prof. Ben-Eliyahu.

"Timing is everything after cancer surgery," says Prof. Ben-Eliyahu. "There is a short window of opportunity, about a week after surgery, when the immune system needs to be functioning maximally in order kill the tiny remaining bits of tumor tissue that are scattered around the body."

### An Early Boost

The main stress hormones that appear to have an impact on immune competence are released before and during surgery, Prof. Ben-Eliyahu has found. He is currently developing a novel intervention program, based on existing generic drugs, to block the influence of these hormones.

Pre-clinical studies in a 2005 study also published in *Brain, Behaviour, and Immunity* reveal that by blocking these stress hormones, cancer metastases in animal models could be reduced. In a recent study (in progress), Prof. Ben-Eliyahu also found that by blocking these hormones, he could increase long-term post-operative survival rates from cancer in animal models, by as much as 200-300 percent.

Prof. Ben-Eliyahu and his students are now also trying to integrate stimulation of the immune system just before surgery and prevent its suppression. This may provide the immune system with an opportunity to eradicate cancer residuals after the surgical removal of the primary tumor, and before these residuals are re-established and become resistant to immunity, he says.

Prof. Ben-Eliyahu concludes, "By boosting the immune system and blocking its suppression by psychological and physiological stress, starting a day or two before surgery, during surgery and after surgery, we may be able to provide an intervention program that can extend people's lives and potentially increase their chances for long-term survival."

He plans on starting clinical trials within the next year or two.

Prof. Ben-Eliyahu is one of about 200 other scientists working in the novel and emerging field of Psychoneuroimmunology. It is an interdisciplinary study of the interaction between the psychological processes of the brain, and the nervous and immune systems of the human body. In this field, Prof. Ben-Eliyahu collaborates regularly with Prof. Gayle Page from the Johns Hopkins School of Nursing and other scientists from the United States and Israel. His work is supported by the U.S. National Institute of Health. In May, he plans on attending the Psychoneuroimmunology Research Society conference in Madison, Wisconsin.

*Article adapted by Medical News Today from original press release.*
CLASSIFICATION OF TUMOURS

Tumours are currently classified according to their behaviour and tissue of origin. On the basis of their behaviour they can be separated into two main groups, benign and malignant. The malignant tumours can then be separated into primary or secondary (metastatic) tumours. The principal points of distinction between the two groups are:

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of growth</strong></td>
<td>Expansive/pushing</td>
<td>Infiltrative</td>
</tr>
<tr>
<td></td>
<td>Circumscribed</td>
<td>Poorly-defined margins</td>
</tr>
<tr>
<td></td>
<td>Encapsulated</td>
<td>Non encapsulated</td>
</tr>
<tr>
<td><strong>Rate of growth</strong></td>
<td>Slow and may cease</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Microscopic structure</strong></td>
<td>Well-differentiated (i.e. closely resembles tissue of origin)</td>
<td>Varying degrees of differentiation</td>
</tr>
<tr>
<td></td>
<td>Cells - regular</td>
<td>Cellular and nuclear pleomorphism (variation in size and shape)</td>
</tr>
<tr>
<td></td>
<td>Absent or scanty mitotic figures</td>
<td>Increased mitoses</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Clinical effects</strong></td>
<td>Mechanical or hormonal</td>
<td>Mechanical, hormonal, systemic effects</td>
</tr>
<tr>
<td>destructive,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Outcome</strong></td>
<td>Rarely fatal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually fatal</td>
</tr>
</tbody>
</table>

These are general points to which there are many exceptions. Some tumours exhibit an intermediate type of behaviour and cannot be allocated to either category, e.g. giant-cell tumour of bone. Benign tumours usually end with the suffix -oma. Malignant epithelial tumours are usually called -carcinoma and malignant tumours derived from mesoderm -sarcoma. Teratomas are derived from germ cells and tumours arising from fetal tissues or their remnants -blastomas. There are exceptions to most of these rules, for example hamartomas are not tumours, seminomas and lymphomas are both malignant, so whilst these rules are helpful, caution is required in the use of terminology.

<table>
<thead>
<tr>
<th><strong>Tissue of origin</strong></th>
<th><strong>Benign</strong></th>
<th><strong>Malignant</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>squamous</td>
<td>Papilloma</td>
<td>Squamous</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glandular</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>


transitional cell carcinoma

Connective tissue
Fibrous tissue
Fat
Bone (osteogenic)
Cartilage
Smooth muscle
Striated muscle
Blood vessels
Lymphoid tissue
lymphoma
Nervous system

Trophoblast
Germ Cells

Embryonic tissues

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Benign Tissue</th>
<th>Malignant Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone (osteogenic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartilage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striated muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trophoblast</td>
<td>Hydatidiform mole</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Germ Cells</td>
<td>Benign teratoma</td>
<td>Malignant teratoma</td>
</tr>
<tr>
<td>Embryonic tissues</td>
<td>Nephroblastoma</td>
<td>Neuroblastoma (sympathetic nerve)</td>
</tr>
</tbody>
</table>

Teratoma
A teratoma is 'a true tumour composed of multiple tissues foreign to the part in which it arises' (Willis).
Teratomas originate by neoplastic change in germ cells (which in some cases may have been arrested in their migration from the yolk sac wall).

Sites
1. Ovary (usually benign)
2. Testis (usually malignant)
3. Anterior mediastinum
4. Presacral
5. Retroperitoneal
6. Intrapericardial
7. Base of skull and nasopharynx
8. Intracranial, including pineal
9. Neck - usually within the thyroid gland

NON NEOPLASTIC CONDITIONS OFTEN CONFUSED WITH TUMOURS

Hamartoma
A hamartoma is a tumour-like malformation composed of a haphazard arrangement of mature tissues appropriate to the particular part of the body in which it is found.
The distinction between a hamartoma and a benign tumour can be very difficult, and very occasionally malignant tumours develop from such malformations.

Examples
1. **Respiratory system**
   (i) Pulmonary hamartoma composed principally of mature cartilage but including columnar or cuboidal epithelium and fibrous tissue
2. **Intestine**
   e.g. Peutz-Jeghers' polyps in the small intestine associated with circumoral pigmentation
3. **Multi-system involvement** e.g. Tuberous sclerosis
   (i) Skin papules - adenoma sebaceum,
   (ii) Angiolipomyoma in the kidney. (These can also occur without tuberous sclerosis.)

**Choristoma**
A choristoma is composed of normal tissue at an abnormal site, e.g. ectopic pancreas in the small intestine or stomach or adrenal cells under the capsule of the kidney. They are not neoplasms but can rarely give rise to tumours.

**COMPLICATIONS OF BENIGN TUMOURS**
1. Pressure effects
   (i) Meningioma compressing brain or spinal cord
   (ii) Uterine leiomyoma (fibroid) compressing endometrium
2. Obstruction
   (i) Bronchial obstruction due to an adenoma
   (ii) Blockage of the mitral valve by an atrial myxoma
   (iii) CSF obstruction by an ependymoma
3. Ulceration and haemorrhage
   (i) Leiomyoma of the stomach wall
   (ii) Adenoma of the colon
4. Infarction, e.g. pedunculated leiomyoma
5. Rupture of cystic neoplasms, e.g. mucin-secreting cystadenoma of the ovary producing myxoma peritonei
6. Hormone production
   (i) Islet-cell tumour of the pancreas producing insulin or glucagon
   (ii) Phaeochromocytoma
   (iii) Adrenal cortical adenoma giving rise to
      a. Cushing's syndrome
      b. Conn's syndrome
   (iv) Pituitary adenoma
      a. Acromegaly
      b. Cushing's syndrome
   (v) Parathyroid adenoma
7. Malignant change
   e.g. Adenomas of large intestine giving rise to adenocarcinoma, as occurs in sporadic adenomas and in familial adenomatous polyposis
COMPLICATIONS OF MALIGNANT TUMOURS

1. Invasion
   (i) Direct spread within the organ of origin, e.g. squamous carcinoma of the lung or hepatocellular carcinoma in the liver
   (ii) Spread to adjacent organ(s), e.g. adenocarcinoma of the pancreas invading duodenum, stomach or colon
   (iii) Invasion through the peritoneal or pleural surface, e.g. adenocarcinoma of the stomach or lung

2. Metastasis
   (i) Carcinomas usually spread by lymphatic invasion and involvement of lymph nodes but also by vascular spread, e.g. squamous carcinoma of the lung invading regional lymph nodes with subsequent haematogenous spread to liver, bone and brain
   (ii) Sarcomas usually spread by vascular invasion, e.g. osteosarcoma spreading to the lung
   (iii) Lymphomas usually spread by vascular and lymphatic routes initially within the immune system

3. Obstruction
   (i) Stenosis of a hollow visceral structure, e.g. colon, bile duct, ureter by primary or secondary tumour
   (ii) Obstruction of lymphatic channels, e.g. peau d'orange of the breast caused by blockage of lymphatic channels by adenocarcinoma of the breast

4. Ulceration and haemorrhage
   (i) Ulceration of a mucosal surface by a primary or secondary tumour, e.g. adenocarcinoma of the colon or squamous carcinoma of the skin or adenocarcinoma of the prostate invading into the rectum
   (ii) Haemorrhage into a tumour, e.g. renal cell adenocarcinoma

5. Infarction

6. Rupture or perforation
   (i) Cystadenocarcinoma of the ovary causing myxoma peritonei
   (ii) Teratoma of the ovary rupturing into the peritoneum
   (iii) Perforation of carcinoma of the colon

7. Hormone production
   (i) Carcinoma of the lung producing
      a. ADH
      b. Parathyroid hormone related peptide (PTH-rp)
      c. ACTH
   (ii) Malignant islet cell tumours
      a. Glucagon
      b. Insulin
   (iii) Malignant carcinoid tumours
      a. Serotonin
      b. 5-Hydroxy indole acetic acid
   (iv) Renal cell adenocarcinoma
      a. Erythropoietin
      b. Parathyroid hormone related protein
GROWTH AND SPREAD OF TUMOURS

The most important characteristics of tumours are their capacity for:
A. Uncoordinated growth
B. Invasion
C. Metastasis

A. Tumour growth
This is the result of:
1. The rate of entry and time spent in the cell cycle
2. Death of cells by:
   (i) Apoptosis
   (ii) Necrosis

In normal tissues the level of mitotic activity (i.e. the cell birth rate) is equal to the rate of cell loss so that the total number of cells is more or less constant. Where injury leads to cell loss in excess of the cell birth rate then atrophy or tissue damage such as ulceration will result. In neoplasia, the cell birth rate exceeds cell loss so that there is progressive accumulation of tumour cells. In some tumours, the cell birth rate although exceeding cell loss, may be lower than the prevailing level of mitosis in the surrounding tissue of origin, and this may explain the poor response of such tumours to radio- or chemotherapy. Tumour growth progresses in two ways:
1. *Expansive growth*. Purely expansive growth is a feature of many benign tumours and produces a circumscribed, encapsulated neoplasm, e.g. fibroadenoma of the breast
2. *Infiltrative growth* is usually a reflection of invasion and can be recognized around the margins of a malignant tumour.

B. Invasion
Direct spread of tumour in continuity occurs along the following:
1. Microscopic tissue spaces (interstitial spread)
2. Lymphatics - permeation as a continuous cord of tumour cells
3. Veins and capillary blood vessels, e.g. renal cell adenocarcinoma along the renal vein
4. Coelomic cavities, e.g. pleural spread of lung cancer or peritoneal spread of colonic adenocarcinoma
5. Cerebrospinal spaces, e.g. malignant gliomas
6. Epithelial cavities, e.g. uterine tumours spreading along the Fallopian tubes or into the cervix

The mechanisms underlying the invasive properties of malignant cells are not known but invasion can be blocked if protein synthesis is inhibited indicating that invasion is an active process. The following factors have been suggested as possible explanations.
1. *Increased motility, loss of adhesiveness, and loss of substrate dependence*
   (i) Loss or down-regulation of laminin or collagen receptors and cell adhesion molecule abnormalities
   (ii) Increased production of autocrine motility factors
2. *Loss of contact and density inhibition*
   The failure of malignant cells to show the normal inhibition of mitosis and movement on contact may be due to:
(i) Loss of responsiveness to inhibitory cytokines
(ii) Defects in trans-membrane communication

3. Fibrin production

Fibrin is deposited around the growing margins of many tumours. The organisation of this deposit may lead to the formation of blood vessels, lymphatics and stroma, bringing nutrition to the tumour and encouraging its growth. On the other hand, the fibrin deposit may be a host reaction tending to limit the growth of the tumour. Its role in tumour spread is therefore doubtful.

4. Enzyme production

Although mention has been made of 'microscopic tissue spaces' and 'lines of cleavage' as routes of invasion, in reality these are filled by a relatively dense interstitial matrix composed of collagen (Types I and III), glycoproteins, and acid mucopolysaccharides (proteoglycans). This matrix forms a dense meshwork which does not normally allow the passage of cells. Furthermore, invasive cells of epithelial origin must first traverse a dense basement membrane composed of Type IV collagen.

It has now been shown that many tumours secrete collagenases capable of digesting the interstitial matrix together with a distinctive metalloproteinase which degrades basement membrane collagen. Such destruction of the extracellular matrix by proteolytic enzymes is believed to facilitate invasion. Elastase is also secreted by some tumour cells. In addition, production of plasminogen activator by tumour cells and the subsequent formation of plasmin might be important in:

   (i) Removing fibrin from around the advancing tumour margin
   (ii) Releasing pro-collagenases from the cell membrane
   (iii) Increasing vascular permeability for tumour cells

Inhibitor proteins from the surrounding tissues or the tumour cells can block metalloproteinase activity. Such factors include tissue inhibitors of metalloproteinases (TIMPS) and plasminogen activator inhibitors (PAIs). Loss of these genes may facilitate invasion.

C. Metastasis

Denotes successful growth of tumour in the body at a site distant from its primary location.

The metastatic potential of a tumour is dependent on:

1. The site, histological type and grade of tumour
2. Access of the tumour to lymphatic, vascular and other tissue/organ spaces and their drainage
3. Specific properties of the tumour cells as well as those of the site of the metastasis

Detached tumour cells take the following paths:

1. Lymphatics
2. Blood vessels
3. Coelomic spaces
4. Cerebrospinal spaces
5. Epithelial cavities
1. **Lymphatic spread**

This is most commonly associated with carcinomas, but is frequently seen with malignant melanoma and malignant teratoma of the testis.

Results of lymph node involvement:

   (i) Invasion of adjacent tissues:
       a. veins
       b. trachea, skin, etc.
   (ii) Compression of neighbouring structures, e.g. superior vena cava syndrome
   (iii) Further dissemination by diversion of lymph flow
   (iv) Lymphoedema of limb or scrotum

2. **Blood spread**

   This occurs typically with sarcomas and as a later feature of spread from carcinomas. There are three continuous phases:

   (i) The invasion of blood vessels by tumour cells *Mechanism*
       a. Production of degradative enzymes weakening blood vessel integrity
       b. Imperfect endothelial lining of tumour blood vessels allowing direct access by tumour cells (especially in sarcomas)
       c. Loss of cell-to-cell adhesiveness
   (ii) The transport of tumour cells by established vascular pathways. The presence of circulating tumour cells may be a common feature of tumours and does not inevitably lead to metastases
   (iii) The lodgement, attachment, and growth of tumour cells at the distant site. The arrest of circulating tumour cells is not a result of non-specific mechanical trapping, but probably is determined by the cell surface properties of the tumour cell such as adhesion molecules. The variation in these surface properties and their differing affinity for arrest may explain the organ specificity of metastatic tumour spread.

   **Examples of organ specificity**
   a. Carcinoma of the breast, thyroid, kidney, lung and prostate frequently metastasise to bone
   b. Carcinoma of the bronchus often involves the liver and adrenals
   c. Carcinoma of the colon and rectum spread to the liver
   d. Seminoma (testis) spreads to the lung
   e. Sarcomas spread principally to the lung but also to liver and brain

3. **Coelomic spaces Examples**

   (i) Spread from a gastric or intestinal primary to the ovaries (Krukenberg tumours)
   (ii) Pleural spread of lung and breast cancer
   (iii) Peritoneal spread of ovarian carcinoma

4. **Cerebrospinal spaces**

   Primary tumours of the CNS may spread via the subarachnoid space or the ventricular system and give rise to seedlings distant from their origin.

5. **Epithelial cavities**

   This mode of spread is rare. One example is implantation of desquamated tumour cells from an intestinal carcinoma into anastomosis sites during surgical
removal.

PATHOLOGICAL ASSESSMENT OF NEOPLASIA
Three features of a tumour must be determined
(i) The tissue of origin and type of tumour
(ii) How far in its natural history has it progressed - the stage of the tumour
(iii) How aggressive is the tumour - the grade of the tumour

Origin and type of tumour
The mode of spread and its extent are strongly influenced by the site and tissue of origin and the nature of the tumour. Furthermore the form of treatment will often be dictated by these factors.

Stage
The stage of a tumour is determined from the degree of invasion and the presence and extent of metastasis. A frequently encountered example is in colorectal cancer Dukes' staging. This is a widely used modified scheme:
(i) Stage A: invasion through the muscularis mucosae has occurred but the tumour has not penetrated through the muscularis propria. Survival 90%
(ii) Stage B: The muscularis propria is breached but no metastases are detected. Survival 60%
(iii) Stage C1: Peri-tumoural lymph node involvement is present. Survival 40%
(iv) Stage C2: The highest lymph node resected, i.e. the node at the vascular tie, is involved. Survival 20%
(iii) Stage D: Distant metastases to the liver or unresectable local disease. Survival 0-5%

Staging systems differ depending on the type, site and clinical behaviour of the tumour.

Grade
Two tumours at the same stage may have very different outcomes as one may behave more aggressively than the other. The aggressiveness of the tumour is often reflected by the 'grade' of malignancy. The grade is usually based on the degree of similarity of the tumour to the fully mature 'differentiated' state of the tissue of origin.
(i) Well differentiated/low grade - closely resembles tissue of origin
(ii) Moderately differentiated/intermediate grade
(iii) Poorly differentiated/high grade - difficult to recognise the tissue of origin

PREMALIGNANCY
It is frequently possible to recognise precursor lesions of malignant tumours. Often these are benign tumours such as colorectal adenomas which precede colorectal adenocarcinomas. In other situations a benign tumour is not present but morphological abnormalities may still be identified. These abnormalities are called dysplasia.
**Dysplasia**
A pre-malignant disturbance of cell proliferation and maturation. It is generally assumed that once initiated dysplasia will inevitably progress (through increasing grades of severity) to an invasive malignant tumour. However, it must be said that evidence is accumulating that dysplasia can remain static or regress. The most severe end of the dysplasia spectrum can be synonymous with intra-epithelial carcinoma or carcinoma-in-situ. Dysplasia is recognized by:

1. Pleomorphism of cells (excessive variation in shape and size)
2. Hyperchromatic nuclei and increased mitotic activity
3. Loss of polarity (orientation) of cells
4. Disordered maturation
5. Absence of invasion

Dysplasia and carcinoma-in-situ are found in:

A. **Squamous epithelia**
   1. Cervix uteri - 'Cervical Intra-epithelial Neoplasia (CIN)'
   2. Vagina and vulva (VIN)
   3. Oro-pharynx and oesophagus
   4. Larynx
   5. Skin
      (i) Paget's disease of the skin
         This is usually (but not invariably) associated with an underlying but separate adenocarcinoma and is found in the nipple, axilla, anus, and vulva
      (ii) Bowen's disease (intra-epidermal carcinoma)
   6. Bronchus in areas of squamous metaplasia

B. **Transitional epithelium of the urinary system, especially in the bladder**

C. **Columnar secretory epithelia**
   1. Gastric mucosa in
      (i) Chronic gastritis
      (ii) Margins of a chronic peptic ulcer (uncommon)
      (iii) Menetrier's disease (rare)
   2. Large intestinal mucosa
      (i) Ulcerative colitis
      (ii) Crohn's disease
   3. Small intestinal mucosa (rare)
      (i) Crohn's disease
      (ii) Coeliac disease
   4. Ductal epithelia
      (i) Breast - atypical hyperplasia and intra-duct carcinoma (also lobular carcinoma-in-situ)
      (ii) Bile ducts
      (iii) Pancreatic duct
   4. Endometrium
Stress Is Back

People who face serious life stress are more likely to develop a peptic ulcer over the next 15 years.

By: Richard Firshein

For years, doctors believed that ulcers were psychosomatic, caused by stress. But then researchers discovered a hardy, virulent little bacterium known as Helicobacter priori. Able to survive and even thrive in stomach acid, this bacterium is so damaging it has been given Class 1 carcinogen status since it's known to be a direct precursor of certain stomach cancers. This led scientists to believe that it caused ulcers.

The discovery of H. priori was revolutionary. Doctors began to treat ulcers with antibiotics. A combination of ampicillin and metronidazole (Flagyl), two common drugs, seemed to work best, and individuals who had been suffering for years with agonizing ulcer pain suddenly became well. Talk about a swing of the pendulum: a shocked medical community concluded that all ulcers were caused by infection. The search for a psychological root was abandoned.

End of story? Not quite. Eight out of 10 people infected with H. priori never get ulcers. As an article in the Journal of the American Medical Association points out, studies show that people who face serious life stress are more likely to develop a peptic ulcer over the next 15 years. Research reported in the Archives of Internal Medicine followed 4500 subjects and found that the incidence of ulcers in those who felt they were stressed was almost twice as great as in those who were stress-free. In addition, the incidence of ulcers seems to rise after national disasters. A review of medical records from 61 hospitals, published in the American Journal of Gastroenterology, found that the Hanshin-Awaji earthquake in Japan was followed by a marked increase in bleeding gastric ulcers.

It's clear to me that the true origin of ulcers lies both in the mind and the body. As a physician, I can see that stress plays a huge role in all my patients' illnesses. I see flare-ups of asthma, hypertension and diabetes during periods of stress. When approaching treatment of any illness, I try to suggest nutritional and lifestyle changes, and when necessary, medicines, to help both mood and body.

For example, a 54-year-old woman recently sought my help. She'd suffered from ulcers for many years, and her doctor had given her multiple courses of antibiotic therapy. The drugs had always helped, but only temporarily; the ulcers always returned. Nobody had asked about her levels of anxiety, but when I inquired, she admitted that she'd just gotten out of a long and difficult marriage and was now a single mother with financial problems. Stress had been her constant companion for years.

I suggested a program of meditation and biofeedback to help her relax. I also prescribed a course of natural supplements, among them DGL (deglycyrrhizinated licorice), a licorice extract that helps heal the lining of the stomach, and aloe, another healing agent which soothes inflammation. That, along with a final course of antibiotics, alleviated her stress and quieted her inflamed gut. She hasn't suffered from an ulcer in over a year.

To understand any disease, we need to realize that illnesses almost always stem
from multiple causes. Psychological factors should never be overlooked when treating disease, and the immune and nervous systems should be examined together. That's why I'm glad that stress is back at least where ulcers are concerned.

Psychology Today Magazine, May/Jun 99
Last Reviewed 25 Apr 2005
Article ID: 487

D. The bone marrow - Myelodysplasia

The importance of the premalignant phase is that removal or treatment of the lesion may prevent it becoming invasive or spreading. Screening for neoplasia is usually based on identifying the premalignant or early malignant stages of the disease.

AETIOLOGY OF TUMOURS

Tumours are induced by a variety of mechanisms including:
1. Chemicals
2. Physical agents
3. Viruses
4. Genetic lesions

Our knowledge is far from complete but these general principles apply:
1. Agents capable of causing tumours usually mediate their effects through damage to DNA
2. Different types of genes are affected
3. A range of genetic lesions occur varying from a single base pair mutation to loss of the entire gene or chromosome. More than one type of lesion may be seen in the same gene on different alleles
4. The number and type of genetic lesions required to induce a tumour depends on the maturity and type of tissue
5. The type and frequency of events differs from tissue to tissue and may be highly specific to one tumour or common to a wide range of tumours
6. The sequence of genetic events may vary in tumours of the same type

A. Chemical

Of largely historical interest, early examples of chemical carcinogenesis are:
1. Carcinomas of the scrotum in chimney sweeps
2. Cancer of the hands and arms in shale-oil workers
3. Cancer of the skin and lung after long-term exposure to arsenic (still seen occasionally)

Present day examples are:
4. Carcinoma of the lung
   (i) Tobacco smoke
   (ii) Asbestos
   (iii) Chromate smelting
5. Carcinoma of the bladder
   (i) Aniline dye production
(ii) Rubber manufacture
6. Carcinoma of the nasal sinuses in wood-workers
7. Carcinoma of the skin in tar-workers
8. Haemangiosarcoma of the liver in vinyl chloride workers

Experimental carcinogenesis
Most, if not all, chemical carcinogens undergo some metabolic conversion to form either intermediate compounds called Proximate carcinogens or active alkylating or arylating products which bind to DNA, and to a lesser extent, RNA and protein. These active products are termed the ultimate carcinogens and can modify the genome of the cell by:
1. Direct action on DNA
2. Modification of TRNA followed by the production of mutant DNA by the reverse transcriptase mechanism

These modifications may have the following effects on the cell:
1. Cell death
2. DNA damage followed by successful repair
3. DNA damage with faulty repair conferring neoplastic potential
4. Stable mutation and transmission of DNA damage to its progeny, possibly leading to neoplasia

Chemical carcinogens
1. Locally-acting chemical carcinogens, e.g. polycyclic aromatic hydrocarbons such as 3:4 benzpyrene, 3:methylcholanthrene These are 'strong' carcinogens characterized by:
   (i) Action at the site of administration
   (ii) Most tissues will respond
   (iii) High tumour yield
2. Remotely-acting carcinogens
   (i) Procarcinogens are either activated through several steps 'proximate carcinogens' to the ultimate carcinogen or the ultimate carcinogen may be formed in one step e.g. N-methyl-4-aminoazobenzene (MAB) produces liver tumours after oral administration because the liver is the site of its metabolic conversion to the carcinogenic N-hydroxy derivative.
   (ii) Detoxification and excretion of a procarcinogen can also lead to cancer if subsequent modification of the detoxified product occurs, e.g. the excretion product of b-naphthylamine is activated in the urine giving rise to bladder tumours

Examples of chemical carcinogenesis
1. Naturally occurring
   (i) Aflatoxin, a product of the fungus Aspergillus flavus, is a frequent contaminant in foodstuffs in the tropics. It produces liver and kidney tumours in animals. Known to induce point mutations in the p53 gene
   (ii) Cycad nuts. The active principal cycasin induces tumours of kidney, liver and colon in animals
   (iii) Senecio alkaloids (ragwort) - ? liver cancer
   (iv) Nitrosamines in certain smoked foods - ? gastric cancer
2. Polycyclic aromatic hydrocarbons
   (i) Pitch, coal-tar, creosote and oil products (skin)
   (ii) Cigarette smoking (lung)

3. Aromatic amines
   (i) b-naphthylamine  - urothelial cancers
   (ii) benzidine
   (iii) auramine and magenta
   (iv) aminoazo dyes - liver tumours
   (v) 2-acetylaminofluorene - liver and bladder tumours

4. Vinyl chloride monomer - haemangiosarcoma of liver

Biology of carcinogenesis
1. The effects of carcinogens are dose-dependent, additive, and irreversible
2. Carcinogenesis occurs after a variable latent period during which a series of modifications occurs converting a normal cell, through successive generations, into a cancer cell. Such modifications are accelerated and enhanced by cell proliferation, and chemicals promoting the change from a modified to malignant cell may not be carcinogenic themselves, e.g. Croton oil

Thus the initial lesions of DNA, although modifying the cell, do not necessarily lead to neoplasia. The modified cell has to come under the influence of promoters which selectively stimulate the cell to divide at the expense of surrounding cells. In this way, the initiated cell population is greatly amplified. Even at this stage the enlarged population of initiated cells may undergo regression or maturation to normal-appearing tissue. The alternative, however, is for persistence and eventual transformation to a self-generating population of cells no longer dependent upon exogenous stimuli and these constitute cancer cells. In embryonal tumours the number of events required may be as little as two whereas in adult tumours multiple episodes of damage are required, in some instances as many as seven have been suggested. This probably explains why tumours predominantly affect the elderly. Once the neoplasm has been formed it then becomes invasive and subsequently undergoes progression. Tumour cells with different biochemical characteristics evolve. Those most suited to the local environment survive and proliferate whereas those not so well adapted decline in number or die. Metastatic variants and cells unresponsive to therapeutic modalities may develop.

B. Physical
1. Solar radiation. Ultraviolet light causes DNA damage by dimerising pyrimidines
   (i) Squamous and basal cell carcinomas of the skin
   (ii) Melanomas
2. X-irradiation
   (i) Skin cancer
   (ii) Leukaemia
3. Radio-active substances - alpha and beta particles, protons and neutrons cause damage by removing electrons from atoms with which they interact forming highly charged radicals which bind to and damage DNA
   (i) Lung cancer due to radon (Schneeburg miners)
   (ii) Osteogenic sarcoma following ingestion of radium, strontium,
mesothorium (luminous paint)
(iii) Liver tumours following 'thorotrast' (thorium dioxide) administration for radiological purposes
4. Heat - this is dubious but it could act by promotion of the effects of a carcinogen possibly present in the fuel, e.g. in Changri cancer of the abdominal wall (charcoal braziers tied around the abdomen in Kashmir)

C. Viruses
Different types of virus induce tumours through different mechanisms.

Retroviruses
These are RNA viruses with a simple RNA genome. Two different types exist, the rapidly transforming retroviruses (RTRV) and the slowly transforming retroviruses (STRV). The former can induce tumours in animals within weeks of infection whereas the STRV take much longer.

Mechanism of action
A RTRV may either infect a cell itself or more usually in association with an STRV. RTRVs have an extra gene over the STRVs called an oncogene. This gene varies between different viruses but it has the same effect in that if it is removed or inactivated the RTRV can no longer rapidly induce tumours. If this gene is isolated and transfected into cells in vitro then the cells will transform and behave as tumour cells. This gene is therefore capable of causing tumours - an oncogene.

It was subsequently discovered that all organisms have a range of these genes and that they are highly conserved at all levels of the animal kingdom. Study of the structure of RTRV oncogenes and the equivalent genes in animals showed that the animal genes had introns (non coding regions) inserted between exons (coding regions) whereas the viral genes did not. It is now known that RTRV oncogenes were obtained by 'hijacking' an animal cellular oncogene mRNA and incorporating it into their genome. This gave the RTRV an advantage over the STRVs as they could control the cell regulatory processes more easily. Thus retroviral induced transformation can come about by two mechanisms:

1. The introduction of 'new' viral oncogenes into cells which following integration bring about the synthesis of virally coded proteins controlling cell growth and division
2. The activation of pre-existing genetic sequences (protooncogenes) and inappropriate production of host proteins controlling cell growth and division.

Such activation can also be produced by carcinogens and irradiation.

Possible RNA virus candidates as human tumour viruses:
1. Human T-cell leukaemia/lymphoma virus (HTLV-1)
2. HTLV-2 and HTLV-5
3. Human immunodeficiency virus and Kaposi’s sarcoma

DNA viruses
DNA viruses act either by inserting close to a proto-oncogene and causing inappropriate expression (? hepatitis B), or by producing viral proteins, e.g. E6 (human papilloma virus) and E1b (adenovirus) which inactivate the product of p53, and E7 (human papilloma virus) and E1a (adenovirus) which bind to the retinoblastoma gene product.
DNA viruses implicated in human neoplasia

1. Human papilloma virus (HPV)
   (i) HPV 1 - plantar warts
   (ii) HPV 5 - squamous carcinoma in epidermodysplasia verruciformis (v. rare)
   (iii) HPV 6 and HPV 11 - condyloma acuminatum and genital verrucous carcinoma
   (iv) HPV 16, 18, 31, 33, 35, 51 - cancer of the cervix

2. Epstein Barr virus in
   (i) Burkitt's lymphoma
   (ii) Nasopharyngeal carcinoma
   (iii) Hodgkin's disease

3. Hepatitis B virus - hepatocellular carcinoma

Warts and Herpes

We are in the midst of a worldwide epidemic of sexually transmitted diseases. At least two of its major diseases are helped by psychological techniques: twenty-six to thirty-one million Americans have genital herpes; forty to fifty million Americans have venereal warts.

We must carefully distinguish between having either the virus and having the symptoms. The both creepy and reassuring reality is that we all swim in a sea of viruses not only outside us but within us. If you have ever had chicken pox, mononucleosis, or other such diseases, the virus is now in your body. Usually its presence has no impact. Although recent figures are lower, at one time as many as 90 percent of Americans had the herpes virus for cold sores in their bodies. Perhaps two-thirds of the people who have the possibility of genital herpes have had one or several outbreaks but do not have subsequent symptoms.

Warts are caused by forty or fifty variants of the human papilloma virus (HPV). While its story is not as clear as herpes, a vast percentage of the world population has had a wart at some time. A British study found that 16.2 percent of schoolchildren had active warts (it is not clear how many had the virus in their bodies but not active). As many as 30 percent of American women may have the virus for venereal warts within their bodies.

Here enters the immune system. Its job is to maintain law and order. When it is functioning well, all of these microscopic predators are kept in their place. It puts an end to herpes recurrences and often produces the spontaneous remission of warts. The emerging field of psychoneuroimmunology studies the impact of psychological factors on the immune system's ability to function effectively.

Preventing transmission and knowing what to say to sexual partners require both specific information and personal judgment. The guidelines are being updated as new research comes in, so consult your health care provider. The key to avoiding transmission is having the partner avoid contact with affected skin when the virus is present. Condoms are effective if they cover the affected area, and nonoxynol-9 spermicides also kill the virus.

A common rule for genital herpes was to avoid intercourse or other contact with
the affected skin from the start of the prodrome (tingling, muscle aches, or other indications of a coming recurrence) until two days after the healing of sores. This has been complicated by a growing awareness of the role of asymptomatic transmission?that is, transmission with no visible sores. It is not clear how common this is. One study concluded that it is quite rare yet another called it the major source of transmission. The danger of asymptomatic transmission appears to diminish sharply after the first six months. The clear message is that there is no clear message.

Venereal warts present similar ambiguities. Warts seem to differ in their incubation periods (how long after exposure you see them) and the presence of virus after apparent clearing. One rule of thumb is to consider the virus as possibly transmissible for six months after possible exposure and for the same time period after visible symptoms have gone away.

Ways of establishing human viral oncogenesis:
1. Isolation of virus from the tumour
2. Isolation of virus-specific products from the tumour
3. Demonstration of cell transformation by virus in culture
4. Cells transformed by the virus in tissue culture are able to produce tumours in animals
5. Infection with the virus precedes the development of cancer
6. Sero-epidemiological studies
7. Vaccination against the virus lowers the incidence of cancer

D. Genetic basis of neoplasia
A variety of types of gene have been implicated in neoplasia:
1. Proto-oncogenes activated to oncogenes
2. Tumour suppressor genes: inactivated or deleted
3. Metastasis genes: decreased expression or deletion
4. Senescence genes: deleted

Proto-oncogenes fall into four groups each class being activated by a variety of methods

Alterations in oncogenes
1. Growth factors (GF)
   (i) Increased production of growth factor(s)
   (ii) Inappropriate production of growth factor(s)
   (iii) Loss of production of inhibitory growth factor(s), e.g. TGF-b
2. Growth factor receptors (GF-r)
   (i) Increased numbers of receptors caused by overexpression or by amplification of the GF-r gene, e.g. erb-B, erb-B-2 in breast cancer
   (ii) Abnormal receptors which do not require GF stimulation, e.g. erb-B in gliomas
3. Signal transduction
   (i) Point mutations in GTPase binding proteins increasing the level of signal transmission, e.g. ras family in colorectal cancer, gsp in pituitary adenoma
   (ii) Over-expression of GTPase binding proteins or tyrosine kinases increasing the level of signal transduction, e.g. ras, src, yes
   (iii) Translocation of a tyrosine kinase to form a new protein product with
increased activity, e.g. abl-bcr in chronic myeloid leukaemia

4. Nuclear factors
   (i) Gene amplification of cell cycle control proteins, e.g. nmyc in neuroblastoma
   (ii) Translocation of inactive gene to an area under the influence of an active promoter, e.g. myc in Burkitt's lymphoma
   (iii) Point mutations increasing the stability of a protein, e.g. p53 in a wide range of tumours
   (iv) Increased expression of a range of nuclear factors, e.g. myb, fos

Tumour suppressor genes

_In vitro evidence_
This class of genes was discovered from fusion experiments between normal and tumour cells. The resultant hybridoma cells showed a non malignant phenotype. These experiments proved that malignancy could be suppressed given the influence of the genes from a normal cell.

_Dominantly inherited cancer_
Tumour suppressor genes have frequently been identified by the analysis of familial cancers. Retinoblastoma - a tumour of the retinoblasts of the retina - can occur sporadically or within a family as a dominantly inherited disease where it is associated with deletions of chromosome 13q14. By restriction fragment length polymorphism analysis, gene probing and DNA sequencing the retinoblastoma gene rb was identified. The retinoblastoma gene product is a nuclear transcription factor. The development of inherited and sporadic retinoblastoma is shown on page 203. The function of the retinoblastoma gene as a tumour suppressor gene has been confirmed by the reintroduction of rb into retinoblastoma cells _in vitro_. The cells reverted towards a normal phenotype.

