UKRAINIAN MINISTRY OF HEALTH CARE

STATE MEDICAL UNIVERSITY OF UKRAINE

“UKRAINIAN ACADEMY OF MEDICINE AND DENTISTRY”

CLINICAL MEDICINE

Part 2. INTERNAL MEDICINE:

DISEASES OF RESPIRATORY, GASTROINTESTINAL, URINATION, ENDOCRINE, BLOOD SYSTEMS, ALLERGY AND IMMUNEDEFICIENCE

EDUCATIONAL MATERIALS FOR INDEPENDENT STUDY WITH TESTS AND EXPLANATIONS INCLUDED

FOR FOUR GRAD DENTAL FACULTY STUDENTS

Lesson 1. DISEASES OF RESPIRATORY SYSTEM.

Lesson 2. GASTROINTESTINAL SYSTEM.

Lesson 3. URINATION SYSTEM.

Lesson 4. ENDOCRINE SYSTEM.

Lesson 5. BLOOD SYSTEM.

Lesson 6. ALLERGY AND IMMUNEDEFICIENCE.

PULMONOLOGY

Asphyxia

Asphyxia can literally be translated from the Greek as meaning 'absence of pulse', but is usually the term given to deaths due to 'anoxia' or 'hypoxia'.

The term 'asphyxia' is thought by some forensic pathologists to be a vague and confusing term. In its broadest sense it refers to a state in which the body becomes deprived of oxygen while in excess of carbon dioxide (ie. hypoxia and hypercapnoea). This results in a loss of consciousness and/or death. However, prior to any death the body usually reaches a low oxygen-high carbon dioxide state, and so an 'asphyxial' death is therefore one in which the oxygen deprived state has been achieved unnaturally.

Categorising asphyxial deaths

- Neck Compression
- Chest Compression
- Postural/ Positional Asphyxia
- Airway Obstruction
- Exhaustion or Displacement of Environmental Oxygen

Neck Compression

Mechanisms of Death

- **mechanical constriction/ squeezing of the soft tissues of the neck** - the most common mechanism is that of compression of the jugular veins, with or without that of the carotid arteries, leads to reduced oxygen reaching the brain, loss of consciousness, and if sustained for a sufficient interval (minutes) death. The time interval of compression to loss of consciousness is approx. 10 secs if both carotid arteries are compressed and a minute if only the jugulars are compressed. The time interval from loss of consciousness to death is said to be in the region of minutes.

- **airway obstruction** - this is a contributory factor in some hangings, where the hyoid bone and tongue are pushed upwards and backwards against the laryngo-pharynx. This type of obstruction produces 'air hunger', which is a frightening sensation and which is not a feature of vascular compression in the neck.

- **cardiac arrhythmia** - this is a controversial postulated mechanism whereby pressure over the carotid artery at the carotid sinus provokes a reflex slowing of the heart (bradycardia), which may provoke a fatal arrythmia (particularly in the elderly or those with underlying cardiac disease). This mechanism is unlikely to be responsible where there are petechiae or congestion which would suggest that the heart had been beating for a more lengthy period than this mechanism would support.

Classic signs of asphyxia ...

- congestion of the face - due to venous congestion (venous return to the heart is prevented)
- facial oedema - increased venous pressure causes tissue fluid transudation (remember those Starling forces !)
- cyanosis - excess de-oxygenated haemoglobin in the venous blood
- petechial haemorrhages in the skin and eyes (particularly the eyelids, conjunctiva, sclera, face, lips and behind the ears) - due to raised venous pressure

Petechial Haemorrhages

Unfortunately the presence of petechial haemorrhages does not automatically point to asphyxia as a cause of death. They are fairly non-specific in that they can be produced whenever there is a marked or sudden increase in vascular congestion of the head that causes rupture of capillaries.

The areas of the head that are most characteristically involved are those that have little surrounding soft tissue support, such as the conjunctiva, eyelids, lining of the mouth/ larynx etc. Petechiae can therefore be produced not only during vascular compression of the neck, but also where valsalva manouvres operate, such as during labour, straining at stool, coughing (eg in asthma), sneezing, vomiting etc.

