Ministry of Defence

Synopsis of Causation

Myeloma and the Paraproteinaemias

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1.   Definition

1.1   **Multiple myeloma** is a progressive malignant disease arising from cells within the bone marrow that form plasma cells.

1.2   **Plasma cells** are white blood cells that normally produce circulating gamma globulin, proteins that combat infection and confer immunity. The condition is characterised by a proliferation of abnormal monoclonal immunoglobulins (M proteins) in the blood, referred to as paraproteinaemia.

1.3   The disease causes localised damage to the skeleton by osteolysis from tumour proliferation in the marrow, anaemia due to disordered blood synthesis, renal damage due to the effect of excess protein in the kidneys, and impaired resistance to infection.

1.4   **Monoclonal (M) proteins** are electrophoretically homologous and consist of two 'heavy' and two 'light' polypeptide molecular chains. Agarose gel electrophoresis shows a dense discrete band that represents the M protein. Heavy or light chain protein can predominate and the clinical presentation can produce a range of disease depending on the type of protein that is found.[1]

1.5   Multiple myeloma is one of a spectrum of diseases arising from abnormal plasma cell proliferation. Of these, **monoclonal gammopathy of unknown significance (MGUS)** is of particular relevance as it may progress to myeloma with a latent period of up to twenty years.

1.6   Synonyms for multiple myeloma include:

- myelomatosis
- Kahler's disease
- bone marrow malignancy
- plasma cell dyscrasia
- plasma cell cancer

1.7   Incidence. In the United States, multiple myeloma accounts for 1% of all malignant diseases and just over 10% of haematological malignancies. Annual incidence is 4-5 per 100,000 population. Recent increase in incidence in the past decade is thought to be due to better recognition of the disease.

    1.7.1   Ethnic differences. Incidence in the American black population is double that of the white population. Rates are lower in Asians.

    1.7.2   Sex differences. Multiple myeloma is slightly more common in men than in women (4.3 men to 3 women per 100,000). This difference also is reflected in the ethnic groups.

    1.7.3   Age incidence. The median age at diagnosis is 65 years with only 18% being younger than 50 years and 2% younger than 40 years.[2]

1.8   In the United Kingdom, incidence is 2 per 100,000 with a mean age of onset and male to female differences similar to that in the United States. [3]

2. Clinical Features[1, 2]

2.1 Multiple myeloma can develop insidiously, potentially with a long period of development of up to twenty years when abnormalities of circulating protein can be found before the symptoms appear. First symptoms may be non-specific with vague fatigue and malaise.

2.2 **Skeletal disease.** About two thirds of cases present with non-specific chronic skeletal pain often in the lower back or thoracic area as a manifestation of osteolysis and expansion of the plasma cell tumour within the vertebral bodies or bones of the ribs and pelvis.

    2.2.1 Tumour may compress the spinal cord producing neurological lesions in the lower limbs. Erosion of the bone of the vertebrae may cause vertebral collapse resulting in spinal deformity or catastrophic spinal compression with paraplegia. Between 10-20% of cases are likely to develop some degree of spinal cord compression over the duration of the condition.

    2.2.2 Pathological fractures affecting the pelvis or long bones following simple injury may be the first manifestation of the disease.

2.3 **Renal disease.** Twenty percent of cases show some degree of renal impairment by the time the disease is diagnosed. Renal damage is primarily due to obstruction of the renal tubules by hyaline casts formed by filtration of the high concentrations of light chain paraproteins. Secondary fibrosis of the renal tissue, renal deposits of extramedullary tumour, degeneration of the epithelial lining of the tubules and secondary amyloidosis add to the problems with renal function.

2.4 **Haematological problems.** Anaemia is found in about two thirds of cases at presentation, and eventually all develop some degree of anaemia. Anaemia is usually normochromic and normocytic suggesting reduced rather than abnormal red cell production.

    2.4.1 Bleeding disorders can occur secondary to impaired platelet production and hyperviscosity of the blood.

    2.4.2 Hyperviscosity of blood due to the raised circulatory level of high density protein may also cause impairment of blood flow, particularly of the cerebral circulation leading to mental health problems and possible cerebrovascular accidents. Myocardial infarction may complicate the picture or high plasma volume may lead to impairment of cardiac output and cardiac failure. Epistaxis, Raynaud's phenomenon and carpal tunnel syndrome are also complications of hyperviscosity.