Other tumour suppressor genes:
   (i) Wilm's tumour genes VT-1 and WT-2 on chromosome 11. Two loci have been identified.
   (ii) Familial adenomatous polyposis (FAP). The APC gene on chromosome 5q21 is mutated or deleted in FAP. An adjacent gene called the MCC gene (mutated in colorectal cancer) also plays a role in sporadic colorectal cancer.
   (iii) Neurofibromatosis. NF-1 on chromosome 17q11. NF-2 is implicated in schwannomas and resides on chromosome 22q.
   (iv) Multiple endocrine neoplasia-1 (MEN-1). The MEN-1 gene is located at 11q12 and MEN-2A between 10p12-ql1. Other abnormalities may be seen on 1p and 22q.
   (v) p53. This gene on 17p is one of the most frequent targets for DNA damage yet known. If it sustains a point mutation in one of several areas it stabilises the protein extending its usually very short half life. This activating point mutation makes p53 act as an activated oncogene. Mutant p53 binds with wild type p53 to create an inactive complex. Thus p53 acts by a dominant negative effect. Loss of the remaining normal (wild type) allele causes complete loss of the tumour suppressor function of p53 leaving the abnormal p53 protein complexes only. p53 can also be bound by viral proteins such as adenovirus E1b an human papilloma virus protein E6. These proteins neutralise its tumour suppressor function
(vi) 3p. Consistent loss of heterozygosity of 3p in small cell lung cancers and other tumours.

**Metastasis genes**
Fusion of metastatic cells with non-metastatic cells can lead to a temporary cessation of the metastatic phenotype. nm23 is a putative metastasis gene that is involved in colorectal and breast cancer. It is down-regulated or deleted in cancers which have metastasised. The gene has homology to the family of nucleoside diphosphate kinases which are involved in microtubule function and interact with G proteins.

**Senescence genes**
A group of genes on a number of different chromosomes are involved in genetically programming senescence. Cell fusion experiments between a normal cell and an immortal cell indicate that these genes can 'remember' the Hayflick number of the normal cell. Deletion of these genes allows the cell to become immortal but not transformed.

**Molecular pathology of colorectal cancer**
The best characterized tumour system with regard to molecular events is the adenoma-carcinoma sequence of the colorectal cancer. The earliest lesion occurs in the APC or MCC genes on chromosome 5. Initially this is thought to be a point mutation with possible subsequent loss of the remaining normal allele. This leads to a hyperplastic mucosa. A variety of genes subsequently become hypomethylated and early adenomas are formed. Kirsten ras mutations at codon 12, 13 or 61 may then occur. At the adenoma-carcinoma interface point mutations of p53 with subsequent loss of the wild type allele occurs. Deletions of the deleted in colorectal cancer gene (DCC), a cell adhesion gene, may then be seen. Abnormalities of nm23, rb and chromosomes 1, 3, 12 and 22 may also occur. The complete dissection of these multiple events requires further research but it is a good example of the multistep pathway of neoplasia.

**BIOLOGY OF NEOPLASTIC CELLS**

**Morphological changes**
Morphological observations on cancer cells have revealed a number of differences from normal cells but these are non-specific:
1. Increase in nuclear and cytoplasmic volume with an increase in the nuclear-cytoplasmic ratio
2. Irregular nuclear shape and multiple nucleoli
3. Numerous misshapen protrusions from the cell surface
4. Disorganised cytoskeleton
5. Simplification of cytoplasmic organelles
6. Formation of tumour giant cells
7. Abnormal mitotic figures

**Biochemical alterations**
1. Composition of the cell surface
   (i) Loss of glycoprotein molecules
   (ii) Deletion of saccharide residues from glycolipids
   (iii) Loss of fibronectin
2. Cell surface properties
   (i) Enhanced mobility of receptor resulting from loss of cytoskeletal attachment to integral glycoproteins
   (ii) Increase in number of cell surface receptors, abnormal structure of receptor or loss of receptors
   (iii) Expression of fetal, viral, or neo-antigens
   (iv) Shedding of antigens (and other glycoproteins)
   (v) Increase in the net negative charge on the plasma membrane
3. Changes in nuclear DNA
   (i) Hypomethylation
   (ii) Increased DNA content expressed as DNA aneuploidy
4. Enzyme production and release
   (i) Increased protease activity (including collagenases and plasminogen activator)
   (ii) Increased release of alkaline phosphatase and glycosyl transferase
5. Transport
   Increased uptake of sugars and amino acids
6. Cyclic nucleotides Increased cyclic GMP

**Behavioural characteristics in vitro**
1. Loss of senescence
   Whilst normal somatic cells can only undergo a finite number of divisions (Hayflick number), neoplastic cells will proliferate *ad infinitum* under ideal culture conditions
2. Loss of contact inhibition
   When normal cells which are proliferating and spreading come into contact, a 'cut-out' mechanism operates and mitosis and movement ceases. Malignant cells show a loss of such 'contact inhibition' and proliferation persists
3. Increased motility
   Compared with normal cells, it is claimed that neoplastic cells migrate more rapidly, probably as a consequence of altered cytoskeletal function
4. Decreased cell-to-cell adhesion
   The presence of specific topographic patterns of macromolecules at the cell surface may serve as a mechanism for cellular recognition and adhesion. Disturbances in the arrangement of macromolecules on tumour cells may explain the breakdown in cell-to-cell signals that underlie such phenomena as contact inhibition and mutual adhesiveness
5. Loss of substrate dependency
   Most normal cells require attachment to a suitable substrate before proliferation can occur; this attachment being mediated by binding proteins such as fibronectin and laminin. Neoplastic cells show a greatly diminished dependence on substrate attachment for proliferation.

**HORMONAL FACTORS IN NEOPLASIA**

Whilst it is well known that hormones can greatly modify the production and growth of tumours, their role in the causation of tumours is less clear. It is probable that hormones act as promoters of malignant change already initiated by some other factor such as a virus or chemicals.
Examples
1. Oestrogens
   (i) In mice oestrogens promote the development of mammary cancer which has been initiated by the Bittner virus
   (ii) Administration of artificial oestrogens to trans-sexual men has resulted in a few cases of mammary carcinoma
   (iii) Breast carcinoma in women may undergo regression after adrenalectomy and oophorectomy
   (iv) Hyperoestrogenism, for example due to a granulosa cell tumour of the ovary, may give rise to endometrial carcinoma
   (v) Adenocarcinoma of the vagina in the daughters of women given stilboestrol in pregnancy
   (vi) Oral contraceptives giving rise to liver cell adenomas and a few cases of hepatocellular carcinoma

2. Trophic hormones
   (i) Gonadotrophins will bring about proliferation and in some cases malignant change in the ovaries of experimental animals which have been transplanted into the spleen. In this site the oestrogens released by the ovary are inactivated by the liver and there is reduced feed-back to the pituitary which responds by excessive production of gonadotrophins (feed-back deletion)
   (ii) Excess TSH and ACTH levels may bring about tumour formation in the corresponding target organs in experimental animals
   (iii) A possible increase in tumours in patients with growth hormone overproduction (acromegaly)

IMMUNOLOGICAL FACTORS IN NEOPLASIA

The immunological theories of oncogenesis depend upon some breakdown of the normal capacity to recognise neoplastic cells as 'foreign' and to react against them. This ability to recognise mutant cells is termed 'immunological surveillance'. The existence of immunological surveillance presumes that there are antigenic differences between normal and neoplastic cells. Evidence for the development of tumour antigens and immune reactions to them has been drawn from animals and humans.

Evidence in animals
1. Syngeneic animals can reject transplanted tumour if previously immunised against it (e.g. with irradiated tumour cells)
2. The presence of circulating antibodies cytotoxic to tumour cells in vitro has been demonstrated in viral-induced animal leukaemias
3. Immune lymphocytes produced in one animal will cause regression of chemically-induced tumours when injected into syngeneic animals
4. After a primary solid tumour has been removed from an animal, it is more difficult to re-establish the tumour and a large inoculum must be given
5. Animals rendered immunodeficient by neonatal thymectomy or made tolerant to tumour antigens are more susceptible to oncogenesis
6. Vaccination against an animal oncogenic virus (turkey herpes virus) can prevent tumour development in chickens

**Evidence in man**
1. Circulating antibodies to tumour antigens have been demonstrated in malignant melanoma, neuroblastoma, Burkitt's lymphoma and nasopharyngeal carcinoma (which cross-react with EB virus), osteogenic sarcoma, etc.
2. Cell-mediated immunity can be demonstrated to tumour specific antigens by macrophage migration inhibition, etc.
3. Histological evidence
   With certain tumours, those that have a prominent lymphocytic stromal infiltrate ('host reaction') have a better prognosis
4. Correlation between prognosis and the number and reactivity of circulating lymphocytes
5. Immunodeficiency or immunosuppression is associated with an increased incidence of non-Hodgkin lymphomas, squamous and basal carcinomas and melanomas
6. Tumour cells which have been inadvertently transplanted into the recipients of renal homografts taken from cancer patients have grown successfully because of immunosuppression of the host
7. Spontaneous full or partial regression of tumours, e.g. melanomas
8. Dramatic response after small doses of chemotherapy, e.g. in Burkitt's lymphoma and choriocarcinoma
9. Removal of a primary tumour may be followed by regression of secondaries
10. Long-standing relapses after presumed 'dormancy' of cancer cells. In some cases relapse has followed an alteration in immune status resulting from immunosuppressive treatment, irradiation, etc.

**Development of tumour antigens**
Alteration of the genome by an oncogenic agent may lead to the formation of new antigens at the cell surface. These might not respond to cytokines and contact stimuli appropriately and react by excessive proliferation or tissue invasion.
1. Virus alterations result in a new surface antigen which is characteristic of the infecting virus and common to all tumours produced by that virus
2. Chemical carcinogens also induce new surface antigens but these differ from tumour to tumour (idiotypic)
3. Some tumours develop fetal antigens not normally expressed in adult tissues, e.g. CEA, (a-fetoprotein

**Effector mechanisms in tumour-cell killing**
1. Sensitized killer T-lymphocytes
2. Natural killer lymphocytes
3. Antibody-dependent cell-mediated cytotoxicity
4. Complement-mediated cytolysis
5. Macrophage killing following:
   (i) Antibody attachment (Fc)
   (ii) Cytokine activation

**Failure of the immune response**
Immune surveillance may fail if the
1. Tumour is non-antigenic
2. Immune system is inefficient because of
   (i) Increasing age
   (ii) Human immunodeficiency virus infection
   (iii) Immune suppression in transplant recipients
3. Cancer cells evade the immune mechanisms
   (i) Tolerance
      a. Oncogenic virus transmitted vertically or present from birth, e.g. hepatitis B
      b. Activation of T-suppressor cells
      c. High dose suppression by antigens shed from tumour cells
   (ii) Blocking of cytotoxic effects on tumour cells by
      a. Formation of soluble Ag/Ab complexes (shedding of tumour antigens leads to production of immune complexes in Ag excess)
      b. Shedding of cell-bound Ag/Ab complexes
      c. Increased endocytosis of cell-bound Ag/Ab complexes
   (iii) Escape from complement-mediated cell lysis
      a. Localized concentration of surface antigens (antigen 'capping') leads to aggregation of Ag/Ab complexes so that steric hindrance prevents complement binding
      b. Changes in the lateral mobility of surface antigens may hinder the critical alignment of Ag/Ab complexes necessary for complement activation

Other factors in tumour formation
Tumour formation is also influenced by:
1. Age
   Carcinoma of the bronchus, colorectum, stomach and pancreas all increase with age whereas carcinoma of the breast and cervix occur earlier with only a small increase with age. Hodgkin's disease and osteogenic sarcoma occur with a bimodal distribution, in young adults and the elderly. Germ cell tumours tend to occur in 30's and 40's and blastomas in children.
2. Sex
   Variability in incidence between sexes for most major types of cancer
3. Genetic background
   Family history of tumours strongly affects predisposition to specific types of tumour
4. Race
5. Geographical location
6. Hormonal status
7. Immune function
8. Diet
9. Chronic inflammation

COMMONEST MALIGNANT TUMOURS IN ADULTS
1. Carcinoma of the bronchus (squamous, small cell and adenocarcinoma)
2. Squamous and basal cell carcinomas of the skin
3. Adenocarcinoma of the colon and rectum
4. Adenocarcinoma of the breast
5. Adenocarcinoma of the stomach
6. Adenocarcinoma of the prostate  
7. Transitional cell carcinoma of the bladder  
8. Lymphoma and leukaemia  
9. Carcinoma of the oesophagus  
10. Adenocarcinoma of the ovary

**COMMONEST MALIGNANT TUMOURS OF CHILDHOOD**

1. Leukaemia (32% of total) of which about 80% are acute lymphocytic leukaemia  
2. Lymphoma (10%)  
   (i) Non-Hodgkin's lymphoma including Burkitt's lymphoma (5%)  
   (ii) Hodgkin's disease (5%)  
3. Brain tumours (25%) including  
   (i) Medulloblastoma (cerebellum) (5%)  
   (ii) Astrocytoma, frequently sub-tentorial (9%)  
   (iii) Ependymoma (5%)  
4. Neuroblastoma (6%)  
   From sympathetic ganglia and adrenal medulla. Some mature into ganglioneuroma  
5. Nephroblastoma (Wilm’s tumour) (5%)  
   Composed of tubules and immature glomeruli in a mesenchymal stroma which may contain striated muscle, fat, cartilage and bone  
6. Retinoblastoma (3%)  
7. Hepatoblastoma (1%)  
8. Germ cell tumours (yolk sac tumour, teratoma) (4%)  
9. Rhabdomyosarcoma and other soft tissue sarcomas (5%)  
10. Osteogenic sarcoma (3%)  
    Most commonly at the lower end of the femur, then the upper part of the tibia  
11. Ewing's tumour (2%)

**NON-METASTATIC EFFECTS OF TUMOURS**

**A. Skin markers of malignancy**

1. Acanthosis nigricans  
   almost always associated with carcinoma - 75% adenocarcinoma  
2. Dermatomyositis  
   about 15% of cases associated with malignancy  
3. Necrolytic migratory erythema  
   with glucagonoma  
4. Exfoliative dermatitis  
   with lymphomas and leukaemias  
5. Erythema gyratum repens  
   with carcinoma of the bronchus  
6. Pigmentation  
   in carcinomatosis  
7. Pruritus  
   in lymphomas and some carcinomas
8. Herpes zoster
   in Hodgkin's lymphomas
9. Bullous pemphigoid (?)
10. Acquired ichthyosis in lymphomas
11. Fixed LE-like eruptions
12. Hypertrichosis

B. Neuromuscular effects
1. Myopathy
   with various carcinomas and lymphomas
2. Myasthenic syndrome
   with intrathoracic tumours usually oat-cell carcinoma of bronchus and thymoma
3. Mixed neuropathy (sensory and motor)
   with many types of carcinoma, e.g. bronchus, stomach, breast, together with
   lymphomas and myeloma
4. Sensory neuropathy
   a rare complication of carcinoma of the bronchus
5. Autonomic neuropathy
6. Dementia or psychosis
7. Cerebellar degeneration
   with carcinoma of bronchus, breast, ovary and lymphomas
8. Brain stem degeneration
   may accompany some other neuromuscular lesion
9. Progressive multifocal leucoencephalopathy caused by papova virus
   very rare; association with lymphoma

C. Haematological effects
1. Thrombotic disorders
   (i) Venous thrombosis
      especially carcinoma of the pancreas and mucinproducing carcinomas
   (ii) Non-bacterial thrombotic endocarditis
   (iii) Disseminated intravascular coagulation - prostate,
      bronchus, stomach, pancreas
   (iv) Microangiopathic haemolytic anaemia, usually advanced carcinoma of
      stomach, pancreas, colon, lung and breast
2. Miscellaneous
   (i) Normocytic normochromic anaemia
   (ii) Autoimmune haemolytic anaemia Hodgkin's disease, lymphomas, thymoma
   (iii) Sideroblastic anaemia
   (iv) Thrombocytopenia
   (v) Red cell aplasia associated with thymoma
   (vi) Polycythaemia with renal carcinoma, etc.

D. Hormonal effects - due to inappropriate production by tumour cells
1. Cushing's syndrome (ACTH production)
   associated with oat-cell carcinoma of the bronchus, thymoma, carcinoid tumours,
   medullary carcinoma of the thyroid
2. Hyponatraemia (ADH-like substance)
   oat-cell carcinoma
3. Hypoglycaemia (insulin-like substance)
   mesothelioma, liver cell carcinoma, adrenal cortical carcinoma
4. Hypercalcaemia (parathyroid hormone related peptide) carcinoma of the
   bronchus and cervix, renal carcinoma, lymphomas, small cell carcinoma of the
   ovary and breast carcinoma
5. Polycythaemia (erythropoietin production)
   renal adenocarcinoma and occasional cases of uterine leiomyoma, hepatocellular
   carcinoma, cerebellar haemangioblastoma, nephroblastoma
6. Carcinoid syndrome (5-H-T)
   oat-cell carcinoma, medullary carcinoma of the thyroid
7. Gynaecomastia (HCG or human placental lactogen)
   with anaplastic or squamous carcinomas of bronchus, testicular tumours,
   hepatocellular carcinoma
8. Hypertension (excess renin production) from nephroblastoma
9. Hyperthyroidism (TSH-like substance)
   (i) Hydatidiform mole and choriocarcinoma
   (ii) Malignant teratoma trophoblastic of testis
10. Pigmentation (melanocyte stimulating hormone - MSH) oat-cell carcinoma of
     bronchus

TUMOUR MARKERS

A tumour marker is a substance, usually detected in the serum, whose concentration
can be related to the presence of a tumour. The substance need not necessarily be
tumour-specific but can be used as a marker because it is secreted in much greater
quantities by tumour cells.
Clinically useful serum markers include:
1. Human chorionic gonadotrophin - HCG
2. Alpha feto-protein - AFP
3. Carcino-embryonic antigen - CEA
4. Pregnancy associated beta1 globulin - PAb1 G
5. Placental alkaline phosphatase
6. Prostatic acid phosphatase and prostate specific antigen
7. Paraproteins (monoclonal immunoglobulins)

These markers are of value in the diagnosis and/or follow-up of the following
tumours:

1. Choriocarcinoma             HCG
2. 'Yolk sac tumour           AFP
3. Malignant teratoma         HCG, AFP, PAb1 G
4. Dysgerminoma               HCG, placental alkaline phosphatase
5. Prostatic cancer           prostatic acid phosphatase, prostate
   specific antigen
6. Colorectal cancer          CEA (in follow-up)
7. Myeloma                    Paraproteins
8. Hepatoma                   AFP
CANCER THERAPY

Treatment of cancer is by surgery, irradiation, chemotherapy or by manipulation of hormonal or immune function.

Chemotherapy
Factors affecting chemotherapy:
1. Efficiency of absorption/delivery
2. Drug concentration
3. Duration of exposure
4. Rate of metabolic breakdown
5. Rate of excretion
6. Development of resistance to agent

Major groups of chemotherapeutic agents
1. Alkylating agents - electron deficient side chains which interact with DNA
   (i) Nitrogen mustards - cyclophosphamide, melphalan and chlorambucil
   (ii) Nitrosoureas - BCNU, CCNU and methyl-CCNU
   (iii) Others - busulphan, thio-TEPA and procarbazine
2. Antimetabolites - inhibit nucleic acid synthesis directly or indirectly
   (i) Methotrexate - analogue of folic acid causes cessation of DNA synthesis
   (ii) 5-fluorouracil - analogue of pyrimidine bases uracil and thymidine interferes
       with RNA processing and DNA synthesis
   (iii) cytosine arabinoside - competitive inhibition of DNA polymerase
   (iv) purine antimetabolites - mercaptopurine and thioguanine interferes with DNA
       synthesis
3. Natural products
   (i) anthracyclines - planar multi ring structures that intercalate into DNA - inhibits
       DNA and RNA synthesis
       a. Doxorubicin
       b. Actinomycin
c. Bleomycin
   (ii) vinca alkaloids - bind to tubulin and disrupt the mitotic spindle
       a. Vinblastine
       b. Vincristine
4. Miscellaneous
   (i) Cisplatin - cross links DNA-DNA and DNA-protein
   (ii) Hydroxyurea - inhibits ribonucleotide reductase
       enzymes that convert ribose nucleotides to deoxyribose nucleotides
   (iii) L-asparaginase - degradation of L-asparagine

Systemic effects of chemotherapy
1. Bone marrow suppression - loss of rapidly proliferating lineages. Granulocytes >
   platelets > red blood cells
2. Intestinal ulceration - inhibition of production of epithelial cells leading to loss of
   function and ulceration
3. Partial or complete loss of hair
4. Inhibition of germ cell development - spermatozoa and oocytes
5. Cessation of ovarian function
6. Nausea and vomiting
7. Mutation of DNA and chromosomal damage - can lead to second malignancies especially leukaemias

**Types of radiation**
1. X-rays are machine-generated electromagnetic radiations of zero mass and charge
2. g-rays are similar to X-rays but are generated by the spontaneous decay of radio-active isotopes
3. a-Particles have a mass of 4 and a positive charge of 2 equivalent to a helium nucleus. They are produced by the nuclear reactions of high-energy electromagnetic radiation and the decay of radio-active elements, such as radium and uranium
4. b-Particles are electrons having negligible mass and one negative charge, which in medical usage are produced by decay of certain isotopes

**Mechanisms of action**
1. Direct action
   One mode of action may be a direct ionisation of part of a molecule by the absorbed energy
2. Indirect action
   A more likely explanation is that highly reactive free radicals, such as uncharged hydrogen atoms or OH° radicals, are formed which subsequently attack intracellular macromolecules causing cell injury

**Cellular effects**
1. Very high dosage leads to rapid cell death
2. Lower doses by affecting DNA synthesis reduce mitotic activity
3. Chromosome abnormalities may appear after cell division

**Tissue effects**
1. Skin, with increasing dosage
   (i) Erythema
   (ii) Abnormalities in pigmentation
   (iii) Hyperkeratosis
   (iv) Loss of skin appendages
   (v) Epidermal atrophy
   (vi) Dermal fibrosis
   (vii) Ulceration
2. Haemopoietic system
   (i) Transient pancytopenia
   (ii) Aplastic anaemia
   (iii) Leukaemic change
3. Testis
   (i) Tubular atrophy and hyalinisation
   (ii) Loss of spermatogonia
4. Ovary
   (i) Destruction of follicles
   (ii) Cessation of menstruation
5. Lungs
   (i) Pulmonary congestion and oedema
(ii) 'Hyaline membrane' reaction
(iii) Interstitial fibrosis
(iv) Bronchial carcinoma following inhalation of radio-active substances, e.g. miners of Schneeberg (pitchblende)

6. Kidneys
(i) Glomerular fibrosis
(ii) Vascular sclerosis
These changes may produce malignant hypertension

7. Gastrointestinal tract
(i) Mucosal oedema and ulceration
(ii) Vascular hyalinisation
(iii) Submucosal fibrosis
(iv) Glandular atrophy
(v) Fibrosis of the muscularis propria
(vi) Stricture formation

8. Salivary glands - decreased function leads to
(i) Xerostomia
(ii) Infections of the mouth
(iii) Dental caries

9. Liver
(i) Diffuse fibrosis
(ii) Veno-occlusive disease

10. Bone
(i) 'Radionecrosis'
(ii) Osteogenic sarcoma from radium and mesothorium

11. Nervous system
(i) White matter oedema
(ii) Astrocyte hypertrophy and hyperplasia
(iii) Vascular hyalinisation
(iv) Microcalcification
(v) Necrosis probably mediated by small vessel fibrosis

Whole body irradiation
With increasing dosage the effects can be grouped into three main syndromes:

1. Haemopoietic syndrome (4-10 Gy)
   (i) Lymphopenia
   (ii) Granulocytopenia
   (iii) Thrombocytopenia
Death may result from infection or haemorrhage

2. Gastrointestinal syndrome (10-15 Gy)
   (i) Villous atrophy
   (ii) Mucous depletion
Death is due to fluid and electrolyte imbalance, infection, or nutritional impairment

3. Cerebral syndrome (>100 Gy)
   Nerve cells are destroyed by either direct radiation injury or secondary to increased vascular permeability with oedema and pressure damage. Nausea and vomiting are followed by tremors and convulsions with death 1-2 days after exposure.
If the patient survives the acute phase then there are a number of possible late effects:
1. Marrow aplasia
2. Cataracts
3. Developmental abnormalities in the fetus
4. Leukaemia, skin cancer, or cancer in other organs such as thyroid, bone, larynx, etc.
5. General effects - premature ageing
6. Pneumonitis; nephritis; myocarditis and pericarditis

**Sensitivity of tumours to irradiation**
The following facts are important:
1. Tissue of origin
2. Degree of differentiation, usually inversely proportional to the sensitivity
3. Mitotic activity, directly proportional to the sensitivity
4. Vascularity of the stroma and general blood supply, which is related to 5
5. Hypoxia reduces the sensitivity of tumours to radiation, conversely hyperbaric oxygen has been used to enhance radiotherapy
6. Recurrent tumours are insensitive as they are probably derived from the most radioresistant cells of the primary neoplasm.

**Other therapeutic agents**
1. Modulation of oestrogens
   (i) Tamoxifen - competes with oestradiol for the high affinity oestrogen receptor
   (ii) Progestational agents - medroxyprogesterone
   (iii) Aminoglutethimide - inhibits synthesis of oestrogen
2. Modulation of androgens - cyproterone acetate, flutamide and synthetic gonadotro-releasing agonists
3. Biological response modifiers (cf. cytokines) - therapeutic agents which help the host's defense mechanisms to act against cancer cells
   (i) Interferons
   (ii) Interleukins-1 and 2
   (iii) Tumour necrosis factors
4. Immunotherapy (mainly experimental)
   (i) Active immunotherapy
      a. Administration of inactivated tumour cells
      b. Administration of immune stimulants such as BCG or *Corynebacterium parvum* vaccine or levamisole
   (ii) Passive immunotherapy
      a. Administration of monoclonal antibodies or fragments of antibodies
      b. Injection of cloned cytotoxic T-cells or natural killer cells
18. Alimentary system

SALIVARY GLANDS

A. Congenital
1. Agenesis of one or more glands
2. Atresia of a duct

B. Acute inflammation
1. Acute suppurative sialadenitis
2. Mumps
3. Cystomegalic inclusion disease
4. Congenital
5. Agenesis of one or more glands

C. Chronic inflammation
1. Non-specific, usually in association with calculi
2. Sjögren's syndrome
   (i) Keratoconjunctivitis sicca
   (ii) Xerostomia
   (iii) Rheumatoid arthritis
   (iv) Enlargement of salivary glands
3. Sarcoidosis
4. Tuberculosis
5. Actinomycosis
6. Syphilis
7. Mikulicz's disease (benign lymphoepithelial lesion)

D. Mechanical disorders
1. Mucocoele resulting from rupture of a duct
2. Ranula resulting from obstruction of a sublingual gland
3. Obstruction by calculus - sialolithiasis

E. Benign tumours
1. Pleomorphic adenoma (mixed parotid tumour)
2. Warthin's tumour
3. Monomorphic adenoma

F. Malignant tumours
1. Mucoepidermoid carcinoma
2. Adenoid cystic carcinoma
3. Carcinoma arising from a pleomorphic adenoma
4. Adenocarcinoma
5. Lymphoma
MOUTH AND PHARYNX

A. Congenital
1. Cleft lip and palate
2. Microstomia and macrostomia
3. Microglossia and macroglossia
4. Median rhomboid glossitis
5. 'Bifid' and 'scrotal' tongue

B. Acute inflammation
1. Non-specific gingivitis
2. Vincent's infection (acute necrotising ulcerative gingivitis)
3. Aphthous stomatitis
4. Herpetic gingivo-stomatitis
5. Moniliasis (thrush)
6. Cancrum oris (noma)

C. Chronic inflammation
1. Chronic desquamative gingivitis
2. Tuberculosis
3. Actinomycosis
4. Syphilis

D. Benign tumours and tumour-like conditions
1. 'Congenital epulis'
2. Giant-cell epulis (probably reactive)
3. Angiomatous 'tumour' of pregnancy (reactive)
4. Fibroma
5. Haemangioma
6. Squamous papilloma
7. Lymphangioma
8. Granular-cell myoblastoma

E. Leucoplakia
1. Aetiology
   (i) Poor dental hygiene
   (ii) Smoking
   (iii) Trauma from rough teeth
   (iv) Syphilis

2. Microscopic appearances
   (i) Hyperplasia of squamous epithelium
   (ii) Hyperkeratosis
   (iii) Chronic inflammatory reaction
   (iv) Dysplasia (may be absent)

F. Malignant tumours
1. Squamous carcinoma
2. Adenocarcinoma (mucous/salivary glands)
3. Intermediate or 'transitional-cell' carcinoma (pharynx)
4. Undifferentiated carcinoma with lymphoid stroma "lymphoepithelioma" (nasopharynx)
5. Malignant melanoma
6. Fibrosarcoma
7. Lymphoma (tonsils)

**OESOPHAGUS**

**A. Congenital**
1. Agenesis (extremely rare)
2. Atresia, usually associated with a fistula into the trachea
3. Stenosis
4. Gastric heterotopia

**B. Inflammation**
1. Reflux oesophagitis
   *Rare causes*
2. Viral oesophagitis, e.g. herpes simplex and CMV
3. Fungal oesophagitis
   (i) Candidiasis
   (ii) Aspergillosis
4. Uraemic oesophagitis
5. Corrosive chemical ingestion
6. Plummer-Vinson syndrome - resulting from long-standing iron deficiency
7. Tuberculosis
8. Crohn's disease
9. Chagas' disease

**C. Vascular disorders**

Oesophageal varices - dilatation of submucosal veins resulting from portal hypertension

**D. Mechanical disorders**
1. Diverticula
   (i) Traction
   (ii) Pulsion
2. Obstruction resulting from:
   (i) Stricture - chronic peptic ulceration or corrosive ingestion
   (ii) Carcinoma
   (iii) Achalasia (cardiospasm)
   (iv) Progressive systemic sclerosis
   (v) Mucosal webs
   (vi) Congenital stenosis
3. Rupture
   (i) Mucosal (Mallory-Weiss syndrome)
   (ii) Full thickness - oesophageal perforation
4. Hiatus hernia
   (i) Sliding type
   (ii) Para-oesophageal perforation
E. Benign tumours
1. Leiomyoma
2. Fibroma
3. Lipoma
4. Granular cell myoblastoma

F. Malignant tumours
1. Carcinoma of the oesophagus
   Predisposing factors, many of which are speculative
   (i) Tobacco and alcohol
   (ii) Barrett's metaplasia
   (iii) Anatomical abnormalities, e.g. hiatus hernia, achalasia
   (iv) Plummer-Vinson syndrome (post cricoid)
   (v) Following corrosive injury
   Types
   (i) Squamous cell, including polypoid or spindle cell variants
   (ii) Adenocarcinoma, arising from-
      a. Metaplastic columnar epithelium in the lower oesophagus (Barrett's oesophagus)
      b. Gastric type epithelium in lower 2 cm
   (iii) Oat-cell carcinoma (rare)
   (iv) Adenosquamous carcinoma (rare)

   Spread
   (i) Direct to:
      a. Mediastinum
      b. Trachea or main bronchi
      c. Lung
      d. Aorta or heart (uncommon)
   (ii) Metastasis to:
      a. Regional lymph nodes
      b. Liver
      c. Lungs
      d. Adrenal

   Prognosis
   5 year survival is below 10%

   The remaining tumours are all very rare:
   2. Sarcoma
      (i) Leiomyosarcoma
      (ii) Fibrosarcoma
   3. Malignant melanoma
   4. Carcino-sarcoma

STOMACH

A. Congenital
1. Diaphragmatic hernia
2. Congenital Pyloric stenosis
B. Inflammations

1. Acute haemorrhagic gastritis

   Causes
   (i) Alcohol excess
   (ii) Salicylates and other drugs
   (iii) Bile reflux
   (iv) Staphylococcal exotoxin in contaminated food
   (v) Irritant chemicals/corrosives
   (vi) After major surgery or trauma

2. Acute neutrophilic gastritis - the acute phase of *Helicobacter pylori* infection of the stomach

3. Chronic gastritis
   (i) Autoimmune gastritis
      a. Anti-parietal cell and anti-intrinsic factor antibodies
      b. Sensitized T-cell attack on corpus glands
      c. Glandular atrophy restricted to the corpus
      d. Intestinal metaplasia
   (ii) *H. pylori*-associated chronic gastritis, pan-gastritis type
      a. Involves entire stomach
      b. Surface epithelial degeneration
      c. Active chronic inflammation
      d. Depending on the duration of infection and the presence of other factors such as bile reflux and dietary irritants, atrophy and intestinal metaplasia are seen in the later stages.
      e. Increased risk of gastric ulcer and gastric cancer
   (iii) *H. pylori*-associated chronic gastritis, antrum predominant type
      a. Active chronic inflammation in the antrum
      b. Corpus is normal or shows only minor involvement
      c. occurs in people with acid-induced gastric metaplasia in the duodenum
      d. Strong association with duodenal ulceration
   (iv) Reflux or chemical type

   Causes
   a. Entero-gastric bile reflux
   b. NSAID usage
   c. Alcohol (possible)

   Features
   a. Foveolar hyperplasia
   b. Lamina propria oedema
   c. Vasodilatation/congestion
   d. Paucity of inflammatory cells

4. Lymphocytic gastritis
   (i) Large numbers of intra-epithelial lymphocytes
   (ii) Maximal in the corpus
   (iii) Enlarged mucosal folds
   (iv) Aphthoid ulcers

5. Hypertrophic gastritis (Ménétrier's disease)
   (i) Rugal hypertrophy
   (ii) Cystic dilatation of glands
(iii) Strands of muscularis mucosae in lamina propria
6. Eosinophilic gastritis
7. Granulomatous gastritis
   (i) Crohn's disease
   (ii) Sarcoidosis
   (iii) Reaction to H. pylori
   (iv) Foreign material, e.g. food particles in the mucosa
   (v) Isolated (i.e. idiopathic)

C. Acute ulceration and erosions
1. Related to acute gastritis
   (i) Aspirin
   (ii) Alcohol excess
   (iii) Bile reflux
2. Related to shock
   (i) Severe burns, major trauma (Curling's ulcers)
   (ii) Cerebrovascular accidents
   (iii) Septicaemia
   (iv) ACTH or corticosteroid therapy

D. Chronic peptic ulcers
1. Sites
   (i) Lesser curve of stomach
   (ii) First part of duodenum
   (iii) Lower oesophagus
   (iv) Gastroenterostomy margins
   (v) Meckel's diverticulum
   (vi) Remainder of duodenum and jejenum in Zollinger-Ellison syndrome
2. Predisposing factors Gastric ulceration
   (i) Chronic H. pylori-associated pan-gastritis
   (ii) NSAID use
   (iii) Alcohol abuse
   (iv) Bile reflux
Duodenal ulceration
   (i) Helicobacter-associated chronic gastritis - antral predominant
   (ii) Gastric metaplasia in the duodenum
3. Pathogenesis
   Chronic peptic ulcers occur when the digestive action of acid and pepsin overcome the natural defenses of the mucosa. Duodenal ulcers develop when:
   (i) Gastric metaplasia appears in the duodenum as a consequence of excessive acid output
   (ii) Subsequent H. pylori infection causes active chronic inflammation in the metaplastic mucosa
   (iii) Active chronic inflammation reduces mucosal resistance and erosions and ulceration ensue
Gastric ulcers are multifactorial
   (i) Long-standing chronic gastritis (H. pylori-associated) reduces mucosal resistance to acid/pepsin
   (ii) In some cases NSAIDs act synergistically with H. pylori-associated mucosal
damage to produce ulcers
(iii) Mucosa which has undergone intestinal metaplasia may be more susceptible to acid attack

4. Complications
(i) Perforation
(ii) Haemorrhage
(iii) Stenosis
   a. Pyloric
   b. Hour-glass deformity
(iv) Malignant change (rare)

E. Benign tumours and polyps
1. Hyperplastic (regenerative) polyps
2. True neoplasms
   (i) Adenoma
   (ii) Stromal tumours (difficult to predict behaviour)
3. Hamartomas and heterotopias
   (i) 'Cystic hamartomatous polyps'- simple fundic polyps
   (ii) Heterotopic pancreas
   (iii) Adenomyoma (myo-epithelial hamartoma)
   (iv) Peutz-Jeghers' polyps
   (v) Cronkhite-Canada syndrome
      a. Polyposis of the stomach and intestines
      b. Abnormal skin pigmentation
      c. Nail dystrophy
      d. Baldness

F. Malignant tumours
1. Carcinoma

   Precancerous conditions
   a. H. pylori-associated chronic gastritis with atrophy and intestinal metaplasia
   b. Adenomatous polyps (rare outside Japan)
   (Chronic peptic ulcer rarely give rise to gastric carcinomas, <1%)

Gross types
   (i) Nodular
   (ii) Ulcerative
   (iii) Polypoid or fungating
   (iv) Linitis plastica

Microscopic appearances
   (i) Intra-mucosal ‘tubular’ or ‘signet-ring cell’ types
   (ii) Adenocarcinoma
      a. Intestinal type
      b. Diffuse type
      c. Mixed showing well, moderate or poor differentiation
   (iii) Anaplastic carcinoma

Spread
   (i) Direct
      a. Confined to mucosa or submucosa = early gastric cancer (even if lymph
nodes involved)
  b. Spread into muscularis propria and beyond advanced gastric cancer
  (ii) Lymphatic to nodes along lesser and greater curve
  (iii) Blood spread to liver
  (iv) Transcoelomic to omentum, peritoneum and ovaries (Krukenberg spread)

2. Carcinoid tumour - increased prevalence in pernicious anaemia
3. Lymphoma - usually melanoma (B-cell lymphoma)
4. Stromal tumours of smooth muscle or neural origin

SMALL INTESTINE

A. Congenital
1. Duodenal diverticula
2. Diverticulosis of jejunum and ileum
3. Meckel's diverticulum
4. Atresia
5. Failures of rotation

B. Inflammation/ulceration
1. Crohn's disease
A chronic granulomatous disease mainly affecting the small intestine but can involve any part from mouth to anus. The aetiology is unknown but there is increasing evidence pointing towards infection by \textit{Mycobacterium paratuberculosis}.

