*Ministry of Defence*

# Synopsis of Causation

## Stroke
## (including Subarachnoid Haemorrhage)

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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. The term **"stroke"** is used to describe a sudden onset of neurological deficit due to vascular disease.

1.1.1. Stroke can be divided into ischaemic (70-80%) and haemorrhagic (20-30%) types. Ischaemic stroke can be further divided into large vessel and small vessel disease, and into thrombotic and embolic types, the latter being more common.

1.1.2. If the interruption is temporary and no infarction has occurred, this is called a transient ischaemic attack or TIA. TIAs usually last about 10 to 15 minutes, but can persist for up to 24 hours.

1.1.3. Occlusion of cerebral veins or dural sinuses can also produce a stroke syndrome.

1.2. **Subarachnoid haemorrhage** may mimic stroke clinically but should be considered as an entirely separate entity in view of its different pathophysiology and aetiology. Consequently, information on this condition is presented separately in section 6 of this synopsis.

1.3. **Subdural haemorrhage** is bleeding between the dura and pia mater and is usually traumatic in origin. The condition is unrelated to stroke and is not considered in this synopsis.

# 2. Clinical Features

2.1. Stroke affects between 174 and 216 per 100,000 population in the UK each year.[1,2] It accounts for 11% of all deaths in England and Wales. The incidence approximately doubles for every decade after 45 years, rising from 104 per 100,000 per year at ages 45-54 to 1113 per 100,000 per year at ages 75-84.

2.2. Stroke is generally regarded as a disease of the elderly, but about 30% occur under the age of 65. In this younger age group, a cause other than atheroma is more likely. Stroke is generally more common in males than in females.

2.3. The clinical picture is often unhelpful in distinguishing the cause of the stroke. With thrombosis of the cerebral veins or dural sinuses, headache is usually a prominent feature, and may precede a stroke by several weeks. Seizures are sometimes seen, and secondary haemorrhage may occur into areas of infarction. The neurological deficit develops over a matter of minutes or hours.[3] It is not uncommon for a person to wake up with a fully developed stroke.

2.4. The commonest presentation is with a unilateral motor deficiency (hemiparesis). Weakness may be localised to the region supplied by the cranial nerves, although this is very rare, or to the upper limb or lower limb only. Alternatively, the weakness may be more extensive, affecting two adjacent areas or even all three. Rarely, both sides of the body are affected. The exact manifestations depend on the area of ischaemia. Weakness of the face is usually unilateral with face drop and drooling. Although a stroke produces an upper motor neurone lesion, the clinical features may resemble Bell's palsy, which is a lower motor neurone lesion of the 7th cranial nerve.

2.5. The distribution of weakness/dysfunction can usually be related to a vascular territory. Hemiparesis occurs with cortical signs such as dysphasia and neglect if the anterior circulation is affected, or alone or with brainstem features in posterior circulation stroke.

2.6. Sensory loss can occur with stroke, but motor loss is more common. Both can be present. The level of consciousness is often affected initially, and there may rarely be complete loss of consciousness. Sometimes there is loss of vision in one or both eyes or visual field defects. Diplopia may occur if the external muscles of the eye are involved.

2.7. Brainstem and cerebellar lesions can cause dysarthria, vertigo and ataxia. Dysarthria or dysphasia is often associated with motor loss, as the speech area is close to the motor cortex.

2.8. Various combinations of presentations may occur, depending on the anatomy of the area involved. Sensory loss usually affects an arm and a leg or an arm and the face on the same side of the body. Sensory loss with a stroke usually affects all digits, unlike peripheral nerve lesions, where more specific areas are usually affected.

2.9. Examination of the cardiovascular system may reveal a reason for generation of emboli such as atrial fibrillation or abnormal heart valves. ECG may confirm atrial fibrillation or reveal a myocardial infarction that may be associated with a mural thrombus. Echocardiography may demonstrate thrombus in the atrium, on the wall of the ventricle or any abnormality of the valves. Brain imaging techniques include computerised

tomography (CT) and magnetic resonance imaging (MRI) which can confirm the nature and extent of the lesion, and MRI especially may give an indication of the integrity of blood vessels in both the head and neck. Carotid duplex scanning is a useful investigation to determine the extent of atheroma in the carotid arteries.