Other examples include chest compression, where the right heart is compressed, but the left heart is still capable of pumping (and acute right heart failure due to disease). In these circumstances, the level of congestion would be just above the heart on the chest wall.

Where bodies are found lying prone with the head at a lower level than the rest of the body, there may be coarse petechiae present in the areas of intense congestion.

Traumatic Asphyxiation

This is the term given to the condition most often seen after mass disasters, such as the Hillsborough football stadium disaster, or where people have been crushed by collapsing trenches, or by the weight of grain etc in silos.

The thorax is transfixed, preventing respiratory movements. There are classic signs of congestion, cyanosis and petechiae, but there may be no other signs of injury on the body. The florid signs of congestion usually finish at the level of the clavicles.

Postural asphyxia is a related condition, recently coming to the fore due to interest in deaths in police custardy etc, and may involve splinting of the diaphragm during restraint, coupled with the additional requirements for oxygen during a struggle. Research into this aspect is ongoing.

Obstruction of the airway

When oxygen is not able to reach the lungs because of external occlusion of the mouth and/ or nose, or the airway at the level of the larynx is obstructed (eg by a bolus of food), the cause of the asphyxial death is 'obstruction of the airways'. There are no specific autopsy findings that would support the main types of airway obstruction deaths, and circumstantial evidence, physical evidence (eg plastic bags used by the deceased) and the scene of death would be relied on to support the diagnosis.

- smothering - the covering of the mouth or nose (or external occlusion) eg by a plastic bag or in overlay deaths (may see abrasions etc in a homicidal smothering if the victim could put up a struggle)
- gagging - the tongue is pushed backwards and upwards, and the gag becomes saturated with saliva and mucus causing further obstruction.
- foreign body obstruction (those at risk being children/ infants, the intoxicated and those with neurological difficulties with swallowing etc)
- swelling of the airway lining (anaphylactic hypersensitivity reactions, or thermal/ heat injury.

Exhaustion or Displacement of Environmental Oxygen (Suffocation)

This may occur in tight or confined spaces, where toxic fumes are released from bedding etc in cots, or in drowning (the inhaled water displaces the oxygen).

This is 'pure' asphyxia and results in a fairly rapid, painless loss of consciousness, followed by death if not discovered. There are no diagnostic autopsy findings.

Pneumonia

Pneumonia is an illness of the lungs and respiratory system in which the alveoli (microscopic air-filled sacs of the lung responsible for absorbing oxygen from the atmosphere) become inflamed and flooded with fluid. Pneumonia can result from a variety of causes, including infection with bacteria, viruses, fungi, or parasites. Pneumonia may also occur from chemical or physical injury to the lungs.

Typical symptoms associated with pneumonia include cough, chest pain, fever, and difficulty in breathing. Diagnostic tools include x-rays and examination of the sputum. Treatment depends on the cause of pneumonia; bacterial pneumonia is treated with antibiotics.

Pneumonia is a common illness which occurs in all age groups, and is a leading cause of death among the elderly and people who are chronically and terminally ill. Vaccines to prevent certain types of pneumonia are available. The prognosis depends on the type of pneumonia, the appropriate treatment, any complications, and the person's underlying health.

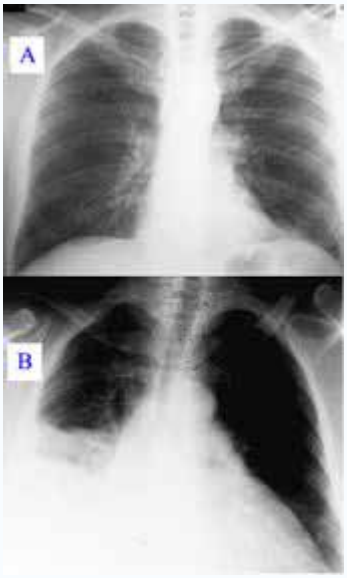
Symptoms

Pneumonia fills the lung's alveoli with fluid, keeping oxygen from reaching the bloodstream. The alveolus on the left is normal, while the alveolus on the right is full of fluid from pneumonia.