  \textbf{Gross features}
  (i) 'Hosepipe' thickening of wall
  (ii) Ulcers - aphthoid or linear
  (iii) Deep fissures
  (iv) 'Cobblestone' mucosa
  (v) 'Skip' lesions (i.e. segmental involvement)
  (vi) Enlarged lymph nodes

\textbf{Microscopic appearances}
  (i) Granulomas (sarcoid-type)
  (ii) Transmural inflammation
  (iii) Aggregated pattern of inflammatory cells
  (iv) Submucosal oedema, lymphangiectasia, and fibrosis
  (v) Fissure ulcers
  (vi) Neuromatoid hyperplasia

\textbf{Complications}
  (i) Malabsorption
  (ii) Obstruction
  (iii) Fistula formation
  (iv) Perforation
  (v) Haemorrhage
  (vi) Liver disease - peri-biliary fibrosis
  (vii) Skin lesions
  (viii) Ocular inflammation
  (ix) Malignancy

2. Infections
  (i) Cholera
(ii) *E. coli* infections in infants  
(iii) Typhoid/paratyphoid  
(iv) Staphylococcal enterocolitis  
(v) Tuberculosis  
(vi) Actinomycosis  
(vii) *Yersinia pseudotuberculosis* (acute terminal ileitis)  
(viii) Viral diseases parvoviruses and reoviruses  
(ix) Whipple's disease  
(x) Giardiasis - found more commonly in:  
   a. Childhood  
   b. Malnutrition  
   c. Following gastrectomy  
   d. Pancreatic disease  
   e. Hypogammaglobulinaemia  
   f. Nodular lymphoid hyperplasia  
   g. Dysgammaglobulinaemia  
   h. Travellers (Leningrad, Indian subcontinent, etc)  

C. Malabsorption  
Due to abnormal small intestinal function  
1. Villous atrophy  
   **Terminology**  
   (i) Villous architecture  
      a. Mild, moderate or severe partial villous atrophy  
      b. Total villous atrophy  
   (ii) Crypt cellularity and mitotic activity  
      a. Crypt hyperplasia  
      b. Crypt hypoplasia  
   **Major causes of crypt hyperplastic villous atrophy**  
   (i) Coeliac disease caused by an abnormal response of the small intestinal mucosa to an unknown peptide found in the wheat protein, gluten. This is likely to be immunologically mediated.  
   **Immunological findings**  
      a. Mucosal plasma cells show diminished IgA, and increased IgM secretion  
      b. IgM is decreased in the serum whilst IgA is increased  
      c. Features of immune dysfunction such as splenic atrophy and impaired lymphocyte transformation  
      d. The serum may contain IgM antibodies to certain fractions of gluten  
      e. IgA deposited on basement t-membrane following gluten challenge. IgG deposits found in untreated coeliacs  
      d. Increased proportion of g/b T-cells in the epithelium  
   **Microscopic features**  
      a. Total or severe partial villous atrophy  
      b. Cuboidal surface epithelium with palisading of nuclei and indistinct brush border  
      c. Heavy infiltration of epithelium by lymphocytes  
      d. Increase in lymphocytes and plasma cells in lamina propria  
   **Complications**  
      a. Enteropathy-associated T-cell lymphoma
b. Ulcerative jejunitis
c. Adenocarcinoma of the small intestine
d. Extra-intestinal malignancy, e.g. carcinoma of the oesophagus

(ii) Tropical sprue
(iii) Stasis syndrome with bacterial overgrowth
(iv) Post-infective malabsorption syndrome
(v) Kwashiorkor
(vi) Severe chronic duodenitis

Causes of crypt hypoplastic villous atrophy
(i) Pernicious anaemia
(ii) Folic acid deficiency
(iii) Carcinomatosis
(iv) Hypopituitarism
(v) Irradiation

2. Biochemical disorders giving rise to malabsorption
(i) Sucrase-isomaltase deficiency
(ii) Lactase deficiency
(iii) Monosaccharide malabsorption
(iv) Hartnup disease
(v) Cystinuria
(vi) Congenital chlorodiarrhoea
(vii) Abeta-lipoproteinaemia

3. Disease of the intestinal wall
(i) Amyloidosis
(ii) Radiation injury
(iii) Collagen disease
(iv) Crohn's disease

4. Altered bacterial flora
(i) Stagnant loop syndrome
(ii) Jejunal diverticulosis
(iii) Multiple strictures as in Crohn's disease
(iv) Fistulae

5. Miscellaneous causes
(i) Whipple's disease
(ii) Lymphangiectasia

D. Vascular disorders
1. Mucosal vessels
   (i) Hereditary haemorrhagic telangiectasia (Osler-Rendu-Weber syndrome)

2. Mesenteric arteries
   (i) Thrombosis/embolus
   (ii) Atherosclerosis
   (iii) Fibro-muscular hyperplasia
   (iv) Polyarteritis nodosa

3. Mesenteric veins
   (i) Thrombosis
   (ii) Strangulation (in later stages leads to arterial occlusion)

Arterial and venous occlusion results in haemorrhagic infarction

4. Non-occlusive ischaemia resulting from
   (i) Cardiac failure
(ii) Shock
(iii) Drug-induced vasoconstriction

E. Mechanical disorders
Obstruction of the small intestine
Causes
1. Hernias
2. Adhesions
3. Neoplasms
4. Intussusception
5. Volvulus
6. Strictures, congenital or acquired
7. Atresia
8. Gall stones or foreign body (including food bolus)
9. Meconium plug (mucoviscidosis)
Obstruction may also result from mesenteric thrombosis and neurogenic paralytic ileus

F. Benign tumours - these are all rare
1. Adenoma - mainly peri-ampullary
2. Lipoma
3. Haemangiomata (may be part of the Osler-Rendu-Weber syndrome)
4. Lymphangioma
5. Peutz-Jeghers’ polyps (hamartomas)
6. Stromal tumour

G. Malignant tumours
1. Carcinoid tumour
2. Lymphoma Predisposed to by:
   (i) Coeliac disease
   (ii) Alpha-chain disease
   (iii) Selective IgA deficiency
   (iv) Common variable hypogammaglobulinaemia
   (v) Crohn's disease
3. Malignant stromal tumour
4. Adenocarcinoma (rare) Predisposed to by:
   (i) Crohn's disease
   (ii) Coeliac disease
   (iii) Familial adenomatous polyposis

APPENDIX
A. Inflammation
1. Acute non-specific
   Predisposing factors (act mainly by causing obstruction)
   (i) Lymphoid hyperplasia
      a. Physiological
      b. Measles and other viral diseases
   (ii) Faecalith/foreign bodies/food residues
   (iii) Mucosal oedema
   (iv) Diverticulosis of the appendix
(v) Carcinoid tumour
(vi) Threadworms

Complications
(i) Perforation leading to:
   a. Generalized peritonitis
   b. Appendicular abscess
   c. Fistula formation
(ii) Suppurative pylephlebitis and liver abscess
(iii) Septicaemia
(iv) Chronic appendicitis
(v) Mucocoele which may rupture and produce pseudomyxoma peritonei

2. Specific bacterial infections
   (i) *Yersinia pseudotuberculosis* appendicitis
   (ii) Typhoid
   (iii) Tuberculosis
   (iv) Actinomycosis

3. Crohn's disease
4. Starch-grain granulomatosis
5. Polyarteritis nodosa
6. Eosinophil granuloma

B. Neoplasms
1. Carcinoid tumour
2. Adenoma
3. Adenocarcinoma
4. Lymphoma

LARGE INTESTINE

A. Congenital
1. Atresia including imperforate anus
2. Stenosis
3. Duplication
4. Hirschsprung's disease - aganglionosis

B. Inflammation
1. Infective colitis *Features*
   (i) Crypt pattern preserved
   (ii) Predominantly neutrophil Polymorph infiltrate
   (iii) Poorly formed 'mucoid' crypt abscesses
   (iv) Marked surface epithelial degeneration and crypt hyperplasia

*Causes*
(i) Bacterial
   a. *Campylobacter jejuni*
   b. Bacillary dysentery (shigellosis)
   c. Salmonella food-poisoning
   d. Tuberculosis
   e. Staphylococcal enterocolitis
   f. Gonorrhoea
   g. Enterotoxic *E. coli*
(ii) Viral / chlamydial
a. CMV
b. Lymphogranuloma venereum
(iii) Others
a. Amoebic dysentery
b. Schistosomiasis
c. Balantidiasis
d. Rectal syphilis

2. Ulcerative colitis
A chronic inflammatory process of unknown aetiology characterized by relapses and remissions leading to persistent diarrhoea and debility.

Sites
Usually starts in rectum and spreads proximally to involve a variable length of colon. Frequently the entire colon is involved.

Gross features
(i) Continuity of involvement
(ii) Confluent irregular mucosal ulceration
(iii) Pseudopolyps’ residual inflamed mucosa
(iv) Intense vascularity

Microscopic features
(i) Continuous inflammation maximal in the mucosa
(ii) Congestion and vasodilatation
(iii) Crypt abscesses
(iv) Undermining ulcers and inflammatory polyps
(v) Crypt atrophy and distortion
(vi) Mucin depletion
(vii) Paneth-cell metaplasia
(viii) Pre-malignant dysplasia may be present in long-standing cases

Complications
(i) Haemorrhage
(ii) Anaemia
(iii) Electrolyte disturbance
(iv) Perforation
(v) Toxic dilatation
(vi) Malignant change - adenocarcinoma, rarely a malignant carcinoid or small cell carcinoma
(vii) Extra-intestinal disease
   a. Skin lesions - pyoderma gangrenosum, erythema nodosum
   b. Arthritis/ankylosing spondylitis
   c. Liver disease - chronic pericholangitis
   d. Eye disease - iritis, uveitis, episceritis
   e. Biliary tract - sclerosing cholangitis, carcinoma

3. Crohn's colitis
4. Irradiation colitis
5. Antibiotic-associated (including pseudomembranous colitis)
6. Mucosal prolapse syndrome - including solitary ulcer
7. Microscopic or lymphocytic colitis
8. Collagenous colitis
9. Diversion colitis

C. Vascular disorders
1. Ischaemia
   The causes of ischaemia are the same as those in the small intestine.
   Ischaemia results in:
   (i) Infarction
   (ii) Ischaemic colitis
   (iii) Stricture
2. Haemorrhoids.
   Varicosities of the superior and inferior rectal veins.
   Causes
   (i) Chronic constipation
   (ii) Heavy physical work
   (iii) Pregnancy
   (iv) Pelvic tumours
   (v) Portal hypertension
   (vi) Rectal carcinoma
3. Angiodysplasia - usually in the caecum

D. Mechanical disorders
1. Diverticular disease
   Outpouchings of the large bowel mucosa through the muscle coat develop in response to prolonged increases in intraluminal pressure. These diverticulae form at the sites of lympho-glandular complexes in the mucosa which overlie defects in the muscularis mucosae. The usual segment to be affected is the sigmoid colon, but infrequently they can be found in the proximal colon. The diverticulae become secondarily infected, probably following minor trauma, and the ensuing diverticulitis can lead to abscess formation and generalized peritonitis.
2. Volvulus
3. Herniation
4. Intussusception

E. Tumour-like conditions
   (i) Peutz-Jeghers’ polyps
   (ii) Juvenile polyposis

F. Benign tumours and polyps
1. Epithelial
   (i) Tubular adenoma (adenomatous polyp)
   (ii) Tubulo-villous adenoma
   (iii) Villous adenoma
   (iv) Metaplastic polyps
2. Lymphoid
   (i) Benign lymphoid polyp
3. Connective tissues
   (i) Lipoma
(ii) Stromal tumours
(iii) Ganglioneuroma
(iv) Haemangioma

G. Malignant tumours

1. Carcinoma

Pre-malignant conditions
(i) Adenomas - adenoma-carcinoma sequence
   a. Familial adenomatous polyposis
   b. Hereditary non-polyposis colorectal cancer syndrome
(ii) Ulcerative colitis - dysplasia-carcinoma sequence

Aetiology
(i) Genetic - familial tendency
(ii) Dietary factors
   a. ? Bile salts and anaerobic organisms
   b. ? Low residue food

Gross features
(i) Annular ulcerated
(ii) Polypoid/fungating

Microscopic appearances
(i) Adenocarcinoma
(ii) Mucoid (colloid) carcinoma
(iii) Small-cell undifferentiated carcinoma and in the lower rectum and anal canal
(iv) Squamous carcinoma (including basaloid variety)

Spread
Direct and lymphatic: Dukes' classification -
   Stage A - does not penetrate through the muscle layer of the colon/rectum
   Stage B - extends into surrounding fat but there is no involvement of regional lymph nodes
   Stage C1 - secondary deposits present in the regional lymph nodes
   Stage C2 - involvement of the highest resected lymph node
   Stage D - distant metastases

Blood spread is mainly to the liver

Complications
(i) Obstruction
(ii) Perforation
(iii) Fistula formation
(iv) Haemorrhoids (with rectal carcinoma)
(v) Anaemia
(vi) Diarrhoea

2. Carcinoid tumour
3. Lymphoma, including malignant lymphoid polyposis
4. Sarcoma
   (i) Malignant stromal tumour
   (ii) Liposarcoma
5. Malignant melanoma (anal region)
19. Liver, gall-bladder-and pancreas

DISEASES OF THE LIVER

A. Congenital
1. Accessory lobes - Riedel's lobe
2. Congenital cystic disease (found in association with polycystic kidneys)
3. Congenital hepatic fibrosis (some cases are associated with renal cysts)
4. (α-1-antitrypsin deficiency

B. Infections
1. Viral hepatitis
   Types
   (i) Hepatitis A - caused by an RNA enterovirus, 2-6 weeks incubation, epidemic, faecal-oral spread
   (ii) Hepatitis B - DNA hepadna Virus, 2-6 months incubation, parenteral, placental or venereal spread Dane particle - complete virion consisting of a core containing circular DNA formed in liver cell nuclei and a coat which is formed in the cytoplasm and is often found detached from the core. The core antigen is termed HBCAG and the surface antigen, HBsAg. A third antigen e antigen, has three variants and e3 is associated with hepatitis-B-specific DNA polymerase.
   (iii) Hepatitis C - RNA virus related to flaviviridae, long incubation, parenteral spread
   (iv) Hepatitis D - defective RNA virus, infection only occurs if patient has hepatitis B, parenteral spread
   (v) Hepatitis E - RNA virus, short incubation, faecal-oral spread
   (vi) Other hepatitis viruses - unexplained outbreaks of hepatitis and sporadic cases
   (vii) Miscellaneous viral diseases involving the liver include
      a. Infectious mononucleosis
      b. Cytomegalovirus
      c. Herpes hominis
      d. Yellow fever

Microscopic features
   (i) Necrosis of hepatocytes, usually single-cell but may be zonal
   (ii) Other degenerative changes - 'ballooning'
      (iii) Inflammatory cell infiltration of portal tracts and parenchyma, mainly lymphocytes and macrophages with small numbers of polymorphs
   (iv) Kupffer cell proliferation
   (v) Variable cholestasis
   (vi) Features of regeneration

Variants of acute viral hepatitis
   (i) With bridging necrosis (subacute hepatic necrosis)
   (ii) With massive necrosis
   (iii) 'Cholestatic' hepatitis

Fate of acute viral hepatitis
   (i) Resolution
Massive necrosis and death
Recurrence of acute hepatitis
Chronic persistent hepatitis
Chronic active hepatitis (hepatitis B, C and D)
Cirrhosis

2. Bacterial infection
   (i) Tuberculosis especially in miliary spread
   (ii) Brucellosis

3. Spirochaetes
   (i) Syphilis
      a. Congenital pericellular fibrosis
      b. Gummata - hepatic lobatum
   (ii) Borrelia recurrentis infection
   (iii) Leptospirosis (Weil's disease)

4. Protozoa
   (i) Amoebiasis
      a. Amoebic hepatitis
      b. Amoebic abscess
   (ii) Toxoplasmosis

5. Rickettsia
   (i) Q fever

6. Fungi
   (i) Histoplasmosis

7. Parasites
   (i) Hydatid cysts - *Echinococcus granulosus*
   (ii) Opisthorchiasis (Clonorchis)
   (iii) *Fasciola hepatica*
   (iv) *Schistosoma mansoni.*
   (v) *Ascaris lumbricoides*

8. Non-specific inflammation
   (i) Abscess (pyaemic)
   (ii) Cholangitis

C. Chronic hepatitis
A diffuse inflammatory condition of the liver in which there are clinical and/or biochemical disturbances for longer than 6 months.

1. Chronic persistent hepatitis
   The liver contains excessive numbers of chronic inflammatory cells but these are confined to the portal tracts.

   Causes
   (i) Prolonged viral hepatitis
   (ii) Non-specific reaction to systemic disease
   (iii) Inflammatory bowel disease
   (iv) Alpha-1-antitrypsin deficiency

   Prognosis
   Good, the disease usually resolves (unless it is secondary to some untreatable condition), but it may progress to chronic active hepatitis

2. Chronic active hepatitis (CAH)
   Excessive numbers of chronic inflammatory cells in portal and peri-portal areas with destruction of liver cells at the interface between connective tissue and
parenchyma - piecemeal necrosis.
There might also be:
(i) Bridging necrosis linking portal tracts
(ii) Lobular hepatitis - inflammatory infiltration and degenerative changes throughout the parenchyma

**Causes**
(i) Primary - ? an auto-immune disease with systemic features
(ii) Secondary
   a. Viral
      Hepatitis B
      Hepatitis C
      Hepatitis D
      Neonatal hepatitis
   b. Drugs (see below)
   c. Alcohol (rare)
   d. Wilson's disease
   e. Alpha-1-antitrypsin deficiency

**Prognosis**
Poor, there is almost invariably progression to cirrhosis but deterioration is delayed by steroid or interferon therapy.

**D. Drugs and the liver**
Drugs may injure the liver by a direct toxic effect or because of an idiosyncratic reaction where the drug is acting as an allergen. Four major categories of liver damage are produced:
1. Direct hepatic necrosis
2. Hepatitis-like reactions
3. Cholestasis and hepatitis
4. Cholestasis alone

1. **Direct hepatic necrosis.** This is usually a predictable injury resulting in zonal or massive necrosis.

**Causes include**
(i) Paracetamol (acetaminophen) in acute overdosage
(ii) Ferrous sulphate in acute overdosage
(iii) Carbon tetrachloride and benzene derivatives
(iv) Methotrexate and 6-mercaptopurine (non-zonal)
(v) Aflatoxin
(vi) Tannic acid

2. **Hepatitis-like reactions.** These are hypersensitivity reactions and may produce a histological picture indistinguishable from acute viral hepatitis or a chronic active hepatitis.

**Causes include**
(i) Halothane
(ii) Monoamine oxidase inhibitors
(iii) (a-Methyldopa
(iv) Isoniazid
(v) Oxyphenisatin
(vi) Nitrofurantoin  
(vii) Sulphonamides  

3. Cholestasis and hepatitis. This also represents a hypersensitivity reaction in which cholestasis is the major feature but some histological evidence of hepatitis is usually present.  

Causes include  
(i) Phenothiazines especially chlorpromazine  
(ii) Tricyclic antidepressants  
(iii) Anxiolytic drugs (chlordiazepoxide, diazepam)  
(iv) Anti-inflammatory drugs (phenylbutazone, indomethacin)  
(v) Anti-tuberculous drugs (PAS, rifampicin)  
(vi) Antibiotics (erythromycin, sulphamethoxazole)  

4. Cholestasis alone  
This injury is not related to hypersensitivity but genetic factors may alter susceptibility:  

Causes  
(i) Anabolic steroids (methyltestosterone/norethandrolone)  
(ii) Contraceptive steroids  

5. Miscellaneous drug injuries  
(i) Diffuse fatty liver - tetracycline  
(ii) Increase in liver cell lipofuscins - phenacetin  
(iii) Fatty change, fibrosis, and cirrhosis - long-term methotrexate therapy for psoriasis  
(iv) Central vein occlusion - Senecio alkaloids, urethane  
(v) Peliosis hepatitis (haemorrhagic cysts) - anabolic steroids  
(vi) Granuloma - phenylbutazone  

6. Alcohol and the liver  
(i) Fatty liver - may be associated with:  
   a. Jaundice  
   b. Portal hypertension  
   c. Encephalopathy  
   d. Fat embolism (very rare)  
(ii) Alcoholic hepatitis  

Features  
 a. Centrilobular single-cell necrosis  
 b. Mallory's hyaline bodies  
 c. Fatty change  
 d. Polymorph infiltration  
 e. Pericellular collagenisation  
 f. Perivenular fibrosis  
 g. Giant mitochondria  
(iii) Cirrhosis  
(iv) Portal fibrosis  
(v) Chronic active hepatitis  
(vi) Cholestasis (unusual)  

E. Degenerative/metabolic disorders  
1. Brown atrophy - lipofuscinosisis  
2. Fatty change  
   (i) Diabetes mellitus
(ii) Starvation
(iii) Alcoholic
(iv) Obesity
(v) Kwashiorkor
(vi) Drugs - methotrexate, corticosteroids
(vii) Reye's syndrome (? viral aetiology, usually preceded by influenza or varicella infection, associated with salicylates)
   a. Fever/vomiting
   b. Hypoglycaemia
   c. Respiratory acidosis
   d. Encephalopathy
   e. Liver shows microvesicular fatty change
3. Amyloidosis - usually secondary type
4. Glycogen deposition
   (i) Diabetes mellitus (with nuclear vacuolation)
   (ii) Von Gierke's disease
5. Lipid storage
   (i) Hand-Schüller-Christian disease
   (ii) Gaucher's disease
   (iii) Niemann-Pick
6. Haemosiderosis/haemochromatosis
7. Wilson's disease

F. Vascular disorders
1. Portal hypertension follows obstruction to the portal blood flow somewhere along its course
   (i) Extrahepatic portal vein
      a. Thrombosis possibly secondary to pancreatitis or pylephlebitis
      b. Pressure from glands in porta hepatitis
      c. Invasion by carcinoma of pancreas or biliary tract
      d. Stricture or ligature following surgery
   (ii) Intrahepatic portal veins
      a. Schistosomiasis
      b. Infiltration of portal tracts by lymphoma, myeloproliferative disease, or sarcoidosis
      c. Congenital hepatic fibrosis
      d. Obliterative portal venopathy
   (iii) Sinusoids or small hepatic veins
      a. Cirrhosis
      b. Veno-occlusive disease resulting from ingestion of Senecio alkaloids, administration of cytotoxic drugs and liver irradiation
   (iv) Hepatic veins (Budd-Chiari syndrome)
      a. Thrombosis
      b. Tumour involvement
   (v) Chronic venous congestion of liver (CVC)
      a. Congestive cardiac failure
      b. Constrictive pericarditis
      c. Tricuspid incompetence
2. Infarcts resulting from occlusion of the hepatic arteries are uncommon and usually result from a severe arteritis or when the additional supply from the portal vein is
diminished.
Occlusion of intrahepatic branches of the portal vein results in haemorrhagic lesions - 'Zahn's infarcts'.
3. Hypoxic centrilobular necrosis is seen in shock.
4. Cardiac 'cirrhosis'
Prolonged and severe CVC leads to centrilobular necrosis, distortion of reticulin framework and scarring. In the most severe cases this scarring may link up adjacent central veins to produce 'reverse lobulation'. The intervening parenchyma rarely shows sufficient evidence of regeneration to justify the term cirrhosis.

G. Bile duct diseases
1. Primary biliary cirrhosis
   (i) Granulomatous inflammation around medium sized bile ducts
   (ii) Destruction and disappearance of ducts
   (iii) Aggregated lymphocytic infiltration
   (iv) Lipid-laden macrophages in portal tracts
   (v) Anti-mitochondrial antibodies in serum
2. Sclerosing cholangitis
   (i) Loss of bile ducts in liver
   (ii) Fibrous obliteration of extra-hepatic biliary system
   (iii) Association with ulcerative colitis
   (iv) Proceeds to biliary cirrhosis (secondary)

H. Cirrhosis
A combination of widespread fibrosis and regenerative nodule formation following necrosis of liver cells.
Aetiological classification
1. Cryptogenic or idiopathic
2. Toxic or drug-induced
   (i) Alcohol
   (ii) Methotrexate
   (iii) Aflatoxins
3. Viral hepatitis (including neonatal hepatitis)
4. Immunologically mediated
   (i) Chronic active hepatitis
   (ii) Primary biliary cirrhosis
5. Secondary biliary cirrhosis, resulting from long standing obstruction
6. Metabolic and inherited disorders
   (i) Haemochromatosis
   (ii) Wilson's disease
   (iii) a,-l-antitrypsin deficiency
   (iv) Cystic fibrosis
   (v) Hereditary haemorrhagic telangiectasia
   (vi) Galactosaemia
   (vii) Hereditary fructose intolerance
7. Intestinal by-pass
8. Indian childhood cirrhosis
Incidence
1. Alcoholic (about 60%)
2. Viral (10%)
3. Biliary (10%)
4. Disordered iron metabolism (5%)
5. Other metabolic disorders (1%)
6. Idiopathic (15%)

Complications of cirrhosis
1. Hepatocellular failure
   (i) Increasing jaundice
   (ii) Coagulopathy - decreased synthesis of factors V, VII, IX and X
   (iii) Encephalopathy
   (iv) Hyperoestrogenism
2. Portal hypertension
   (i) Splenomegaly
   (ii) Enlargement of porto-systemic anastomoses
   (iii) Ascites
3. Intercurrent infection, e.g. suppurative peritonitis
4. Development of liver-cell carcinoma

I. Tumour-like lesions
1. Cavernous haemangioma
2. Mesenchymal hamartoma
3. Focal nodular hyperplasia
4. Diffuse nodular hyperplasia
5. Partial nodular transformation

J. Benign tumours
1. Adenoma
   (i) Bile duct adenoma
   (ii) Liver cell adenoma (associated with contraceptive steroids)
2. Infantile haemangioendothelioma

K. Malignant tumours
1. Liver cell carcinoma predisposing factors
   (i) Cirrhosis, especially haemochromatosis
   (ii) Aflatoxins?
   (iii) Hepatitis B infection
2. Bile duct carcinoma Predisposing factors
   (i) Clonorchis sinensis infestation
   (ii) Arsenic
   (iii) Ulcerative colitis
3. Haemangiosarcoma Predisposing factors
   (i) Polyvinyl chloride manufacture
   (ii) Thorotrast
4. Hepatoblastoma
5. Lymphoma
6. Fibrosarcoma/neurogenic sarcoma (very rare)
7. Metastatic carcinoma is very common. The main sources are:
   (i) Gastrointestinal tract
Likewise involvement by leukaemias and lymphomas arising elsewhere is common.

L. Hyperbilirubinaemia (jaundice)

Causes of jaundice:

1. Excessive bilirubin production capacity of the liver
   (i) Haemolysis due to
      a. Hereditary spherocytosis
      b. Hereditary red-cell enzyme defects
      c. Thalassaemia
      d. Sickle-cell disease
      e. Auto-immune haemolytic anaemia
      f. Secondary to Hodgkin's disease, leukaemias, etc.
   (ii) Increased production by the bone marrow – primary, 'shunt' hyperbilirubinaemia

2. Decreased uptake of bilirubin into liver cells and transport to the smooth endoplasmic reticulum
   (i) Gilbert's disease. A familial condition resulting in mild intermittent jaundice
   (ii) Viral hepatitis

3. Defective conjugation of bilirubin
   (i) Glucuronyl transferase deficiency
      a. Neonatal jaundice ('physiological')
      b. Crigier-Najjar disease. A very rare condition giving rise to severe persistent jaundice and deposition of bilirubin in the brain - kernicterus
   (ii) Glucuronyl transferase inhibitor in the maternal serum familial neonatal hyperbilirubinaemia (Lucey-Driscoll syndrome)

4. Disturbances of bilirubin excretion
   
   Intrahepatic:
   (i) Impaired cellular excretion into canaliculi
      a. Viral hepatitis (cholestatic type)
      b. Alcoholic hepatitis
      c. Dubin-Johnson syndrome, associated with marked lipofuscin deposition in liver cells
      d. Rotor syndrome, without such pigment
   (ii) Canalicular or ductular obstruction
      a. Drug hypersensitivity, e.g. chlorpromazine
      b. C-17 substituted steroids such as methyl testosterone
      c. Cholestatic jaundice of pregnancy and the pill
      d. Breast-milk jaundice of neonates
      e. Associated with Hodgkin's disease and other lymphomas
      f. Severe infections
      g. Idiopathic recurrent cholestasis
   (iii) Bile duct obstruction
      a. Primary biliary cirrhosis
      b. Sclerosing cholangitis
      c. Intrahepatic biliary atresia
      d. Cholangiocarcinoma

   Extrahepatic bile duct obstruction
   (i) Gall stones
(ii) Carcinoma of the pancreas/ampulla
(iii) Pressure by tumour involved lymph glands at the porta hepatis
(iv) Sclerosis of the extrahepatic ducts
(v) Postoperative stricture
(vi) Extrahepatic atresia

5. Hepatic failure
The jaundice of hepatic failure may result from several disturbances but the principal
defect is that there are insufficient functioning liver cells to conjugate the normal
bilirubin load. The major causes are:
(i) Terminal cirrhosis
(ii) Massive necrosis
   a. Fulminant viral hepatitis
   b. Drug hepatotoxicity, e.g. paracetamol (acetaminophen) overdosage,
      halothane hepatitis

DISEASES OF THE GALL-BLADDER AND EXTRA-HEPATIC BILE DUCTS

A. Congenital
1. Atr r of any part of the hepatic or common bile ducts
2. Folded gall-bladder
3. Complete or incomplete septum across the lumen
4. 'Floating' gall-bladder
5. Anomalies of the Cystic duct and artery
6. Choledocal cyst

B. Inflammation
1. Acute cholecystitis Results
   (i) Resolution
   (ii) Empyema
   (iii) Gangrene which may perforate and produce
      a. Generalized peritonitis
      b. Local abscess
   (iv) Ascending cholangitis
2. Chronic cholecystitis Features
   (i) Fibrosis
   (ii) Mucosal herniations (Aschoff-Rokitansky sinuses)
   (iii) Chronic inflammatory cell infiltrate
   (iv) Muscular hypertrophy

C. Cholelithiasis
Factors involved
(i) Production of abnormal bile
   a. Excess bile pigment
   b. Excess of cholesterol relative to bile salts and lecithin
(ii) Infection and inflammation
(iii) Stasis
Composition
(i) Mixed stones (about 90%)
(ii) Pure stones
a. Cholesterol
b. Calcium bilirubinate
c. Calcium carbonate

**Effects**
(i) Clinically 'silent'
(ii) Inflammation - provoke acute and chronic cholecystitis
(iii) Obstruction
   a. Cystic duct; leading to empyema and mucocoele
   b. Common bile duct; producing obstructive jaundice
   c. Ampulla of Vater; jaundice and in some cases acute pancreatitis
(iv) Erosion and perforation
   a. Biliary peritonitis
   b. Gall-stone ileus
(v) Malignant change
Gall-stones are present in about 90% of cases of carcinoma of the gall-bladder

**Risk factors**
(i) Obesity
(ii) Diet
(iii) Race
(iv) Sex
(v) Reduced entero-hepatic circulation

**D. Mechanical disorders**
1. Diverticulosis of the gall-bladder
   (i) Fundal, usually in relation to a congenital septum (socalled 'adenomyoma')
   (ii) Generalized - 'cholecystitis glandularis proliferans'
2. Obstruction to the extra-hepatic bile ducts
   (i) Gall stones
   (ii) Benign stricture
      a. Following surgery
      b. Traumatic
      c. Fibrosis around a peptic ulcer
      d. Chronic pancreatitis
      e. Benign bile duct tumours
      f. Sclerosing cholangitis
   (iii) External pressure
      a. Carcinoma of the pancreas
      b. Enlarged lymph glands at the porta hepatis
      c. Duodenal diverticulum
   (iv) Malignant stricture/occlusion
      a. Carcinoma of the Ampulla
      b. Carcinoma of the bile ducts
      c. Invasion by neighbouring carcinoma
   (v) Atresia

**E. Benign tumours**
1. Papilloma
2. Adenoma
3. Papillary adenomatosis (widespread)
F. Malignant tumours
Carcinoma
(i) Gall-bladder
   a. Papillary
   b. Diffuse infiltration
      *Microscopic appearances*
      a. Adenocarcinoma
      b. Squamous carcinoma (metaplasia)
      c. Anaplastic
(ii) Extra-hepatic ducts *Gross features*
   a. Papillary nodule
   b. Thickening of the wall
      *Microscopical appearances*
      a. Papillary adenocarcinoma
      b. Scirrhoux, mucus-secreting adenocarcinoma

G. Stricture of the bile ducts
1. Congenital biliary atresis
2. Surgery and post-traumatic
3. Post-inflammatory
   (i) Gall-stones
   (ii) Local inflammation - duodenal ulcer or pancreatitis
   (iii) Parasites
4. Tumours
   (i) Adenoma
   (ii) Adenocarcinoma
   (iii) Extrinsic lymph node involvement

DISEASES OF THE PANCREAS

A. Congenital
1. Aplasia and hypoplasia
2. Ectopic pancreas in
   (i) Stomach and duodenum
   (ii) Jejunum
   (iii) Meckel's diverticulum
   (iv) Ileum
3. Anomalies of the ducts
4. Annular pancreas
5. Mucoviscidosis (cystic fibrosis)
   Lesions mainly due to exocrine gland obstruction by secretions. Pathogenesis unknown.
   *Autosomal recessive inheritance*

Lesions
   (i) Meconium ileus
   (ii) Pancreas - fibrocystic changes
   (iii) Lungs - recurrent bronchopneumonia usually staphylococcal
   (iv) Liver - biliary cirrhosis
(v) Salivary glands - acinar atrophy and fibrosis

6. Congenital cysts

B. Inflammations
1. Acute haemorrhagic pancreatitis *Aetiological factors*
   (i) Alcohol excess - causes hypersecretion and protein-plugging
   (ii) Bile reflux - biliary tract disease and gall-stones
   (iii) Ischaemia
   (iv) Reflux of duodenal juice

   A small proportion of cases are associated with:
   (i) Hypothermia in the aged
   (ii) Mumps
   (iii) Primary hyperparathyroidism
   (iv) Hyperlipoproteinaemia
   (v) Pregnancy and gall-stones
   (vi) Trauma
   (vii) Carcinoma of the pancreas
   (viii) Corticosteroid and azathioprine therapy

   *Effects* (in severe cases)
   (i) Hypovolaemic shock
   (ii) Paralytic ileus
   (iii) Hypocalcaemia (tetany)
   (iv) Hypomagnesaemia

   *Results*
   (i) Resolution, usually incomplete
   (ii) Abscess
   (iii) Pseudocyst formation in lesser-sac
   (iv) Recurrent acute pancreatitis
   (v) Chronic pancreatitis

2. Chronic pancreatitis
   *Aetiology*
   (i) Idiopathic
   (ii) Alcohol excess
   (iii) Following acute pancreatitis
   (iv) Biliary tract disease
   (v) Haemochromatosis

   *Effects*
   (i) Exocrine insufficiency – steatorrhoea
   (ii) Diabetes mellitus
   (iii) Obstructive jaundice
   (iv) Haematemesis and melaena

C. Degenerative disorders
1. Fatty infiltration (adiposity)
2. Atrophy
   (i) Atherosclerotic
(ii) Obstruction of major ducts resulting from
   a. Atresia or congenital stenosis
   b. Pancreatic calculi
   c. Squamous metaplasia
   d. Carcinoma involving ducts
   e. Ligature
   f. Inflammatory stenosis
3. Acinar ectasia in uraemia

D. Benign tumours
1. Cystadenoma - microglandular, glycogen-rich type
2. Fibroma
3. Lipoma
4. Haemangioma

E. Carcinoma of the pancreas
Microscopic types
1. Adenocarcinoma
   (i) Mucus-secreting (mucinous cystadenocarcinoma)
   (ii) Acinar, non-mucus secreting
2. Anaplastic (uncommon)
3. Solid and cystic tumour
Complications
1. Biliary obstruction
   (i) Obstructive jaundice
   (ii) Cholangitis
   (iii) Biliary cirrhosis
2. Invasion of duodenum - bleeding
3. Diabetes mellitus
4. Venous thrombosis
   (i) Portal vein
   (ii) Thrombophlebitis migrans
5. Acute and chronic pancreatitis
6. Excessive lipase secretion by widespread tumour may give
   (i) Polyarthritis
   (ii) Panniculitis (fat necrosis)
   (iii) Eosinophilia
7. Myopathy/peripheral neuropathy
8. Thrombotic endocarditis
9. Fibrinolysis and haemorrhage