2.10. Transient ischaemic attack (TIA) is a syndrome characterised by an acute loss of focal brain or eye function with symptoms lasting less than 24 hours. It affects 35 people per 100,000 per year. A third of those who have a TIA will develop a full stroke at some stage, although not necessarily in the same anatomical area.

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# 3. Aetiology

3.1. Cerebral infarction accounts for 69% of strokes, primary haemorrhage for 13%, and 18% are due to other causes.[4]

3.2. **Ischaemic stroke:** The main predisposing factors for stroke are hypertension (which demonstrates a linear relationship) and age. A positive family history is significant. For individuals who have experienced a TIA, the commonest causes of death subsequently are myocardial infarction and stroke. A TIA may be an indicator of general atheroma. The risk factors are all modifiable,[5] and they include:

- Blood pressure. The recommended target is 140/85 mmHg or less[6] except in people with diabetes where the target should be 130/80 mmHg or less[7]. Under normal circumstances, autoregulation maintains a constant cerebral blood flow at mean arterial pressures ranging from 50-170 mmHg
- Cholesterol is important, but probably makes less contribution to the overall risk in stroke than it does in coronary heart disease. Total cholesterol is a risk factor but high density lipoprotein (HDL) cholesterol is protective, and so the ratio of total cholesterol to HDL cholesterol is a more accurate indicator
- Smoking is a critical risk factor
- Diabetes, especially type 2, also increases risk. Good control of diabetes has a beneficial effect in lessening the risk
- Overweight status (or elevated body mass index (BMI)), diet, lack of exercise, salt and alcohol consumption all contribute, possibly through their effects on blood pressure and cholesterol

3.3. In ischaemic stroke, the possible presence of a source of **emboli** should be considered. The commonest site is an atheromatous plaque in the carotid arteries in the neck. There may be partial or even complete occlusion. If occlusion is 70% or more, there is often benefit from carotid endarterectomy. Another common source of emboli is the heart. Atrial fibrillation, especially if associated with dilatation of the atrium, is an indication for anticoagulation because this significantly reduces the likelihood of thrombi forming in the left atrium. A mural thrombus may follow a myocardial infarct, especially if there is aneurysm of the anterior wall of the left ventricle. Emboli can also originate from heart valves. These may be due to a thrombotic event, arising from a replaced mitral or aortic valve, or from vegetations caused by subacute bacterial endocarditis.

3.4. When an ischaemic stroke occurs in a younger patient, the underlying cause is less likely to be attributable to atheroma than in an older person. In such circumstances, likely causes include:

- Dissection of an extra-cranial vessel, which may occur in predisposed individuals following neck extension injury
- Paradoxical embolisation of a venous thrombus that enters the arterial circulation through a patent foramen ovale. This may occur when the direction of blood flow through the defect is reversed (right-to-left shunting), a situation that is facilitated during the Valsalva manoeuvre
- Drug or substance misuse

3.5. Conditions that predispose to venous or arterial thrombosis include pregnancy, use of a combined oral contraceptive or, to a lesser extent, hormone replacement therapy.[8] The risk of stroke is also increased in a number of haematological conditions including those that give rise to an increased number of platelets in the blood such as the myeloproliferative diseases. Polycythaemia increases blood viscosity and the risk of sludging. Antiphospholipid syndrome also needs to be considered.

3.6. **TIAs** are due to temporarily inadequate cerebral or ocular blood supply as a result of low blood flow, arterial spasm, thrombosis, or embolism.[9]

3.7. **Primary intracerebral haemorrhage** may be associated with severe hypertension or an abnormality of the blood vessels. It is worth noting that abuse of cocaine often causes a large transient rise in blood pressure and that this may play a part in triggering a haemorrhagic stroke. Stroke has occasionally also been associated with the use of cannabis.[10]

3.8. Occlusion of cerebral veins or dural sinuses may occur for no apparent reason, but usually arises in the setting of thrombophilic factors. These situations, in which there is an increased tendency to thrombosis, include the inherited hypercoagulable states such as factor V Leiden and acquired disorders such as disseminated malignancy. Risk factors include the post-partum period, the contraceptive pill, dehydration or, more rarely, intracranial infection or infection of the ear or sinuses. This event can produce a stroke syndrome, subarachnoid haemorrhage or isolated raised intracranial pressure.

