Disease is disturbance of normal structure or function. This can result from many factors as outlined below. Some are transient whereas other permanent. Consider the implications of these at the level of the tissue, the cell and the molecular organisation. See at what point the problem occurs. Can the problem be minimised? Can the problem be solved? Think of strategies to develop therapies.

This lecture indicates only a tiny proportion of the many many diseases that exist. It is designed to introduce you to different ways of viewing the disease process from the cellular perspective. Some useful references are cited in the text and numerous excellent Pathology text books readily provide additional classical information e.g. Robbins SL and Cotran RS (1979) “Pathologic basis of disease” Saunders, Philadelphia. Brunson JG, Gall EA (1971) “Concepts of Disease” Macmillan, New York.

Developmental abnormalities
Due to something going wrong during development (due to environmental or genetic causes). Some environmental examples are:

- Physical deformities resulting from an error during embryogenesis (see below)
- Lack of amniotic fluid means the embryo cannot move limbs around as much as needed and therefore can get joint malformation - arthrogroposis
- Exposure to a teratogen during a critical stage of development e.g. thalidomide during time of limb formation gives no limbs. Infection of the mother by rubella virus during pregnancy results in many severe defects, the most common being heart disease, cataracts and deafness. Iodine deficiency in the pregnant mother results in cretinism in the infant. Other drugs can produce very delayed effects on the baby. e.g. diethylstilbestrol (a synthetic form of oestrogen) was given to mothers (in the 1960s) to help maintain pregnancy. It was subsequently found that this resulted in lethal cancer of the cervix (adenocarcinoma) in their daughters at around 15 to 20 years of age.
- Specific nutritional deficiency e.g. rickets - (manifesting between 6-18 months after birth) results from a lack of vitamin D (e.g. lack of sunlight) which causes a failure of osteoid mineralisation, the cartilage does not calcify but continues to proliferate and this leads to bone deformities.
- General under-nutrition leading to low birth weight. May be due to malnutrition of the mother, and occur with multiple births which can be more frequent with in vitro fertilisation programmes. Under-nutrition in utero (resulting in low birth weight) leads to persisting changes in blood pressure, cholesterol metabolism and a range of other metabolic, endocrine and immune functions known to be important in human disease. These latent effects resulting from low birth weight are associated in adults with insulin-dependent diabetes and cardiovascular disease.

Genetic disorders
A huge number of inherited defects lead to various diseases. These are irreversibly programmed into the genome. (1) Some result in the lack of some critical factor and always result in a particular disease. A devastating disease can result from even a point mutation in a critical part of a gene that affects one particular protein. Certain genetic diseases may manifest during
development, others during childhood and others later in life. Cell and gene therapy to replace the defective gene has already been attempted in a few of these diseases. (Sometimes the heterozygote condition may confer some advantage under certain conditions e.g. sickle cell anaemia and malaria). A few examples of genetic diseases that develop at different ages are:

- Cystic fibrosis is due to defect in a chloride channel and results in excessive mucous and chronic bacterial infection in the lungs (it appears the low Cl affects the bacteriocidal action of the surfactant). The children need extensive and constant physiotherapy to keep the lungs cleared of mucous. Gene therapy has attempted to introduce DNA for the missing gene in an adenovirus vector into the lung by aerosol inhalation. This is rapidly absorbed into the defective cells and is very effective. Unfortunately, the virus disappears within a month and readministration of the virus/gene produces an immune response since the host has been already exposed, and is sensitised, to the virus. (Yang Y et al (1994) Nature Genetics 7: 362-369; also comments by Crystal et al (1994) Nature Genetics 8:8-9; Goldman et al (1995) Nature Genetics 9: 132-131.).

- A defect in keratin 14 affects epithelial cells in the basal layer of the dermis and leads to ulceration of the skin; to produce a condition called Epidermolysis bulosa simplex: this is pronounced during childhood and less severe in later life.