F Islet cell tumours
1. Insulinoma (B-cell tumour)
   Usually solitary but in about 10% of cases are multiple. 10-15% are malignant
2. Gastrinoma (delta-cell tumour) associated with the Zollinger-Ellison syndrome
   About 60% are malignant
3. Glucagonoma
20. Cardiovascular system

PERICARDIUM

A. Inflammation
1. Acute pericarditis
   (i) Secondary to myocardial infarction
   (ii) Uraemia
   (iii) Rheumatic fever
   (iv) Infectious causes
      a. Bacterial - staphylococcal, pneumococcal
      b. Viral - especially Coxsackie B
   (v) Drug reactions
   (vi) Postmyocardial infarction/postcardiotomy syndromes
   (vii) Idiopathic
2. Chronic pericarditis
   (i) Tuberculosis
   (ii) Rheumatoid disease
   (iii) SLE
   (iv) Systemic sclerosis
   (v) Idiopathic constrictive pericarditis
   (vi) Actinomycosis
   (vii) Amoebiasis

B. Tumours of the pericardium
1. Secondary involvement by:
   (i) Carcinoma
      a. Bronchus
      b. Oesophagus
      c. Breast
   (ii) Lymphoma/leukaemia
   (iii) Thymoma
2. Mesothelioma

HEART
A. Congenital
1. Disorders of the entire heart
   (i) Dextrocardia - with or without Situs inversus
   (ii) Laevocardia
   (iii) Cardiomegaly
      Causes
      a. Shunts
      b. Anomalies of the coronary arteries
      c. Myocarditis
      d. Infantile endocardial fibroelastosis
      e. Hereditary diseases - Friedreich's ataxia, Refsum's syndrome
      f. Storage disorders - Glycogen storage (Pompe's disease)
   (iv) Congenital 'rhabdomyomas', as in tuberous sclerosis
2. Acyanotic shunts (left-right)
   (i) Ventricular septal defect (VSD)
(ii) Atrial septal defect (ASD)
(iii) Patent ductus arteriosus

3. Cyanotic shunts (right-left)
   (i) Tetralogy of Fallot
       a. Pulmonary stenosis
       b. Ventricular septal defect
       c. Dextraposition and over-riding of the aorta
       d. Right ventricular hypertrophy
   (ii) Eisenmenger complex
       VSD with reversal of shunt resulting from pulmonary hypertension
   (iii) Transposition of the great vessels

4. Valvular abnormalities
   (i) Additional cusps
       a. Aortic
       b. Pulmonary
   (ii) Missing cusps
       a. Bicuspid aortic
       b. Bicuspid pulmonary
   (iii) Malpositioning
       a. Ebstein's anomaly - malformation of the tricuspid with downward displacement
   (iv) Atresia
       a. Aortic
       b. Pulmonary (+VSD)
       c. Tricuspid (+ASD)
       d. Mitral (+ASD)
   (v) Stenosis
       a. Aortic
       b. Pulmonary - isolated or associated with other defects in Fallot's tetralogy
   (vi) 'Floppy' valve - deposition of proteoglycans in the mitral valve sometimes associated with Marfan's syndrome

*Effects of congenital heart disease*
1. Shunting - initially left to right but with the development of pulmonary hypertension the shunt is reversed and cyanosis appears
2. Overloading of the right ventricle leading to hypertrophy and failure
3. Pulmonary hypertension
4. Infective endocarditis
5. Secondary polycythaemia
6. Conduction disturbances
7. General predisposition to infection

**B. Myocarditis**
Inflammation of the myocardium caused by:
1. Rheumatic fever
2. Viral diseases
   (i) Coxsackie B
   (ii) Echo virus
   (iii) Poliomyelitis
   (iv) Mumps
3. Bacterial infections
   (i) Diphtheria
   (ii) Typhoid
   (iii) Spread from pericarditis, infective endocarditis
   (iv) Pyaemic spread, staphylococci, streptococci, etc.
4. Parasitic diseases
   (i) Toxoplasmosis
   (ii) Trichinosis
   (iii) Trypanosomiasis (Chagas' disease)
5. Acute idiopathic myocarditis (Fiedler's)
   (i) Diffuse interstitial form
   (ii) Giant-cell (tuberculoid) form
6. Sarcoidosis
7. Syphilis

C. Cardiomyopathy

Definition
'Diffuse myocardial disease not attributable to ischaemia, or pressure or volume overload'

Types
1. Dilated
2. Hypertrophic
3. Restrictive, including obliterative

Causes
1. Dilated
   (i) Systemic disorders Some cases of:
      a. Amyloidosis
      b. Sarcoidosis
      c. Haemochromatosis
   (ii) Toxicity
      a. Alcohol
      b. Cobalt
      c. Lithium
      d. Nickel
      e. Anthracyclins
         Adriamycin
         Daunorubicin
         Cyclophosphamide
   (iii) Nutritional deficiencies
      a. Beri-beri
      b. Chronic alcoholism
      c. ? Post-partum
   (iv) Post-infection
      a. Viral myocarditis Coxsackie Herpes simplex
      b. Chagas' disease
   (v) Idiopathic
2. Hypertrophic
   (i) Inherited - as an autosomal dominant
   (ii) Idiopathic
3. Restrictive
   (i) Idiopathic diffuse myocardial fibrosis
   (ii) Endocardial fibro-elastosis
   (iii) Endomyocardial fibrosis (obliterative)
   (iv) Some cases of:
       a. Amyloidosis
       b. Sarcoidosis
       c. Haemochromatosis

D. Rheumatic fever

Aetiology
An allergic reaction to streptococcal antigens
1. ? Antibodies to these antigens cross-react with myocardial fibres, arterial smooth muscle cells, and connective tissue proteoglycans
2. ?? Immune complexes are formed which are deposited at the site of the lesions.
The Aschoff nodule
   1. Fibrinoid degeneration of collagen
   2. Mixed inflammatory cells
   3. Large mesenchymal cells (Anitschkow myocytes) which are probably altered fibroblasts
   4. Occasional Aschoff giant-cells

Lesions
   1. Heart
      (i) Pericarditis - 'bread and butter' type
      (ii) Myocarditis
      (iii) Endocarditis
         Valvulitis with vegetations
         a. Mitral
         b. Aortic
         c. Pulmonary (uncommon)
         d. Tricuspid (rare)
      (iv) Chronic deformity
         a. Mitral stenosis/incompetence
         b. Aortic stenosis/incompetence
      (v) Atrial fibrillation
   2. Joints
      Synovitis and inflammation of the capsule
   3. Brain
      (i) Sydenham's chorea
      (ii) Acute meningo-encephalitis
   4. Skin
      (i) Subcutaneous nodules
      (ii) Erythema nodosum
      (iii) Erythema marginatum
      (iv) Erythema multiforme
      (v) Petechiae
      (vi) Urticaria
(vii) Livedo reticularis

5. Lungs
   Acute pneumonitis

6. Arteries
   Acute fibrinoid arteritis affecting coronary, cerebral, renal and mesenteric vessels

E. Infective endocarditis

Causes
1. *Streptococcus viridans*
2. Staphylococci
3. Enterococci (*Streptococcus faceless*)
4. Brucella
5. Haemophilus group
6. *Coxiella burnetii*
7. *Candida albicans*
8. *Histoplasma capsulatum*
9. *Aspergillus fumigatus*
10. *Cryptococcus neoformans*

Predisposing lesions
1. Valves previously damaged by rheumatic fever
2. Congenital valvular abnormalities, e.g. bicuspid aortic valve
3. Interstitial valvulitis due to stress, hypersensitivity reactions, exposure to cold or high altitudes
4. ? Valvular endocarditis resulting from virus infections

Mechanism
1. Development of bland, fibrin-platelet thrombi on distorted or inflamed myocardium
2. Seeding of these small vegetations by organisms from the bloodstream
3. Further fibrin deposition and proliferation or organisms give rise to larger, friable vegetations characteristic of infective endocarditis

Lesions of infective endocarditis
1. Features of infection and toxaemia
   (i) Weight loss
   (ii) Anaemia
   (iii) *Cafe au lait* skin pigmentation
   (iv) Splenomegaly
2. Embolic features
   (i) Infarcts - brain, kidney, spleen
   (ii) Splinter haemorrhages
   (iii) Metastatic abscesses
   (iv) Mycotic aneurysms
3. Immune-complex deposition
   (i) Kidney lesions
      a. Focal glomerulonephritis ('embolic nephritis')
      b. Diffuse proliferative glomerulonephritis
(ii) Brain
   a. Focal encephalitis
   b. Cerebral arteritis
(iii) 'Microembolic lesions'
   a. Petechial rash
   b. Osier's nodes
   c. Roth's spots in the retina
   d. Retinal haemorrhage
   e. Nodular haemorrhagic lesions on palms and soles

*Causes of death*
1. Acute valve perforation
2. Embolism
3. Ruptured mycotic aneurysm
4. Renal failure - diffuse glomerulonephritis

**F Ischaemic heart disease**

*Aetiology*
1. Coronary atherosclerosis alone or complicated by
   (i) Thrombosis
   (ii) Haemorrhage into a plaque
   (iii) Rupture of a plaque
2. Narrowing of the coronary ostia due to
   (i) Atherosclerosis of the aorta or rarely,
   (ii) Syphilitic aortitis
   (iii) Dissecting aneurysms
3. Coronary arteritis
4. Embolism
5. Trauma
6. Thrombotic haematological diseases
7. Congenital abnormalities of the arteries
8. Irradiation

*Types*
1. Chronic ischaemic fibrosis
2. Infarction
   (i) Subendocardial
   (ii) Transmural

*Sequence of events*
6-12 h fibres show degenerative changes
   (i) Increased eosinophilia
   (ii) Swelling
12 h polymorphs appear
18-24 h area paler than normal
48 h area outlined by a hyperaemic border, fibres become coagulated, and nuclear pyknosis increases
4-10 days muscle becomes yellow and necrotic (myomalacia cordis) and there is increasing granulation tissue formation
12 days collagen appears
3 weeks infarct totally replaced by granulation tissue
3 months shrunken scar

Complications
1. Conduction defects and rhythm disturbances
2. Fibrinous or haemorrhagic pericarditis
3. Mural thrombosis and embolism
4. Rupture giving rise to:
   (i) Massive haemorrhage into the pericardium (cardiac tamponade)
   (ii) Breach in the septum resulting in acute cardiac failure
5. Cardiac aneurysm
6. Cardiac failure

H. Tumours
1. Benign (rare)
   (i) Atrial myxoma
   (ii) Congenital rhabdomyoma (hamartoma)
2. Malignant (all very rare)
   (i) Undifferentiated spindle-cell sarcoma
   (ii) Rhabdomyosarcoma
   (iii) Fibrosarcoma
   (iv) Secondary tumours

BLOOD VESSELS

A. Arteriosclerosis and atherosclerosis

B. Vasculitis

Features
1. Swelling, separation or necrosis of endothelial cells
2. Intimal thickening
3. Leucocyte infiltration of the wall
   (i) Acute
      a. Neutrophilic vasculitis
      b. Eosinophilic (allergic) vasculitis
   (ii) Chronic
      a. Lymphocytic
      b. Granulomatous
4. Destruction of the elastica and media
5. Superimposed thrombosis

Causes
1. Immune mechanisms
   (i) immune complex deposition
   (ii) Cell-mediated damage
2. Infections
   (i) Acute pyogenic infections by
      a. Direct extension
b. Infected thromboemboli
(ii) Chronic
  a. Syphilis
  b. Tuberculosis
3. Chemical agents
(i) Endogenous
  a. Gastric acid
  b. Bile
(ii) Exogenous
  a. Sclerosing agents
  b. Caustic or irritant chemicals
4. Physical agents
(i) Trauma
  a. Vibrating tools
  b. Intravascular catheters
  c. Pacemaker leads
(ii) Ionizing radiation

Vasculitis syndromes
1. Connective tissue diseases
   (i) Rheumatic fever
   (ii) Rheumatoid disease
   (iii) Ankylosing spondylitis
   (iv) SLE
   (v) Polyarteritis nodosa
2. Wegener’s granulomatosis Features
   (i) Ischaemic necrosis in
   (ii) Facial ulceration
   (iii) Glomerulonephritis
3. Thromboangiitis obliterans Features
   (i) Segmental involvement of medium and small arteries often involving the adjacent vein
   (ii) Superimposed thrombosis with recanalisation and fibrosis
   (iii) Leads to progressive ischaemia of the extremities and ultimately to gangrene
4. Takayasu’s disease (syn. pulseless disease) Features
   (i) Fibrous thickening of the intima
   (ii) Chronic inflammation of the media
   (iii) Adventitial fibrosis
   Primarily affects the arch of the aorta and the proximal branches
5. Giant-cell arteritis Features
   (i) Systemic arteritis dominated by temporal artery involvement upper and lower respiratory tract
   (ii) Disruption of the elastica with giant cell formation
   (iii) Association with polymyalgia rheumatica
6. ‘Allergic’ vasculitis
   (i) Visceral
     a. Appendix
     b. Gall-bladder
     c. Breast
d. Urinary bladder
(ii) Skin
   a. Erythema nodosum
   b. Erythema induratum
   c. Drug reactions
   d. Weber-Christian disease
   e. Nodular vasculitis
(iii) Allergic granulomatosis
   a. Asthma and pulmonary vasculitis
   b. Blood eosinophilia
   c. Elevated IgE levels
7. Serum or drug-induced vasculitis
8. Post-infection vasculitis Causes
   (i) Infective endocarditis
   (ii) Infected shunts
   (iii) Leprosy
   (iv) Malaria
Features
   (i) Fever and skin rash
   (ii) Arthritis
   (iii) Focal segmental glomerulonephritis
9. Kawasaki's disease syndrome (syn. mucocutaneous lymph node)
Features
   (i) Fever and erythematous rash
   (ii) Oedema and congestion of conjunctivae and mucous membranes
   (iii) Non-suppurative cervical lymphadenopathy

21. Respiratory system

NOSE AND NASAL SINUSES

A. Congenital
   1. Choanal stenosis or atresia
   2. Involvement in cleft palate
   3. Saddle nose in hypertelorism

B. Inflammation
   1. Acute rhinitis
      (i) Common cold
      (ii) Allergic
      (iii) Measles
      (iv) Irritant fumes
      (v) Diphtheria
   2. Acute sinusitis - non-specific, bacterial
   3. Chronic hypertrophic rhinitis
   4. Chronic atrophic rhinitis
(i) Simple atrophy
(ii) Ozaena caused by Klebsiella infection

5. Chronic specific infections of the nose
   (i) Tuberculosis
   (ii) Leprosy
   (iii) Syphilis
   (iv) Rhinoscleroma
   (v) Fungal infections
       a. Candidacies
       b. Aspergillosis
       c. Phycomycosis
       d. Rhinosporidiosis
       e. S. American blastomycosis
   (vi) Leishmaniasis

6. Wegener's granulomatosis

C. Nasal polyps
1. Allergic
   (i) Allergic rhinitis
   (ii) Vasomotor rhinitis
2. Non-allergic including antro-choanal polyps

D. Tumours of the nose and naso-pharynx
1. Epithelial
   (i) Squamous papilloma
   (ii) Transitional-type ('inverted') papilloma
   (iii) Keratoacanthoma
   (iv) Adenoma arising from mucous glands
   (v) Carcinoma
       a. Squamous
       b. Transitional-type
       c. Adenocarcinoma
       d. Anaplastic including 'lymphoepithelioma'
   (vi) Malignant melanoma
2. Vascular
   (i) Capillary haemangioma
   (ii) Juvenile angiofibroma
   (iii) Haemangiopericytoma
   (iv) Haemangioendothelioma (angiosarcoma)
3. Lymphoid tissue
   (i) Lymphoma
   (ii) Malignant histiocytosis
   (iii) Myeloma
4. Neurogenic
   (i) Neurilemmoma
   (ii) Neurofibroma
   (iii) Nasal 'glioma' (ectopic glial tissue)
   (iv) Olfactory neuroblastoma
5. Bone and connective tissues
   (i) Osteoma
(ii) Chondroma
(iii) Ossifying fibroma
(iv) Fibrosarcoma
(v) Chondrosarcoma
(vi) Osteogenic sarcoma
(vii) Chordoma

LARYNX

A. Congenital
1. Laryngeal web
2. Stenosis
3. Laryngoecele

B. Inflammation
1. Acute laryngitis (bacterial and viral)
2. Acute epiglottis (*Haemophilus influenzae* type B)
3. Chronic laryngitis
   (i) Non-specific
   (ii) Tuberculosis
   (iii) Syphilis
   (iv) Fungal infections
   (v) Scleroma
   (vi) Leprosy

C. Polyps, cysts and benign tumours
1. Vocal cord polyps and nodules (Singer's nodes)
2. Cysts
   (i) Mucus retention cysts
   (ii) Epidermoid cysts
   (iii) Branchial cysts
3. Benign tumours
   (i) Juvenile papillomatosis
   (ii) Adult papilloma
   (iii) Adenoma of sero-mucinous glands
   (iv) Papillary cystadenoma
   (v) Chondroma
   (vi) Neurogenic tumours
   (vii) Lipoma
   (viii) Granular cell myoblastoma
   (ix) Amyloid 'tumour'

D. Pre-malignant and malignant lesions
1. 'Keratosis'
   Keratinisation and epithelial hyperplasia with or without dysplasia (laryngeal intra-epithelial neoplasia I and II)
2. Carcinoma-in-situ / LIN III
3. Invasive carcinoma
   Sites
   (i) Supraglottic
(iii) Glottic - vocal cords and the commissures. This is the most frequent site and carries the best prognosis.

(iii) Subglottic
(iv) Transglottic - extensive tumours with a poor prognosis.

**Microscopic appearances**

(i) Squamous
(ii) Spindle squamous cell
(iii) Verrucous squamous cell
(iv) Anaplastic
(v) Adenocarcinoma (from mucous glands)

4. Sarcoma
   (i) Fibrosarcoma
   (ii) Chondrosarcoma

**TRACHEA, BRONCHI AND LUNGS**

**A. Congenital**
   1. Agenesis of one lung
   2. Hypoplasia of one or both lungs
   3. Bronchogenic cystic disease of the lung
      (i) Multiple
      (ii) Single - pneumatocele
   4. Cystic adenomatoid malformation
   5. Accessory lobes
      (i) Azygos
      (ii) Cardiac
   6. Absence of bronchial connections - sequestration
   7. Abnormalities of the pulmonary arteries
   8. Tracheo-oesophageal fistula

**B. Inflammation of trachea and bronchi**
   1. Acute laryngo/tracheo-bronchitis
      (i) Bacterial/viral
      (ii) Atmospheric pollution or irritant gases
      (iii) Allergic
   2. Chronic bronchitis
      A chronic inflammatory condition resulting in the 'Expectoration of sputum on most days for three months or more, for at least two years.'
      **Types**
      (i) Simple - only hypersecretion of Mucus
      (ii) Obstructive - where the hypersecretion is combined with airways obstruction
      **Aetiology**
      (i) Smoking
      (ii) Atmospheric pollution
      (iii) Persistent or recurrent infection, especially *Haemophilus influenzae*
      (iv) Familial predisposition
      **Gross features**
(i) Muco-puruient secretion
(ii) Symmetrical mild dilatation of bronchi
(iii) Prominent mucous glands which elevate the mucosa
(iv) Frequently associated with emphysema

**Microscopic appearances**

(i) Bronchial epithelium
   a. Goblet-cell hyperplasia
   b. Variable squamous metaplasia
   c. (ii) Bronchial sero-mucinous glands
   d. a. Hypertrophy
   e. b. Increased proportion of mucous to serous acini
   f. c. Gland to wall-thickness ratio (Reid index) increased
   g. (iii) Submucosa
   h. Chronic inflammatory cell infiltration

**Effects**

(i) Progressive dyspnoea
(ii) Cor pulmonale
(iii) Cardiac failure
(iv) Respiratory failure
   a. Hypercapnia
   b. Hypoxaemia

3. Bronchiectasis

Irreversible dilatation of the bronchi, usually associated with inflammation

**Aetiology**

(i) Inflammatory disease of bronchial walls
   a. Unresolved pneumonia
   b. Pneumococcal bronchopneumonia
   c. Whooping cough
   d. Influenza
   e. Complicating chronic sinusitis

(ii) Extrinsic pressure on bronchi
   a. Lymph node enlargement, e.g. primary tuberculosis, measles
   i. Tumours
      (iii) Intra-luminal obstruction
   a. Pus and/or fibrinous exudates
   b. Foreign bodies
   c. Adenoma/carcinoma
   d. Tenacious mucus in mucoviscidosis

(iv) impaired pulmonary defense mechanisms
   a. Kartagener's syndrome
   b. Primary ciliary dyskinesia
   c. Congenital immunodeficiency

**Complications**

(i) Lung abscess
(ii) Empyema thoraces
(iii) Pyaemia - metastatic abscesses
(iv) Pulmonary fibrosis
(v) Cor pulmonale and cardiac failure
(vi) Secondary to amyloidosis

4. Bronchial asthma
   Types
   (i) Extrinsic
   a. Atopic asthma, Type I hypersensitivity to exogenous allergens
   b. Non-atopic, Type III hypersensitivity mediated by circulating precipitins

   (ii) Intrinsic - attacks provoked by a wide variety of stimuli such as anxiety, infection, exercise, smoke, etc.
   (iii) Mixed type
   Gross features
   (i) Tenacious mucus plugs
   (ii) Over-distension of lungs
   (iii) Desquamation of epithelium
   (iv) Sputum findings
       a. Curschmann's spirals
       b. Charcot-Leyden crystals
   Microscopic features in the bronchi
   (i) Lumen filled with basophilic secretion
   (ii) Eosinophils and desquamated epithelium in these plugs
   (iii) Submucosal oedema
   (iv) Infiltration by lymphocytes and eosinophils
   (v) Serous acini increased relative to mucous acini
   (vi) Muscular hypertrophy
   (vii) Thickened basement membrane
   Complications
   (i) Status asthmaticus
   (ii) Sudden death
   (iii) Mucus plugging and pulmonary collapse
   (iv) Allergic broncho-pulmonary aspergillosis
   (v) Pneumothorax
   (vi) Mucus hypersecretion

C. Acute pulmonary infections
1. Acute bacterial pneumonia
   (i) Lobar pneumonia - acute diffuse inflammation involving an entire lobe of lung and limited only by the pleura Causes
       a. Pneumococci; Types 1,2,3 and 5 account for 90-95% of cases
       b. Klebsiella
       c. Staphylococci
       d. Streptococci
       e. H. influenzae?
       f. Legionella
   Stages
       a. Congestion
       b. Red hepatisation
       c. Grey hepatisation
Complications
a. Carnification if resolution is incomplete
b. Empyema
c. Suppurative pericarditis
d. Metastatic abscesses, e.g. in brain, kidney
e. Acute endocarditis
f. Meningitis
g. Arthritis
h. Peritonitis

(ii) Bronchopneumonia (lobular) - patchy, often multifocal inflammatory consolidation of lung tissue centred around small airways

Causes
a. Pneumococci
b. *H. influenzae*
c. Staphylococci
d. Streptococci
e. Pseudomonas
f. Klebsiella
g. *Yersinia pestis* (plague)
h. Anthrax ('wool-sorter's disease')

Complications
a. 'Carnification' - organisation of exudate
b. Pulmonary fibrosis - scarring in areas destroyed by suppuration
c. Bronchiectasis
d. Lung abscess
e. Empyema
f. Pericarditis
g. Metastatic abscesses

2. Lung abscess
Causes
(i) Inhalation of infected material, e.g. food, blood clot, teeth, etc.
(ii) Complicating pneumonia/bronchiectasis
(iii) Following bronchial obstruction especially due to carcinoma
(iv) Pyaemic (secondary) abscesses
(v) Infected thrombo-emboli (especially in drug addicts)
(vi) Penetrating injuries

Complications
(i) Scarring and deformity of the lung
(ii) Empyema
(iii) Broncho-pleura fistula
(iv) Pyaemia

3. Viral pneumonia Causes
a. Influenza
b. Adenovirus
c. Measles
d. Herpes virus (H. simplex and chickenpox)
e. Cytomegalovirus
f. Respiratory syncitial virus

4. Chlamydiae (Bedsonia)
a. Psittacosis
b. Ornithosis
5. Mycoplasmal pneumonia - *M. Pneumoniae*
6. Rickettsial pneumonia - *Coxiella burnetii*

D. Chronic Pulmonary infections
1. Tuberculosis
2. Actinomycosis
3. Nocardiosis
4. Fungal infections
   (i) Aspergillosis
   (ii) Candidiasis
   (iii) Phycomycosis
   (iv) Cryptococcosis
   (v) Blastomycosis
   (vi) Histoplasmosis
   (vii) *Torulopsis glabrata*
   (viii) Coccidioidomycosis
5. Protozoan infections
   (i) *Pneumocystis carinii*
   (ii) Amoebiasis
6. Metazoan infections
   (i) Schistosomiasis
   (ii) Paragonimiasis
   (iii) Ascariasis
   (iv) Hydatid disease

E. The Lung in AIDS
1. Opportunistic infections
   (i) Mycobacteria - tuberculosis and atypical species (e.g. *M. avium intracellulare*)
   (ii) Fungi - Candida, aspergillus, cryptococcus
   (iii) Virus - cytomegalovirus, herpes virus
   (iv) Protozoan -
      a. *Pneumocystis carinii*
      b. Toxoplasmosis
2. Lymphoproliferative disorders
   (i) Pulmonary lymphoid hyperplasia
   (ii) Lymphoid interstitial pneumonia
   (iii) Lymphoma
3. Tumours
   (i) Kaposi's sarcoma

F. Diffuse infiltrative lung diseases

Diseases characterized by diffuse inflammation and fibrosis of the connective tissue of the alveolar walls (interstitial fibrosis).
1. Pneumoconioses - diseases caused by the inhalation of dust
   (i) Coal workers’
      a. Simple pneumoconiosis
      b. Progressive massive fibrosis
c. Caplan’s type (with rheumatoid arthritis)

(ii) Silicosis

(iii) Asbestosis - also gives rise to:

a. Pleural fibrosis
b. Bronchial carcinoma (especially in cigarette smokers)
c. Mesothelioma

(iv) Berylliosis

(v) Siderosis (iron oxide)

(vi) Stannosis (tin ore particles)

2. Physical and chemical agents

(i) Cytotoxic drugs - busulphan, bleomycin, cyclophosphamide

(ii) Hypersensitivity to drugs - nitrofurantoin, salazopyrine, amiodorone, hexamethonium,

(iii) Toxic substances - paraquat poisoning (herbicide)

(iv) Radiation

3. Immunological diseases

(i) Extrinsic allergic alveolitis

a. Farmer’s lung - *Micropolyspora faeni* in mouldy hay
b. Maltworker’s lung - *Aspergillus clavatus* in malting barley
c. Bagassosis - mouldy sugar cane fibres
d. Maple bark stripper’s disease - *Coniosporium corticale* in the bark of maple trees
e. Bird fancier’s lung - avian proteins in bird droppings

(ii) Interstitial pneumonias (fibrosing alveolitis)

Types

a. Usual interstitial pneumonia
b. Desquamative interstitial pneumonia
c. Lymphocytic interstitial pneumonia

(iii) Connective tissue disorders

a. Rheumatoid disease
b. Systemic lupus erythematosus
c. Progressive systemic sclerosis

(iv) Goodpasture’s syndrome - pulmonary fibrosis and glomerulonephritis

(v) Idiopathic

a. Sarcoidosis
b. Alveolar proteinosis

Controlling Stress Helps Fight Chronic Diseases Such As Lupus

*ScienceDaily* (Aug. 6, 2007) — Lupus is an autoimmune disease which produces antibodies causing injuries to the body’s cells and tissue. It makes the immune system go out of control and the organism attack healthy cells instead of the germs on them. This pathology, which affects more than 5 million people around the world, is more developed in women of fertile age between 15 and 44 years old.

A study conducted in the Department of Medicine at the University of Granada determined that daily stress (which occurs in circumstances of little importance but of high frequency) could exacerbate the symptoms of patients suffering from lupus. In other words, controlling the stress level of those suffering from this disease allows the determination of its negative effects, such as inexplicable loss of weight, feeling of
fatigue, continuous fever or pain and inflammation in joints.

This study, carried out by Dr. Nuria Navarrete Navarrete and led by researchers Juan Jiménez Alonso and María Isabel Peralta Ramírez, aimed to check the effects of stress treatment in patients suffering from lupus and with high levels of stress. A team of psychologists from the University of Granada applied a therapy to fight stress in a group of 45 patients suffering from lupus to teach them how to manage their stress to reduce the negative effects of this disease.

Results showed that patients who received psychological therapy significantly reduced their levels of stress, anxiety and depression, achieving levels even lower than those of the general population. Furthermore, they significantly improved their quality of life both at a physical and psychological level and presented fewer skin and muscloskeletal symptoms, which usually appear in patients suffering from lupus.

**Managing daily stress**

Nuria Navarrete explains that lupus is a chronic disease whose course is unpredictable. Patients alternate periods of clinical stability with others in which there are symptoms and signs showing that the disease is active. In addition, there are certain factors such as stress which may cause crisis and, therefore, worsen the prognosis of the disease.

Daily stress is very common in patients suffering from lupus. Apart from the usual circumstances which produce anxiety in a healthy population, other effects include knowing that your body suffers from a chronic disease which is controllable but incurable and of uncertain prognosis that requires chronic treatment (in some cases for the rest of their life) and which have important secondary effects.

The results of this study highlighted the importance of dealing appropriately with patients suffering from lupus and, by extension, from other chronic diseases. “According to our results, attention on other psychological aspects is essential to achieve an effective global treatment of the patient”, says Navarrete.

In other words, the treatment of daily stress, together with the usual pharmacological treatment, is a useful weapon when treating patients suffering from lupus. “We think that this treatment could be useful from the moment in which the disease is diagnosed, as patients may require help to manage their stress and minimise its negative effects,” says researcher Navarrete.

Part of the results of this study were published in the journals “Psychosomatic Medicine” and “Revista Clínica Española”.

Adapted from materials provided by University of Granada.

**G. Pulmonary emphysema**

**Classification**

1. Interstitial emphysema - the presence of air in the interstitial tissue of the lung

   **Causes**

   (i) Tearing of alveolar walls by excessive pressure

   a. Severe asthma

   b. Whooping cough
2. Vesicular emphysema - an increase in size beyond the normal in air spaces distal to terminal bronchioles, that is the pulmonary acini. An acinus contains the respiratory bronchioles, alveolar ducts, and alveoli arising from one terminal bronchiole.
   (i) Centriacinar (centrilobular) emphysema Distensive type found in
   a. Urban dwellers
   b. Coal-miners
   Destructive types -more severe form in
   a. Chronic bronchitis
   b. Smoking (inhibition of anti-proteases)
   Paraseptal (periacinar) emphysema
   Distensive type
   a. Lobar emphysema of infancy and childhood
   b. Compensatory emphysema following collapse, agenesis, surgical removal of a lobe(s)
   Destructive type
   a. Chronic bronchitis and recurrent bronchopneumonia
   b. a-l-antitrypsin deficiency
   c. Inhalation of cadmium fumes (? in cigarette smoke)
   (iii) Paraseptal (periacinar) emphysema
   ? results from inflammation
   (iv) Irregular emphysema
   This does not affect the acini in a uniform manner.
   Occurrence
   a. relation to scars
   b. giant bullous emphysema
   c. acute tension cysts in infancy

When stress levels go up, asthma symptoms can go into overdrive.

What’s the link, and how can asthma and anxiety be managed?

By Heather Hatfield
WebMD Feature

Reviewed by Charlotte E. Grayson Mathis, MD

When stress levels start to creep upward -- whether it's over bills, work, or your kids -- jam-packed calendar -- asthma symptoms can kick into overdrive. As the wheezing and coughing gets worse, your health becomes one more reason to worry. Asthma and anxiety make for a vicious circle, and one that can spiral downward quickly.

"Asthma is triggered by many things, and one of them is stress," says Pramod Kelkar, MD, a fellow with the American Academy of Asthma Allergy and Immunology (AAAAI).

"So look at the big picture: just as you manage exposure to triggers like cigarette
smoke and pet dander to keep symptoms from getting worse, stress -- as a trigger -- needs to be managed as well."

**Stress and Asthma: What’s the Connection?**

"Stress can affect the cardiovascular, gastrointestinal, musculoskeletal, immune, and central nervous systems," says Paul Rosch, MD, president of the American Stress Institute. "In fact, it's difficult to think of any disorder in which stress has not been shown to have an aggravating role.

Asthma is no exception.

Stress can create strong physiologic reactions that lead to airway constriction and changes in the immune system, which can worsen asthma symptoms.

"The mechanism between asthma and anxiety is many-fold," says Kelkar, a physician at Allergy and Asthma Care in Maple Grove, Minn. "Uncontrolled emotions can work the nerves and cause constriction of muscles, like the smooth muscles of the airways in the lungs. They tighten up and constrict, which can worsen wheezing, coughing, and chest tightness in people with asthma."

Although stress and anxiety start in your mind, asthma is a physical disease of the lungs.

"It is important to note that asthma is not a psychosomatic disease," Kelkar tells WebMD. "It's not in your head. Stress can trigger symptoms if you already have the disease, but if you don't have it, stress does not all of a sudden cause a person to develop the disease of asthma."

**The Brain’s Impact on Asthma and Stress**

The brain-body link between asthma and anxiety is starting to be better understood. Led by researchers from the University of Wisconsin, a group of scientists found that certain areas of the brain cause worsening asthma symptoms when a person is under stress.

Researchers exposed a group of people with mild asthma to triggers that caused both inflammation and muscle constriction. When symptoms flared, the participants were asked to read words that were either emotionally charged, such as "lonesome"; neutral, such as "curtains"; or asthma-related, such as "wheezing."

They found that the words linked with asthma increased inflammation and activity in parts of the brain that control emotions.

The results, published in the Proceedings of the National Academy of Science, show a possible link between emotions and asthma. Although it's only preliminary research, it does start to connect the dots. Until researchers find a clear link between anxiety and asthma, keep symptoms in check by managing stress and treating asthma with appropriate medication.

Persistent asthma means you have symptoms more than once a week, but not constantly. Treating persistent asthma requires long-term maintenance therapy, such as an inhaled corticosteroid, plus rescue therapy when something triggers symptoms.
And when your symptoms are out of control, an anti-inflammatory, such as the oral steroid **prednisone**, might be necessary. The problem is that prednisone can cause mood swings as a side effect, adding fuel to the anxiety fire.

"The good news is that prednisone is only a short-term treatment," explains Kelkar. "When a course of oral steroids ends, a person should go back to a long-term maintenance therapy like **inhaled steroids**, which do not have an impact on mood and anxiety."

Sometimes a long-term **asthma medication** doesn't work well, and wheezing and chest tightness occurs all too often. Then, a vicious circle can begin, where anxiety worsens asthma, and asthma worsens anxiety, says Kelkar.

The solution is to talk to a health-care provider about your symptoms, triggers, and stress. Also discuss other treatment options that can help get your asthma under control again.

**Managing Asthma and Anxiety**

"There are numerous stress-reduction techniques, ranging from **meditation**, **yoga**, and **Pilates** to jogging, listening to music, and hobbies," says Rosch. "You have to find out what works best for you."

Here are stress-reduction tips from the Cleveland Clinic. They can help you make anxiety one less **asthma trigger** for you to worry about:

- Keep your mind free of stressful thoughts. Use the power of positive thinking to keep your mind going in the right direction. When you feel anxious about something, try to stay positive. How you think and what you think both play a role in managing stress levels.

- Identify your stressors. What stresses you out? Is it money, your mother-in-law, a hectic lifestyle? Once you know what your stress triggers are, work on resolving them. If you can't do it on your own, get help from a professional. This might be a financial counselor, psychologist, or family therapist. Link your health-care providers together, as well. Let your allergist know that stress is a trigger, so she or he can keep your anxiety in mind when treating your symptoms.

- Don't try to do it all. Manage your time wisely. Don't cram two days' worth of errands into one day. If you know you need to get everything done before a deadline, delegate so you can take some time for yourself. With more hands pitching in, you can avoid being overburdened.

- Say ohm. Practicing relaxation exercises can help lessen the negative effects of stress and asthma. Try deep breathing, progressive muscle relaxation, and clearing negative thoughts.

- Eat right and **exercise**. Exercise is a great way to let go of stress. Also, eat right and avoid junk food, coffee, and soda -- which can make you feel drained after the sugar-high and caffeine effects wear off. This can help your overall health, give you more energy to combat stress, and put you in a better position to manage asthma.
• Get by with a little help from your friends and family. When it comes to asthma and anxiety, no one should go it alone. Having support from your loved ones can help you tackle stressful situations. They can provide an emotional hand when things get tough as well as offer friendly reminders when it's time to take your medication.