3.9. Migraine, especially with aura, is weakly associated with an increased risk of ischaemic but not haemorrhagic stroke. As the use of combined hormonal contraceptives constitutes an independent risk factor for ischaemic stroke, a range of contraindications and special precautions applies to the prescription of such drugs to women who suffer from migraine.[11,12]

3.10. Heavy consumption of alcohol is sometimes suggested as an independent risk factor for stroke, but the effects are difficult to evaluate as alcohol intake raises blood pressure and high consumption is often associated with smoking and lack of exercise. The possible role of binge drinking in the aetiology of stroke is also difficult to assess, since there is no reliable data.

3.11. A raised haematocrit is known to increase the risk of stroke. The haematocrit rises with dehydration and in various medical conditions that cause an increased number and volume of red blood cells. However, as the haematocrit is also raised by the effect of carbon monoxide in tobacco smoke, it is difficult to substantiate this factor as an independent variable.

3.12. Vigorous exercise, especially in a hot environment, will lead to dehydration, concentration of the blood and an increased risk of blood sludging in the vessels. These effects are almost certainly short-lived, but every reasonable effort should be made to limit dehydration during vigorous exercise, including the avoidance of heavy alcohol consumption shortly beforehand, because the diuretic effect of alcohol will, in itself, lead to dehydration. On the other hand, regular exercise is beneficial in reducing the risk of stroke. Endurance training appears to increase total blood volume but, as the increase is especially evident with regard to the plasma volume, this feature appears to offer protection against acute dehydration during endurance exercise.[13]

3.13. A number of authors have investigated the relationship between stress, including post-traumatic stress disorder (PTSD), and stroke. Stress reactions may arise in response to a wide range of external stimuli. These stimuli may be mental or physical, and either of these can be acute or chronic. Acute mental stress can be caused by accidents, natural disasters, assaults or warfare. Chronic mental stress is associated with psychosocial factors such as family conflict, terminal illness in the family, financial worries, divorce, and redundancy, or various workplace factors including time pressures, excess working hours and bullying. Physical stressors include very high or low external temperature, extreme exertion, injury, pain and sleep deprivation. A number of these factors may coexist, and they may also be inter-related. The net effects of acute stress are mediated mainly through secretion of adrenaline and noradrenaline, and these raise blood pressure, heart rate, fibrinogen levels, haematocrit and blood viscosity, all of which may in theory predispose to stroke.[14] Chronic stress elicits a more complicated neuroendocrine response, the effects of which are less predictable. Direct evidence linking stress with stroke is inconclusive and is certainly not of the same order as that with heart disease. The difficulties in evaluating the evidence are compounded by the fact that there is no consensus on how stress should be measured.

3.13.1. One small controlled study found a doubling of the incidence of stroke within a year of exposure to severely threatening long-term stressors, a description applied to such events as bereavement, break-up of an intimate relationship and job loss.[15] Prior risk factors for stroke were comparable with a control group. The increased risk was manifested throughout the one year following the onset of the event, not merely in the immediate aftermath.

3.13.2. One paper from Serbia reported an association between exposure to conflict and the risk of stroke,[16] but detail is lacking, and it is extremely difficult to assess the validity of the evidence, particularly in relation to causality and confounding factors.

3.13.3. A group from Croatia demonstrated increased susceptibility to cerebral vasospasm in men who had been in conflict situations,[17] but again detail is lacking, and no direct association with stroke was shown.

3.13.4. One Swedish study demonstrated an increase in strokes in hypertensive men shown in experimental conditions (serial colour-word tests) to adapt poorly to changing circumstances.[18] The authors propose that this adaptive pattern might also in life predispose to stroke, but they present no supporting evidence for this.

3.13.5. A large study from Denmark found an increase in the rate of fatal strokes in people who reported feeling highly stressed at least once weekly.[19] However, the subjects who reported stress also had more in the way of established adverse risk factors for stroke, and there was no association between non-fatal stroke and self-reported stress. The authors concluded that their study provided no evidence for an independent effect of stress as a risk factor for stroke.