People with infectious pneumonia often have a cough that produces greenish or yellow sputum and a high fever that may be accompanied by shaking chills. Shortness of breath is also common, as is pleuritic chest pain, a sharp or stabbing pain, either felt or worse during deep breaths or coughs. People with pneumonia may cough up blood, experience headaches, or develop sweaty and clammy skin. Other symptoms may include loss of appetite, fatigue, blueness of the skin, nausea, vomiting, mood swings, and joint pains or muscle aches. Less common forms of pneumonia can cause other symptoms. For instance, pneumonia caused by *Legionella* may cause abdominal pain and diarrhea, while pneumonia caused by tuberculosis or *Pneumocystis* may cause only weight loss and night sweats. In elderly people the manifestations of pneumonia may not be typical. Instead, they may develop new or worsening confusion or may experience unsteadiness leading to falls. Infants with pneumonia may have many of the symptoms above, but in many cases, they are simply sleepy or have decreased appetite.

Physical examination

Individuals with symptoms of pneumonia need medical evaluation. Physical examination by a health care provider may reveal fever or sometimes low body temperature, an increased respiratory rate, low blood pressure, a fast heart rate, or a low oxygen saturation, which is the amount of oxygen in the blood as indicated by either pulse oximetry or blood gas analysis. People who are struggling to breathe, confused, or who have cyanosis (blue-tinged skin) require immediate attention.



Pneumonia as seen on chest x-ray. *A*: Normal chest x-ray. *B*: Abnormal chest x-ray with shadowing from pneumonia in the right lung (left side of image).

Listening to the lungs with a stethoscope (auscultation) can reveal several things. A lack of normal breath sounds, the presence of crackling sounds (rales), or increased loudness of whispered speech (whispered pectoriloquy) can identify areas of the lung that are stiff and full of fluid, called "consolidation." The examiner may also feel the way the chest expands (palpation) and tap the chest wall (percussion) to further localize consolidation. The examiner may also palpate for increased vibration of the chest when speaking (tactile fremitus).[1]

Chest X-rays, sputum cultures, and other tests

An important test for detecting pneumonia in unclear situations is a chest x-ray. Chest x-rays can reveal areas of opacity (seen as white) which represent consolidation. Pneumonia is not always seen on x-rays, either because the disease is only in its initial stages, or because it involves a part of the lung not easily seen by x-ray. In some cases, chest CT (computed tomography) can reveal pneumonia that is not seen on chest x-ray. X-rays can be misleading, because other problems, like lung scarring and congestive heart failure, can mimic pneumonia on x-ray.[2] Chest x-rays are also used to evaluate for complications of pneumonia. (*See below.*)

If an individual is not getting better with antibiotics, or if the health care provider has concerns about the diagnosis, a culture of the person's sputum may be requested. Sputum cultures generally take at least two to three days, so they are mainly used to confirm that the infection is sensitive to an antibiotic that has already been started. A blood sample may similarly be cultured to look for infection in the blood (blood culture). Any bacteria identified are then tested to see which antibiotics will be most effective.

A complete blood count may show a high white blood cell count, indicating the presence of an infection or inflammation. In some people with immune system problems, the white blood cell count may appear deceptively normal. Blood tests may be used to evaluate kidney function (important when prescribing certain antibiotics) or to look for low blood sodium. Low blood sodium in pneumonia is thought to be due to extra anti-diuretic hormone produced when the lungs are diseased (SIADH). Specific blood serology tests for other bacteria (*Mycoplasma*, *Legionella* and *Chlamydophila*) and a urine test for *Legionella* antigen are available. Respiratory secretions can also be tested for the presence of viruses such as influenza, respiratory syncytial virus, and adenovirus.