• Get a good night's sleep. Sleep helps you recharge your batteries -- physically, emotionally, and even cognitively -- according to the National Sleep Foundation. Without a solid night's sleep, mood, behavior, and performance can be affected, and so can asthma.

H. Effects of cigarette smoke
1. Mucus hypersecretion
   (i) Epithelial goblet cells increase and extend into bronchioles
   (ii) Hyperplasia of mucus cells in sero-mucinous glands
   (iii) Composition of mucus changes - hyperviscous and tenacious
2. Infection resulting from
   (i) inefficient muco-ciliary escalator
   (ii) Loss of protective proteins from serous cells of glands and clara cells
   (iii) Loss of ciliary action in squamous metaplasia
3. Emphysema
   (i) Proteases increase - from inflammatory cells
   (ii) Anti-proteases decrease - reduced clara cells
   (iii) Anti-proteases inhibited - direct action of smoke

I. Mechanical disorders
1. Pulmonary atelectasis
   A failure of full expansion of the lungs after birth
   Causes
   (i) Bronchial obstruction
      a. Viscid mucus
      b. Liquor amnii
   (ii) In association with hyaline membrane disease
   (iii) Brain damage involving the respiratory centre
2. Lung collapse (after full aeration) Causes
   (i) Obstruction of the bronchial lumen
      a. Mucus in asthma mucoviscidosis
      b. Aspirated material
      c. After anaesthesia/operations
      d. Foreign bodies
   (ii) Extreme narrowing of a bronchus
      a. Carcinoma
      b. Inflammatory fibrosis
   (iii) External pressure on a bronchus
      a. Enlarged lymph gland
      b. Aortic aneurysm
      c. Tumour
   (iv) Pressure on the lung
a. Pneumothorax
b. Pleural effusion
c. G-forces in aircrew

**J. Tumours**

**Benign**
1. Epithelial
   (i) Papilloma
      a. Squamous
      b. Transitional
      Both types are exceedingly rare in the bronchi
   (ii) Adenoma These can arise from MUCOUS glands and are either:
      a. Pleomorphic
      b. Monomorphic
2. Connective tissue
   (i) Angioma and sclerosing angioma
   (ii) Chondroma
   (iii) Lipoma
   (iv) Fibroma
   (v) Neurofibroma
3. Mixed 'tumour'- chondroadenoma (? hamartoma)

**Malignant**
1. Carcinomas *Aetiology*
   (i) Cigarette smoking
   (ii) Atmospheric pollution (?)
   (iii) Asbestosis
   (iv) Exposure to arsenic, nickel, haematite, and chromates
   (v) Exposure to radio-active materials

**Varieties**
   (i) Squamous carcinoma (via squamous metaplasia)
   (ii) Small cell carcinoma
   (iii) Adenocarcinoma
      a. Acinar or tubular
      b. Papillary
      c. Bronchiolo-alveolar
   (iv) Large cell carcinoma

**Rare varieties**
   (v) Giant cell carcinoma
   (vi) Clear cell
   (vii) Adeno-squamous
   (viii) Adenoid cystic
   (ix) Muco-epidermoid

**Spread**
   (i) Local - to pleura, diaphragm, and pericardium
   (ii) Lymphatic - to ipsilateral and contralateral lymph nodes and then to mediastinal, and cervical nodes
   (iii) Blood stream - to:
      a. Liver
      b. Adrenals
      c. Brain
2. Carcinoid tumours
   Tumours of low-grade malignancy arising from bronchial APUD cells. Part of the spectrum of neuro-endocrine tumours ranging from classical carcinoid tumours through atypical carcinoids to small cell carcinoma.

3. Carcin-sarcoma
4. Sarcomas
5. Pulmonary blastoma
6. Malignant lymphoma

PLEURA

A. Inflammation

Acute
1. Pleurisy
   (i) Primary viral infections, e.g. Coxsackie B
   (ii) Traumatic injury
   (iii) Secondary to underlying lung disease
       a. Pneumonia
       b. Lung abscess
2. Empyema - a collection of pus in the pleural space resulting from the introduction of pyogenic organisms through trauma to the chest wall or by spread of infection from:
   (i) Bacterial pneumonia
   (ii) Lung abscess
   (iii) Broncho-pleural fistula
   (iv) An infected neoplasm
   (v) Abdominal sepsis

Chronic
1. Non-specific, following acute infections
2. Tuberculosis
3. Asbestosis
4. SLE
5. Rheumatoid disease
6. Actinomycosis
7. Fungal infections

B. Pneumothorax

C. Causes
1. Rupture of sub-pleural bulla
2. Trauma (including injection sites)
3. Broncho-pleural fistula
4. Perforation of the oesophagus with rupture of pleura

C. Tumours

Primary
   (i) Fibrous tumour of pleura - rare and usually benign
   (ii) Mesothelioma - related to previous exposure to asbestos.
6 The tumours are associated with:
a. Fibrous or calcified pleural plaques in about 2/3 cases
b. Pulmonary asbestosis in 12-45%

They show heterogeneous histological patterns:
  a. 'Epithelial' type - acinar or papillary formations resembling adenocarcinoma
  b. Sarcomatous type resembling fibrosarcoma
  c. Mixed types

Secondary
Involvement of the pleura by metastatic tumour is relatively common and frequently presents as a pleural effusion. The major causes of a malignant pleural effusion are:

1. Breast carcinoma
2. Carcinomas of the lung
3. Malignant lymphomas
4. Ovarian carcinomas

22. Urinary system

KIDNEY

A. Renal cystic and dysplastic lesions
1. Developmental lesions
   (i) Agenesis
   (ii) Hypoplasia
   (iii) Heterotopia, e.g. in the pelvis
   (iv) Fusion - horseshoe kidney
   (v) Renal dysplasia
      a. Multicystic (unilateral or bilateral)
      b. Segmental
      c. With lower urinary tract obstruction (e.g. posterior urethral valves)

2. Hereditary lesions
   (i) Polycystic disease
      a. Infantile
      b. Adult
   (ii) Renal medullary cystic disease
      a. Medullary cystic disease/familial juvenile nephronophthisis
      b. Medullary sponge kidney
   (iii) Renal cysts in hereditary syndromes, tuberous sclerosis, etc.

3. Acquired renal cortical cysts
   (i) Simple
   (ii) Multilocular
   (iii) End stage disease of patients receiving maintenance dialysis

B. Inflammatory disorders (mainly affecting the interstitium)

1. Acute pyelonephritis
   Acute bacterial infection of the kidney and renal pelvis, usually resulting from ascending infection of the urinary tract, but some cases may result from haematogenous or lymphatic spread.
Pathogenesis
Ascending infection usually follows bacterial contamination of the urine in the bladder with or without true infection of the bladder wall - cystitis

Predisposing factors
(i) Obstruction, of which the major causes are
   a. Malformations of the GU tract in childhood
   b. Pregnancy
   c. Prostatic hyperplasia and uterine prolapse in the elderly
(ii) Urethral reflux
(iii) Catheterisation
(iv) Diabetes mellitus

Pathological features
(i) Kidney is swollen and hyperaemic
(ii) Surface studded with small abscesses
(iii) Scattered, rounded or linear abscesses in the cortex and medulla
(iv) Polymorphs in tubules and interstitium

Complications
(i) Renal carbuncle
(ii) Peri-nephric abscess
(iii) Renal papillary necrosis
(iv) Acute renal failure
(v) Pyonephrosis
(vi) Chronic pyelonephritis
(vii) Septicaemia
(viii) Metastatic abscesses

2. Chronic pyelonephritis
Chronic inflammation and fibrosis associated with persistent infection or initiated by infection but becoming self-perpetuating

Pathological features
(i) Granular, shrunken kidneys
(ii) Cortical scarring
(iii) Deformity of the pelvi-calyceal system

Microscopic
(iv) Tubular atrophy
(v) Interstitial fibrosis
(vi) Periglomerular fibrosis
(vii) Glomerular hyalinisation
(viii) Chronic inflammatory cell infiltration

Complications
(i) Hypertension
(ii) Chronic renal failure

3. Tuberculosis
(i) Miliary
(ii) Fibro-caseous, nodular tuberculosis
(iii) Tuberculous 'pyonephrosis'

C. Glomerular disorders
Definitions
Patterns of involvement by disease are designated:
(i) Diffuse - all the glomeruli are affected
(ii) Focal - occasional glomeruli are affected
(iii) Segmental - only parts of glomeruli are affected

Classification is based on the presence or absence of:

(i) Mesangial cell and matrix increase if present: proliferative glomerulonephritis (GN)
(ii) Glomerular basement membrane thickening if present with proliferation: membranoproliferative GN if present alone: membranous GN
(iii) Crescents
>Cr50% of glomeruli: crescentic GN

1. Proliferative glomerulonephritis (GN)

(i) Diffuse endocapillary (exudative) GN
Mesangial cell and matrix increase with swollen endothelial cells and an excess of polymorphs Subepithelial and mesangial deposits containing lg and complement, i.e. immune complexes

The antigens responsible for these reactions are ill-defined. The classical form of acute diffuse proliferative GN is provoked by streptococcal infection elsewhere in the body, but most cases do not fall into this category.

Other antigens include:
- a. Bacterial endotoxins
- b. Schistosomes
- c. Trypanosomes
- d. Plasmodia
- e. Viral antigens, e.g. hepatitis B, mumps, chicken pox measles
- f. Endogenous DNA

(ii) Diffuse or focal segmental mesangial proliferative GN This pattern of proliferation is a variant also resulting from immune complex deposition. A special form is deposition of IgA in the mesangium seen in Berger's disease (recurrent haematuria syndrome). Affected patients show an elevated serum IgA and have increased titres to respiratory pathogens including Mycoplasma pneumoniae and influenza virus. The disease may be initiated by respiratory infection.

(iii) Crescentic (excracapillary or rapidly progressive GN)

Pathological features
Segmental necrosis and fibrin deposition in Bowman's space lead to epithelial crescent formation with exudation of inflammatory cells. Superimposed on underlying disease.
This condition has a poor prognosis.

Aetiology
Crescentic GN can supervene on 'acute' proliferative GN, most cases of which are idiopathic, but is also regularly encountered in multisystem diseases:
- a. Malignant hypertension
- b. Infective endocarditis
- c. SLE
- d. Polyarteritis nodosa
- e. Wegener's granulomatosis
- f. Goodpasture's syndrome
- g. Rheumatoid vasculitis
- h. Henoch-Schönlein syndrome
Immunostaining helps to determine the diagnostic category
a. Linear staining along GBM for IgG, associated with anti-GBM antibody (Goodpasture's)
b. Granular staining for immune complex
c. Negative in vasculitis such as polyarteritis nodosa or Wegener's
(iv) Membranoproliferative GN. Often persistent hypocomplementaemia

Type I (mesangiocapillary GN)
Mesangial interposition and 'double contour' GBM Mesangial and subendothelial deposit of Ig and complement

Type II (dense deposit disease)
Intramembranous ribbon-like deposit of extremely electron dense material, also in Bowman's capsule and tubular basement membrane - C3 often, usually no Ig

Type III
As type I and numerous subepithelial and intramembranous deposits
Aetiology- idiopathic (rarely associated with immunisation)
Prognosis: usually slowly progressive

2. Minimal change GN
This is the most common cause of the nephrotic syndrome in childhood.
Aetiology
- a reaction to lymphokines produced as a hypersensitivity response to toxins, insect stings, pollens, foodstuffs, etc.

Pathological features
(i) Fusion of epithelial foot processes (EM)
(ii) Fat droplets in the tubular epithelium

Prognosis
Excellent when treated with corticosteroids or cyclophosphamid

3. Focal glomerulosclerosis
Hyaline thickening of mesangial regions and capillary loops of focal and segmental distribution, usually presenting in childhood as the nephrotic syndrome. The response to treatment is poor. An identical picture can be seen in adults with a wide variety of renal disorders.

4. Membranous GN

Aetiology
- in-situ formation of immune complexes within the GBM which activate complement. The increased GBM permeability may be a consequence of membrane attack by the final sequence (C5-9) of complement. Most cases are idiopathic but known causes include:
  (i) Drug hypersensitivity, particularly to gold and penicillamine
  (ii) Quartan malaria
  (iii) Tumour antigens - e.g. colonic, gastric, and renal adenocarcinoma
  (iv) Hepatitis B
  (v) SLE and rheumatoid disease

Pathological features
(i) Diffuse thickening of the GBM with 'spike' formation
(ii) Deposits of immunoglobulin (mainly IgG) and complement C3 beneath the epithelium which later becomes incorporated into the BM
(iii) Loss of foot processes from the epithelial cells
(iv) Progressive sclerosis of glomeruli

_Prognosis_
Usually presents with the nephrotic syndrome and deteriorates slowly to renal failure in 5-10 years

5. Glomerulosclerosis (advanced GN)
The end result of a variety of progressive destructive lesions.

_Aetiologies_
The main causes are:
(i) Progressive GN
(ii) Hypertensive nephrosclerosis
(iv) Diabetes mellitus
(v) (iv) Amyloidosis
(vi)

_Pathological features_
(i) Contracted kidneys
(ii) Hyaline fibrosis of glomeruli
(iii) Secondary tubular atrophy
(iv) Interstitial fibrosis
(v) Associated hypertensive changes

_Prognosis_
Deterioration to chronic renal failure and death

**Pathological basis of the clinical syndromes**
(i) Acute nephritis syndrome
   a. Diffuse proliferative GN
   b. Crescentic (rapidly progressive) GN
   c. Membrano-proliferative GN
   d. SLE
   e. Polyarteritis nodosa
   f. Henoch-Schönlein syndrome
   g. IgA nephropathy
   h. Hereditary nephritis
(ii) Nephrotic syndrome
   a. Minimal change GN
   b. Membranous GN
   c. Proliferative GN
   d. Focal glomerulosclerosis
   e. Amyloidosis
   f. Diabetes mellitus
   g. SLE
   h. Renal vein thrombosis
   i. Congenital nephrotic syndrome
(iii) Acute renal failure
   a. Acute tubular necrosis
   b. Crescentic
   c. Diffuse proliferative GN
   d. Severe acute pyelonephritis
   e. Malignant hypertension
   f. Polyarteritis nodosa
g. SLE  
h. Eclampsia  
i. Hypercalcaemia  
j. Haemolytic-uraemic syndrome  
(iv) Chronic renal failure  
a. Glomerulosclerosis (advanced GN)  
b. Chronic pyelonephritis  
c. Hypertensive nephrosclerosis  
d. Diabetes mellitus  
(v) Painless haematuria  
a. Berger's (IgA) nephropathy  
b. Mesangial proliferative GN  
c. Progressive proliferative GN  
d. Chronic pyelonephritis  
e. Hydronephrosis  
f. Calculus  
g. Tumours  
h. Benign recurrent haematuria  

D. Tubular disorders  
1. Acute tubular necrosis  
   (i) Nephrotoxic  
      a. Heavy metals  
      b. Organic solvents  
      c. Ethylene glycol  
      d. Mushroom poisoning  
   (ii) Ischaemic  
   The causes are those of 'shock'  
   
   Pathological features  
   (i) Kidneys are swollen and pale  
   (ii) Tubular epithelial necrosis, with desquamation of cells forming casts  
   (iii) Calcium oxalate crystals in the lumen in some cases  
   (iv) Rupture of the tubular basement membrane tubulorrhexis  
   (v) Regeneration of epithelium in later stages  

2. Myeloma kidney  

3. Bile nephrosis  

4. Glycogen accumulation  
   (i) Diabetes mellitus  
   (ii) Glycogenoses  

5. Tubular vacuolation  
   (i) Hypokalaemia  
   (ii) Administration of hypertonic solutions  

6. Disorders of tubular function  
   (i) Defects in transport mechanisms
a. Renal glycosuria
b. Phosphaturia
c. Renal tubular acidosis
d. Familial phospho-gluco-aminoaciduria
e. Cystinuria
f. Hartnup disease
g. Glycine-iminoaciduria
h. Glycinuria

(ii) Abnormal tubular response to hormones
a. Nephrogenic diabetes insipidus
b. Pseudohypparathyroidism
c. Pseudohyperaldosteronism
d. Pseudohyperaldosteronism

E. Urinary calculi and nephrocalcinosis

Calculi
Calculi are composed of amorphous urinary crystalloids bound by a mucoprotein matrix. They may be found anywhere in the urinary tract but most are formed in the calyces and renal pelvis. The major crystalloids are:
1. Uric acid
2. U rates
3. Oxalates
4. Calcium or magnesium phosphate

Pathogenesis
1. Increased concentration of crystalloids in the urine resulting from:
   (i) Reduced urine volume as in dehydration
   (ii) Increased excretion of crystalloids
      a. Hypercalciuria
      b. Cystinuria
      c. Gout - (uric acid excess)
2. Factors favouring the precipitation of crystalloids from 'normal' urine
   (i) Stasis
   (ii) Infection. Organisms may split urea and produce alkalinity of the urine which favours the formation of magnesium-ammonium phosphate
   (iii) Foreign bodies, clumps of bacteria, desquamated epithelial cells, these may act as a nidus for crystallisation
   (iv) Deficiency of stabilising factors such as citrate, colloids, amino acids

Effects
1. Obstruction - hydronephrosis
2. Chronic infection - pyelonephritis
3. Squamous metaplasia

Nephrocalcinosis

Aetiology
1. Hyperparathyroidism
2. Malignancy
   (i) Hypercalcaemia due to osteolytic deposits
   (ii) Secretion of parathormone-like hormone by tumour cells
3. Paget's disease of bone particularly during immobilisation
4. Sarcoidosis
5. Vitamin D excess
6. Milk-alkali syndrome
7. Renal tubular acidosis
8. Idiopathic hypercalcaemia of infancy
9. Hyperoxaluria
10. Hyperthyroidism
11. Hypothyroidism in infants

F Vascular disorders
1. Benign nephrosclerosis in essential hypertension
2. Malignant nephrosclerosis
3. Senile arteriosclerotic disease
4. Infarction
   (i) Arterial embolism
      a. Atrial or mural thrombosis in the heart
      b. Thrombus from the aorta
      c. Atherosclerotic debris from ruptured plaques in the upper aorta
      d. Vegetations from the aortic or mitral valves
   (ii) Arterial thrombosis
      a. Superimposed on atherosclerosis
      b. Aortic thrombosis occluding the renal ostium
      c. Polyarteritis nodosa
   (iii) Involvement of renal ostia by aneurysm
   (iv) Sudden venous occlusion - renal vein thrombosis
5. Acute cortical necrosis resulting from DIC in various forms of shock.

G. Tumours
1. Benign
   (i) Cortical adenoma
      a. Clear cell
      b. Papillary
      c. Oxyphil cell
   (ii) Fibroma
   (iii) Haemangioma
   (iv) Angiolipom
2. Malignant
   (i) Adenocarcinoma (hypernephroma)
      a. Solid-cell type often found in the same tumour
      b. Clear-cell type
   (ii) Nephroblastoma (Wilms'tumour)
   (iii) Sarcomas (very rare)
   (iv) Transitional cell carcinoma of the renal pelvis
   (v) Squamous cell carcinoma of the renal pelvis (very rare)
BLADDER

A. Congenital
1. Diverticula
2. Ectopia vesicae
3. Persistent urachus

B. Inflammations
Types
1. Acute cystitis
2. Chronic cystitis
3. Special forms of cystitis
   (i) Follicular
   (ii) Encrusted - phosphates
   (iii) Polypoid, including bullous
   (iv) Interstitial
   (v) Cystitis cystica
   (vi) Tuberculous
   (vii) Malakoplakia
   (viii) Irradiation
   (ix) Schistosomiasis (haematobium)

C. Miscellaneous conditions
1. Calculi
2. Diverticulae
3. Fistula
   (i) Crohn's disease
   (ii) Malignancy
4. Perforation, most commonly traumatic

D. Tumours
1. Benign or premalignant
   (i) Transitional cell papilloma. To be classified as a papilloma the tumour must:
      a. Be strictly papillary in pattern
      b. Show normal transitional cell differentiation throughout
      c. At no point be more than four cells thick
      d. Show no invasion
   (ii) Dysplasia - mild, moderate, severe or carcinoma-in-situ
2. Malignant
   (i) Transitional cell carcinoma Growth pattern
      a. Intra-epithelial (carcinoma-in-situ)
      b. Papillary
      c. Solid
      d. Mixed papillary and solid
   Cellular structure
   Three grades showing progressive anaplasia have been described corresponding to well, moderately and poorly differentiated.
   Pathological staging
   pTis - Pre-invasive carcinoma
   pT1 - Infiltration of subepithelial connective tissue
pT2 - Infiltration of superficial muscle (<halfway)
pT3 - Infiltration of deep muscle
pT4 - Invasion of prostate or other extra-vesical structures

(ii) Squamous carcinoma (arising via metaplasia)
(iii) Adenocarcinoma
(iv) Sarcomas, e.g. rhabdomyosarcoma
(v) Phaeochromocytoma (very rare)

23. Reproductive system

MALE

PROSTATE

A. Inflammations
1. Non-specific prostatitis
   (i) Acute
   (ii) Chronic
   (iii) Granulomatous
2. Gonococcal
3. Chlamydial
4. Tuberculous prostatitis
5. Eosinophilic (allergic) prostatitis
6. Malakoplakia

B. Nodular hyperplasia
Types Of nodule
1. Mixed stroma and acini (fibromyo-adenomatous)
2. Fibrous or fibrovascular - possibly resulting from previous infarction or foci of inflammation
3. Muscular

Additional features
1. Focal inflammation - acute or chronic
2. Corpora amylacea
3. Calculi
4. Cystic degeneration
5. Infarcts
6. Squamous metaplasia/hyperplasia of the peri-urethral glands

C. Neoplasms
1. Carcinoma

Aetiological factors
   (i) Age - rare under 50
   (ii) Hormones
      a. ? steroid imbalance
      b. ? altered sensitivity of prostatic epithelium
(iii) Race - low incidence in Orientals

**Histological types**
(i) Adenocarcinoma
(ii) Anaplastic
(iii) Squamous carcinoma arising from metaplastic epithelium in ducts

**Behavioural types**
(i) Clinical prostatic cancer - where the disease is producing symptoms
(ii) Latent cancer - foci of carcinoma found incidentally:
   - at prostatectomy: if multifocal (even low grade), associated with a significant rate of progression if patient less than 60
   - at autopsy: incidence increases with age
(iii) Occult cancer - the appearance of metastases whilst the primary remains covert

**Stages**
A = Occult carcinoma
B = Nodule of carcinoma confined within the prostatic capsule
C = Carcinoma has spread outside the capsule with extension into surrounding structures,
   or confined within the capsule but with elevated serum acid phosphatase
D = Demonstrable skeletal or extra-pelvic involvement

**Spread**
(i) Direct: seminal vesicles, rectum, bladder
(ii) Lymphatic: iliac, para-aortic glands
(iii) Blood: bone, particularly the sacrum and vertebrae

2. Embryonal rhabdomyosarcoma
3. Leiomyosarcoma
4. Lymphoma

**TESTIS AND EPIDIDYMIS**

**A. Congenital**
1. Undescended testis (cryptorchidism)
2. Absence of one or both testes
3. Fusion
4. Simple cysts
5. Ectopic testes

**B. Inflammatory disorders**
1. Non-specific epididymo-orchitis
2. Gonococcal epididymo-orchitis
3. Mumps orchitis
4. Tuberculosis (starts in epididymis)
5. Syphilis (starts in testis)
6. Granulomatous orchitis

**C. Degenerative disorders**
1. **Causes**
   (i) Increasing age - ? ischaemic
   (ii) Following orchitis
   (iii) Administration of anabolic steroids
(iv) Malnutrition
(v) Post-vasectomy
(vi) Hyrhoestrogenic states
(vii) Hypopituitarism

D. Vascular disorders
1. Torsion of the testis
2. Varicocele (varicosity of the pampiniform plexus)

**Germ cell tumours**
1. Seminoma
   The most common testicular tumour - about 40%.
   Highly radiosensitive, therefore a good prognosis.

*Spread*
   (i) Lymphatic: iliac and para-aortic nodes
   (ii) Blood: late spread to liver and lungs

2. Teratoma
   Second most common tumour of testes. The prognosis is good with combination chemotherapy unless the disease is extremely advanced at presentation.
   (i) Malignant teratoma differentiated
   (ii) Malignant teratoma intermediate
   (iii) Malignant teratoma undifferentiated
      No mature elements are present
      This category includes tumours that can be entirely undifferentiated or show some areas of either trophoblastic or yolk sac differentiation.
      Trophoblastic (malignant teratoma trophoblastic) and yolk sac tumours can also exist as distinct neoplasms

3. Combined tumours Seminomas and any type of teratoma can coexist.

**Miscellaneous tumours**
1. Malignant lymphoma
   These are more common in older men
2. Spermatocytic seminoma
3. Sertoli cell tumour - rare
4. Leydig cell tumour - mainly benign tumours secreting androgenic hormones and presenting in childhood with sexual precocity, in adults as a testicular swelling
5. Carcinoma of the rete and appendix testis

**FEMALE**

**CERVIX**

**A. Inflammation**
1. Acute cervicitis
2. Chronic cervicitis - increased numbers of chronic inflammatory cells with, in a few cases, follicle formation. These may indicate chlamydial infection.
3. Viral infections
   (i) Herpes simplex
   (ii) Human papilloma virus infection which is manifest as:
      a. Condyloma acuminata
      b. Non-condylomatous wart virus infection – koilocytosis
B. Squamous metaplasia and 'erosion'
At puberty and during pregnancy the columnar epithelium of the endocervix extends downwards and occupies part of the ectocervix. This change, which is physiological, is clinically termed an 'erosion'. Subsequently this columnar epithelium undergoes metaplasia to squamous type. This labile area at the squamo-columnar junction is known as the 'transformation zone'.

D. Tumour-like lesions
Cervical polyps
(i) Endocervical or mucous polyp
(ii) Inflammatory polyp (granulation tissue)

D. Tumours
Benign
Leiomyoma
Malignant
1. Carcinoma
Predisposing factors
(i) Viral infection (HPV)
(ii) Low social class
(iii) Prematurity, frequency of intercourse, early age of onset of sexual relations
(iv) Cigarette smoking
Pre-invasive neoplasia (cervical intra-epithelial neoplasia)
CIN I (mild dysplasia)
CIN II (moderate dysplasia)
CIN III (severe/carcinoma-in-situ)
Micro-invasive carcinoma
This is where invasion into sub-epithelial stroma is less than 3 mm. Such carcinomas carry a low risk of lymph node involvement
Histological types of invasive carcinoma
(i) Squamous carcinoma (70%)
(ii) Adenocarcinaoma (5%)
(iii) Adeno-squamous (25%)
Staging
Stage 0 = Carcinoma-in-situ (CIN III)
Stage I = Invasive carcinoma confined to the cervix
Stage II = Carcinoma extends beyond the cervix but not to the pelvic wall or lower 1/3 of vagina
Stage III = Carcinoma extends to pelvic wall and/or the lower 1/3 of vagina
Stage IV = Extension beyond the true pelvis or involvement of mucosa of bladder or rectum
Metastatic spread of cervical carcinoma is by Pelvic lymphatics to the para-aortic lymph nodes.
2. Sarcomas
(i) Leiomyosarcoma
(ii) Embryonal rhabdomyosarcoma (sarcoma botryoides)
UTERUS

A. Congenital
Abnormal fusion of the Mullerian ducts leads to:
(i) Double uterus
(ii) Septate
(iii) Bicornuate
(iv) Bicollis

B. Endometrial inflammation
1. Acute endometritis may result in pyometra
2. Chronic endometritis
   (i) Post-partum
   (ii) IUCD associated
   (iii) Salpingitis associated
   (iv) Tuberculous

C. Adenomyosis
Is the presence of endometrial elements in the myometrium. The aetiology is unknown but may represent herniation into the muscle

D. Hormone induced changes in the endometrium
1. Dysfunctional uterine bleeding
   (i) Anovulation
   (ii) Persistent corpus luteum (delayed shedding)
2. Arias-Stella phenomenon - nuclear enlargement and glandular hypersecretion usually found in pregnancy. In the absence of a uterine pregnancy the finding of an Arias-Stella change suggests an ectopic pregnancy.
3. Oral contraceptive pill effects
4. Senile cystic atrophy
5. Hyperplasia
   (i) Simple hyperplasia - no risk of malignant change
   (ii) Complex hyperplasia (architectural abnormalities) – low risk
   (iii) Complex atypical hyperplasia (architectural and cytological abnormalities) - greatest risk of malignancy
6. Endometrial polyps

E. Tumours
1. Endometrium
   (i) Adenoma (rare)
   (ii) Carcinoma
   
   Predisposing factors
   Hyperplasia especially complex atypical hyperplasia which may be a consequence of
   a. Obesity
   b. Exogenous oestrogens
   c. Ovarian stromal hyperplasia
   d. Granulosa cell tumours of the ovary
   e. Polycystic ovary syndrome

   Histological types
Hyperplasia related:
a. Adenocarcinoma

Unrelated to hyperplasia:
a. Adenosquamous, where there is a mixture of adenocarcinoma and malignant squamous elements
b. Papillary serous
c. Clear cell

Spread
The prognosis is determined by the depth of myometrial invasion.
a. Direct to cervix, vagina, vulva and parametrium
b. Direct to tubes and ovaries
c. Lymphatic to iliac and para-aortic glands
d. Blood spread is late - lungs, liver, adrenals and bone

(ii) Endometrial stromal sarcoma - low-grade or high-grade
(iii) Mixed Mullerian tumours (carcino-sarcomas)
 a. Homologous - derived from uterine components
 b. Heterologous - from tissues not normally present in the uterus

2. Myometrium
 (i) Leiomyoma (fibroid)
 (ii) Smooth muscle tumour of uncertain malignant potential
 (iii) Leiomyosarcoma

OVARY

1. Endometriosis
Endometriosis is the presence of endometrial glands and stroma in sites other than the uterine corpus. Aetiological theories include retrograde menstruation and Mullerian metaplasia of the mesothelium.

Sites
 (i) Ovaries
 (ii) Fallopian tubes
 (iii) Rectovaginal septum - pouch of Douglas
 (iv) Peritoneum
 (v) Umbilicus
 (vi) Rare sites - vulva, vagina, appendix, intestinal wall

Effects
 (i) 'Chocolate' cyst formation
 (ii) Intra-pelvic haemorrhage
 (iii) Formation of adhesions
 (iv) Endometrioid adenocarcinoma of the ovary
 (v) Infertility

2. Neoplasms
 (i) Epithelial - benign, borderline or malignant
   a. Serous
   b. Mucinous
   c. Brenner
   d. Endometrioid
 (ii) Germ cell tumours
a. Teratoma
   Mature cystic
   Immature solid
b. Extra-embryonic
   Yolk sac tumour
   Choriocarcinoma
c. Dysgerminoma
d. Malignant mixed germ cell tumours

(iii) Sex-cord stromal tumours
   a. Thecoma
   b. Granulosa cell tumour
   c. Sertoli-Leydig cell tumour
   d. Mixed germ cell / stromal tumour (gonadoblastoma)

PLACENTA

1. Hydatidiform mole
   The placenta is composed of swollen chorionic villi showing trophoblastic hyperplasia. There is an associated high HCG level and the condition may be complicated by choriocarcinoma. Two types are recognized:
   (i) Complete mole - this has a triploid karyotype consisting of male (2n) and female (1n). No fetus.
   (ii) Partial mole - this has a triploid karyotype consisting of male (2n) and female (1n). A fetus may be present.

2. Abnormalities of placentation
   (i) Extrachorial
      a. Circum-vallate
      b. Circum-marginate
   (ii) Accessory lobe
   (iii) Placenta accreta - penetration of the myometrium by chorionic villi

3. Inflammation
   Inflammation (villitis) is associated with fetal growth retardation and death. Most cases are idiopathic but recognized causes include:
   (i) Listeriosis
   (ii) Cytomegalovirus
   (iii) Toxoplasmosis

4. Chorionic villous immaturity
   Immaturity can give rise to hypoxia, low birth weight and perinatal death.

5. Vascular lesions
   (i) Infarcts - occlusion of maternal spiral arteries
   (ii) Thrombosis of fetal villous stem arteries
   (iii) Haemangioma
24. Breast

A. Congenital
1. Supernumerary nipples - polythelia
2. Supernumerary breasts - polymastia

B. Inflammation
1. Acute suppurative mastitis
2. Breast abscess
3. Mammary duct ectasia (plasma-cell mastitis)
4. Fat necrosis
5. Tuberculosis
6. Silicone mastitis following cosmetic surgery

C. Cystic disease
Fibrocystic disease, cystic mastopathy, mammary dysplasia Microscopic features (found in various combinations)
1. Cyst formation (macro- or microcysts)
2. Intercalated and intralobular fibrosis
3. Apocrine metaplasia
4. Epithelial proliferation (epitheliosis)
5. Ductular proliferation (adenosis)
6. Papillomatosis
7. Lobular sclerosis (sclerosing adenosis)
8. Radial scar
Occasionally, sclerosing adenosis is found as a solitary lesion. In some young women fibrosis is the dominant feature and is associated with premature involution. This form has been designated fibrous disease of the breast.

D. Tumour-like lesions
1. Hamartoma
2. Microglandular adenosis

E. Tumours
Benign
1. Fibroadenoma
   (i) Intracanalicular
   (ii) Pericanalicular, including 'giant fibroadenoma'
2. Intraduct papilloma
3. Adenoma of the nipple
4. Tubular adenoma
5. Ductal adenoma
6. Lactating adenoma
7. Lipoma
8. Fibroma, haemangioma, etc.
Phyllodes tumour
These tumours (formerly included with giant fibroadenomas) have a structure resembling an intracanalicular fibroadenoma but have a cellular stroma showing varying degrees of atypia. They can be benign, borderline, or malignant.

Malignant
1. In-situ (non-invasive) carcinoma
   (i) Ductal
   (ii) Lobular
2. Infiltrating (invasive) carcinoma
   (i) Ductal
      Varieties
      a. Classical
      'Special' types
      b. Medullary
      c. Mucinous
      d. Tubular
      e. Papillary
      f. Apocrine
      g. Squamous (?tumour metaplasia)
   (ii) Lobular Varieties
      a. Classical
      b. Sparse (paucicellular)
      c. Solid and pleomorphic - worse prognosis
      d. Alveolar
      e. Tubulo-alveolar
   (iii) Adenoid cystic carcinoma
   (iv) Carcinoid (very rare)
3. Paget's disease of the nipple

Spread of mammary carcinoma
1. Direct
   (i) Skin - fungating growths
   (ii) Deep fascia
   (iii) Muscle
2. Lymphatic
   (i) Axillary and internal mammary lymph nodes
   (ii) Dermal lymphatics
   (iii) Widespread dissemination - mediastinal, abdominal, pelvic and inguinal glands
3. Serous cavities with effusions
   (i) Pleura
   (ii) Pericardium
4. Blood stream
   (i) Lungs
   (ii) Bone
   (iii) Adrenals
   (iv) Ovaries
   (v) Kidneys
   (vi) Brain, etc.
Other malignant tumours of the breast
All are rare
1. Fibrosarcoma
2. Liposarcoma
3. Haemangiosarcoma
4. Lymphoma

25. Endocrine system

ADRENAL GLANDS

A. Reactions to stress
1. Lipid depletion (compact-cell change)
   (i) Focal
   (ii) Diffuse
2. Degenerative changes in the zone fascicular cells
3. Hemorrhage

B. Hypercorticalism
1. Cushing's syndrome
   Primary
   (i) Cortical hyperplasia
      a. Diffuse
      b. Nodular
   (ii) Adenoma
   (iii) Carcinoma
   Secondary
   (i) ACTH and corticosteroid administration
   (ii) Pituitary adenoma (basophil or chromophobe)
   (iii) Non-endocrine tumours producing ACTH
      a. Carcinoma of the bronchus (oat-cell type)
      b. Thymoma
      c. Medullary carcinoma of thyroid
      d. Islet cell tumours of pancreas
   Effects
      (i) Obesity
      (ii) Hypertension
      (iii) Osteoporosis
      (iv) Hyperglycaemia
      (v) Myopathy
      (vi) Atrophic change in skin
      (vii) Polycythaemia
      (viii) Pituitary changes - Crooke's hyaline degeneration in basophils
      (ix) Susceptibility to infection
2. Conn's syndrome - (Primary aldosteronism)
   Causes
(i) Cortical adenoma
(ii) Diffuse or nodular hyperplasia
(iii) Carcinoma

**Effects**
(i) Hypertension
(ii) Muscle weakness (hypokalaemia)
(iii) Polyuria and polydipsia
(iv) Hypernatraemia

3. Adreno-genital syndrome **Causes**
(i) Congenital adrenal hyperplasia resulting from a specific enzyme deficiency
(ii) Cortical adenoma in older children and in adults
(iii) Carcinoma

**Effects**
(i) Congenital type
   a. Male - enlargement of the penis, rapid growth, early fusion of epiphyses
   b. Female - pseudohermaphrodite, hirsutism, rapid growth
      In addition both may develop hypertension and salt-losing crises
(ii) Adults
   a. Female - amenorrhoea, hirsutism, atrophy of the breasts, enlarged clitoris, male musculature
   b. Male - no clinical effects

C. **Hypocorticalism**
1. Acute adrenal insufficiency resulting from
   (i) Haemorrhagic necrosis
      a. Shock and stress reactions
      b. Septicaemia (Waterhouse-Friderichsen syndrome)
      c. Neonatal hypoxia/birth injury
      d. Abdominal trauma
   (ii) Sudden deterioration of chronic insufficiency of the adrenal cortex
2. Chronic adrenal insufficiency resulting from:
   (i) Pituitary/hypothalamic disorders
      a. Simmond's disease
      b. Sheehan's syndrome
      c. Iatrogenic
   (ii) Adrenal diseases
      a. Atrophy (idiopathic)
      b. Tuberculosis
      c. Amyloidosis
      d. Fungal infections - histoplasmosis, torulosis, coccidioidomycosis, blastomycosis
      e. Metastatic carcinoma
      f. Haemochromatosis
      g. Following haemorrhagic necrosis
      h. Congenital disorders - hypoplasia with cytomegaly, adreno-genital syndrome
   (iii) Suppression of ACTH production by corticosteroid treatment

**Effects**
   a. Increased skin pigmentation
b. Hypotension
c. Muscle weakness
d. Hypoglycaemia
e. Normochromic anaemia
f. Hyponatraemia
g. Hyperkalaemia
h. Reduced renal excretion of water, ammonium ions and urea

D. Tumours
Adrenal cortex
1. Adenoma (the majority are non-functional)
2. Carcinoma
3. Myelolipoma
Adrenal medulla
1. Phaeochromocytoma
A tumour of the catecholamine-producing chromatin cells resulting in paroxysmal hypertension.