- Duchenne muscular dystrophy, carried on the X-chromosome affects only boys, manifests around 2-4 years, results in necrosis of skeletal muscle and the progressive replacement of muscle by fat and fibrous connective tissue, leading to death (often from respiratory failure) by the 2nd decade. The gene defect was only identified in 1987 and it produces a defect/lack of the protein dystrophin which is normally located beneath the cell membrane (sarcolemma of skeletal muscle). The lack of dystrophin makes the muscle fibre very vulnerable to damage. Why muscle regeneration fails after the repeated cycles of necrosis is unclear. Cell replacement therapy is designed to introduce normal muscle nuclei with the dystrophin gene into the dystrophic muscle fibres, since multinucleated muscle fibres are formed by fusion of mononucleated precursor cells. (See Partridge TA (1991) Myoblast transfer: a possible therapy for inherited myopathies? Muscle & Nerve 14:197-212; Grounds MD (1996) Commentary on the present state of knowledge for myoblast transfer therapy. Cell Transplantation. 5(3):431-433.)

- Huntington’s disease shows no symptoms until after 30-50 years and then leads to dementia and death. This gene is passed down through many generations and has only recently been identified. It is due to massive loss of neurones in the striatum of the brain. Transplantation of embryonic striatal tissue to replace the missing cells is being explored. (Sanberg et al (1992) Cell transplantation for Huntington’s disease Transpl. Proc. 24:3015-3016; Peschanski et al (1995) Rational for intrastriational grafting of striational neuroblasts in patients with Huntington’s disease Neuroscience 68:273-285)

(2) Many other genes just predispose the individual (i.e load the dice) towards a particular disease and the final outcome will depend on a whole range of multifactorial events, including environmental. Examples of some of these are, breast cancer (e.g. about 15% of women with the breast cancer gene BRCA1 do not get the disease), bowel cancer, schizophrenia (can be triggered by maternal malnutrition), emphysema.

**Damage (and impaired repair)**

- Injury e.g. spinal damage leads to permanent paralysis, since nerves of the central nervous system do not undergo repair (unlike axons of peripheral nerves).
• Drugs e.g. alcohol can produce irreversible liver damage called cirrhosis, which is progressive fibrosis of the liver that can lead to liver failure. (Alcohol abuse accounts for 30-60% of cases of cirrhosis). Remember that the liver normally has an excellent capacity for regeneration.

• Viral infection e.g. hepatitis; the virus itself appears not to be cytopathic, but it induces an immune response which leads to necrosis of the liver. This can be mild with good recovery of the liver or severe and lead to cirrhosis. 
Myocarditis; viral infection can lead to inflammation of the heart muscle. Sometimes this is severe resulting in muscle necrosis; since cardiac muscle cannot regenerate, scar tissue is formed and this can lead to sudden heart failure.

• Inherited diseases e.g. Duchenne Muscular Dystrophy (discussed above).

**Nutritional**

Undernourishment (starvation, famine), either a calorie or protein deficiency, is very damaging to the body (see also ‘Developmental abnormalities’ above). Beyond problem of general under nutrition, some 50-60 organic and inorganic substances are essential dietary components and are required in amounts ranging from microgram to gram quantities. These are usually provided by a balanced diet. Deficiencies in many of these are known to lead to specific diseases. e.g. rickets results from a vitamin D deficiency (see above); Vitamin C is essential for the formation of collagen (e.g. required for the hydroxylation of proline to hydroxyproline in fibroblasts), and a defect lead to impaired wound healing and results in scurvy (cured by giving sailors limes to eat - hence the term limey); vitamin B1 (thiamine) is required on a daily basis and deficiencies lead to neuromuscular problems (Beri-beri).