Community-acquired pneumonia

Community-acquired pneumonia (CAP) is infectious pneumonia in a person who has not recently been hospitalized. CAP is the most common type of pneumonia. The most common causes of CAP differ depending on a person's age, but they include *Streptococcus pneumoniae*, viruses, the atypical bacteria, and *Haemophilus influenzae*. Overall, *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia worldwide. Gram-negative bacteria cause CAP in certain at-risk populations. CAP is the fourth most common cause of death in the United Kingdom and the sixth in the United States. An outdated term, walking pneumonia, has been used to describe a type of community-acquired pneumonia of less severity (hence the fact that the patient can continue to "walk" rather than require hospitalization). Walking pneumonia is usually caused by a virus or by atypical bacteria.

Hospital-acquired pneumonia

Hospital-acquired pneumonia, also called nosocomial pneumonia, is pneumonia acquired during or after hospitalization for another illness or procedure with onset at least 72 hrs after admission. The causes, microbiology, treatment and prognosis are different from those of community-acquired

pneumonia. Up to 5% of patients admitted to a hospital for other causes subsequently develop pneumonia. Hospitalized patients may have many risk factors for pneumonia, including mechanical ventilation, prolonged malnutrition, underlying heart and lung diseases, decreased amounts of stomach acid, and immune disturbances. Additionally, the microorganisms a person is exposed to in a hospital are often different from those at home . Hospital-acquired microorganisms may include resistant bacteria such as MRSA, *Pseudomonas*, *Enterobacter*, and *Serratia*. Because individuals with hospital-acquired pneumonia usually have underlying illnesses and are exposed to more dangerous bacteria, it tends to be more deadly than community-acquired pneumonia. Ventilator-associated pneumonia (VAP) is a subset of hospital-acquired pneumonia. VAP is pneumonia which occurs after at least 48 hours of intubation and mechanical ventilation.

Treatment

Most cases of pneumonia can be treated without hospitalization. Typically, oral antibiotics, rest, fluids, and home care are sufficient for complete resolution. However, people with pneumonia who are having trouble breathing, people with other medical problems, and the elderly may need more advanced treatment. If the symptoms get worse, the pneumonia does not improve with home treatment, or complications occur, the person will often have to be hospitalized.

Antibiotics are used to treat bacterial pneumonia. In contrast, antibiotics are not useful for viral pneumonia, although they sometimes are used to treat or prevent bacterial infections that can occur in lungs damaged by a viral pneumonia. The antibiotic choice depends on the nature of the pneumonia, the most common microorganisms causing pneumonia in the local geographic area, and the immune status and underlying health of the individual. Treatment for pneumonia should ideally be based on the causative microorganism and its known antibiotic sensitivity. However, a specific cause for pneumonia is identified in only 50% of people, even after extensive evaluation. Because treatment should generally not be delayed in any person with a serious pneumonia, empiric treatment is usually started well before laboratory reports are available. In the United Kingdom, amoxicillin is the antibiotic selected for most patients with community-acquired pneumonia, sometimes with added clarithromycin; patients allergic to penicillins are given erythromycin instead of amoxicillin. In North America, where the "atypical" forms of community-acquired pneumonia are becoming more common, azithromycin, clarithromycin, and the fluoroquinolones have displaced amoxicillin as first-line treatment. The duration of treatment has traditionally been seven to ten days, but there is increasing evidence that shorter courses (as short as three days) are sufficient.[7][8][9]

Antibiotics for hospital-acquired pneumonia include vancomycin, third- and fourth-generation cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides. These antibiotics are usually given intravenously. Multiple antibiotics may be administered in combination in an attempt to treat all of the possible causative microorganisms. Antibiotic choices vary from hospital to hospital because of regional differences in the most likely microorganisms, and because of differences in the microorganisms' abilities to resist various antibiotic treatments.

People who have difficulty breathing due to pneumonia may require extra oxygen. Extremely sick individuals may require intensive care treatment, often including intubation and artificial ventilation.