2.5 **Infection.** Abnormal immunoglobulin production and leucopenia leads to a defective immune response. The patient is prone to recurrent bacterial infection particularly from pneumococcal and haemophilus organisms. Exacerbation of herpes zoster is also common.

2.6 **Diagnosis** can be confirmed using a series of investigations.

- **Haematology** including full blood count, measurement of total serum protein and albumin/globulin ratio, and protein electrophoresis
- **Urinalysis** may show proteinuria and Bence-Jones protein but paper strip tests are not always reliable. Protein electrophoresis of urine more reliably shows Bence-Jones protein.
- **Bone marrow biopsy** may indicate an increase in plasma cells
- **Radiology** of bone may identify areas of osteolysis. A full skeletal survey including the skull may identify bone lesions. MRI scan may be more reliable in identifying lesions or confirming those found on plain radiology.[2]

2.7 Other forms of paraproteinaemia occur and need to be differentiated from multiple myeloma because of the differing methods of treatment and prognosis.

2.7.1 **Monoclonal gammopathy of unknown significance (MGUS)** is the presence of serum M protein in an apparently healthy person. This condition mainly seems benign but may progress to myeloma with a latent period of up to twenty years. Raised serum levels of protein remain stable over a prolonged period. MGUS occurs in 1% of individuals older than 40 years and frequency rises with age. An increase in incidence of MGUS was seen in survivors of the atomic bomb explosions in Japan with the rate of progression to myeloma being higher after age 60 years in the radiation exposed group. However, progression to myeloma is generally slow and management by long-term follow-up is recommended with no active treatment.[4]

2.7.2 **Waldenström's macroglobulinaemia** is a malignant plasma cell disease of cells that normally secrete IgM immunoglobulin. It is a rare condition that is more typical of lymphoma than myeloma. It is clinically distinct from myeloma with hyperviscosity syndrome predominating. It usually affects older persons with a median age of 65 years, more commonly in men. Around 12% of patients with MGUS show evidence of macroglobulinaemia and the condition may be found in a small proportion of patients with non-Hodgkin's lymphoma.

2.7.3 **Smouldering multiple myeloma** shows abnormality of blood protein and bone marrow changes but no anaemia or renal changes. This can advance to progressive myeloma.

2.7.4 **Heavy chain disease** is a plasma cell dyscrasia with production of heavy chain M protein with abnormally high levels of lymphocytes. The clinical picture is more like lymphoma than myeloma. There are three main variants depending on the form of heavy chain M protein that predominates.

2.7.5 **Extramedullary plasmocytosis** is a plasma cell tumour arising outside the bone marrow, often from the respiratory tract (80%).

2.7.6 **Solitary plasmocytoma of bone** is a localised plasma cell tumour without evidence of widespread multiple myeloma.

2.7.7 **Osteosclerotic myeloma (POEMS syndrome)** is characterised by Polyneuropathy, Organomegaly, Endocrine disease, M protein in the blood and

Skin lesions. It primarily presents as a marked polyneuropathy with widespread neurological problems. Sclerotic bone lesions occur with hepatomegaly, splenomegaly, skin pigmentation and diffuse endocrine manifestations such as gynæcomastia.

2.7.8   **Plasma cell leukaemia** is a form of malignant abnormality of white blood cell production with a predominance of abnormal plasma cells.

2.7.9   **Primary amyloidosis** results from the formation of protein containing fibrillous substance being laid down in tissue of organs. It occurs secondary to chronic inflammatory diseases and chronic infection but the high level of paraprotein in myeloma and associated diseases can result in significant amyloid disease.

3. Aetiology

3.1   The cause of multiple myeloma is unknown but it appears to be due to an interaction of constitutional and environmental influences. Various factors have been considered as potential causes. These an be considered under the headings of:

3.1.1   **Genetic Factors.** Attempts are continuing to try to establish whether there is an inherited trait that increases the chances of developing myeloma or whether damage or mutation to specific genes causes the bone marrow to produce abnormal cells. Advances in this area could potentially allow treatment by gene therapy to reverse the process.

