Ministry of Defence

Synopsis of Causation

Cancer of the Stomach

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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. Cancer of the stomach (*syn* gastric cancer, malignant neoplasm of the stomach, adenocarcinoma of the stomach) is the second most common cause of cancer-related death in the world; indeed in some areas it is the commonest. The condition exhibits very marked geographical variation and is particularly prevalent in Asian countries, including Korea, China, Taiwan, and Japan. By 2010 it is expected that there will be 1.1 million cases annually in the world.

1.2. In the UK about 10,000 people are diagnosed with gastric cancer each year. It is the 6th commonest cancer in the UK and represents approximately 10% of all cancer deaths in this country.[1]

1.3. In Western countries, the incidence of cancer localised to the distal part of the stomach has declined steadily in recent decades, whereas the incidence of proximal gastric cancer, cancers of the gastroesophageal junction and lower oesophageal adenocarcinoma have been steadily increasing, perhaps reflecting differences in causative factors. The condition affects slightly more men than women, and is commoner in older age groups; the median age at diagnosis is 65 years (range 40-70 years). The cases which occur in younger patients may represent a more aggressive variant.

1.4. **Classification** In 1965, Laurén classified gastric carcinoma into two subtypes; an intestinal type, and a diffuse type.

Intestinal-type carcinomas are characterised by cohesive neoplastic cells and the formation of bulky tumours composed of glandular structures. They develop from precursor lesions, are often ulcerated and occur more frequently in the distal stomach. The decline in prevalence of gastric cancer in certain geographical areas is largely due to a reduction in the number of these intestinal-type tumours.

Diffuse carcinomas In these neoplasms cells infiltrate and thicken the wall of the stomach without forming a discrete tumour mass. They may develop anywhere in the stomach but arise more often in the cardia[2] and may ultimately result in linitis plastica, a condition in which the stomach is constricted, inelastic, and rigid. Diffuse carcinoma is commoner in younger patients and carries a worse prognosis than the intestinal type. The incidence of this variety is similar in most populations throughout the world.

1.5. 90-95% of gastric cancers are adenocarcinomas; the remainder includes lymphomas (5%), stromal tumours, and other rare varieties.[3]

1.6. **Cancers of the gastroesophageal junction**, which have been increasing in frequency in the West since 1970 may represent a third and separate form of gastric cancer. These lesions are often associated with chronic gastroesophageal reflux and Barrett's dysplasia and are discussed in the Synopsis *Cancer of the oesophagus*.

1.7. **Gastric lymphoma** This is an uncommon malignant neoplasm usually consisting of fairly mature B lymphocytes. Most are classified either as marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, or as diffuse large B cell lymphoma. Lymphoma may arise from lymphoid tissue which is normally found in the intestinal wall (e.g., in Peyer's patches) or from lymphoid tissue that has arisen due to inflammation in

response to infection or some autoimmune process. Gastric tissue does not normally contain mucosa-associated lymphoid tissue but it may be acquired as a result of chronic *Helicobacter pylori* infection.

2. Clinical features

2.1. Gastric carcinoma presents many difficulties for the clinician because 80 to 90% of all patients with the disease are either diagnosed at an advanced stage when the tumour is inoperable, or develop a recurrence within five years.[4] Even patients who present with local tumours still die of the disease.

2.2. **Signs and symptoms** There are no signs or symptoms that are typically associated with early gastric carcinoma, and the condition may be diagnosed incidentally in a patient undergoing investigation for another complaint. Most symptoms of gastric carcinoma reflect advanced disease, such as indigestion, nausea or vomiting, dysphagia, postprandial fullness, loss of appetite, and weight loss.[5]

2.3. **Metastasis** Spread to the peritoneum is frequent, usually accompanied by ascites, and liver metastases are common. Spread to distant lymph nodes is very common. Cachexia is usually an early feature. In advanced cases more distant sites may be involved, such as peritoneal and pleural effusions, obstruction of the gastric outlet, gastroesophageal junction or small bowel, bleeding from oesophageal varices and jaundice.

2.4. **Surgical treatment** usually consists of partial or total surgical removal of the stomach, along with lymph node resection. Details of the extent and scope of the surgery vary between centres.[6] Adjuvant therapy may also be given, in the form of chemotherapy and/or radiotherapy.