Viral pneumonia caused by influenza A may be treated with rimantadine or amantadine, while viral pneumonia caused by influenza A or B may be treated with oseltamivir or zanamivir. These treatments are beneficial only if they are started within 48 hours of the onset of symptoms. Many strains of H5N1 influenza A, also known as avian influenza or "bird flu," have shown resistance to

rimantadine and amantadine. There are no known effective treatments for viral pneumonias caused by the SARS coronavirus, adenovirus, hantavirus, or parainfluenza virus.

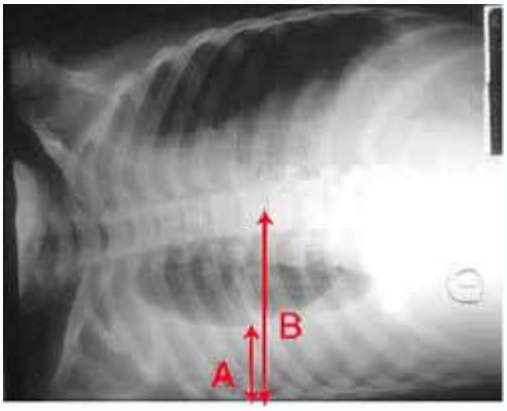
Complications

Sometimes pneumonia can lead to additional complications. Complications are more frequently associated with bacterial pneumonia than with viral pneumonia. The most important complications include:

Respiratory and circulatory failure

Because pneumonia affects the lungs, often people with pneumonia have difficulty breathing, and it may not be possible for them to breathe well enough to stay alive without support. Non-invasive breathing assistance may be helpful, such as with a bilevel positive airway pressure machine. In other cases, placement of an endotracheal tube (breathing tube) may be necessary, and a ventilator may be used to help the person breathe.

Pneumonia can also cause respiratory failure by triggering acute respiratory distress syndrome (ARDS), which results from a combination of infection and inflammatory response. The lungs quickly fill with fluid and become very stiff. This stiffness, combined with severe difficulties extracting oxygen due to the alveolar fluid, create a need for mechanical ventilation.



Pleural effusion. Chest x-ray showing a pleural effusion. The A arrow indicates "fluid layering" in the right chest. The B arrow indicates the width of the right lung. The volume of useful lung is reduced because of the collection of fluid around the lung.

Sepsis and septic shock are potential complications of pneumonia. Sepsis occurs when microorganisms enter the bloodstream and the immune system responds by secreting cytokines. Sepsis most often occurs with bacterial pneumonia; *Streptococcus pneumoniae* is the most common cause. Individuals with sepsis or septic shock need hospitalization in an intensive care unit. They often require intravenous fluids and medications to help keep their blood pressure from dropping too low. Sepsis can cause liver, kidney, and heart damage, among other problems, and it often causes death.

Pleural effusion, empyema, and abscess

Occasionally, microorganisms infecting the lung will cause fluid (a pleural effusion) to build up in the space that surrounds the lung (the pleural cavity). If the microorganisms themselves are present in the pleural cavity, the fluid collection is called an empyema. When pleural fluid is present in a person with pneumonia, the fluid can often be collected with a needle (thoracentesis) and examined.

Depending on the results of this examination, complete drainage of the fluid may be necessary, often requiring a chest tube. In severe cases of empyema, surgery may be needed. If the fluid is not drained, the infection may persist, because antibiotics do not penetrate well into the pleural cavity.

Rarely, bacteria in the lung will form a pocket of infected fluid called an abscess. Lung abscesses can usually be seen with a chest x-ray or chest CT scan. Abscesses typically occur in aspiration pneumonia and often contain several types of bacteria. Antibiotics are usually adequate to treat a lung abscess, but sometimes the abscess must be drained by a surgeon or radiologist.