3.1.2   **Environmental factors.** Several environmental factors have been implicated as potential causes of multiple myeloma and MGUS as well as possible factors in increasing the rate of transition of MGUS to multiple myeloma. These include:

- Exposure to ionising radiation
- Exposure to organic solvents
- Exposure to benzene derivatives – mainly in the petrochemical industry
- Area of residence – particularly agricultural communities
- Exposure to herbicides and pesticides
- Infection – particularly viral infection
- Immune system overload

3.2   **Genetic factors**

3.2.1   Differences in incidence between ethnic and racial groups suggest a genetic susceptibility to multiple myeloma. Even with the effects of environmental influences, genetic tendencies appear to aggregate within families or populations. Groups of families with clustering of multiple myeloma have been investigated. One study of 25 family members of a patient with multiple myeloma identified two other siblings out of seven with asymptomatic multiple myeloma and two other family members with MGUS. Other haematological cancers were also identified in the family group.[5]

3.2.2   Several studies have identified an increased risk of developing myeloma among persons with a member of the family with the disease.[6] One study showed a relative risk of 2.36 among first degree relatives.[7]

3.2.3   Wide genetic variability between individuals confounds comparison of gene profiles in normal plasma cells and myelomatous cells. A recent study looked at genetic expression profiles of bone marrow samples from monozygotic twins. Some genes were highly expressed in myeloma cells compared with normal cells whereas others were downgraded. Three genes in particular were identified that mediate transformation and differentiation of malignant cells. It therefore appears that genes can be identified that have been uniquely altered in myeloma. If this is confirmed by further research it may identify a method of therapeutically modifying the disease.[8]

3.2.4   Specific absences or mutations of genes 1 and 13 have been found in malignant plasma cells in some cases and these seem to have a less favourable prognosis but the reason for the abnormality and its association with the disease is not fully explained. Abnormalities of other chromosomes including 14 and 32 have also been observed.

3.3   **Environmental factors.** A number of environmental factors have been postulated as potential causes of myeloma including living in agricultural areas and exposure to herbicides, pesticides petrochemical agents particularly benzene and organic solvents, cutting oils, wood dust, arsenic, and ionising radiation. Viral infection, especially the effect of human herpesvirus (HHV-8) which is associated with Kaposi's sarcoma has also been implicated. These many suggested links have yet to be substantiated.

3.3.1   **Ionising radiation – general considerations.** Ionising radiation can cause damage to living tissue, the extent of which relates to the dose of radiation and the duration of exposure. Everyone is exposed to a background radiation exposure from naturally occurring sources including cosmic radiation, and this varies depending on geographic location. Some of this will be linked to cancers in the population as a whole. Radiation equivalent dose is measured in units of Sieverts (Sv) The Sievert represents a high dose of radiation and measurements are usually given in millisieverts (mSv). The amount of radiation energy absorbed by unit weight of a body organ is expressed in units of Gray (Gy). The equivalent dose in Sieverts reflects the differing sensitivity of different tissues and different types of radiation which produce different relative amounts of tissue damage. The equivalent dose is determined by multiplying the absorbed dose in Gy by a weighting factor that reflects both tissue sensitivity and radiation type. Background radiation in the UK is on average 2mSv per annum, being up to 8 mSv in some areas such as Cornwall with a high geological content of granite which is associated with a natural occurrence of radioactive radon gas.

3.3.2   Adverse effects are proportional to the dose of radiation absorbed and there is no lower threshold below which ionising radiation is safe. However, total body doses up to 10 mSv are not likely to produce an adverse effect but 100mSv is likely to cause radiation sickness. A total equivalent dose of 10,000 mSv (10Sv) is likely to be lethal. Limits of annual radiation exposure are set for those working with ionising radiation. From 1 January 2000 these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers. The recommended dose limit for the general public is 1mSv per annum above background levels.

3.3.3   High doses (1Sv or above) can cause immediate severe illness. Early effects usually arise within hours or weeks of exposure. The severity of effect is proportional to radiation dose and there is a threshold below which no effects are evident. This threshold is relatively high, exceeding natural background levels by several hundred fold. Late effects, arising between 2 to 40 years after exposure, appear to have no threshold level of risk and probability of effect is proportional to dose. There is a finite risk from any exposure including background radiation. Long-term exposure to lower doses of ionising radiation in excess of background levels has been implicated in causation of many malignant diseases. However, UK overall cancer rates are higher than expected

for the generally low background radiation levels indicating that factors other than radiation are involved in causation of malignancies.