2.5. **Chemotherapy** is now generally employed as a combination regimen and significantly improves survival in comparison to best supportive care. Best survival results are achieved with regimens containing 5-fluorouracil (5-FU), anthracyclines and cisplatin, and of these, ECF (epirubicin, cisplatin and continuous infusion 5-FU) is tolerated best.[7] Recent trials have shown that in patients with operable gastric or lower oesophageal adenocarcinomas, a perioperative (i.e. preoperative and postoperative) regimen of ECF decreased tumour size and stage and significantly improved progression-free and overall survival.[8] However there are now newer and less complex chemotherapy regimens with activity against advanced gastric cancer, and further clinical trials are awaited.[9]

2.6. **Radiotherapy** Gastric cancer is relatively resistant to radiotherapy and it was thought that adequate control of the primary tumour could only be achieved at a dosage which compromised adjacent structures such as bowel mucosa and the spinal cord. Until recently it was therefore largely employed as a palliative measure. However, concurrent chemotherapy and radiotherapy have been investigated as an adjuvant postoperative measure[10] and researchers have concluded that postoperative chemoradiotherapy should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastroesophageal junction who have undergone curative resection.[11]

2.7. **Gastric lymphoma** Gastric lymphomas may be of low-grade indolent type, or high-grade aggressive type. The condition usually occurs in patients over 40 years of age but can occur at any age. Gastric lymphomas often present with non-specific dyspepsia. Endoscopy reveals inflamed, sometimes eroded mucosa more suggestive of gastritis or peptic ulcer than a tumour mass. Low grade lymphoma is usually secondary to chronic *H. pylori* infection and may respond to elimination of the organism. High grade lymphoma is often treated in the same way as systemic lymphoma; medical treatment is usually effective in both varieties.[12]

3. Aetiology

3.1. The typical progression in **intestinal type tumours** is from chronic gastritis to chronic atrophic gastritis (usually mediated by *H. pylori* infection), followed by intestinal metaplasia of the gastric mucosa (replacement of the normal gastric mucosa with cells resembling intestinal epithelium). This may be followed in turn by dysplasia and ultimately carcinoma.[1] It is notable that in 90% of patients who develop gastric carcinoma, gastric acid production is lost decades before the development of the tumour. This succession of events probably results from the interaction of a number of factors related to diet, environment and individual genetic susceptibility, but the precise role of these various agents is at present undefined.[13,14,15] It is probable that *H. pylori* alone does not directly cause gastric cancer but appears to influence the development of the disease through the development of chronic atrophic gastritis.[16]

3.2. The development of the **diffuse type** follows a less clearly defined progression, although intestinal metaplasia is encountered frequently.

3.3. The development of gastric MALT **lymphoma** is thought to be a multi-stage process, involving the development of *H. pylori* gastritis, low-grade B cell lymphoma, and then high-grade B cell lymphoma. *H. pylori* infection probably elicits an immune response in which T cells and B cells are recruited to the gastric mucosa, where MALT is then formed. However, gastric lymphoma develops in only a very small percentage of individuals infected by *H. pylori*, and additional environmental, microbial, or genetic factors probably play a contributory role. So far, these factors have not been identified and studies have produced conflicting results.

3.4. **Genetic factors** Evidence for a genetic predisposition to the disease comes from both epidemiological studies and case reports of gastric cancer families. Clustering of the disease within families has been recognised for many years, and a number of studies suggest that first-degree relatives of patients with gastric cancer have a two- to threefold increase in the risk of contracting the disease.[17,18,19] An increased incidence of the disease, particularly the diffuse variety, has been reported in individuals with blood type A, an observation which lends further support for a genetic influence. The high incidence of gastric cancer in certain countries such as Japan may be due to genetic factors that cause specific varieties of response to sub-types of *H. pylori.*

3.5. A number of abnormalities have been identified in gastric cancer, most notably loss of heterozygosity (LOH) of tumour suppressor genes. The gene that has attracted most attention is the tumour suppressor gene p53. Initial studies found that LOH (60% to 70%) and mutations (38% to 71%) of the p53 gene are quite common in gastric cancer. Furthermore, p53 mutations are also common in intestinal metaplasia (38%) and gastric dysplasia (58%) (see 3.1 above), suggesting that mutations of the p53 gene may be an early event in the pathogenesis of the disease. The role of gastric adenomatous polyps is discussed later (3.9.14).