Pneumothorax

In medicine (pulmonology), a **pneumothorax**, or **collapsed lung**, is a potential medical emergency caused by accumulation of air or gas in the pleural cavity, occurring as a result of disease or injury

Aetiology

It can result from:

- A penetrating chest wound
- Barotrauma to the lungs
- Spontaneously (most commonly in tall slim young males and in Marfan syndrome)
- Chronic lung pathologies including emphysema, asthma
- Acute infections
- Acupuncture
- Chronic infections, such as tuberculosis
- Cancer
- Catamenial pneumothorax (due to endometriosis in the chest cavity)

Pneumothoraces are divided into tension and non-tension pneumathoraces. A tension pneumothorax is a medical emergency as air accumulates in the pleural space with each breath. The remorseless increase in intrathoracic pressure results in massive shifts of the mediastinum away from the affected lung compressing intrathoracic vessels. A non-tension pneumothorax by contrast is a less severe pathology because the air in the pneumothorax is able to escape.

The accumulation of blood in the thoracic cavity (hemothorax) exacerbates the problem, creating a pneumohemothorax.

Signs and symptoms

Sudden shortness of breath, cyanosis (turning blue) and pain felt in the chest and/or back are the main symptoms. In penetrating chest wounds, the sound of air flowing through the puncture hole may indicate pneumothorax, hence the term "sucking" chest wound. The flopping sound of the punctured lung is also occasionally heard.

If untreated, hypoxia may lead to loss of consciousness and coma. In addition, shifting of the mediastinum away from the site of the injury can obstruct the superior and inferior vena cava resulting in reduced cardiac preload and decreased cardiac output. Untreated, a severe pneumothorax can lead to death within several minutes.

Spontaneous pneumothoraces are reported in young people with a tall stature. As men are generally taller than women, there is a preponderance among males. The reason for this association, while unknown, is hypothesized to be the presence of subtle abnormalities in connective tissue.

Pneumothorax can also occur as part of medical procedures, such as the insertion of a central venous catheter (an intravenous catheter) in the subclavian vein or jugular vein. While rare, it is considered a serious complication and needs immediate treatment. Other causes include mechanical ventilation, emphysema and rarely other lung diseases (pneumonia).

Diagnosis

The absence of audible breath sounds through a stethoscope can indicate that the lung is not unfolded in the pleural cavity. This accompanied by hyperresonance (higher pitched sounds than normal) to percussion of the chest wall is suggestive of the diagnosis. If the signs and symptoms are doubtful, an X-ray of the chest can be performed, but in severe hypoxia, emergency treatment has to be administered first.

In a supine chest X-ray the *deep sulcus sign* is diagnostic[2], which is characterized by a low lateral costophrenic angle on the affected side.[3] In layman's terms, the place where rib and diaphragm meet appears lower on an X-ray with a *deep sulcus sign* and suggests the diagnosis of pneumothorax.

Differential Diagnosis

When presented with this clinical picture, other possible causes include:

- Acute Myocardial Infarction: presents with shortness of breath and chest pain, though MI chest pain is characteristically crushing, central and radiating to the jaw, left arm or stomach. Whilst not a lung condition, patients having an MI often happen to also have lung disease.
- Emphysema: here, delicate functional lung tissue is lost and replaced with air spaces, giving shortness of breath, and decreased air entry and increased resonance on examination. However, it is usually a chronic condition, and signs are diffuse (not localised as in pneumothorax).

First Aid

Chest wound

Penetrating wounds require immediate coverage with an occlusive dressing, field dressing, or pressure bandage made air-tight with petroleum jelly or clean plastic sheeting. The sterile inside of plastic bandage packaging is good for this purpose; however any airtight material, even the cellophane of a cigarette pack, can be used. A small opening, known as a flutter valve, needs to be left open, so the air can escape while the lung reinflates. Any patient with a penetrating chest wound must be closely watched at all times and may develop a tension pneumothorax or other immediately life-threatening respiratory emergency at any moment. They cannot be left alone.

Blast injury or tension

If the air in the pleural cavity is due to a tear in the lung tissue (in the case of a blast injury or tension pneumothorax), it needs to be released. A thin needle can be used for this purpose, to relieve the pressure and allow the lung to reinflate.

Pre-hospital care

Many paramedics can perform needle thoracocentesis to relieve intrathoracic pressure. Intubation may be required, even of a conscious patient, if the situation deteriorates. Advanced medical care and immediate evacuation are strongly indicated.