Associations
(i) Multiple endocrine neoplasia syndrome (MEN-2, Sipple's syndrome)
(ii) Neufibromatosis
(iii) von Hippel-Lindau disease
(iv) Medullary carcinoma of thyroid
(v) Parathyroid adenomas

Behaviour
Most are benign, about 10% are malignant.
Metastases are found in lymph glands, lungs, liver and bone

2. Neuroblastoma
A highly malignant tumour of neuroblasts, cells which normally mature into sympathetic ganglion cells. It is a common tumour of childhood.

Sites
(i) Adrenal medulla
(ii) Sympathetic chain in posterior mediastinum and abdomen
(iii) Rare sites, e.g. jaw, bladder

Spread
(i) Direct local infiltration
(ii) Lymph glands
(iii) Blood spread
   a. Skeletal metastases especially to skull and orbit (Hutchinson type)
   b. Multiple deposits in the liver (Pepper type)

3. Ganglioneuroma
'Mature' form of neuroblastic tumour with plentiful ganglion cells. These have a much better prognosis.
Both tumours may be associated with catecholamine production.

DIABETES MELLITUS

A metabolic disorder characterized by impaired utilisation of carbohydrates and disturbances in lipid and protein metabolism resulting from an absolute or relative deficiency of insulin.
Aetiology

1. Primary (idiopathic)
   (i) Juvenile
   (ii) Maturity-onset

2. Secondary
   (i) Pancreatic causes
      a. Pancreatitis
      b. Carcinoma of the pancreas
      c. Haemochromatosis
      d. Pancreatectomy
      e. 'Glucagonoma'
   (ii) Adrenal causes
      a. Cushing's syndrome
      b. Phaeochromocytoma
   (iii) Pituitary - acromegaly
   (iv) Thyroid - thyrotoxicosis
   (v) Drugs - thiazides

Pathological features

1. Islets of Langerhans
   (i) Degranulation of b-cells
   (ii) Hyaline deposits and amyloidosis
   (iii) Fibrosis
   (iv) Hydropic degeneration of b-cells
   (v) Lymphocytic infiltration

2. Kidney
   (i) Arteries and arterioles
      a. Atherosclerosis
      b. Arteriolosclerosis - afferent and efferent
   (ii) Glomeruli
      a. Diffuse glomerulosclerosis
      b. Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion)
      c. Exudative lesions - fibrin cap, capsular drops
   (iii) Tubules
      a. Glycogen accumulation (Armanni-Ebstein lesion)
      b. Fatty change
   (iv) Interstitium
      a. Acute or chronic pyelonephritis
      b. Fibrosis

3. Cardiovascular lesions
   (i) Arteries
      a. Atherosclerosis - gangrene, myocardial infarction
      b. Monckeberg's sclerosis (more common in diabetics)
   (ii) Arteriolosclerosis
   (iii) Microangiopathy

4. Ocular lesions
   (i) Capillary microaneurysms
   (ii) Retinitis proliferans resulting from repeated haemorrhages
   (iii) Thrombosis of the central retinal vein
   (iv) Cataracts
5. Liver
   (i) Fatty change
   (ii) Glycogenic vacuolation of hepatocyte nuclei
6. Gall-bladder
   (i) Cholesterolosis increased incidence
   (ii) Gall-stones
7. Neurological lesions
   (i) Atherosclerotic neuropathy
   (ii) Diabetic pseudotabes
   (iii) Motor neuropathy
   (iv) Autonomic neuropathy
      a. Impotence
      b. Diarrhoea
      c. Atonic stomach
      d. Disturbed oesophageal peristalsis
      e. Bladder dysfunction
8. Skin
   (i) Xanthomata
   (ii) Necrobirosis lipoidica diabeticorum
   (iii) Infections
      a. Pyogenic - boils, carbuncles
      b. Fungal
9. Lungs
   Increased risk of infection
   a. Bronchopneumonia
   b. Tuberculosis
10. Fetus
     a. Infants of diabetic mothers show hyperplasia of b-cells (nesidioblastosis) which can cause hypoglycaemia
     b. Increased birth weight

PITUITARY

1. Pituitary insufficiency
   Aetiology
   (i) Ischaemic necrosis, especially postpartum (Sheehan's syndrome)
   (ii) Tumours
      a. Chromophobe adenoma
      b. Craniopharyngioma
      c. Cholesteatoma
      d. Metastatic
   (iii) Granulomata
      a. Sarcoidosis
      b. Tuberculosis
      c. Congenital syphilis
      d. Idiopathic giant-cell type
   (iv) Infiltrations
      a. Amyloidosis
b. Hand-Schüller-Christian disease
(v) Trauma

Anterior pituitary failure leads to
(i) Simmond's disease
   a. Loss of pigment
   b. Loss of hair
   c. Mental deterioration
   d. Genital atrophy
   e. Myxoedema
(ii) Frohlich's syndrome - adipose-genital dystrophy
(iii) Lorain-type dwarfism

Posterior pituitary failure leads to diabetes insipidus

2. Pituitary hyperfunction results from functioning adenomas
   (i) ACTH - Cushing's syndrome
   (ii) Somatotropin
       a. Gigantism
       b. Acromegaly
   (iii) Prolactin
       a. Galactorrhoea
       b. Amenorrhoea
       c. Impotence

THYROID

A. Congenital disorders
1. Aplasia
2. Hypoplasia
3. Thyroglossal duct/cyst/fistula
4. Lingual thyroid

B. Thyroiditis
1. Infection
   (i) Acute non-specific
   (ii) Tuberculosis
   (iii) Sarcoidosis
   (iv) Actinomycosis
2. Immune mechanisms
   (i) Hashimoto's disease
   (ii) Focal lymphocytic thyroiditis
3. Physical agents
   (i) Irradiation
   (ii) Trauma
4. Unknown aetiology
   (i) Subacute (giant-cell) thyroiditis - de Quervain's disease
   (ii) Fibrous thyroiditis (Riedel's struma)

C. Hyperthyroidism

Aetiology
1. Diffuse thyroid hyperplasia but may result from:
2. Overactivity of a multinodular goitre
3. Functional (toxic) adenoma
4. Hashimoto's disease (rarely)

**Diffuse thyroid hyperplasia (Graves' disease)**

**Aetiology**

(i) Long-acting thyroid stimulator - an immunoglobulin
(ii) Pituitary hyperfunction with excess TSH production

**Organ changes**

(i) Thyroid
   - Enlargement
   - Columnar epithelial cells
   - Papillary infoldings of epithelium
   - Diminished colloid
   - Focal lymphocytic infiltration
(ii) Exophthalmos
   - Oedema of the orbital contents
   - Increase in adipose tissue in orbits
   - Degeneration and fibrosis in extra-ocular muscles
(iii) Pre-tibial myxoedema
(iv) Lymphoid hyperplasia
(v) Heart
   - Left ventricular hypertrophy
   - Focal myocardial necrosis
(vi) Adrenal - hyperplasia
(vii) Skeletal muscle
   - Atrophy
   - Adipose infiltration
   - Vacuolisation
(viii) Bones
   - Osteoporosis
   - 'Thyroid acropachy' - finger-clubbing resulting from subperiosteal new bone formation

**D. Goitre**

**Types**
1. Diffuse colloid
2. Multinodular

**Aetiology**
1. Iodine deficiency
2. Drug-induced (goitrogens)
   (i) Iodides
   (ii) Thioureas
   (iii) PAS, etc.
3. Inborn errors of metabolism (dyshormonogenic goitre)
   (i) Defective iodide trapping
   (ii) Failure to oxidise iodide to iodine prior to incorporation into tyrosine
   (iii) Failure to couple mono- and diiodotyrosine to form T3 and T4
(iv) Failure to de-iodinate iodine-containing by-products of T3/T4 synthesis resulting from a lack of iodotyrosine dehalogenase
(v) An abnormal iodoprotein is produced instead of synthesis of thyroid hormones

Effects
1. Overactivity in some cases, hypofunction in others. Most are euthyroid
2. Pressure on the trachea and oesophagus
3. Haemorrhage into a nodule
4. Malignant change

E. Hypothyroidism
1. Cretinism Aetiology
   (i) Aplasia
   (ii) Hypoplasia
   (iii) Inborn error of hormone synthesis

2. Myxoedema
Aetiology
   (i) Primary
   a. Hashimoto's disease
   b. Other forms of thyroiditis
   c. Senile atrophy
   d. Iodine deficiency
   e. Goitrogenic drugs
   f. Thyroidectomy
   g. Irradiation
   (ii) Secondary
   a. Pituitary insufficiency (low TSH)

Organ changes
1. Cardiovascular system
   (i) Congestive cardiomyopathy
      a. Increased mucopolysaccharide in the interstitium
      b. Mucoid vacuolation of myocardial fibres
   (ii) Atherosclerosis resulting from hypercholesterolaemia
2. Myxoedema
   Infiltration of the skin and other tissues by mucoid oedema
3. Central nervous system
   (i) Mental deterioration
   (ii) Psychosis
   (iii) Stupor and coma

F. Tumours
1. Benign
   (i) Follicular adenoma Variants
      a. Colloid adenoma
      b. Fetal adenoma
      c. Hürthle cell adenoma
   (ii) Teratoma (very rare)
2. Malignant  
   (i) Carcinoma arising from thyroid epithelium  
      a. Follicular  
      b. Papillary  
      c. Hürthle cell  
   (ii) Carcinoma arising from calcitonin-producing cells Medullary carcinoma  
      (with amyloid in stroma)  
   (iii) Rare tumours  
      a. Squamous carcinoma (by metaplasia)  
      b. Mucoepidermoid  
      c. Undifferentiated carcinoma  
         Spindle cell  
         Giant cell  
      d. Sarcoma  
      e. Lymphoma

PARATHYROID

A. Congenital  
1. Abnormal number 2-5  
2. Abnormal position, e.g. mediastinum

B. Hyperparathyroidism

Aetiology

Effects
1. Bone  
   (i) Osteitis fibrosa cystica  
   (ii) Giant-cell granulomas ('brown tumours')  
2. Metastatic calcification in  
   (i) Kidneys  
      a. Nephrocalcinosis  
      b. Renal calculi  
   (ii) Blood vessels  
   (iii) Lung  
   (iv) Stomach  
3. Peptic ulceration  
4. Chronic pancreatitis

C. Hypoparathyroidism

Aetiology
1. Surgical removal in thyroidectomy  
2. 'Idiopathic'  
   (i) Hypoplasia/aplasia (as in Di George's syndrome)  
   (ii) Atrophy (? auto-immune)  
3. Pseudo-hypoparathyroidism (Albright)

Effects  
1. Tetany  
2. Mental disturbances
3. Epilepsy  
4. Papilloedema  
5. Ectodermal changes  
   (i) Dry skin/brittle nails  
   (ii) Eczema  
   (iii) Moniliasis  
6. Cataracts  
7. Calcification of the basal ganglia  

26. Haemopoietic and lymphoid tissues  

HAEMOGLOBIN  
Haemoglobin is a conjugated protein composed of four haem groups attached to globin. Haem consists of a tetrapyrrole (porphyrin) ring with a ferrous ion at its centre.  
Haemoglobin from effete red cells is normally broken down in reticuloendothelial cells of the spleen, bone marrow, and liver. The protein moiety is detached and broken down into its constituent amino acids which are re-metabolised. The Porphyrin moiety is converted into bilirubin and excreted. The iron (now ferric) combines with protein (apoферритин) to form ferritin. It can be stored in this form, or as a more concentrated iron-protein complex haemosiderin. Iron is transported in the plasma as ferric ion bound to the β globulin transferrin.  
Apart from the inherited disorders of globin synthesis (the haemoglobinopathies), haemoglobin and its products are subject to the following disturbances:  
A. Disordered synthesis of haem resulting from abnormal porphyrin metabolism  
B. Formation of abnormal haemoglobin compounds  
C. Abnormal storage of iron  
D. Abnormal bilirubin metabolism and excretion leading to hyperbilirubinaemia  

A. Porphyrin metabolism and its abnormalities  
1. Disordered synthesis in the liver (hepatic porphyrias)  
   (i) Inherited as autosomal dominants  
      a. Acute intermittent porphyria  
      b. Porphyria variegate (South African type)  
      c. Hereditary coproporphyria  
      Mechanism  
      Increased activity of d-aminolaevulate synthetase (ALA-S) in response to a partial blockage of haem formation operating at different points in its synthesis for each disease  
      Results  
      a. Acute abdominal pain  
      b. Neuro-psychiatric attacks  
      c. Excretion of large quantities of porphobilinogen (PBG) and
d-aminolaevulinic acid (ALA) in the urine. The attacks may be precipitated by drugs, especially barbiturates

(ii) Sporadic - symptomatic cutaneous hepatic porphyria. This is usually a consequence of chronic liver disease, especially chronic alcoholism

Results
a. Skin photosensitivity
b. Hypermelanosis
c. Hypertrichosis
d. Excretion of large quantities of red-coloured uroporphyrin in the urine

2. Disordered synthesis in the bone marrow (erythropoietic porphyries)

(i) Congenital erythropoietic porphyria (recessive) Results
a. Bulla formation in the skin in response to light and trauma
b. Accumulations of uro- and coproporphyrins in the bone marrow, red blood cells and teeth
c. Excess excretion of uro- and coproporphyrins in the urine and faeces

(ii) Erythropoietic protoporphyria (dominant)
a. Photosensitivity of the skin but no bullae in response to trauma
b. Increased amounts of protoporphyrin in red cells and faeces but not in the urine
c. Cirrhosis of the liver
d. Cholelithiasis

(iii) Erythropoietic coproporphria
a. Photosensitivity
b. Increased coproporphyrins in faeces

B. Abnormal haemoglobin compounds

1. Carboxyhaemoglobin resulting from combination with carbon monoxide and producing a characteristic cherry-red colour in the blood

2. Methaemoglobin results from the conversion of the ferrous to a ferric ion, and in this form cannot combine with oxygen
   (i) Congenital - due to either a haemoglobinopathy (Hb-M) or a deficiency of methaemoglobin reductase (diaphorase)
   (ii) Acquired - drug induced, e.g. phenacetin, sulphonamides, nitrates, and other oxidising drugs

3. Sulphaemoglobin - drug induced, e.g. phenacetin, acetanilide

C. Abnormal storage of iron

Iron is normally stored as ferritin or as haemosiderin, which consists of partly denatured ferritin. When excessive quantities require to be stored clumps of haemosiderin appear in the tissues and can be readily demonstrated by Prussian Blue reaction.

Haemosiderin deposition may be localized or generalized:

1. Localized deposits are found in:
   (i) Areas of haemorrhage in haemosiderin-laden macrophages
   (ii) Renal tubular cells in haemoglobinuria
   (iii) Siderotic nodules (Gamna-Gandy bodies) in splenomegalgy with hepatic cirrhosis

2. Generalized deposition may result from:
   (i) Excessive absorption of iron from the diet due to
a. An inborn error of metabolism  
b. A greatly increased dietary intake  
c. In thalassaemia, sideroblastic anaemia, and spherocytosis (in the absence of transfusions)

Prolonged increased absorption leads to complete saturation of circulating transferrin and thereafter absorbed iron is present in portal blood in the unbound form. Free iron is toxic and produces chronic cell injury in vascular shunts in the cirrhosis liver, free iron enters the liver resulting in cirrhosis. With the development of systemic circulation and affects other organs, notably the heart and pancreas. A variety of functional disturbances may ensue and this parenchymatous iron storage disease is **haemochromatosis**.

(ii) Excessive administration of iron by multiple transfusions or parenteral injections

This usually results in iron deposition in macrophages of the bone marrow, liver, and spleen and is termed **haemosiderosis**. If administration is prolonged or massive amounts are given, then saturation followed by parenchymatous deposition and fibrosis may result in a picture indistinguishable from haemochromatosis.

**Haemochromatosis may affect many organs:**  
a. Liver - producing cirrhosis which in turn is associated with an increased incidence of hepatocellular carcinoma  
b. Pancreas - interacinar fibrosis with Pigmentation and atrophy of islets leading to diabetes mellitus  
c. Skin - increase in melanin in the basal layer of the epidermis. Haemosiderin is also present mainly around skin appendages  
d. Heart - pigmentation and atrophy of myocardial fibres resulting in arrhythmias and cardiac failure  
e. Stomach - rare cases show deposition of haemosiderin in effect on pepsin secretion chief cells of the gastric mucosa but the pigment has little  
f. Spleen - pigmentation and fibrosis  
g. There may be pigmentation and atrophy in testes, thyroid, adrenals and pituitary

**ANAEMIA**

Anaemia can be defined as a reduction below normal limits of the total circulating red cell mass.  
**Causes**

The major causes of anaemia are blood loss, haemolysis and diminished production.  
A. Blood loss  
   Chronic blood loss, e.g. from the gastrointestinal tract or menorrhagia, results in a microcytic, hypochromic anaemia  
B. Haemolysis  
   1. Hereditary  
      (i) Enzyme deficiency  
         a. Hexose monophosphate shunt enzymes, such as G6PD and glutathione synthetase  
         b. Glycolytic enzymes - pyruvate kinase, hexokinase
(ii) Membrane defects
   a. Disorders of the cytoskeleton - spherocytosis
   b. Increased membrane lipids
(iii) Abnormal haemoglobin synthesis
   a. Production of abnormal P globin chains - sickle cell anaemia (HBSS), sickle cell trait (HBAS)
   b. Deficient P globin synthesis - thalassaemia

2. Acquired
   (i) Immune mechanisms
      a. Autoimmune reactions which may be idiopathic (primary) or associated with mycoplasma infection, SLE and various malignancies
      b. Iso-immune reactions such as drug (hapten) induced haemolysis, transfusion reactions, haemolytic disease of the newborn (erythroblastosis fetalis)
   (ii) Membrane defects - paroxysmal nocturnal haemoglobinuria (sensitivity to complement mediated lysis)
   (iii) Toxin or chemical injury - snake venoms, lead poisoning
   (iv) Infection - malaria
   (v) Physical trauma to red cells
      a. microangiopathic haemolytic anaemias thrombotic thrombocytopenic purpura, DIC
      b. Mechanical injury produced by prosthetic heart valves

C. Diminished red cell production
1. Replacement of the bone marrow
   (i) Malignancy
   (ii) Myelofibrosis
2. Erythroid stem cell failure
   (i) Aplastic anaemia - idiopathic or drug-related
   (ii) Pure red cell aplasia
3. Inadequate erythropoietin stimulation
   (i) Chronic renal disease
4. Defective DNA synthesis
   (i) Folic acid deficiency and folic acid antagonists
      a. Malnutrition
      b. Chronic alcoholism
      c. Malabsorption states
      d. Pregnancy
      e. Anti-cancer drugs such as methotrexate
      f. Anticonvulsant drugs
   (ii) Vitamin B$_{12}$ deficiency
      a. Pernicious anaemia
      b. Post-gastrectomy
      c. Malabsorption states
      d. Ileal resection
      e. Diffuse intestinal diseases - systemic sclerosis
      f. Competition for uptake - fish tapeworm infestation or bacterial overgrowth in 'blind loops'
5. Defective haemoglobin synthesis
   (i) Iron deficiency
   (ii) Thalassaemia
   (iii) 'Anaemia of chronic disease'
   (iv) Sideroblastic anaemia

LEUKAEMIA AND MYELOPROLIFERATIVE DISORDERS

These disorders are characterized by replacement of the bone marrow by the progeny of a neoplastic stem cell resulting in disordered haematopoiesis. In acute leukaemia the marrow is rapidly replaced by a population of immature cells which leads to the acute effects of marrow failure - anaemia, bleeding and susceptibility to infection. In myelodysplasia the marrow is gradually replaced by a neoplastic clone which results in ineffective haemopoiesis with release of abnormal cells into the circulation, inadequate production (pancytopenia), and a variable rate of evolution towards acute leukaemia. A chronic myeloproliferative disorder (CMPD) is one in which the presence of an abnormal clone leads to the over-production of one or more cell lines which can be either red cells, granulocytes, platelets or bone marrow stromal cells. However, these distinctions are blurred by the tendency for both myelodysplasia and chronic myeloproliferative disorders to undergo transformation to leukaemias. CMPD may undergo blast transformation leading to the production of immature cells, frequently of lymphoid type.

Acute leukaemia
Acute leukaemia may arise de novo as well as developing from myelodysplasia or by blast transformation of CMPD. It is divided into myeloid (AML) and lymphoid (lymphoblastic - ALL) types. These are subdivided according to T or B or common differentiation and by some aspects of cellular morphology. Thus AML is subclassified according to whether there is differentiation towards granulocytes, monocytes, erythroid cells or megakaryocytes.

Myelodysplasia
Myelodysplasia (MDS) is probably quite common but in many people remains as a sub-clinical condition. Dysplastic changes can be found as a secondary phenomenon in a large number of conditions such as marrow replacement by carcinoma and following drug treatment. The primary form, however, is characterized by several chromosomal abnormalities including monosomy 7 which points to its essentially neoplastic nature. The proportion of immature myeloid cells in the marrow appears to determine the prognosis: when less than 5% MDS is an indolent disease whereas with levels between 5 and 30% survival declines rapidly. When the proportion of myeloblasts exceeds 30% the diagnosis becomes acute leukaemia.

Chronic myeloproliferative disorders
Over-production of granulocytes, red cells, platelets and stromal cells gives rise to:
1. Chronic myeloid leukaemia (CML) characterized by:
   (i) Fever
   (ii) Splenomegaly
   (iii) Anaemia
(iv) Bleeding  
(v) Hyperviscosity  
(vi) Progression to acute leukaemia  
(vii) Presence of the Philadelphia chromosome, a translocation between chromosomes 9 and 22 which results in the transcription of a hybrid gene composed of c-abl - bcr.

2. Primary proliferative polycythaemia (PPP or polycythaemia rubra vera)  
   (i) Raised haemoglobin and packed cell volume  
   (ii) Thrombotic tendency - splenic and renal infarcts  
   (iii) Bleeding

3. Primary thrombocythaemia  
   Although there are increased numbers of platelets, bleeding occurs because there is a poor response to aggregating agents. Thrombosis in small vessels is another consequence.

4. Myelofibrosis  
   (i) Splenomegaly  
   (ii) Extra-medullary haemopoiesis  
   (iii) Normocytic, normochromic anaemia  
   (iv) Deformed red cells - tear-drop poikilocytes  
   (v) Leukoerythroblastic cells

LYMPHADENOPATHY

A. Non-neoplastic causes of lymphadenopathy
1. Immune response to local infection or inflammation  
   (i) Naso-pharyngeal infection  
   (ii) Genital infection  
   (iii) Dermatopathic reactions  
   (iv) Crohn's disease

2. Systemic infections involving lymph nodes  
   (i) Infectious mononucleosis  
   (ii) Toxoplasmosis  
   (iii) Tuberculosis  
   (iv) Cat-scratch disease  
   (v) Yersiniosis  
   (vi) Chlamydial infection  
   (vii) Viral infections

3. Foreign material  
   (i) Silicosis  
   (ii) Anthracosis  
   (iii) Lipid deposits - lipogranulomas

4. Miscellaneous causes  
   (i) Sarcoidosis  
   (ii) Drug reactions - e.g. phenytoin

B. Neoplastic causes of lymphadenopathy
1. Metastatic tumours - carcinomas, malignant melanoma, seminoma, etc.  
2. Malignant lymphomas which can be divided into:  
   (i) Hodgkin's disease characterized by  
      a. Reed-Sternberg cells which can be either of B or T cell type
b. A large population of reactive lymphocytes and histiocytes
c. Eosinophils
d. Contiguous spread along lymph node chains

Prognosis is largely governed by pathological type (lymphocyte predominant better than lymphocyte depleted) and the extent of spread (stage) present a diverse and highly

(ii) Non-Hodkins lymphoma (NHL). These lymphomas represent a diverse and highly complex group of neoplasms with currently over 60 different subtypes being recognized. Classification is based on the predominant cell present, the cells corresponding to a certain developmental stage in the differentiation and maturation of lymphocytes. Lymphomas of precursor cells are typically the T-and B-lymphoblastic lymphomas and ALL, whereas neoplastic proliferation of cells in the antigen-dependent phase are much more diverse and consist of either small lymphocytes, germinal centre cells, activated T-cells, or plasmacytoid cells. Grading is derived from the classification into high, intermediate and low grade types. Low grade lymphomas progress slowly but usually show a poor response to chemotherapy. High grade lymphomas progress rapidly but can respond moderately well to chemotherapy.

(iii) Histiocytosis and myeloid malignancy
Examples:
   a. Langerhans cell histiocytosis
   b. Chronic myeloproliferative disorder

**MALIGNANT LYMPHOMA AT OTHER SITES**

1. Mucosa associated B-cell lymphoma
   (i) Stomach
   (ii) Lung
   (iii) Thyroid
   (iv) Salivary gland
2. Cutaneous T-cell lymphoma
3. Enteropathy associated T-cell lymphoma of the intestine
4. Myeloma - a neoplasm of bone marrow plasma cells

**LYMPHOMAS WITH A LEUKAEMIC PHASE**

1. Precursor B- and T- cells - ALL
2. CD5+ B-cells - CLL
3. Pre-plasma cells - hairy cell and lymphoplasmacytoid leukaemia

**THYMUS**

1. Congenital disorders associated with immune deficiency
   (i) Aplasia
   (ii) Hypoplasia
2. Thymic B-cell hyperplasia
3. Thymoma - a malignant tumour of thymic epithelium

Varieties
   (i) Lymphocytic
   (ii) Lymphoepithelial
(iii) Epithelial
(iv) Spindle cell

**Associations** with thymoma
(i) Myasthenia gravis
(ii) Red cell aplasia
(iii) Agammaglobulinaemia
(iv) Thrombocytopenia
(v) Cushing's syndrome
(vi) Auto-immune conditions especially SLE
(vii) Dermatomyositis and polymyositis
(viii) Myocarditis

**Spleen**

**A. Congenital**
1. Agenesis
2. Splenunculi- small rounded nodules of splenic tissue found around the hilum or in the omentum.

**B. Inflammation**
1. Acute non-specific inflammation - the 'septic' spleen
2. Chronic inflammation
   (i) Non-specific, as part of a systemic lymphoid hyperplasia
   (ii) Specific
      a. Malaria
      b. Infectious mononucleosis
      c. Salmonellosis
      d. Tuberculosis (miliary)
      e. Sarcoidosis
      f. Brucellosis

**C. Haematological diseases**
1. Myeloproliferative
   (i) Leukaemias, especially chronic myeloid
   (ii) Myelofibrosis - extramedullary haematopoiesis
2. Red cell disorders
   (i) Autoimmune haemolytic anaemia
   (ii) Hereditary micro-spherocytosis
   (iii) Sickle-cell anaemia
   (iv) Thalassaemia
   (v) Polycythaemia rubra vera
3. Platelet disorders
   (i) Idiopathic thrombocytopenic purpura
   (ii) Thrombotic thrombocytopenic purpura

**D. Vascular disorders**
1. Acute congestion
2. Chronic congestion (see p. 137)
   (i) Congestive cardiac failure
(ii) Portal hypertension

E. *Storage* disease
1. Carbohydrates
   (i) Galactosaemia
   (ii) Type IV glycogenosis (amylopectinosis)

2. Lipids
   (i) Gaucher's disease (glucosyl ceramide a sphingolipid)
       (ii) Niemann-Pick's disease (sphingomyelin)
   (iii) Generalized (GM) gangliosidosis
   (iv) Wolman's disease (neutral lipids triglyceride/cholesterol esters)

3. Glycosaminoglycans
4. Miscellaneous
   (i) Mannosidosis
   (ii) Cystinosis

F. Tumours
*Benign*
   (i) Cavernous haemangioma
   (ii) Lymphangioma

*Malignant*
   (i) Lymphoma, usually secondary involvement
   (ii) Metastases, these are uncommon. They can be seen in malignant melanoma and in some patients with carcinoma who are immuno-suppressed

---

27. **Connective tissue diseases**

A miscellaneous collection of multisystem disorders in which connective tissue effects are prominent. Although formerly called I collagen diseases', changes in collagen synthesis may not be important clinically nor do they indicate the pathogenesis of the condition. Most are thought to be immunologically mediated.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

*Aetiology*

Auto-immune B cell reactions initiated by
1. Genetic predisposition
2. Drugs
   (i) Hydralazine
   (ii) Procainamide
   (iii) Penicillin
(iv) a-Methyldopa
3. Viruses (?)
4. Ultra-violet light
5. Sex hormones

Features
1. Skin
   (i) Liquefaction/degeneration at the dermal-epidermal junction
   (ii) Homogenisation of collagen fibres
   (iii) Fibrinoid necrosis in blood vessels (distinguish from discoid LE)
2. Kidneys
   (i) Diffuse proliferative GN (immune complex type)
   (ii) Focal proliferative GN
   (iii) Membranous GN -‘wire loop’ lesions
   (iv) Vasculitis
3. Heart
   (i) Pericarditis
   (ii) Myocarditis
   (iii) Endocarditis atypical verrucous endocarditis (Libman-Sacks)
4. Lung and pleura
   (i) Pleurisy
   (ii) Pneumonitis
   (iii) Arteritis
5. Joints - inflammation, but not destruction as in RA
6. Spleen
   (i) Perisplenitis
   (ii) 'Onion skin' arteriolar thickening
7. Lymph nodes
   (i) Follicular hyperplasia
   (ii) Focal necrosis
8. CNS
   (i) Epilepsy
   (ii) Mental/hypothalamic features
   (iii) Myasthenic syndrome

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

A disease characterized by excessive fibrosis throughout the body.
Features
1. Skin
   (i) Pigmentation
   (ii) Epidermal atrophy with loss of appendages
   (iii) Dermal oedema and separation of collagen
   (iv) Calcinosis
2. Lungs
   (i) Interstitial fibrosis - honeycomb lung
   (ii) Vascular changes
3. Kidneys
(i) Basement membrane thickening
(ii) Fibrinoid necrosis in arterioles
(iii) Cortical infarcts
4. Alimentary tract
   (i) Collagenous thickening - hypomotility
   (ii) Pseudo-obstruction
5. Blood vessels
   (i) Intimal proliferation and medial hypertrophy
   (ii) Fibrinoid necrosis
6. Muscle
   (i) Atrophy
   (ii) Myositis
7. Joints
   (i) Synovitis
   (ii) Synovial sclerosis
8. Heart
   (i) Myocardial fibrosis
   (ii) Pericarditis
9. Thymus
   (i) Lympho-epithelial proliferation
   (ii) Enlarged Hassall's corpuscles

POLYARTERITIS NODOSA

Disseminated necrotising inflammation affecting medium-sized and small arteries.

Features
1. Medial fibrinoid necrosis
2. Polymorph infiltration
3. Destruction of the internal elastic lamina
4. Super-imposed thrombosis
5. Fibroblastic proliferation
6. Infiltration by lymphocytes, plasma cells, eosinophils
7. Increasing collagenisation

Results
1. Haemorrhage
2. Infarction
3. Aneurysmal dilatation

Organs affected
1. Kidneys
   (i) Focal necrosis
   (ii) Proliferation - crescent formation
   (iii) Granular deposits and fibrin (GBM)
2. Heart
3. Liver
4. Gastrointestinal tract
5. Lungs
6. Peripheral ner
RHEUMATOID DISEASE

This is a chronic relapsing multisystem disease of unknown aetiology.  

Extra-articular lesions

1. Nodules  
   (i) Subcutaneous tissue  
   (ii) Lungs and pleura  
   (iii) Heart - base of valves  
   (iv) Dura mater

2. Bones  
   (i) Periarthrodal osteoporosis  
   (ii) Generalized osteoporosis resulting from:  
      a. immobilisation  
      b. steroid therapy

3. Heart  
   (i) Nodules  
   (ii) Pericarditis  
   (iii) Coronary arteritis

4. Blood vessels  
   (i) Vasculitis  
   (ii) Intimal proliferation leading to occlusion

5. Lungs  
   (i) Diffuse interstitial fibrosis  
   (ii) Nodular lung disease  
   (iii) Rheumatoid pneumoconiosis (Caplan's syndrome)

6. Lymph nodes - follicular hyperplasia

7. Secondary amyloidosis

8. Kidneys - secondary involvement due to  
   (i) Arteritis  
   (ii) Amyloid  
   (iii) Analgesics

9. Eyes  
   (i) Keratoconjunctivitis sicca  
   (ii) Episcleritis  
   (iii) Scleromalacia perforans  
   (iv) Uveitis

10. Nerves  
    (i) Secondary to vasculitis  
    (ii) Compression  
    (iii) Amyloidosis  
    (iv) Drugs

11. Muscle  
    (i) Atrophy secondary to neuropathy  
    (ii) Steroid myopathy

12. Thyroid  
    Increased incidence of  
    (i) Thyrotoxicosis  
    (ii) Hashimoto's disease

13. Sjögren's syndrome (kerato-conjunctivitis sicca)
28. Musculo-skeletal system

SKELETAL MUSCLE

A. Muscular dystrophy
1. Myotonic
   (i) Myotonia dystrophica
   (ii) Congenital myotonia (Thomsen's disease)
   (iii) Paramyotonia congenita
2. Non-myotonic
   (i) Duchenne type (pseudo-hypertrophic)
      (ii) Becker type
      (iii) Facioscapulohumeral
      (iv) Limb-girdle
      (v) Distal muscular type
      (vi) Ocular muscular type

B. Myopathies
1. Congenital
   (i) Benign congenital hypotonia
   (ii) Fibre type disproportion
   (iii) Central core disease
   (iv) Nemaline myopathy
   (v) Myotubular myopathy
   (vi) Arthrogryposis multiplex congenita
2. Metabolic
   (i) Glycogenoses
      a. Type V (McArdle's)
      b. Type VII (Tare's)
      c. Also in type II (Pompe's disease), type III and sometimes type IV
   (ii) Periodic paralysis syndromes
      a. Hypokalaemic
      b. Hyperkalaemic
      c. Normokalaemic
   (iii) Hypercalcaemia

3. Endocrine
   (i) Hyperthyroidism
   (ii) Hypothyroidism
   (iii) Hyperparathyroidism (unrelated to plasma calcium)
   (iv) Cushing's syndrome
   (v) Hyperaldosteronism
   (vi) Hypopituitarism

4. Toxic
   (i) Steroids
   (ii) Chloroquine
   (iii) Alcohol
   (iv) ? Malignant hyperpyrexia after general anaesthesia
5. Collagen diseases
   (i) Acute rheumatic fever
   (ii) SLE
   (iii) Polyarteritis nodosa
   (iv) Polymyalgia rheumatica
6. Infection/infestation
   (i) Coxsackie B virus (Bornholm)
   (ii) Syphilis
   (iii) Toxoplasmosis
   (iv) Trypanosomiasis
   (v) Trichinosis
   (vi) Cysticercosis
7. Carcinoma-associated
   (i) Neuromyopathy
   (ii) Myopathy
   (iii) Myasthenic-myopathic syndrome
8. Sarcoidosis

C. Myasthenia gravis
Muscle disease characterized by weakness and resulting from a deficiency, or premature breakdown, of acetylcholine.