3.5.1. **Hereditary nonpolyposis colorectal cancer** (HNPCC) is a genetically-determined condition inherited as an autosomal dominant pattern with 70% to 80% penetrance of colorectal cancer. All first-degree relatives of a patient with HNPCC have a 50% risk of carrying one of the deleterious genes. One of the major subtypes, Lynch type II, is characterised by carcinomas in the colon and other organs including the stomach.

3.5.2. **Peutz-Jeghers syndrome** This is an autosomal dominant inherited disorder which is characterised by intestinal polyps and mucocutaneous melanocytic macules. There is a 15-fold elevated relative risk of developing intestinal cancer in this syndrome over that of the general population; cancer primarily is of the gastrointestinal tract. Patients with this syndrome carry a 29% lifetime risk for developing gastric cancer and a 36% risk of developing pancreatic cancer.[20,21]

3.6. **Chronic atrophic gastritis** Chronic atrophic gastritis may be defined as the presence of chronic inflammatory changes of the gastric mucosa which lead eventually to mucosal atrophy and intestinal metaplasia. The changes in the epithelium may become dysplastic and constitute a background for the development of gastric cancer. *H. pylori* infection, discussed below, is the commonest cause of chronic atrophic gastritis but there are a number of others, of which the most important is autoimmune gastritis. Patients with autoimmune gastritis have a significant risk for developing gastric cancer. Although this form accounts for less than 10% of cases of chronic gastritis, in severe cases it may lead to pernicious anaemia which carries a three-fold increase in gastric cancer risk.

3.7. ***Helicobacter pylori* infection** There is a strong association between *H. pylori* infection and gastric cancer. However, the precise mechanisms of this interaction are still unclear.[22,23,24] *H. pylori* are Gram-negative bacteria that have the ability to colonise and infect the human stomach. The infection is usually acquired during childhood and the organisms reside within the mucous layer that covers the gastric surface epithelium. The presence of this organism in the stomach is always associated with tissue damage and histologically apparent gastritis. Typically, the patient initially develops active gastritis, and small microabscesses may be formed. In disease of longer duration, gastric atrophy develops, with significant loss of gastric glands. In advanced stages of chronic atrophic gastritis associated with *H. pylori* infection, there is extensive replacement by intestinal metaplasia, and associated hypochlorhydria. The risk of gastric cancer increases exponentially with increasing grade of gastric atrophy and intestinal metaplasia.

3.8. **Social and occupational factors** A large number of social and occupational agents have been proposed as possible risk factors for gastric cancer and many occupations have been subjected to detailed scrutiny. Coal mining and construction work appear in some studies to present an increased risk of gastric cancer but no clear pattern has emerged.[25,26,27] Similarly, an excess risk of gastric cancer has in some studies been demonstrated in steel foundry workers, nickel and copper workers, metal component manufacturing workers and tin and gold miners. Oil refinery and other chemical industry workers have been found by some researchers to have an increased risk of the disease, and those employed in the rubber, leather and shoe industries and in the wood product industry. An increased risk of gastric cancer has also been found in such diverse occupations as coking plant workers, farmers, fishermen and jewellery workers.[28] In one series workers found an increased risk of gastric cancer among professional drivers in one Italian city, although numbers were small. Similar findings have been reported from a longitudinal study of London drivers[29] although this has not been confirmed.

3.8.1. **Workplace hazards** The authors of one large case control study point out that most studies of gastric cancer and occupation rely on poor environmental data, and are hampered by variation in occupational definition. Their study was based on data from 41,957 subjects who died from gastric cancer in 1984-1996, and evaluated the association of risk with a number of workplace exposures, including asbestos, inorganic dust, metals, polycyclic aromatic hydrocarbons, nitrosamines, herbicides and pesticides. They concluded that occupational factors appear to contribute little to the aetiology of

the disease.[30] Only a weak association between exposure to inorganic dust and risk of gastric cancer was found.

3.8.2. **Socioeconomic group** There is some evidence of an inverse association between gastric cancer and socioeconomic group. This does not appear to be related to lifestyle factors and is as yet unexplained. Indeed not all authorities agree with the premise and although higher levels of education were shown to have a protective effect (risk ratio of 0.6), in a prospective cohort study of 58,279 Dutch men followed for 4.3 years, there was no clear association of gastric cancer with socioeconomic group.[31,32] The association is therefore still in contention.

3.9. **Dietary and allied factors** Certain dietary factors have been associated with intestinal-type gastric cancer, and one commonly-held view is that different dietary components, in the presence of *H. pylori* infection, act in different ways in the succession of events described in 3.1 above.