3.3.4   **Ionising radiation – specific studies.** Speculation of a causal link between myeloma and exposure to ionising radiation has been ongoing over the years since nuclear hazards have existed. Initial studies on survivors of the World War 2 atomic bomb detonations in Japan showed an increased incidence of several haematological cancers including multiple myeloma and appeared to show an increasing risk for this disease with increasing radiation dose.[9] An increase in MGUS was also found in this group. Further follow up of survivors appeared to show a significant link with myeloblastic leukaemia, lymphomas and multiple myeloma but continuing prospective follow up of that cohort has shown the link with multiple myeloma has weakened.[10] However, overall data provides support for a causative link with ionising radiation for both MGUS and multiple myeloma. Transition from MGUS to multiple myeloma has been found to be faster in radiation-exposed than non-exposed persons.[11]

3.3.5   Evidence relating to the link between multiple myeloma and radiation exposure, as encountered in various circumstances, is summarised below:

- **Nuclear industry.** The nuclear industry clearly has a potential for excessive exposure to radiation. Strict health and safety controls and surveillance have been applied and much research has been done into the potential long-term effects of work in this type of industry. In general there is not considered to be an increased risk of multiple myeloma in radiation workers. One large cohort study of workers in the nuclear industry found overall levels of mortality among the cohort were less than expected from national rates of diseases. Although there was some increase in risk for leukaemia (excluding chronic lymphatic leukaemia) in proportion to dosage, no increase in risk for multiple myeloma was found.[12]

- **UK Nuclear Tests.** During the 1950s the UK carried out a series of 21 atmospheric tests of nuclear weapons in Australia and the Pacific. Concern has been expressed by service personnel and other participants who were involved in these tests or serving in the vicinity that this had lead to an increased risk of ill health and malignancies, including multiple myeloma. An independent study to examine this was commissioned by the Ministry of Defence in 1983. The study was carried out by the National Radiation Protection Board and involved an historical cohort study which compared mortality and incidence of cancer in over 20,000 test participants with that of other service personnel. This found no reduction in overall life expectancy in participants compared with control cases, and no increase in cancers with the exception of an increased incidence of multiple myeloma and leukaemia (excluding chronic lymphatic leukaemia). However this last finding was not considered to be due to radiation as the rate for these conditions was particularly low in the service controls and those subgroups considered most highly exposed to radiation did not show the highest rates of the conditions. This study was extended and in 1993 a second report was published which concluded that the extended evidence did not support the original finding of an increased incidence of myeloma. A third report published in 2003 which further extended the follow up period to 1998

supported the findings of the second report.[13] It concluded that the overall levels of mortality in the UK nuclear weapons test participants had continued to be similar to those in a matched control group and overall mortality from all causes was lower than expected from national rates. Notwithstanding subsequent debate, the validity of the extended findings is accepted by the scientific community. Current evidence therefore does not support a causal link between multiple myeloma and participation in the UK nuclear testing programme.

- **Medical exposure – diagnostic procedures.** There is some evidence from American studies in the 1960s of an increased risk of multiple myeloma in radiologists and radiotherapists. These findings were not repeated in a study of a large number of radiological diagnosticians in China. Although an increased risk of some cancers and leukaemias was apparent, the evidence did not support an increased risk of multiple myeloma in this group. [3,14] Although there is a potential risk from any dose of ionising radiation, there is no significant risk from routine diagnostic exposure of patients to X-rays other than some evidence of an increased risk for those receiving numerous diagnostic exposures due to difficulties with diagnosis or long-term radiological follow-up.[15,16]

- **Medical exposure – therapeutic procedures.** There is a significant risk from therapeutic radiation exposure to various parts of the body. Experimental treatment of non-malignant conditions such as ankylosing spondylitis or metropathia haemorrhagica has been shown to result in an increase incidence in several malignancies including multiple myeloma. In one study of radiation-treated metropathia haemorrhagica, the standardised mortality ratio for multiple myeloma was 2.59 at 5+ years following radiation. Radiation absorbed doses in this group were in the range of 2.6-5.3 Gy.[17, 18]

3.3.6 **Occupational exposure** to a wide variety of substances has been investigated over the years with varying results and conclusions. In a study of Norwegian agricultural workers, multiple myeloma was found to be positively associated with pesticide indicators for both men and women working in potato cultivation.[19] Conversely a large case-control study from hundreds of occupational exposures and 19 cancer sites showed a small association of myeloma in sheet metal workers but nothing else.[20] Evidence of an association with pesticides, herbicides, organic chemicals, wood dust, and asbestos is equivocal with causal associations being countered by negative findings.