3.13.6. Overall, the quality of available evidence relating stress and stroke is poor, and there is no convincing evidence of an important causal relationship.

3.14. There are no demonstrable associations between stroke of any type and exposure to ionising or non-ionising radiation, except when a patient has received radiotherapy to

the neck for laryngeal carcinoma, in which case there is a risk of inducing carotid artery stenosis. Specifically, there is no increased frequency of stroke in service personnel who participated in the UK's atmospheric nuclear weapons tests.[20]

# 4. Prognosis

4.1. Until fairly recently the management of stroke was purely expectant. Nowadays it is much more active. There is very good evidence that prognosis is improved if the patient is managed in a dedicated stroke unit. In such a unit, early thrombolysis is possible and, used appropriately, this improves outcome, both in terms of immediate survival and in subsequent degree of recovery.[21] Although clinical features are unhelpful in distinguishing between ischaemic and haemorrhagic stroke, CT or MRI scanning in the early hours after an event can differentiate between the two types.[22] However, interpretation of the images is not easy and requires considerable experience. Provided that a scan has confirmed an ischaemic area and less than 3 hours have passed since the onset of symptoms,[23] thrombolysis is an effective intervention.[24] However, this is a much more high risk intervention than thrombolysis for myocardial infarction, and the Royal College of Physicians is insistent that strict protocols must be followed.[25] As well as such risks as gastro-intestinal bleeding, as may occur with thrombolysis for myocardial infarction, there is risk of haemorrhage into the infarcted area of brain. In addition, if a scan had been misread and thrombolysis was given for a haemorrhagic rather than ischaemic event, the consequences would be disastrous. Such an error is unlikely, but always possible.

4.2. In the acute stage, blood pressure should be lowered only in malignant hypertension. Otherwise it is better to wait 2 weeks before starting treatment, since a reduction in diastolic blood pressure of 20 mmHg or more carries a three-fold increase of adverse outcome.[26]

4.3. In the beginning, attention is directed towards preventing extension of the infarction, and active management may reduce the risk of complications such as pneumonia, deep vein thrombosis, pressure sores and urinary tract infection. Longer-term management includes addressing the many risk factors to reduce the chance of a further episode or myocardial infarction.

4.4. The overall mortality of strokes is 20%, although this varies greatly between hospitals and with a variety of other factors including type of stroke, age of the patient and comorbidity. Of the survivors, it is estimated that 10% have no residual defect, 80% respond to rehabilitation, whilst the remaining 10% are unable to participate in rehabilitation.

4.5. In those who survive, muscle strength tends to reach a plateau faster than functional recovery because control of movement also needs to be regained. Maximum neurological recovery has been achieved by 11 weeks in 95% of patients and maximum functional recovery by 12½ weeks, as subtleties of movement are re-learned. Although recovery proceeds most rapidly in the first 3 months, improvement may continue for more than a year.[27] By the end of the first year 75-85% of patients are walking, 48-58% are independent in activities of daily living and 10-29% require residential care.[28]

4.6. Less high quality function is usually regained in the arms than in the legs. Lack of early improvement and grip strength at 4 weeks carries a poor prognosis for functional recovery.[29] Early evaluation of effective movement of an arm or leg is a simple way of making a fairly reliable assessment of functional prognosis.[30] Language improves unevenly. Improvement of dysphasia appears to occur independently of recovery from

hemiparesis. Persistence of poor swallowing ability at 3 weeks carries a high mortality rate, probably because of inhalation.[31]

4.7. Outcome is worse in those with diabetes, ischaemic heart disease, previous stroke, previous dependence on others, sensory and visual loss, severe motor deficit, loss of consciousness, cognitive defects and incontinence.

4.8. The use of certain drugs may have an adverse outcome on recovery from stroke. These include benzodiazepines, phenytoin, barbiturates, and some hypotensive agents such as clonidine and prazosin. Even single doses may have long-term harmful effects.[32] However, given the relative uncertainty of the clinical evidence, these drugs should not be withheld if the clinical indications for their use are strong.