3.9.1. **Diet low in fruit and vegetables** A high intake of fresh fruit and raw vegetables has been found by some investigators to protect against gastric cancer, with a reduction in risk of 30% to 50%.[33,34] The factors responsible for this observation are not known with certainty, but candidates include vitamins C and E, carotenoids (particularly beta carotene), and selenium. Conversely a diet deficient in these factors is thought to predispose to gastric cancer. However intervention studies with vitamin C supplements have not yet demonstrated chemopreventive activity; indeed as it is an acid it increases the risk of gastric erosions and gastric ulcers if taken in high doses. Furthermore in recent years, large-scale, randomised clinical trials have reached inconsistent conclusions regarding the ability of antioxidant agents to prevent cancer.

3.9.2. **The consumption of salted or poorly preserved foods** A number of studies have implicated salted food in the aetiology of gastric cancer. It is suggested that the use of high doses of salt over many years would result in the early onset of atrophic gastritis, so increasing the later risk of gastric cancer. Since the theory was proposed a number of studies have seemed to confirm that high salt consumption is associated with a greater risk of gastric cancer, but reliable quantitative data is lacking.

3.9.3. **Polycyclic aromatic hydrocarbons** These substances are a heterogeneous class of lipophilic compounds, many of which are carcinogenic and mutagenic. In experimental settings several have been reported to produce gastric tumours when administered orally. They are produced during the heating of foods to high temperatures or incorporated into foods that are cooked over a flame or smoked and are found in high quantities in grilled, charbroiled, and smoke-cured meats. However, dietary exposure to polycyclic aromatic hydrocarbons has not been fully evaluated in large populations.

3.9.4. **Nitrosamines** It has been suggested that nitrosamines originating in food or produced in the stomach from precursors may have a role in the aetiology of gastric cancer. Many nitrosamines are potent mutagens and stomach carcinogens in the experimental setting, and several studies have suggested an association between increased levels of nitrate in the diet or drinking water and the risk of gastric cancer. However nitrates themselves are not carcinogenic and dietary nitrate must first undergo reduction to nitrite, which in turn nitrosates other compounds in the stomach contents, thus producing nitrosamines. Despite this avenue of research human epidemiological studies have failed to observe a consistent relationship between dietary nitrate and gastric cancer. A large prospective cohort study analysed food and water nitrate and nitrite content in 120,852 men and

women. The mean follow-up was 6.3 years, and in the 282 cases of gastric cancer, there was no association with dietary nitrate intake.[35]

3.9.5. **Other foods** Other dietary elements that have been implicated as risk factors for gastric cancer include a high intake of fried food, and a diet which is generally high in fat. A high intake of red meat has also been thought to increase vulnerability to the disease,[36] and aflatoxins, metabolites of the fungus *Aspergillus flavus*, have also been implicated. However there is insufficient information to reach any definite conclusions regarding these possible dietary factors. A synergism between *H. pylori* infection and dietary salt intake has been proposed, but confirmatory data is lacking.[37]

3.9.6. **Excess alcohol ingestion** It has been held that excess alcohol ingestion is a risk factor for gastric cancer.[38] However a number of investigators have now shed doubt on the suggestion that alcohol is an independent risk factor for the disease.[39,40,41]

3.9.7. **Cigarette smoking** The relationship between smoking and stomach cancer has been recognised for some years and has been reported in a number of case-control studies. The association is thought to be particularly strong in heavy smokers and those who began smoking at a young age.[39,40,41,42]. The European Prospective Investigation Into Cancer and Nutrition (EPIC) project found a significant association between cigarette smoking and gastric cancer risk: the hazard ratio was 1.45, 1.7 and 1.8 for ever smokers, current male and current female smokers, respectively, and increased with intensity and duration of cigarette smoking. A number of other workers report a linear relationship between the number of cigarettes smoked per day and the risk of gastric cancer.[43,44,45,46,47] This dose-response effect is thought to represent one of the more compelling arguments for a causal relationship.[48] In one meta-analysis of 40 studies examining a quantitative link between smoking and gastric cancer the authors concluded that 11% of all cases of the disease may be attributed to tobacco smoking each year.[49]

3.9.8. The risk of gastric cancer among *H. pylori*-infected individuals is further increased by smoking. A cohort of almost 33,000 Swedish city residents was investigated over a period of 8 years. The proportion of current smokers was 61% among gastric cancer cases, versus 41% among controls. *H. pylori* seropositivity was present in 82% of the cases and 49% of the controls. The authors conclude that the risk of gastric cancer in *H. pylori*-infected current smokers is 11 times that of non-infected individuals not currently smoking.[50]

3.9.9. In most cases low grade gastric lymphoma regresses completely following antibiotic therapy designed to eliminate *H. pylori* infection, but it is not clear whether this can suppress the disease in the long-term or change overall survival. However the aetiological role of the organism in these cases is generally accepted. The cause of the more aggressive cases of gastric lymphoma is however unknown, although some appear to evolve from the low-grade form.