3.3.7 **Benzene exposure.** Benzene has a molecular structure that could be associated with haematological malignancy and much work has been done on the incidence of myeloma in workers in the petrochemical industry. One reliable study showed a 2-3 fold increase in risk of multiple myeloma and a similar increase in leukaemia among workers exposed to benzene for more than 20 years but no increase in workers exposed intermittently in jobs such as maintenance work. A large meta-analysis in 1997 of data from 22 cohort studies of petroleum workers in Canada, United States, United Kingdom and Australia found no increase in incidence of multiple myeloma in these groups.[21] Overall

results therefore have been variable and a causal link with benzene remains controversial.

3.3.8   **Lifestyle factors.** Socio-economic class, smoking habits, diet, alcohol intake and use of permanent hair dyes have been considered as potential links. No reliable repeatable evidence has been established to confirm any of these factors as causes.

3.3.9   **Infection.** Human herpesvirus (HHV-8) can be isolated from a variety of body tissue cells including the dendritic cells of bone marrow and has been implicated as a possible cause of bone marrow dysplasia. This has been considered as a specific cause but this has not been substantiated other than in a possible association with severe immune dysfunction.

3.3.10   **Immune system dysfunction.** Acquired immune deficiency syndrome (AIDS) is probably the most common form of severe immune deficiency. In a study linking population-based cancer and AIDS registries in the USA, a 4.5-fold increase in risk was found for myeloma in those with accepted AIDS.[22] In a similar study in Australia, a 12-fold increase in multiple myeloma was found. Other forms of challenge to the immune system have been implicated including rheumatoid arthritis, allergies and atopic eczema, herpes zoster, chronic bacterial disease and BCG vaccination. The evidence for any of these as a causative link is inconsistent.

4.   Prognosis

4.1   Multiple myeloma is treatable but not curable. It is a progressive disease with a median survival time of around three years, although with current treatment regimes around 20% survive without complication for 5 years or longer. Survival rate depends on the extent of disease at diagnosis and the response to treatment. Best prognostic indicators are said to be the plasmas-cell labelling index and β2-macroglobulin level. Low plasma cell index and low β2 macroglobulin level are associated with a survival rate of 6 years with chemotherapy.[1]

4.2   Several systems of staging of multiple myeloma are in use and these have prognostic value. The Durie-Salmon system has been most commonly used, particularly for clinical trials. This system stages cell mass categories as high (stage 3), intermediate (stage 2), and low (stage 1) based on haemoglobin level, serum calcium level, M-component and the number of bone lesions found on skeletal survey.[23] Another system developed by the Medical Research Council also uses three stages but defined as 'poor prognosis (stage 3), ''intermediate' (stage 2), and good prognosis' (stage 1). These stages are based on blood urea concentration, haemoglobin level and patient activity performance status. Newer systems of staging for diagnosis of multiple myeloma and other paraproteinaemias are being developed.

4.3   Based on the various staging systems, unfavourable prognostic signs at presentation, apart from high plasma cell indexes and β2- macroglobulinaemia, therefore are:

- Diffuse multiple bone lesions
- Marked anaemia
- Hypercalcaemia
- Very high levels of M protein in blood and urine
- Renal failure

4.4   Good management can extend the period of survival and improve quality of life. Treatment is aimed at reducing tumour mass with an aim of ablating the tumour cells, treating localised areas of bone erosion and general management of the patient's well-being by managing effects of bone pain, anaemia, renal impairment, hypercalcaemia and other systemic symptoms.

4.5   Chemotherapy is preferred as first line treatment for patients over 70 years.[1] Various combinations of chemotherapeutic agents are being tried, with or without prednisolone. Treatment is given by repeated courses until a plateau state has been reached with stable urine and serum levels of paraprotein.

4.6   In younger patients, ablation of the bone marrow using high dose combination chemotherapy and transplantation with autologous stem cells to restore marrow function has had significant success. A recent study of the outcome of autologous transplantation at a single institution showed that complete response was obtained in 36% and transplant mortality was 7% of cases. The disadvantage of autologous transplantation is that the transplanted stem cells may be contaminated with abnormal plasma cells but the much lower post transplant mortality rate makes this far more acceptable.

4.7   Allogenic transplantation has the apparent advantage of using marrow which has no malignant cells but mortality rates are much higher from complications of the transplant procedure and, at present, it cannot be recommended as a routine procedure.

4.8   Skeletal problems and complication such as pathological fracture and spinal compression can be helped by treatment with bisphosphonate drugs which inhibit bone resorption and reduce osteolysis.

4.9   Management of other complications such as hypercalcaemia, anaemia, infection, neurological complications and the effects of increased blood viscosity all need to be addressed.