   Associations
   (i) Thymoma
   (ii) Hyperthyroidism
   (iii) Diabetes mellitus
   (iv) SLE
   (v) Rheumatoid disease

D. Rhabdomyolysis
   Acute muscle breakdown with myoglobinuria resulting from:
   (i) Excessive physical exertion (e.g. marathon running)
   (ii) Virus infection
   (iii) Alcohol excess
   (iv) Drugs
   (v) Trauma (crush syndrome)

E. Tumours
   1. Granular cell myoblastoma
   2. Rhabdomyosarcoma
      (i) Embryonal alveolar type
      (ii) Embryonal botryoid type
      (iii) Adult pleomorphic type

FIBROMATOSES

A. Congenital and juvenile
   1. Fibrous hamartoma of infancy
   2. Fibromatosis colli (congenital torticollis)
   3. Infantile fibromatosis
(i) Dermal
(ii) Diffuse
4. Juvenile fibromatosis
5. Juvenile aponeurotic fibroma
6. Congenital generalized fibromatosis

B. Miscellaneous types
1. Palmar fibromatosis (Dupuytren’s contracture) and its plantar variant
2. Musculo-aponeurotic fibromatosis (desmoids)
3. Mesenteric fibromatosis
4. Hereditary gingival fibromatosis
5. Generalized multifocal fibromatosis

BONES

A. Congenital
1. Achondroplasia
2. Dyschondroplasia
3. Chondro-osteodystrophy (Morquio)
4. Osteogenesis imperfecta
5. Osteopetrosis
6. Marfan’s syndrome
7. Gargoyleism (Hunter-Hurler)

B. Inflammatory
1. Non-specific suppurative osteomyelitis
   **Features**
   (i) Pus formation
   (ii) Necrosis of bone resulting from toxic and ischaemic injury (sequestrum)
   (iii) Reactive new bone formation (involucrum)
   (iv) Drainage of pus via cloacae and sinuses to the skin
   **Complications**
   (i) Septicaemia
   (ii) Metastatic abscesses
   (iii) Suppurative arthritis
   (iv) Amyloidosis
2. Tuberculosis
3. Syphilis
   (i) Osteochondritis
   (ii) Periostitis with cortical thickening - sabre tibia
   (iii) Gummatous destruction -’worm-eaten’ skull
4. Fungal
   (i) Blastomycosis
   (ii) Coccidioidomycosis
5. Actinomycosis

C. Osteoporosis
Reduction in calcified bone mass - generalized atrophy of bone. The disease probably represents an involutional or ageing phenomenon in which there is
diminished osteoblastic activity without a corresponding reduction in osteoclasia.

Aetiology
1. Idiopathic
   (i) Senile
   (ii) Postmenopausal
2. Malnutrition
3. Hypovitaminosis C
4. Prolonged immobilisation
5. Endocrine
   (i) Corticosteroid treatment/Cushing's syndrome
   (ii) Hyperthyroidism
   (iii) Acromegaly
   (iv) Hypopituitarism
6. Chronic liver and renal disease

D. Osteomalacia/rickets
Inadequate mineralisation of bone matrix resulting in a relative increase in the amount of osteoid.

Aetiology
1. Vitamin D deficiency
   (i) Malabsorption syndromes
   (ii) Dietary deficiency
   (iii) No exposure to sunlight
2. Associated with hypophosphataemia
   (i) Renal tubular acidosis
   (ii) Familial hypophosphataemia (vitamin-D resistant)
   (iii) Fanconi's syndrome
   (iv) Part of renal osteodystrophy
3. Defective mineralisation but with normal calcium, phosphorus and vitamin D levels
   (i) Hypophosphatasia
   (ii) Fluoride excess

E. Paget's disease (osteitis deformans)
A combination of osteoclastic resorption of normal bone and osteoblastic regeneration or primitive coarse-fibred bone lying in a richly vascular fibrous stroma.

Types
1. Monostotic - e.g. tibia
2. Polyostotic - pelvis, skull, femur, tibia
3. Localized - sharply outlined resorptive area in the skull (osteoporosis circumscripta)

Complications
1. Deformity
2. Pathological fracture
3. Encroachment on foramina producing nerve defects
4. Flattening of the base of the skull (platybasia)
5. Cardiac failure - high output required because of vascular shunts
6. Development of sarcoma (1-2%)
7. Hypercalcaemia when immobilised

F. Tumours

Osteogenic tumours

Benign
1. Osteoma
2. Osteoid osteoma
3. Osteoblastoma - ‘giant osteoid osteoma’

Malignant
1. Osteogenic sarcoma
2. Parosteal osteosarcoma

Cartilaginous tumours

Benign
1. Osteochondroma - osteocartilaginous exostosis
   (i) Single
   (ii) Multiple
2. Chondroma
   (i) Ecchondroma
   (ii) Enchondroma
      Multiple in Ollier's disease
      Associated with haemangiomata in Maffucci's syndrome
3. Chondroblastoma - Codman’s tumour
4. Chondromyxoid fibroma

Malignant
1. Chondrosarcoma
2. Mesenchymal chondrosarcoma

Fibrous tumours

Benign
1. Non-osteogenic fibroma
2. Ossifying fibroma
3. Fibromyxoma

Malignant
1. Fibrosarcoma
2. Malignant fibrous histiocytoma

Giant-cell ‘tumours’
1. True giant-cell tumour
2. Giant-cell reparative granuloma of jaw
3. 'Brown tumours' of hyperparathyroidism
5. Simple bone cyst
6. Aneurysmal bone cyst.

Tumours arising from bone-marrow
1. Leukaemias
2. Multiple myeloma
3. Malignant lymphomas
Other tumours
1. Ewing's tumour
2. Chordoma
3. Haemangioma
4. Neurofibroma
5. Adamantinoma of long bones

Metastatic tumours
Childhood - neuroblastoma
Adult -
1. Osteosclerotic carcinomas
   (i) Prostate
   (ii) Breast
   (iii) Adenocarcinoma of bronchus
   (iv) Signet-ring type of gastric carcinoma
2. Osteolytic carcinomas
   (i) Renal
   (ii) Thyroid
   (iii) Colon
   (iv) Breast
3. Unchanged - oat-cell carcinoma of bronchus

Histiocytosis X
1. Eosinophil granuloma
2. Hand-Schüller-Christian disease
3. Letterer-Siwe disease

JOINTS

A. Arthritis in systemic diseases
1. Gout
2. Psoriasis
3. Ulcerative colitis and Crohn's disease
4. Sarcoidosis
5. Immune-complex deposition
   (i) Rubella
   (ii) Hepatitis B
   (iii) Serum sickness

B. Osteoarthritis
Aetiology
1. Primary - degeneration
2. Secondary
   (i) Trauma
   (ii) Obesity
   (iii) Osteochondritis
   (iv) Developmental - e.g. congenital dislocation
   (v) Haemophilia
(vi) Ochronosis
(vii) Acromegaly

Features
1. Fibrillation of cartilage
2. Fragmentation
3. Exposure of bone with thickening - eburnation
4. Marginal new bone formation - osteophytes
5. Fibrosis of underlying bone - radiological 'cysts'

C. Rheumatoid arthritis

Features
1. Synovial inflammation
2. Accumulation of fibrinoid material on the synovium
3. Enlargement of synovial villi resulting from oedema, proliferation and cellular infiltration (lymphocytes and plasma cells)
4. Erosion of cartilage at the margins
5. Replacement by granulation tissue - pannus
6. Fusion of articular surfaces by fibrosis ankylosis, or subluxation of the joint

29. Nervous system

A premorbid blunting of normal diurnal corticosterone levels in both Lewis and DA rats has been shown in animals susceptible to experimentally induced arthritis [162]. In adjuvant-induced arthritis, chronic activation of the HPA axis is seen 7–21 days after adjuvant injection, together with loss of circadian rhythm [163]. This chronic activation of the HPA axis was shown to be due to increased corticosterone secretion due to an increase in the pulse frequency of secretion in adjuvant-induced arthritis [164]. During this chronic activation of the HPA axis, rats with adjuvant-induced arthritis are incapable of mounting an HPA axis response to acute stress (such as noise) but are still able to respond to an acute immunological stress [165]. Adrenalectomy or glucocorticoid receptor blockade exacerbates the disease state and results in death or disease expression in surviving animals [139,166,167]. It has been suggested that mortality from such shock-like responses is due to the increased cytokine production that occurs in adrenalectomized animals exposed to proinflammatory stimuli [166,168].

In addition to the role of HPA axis dysregulation, a dual role for the sympathetic nervous system in animal models of RA has been suggested. Activation of β-adrenoceptors or A2 receptors by high concentrations of norepinephrine or adenosine results in increased intracellular concentrations of cAMP and anti-inflammatory responses, whereas activation of α2-adrenoceptors and A1 receptors by low concentrations of norepinephrine or adenosine results in proinflammatory events, such as the release of substance P [169]. Consistent with this is the observation that β-adrenergic agonists attenuate RA in animal models [170,171]. Rolipram, an inhibitor of the PDE-IV phosphodiesterase, an enzyme that
degrades cAMP, has been shown to reduce inflammation in several rodent models [170,172-174]. The effects of rolipram have also been suggested to be mediated by catecholamines [175] or by the stimulation of the adrenal and HPA axis [176,177]. There is also a loss of sympathetic nerve fibers during adjuvant-induced arthritis [178]. The peripheral natural anti-inflammatory agent, vasoactive intestinal peptide, has been shown to reduce the severity of arthritis symptoms in the mouse model of collagen-induced arthritis [179,180].

In addition to the sympathetic nervous system, the parasympathetic nervous system is also important in immune regulation. A role of the cholinergic parasympathetic nervous system in an animal model of RA was suggested because direct stimulation of the vagus nerve was shown to inhibit the inflammatory response [181]. Impairment of the cholinergic regulation also exacerbates an inflammatory response to adjuvant in the knees of rats [182].

**Summary of animal model studies and therapeutic correlates**

Thus, animal models for arthritis have shown a role for the HPA axis, sympathetic, parasympathetic, and peripheral nervous systems. They have shown the necessity of endogenous glucocorticoids in regulating the immune response after exposure to antigenic or proinflammatory stimuli, and severity of inflammatory/autoimmune disease or mortality after removal of these endogenous glucocorticoids by adrenalectomy or GR blockade. Animal models have enabled genetic linkage studies, which have demonstrated the multigenic, polygenic nature of such inflammatory diseases with genes on more than 20 different chromosomes being linked to inflammatory arthritis. Finally, animal models have shown defects in the sympathetic and parasympathetic nervous system in arthritis. These findings have led to the development and testing of novel therapies (see the penultimate section, 'New therapies').

**Human studies**

In humans, ovine CRH, hypoglycemia, or psychological stresses have been used to stimulate the HPA axis. In such studies, blunted HPA axis responses have been shown in a variety of autoimmune/inflammatory or allergic diseases such as allergic asthma and atopic dermatitis [183-186], fibromyalgia [187-190], chronic fatigue syndrome [188,189,191,192], Sjögren's syndrome [2,193], systemic lupus erythematosus [2,194], multiple sclerosis [195,196], and RA [1,197-202]. Conversely, chronic stimulation of the stress hormone response, such as experienced by caregivers of Alzheimer's patients, students taking examinations, couples during marital conflict, and Army Rangers undergoing extreme exercise, results in chronically elevated glucocorticoids, causing a shift from Th1 to Th2 immune response, and is associated with an enhanced susceptibility to viral infection, prolonged wound healing, or decreased antibody production in response to vaccination [203-206].

**Rheumatoid arthritis**

RA is more common in women than in men, with onset usually occurring between menarche and menopause [207,208]. However, the incidence of RA becomes much less gender specific in elderly men and women [207]. In women, RA activity is reduced during pregnancy but returns postpartum, suggesting a role for the
hormones that are fluctuating at this time (cortisol, progesterone, and estrogen) in the regulation of RA activity [33,209-212].

Glucocorticoids have been used for therapy for RA since the 1950s [213,214], when the Nobel Prize was awarded for the discovery of this effect. They are effective because of their anti-inflammatory actions in the suppression of many inflammatory immune molecules and cells. In patients with RA, administration of glucocorticoids decreases the release of TNF-α into the bloodstream [215]; however, there are many debilitating side effects including weight gain, bone loss, and mood changes.

The HPA axis in RA

Human clinical studies are much more difficult to perform than animal models. However, some evidence exists supporting the involvement of the HPA axis in RA. Alterations in the diurnal rhythm of cortisol secretion have been documented in patients with RA [216,217]. An association between the cortisol diurnal cycle and diurnal variations in RA activity has been made, although it still remains to be determined whether this is cause or effect [218]. One of the most pertinent observations for the regulation of RA by endogenous cortisol comes from a study in which RA was exacerbated by inhibition of adrenal glucocorticoid synthesis by the 11β-hydroxylase inhibitor metyrapone [219].

Several studies have looked for abnormalities in the HPA axis of patients with RA. In general, these point to an inappropriately low cortisol response. Subtle changes in cortisol responses have been reported in response to insulin-induced hypoglycemia [201]. However, another study, also using insulin-induced hypoglycemia, described a blunted HPA axis in patients with RA [220]. In one study, lower cortisol responses to surgical stress were shown in patients with RA compared with healthy controls and an inflammatory control group, whereas normal responses of ACTH and cortisol to ovine CRH were seen in the same patients [198]; however, these results are complicated by the steroid therapy that these patients were taking. Other studies have shown increased peripheral ACTH levels in patients with RA without increases in cortisol [221-223], whereas other studies have shown a normal HPA axis in patients with RA [200]. Some studies have suggested that, given the inflammatory state of RA, a normal cortisol response is in fact indicative of an under-responsive HPA axis [224,225]. It has become generally accepted that lower than normal cortisol responses to stimulation are characteristic of RA [169,197,201,216,221,223,225-227]. Most recently Straub and colleagues have shown that the most sensitive indicator of blunted HPA axis responsiveness in early, untreated PA is an inappropriately low ratio of cortisol to IL-6 in these subjects [228].

Such defects in the stress response system are in agreement with patients' descriptions of RA 'flare up' during stress [229], which are likely to be caused by imbalances of the neuroendocrine and immune systems induced by psychosocial stressors [230]. It is worth noting that psychosocial stress is important in RA disease activity [231-233]. However, this will not be reviewed here and readers are referred to reviews by Walker and colleagues [234] and Herrmann and colleagues [235].

Glucocorticoid receptors in RA

Quantification of the numbers of GRs by ligand binding studies has produced contrasting results. In one study, normal or even slightly elevated numbers of GRs in
Peripheral blood mononuclear cells (PBMCs) were seen in untreated patients with RA [236], whereas other studies have shown a decrease in the number of GR molecules in the lymphocytes of patients with RA in comparison with controls [237]. Others have also shown a downregulation of GR during early RA [238,239]. Recently, Neeck and colleagues, evaluating the expression of GR by immunoblot analysis, showed a higher expression of GR in untreated patients with RA in comparison with controls but a decreased GR expression in glucocorticoid-treated patients with RA in comparison with controls [202]. This has been confirmed by others [240]. A polymorphism in the 5' untranslated region of exon 9 of the GR gene, which is associated with enhanced stability of the dominant-negative splice variant, GRβ, has been shown in patients with RA [31]. Enhanced expression of GRβ has also been shown in the PBMCs of steroid-resistant patients with RA [241]. A polymorphism in the CRH gene has also been described as a susceptibility marker for RA in an indigenous South African population [242-244].

Other hormone measures in RA

Patients with RA also show abnormalities in other endocrine hormones. Like other inflammatory diseases, they have been shown to have low serum androgen levels but unchanged serum estrogen levels [245-252]. Growth retardation is a phenomenon seen in juvenile RA [253], and an impairment of the GH axis has been shown in patients with active and remitted RA [220,225]. An increased expression of IGF-1-binding protein, resulting in a decreased concentration of free IGF-1, was also observed in patients with RA [254-256]. However, another study has attributed this difference in IGF-binding proteins to physical activity rather than inflammation [257].

An association between thyroid and rheumatoid disorders, such as RA and autoimmune thyroiditis, has been known for many years [258] although little is known about the thyroid involvement in RA. One study has shown that patients with RA have increased free T₄ levels, and consequently lower free T₃, than normal controls [259], although other studies were unable to confirm low levels in T₃ patients with RA [260]. However, a higher incidence of thyroid dysfunction has been shown in women with RA [261,262].

Sympathetic nervous system in RA

The extent to which the sympathetic nervous system is involved in human RA is unclear. In one study, a decreased number of β-adrenoceptors in the PBMCs and synovial lymphocytes of patients with RA was described, suggesting a shift to a proinflammatory state [263,264]. Regional blockade of the sympathetic nervous system in patients with RA has been described to attenuate some of features of RA [265]. Others were unable to confirm this result but found defects in other aspects of this signaling pathway [266]. However, as in animal models, β-adrenergic agonists have been shown to attenuate RA in humans [267].

For the sympathetic nervous system to be able to modulate inflammation in RA it is necessary for the synovial tissue to be innervated by sympathetic nerve fibers. In patients with long-term RA there is a significant decrease in sympathetic nerve fibers but an increase in substance P-producing sensory nerve fibers [268,269], suggesting a decrease in the anti-inflammatory effects of the sympathetic nervous system and an increase in the proinflammatory effects of the peripheral nervous system.
Peripheral neuropeptides in RA

Consistent with these changes in peripheral and autonomic innervation in RA are findings of altered peripheral neuropeptides in RA. Proinflammatory CRH is locally secreted in the synovium of patients with RA and at a lower level than in osteoarthritis [199,270]. Human T lymphocytes have been shown to synthesize and secrete CRH [271]. Inflammation in chronic RA has also been shown to be attenuated with the μ-opioid-specific agonist morphine [272]. In animal models, infusion of substance P into the knee exacerbated RA [273].

Summary of hormonal findings in RA

Studies of patients with RA are difficult to interpret and some might be tainted by a prior use of glucocorticoids used generally in the treatment of RA. However, these studies have generally shown a defect in cortisol secretion after HPA axis stimulation, decreased androgen levels, a blunted GH response, and dysregulation of the thyroid response. In addition there is evidence of an impaired response of the sympathetic nervous system and enhanced levels of the peripheral proinflammatory neuropeptides CRH and substance P. In some cases, a decrease in the number of GRs has been shown in RA, or reduced glucocorticoid sensitivity has been observed due to GRβ overexpression, which is consistent with relative glucocorticoid resistance in some patients. Furthermore, a polymorphism of the GRβ associated with the enhanced stability of that receptor has also been shown in RA [31]. It still remains to be fully determined whether these alterations in neuroendocrine pathways and receptors are involved in the pathogenesis of RA or whether they are a result of the inflammatory status of the disease.

Conclusion

The CNS and immune system communicate through multiple neuroanatomical and hormonal routes and molecular mechanisms. The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to, and severity of, autoimmune/inflammatory disease. A thorough understanding of the mechanisms by which the CNS and immune systems communicate at all levels will provide many new insights into the bidirectional regulation of these systems and the disruptions in these communications that lead to disease, and ultimately will inform new avenues of therapy for autoimmune/inflammatory disease. Animal models of arthritis have shown changes in both the HPA axis and the sympathetic nervous system during inflammation. More importantly, these models have demonstrated the importance of endogenous glucocorticoids in the regulation of immunity and the prevention of lethality from an uncontrolled immune response. Furthermore, in both animals and humans, RA is associated with dysregulation of the HPA, HPT, HPG, and GH axes. There is also evidence of an impaired regulation of immunity by the sympathetic nervous system and of defects in glucocorticoid signaling. These principles are now being used to test novel therapies for RA based on addressing and correcting the dysregulation of these neural and neuroendocrine pathways.
BRAIN AND SPINAL CORD

A. Congenital

1. Abnormalities of fusion
   (i) Spina bifida occulta
   (ii) Meningocele
   (iii) Meningomyelocele
   (iv) Myelocele-rachiscisis
   (v) Encephalocele
   (vi) Anencephaly - cranioscisis

2. Abnormalities of cleavage
   (i) Cyclopia
   (ii) Arrhinencephaly
   (iii) Telencephalon impar

3. Abnormalities of migration of neuroblasts
   (i) Ectopias
   (ii) Pachygyria
   (iii) Microgyria

4. Others
   (i) Porencephaly - communication between the ventricular system and the sub-arachnoid space
   (ii) Hypoplasia of the cerebellum
   (iii) Absence of the corpus callosum

B. Hydrocephalus

1. Obstruction to CSF flow
   (i) Congenital malformations
      a. Arnold-Chiari malformation
      b. Stenosis of the aqueduct
      c. Dandy-Walker syndrome
      d. Atresia or stenosis of the foramina of Magendie and Luschka
   (ii) Post-inflammatory
      a. Meningitis
      b. Trauma
   (iii) Space-occupying lesions
      a. Neoplasms
      b. Cysts
      c. Abscesses
      d. Haematomata

2. Defective absorption
   (i) Adhesions over the cerebral hemispheres
   (ii) Organised exudate around arachnoidal villi
   (iii) Thrombosis of the major venous sinuses

3. Excessive production of CSF. Papilloma of the choroid plexus (very rare)

4. Mechanism unknown
   (i) Idiopathic cases
   (ii) 'Normal pressure hydrocephalus'
C. Meningitis

Predisposing factors
1. Local infection, e.g. otitis media, mastoiditis
2. Distant infection, e.g. tuberculosis, pneumococcal pneumonia
3. Trauma, e.g. frontal fractures

Varieties
1. Pyogenic (purulent or suppurative)
   (i) Neonatal
      a. Gram-negative bacilli:
         E. coli
         Proteus spp
         Pseudomonas spp
   b. Streptococcus
   c. Staphylococcus
   d. Haemophilus influenzae
   e. Listeria monocytogenes
   (ii) Infant
      a. H. influenzae
      b. Meningococcus
      c. Pneumococcus, etc.
   (iii) Children and young adults
      a. Meningococcus
      b. Pneumococcus, etc.
   (iv) Elderly
      a. Pneumococcus, etc.
2. Viruses
   (i) Mumps
   (ii) Enteroviruses:
      a. Echo
      b. Coxsackie
      c. Poliomyelitis
   (iii) Herpes zoster
   (iv) EB virus
   (v) Lymphocytic choriomeningitis virus
3. Granulomatous diseases
   (i) Tuberculosis
   (ii) Syphilis
   (iii) Sarcoidosis
   (iv) Cryptococcus neoformans infection
4. Fungi
   (i) Histoplasmosis
   (ii) Coccidioidomycosis
   (iii) Mucormycosis
   (iv) Torulosis
5. Rickettsia
6. Protozoa
   (i) Toxoplasmosis
   (ii) Free-living amoebae:
a. Hartmanella
b. Naegleria

D. Cerebral abscess

Predisposing factors
1. Local infection, e.g.
   (i) Otitis media/mastoiditis
   (ii) Sinusitis
   (iii) Venous sinus phlebitis
2. Distant infection with blood spread, e.g.
   (i) Bronchiectasis
   (ii) Empyema
   (iii) Lung abscess
   (iv) Acute endocarditis
3. Penetrating injury or surgery
4. Cyanotic heart disease, with R to L shunts organisms by -pass the Pulmonary vascular ‘filter’

E. Viral encephalitis
1. Primary-arboviruses
   (i) Transmitted by mosquitoes:
      Group A - Eastern equine encephalitis; Western equine encephalitis; Venezuelan equine encephalitis
      Group B - St Louis encephalitis; Murray Valley encephalitis; Japanese encephalitis
   (ii) Tick-borne encephalitis: Russian spring-summer Central European
2. Secondary to Systemic infection (which may be inapparent)
   (i) Herpesvirus hominis
   (ii) Mumps
   (iii) Varicella
   (iv) Measles
   (v) Echo viruses
   (vi) Cytomegalovirus
3. Slow-virus infections
   (i) Kuru
   (ii) Jakob-Creutzfeldt disease

F. Vascular disorders
1. Meningeal haemorrhage
   (i) Extradural - haemorrhage between the skull and the dura resulting from trauma
   (ii) Subdural - haemorrhage from cortical veins between the dura and the arachnoid, usually a result of trauma but may occasionally follow rupture of a berry aneurysm
   (iii) Subarachnoid - haemorrhage between the arachnoid and pia resulting from:
      a. Rupture of a ‘berry’ aneurysm
      b. Extension from an intracerebral haemorrhage
      c. Traumatic
2. Intracerebral haemorrhage
(i) Massive haemorrhage resulting from
   a. Hypertensive cerebral vascular disease
   b. Ruptured aneurysm
   c. Trauma
   d. Bleeding diathesis
   e. Angiomas/vascular malformations
   f. Bleeding into a tumour
(ii) Scattered punctate haemorrhages
   a. Cerebral contusion
   b. Asphyxia
   c. Fat or air embolism
   d. Infections - viral encephalitis, septicaemia
   e. Bleeding diathesis

3. Anoxic - ischaemic injury
   
   **Aetiology**
   - (i) Cardiac arrest
   - (ii) Systemic hypotension
   - (iii) Respiratory failure
   - (iv) Severe anaemia
   - (v) Poisoning - carbon monoxide, nitrous oxide, etc.
   - (vi) High altitude

   **Regions most vulnerable to hypoxia**
   - (i) Hippocampus
   - (ii) Purkinje cells of the cerebellum
   - (iii) Small pyramidal cells of frontal and occipital cortex
   - (iv) Amygdaloid nucleus
   - (v) Brain stem

   **Cellular changes**
   - (i) Neuronal degeneration and disappearance
     - a. Swelling and pallor of cytoplasm
     - b. Loss of Nissl substance
     - c. Pyknosis and acidophilic shrinkage necrosis
     - d. Karyolysis
     - e. Neuronophagia
   - (ii) Astrocyte proliferation and glial scarring

4. Non-infarctive ischaemia resulting from gradual narrowing of small arteries and arterioles by
   - (i) Hyaline thickening of the media (hypertension/diabetes)
   - (ii) Adventitial sclerosis

   **Effects**
   - (i) Formation of lacunae - small cystic cavities 2-10 mm diameter
   - (ii) Granular cortical atrophy in 'watershed' areas
   - (iii) Status cribrosus - 1-2 mm zones of degeneration around small perforating vessels of the basal ganglia
   - (iv) Binswanger's subcortical encephalopathy - focal demyelination of white matter due to selective involvement of deeper arterial branches

5. Cerebral infarction **Aetiology**
   - (i) Occlusion or narrowing of cerebral, vertebral and internal carotid arteries by
     - a. Atherosclerosis
b. Thrombosis
c. Embolism
(ii) Arteritis/thrombosis
  a. Complicating meningitis
  b. Endarteritis obliterans in syphilis
  c. Polyarteritis nodosa
d. SLE
e. Giant-cell arteritis

Cellular changes
(i) Ischaemic degeneration of neurones
(ii) Myelin pallor
(iii) Destruction of myelin sheaths and axis cylinders
(iv) Macrophage activity - ingestion of myelin and red blood cells
(v) Astrocytic proliferation - gliosis

Macroscopic changes
(i) Softening
(ii) Liquefactive (colliquative) necrosis
(iii) Cyst formation

G. Disorders of myelination
1. Defective myelination due to an inherited defect
   (i) Metachromatic leucodystrophy (accumulation of sulphatide)
   (ii) Krabbe's disease (galactocerebroside)
   iii) Pelizaeus-Merzbacher disease
   (iv) Spongiform degeneration of the white matter - Canavan disease
2. Acquired demyelination
   (i) Multiple sclerosis
   Lesions (plaques) most commonly found in
     a. Optic nerves
     b. Around the lateral ventricles
     c. Brain stem
     d. Cerebellar peduncles
     e. Dorsal spinal cord

Microscopic features
  a. Loss of myelin
  b. Perivascular lymphocytic infiltration
  c. Marked reactive gliosis
(ii) Neuromyelitis optica (Devic's disease - probable variant of MS)
(iii) Acute disseminated encephalomyelitis
(iv) Diffuse cerebral sclerosis (Schilder's disease)
(v) Subacute sclerosing panencephalitis (prolonged cerebral measles virus)
(vi) Progressive multifocal leuencephalopathy caused by papova virus infection in immuno-compromised individuals
(vii) Post-vaccination encephalitis
(viii) Post-infectious encephalitis

H. Metabolic disorders
1. Neuronal storage disorders
   (i) Tay-Sachs' disease
(ii) Niemann-Pick's disease  
(iii) Gaucher's disease  
(iv) Hunter-Hurler disease

2. Phenylpyruvic oligophrenia
3. Maple-syrup urine disease
4. Galactosaemic oligophrenia
5. Porphyric myelopathy
6. Wilson's disease
7. Hallervorden-Spatz disease (iron-containing pigment in the globus pallidus and substantia nigra)

I. Degenerative disorders
1. Alzheimer's disease
   
   **Features**
   
   (i) Cerebral atrophy  
   (ii) Neuronal loss  
   (iii) Senile plaques in grey matter  
   (iv) Neurofibrillary degeneration ('tangles')

2. Parkinson's disease
   
   (i) Idiopathic (paralysis agitans)
   
   **Features**
   
   a. Loss of pigmented neurones from the substantia nigra, locus ceruleus, and motor nucleus of X  
   b. Rounded acidophilic inclusions in neurones - Lewy bodies  
   c. Gliosis some cases have  
   d. Autonomic degeneration with postural hypotension (Shy-Drager syndrome)

   (ii) Postencephalitic
   
   **Features**
   
   a. Loss of pigmented neurones from the substantia nigra and occasionally from the locus ceruleus  
   b. Neurofibrillary tangles in affected neurones  
   c. Gliosis

   (iii) Other conditions producing lesions in striato-nigral pathways (Parkinsonism)
   
   a. Cerebrovascular disease  
   b. Wilson's disease  
   c. Head injury (punch-drunk syndrome)  
   d. Meningovascular syphilis  
   e. Carbon-monoxide poisoning  
   f. Manganese poisoning

   (iv) Drug-induced Parkinsonism
   
   a. Reserpine  
   b. Methyldopa  
   c. Phenothiazines

3. Pick's disease - rare cause of pre-senile dementia
4. Huntington's chorea
   
   (i) Atrophy of caudate nucleus and putamen  
   (ii) Neuronal loss in frontal cortex gives rise to dementia and involuntary movements
5. Spinocerebellar degenerations
   (i) Friedreich’s ataxia
   (ii) Carcinomatous cerebellar degeneration
   (iii) Alcoholic cerebellar degeneration
   (iv) Bassen-Kornzweig syndrome
       a. Cerebellar ataxia
       b. Fat retention in surface enterocytes of jejunum
       c. Abetalipoproteinaemia
       d. Acanthocytosis (red blood cells)
6. Motor neurone disease
   (i) Progressive muscular atrophy - lower motor neurones
   (ii) Amyotrophic lateral sclerosis - upper and lower motor neurones
   (iii) Primary lateral sclerosis - upper motor neurones
   (iv) Bulbar palsy - localized
7. Subacute combined degeneration of the cord. Demyelination of posterior and, later, lateral columns associated with pernicious anaemia

J. Tumours
The commonest cerebral tumour is a metastatic deposit.
Metastases arise from:
1. Carcinoma of bronchus, breast, kidney, gastrointestinal tract
2. Malignant in particular, but most malignant tumours metastasise to the brain.

Neuroectodermal tumours
1. Gliomas
   (i) Astrocytoma: Grade. I-IV
      (Grade IV equivalent to glioblastoma multiforme) Descriptive varieties of astrocytoma
       a. Fibrillary
       b. Pilocytic
       c. Gemistocytic
   Sites
       a. Cerebral - usually found in adults. Variable growth rate and prognosis
       b. Cerebellar - occurs in children. Usually pilocytic and complete removal generally results in cure
       c. Spinal cord - difficult to treat with poor prognosis
   (ii) Oligodendroglioma
   (iii) Ependymoma - develop from the lining of the ventricular system. Myxopapillary ependymoma arises from the filum terminale
   (iv) Polar spongioblastoma (very rare)
2. Medulloblastoma
3. Ganglieneuroma and ganglioglioma

Mesodermal tumours
1. Meningioma
   Sites
   (i) Parasagittal
   (ii) Spinal cord
   (iii) Sphenoidal ridge
(iv) Olfactory groove

Microscopic appearances
(i) Transitional psammomatous
(ii) Meningothelial
(iii) Fibroblastic
(iv) Angioblastic (? haemangiopericytoma)

2. Neurilemmoma, e.g. of the VIII nerve, and dorsal spinal roots
3. Haemangioblastoma - sometimes part of the von Hippel-Lindau syndrome
4. Lymphoma
   (i) Primary
   (ii) Secondary

Tumours of developmental origin
1. Craniopharyngioma
2. Epidermoid and dermoid cysts
3. Chordoma

PERIPHERAL NERVES

Types of injury
1. Wallerian degeneration - demyelination and loss of the axon distal to the site of injury
2. Demyelination alone - i.e. survival of axons
3. Axonal degeneration (dying back phenomenon)
   These types are seen to varying degrees in all the conditions listed below.

Mononeuropathy
Lesions of individual peripheral nerves

Aetiology
1. Penetrating injury
2. Traction
3. Compression
   (i) External, e.g. tourniquet or crutch
   (ii) Internal, e.g. carpal tunnel syndrome
4. Haemorrhage into the nerve
5. Infarction, e.g. in diabetes
6. Cold injury

Multiple mononeuropathy (mononeuritis multiplex)
Discrete lesions of several nerves arising simultaneously or in succession
1. Diabetes
2. Leprosy
3. Sarcoidosis
4. Polyarteritis nodosa
5. Amyloidosis

Polyneuropathy
Generalized involvement
1. Dietary deficiencies
   (i) Chronic alcoholism
(ii) Sprue  
(iii) Pellagra  
(iv) Beri-beri  
(v) Subacute combined degeneration

2. Related to infections  
(i) Acute post-infective polyneuritis (Guillain-Barré)  
(ii) Leprosy  
(iii) Diphtheria  
(iv) Infectious mononucleosis

3. Metabolic  
(i) Diabetes mellitus  
(ii) Uraemia  
(iii) Hepatic failure  
(iv) Acute intermittent porphyria  
(v) Amyloidosis  
(vi) Myxoedema

4. Vascular  
(i) Polyarteritis  
(ii) SLE

5. Toxic  
(i) Heavy metals  
(ii) Organo-phosphorus compounds  
(iii) Drugs, isoniazid and many others

6. Carcinomatous, especially bronchial

7. Heredofamilial disorders  
(i) Peroneal muscular atrophy (Charcot-Marie-Tooth)  
(ii) Hypertrophic interstitial polyneuritis (Dejerine-Sottas)  
(iii) Hereditary sensory radicular polyneuropathy  
(iv) Refsum's disease  
   a. Polyneuritis  
   b. Ichthyosis  
   c. Retinopathy  
   d. Deafness and anosmia

**Tumours**

*Benign*  
1. Neurofibroma  
   (i) Solitary  
   (ii) Multiple - von Recklinghausen's disease

2. Neurilemmoma

*Malignant*  
1. Neurofibrosarcoma  
2. Malignant neurilemmoma  
3. Ganglioneuroma autonomic nervous system  
4. Ganglioneuroblastoma autonomic nervous system  
5. Neuroblastoma
Neural immune pathways and their connection to inflammatory diseases

Farideh Eskandari, Jeanette I Webster and Esther M Sternberg

Section on Neuroendocrine Immunology and Behavior, NIMH/NIH, Bethesda, MD, USA

Keywords: cytokine, hypothalamic–pituitary–adrenal axis, immune, inflammatory, neural, rheumatoid arthritis

Abstract

Inflammation and inflammatory responses are modulated by a bidirectional communication between the neuroendocrine and immune system. Many lines of research have established the numerous routes by which the immune system and the central nervous system (CNS) communicate. The CNS signals the immune system through hormonal pathways, including the hypothalamic–pituitary–adrenal axis and the hormones of the neuroendocrine stress response, and through neuronal pathways, including the autonomic nervous system. The hypothalamic–pituitary–gonadal axis and sex hormones also have an important immunoregulatory role. The immune system signals the CNS through immune mediators and cytokines that can cross the blood–brain barrier, or signal indirectly through the vagus nerve or second messengers. Neuroendocrine regulation of immune function is essential for survival during stress or infection and to modulate immune responses in inflammatory disease. This review discusses neuroimmune interactions and evidence for the role of such neural immune regulation of inflammation, rather than a discussion of the individual inflammatory mediators, in rheumatoid arthritis.

Introduction

The inflammatory response is modulated in part by a bidirectional communication between the brain and the immune systems. This involves hormonal and neuronal mechanisms by which the brain regulates the function of the immune system and, in the reverse, cytokines, which allow the immune system to regulate the brain. In a healthy individual this bidirectional regulatory system forms a negative feedback loop, which keeps the immune system and central nervous system (CNS) in balance. Perturbations of these regulatory systems could potentially lead to either overactivation of immune responses and inflammatory disease, or oversuppression of the immune system and increased susceptibility to infectious disease. Many lines of research have recently established the numerous routes by which the immune system and the CNS communicate. This review will focus on these regulatory systems and their involvement in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA). For other reviews on the involvement of these regulatory pathways in RA and other inflammatory diseases, see reviews by Eijsbouts and...
Murphy [1], Crofford [2], and Imrich [3].

There are two major pathways by which the CNS regulates the immune system: the first is the hormonal response, mainly through the hypothalamic–pituitary–adrenal (HPA) axis, as well as the hypothalamic–pituitary–gonadal (HPG), the hypothalamic–pituitary–thyroid (HPT) and the hypothalamic–growth-hormone axes; the second is the autonomic nervous system, through the release of norepinephrine (noradrenaline) and acetylcholine from sympathetic and parasympathetic nerves. In turn, the immune system can also regulate the CNS through cytokines.

Conversely, cytokines released in the periphery change brain function, whereas cytokines produced within the CNS act more like growth factors. Thus, cytokines produced at inflammatory sites signal the brain to produce sickness-related behavior including depression and other symptoms such as fever [4-7]. In addition, cytokines produced locally exert paracrine/autocrine effects on hormone secretion and cell proliferation [8,9].