3.9.10. It is proposed by some authorities that smoking and exposure to coal dust may have a synergistic effect, whereby the two factors interact locally to promote gastric carcinogenesis.

3.9.11. **Precursor conditions** The disease is more likely to develop in the presence of other conditions. These include:

- Previous partial gastrectomy

- Gastric adenomatous polyps
- Ménétrier's disease

3.9.12. **Previous subtotal gastrectomy** Gastric ulcers themselves do not appear to predispose to gastric cancer. However, patients who have a gastric remnant after subtotal gastrectomy for benign disorders have a relative risk of gastric cancer of 1.5 to 3.0 by 15 to 20 years after surgery. The reason for this is unknown.

3.9.13. **Gastric adenomatous polyps** A higher risk of gastric carcinoma has been reported in patients with gastric adenomatous polyps. These are uncommon, usually solitary growths which consist of localised, polypoid proliferations of dysplastic epithelium. Although their cause is unknown they most often arise in patients who have gastric mucosal atrophy and intestinal metaplasia. Furthermore, some gastric adenomatous polyps themselves undergo neoplastic progression to infiltrating adenocarcinoma.[51] The overall incidence of malignant transformation in adenomatous polyps is about 3.4%.

3.9.14. **Ménétrier's disease** This is a rare condition, characterised by giant gastric folds and epithelial hyperplasia. It is typically associated with protein-losing gastropathy and hypochlorhydria, and the incidence of gastric adenocarcinoma in these patients is said to be about 15%.

3.10. **Epstein-Barr virus (EBV) infection** The role of this virus in the aetiology of gastric cancer is uncertain. The organism is detected in the tissue of about 10% of gastric cancer cases throughout the world, and in each case, 100% of carcinoma cells are infected with EBV.[52] However, recent work suggests that EBV can only infect neoplastic gastric cells and thus is a late event in gastric carcinogenesis.[53]

4. Prognosis

4.1. Survival rates for gastric cancer depend upon site, tumour penetration, lymph node invasion, and dissemination. Only 10% to 20% of all cases are diagnosed in the early stages and the remaining patients present with metastatic disease. The overall 5-year survival rate ranges from almost no survival if the disease is widely disseminated to almost 50% survival for patients with earliest-stage distal gastric cancer. In proximal gastric cancer even when apparently localised, the 5-year survival rate is only 20% to 30% at best, and the majority of patients who present with local tumours still die of the disease. Palliative treatment of disseminated gastric cancer may result in improvement of symptoms and some prolongation of life, but long remissions are rare.

4.2. Treatment with surgery alone has a high failure rate, and one study reported a local recurrence rate of 80%. However adjuvant chemoradiotherapy has improved survival rates.[4,54]

4.3. The mortality rate within 30 days after a surgical procedure for gastric cancer is in the region of 1-2%. Early complications of surgery include failure of the anastomosis, ileus, bleeding, cholecystitis due to infection, pancreatitis, chest infections, and embolism. Late complications include dumping syndrome, vitamin B12 deficiency, reflux oesophagitis, osteoporosis and immunological deficiency.

4.4. In metastatic and advanced disease, the median survival is 3-4 months with best supportive care. Chemotherapy regimens have response rates of 11-20 percent with 5-fluorouracil chemotherapy alone, and up to 40% with combination regimens which improve median survival to approximately 9 months. Long term survivors beyond 3 years are rare once cancer has spread from the stomach.

4.5. MALT lymphoma is not usually at an advanced stage when diagnosed and is slow to disseminate. For this reason low-grade MALT lymphomas respond favourably to therapy and overall survival is approximately 90 per cent at 10 years. The survival for diffuse large B cell lymphoma is significantly worse, in the region of 45 per cent at 10 years.