An untreated pneumothorax is an absolute contraindication of evacuation or transportation by flight.

Clinical treatment

Small pneumothoraces often are managed with no treatment other than repeat observation via Chest X-rays, but most patients admitted will have oxygen adminstrated since this has been shown to speed resolution of the pneumothorax. [4]

Pneumothoraces which are too small to require tube thoracostomy and too large to leave untreated, have been aspirated with a needle to remove the pressure, although this technique is usually reserved for tension pneumothoraces

Larger pneumothoraces may require tube thoracostomy, also known as chest tube placement. A tube is inserted into the chest wall outside the lung and air is extracted using a simple one way valve or vacuum and a water valve device, depending on severity. This allows the lung to re-expand within the chest cavity. The pneumothorax is followed up with repeated X-rays. If the air pocket has become small enough, the vacuum drain can be clamped temporarily or removed.

In case of penetrating wounds, these require attention, but generally only after the airway has been secured and a chest drain inserted. Supportive therapy may include mechanical ventilation.

Recurrent pneumothorax may require further corrective and/or preventive measures such as *pleurodesis*. If the pneumothorax is the result of bullae, then bullectomy (the removal or stapling of *bullae* or other faults in the lung) is preferred. Chemical pleurodesis is the injection of a chemical irritant that triggers an inflammatory reaction, leading to adhesion of the lung to the parietal pleura. Substances used for pleurodesis include talc, blood, tetracycline and bleomycin. Mechanical pleurodesis does not use chemicals. The surgeon "roughs" up the inside chest wall ("parietal pleura") so the lung attaches to the wall with scar tissue. This can also include a "parietal" pleurectomy, which is the removal of the "parietal" pleura; "parietal" pleura is the serous membrane lining the inner surface of the thoracic cage and facing the "visceral" pleura, which lies all over the lung surface. Both operations can be performed using keyhole surgery to minimise discomfort to the patient.

Spontaneous Pneumothorax

Spontaneous Pneumothorax can be classified as primary spontaneous pneumothorax and secondary spontaneous pneumothorax. In primary spontaneous pneumothorax, it is usually characterized by a rupture of a bleb in the lung while secondary spontaneous pneumothorax mostly occurs due to chronic obstructive pulmonary disease (COPD).

Primary spontaneous pneumothorax

A primary spontaneous pneumothorax may occur without either trauma to the chest or any kind of blast injury. This type of pneumothorax is caused when a bleb (an imperfection in the lining of the lung) bursts causing the lung to deflate. If a patient suffers two or more instances of a spontaneous pneumothorax, surgeons often recommend a bullectomy and pleurectomy. Primary spontaneous pneumothorax is most evident to people without any previous history of lung disease and in tall, thin men whose age is between 20 to 40 years old. But it can often occur in teenagers and young adults.Secondary spontaneous pneumothorax

A known lung disease is present in secondary spontaneous pneumothorax[5]. The most common cause is chronic obstructive pulmonary disease (COPD). However, there are several diseases that may lead to spontaneous pneumothorax:COPD

- Tuberculosis
- Pneumonia
- Asthma
- Cystic fibrosis
- Lung cancer
- Interstitial lung disease

Pulmonary embolism

Pulmonary embolism *is the occlusion of one or more pulmonary arteries by thrombi that originate elsewhere, typically in the large veins of the lower extremities or pelvis. Risk factors are conditions that impair venous return and that cause endothelial injury or dysfunction, especially in patients with an underlying hypercoagulable state. Symptoms include dyspnea, pleuritic chest pain, cough, and, in severe cases, syncope or cardiorespiratory arrest. Signs are nonspecific and may include tachypnea, tachycardia, hypotension, and loud pulmonic component of the 2nd heart sound. Diagnosis is based on a ventilation/perfusion scan, a CT angiogram, or a pulmonary arteriogram. Treatment is with anticoagulants, thrombolytics, and, occasionally, surgery to remove the clot.*

Pulmonary embolism (PE) affects an estimated 650,000 people and causes up to 200,000 deaths/yr, accounting for an estimated 15% of all hospital deaths/yr. The incidence of PE in children is about 5/10,000 admissions.