The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to or severity of infectious, inflammatory or autoimmune diseases.

**Regulation of the immune system by the CNS**

**Hormonal pathways**

**HPA axis**

On stimulation, corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply. CRH then stimulates the expression and release of adrenocorticotropic (ACTH) from the anterior pituitary gland. Arginine vasopressin (AVP) synergistically enhances CRH-stimulated ACTH release [10,11]. ACTH in turn induces the expression and release of glucocorticoids from the adrenal glands.

Glucocorticoids regulate a wide variety of immune-related genes and immune cell expression and function. For example, glucocorticoids modulate the expression of cytokines, adhesion molecules, chemoattractants and other inflammatory mediators and molecules and affect immune cell trafficking, migration, maturation, and differentiation [12,13]. Glucocorticoids cause a Th1 (cellular immunity) to Th2 (humoral immunity) shift in the immune response, from a proinflammatory cytokine pattern with increased interleukin (IL)-1 and tumor necrosis factor (TNF)-α to an anti-inflammatory cytokine pattern with increased IL-10 and IL-4 [14,15]. Pharmacological doses and preparations of glucocorticoids cause a general suppression of the immune system, whereas physiological doses and preparations of glucocorticoids are not completely immunosuppressive but can enhance and specifically regulate the immune response under certain circumstances. For example, physiological concentrations of natural glucocorticoids (i.e. corticosterone) stimulate delayed-type hypersensitivity reactions acutely, whereas pharmacological preparations (i.e. dexamethasone) are immunosuppressive [16].
Glucocorticoids exert these immunomodulatory effects through a cytosolic receptor, the glucocorticoid receptor (GR). This is a ligand-dependent transcription factor that, after binding of the ligand, dissociates from a protein complex, dimerizes, and translocates to the nucleus, where it binds to specific DNA sequences (glucocorticoid response elements) to regulate gene transcription [17]. GR can also interfere with other signaling pathways, such as nuclear factor (NF)-κB and activator protein-1 (AP-1), to repress gene transcription; it is through these mechanisms that most of the anti-inflammatory actions are mediated [18-21]. A splice variant of GR, GRβ, that is unable to bind ligand but is able to bind to DNA and cannot activate gene transcription [22] (although this is still under some dispute), has been suggested to be able to act as a dominant repressor of GR [23,24]. Increased GRβ expression has been shown in several inflammatory diseases including asthma [25-28], inflammatory bowel disease/ulcerative colitis [29,30], and RA [31].

**HPG axis**

In addition to the HPA axis, other central hormonal systems, such as the HPG axis and in particular estrogen, also modulate the immune system [32]. In general, physiological concentrations of estrogen enhance immune responses [33,34] whereas physiological concentrations of androgens, such as testosterone and dehydroepiandrosterone (DHEA), are immunosuppressive [34]. Females of all species exhibit a greater risk of developing many autoimmune/inflammatory diseases, such as systemic lupus erythematosus, RA and multiple sclerosis, ranging from a 2-fold to a 10-fold higher risk compared with males [35,36]. Animal models have provided evidence for the importance of in vivo modulation of the immune system by the estrogen receptors [37,38]. Knockout mouse models indicate that both estrogen receptors α and β are important for thymus development and atrophy in a gender-specific manner [39].

In contrast, immune stress, such as occurs during inflammation, has an inhibitory effect on the HPG axis and thus gonadal function is reduced in conditions associated with severe inflammation such as sepsis and trauma. This effect is mediated either through a direct cytokine effect on hypothalamic neurons secreting luteinizing hormone releasing hormone [40,41] or through other factors such as CRH [42,43] and endogenous opioids [44]. Cytokines also affect gonadal sex steroid production by acting directly on the gonads [45].

**Hypothalamic–growth-hormone axis**

Growth hormone (GH) is a modulator of the immune system [46,47]. The effects of GH are mediated primarily through insulin-like growth factor-1 (IGF-1). GH and IGF-1 have been shown to modulate the immune system by inducing the survival and proliferation of lymphoid cells [48], leading some to suggest that GH functions as a cytokine [49]. Thus, immune cells including T and B lymphocytes [50] and mononuclear cells [51] express IGF-1 receptor. After binding to these receptors, GH activates the phosphoinositide 3-kinase/Akt and NF-κB signal transduction pathways, leading to the expression of genes involved in the cell cycle. The NF-κB pathway is also important in immunity, and therefore some of the GH effects on the immune system might be mediated through this signal transduction pathway [49]. However, the role of GH in regulation of the immune system is somewhat controversial. Studies in GH knockout animals have shown that this hormone is only minimally required for immune function [52], leading to an alternative hypothesis in which the primary role of
GH is proposed to be protection from the immunosuppressive effects of glucocorticoids during stress [53].

GH might also modulate immune function indirectly by interacting with other hormonal systems. Thus, short-term increases in glucocorticoids increase GH production [54], whereas long-term high doses result in a decrease in the hypothalamic–GH axis and even growth impairment [55]. Conversely, prolonged HPA axis activation and resultant excessive glucocorticoid production, as occurs during chronic stress, also inhibits the hypothalamic–GH axis [56-58]. Consistent with this is the observation that children with chronic inflammatory disease exhibit growth retardation. During the early phase of inflammatory reactions, the concentration of GH is increased. In spite of an initial rise in GH secretion, GH action is reduced because of GH and IGF-1 resistance induced by inflammation. IL-1α initially stimulates GH [59], but subsequently inhibits its secretion [60].

**HPT axis**

As with the interaction between the HPA axis and the immune system, there is a bidirectional interaction between the HPT axis and immune system [61]. The HPT axis has an immunomodulatory effect on most aspects of the immune system. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the thyroid hormones triiodothyronine (T₃) and thyroxine (T₄) all have stimulatory effects on immune cells [62-64]. As for GH, the role of thyroid hormones in the regulation of immunity is somewhat controversial, and for the same reasons the alternative hypothesis of protection from the immunosuppressive effects of glucocorticoids has also been suggested for thyroid hormones [53]. Inflammation inhibits TSH secretion because of the inhibitory effect of cytokines on TRH [62]. IL-1 has been shown to suppress TSH secretion [59], whereas IL-2 has been shown to stimulate the pituitary–thyroid axis [65]. IL-6 and its receptor have been shown to be involved in developing euthyroid sick syndrome in patients with acute myocardial infarction [66].

In addition to direct effects of thyroid hormones on immune response, there is also interaction between the HPA and HPT axes. Hyperthyroid and hypothyroid states in rats have been shown to alter responses of the HPA axis, with hypothyroidism resulting in a reduced HPA axis response and hyperthyroidism resulting in an increased HPA axis response [67]. In agreement with this, administration of thyroxine, inducing a hyperthyroid state, has been shown to activate the HPA axis and be protective against an inflammatory challenge in rats [68], and hypothyroidism has been shown to cause a reduction in CRH gene expression [69]. Chronic HPA axis activation also represses TSH production and inhibits the conversion of inactive T₄ to the active T₃ [70].

**Neural pathways**

**Sympathetic nervous system**

The sympathetic nervous system regulates the immune system at regional, local, and systemic levels. Immune organs including thymus, spleen, and lymph nodes are innervated by sympathetic nerves [71-73]. Immune cells also express neurotransmitter receptors, such as adrenergic receptors on lymphocytes, that allow them to respond to neurotransmitters released from these nerves.
Catecholamines inhibit production of proinflammatory cytokines, such as IL-12, TNF-α, and interferon-γ, and stimulate the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β [15]. Through this mechanism, systemic catecholamines can cause a selective suppression of Th1 responses and enhance Th2 responses [15,74]. However, in certain local responses and under certain conditions, catecholamines can enhance regional immune responses by inducing the production of IL-1, TNF-α, and IL-8 [75]. Interruption of sympathetic innervation of immune organs has been shown to modulate the outcome of, and susceptibility to, inflammatory and infectious disease. Denervation of lymph node noradrenergic fibers is associated with exacerbation of inflammation [76,77], whereas systemic sympathectomy or denervation of joints is associated with decreased severity of inflammation [77]. However, mice lacking β2-adrenergic receptor from early development (β2AR−/− mice) maintain their immune homeostasis [78]. Therefore, dual activation of the sympathetic nervous system and HPA axis is required for full modulation of host defenses to infection [16,79].

Opioids

Opioids suppress many aspects of immune responses, including antimicrobial resistance, antibody production, and delayed-type hypersensitivity. This occurs in part through the desensitization of chemokine receptors on neutrophils, monocytes, and lymphocytes [80,81]. Morphine decreases mitogen responsiveness and natural killer cell activity [82-86]. In addition to these direct effects, morphine could also affect immune responses indirectly through adrenergic effects, because it increases concentrations of catecholamines in the plasma [87].

Parasympathetic nervous system

Activation of the parasympathetic nervous system results in the activation of cholinergic nerve fibers of the efferent vagus nerve and the release of acetylcholine at the synapses. Together with the inflammation-activated sensory nerve fibers of the vagus nerve (discussed below) this forms the so-called 'inflammatory reflex'. This is a rapid mechanism by which inflammatory signals reach the brain; the brain responds with a rapid anti-inflammatory action through cholinergic nerve fibers [88]. Acetylcholine attenuates the release of proinflammatory cytokines (TNF, IL-1β, IL-6, and IL-18) but not the anti-inflammatory cytokine IL-10, in lipopolysaccharide-stimulated human macrophage cultures through the post-transcriptional suppression of protein synthesis. This effect seems, at least in part, to be independent of the HPA axis, because direct electrical stimulation of the peripheral vagus nerve does not stimulate the HPA axis but decreases hepatic lipopolysaccharide-stimulated TNF synthesis and the development of shock during lethal endotoxemia [89].

Peripheral nervous system

The peripheral nervous system regulates immunity locally, at sites of inflammation, through neuropeptides such as substance P, peripherally released CRH, and vasoactive intestinal polypeptide. These molecules are released from nerve endings or synapses, or they may be synthesized and released by immune cells and have immunomodulatory and generally proinflammatory effects [90-92].
Neuropeptides

The HPA axis is also subject to regulation by both neurotransmitters and neuropeptides from within the CNS. CRH is positively regulated by serotonergic [93-95], cholinergic [96,97], and catecholaminergic [98] systems. Other neuropeptides, such as γ-aminobutyric acid/benzodiazepines (GABA/BZD) have been shown to inhibit the serotonin-induced secretion of CRH [99].

Regulation of the CNS by the immune system

Cytokines

Cytokines are important factors connecting and modulating the immune and neuroendocrine systems. Cytokines and their receptors are expressed in the neuroendocrine system and exert their effects both centrally and peripherally [100-102].

Systemic cytokines can affect the brain through several mechanisms, including active transport across the blood–brain barrier [103], through leaky areas in the blood–brain barrier in the circumventricular organs [104] or through the activation of neural pathways such as the vagal nerve [105]. The blood–brain barrier is absent or imperfect in several small areas of the brain, the so-called circumventricular organs, which are located at various sites within the walls of the cerebral ventricles. These include the median eminence, the organum vasculosum of the laminae terminalis (OVLT), the subfornical organ, the choroid plexus, the neural lobe of the pituitary, and the area postrema. In addition, in the presence of inflammation, the permeability of the blood–brain barrier might be generally altered [106-108]. Moreover, circulating IL-1 can interact with IL-1 receptors on endothelial cells of the vasculature and thereby stimulate signaling molecules such as nitric oxide or prostaglandins, which can locally influence neurons [109].

Cytokines signal the brain not only to activate the HPA axis but also to facilitate pain and induce a series of mood and behavioral responses generally termed sickness behavior [110,111]. Cytokines, such as IL-1, IL-6, and TNF-α, are also produced in the brain [112-114]. Thus, these brain-derived cytokines can stimulate the HPA axis. For example, IL-1 stimulates the expression of the gene encoding CRH and thereby the release of the hormone from the hypothalamus [115], the release of AVP from the hypothalamus [116], and the release of ACTH from the anterior pituitary [117]. IL-2 stimulates AVP secretion from the hypothalamus [118]. IL-6 [119] and TNF-α [120] also stimulate ACTH secretion. In chronic inflammation there seems to be a shift from CRH-driven to AVP-driven HPA axis response [121].

However, in contrast to these effects of peripheral cytokines on neuroendocrine responses in the CNS, cytokines produced within the brain by resident glia or invading immune cells act more like growth factors protecting from or enhancing neuronal cell death. Cytokines might therefore have a pathological consequence, because cytokine-mediated neuronal cell death is thought to be important in several neurodegenerative diseases such as neuroAIDS, Alzheimer’s disease, multiple sclerosis, stroke, and nerve trauma [100-102]. In contrast, activated immune cells and cytokines might also protect neuronal survival after trauma and contribute to
Vagus nerve

The vagus nerve is involved in signaling of the CNS to the immune system. The vagus innervates most visceral structures such as the lung and the gastrointestinal tract, where there may be frequent contact with pathogens. Immune stimuli activate vagal sensory neurons, possibly after binding to receptors in cells in paraganglial structures [123-126]. Administration of endotoxins and IL-1 has been shown to induce Fos expression in the vagal sensory ganglia, and vagotomy abolishes this early activation gene response [124-126]. Vagal afferents terminate in the dorsal vagal complex of the caudal medulla, which consists of the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus. These nuclei integrate sensory signals and control visceral reflexes, and also relay visceral sensory information to the central autonomic network [127]. Subdiaphragmatic vagotomy inhibits activation of the paraventricular nucleus and subsequent secretion of ACTH in response to lipopolysaccharides and IL-1 [128, 129].

Correlation between blunted HPA axis and disease

A blunted HPA axis has been associated with increased susceptibility to autoimmune/inflammatory disease in a variety of animal models and human studies. In general, at the baseline the HPA axis parameters do not differ in individuals susceptible and resistant to inflammatory disease. However, differences become apparent with stimulation of the axis.

Animal models

A blunted HPA axis has been associated with susceptibility to autoimmune/inflammatory diseases in several animal models. These include the Obese strain (OS) chickens, a model for thyroiditis [130]; MRL mice, which develop lupus [131]; and Lewis (LEW/N) rats. A region on rat chromosome 10 that links to the innate carrageenan inflammation [132] is syntenic with a region on human chromosome 17 that is known to link to susceptibility to a variety of autoimmune diseases [133] and is also syntenic with one of the 20 different regions on 15 different chromosomes shown to link to inflammatory arthritis in other linkage studies [134-136]. Several candidate genes within the rat chromosome 10 linkage region are known to have a role in hypothalamic CRH regulation as well as inflammation, including the CRH R1 receptor, angiotensin-converting enzyme, and STAT3 and STAT5a/5b [132]. However, these candidate genes either show no mutation in the coding region and no differences in regulation between susceptible and resistant strains, or show a mutation in the coding region that does not seem to have a role in expression of the inflammatory trait [137]. As in most complex illnesses and traits, the genotypic contribution to variance in the trait is small: about 35%, which is consistent with such multigenic and polygenic conditions.

Inbred rat strains provide a genetically uniform system that can be systemically manipulated to test the role of neuro-endocrine regulation of various aspects of immunity. Lewis (LEW/N) rats are highly susceptible to the development of a wide range of autoimmune diseases in response to a variety of proinflammatory/antigenic
stimuli. Fischer (F344/N) rats are relatively resistant to development of these illnesses after exposure to the same dose of antigens or proinflammatory stimuli. These two strains also show related differences in HPA axis responsiveness. The inflammatory-susceptible LEW/N rats exhibit a blunted HPA axis response, compared with inflammatory-resistant F344/N rats with an exaggerated HPA axis response [138-140]. Differences in the expression of hypothalamic CRH [141], pro-opiomelanocortin, corticosterone-binding globulin [142] and glucocorticoid expression and activation [143,144] have been shown in these two rat strains.

Disruptions of the HPA axis in inflammatory resistant animals, through genetic, surgical, or pharmacological interventions, have been shown to be associated with enhanced susceptibility to, or increased severity of, inflammatory disease [139,145-148]. Reconstitution of the HPA axis in these inflammatory-susceptible animals, either pharmacologically with glucocorticoids or surgically by intracerebral fetal hypothalamic tissue transplantation, has been shown to attenuate inflammatory disease [139,149].

Animal models of arthritis

Several animal models exist for RA in rodents. Lewis rats develop arthritis in response to streptococcal cell walls [138,139], heterologous (but not homologous) type II collagen in incomplete Freund's adjuvant (IFA) [150], and various adjuvant oils – including mycobacteria (MTB-AIA) [109], pristine [151], and avridine, but not IFA alone [152]. Inbred dark Agouti (DA) rats develop arthritis in response to heterologous and homologous type II collagen in IFA [153-156], cartilage oligomeric matrix protein [109], MTB-AIA [152], pristine, avridine [157], and ovalbumin-induced arthritis. DBA mice develop arthritis in response to type II collagen in complete Freund's adjuvant [158,159]. For specific reviews on animal models for RA, refer to reviews by Morand and Leech [160] and Joe and Wilder [161].

A premorbid blunting of normal diurnal corticosterone levels in both Lewis and DA rats has been shown in animals susceptible to experimentally induced arthritis [162]. In adjuvant-induced arthritis, chronic activation of the HPA axis is seen 7–21 days after adjuvant injection, together with loss of circadian rhythm [163]. This chronic activation of the HPA axis was shown to be due to increased corticosterone secretion due to an increase in the pulse frequency of secretion in adjuvant-induced arthritis [164]. During this chronic activation of the HPA axis, rats with adjuvant-induced arthritis are incapable of mounting an HPA axis response to acute stress (such as noise) but are still able to respond to an acute immunological stress [165]. Adrenalectomy or glucocorticoid receptor blockade exacerbates the disease state and results in death or disease expression in surviving animals [139,166,167]. It has been suggested that mortality from such shock-like responses is due to the increased cytokine production that occurs in adrenalectomized animals exposed to proinflammatory stimuli [166,168].

In addition to the role of HPA axis dysregulation, a dual role for the sympathetic nervous system in animal models of RA has been suggested. Activation of β-adrenoceptors or A2 receptors by high concentrations of norepinephrine or adenosine results in increased intracellular concentrations of cAMP and anti-inflammatory responses, whereas activation of α1-adrenoceptors and A1 receptors by low concentrations of norepinephrine or adenosine results in proinflammatory events, such as the release of substance P [169]. Consistent with
this is the observation that β-adrenergic agonists attenuate RA in animal models [170,171]. Rolipram, an inhibitor of the PDE-IV phosphodiesterase, an enzyme that degrades cAMP, has been shown reduce inflammation in several rodent models [170,172-174]. The effects of rolipram have also been suggested to be mediated by catecholamines [175] or by the stimulation of the adrenal and HPA axis [176,177]. There is also a loss of sympathetic nerve fibers during adjuvant-induced arthritis [178]. The peripheral natural anti-inflammatory agent, vasoactive intestinal peptide, has been shown to reduce the severity of arthritis symptoms in the mouse model of collagen-induced arthritis [179,180].

In addition to the sympathetic nervous system, the parasympathetic nervous system is also important in immune regulation. A role of the cholinergic parasympathetic nervous system in an animal model of RA was suggested because direct stimulation of the vagus nerve was shown to inhibit the inflammatory response [181]. Impairment of the cholinergic regulation also exacerbates an inflammatory response to adjuvant in the knees of rats [182].

**Summary of animal model studies and therapeutic correlates**

Thus, animal models for arthritis have shown a role for the HPA axis, sympathetic, parasympathetic, and peripheral nervous systems. They have shown the necessity of endogenous glucocorticoids in regulating the immune response after exposure to antigenic or proinflammatory stimuli, and severity of inflammatory/autoimmune disease or mortality after removal of these endogenous glucocorticoids by adrenalectomy or GR blockade. Animal models have enabled genetic linkage studies, which have demonstrated the multigenic, polygenic nature of such inflammatory diseases with genes on more than 20 different chromosomes being linked to inflammatory arthritis. Finally, animal models have shown defects in the sympathetic and parasympathetic nervous system in arthritis. These findings have led to the development and testing of novel therapies (see the penultimate section, 'New therapies').

**Human studies**

In humans, ovine CRH, hypoglycemia, or psychological stresses have been used to stimulate the HPA axis. In such studies, blunted HPA axis responses have been shown in a variety of autoimmune/inflammatory or allergic diseases such as allergic asthma and atopic dermatitis [183-186], fibromyalgia [187-190], chronic fatigue syndrome [188,189,191,192], Sjögren’s syndrome [2,193], systemic lupus erythematosus [2,194], multiple sclerosis [195,196], and RA [1,197-202]. Conversely, chronic stimulation of the stress hormone response, such as experienced by caregivers of Alzheimer’s patients, students taking examinations, couples during marital conflict, and Army Rangers undergoing extreme exercise, results in chronically elevated glucocorticoids, causing a shift from Th1 to Th2 immune response, and is associated with an enhanced susceptibility to viral infection, prolonged wound healing, or decreased antibody production in response to vaccination [203-206].

**Rheumatoid arthritis**

RA is more common in women than in men, with onset usually occurring between menarche and menopause [207,208]. However, the incidence of RA becomes much
less gender specific in elderly men and women [207]. In women, RA activity is reduced during pregnancy but returns postpartum, suggesting a role for the hormones that are fluctuating at this time (cortisol, progesterone, and estrogen) in the regulation of RA activity [33,209-212].

Glucocorticoids have been used for therapy for RA since the 1950s [213,214], when the Nobel Prize was awarded for the discovery of this effect. They are effective because of their anti-inflammatory actions in the suppression of many inflammatory immune molecules and cells. In patients with RA, administration of glucocorticoids decreases the release of TNF-α into the bloodstream [215]; however, there are many debilitating side effects including weight gain, bone loss, and mood changes.

The HPA axis in RA

Human clinical studies are much more difficult to perform than animal models. However, some evidence exists supporting the involvement of the HPA axis in RA. Alterations in the diurnal rhythm of cortisol secretion have been documented in patients with RA [216,217]. An association between the cortisol diurnal cycle and diurnal variations in RA activity has been made, although it still remains to be determined whether this is cause or effect [218]. One of the most pertinent observations for the regulation of RA by endogenous cortisol comes from a study in which RA was exacerbated by inhibition of adrenal glucocorticoid synthesis by the 11β-hydroxylase inhibitor metyrapone [219].

Several studies have looked for abnormalities in the HPA axis of patients with RA. In general, these point to an inappropriately low cortisol response. Subtle changes in cortisol responses have been reported in response to insulin-induced hypoglycemia [201]. However, another study, also using insulin-induced hypoglycemia, described a blunted HPA axis in patients with RA [220]. In one study, lower cortisol responses to surgical stress were shown in patients with RA compared with healthy controls and an inflammatory control group, whereas normal responses of ACTH and cortisol to ovine CRH were seen in the same patients [198]; however, these results are complicated by the steroid therapy that these patients were taking. Other studies have shown increased peripheral ACTH levels in patients with RA without increases in cortisol [221-223], whereas other studies have shown a normal HPA axis in patients with RA [200]. Some studies have suggested that, given the inflammatory state of RA, a normal cortisol response is in fact indicative of an under-responsive HPA axis [224,225]. It has become generally accepted that lower than normal cortisol responses to stimulation are characteristic of RA [169,197,201,216,221,223,225-227]. Most recently Straub and colleagues have shown that the most sensitive indicator of blunted HPA axis responsiveness in early, untreated RA is an inappropriately low ratio of cortisol to IL-6 in these subjects [228].

Such defects in the stress response system are in agreement with patients' descriptions of RA 'flare up' during stress [229], which are likely to be caused by imbalances of the neuroendocrine and immune systems induced by psychosocial stressors [230]. It is worth noting that psychosocial stress is important in RA disease activity [231-233]. However, this will not be reviewed here and readers are referred to reviews by Walker and colleagues [234] and Herrmann and colleagues [235].
**Glucocorticoid receptors in RA**

Quantification of the numbers of GRs by ligand binding studies has produced contrasting results. In one study, normal or even slightly elevated numbers of GRs in peripheral blood mononuclear cells (PBMCs) were seen in untreated patients with RA [236], whereas other studies have shown a decrease in the number of GR molecules in the lymphocytes of patients with RA in comparison with controls [237]. Others have also shown a downregulation of GR during early RA [238,239]. Recently, Necek and colleagues, evaluating the expression of GR by immunoblot analysis, showed a higher expression of GR in untreated patients with RA in comparison with controls but a decreased GR expression in glucocorticoid-treated patients with RA in comparison with controls [202]. This has been confirmed by others [240]. A polymorphism in the 5' untranslated region of exon 9 of the GR gene, which is associated with enhanced stability of the dominant-negative splice variant, GRβ, has been shown in patients with RA [31]. Enhanced expression of GRβ has also been shown in the PBMCs of steroid-resistant patients with RA [241]. A polymorphism in the CRH gene has also been described as a susceptibility marker for RA in an indigenous South African population [242-244].

**Other hormone measures in RA**

Patients with RA also show abnormalities in other endocrine hormones. Like other inflammatory diseases, they have been shown to have low serum androgen levels but unchanged serum estrogen levels [245-252]. Growth retardation is a phenomenon seen in juvenile RA [253], and an impairment of the GH axis has been shown in patients with active and remitted RA [220,225]. An increased expression of IGF-1-binding protein, resulting in a decreased concentration of free IGF-1, was also observed in patients with RA [254-256]. However, another study has attributed this difference in IGF-binding proteins to physical activity rather than inflammation [257].

An association between thyroid and rheumatoid disorders, such as RA and autoimmune thyroiditis, has been known for many years [258] although little is known about the thyroid involvement in RA. One study has shown that patients with RA have increased free T4 levels, and consequently lower free T3, than normal controls [259], although other studies were unable to confirm low levels in T3 patients with RA [260]. However, a higher incidence of thyroid dysfunction has been shown in women with RA [261,262].

**Sympathetic nervous system in RA**

The extent to which the sympathetic nervous system is involved in human RA is unclear. In one study, a decreased number of β-adrenoceptors in the PBMCs and synovial lymphocytes of patients with RA was described, suggesting a shift to a proinflammatory state [263,264]. Regional blockade of the sympathetic nervous system in patients with RA has been described to attenuate some of features of RA [265]. Others were unable to confirm this result but found defects in other aspects of this signaling pathway [266]. However, as in animal models, β-adrenergic agonists have been shown to attenuate RA in humans [267].

For the sympathetic nervous system to be able to modulate inflammation in RA it is necessary for the synovial tissue to be innervated by sympathetic nerve fibers. In patients with long-term RA there is a significant decrease in sympathetic nerve fibers
but an increase in substance P-producing sensory nerve fibers [268,269], suggesting a decrease in the anti-inflammatory effects of the sympathetic nervous system and an increase in the proinflammatory effects of the peripheral nervous system.

**Peripheral neuropeptides in RA**

Consistent with these changes in peripheral and autonomic innervation in RA are findings of altered peripheral neuropeptides in RA. Proinflammatory CRH is locally secreted in the synovium of patients with RA and at a lower level than in osteoarthritis [199,270]. Human T lymphocytes have been shown to synthesize and secrete CRH [271]. Inflammation in chronic RA has also been shown to be attenuated with the µ-opioid-specific agonist morphine [272]. In animal models, infusion of substance P into the knee exacerbated RA [273].

**Summary of hormonal findings in RA**

Studies of patients with RA are difficult to interpret and some might be tainted by a prior use of glucocorticoids used generally in the treatment of RA. However, these studies have generally shown a defect in cortisol secretion after HPA axis stimulation, decreased androgen levels, a blunted GH response, and dysregulation of the thyroid response. In addition there is evidence of an impaired response of the sympathetic nervous system and enhanced levels of the peripheral proinflammatory neuropeptides CRH and substance P. In some cases, a decrease in the number of GRs has been shown in RA, or reduced glucocorticoid sensitivity has been observed due to GRβ overexpression, which is consistent with relative glucocorticoid resistance in some patients. Furthermore, a polymorphism of the GRβ associated with the enhanced stability of that receptor has also been shown in RA [31]. It still remains to be fully determined whether these alterations in neuroendocrine pathways and receptors are involved in the pathogenesis of RA or whether they are a result of the inflammatory status of the disease.

**Conclusion**

The CNS and immune system communicate through multiple neuroanatomical and hormonal routes and molecular mechanisms. The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to, and severity of, autoimmune/inflammatory disease. A thorough understanding of the mechanisms by which the CNS and immune systems communicate at all levels will provide many new insights into the bidirectional regulation of these systems and the disruptions in these communications that lead to disease, and ultimately will inform new avenues of therapy for autoimmune/inflammatory disease. Animal models of arthritis have shown changes in both the HPA axis and the sympathetic nervous system during inflammation. More importantly, these models have demonstrated the importance of endogenous glucocorticoids in the regulation of immunity and the prevention of lethality from an uncontrolled immune response. Furthermore, in both animals and humans, RA is associated with dysregulation of the HPA, HPT, HPG, and GH axes. There is also evidence of an impaired regulation of immunity by the sympathetic nervous system and of defects in glucocorticoid signaling. These principles are now being used to test novel therapies for RA based on addressing
and correcting the dysregulation of these neural and neuroendocrine pathways.

**SUMMARY:**

I have spent a life time trying to build an educational system and a program to make health care more available the Nelson Method of medicine is as follows.

1. Reduce the Causes of Disease
2. Repair the organs weakened by the Causes
3. Unblock the Blockages to energy, nutrition, Oxygen, waste FLOW
4. Treat the symptoms with natural means before resorting to Synthetic
5. Balance the metabolic typing or constitutional imbalances

The next step is to design a system to work with the body electric. A system to use the advances in science such as electronics, fractal chaos and Quantum Electro Dynamics. A new style of much more modern medicine. A device to find disease at the earliest level and reduce it.

I have been able to make such a machine in 1985, legalize it in 1989, sell it around the world in compliance fashion. It is completely tested, safe, completely tested, and effective. It works and it helps people in many different ways. There have been over one hundred studies published on the Device the EPFX / SCIO.

The frustration of lack of education and the lack of opportunity it conveys, leads many of the poor children to resorting to drugs and crime. Addiction develops and spreads. **Equal Economic Education** will also help the society reduce degenerative disease and the costs it incurs. As well as when there is better education there will be more intelligent selection of foods and the ability to resist drugs.

I have dedicated my life to helping reduce degenerative disease. If we can see the problems of Big Tobacco, Big Sugar, Big Pharma and
just how the medical community fights any change. I have dedicated my
life and intellect to make a new system of medicine and the tools to do it
with a system that is safe and effective. But instead of me being
applauded for the work that I have done, I am attacked. I am vilified.

As you read the EPFX / SCIO testimonials you will see incredible
results. As you read these testimonials, these stories, recognize that this
is the tip of the iceberg. Is that we have been hearing these stories for
20 years. The wondrous stories of how people’s lives have been
changed.

So to end degenerative disease we must
1. Make Big Tobacco pay for the damages they incur
2. Make Big Sugar pay for the damages they incur
3. Make Big Pharma pay for the damages they incur
4. End Allopathic philosophy and develop a new stressor reducing
   based medicine
5. Avoid Bad sugars white processed. Eat Good Sugars from fresh
   fruit, Avoid bad oils cooked or saturated. Eat good oils from fresh
   and raw vegetable and uncooked low temperature made oils.
6. Equal Economic Education- and a new medical education
   based on natural
7. Safe forms of early intervention medicine such as energetic
   biofeedback

With these social changes degenerative disease could be so greatly
reduced to allow for an inexpensive medicine.

WWW Sources
1) Mind/Body Medicine
2) Mayo Clinic-- Stress
3) Psychosomatic Medicine
4) Center for the Advancement of Health
5) Alternative Therapies

7) Physiological Response to Humor

8) Hypnosis


Endnotes

1- the study of behavioral-neural-endocrine-immune system interactions

2-NK cells are natural killer cells which are important in fighting viruses

3- helper T cells invoke an immune system response to infection

4- secreted immunoglobulins are antibodies which are critical in defense against bacteria and viruses

5- psychosomatic conditions involve both psychological and physiological problems

6- salivary IgA is a first line of defense mechanism against the entry of infectious organisms

References


23. Ferrari E, Casarotti D, Muzzoni B, et al. Age-related changes of the adrenal


Imrich R: The role of neuroendocrine system in the pathogenesis of rheumatic diseases (minireview).


Reichenberg A, Kraus T, Haack M, Schuld A, Pollmacher T, Yirmiya R: Endotoxin-induced changes in food consumption in healthy volunteers are associated with TNF-alpha and IL-6 secretion.


Watkins LR, Maier SF, Goehler LE: Cytokine-to-brain communication: a review and analysis of alternative mechanisms.


Ritchlin C, Haas-Smith SA: Expression of interleukin 10 mRNA and protein by synovial fibroblastoid cells.


Lamberts SW, Verleun T, Oosterom R, de Jong F, Hackeng WH: Corticotropin-releasing factor (ovine) and vasopressin exert a synergistic effect on adrenocorticotropin release in man.


Antoni FA: Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age.

*Front Neuroendocrinol* 1993, 14:76-122.

Barnes PJ: Anti-inflammatory actions of glucocorticoids: molecular mechanisms.


Adcock IM, Ito K: Molecular mechanisms of corticosteroid actions.


DeRijk R, Michelson D, Karp B, Petrides J, Galliven E, Deuster P, Paciotti G, Gold...
PW, Sternberg EM: Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha (TNF alpha) production in humans: high sensitivity of TNF alpha and resistance of IL-6.

*J Clin Endocrinol Metab* 1997, **82**:2182-2191.

Elenkov IJ, Chrousos GP: Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease.

*Trends Endocrinol Metab* 1999, **10**:359-368.

Dhabhar FS, McEwen BS: Enhancing versus suppressive effects of stress hormones on skin immune function.


Aranda A, Pascual A: Nuclear hormone receptors and gene expression.

*Physiol. Rev* 2001, **81**:1269-1304.

Karin M, Chang L: AP-1-glucocorticoid receptor crosstalk taken to a higher level.


Herrlich P: Cross-talk between glucocorticoid receptor and AP-1.

*Oncogene* 2001, **20**:2465-2475.

Adcock IM: Molecular mechanisms of glucocorticosteroid actions.

*Pulm Pharmacol Ther* 2000, **13**:115-126.

Encio IJ, Detera-Wadleigh SD: The genomic structure of the human glucocorticoid receptor.


Vottero A, Chrousos GP: Glucocorticoid receptor β: view I.

*Trends Endocrinol Metab* 1999, **10**:333-338.

Carlstedt-Duke J: Glucocorticoid receptor β: view II.

*Trends Endocrinol Metab* 1999, **10**:339-342.

Sousa AR, Lane SJ, Cidlowski JA, Staynov DZ, Lee TH: Glucocorticoid resistance in asthma is associated with elevated in vivo expression of the glucocorticoid receptor beta-isoform.


Imrich R: The role of neuroendocrine system in the pathogenesis of rheumatic diseases (minireview).


Reichenberg A, Kraus T, Haack M, Schuld A, Pollmacher T, Yirmiya R: Endotoxin-induced changes in food consumption in healthy volunteers are associated with TNF-alpha and IL-6 secretion.


Watkins LR, Maier SF, Goehler LE: Cytokine-to-brain communication: a review and analysis of alternative mechanisms.


Ritchlin C, Haas-Smith SA: Expression of interleukin 10 mRNA and protein by synovial fibroblastoid cells.


Lamberts SW, Verleun T, Oosterom R, de Jong F, Hackeng WH: Corticotropin-releasing factor (ovine) and vasopressin exert a synergistic effect on adrenocorticotropic release in man.  
*J Clin Endocrinol Metab* 1984, **58**:298-303.

Antoni FA: Vasopressinergic control of pituitary adrenocorticotropic secretion comes of age.  
*Front Neuroendocrinol* 1993, **14**:76-122.

Barnes PJ: Anti-inflammatory actions of glucocorticoids: molecular mechanisms.  
*Clin Sci (Lond)* 1998, **94**:557-572.

Adcock IM, Ito K: Molecular mechanisms of corticosteroid actions.  
*Monaldi Arch Chest Dis* 2000, **55**:256-266.

*J Clin Endocrinol Metab* 1997, **82**:2182-2191.

Elenkov IJ, Chrousos GP: Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease.  
*Trends Endocrinol Metab* 1999, **10**:359-368.

Dhabhar FS, McEwen BS: Enhancing versus suppressive effects of stress hormones on skin immune function.  

Aranda A, Pascual A: Nuclear hormone receptors and gene expression.  
*Physiol. Rev* 2001, **81**:1269-1304.

Karin M, Chang L: AP-1-glucocorticoid receptor crosstalk taken to a higher level.  


Herrlich P: Cross-talk between glucocorticoid receptor and AP-1.

Adcock IM: Molecular mechanisms of glucocorticosteroid actions.


Encio IJ, Detera-Wadleigh SD: The genomic structure of the human glucocorticoid receptor.


Vottero A, Chrousos GP: Glucocorticoid receptor β: view I.

Trends Endocrinol Metab 1999, 10:333-338.

Carlstedt-Duke J: Glucocorticoid receptor β: view II.


Sousa AR, Lane SJ, Cidlowski JA, Staynov DZ, Lee TH: Glucocorticoid resistance in asthma is associated with elevated in vivo expression of the glucocorticoid receptor beta-isoform.