4.10   The other plasma cell dyscrasias or paraproteinaemias vary from asymptomatic stable conditions to symptomatic, progressive conditions with limited life expectancy. MGUS progression to myeloma is generally low but may occur over a period of 20 years. Waldenström's macroglobulinaemia tends to be more benign than multiple myeloma with life expectancy of 5-7 years. Solitary plasmocytoma tends to run a longer course although often progresses to multiple myeloma with only 20-30% of patients remaining well for 10 years. The various forms of heavy chain disease present a variety of complications, and treatment type and prognosis may be as for lymphoma or leukaemia. Amyloidosis occurs in around 10% of myeloma patients has a median survival time of 13 months with complications due to cardiac and renal failure reducing prognosis.

4.11   Significant emotional support is needed both for the patient and family members and the medical approach needs to be positive and reassuring as, although the overall prognosis is poor, it is possible for some to survive for at least ten years.

5.   Summary

5.1   Multiple myeloma is a progressive malignant disease of bone marrow due to abnormal production of plasma cells forming a tumour within the bone.

5.2   It is one of a group of diseases where abnormal plasma cell growth results in the production of abnormal proteins in the blood known as paraproteins. Some of these forms are asymptomatic but transition to malignant multiple myeloma occurs in a significant number.

5.3   The cause of multiple myeloma and its precursors is not known but they appear to be due to a combination of external factors with a genetic predisposition. Many factors have been considered and there is probably a causal link between multiple myeloma and exposure to ionising radiation although recent studies have cast doubt on the strength of the link. Other factors such as work in agriculture, exposure to benzene, organic solvents, hair dyes, smoking, asbestos, viral infection and several other agents have been shown to produce an increased risk of developing multiple myeloma but there is much conflicting evidence which makes these associations controversial.

5.4   The prognosis of the disease is poor but modern methods of treatment with a variety of methods using chemotherapy, radiotherapy and bone marrow replacement procedures do prolong survival and maintain quality of life. Some of the variants of plasma cell dyscrasia have a better prognosis than multiple myeloma.

6. Related synopses

Acute Myeloid Leukaemia

Chronic Myeloid Leukaemia

HIV Infection and AIDS

Chronic Lymphoproliferative Disorders

7. Glossary

ablation	The removal of diseased or unwanted tissue from the body by surgical or other means.
allogenic	Tissues that are genetically different and not compatible when transplanted.
ankylosing spondylitis	An inflammatory disease of the spine that causes the vertebrae to form a solid inflexible column.
autologous	Derived from the patient's own body – of identical genetic content.
Bence-Jones protein	An abnormal protein found in the blood and urine of patients with multiple myeloma, traditionally demonstrated when, by heating a urine sample, a precipitate forms that disappears as the liquid reaches boiling point.
dyscrasia	Any abnormal condition of blood cells.
dysplasia	Abnormal development or growth of a part of the body, for example an organ, bone, or cell.
electrophoresis	A method of separating and identifying large molecule proteins and carbohydrates by passing an electrical current through a solution or gel containing the substances.
epistaxis	Bleeding from the nose.
extramedullary	Occurring outside the bone marrow.
haematological problems	Disorders of the blood or blood forming tissues.
haematopoietic	Pertaining to the tissues that produce blood.
hepatomegaly	Enlargement of the liver.
herpes zoster	A viral condition commonly known as shingles.
homologous	Corresponding in origin and structure.
immunoglobulins	A class of proteins that function as antibodies in the immune response.
leucopenia	An abnormal reduction in the number of white blood cells (leucocytes).
lymphoma	Tumour of the lymphatic system and lymph nodes.

metropathia haemorrhagica	Excessive irregular uterine bleeding usually associated with overproduction of circulating oestrogen hormones.
monozygotic twins	Twins developed from a single egg – identical twins.
normochromic	Red blood cells of normal colour, usually as they contain the normal amount of haemoglobin pigment.
normocytic	Red blood cells of normal size and shape.
osteosclerosis	Abnormal increase in density of bone – opposite of osteoporosis.
osteolysis	The destruction or breakdown of bone tissue caused by disease.
pathological fracture	A fracture occurring from minor injury due to abnormal weakness of the bone structure.
polyneuropathy	Widespread disorder of the nervous system.
Raynaud's phenomenon (or disease)	A condition affecting the circulation to the hands and feet typified by attacks of severe whitening of the skin of fingers or toes.
splenomegaly	Enlargement of the spleen.

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