4.6. In many Asian studies, patients with the disease tend to have better outcomes than similarly staged patients treated in Western countries. The reason for this is unknown, but some researchers suggest that it reflects a fundamental biological difference between the disease as it manifests itself in Asia and in Western countries. An additional explanation may be that the effects of endoscopic surveillance – for example in Japanese populations – identifies early gastric cancer, with favourable outcomes.

5. Summary

5.1. Gastric cancer is the second most common cause of cancer-related death in the world and exhibits very marked geographical variation.

5.2. The disease almost certainly arises as a result of the interaction of dietary, environmental and genetic factors, but the precise role of these various agents is at present unclear. However, *H. pylori* appears to play a central role in the pathogenesis.

5.3. The prognosis depends upon the stage of the disease when first diagnosed, but in general recurrence rates are high and the aggregate 5-year survival rate is less than 15%.

6. Related Synopses

Cancer of the Oesophagus

Colorectal Cancer

7. Glossary

adenocarcinoma	A form of cancer that forms from cells originating in the lining of the walls of certain organs.
anastomosis	An opening or communication created by surgical, traumatic or pathological means between two normally separate spaces or organs.
Aspergillus flavus	A species of fungus which produces the carcinogenic substance aflatoxin.
atrophic	Wasting, diminution in size.
autoimmune	Of an illness which occurs when the tissues are attacked by the body's own immune system.
autosomal dominant	Requires that only one parent need have the trait (characteristic) in order to pass it to the offspring.
Barrett's dysplasia	A disorder in which the lining of the oesophagus undergoes cellular changes as a result of chronic irritation and inflammation of acid reflux.
cachexia	The appearance of widespread wasting of the body.
cardia	The part of the stomach immediately adjacent to and surrounding the lower opening of the oesophagus.
cholecystitis	Inflammation of the gall bladder.
distal	More remote, farther from any point of reference, opposed to proximal.
dysphagia	Difficulty swallowing.
dysplasia	Abnormality in size, shape and organisation of adult cells. Hence *dysplastic*.
effusion	The escape of fluid into a part or tissue; hence peritoneal effusion into the peritoneal cavity, and pleural effusion into the pleural cavity.
embolism	The sudden blocking of an artery by a clot carried by the bloodstream.
familial adenomatous polyposis	Genetic disease characterised by numerous precancerous polyps in the colon and rectum.
gastritis	Inflammation of the stomach.
gastroesophageal junction	Junction of the oesophagus and stomach.

heterozygosity	Having two versions of the same gene, one version on one chromosome and the second version on the other.
hypochlorhydria	Abnormally low level of acid in the stomach.
ileus	An obstruction of the intestine due to paralysis of its normal muscular movement.
intestinal metaplasia	The transformation of normal mucosa, particularly in the stomach, into glandular tissue resembling that of the intestine.
lipophilic	Having an affinity for fat.
lymphoblast	A differentiation of a T or B lymphocyte, brought about by infection.
lymphocyte	White cell of the blood derived from stem cells of the lymphoid series. There are two main classes; T and B lymphocytes.
lymphoid tissue	Tissue that is particularly rich in lymphocytes and accessory cells, particularly the lymph nodes, spleen, thymus, Peyer's patches, tonsils and adenoids.
macule	A small patch of skin that is altered in colour but usually not elevated.
melanocytic	Relating to special cells in the skin and the eye that synthesise melanin pigments.
mucocutaneous	Pertaining to the skin and mucous membranes, i.e. inner lining of body cavities/passages that communicate with the exterior.
mucosal	Pertaining to the membrane that lines body cavities.
mutagenic	A permanent change in genetic material that can be transmitted to future generations.
neoplastic	New growth, usually cancerous.
oesophagitis	Inflammation of the oesophagus.
osteoporosis	A reduction in bone mass.
pancreatitis	Inflammation of the pancreas.
penetrance	The proportion of individuals with a specific genetic characteristic who demonstrate its effect.
Peyer’s patches	Follicles similar in many ways to lymph nodes, located in the small intestine. In adults, B lymphocytes predominate in Peyer's patches.

pernicious anaemia	A type of anaemia associated with a reduced ability to absorb vitamin B12 due to the absence of intrinsic factor.
proximal	Nearest to or closer to any point of reference, as opposed to distal.
reflux	Reversal of the normal direction of flow.
seropositivity	Having a positive serum reaction especially in a test for the presence of an antibody.
varices	Uneven, permanent dilatation of veins. *Sing* varix.

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