4.9. Active attention to blood pressure, cholesterol and control of diabetes is important to reduce subsequent mortality and morbidity.[33]

4.10. It is now realised that the risk of stroke following TIA is much higher than previously thought. This is because many studies of TIA patients who have already suffered stroke have been excluded from earlier estimates. When looking at stroke, approximately 30% of people reported preceding TIA and the risk of stroke following any TIA may be as high as 10% in the first week.

# 5. Summary

5.1. The term **"stroke"** is used to describe a sudden onset of neurological deficit due to vascular disease. Stroke can be divided into ischaemic (70-80%) and haemorrhagic (20-30%) types. Ischaemic stroke can be further divided into large vessel and small vessel disease, and into thrombotic and embolic types, the latter being more common.

5.2. The interruption of blood flow may be temporary, without any irreversible damage occurring. Attacks of this nature last from a few minutes up to 24 hours, and are called transient ischaemic attacks or TIAs.

5.3. Occlusion of cerebral veins or dural sinuses can also produce a stroke syndrome.

5.4. The main risk factors are high blood pressure, smoking, family history of stroke or heart disease, raised cholesterol and overweight. Physical and psychological stress may also contribute, but the evidence for this is not strong. Stroke is probably most often due to a combination of risk factors being present at the same time.

5.5. Clinical presentation depends on the site and nature of the disturbance of blood flow.

5.6. Prognosis, as with clinical features, depends on the site, nature and severity of the disturbance of blood flow, and also on whether hyper-acute treatment is available and whether the patient is looked after by a trained and co-ordinated stroke team.

# 6. Subarachnoid Haemorrhage

6.1. Subarachnoid haemorrhage (SAH) is bleeding from a cerebral blood vessel, aneurysm or vascular malformation into the subarachnoid space. Although the condition may mimic stroke clinically, it should be considered as an entirely separate entity in view of the different pathophysiology and aetiology.

6.2. Subarachnoid haemorrhage usually presents with sudden onset of headache and vomiting, with or without loss of consciousness. It affects 6-12 people per 100,000 each year and, especially in the younger age group, occurs more frequently in women.

6.3. Approximately 85% of patients with subarachnoid haemorrhage bleed from an intracranial aneurysm, 10% from a non-aneurysmal peri-mesencephalic source and 5% from other vascular abnormalities including arteriovenous malformations.[34] Many of these vascular abnormalities are probably present from birth and the majority never give rise to any problems. Apart from rises in blood pressure, the exact factors that cause some to bleed are poorly understood.

6.4. The commonest source of a subarachnoid haemorrhage is bleeding from a **berry aneurysm,** a small round aneurysm protruding from a cerebral blood vessel. 90% occur in the anterior part of the circle of Willis and 20-30% are multiple. There may sometimes be a family history and they are often referred to as congenital, but this is a misnomer since they are not discernible at birth.[35] They rarely present below 10 years of age. Certain diseases of connective tissue predispose to their development. These include polycystic kidneys, Ehlers-Danlos syndrome type IV, neurofibromatosis type I and Marfan's disease. Other accepted contributing factors are cigarette smoking and hypertension. Berry aneurysms can be found in 2% of people at post mortems that are carried out for other causes of death.

6.5. Other rare causes of aneurysms also carry an attendant risk of SAH. Charcot-Bouchard aneurysms affect tiny blood vessels and may cause multiple small haemorrhages. Mycotic aneurysms are due to infection of the arterial wall with the fungus *Aspergillus*, which results in damage and weakening.

6.6. Prognosis in subarachnoid haemorrhage depends on a number of factors, primarily age, Hunt and Hess grade (see below), location of the aneurysm, and smoking history. Younger patients tend to fare better. Smoking adversely affects the prognosis. Anterior circulation aneurysms carry a better prognosis.

6.7. Hunt and Hess suggested a clinical grading system, ranging from 0 (unruptured aneurysm) to 5 (deep coma, decerebrate rigidity, moribund appearance).[36] Grades 1-3 are associated with a good outcome. These are the patients who are suitable for early surgery. Grades 4 and 5 indicate a poor prognosis, and these patients need supportive treatment and improvement to grade 3 before surgery can be undertaken.