**Infection**

Microorganisms are ubiquitous in our environment. Thus man is infected virtually from birth, but infection does not necessarily mean disease. Indeed, infection may be of benefit to the host e.g. synthesis of vitamin K in the large intestine is dependent on the normal intestinal flora. Disease results only when the microorganism causes functional and structural harm. Infectious diseases provide some of the rare opportunities in medicine to actually effect a complete (and rapid) cure. However, many infectious diseases are highly communicable.

• Bacterial: Streptococcal infection is responsible for scarlet fever and sensitisation to streptococcal antigens leads to post-streptococcal diseases such as rheumatic fever (inflammatory disease which affect the joints and the heart); other well known infectious diseases are pneumonia (pneumococci); meningitis (meningococci), gonorrheae (gonococci); typhoid fever (Salmonella); tuberculosis (Mycobacterium tuberculosis), leprosy (M. leprae); tetanus (Clostridia tetani);

• Viral infections are the commonest ailments e.g. colds and influenza, measles. They are also implicated in cancer. Examples of viral diseases are: Hepatitis (affects the liver), multiple sclerosis (see below under Immunology); Human immunodeficiency virus (HIV) impairs the response of the effector cells of the immune system (the T cells which include T-lymphocytes, macrophages and dendritic cells) and the body becomes super vulnerable to all sorts of opportunistic infections and cancer cells - this is called Acquired Immunodeficiency Disease (AIDS).

• Fungal; thrush or Candida

• Protozoan (parasitic diseases): malaria is a protozoan disease transmitted by the bite of the female Anopheles mosquito; sleeping sickness (trypanosomes).
Immunological

- Immunodeficiency makes the whole organism vulnerable to many other infections, cancer etc. Immunodeficiency may be the result of genetic factors; be acquired (e.g. AIDS); or result from stress or other health aspects that can reduce the overall efficiency of immune function.
- Inflammatory e.g. Arthritis,
- Hypersensitive e.g. Asthma
- Autoimmune diseases result from immune reactions against ‘self-antigens’, there are many examples of this e.g. Multiple sclerosis in which the body attacks it’s own myelin sheath around axons. The trigger is uncertain, but is thought to be virus infection (cat) that the person reacts to by the production of specific antibodies, and these antibodies then (unfortunately) also recognise myelin and destroy it. In Myasthenia gravis, the body produces antibodies to receptors for the neurotransmitter molecule acetylcholine (Ach) and the binding of Ach to its receptor is responsible for transmitting signals between nerves. The antibodies bind onto the receptor and block the action of the nerve. One treatment involves plasmapheresis, where all proteins (including antibodies) are removed from the patients blood which is then replaced - this treatment is effective for several months until the amount of antibody builds up again.

Cancer

Cancer is also referred to as neoplasia (= new growth). A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which caused the change. Cancers are highly invasive and can spread and form tumours (metastases) in distant parts. The causes of many cancers are unknown and are undoubtedly multifactorial i.e. changes in several aspects of cell behaviour must occur before a neoplasm is manifested. Therefore some agents increase the chance of developing cancer, although alone they will not result in cancer. Examples of agents that cause cancer (carcinogens) are:

- Viruses. A range of viruses have been implicated in cancer although in many cases the relationship and mechanism is not clear. Oncogenes derived from viruses mimic normal cellular signalling molecules, such as growth factors, receptors etc. (See lecture on Growth factors in week 2).
- Chemicals. There are many many examples of these, a few are: polycyclic hydrocarbons which produced scrotal cancer in chimney sweeps and may be responsible for lung cancer resulting from smoking; aflotoxin mould which grows on peanuts etc causes liver cancer; betel nut which is widely chewed in some countries gives cancer of the mucous membranes of the oral cavity.
- Radiation e.g. the danger of ionising radiation from X-rays and nuclear bombs is well documented; non-ionising radiation is also recognised as dangerous - e.g. ultraviolet light and skin cancers; lower frequency electromagnetic radiation from power lines and mobile phones has also been implicated in cancers (French P (1997) The cost of keeping in touch. Life Science 9:14-20).