# 7. Related Synopses

Atherosclerosis

Atrial fibrillation

Hypertension

Migraine

# 8. Glossary

| | |
|---|---|
| aneurysm | Dilatation of a blood vessel caused by weakening of the vessel's wall. |
| anticoagulation | Thinning of the blood with drugs to prevent clotting. |
| ataxia | Failure of co-ordinated muscle movements. |
| atheroma | Fatty deposits (plaques) that build up inside an artery. Hence: *atheromatous*. |
| atrial fibrillation | Irregular beating of the heart due to rapid and uncoordinated atrial electrical activity. |
| aura | Abnormal sensations or disturbances of perception preceding migraine. |
| brainstem | The medulla oblongata, midbrain and pons. The part of the brain concerned with control of basic physiological functions. |
| cerebellar | Relating to the cerebellum of the brain. This controls balance and co-ordination of movement. |
| cerebral | Relating to the brain. |
| circle of Willis | A circle of arteries at the base of the brain. It is formed by the internal carotid arteries and the basilar artery. |
| cognitive | Referring to the ability to think, learn and remember. |
| cortex | The superficial part of the brain containing the bodies of the neurones. |
| cranial nerves | Nerves with origins within the skull. |
| diastolic | During the phase of the cardiac cycle when the ventricles are not contracting. |
| dilatation | Increase in diameter, stretching. |
| diplopia | Double vision. |
| duplex scanning | A method of ultrasound scanning used to investigate blood flow. |
| dural | Relating to the dura mater, the outer membrane covering the brain and spinal cord. |

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|---|---|
| dysarthria | A problem with speech due to difficulty with articulation resulting from a disorder of muscle control or structural damage to the organs of speech. |
| dysphasia | Non-mechanical difficulties with speech, problems with finding or understanding words. |
| echocardiography | A technique which uses ultrasound waves to make images of the heart chambers, valves and surrounding structures. |
| embolism | The sudden blocking of an artery caused by a clot carried by the blood flow. Hence: *embolic*. |
| endarterectomy | A surgical procedure to alleviate obstruction of a blood vessel due to atheromatous *(q.v.)* plaque. |
| endocarditis | Inflammation of the inner lining of the heart. |
| fibrinogen | A blood protein involved in the clotting process. |
| foramen ovale | An oval hole in the foetal heart between the right and left atria, which normally closes shortly after birth. |
| haematocrit | The proportion of the blood occupied by red blood cells. |
| haemorrhagic | Due to bleeding. |
| hemiparesis | Paralysis of one side of the body. |
| hypotensive | Associated with low blood pressure. |
| infarction | Death of tissue due to lack of blood supply. |
| intracranial | Inside the skull. |
| ischaemic | Due to lack of blood supply. |
| lower motor neurone | The nerve cell found in peripheral nerves. Damage causes wasting of muscles and a flaccid weakness. |
| mural | Refers to a wall (usually of the heart). |
| myeloproliferative diseases | Malignant conditions originating from the bone marrow. |
| myocardial | Refers to the heart muscle. |
| neurone | Nerve cell. |
| occlusion | Blockage. |
| peri-mesencephalic | In the region surrounding the midbrain. |
| pia mater | The innermost membrane surrounding the brain and spinal cord. |

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|---|---|
| polycythaemia | A malignant condition of the bone marrow resulting in excess production of red blood cells. |
| sinus | A cavity. In the context of this file, refers to spaces in the bones of the skull filled with venous blood. |
| subarachnoid | Between the middle membrane covering of the brain and the brain itself, within the cerebrospinal fluid-filled spaces surrounding the brain. |
| thrombolysis | The use of drugs to break up a blood clot. |
| thrombosis | Formation of a blood clot. |
| thrombus | A blood clot. Hence: *thrombotic*. |
| upper motor neurone | A nerve cell with its body in the brain which transmits impulses to lower motor neurones in the spinal cord. |
| Valsalva manoeuvre | Attempted exhalation against a closed glottis or against a closed mouth and nose, which raises intrathoracic and intra-abdominal pressure. |
| vegetations | Frond-like growths on the heart valves consisting of platelets and fibrin, associated with bacterial infection. |
| vertigo | Dizziness or abnormality of balance that usually causes a spinning sensation. |
| viscosity | Stickiness (in relation to flow). |

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