Etiology and Pathophysiology

Nearly all PEs arise from thrombi in the lower extremity or pelvic veins (deep venous thrombosis [DVT]—see Peripheral Venous and Lymphatic Disorders: Deep Venous Thrombosis (DVT)). Thrombi in either system may be occult. Thromboemboli can also originate in upper extremity veins or in right cardiac chambers. Risk factors for DVT and PE are similar in children and adults and include conditions that impair venous return or that cause endothelial injury or dysfunction particularly in patients with an underlying baseline hypercoagulable state (see Table 1: Pulmonary Embolism (PE): Risk Factors for Deep Venous Thrombosis and Pulmonary Embolism). Bed rest and confinement without walking, even for a few hours, are common precipitators.

GASTROENTEROLOGY

Gastritis

Gastritis is inflammation of the gastric mucosa. The word comes from the Greek gastro- meaning of the stomach and -itis meaning inflammation. Depending on the cause, it may persist acutely or chronically and may coincide with more serious conditions such as atrophy of the stomach.

- **GASTRITIES**

Causes

[edit] Symptoms

The following symptoms can be a result of gastritis or can be related to the underlying cause:

- Upper abdominal pain or discomfort
- Gastric hemorrhage
- Hypochlorhydria
- Appetite loss
- Belching
- Nausea
- Vomiting
- Fever
- Lethargy
- Bits of blood/pink flesh in vomit
- Black specks (blood) in stool

Diagnosis

In suspected cases, a doctor usually orders a barium meal test and gastroscopy to determine gastritis and related conditions such as peptic ulcers and gastric cancer. It is always important that the doctor reviews a patient's history regarding medications, alcohol intake, smoking, and other factors that can be associated with gastritis. In some cases, the appearance of the stomach lining seen during gastroscopy and the results of the barium meal test are reliable in determining gastritis and the cause. However, the most reliable method for determining gastritis is doing a biopsy during gastroscopy and checking for histological characteristics of gastritis and infection. For Helicobacter infection (the most common cause), one can test non-invasively with a urea breath test, stool antigen test, or blood antibody test.

Treatment

Treatment usually consists of removing the irritant or the infection. In cases of infection, a doctor will most often prescribe antimicrobial drugs. Helicobacter infection typically responds well to the triple therapy protocol (consisting of two antibiotics, and a proton pump inhibitor).

PEPTIC ULCER

A **peptic ulcer** , also known as **PUD** or **peptic ulcer disease**[1] is an ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. Most ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also be caused or worsened by drugs such as Aspirin and other NSAIDs. Contrary to general belief, more peptic ulcers arise in the duodenum (first part of the small intestine, just after the stomach) than in the stomach. About 4% of stomach ulcers are caused by a malignant tumor, so multiple biopsies are needed to make sure. Duodenal ulcers are generally benign.

Symptoms and signs

Symptoms of a peptic ulcer can be:

- Abdominal pain, classically epigastric with severity relating to mealtimes, after around 3 hours of taking a meal (duodenal ulcers are classically relieved by food, while gastric ulcers are exacerbated by it);
- Bloating and abdominal fullness
- Waterbrash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus)
- Nausea, and lots of vomiting
- Loss of appetite and weight loss;
- Hematemesis (vomiting of blood);
- Melena (tarry, foul-smelling faeces due to oxidised iron from hemoglobin)
- Rarely, an ulcer can lead to a gastric or duodenal perforation. This is extremely painful and requires immediate surgery.

A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAID (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, and most glucocorticoids (e.g. dexamethasone and prednisolone).

In patients over 45 with more than 2 weeks of the above symptoms, the odds for peptic ulceration are high enough to warrant rapid investigation by EGD (see below).

The timing of the symptoms in relation to the meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid is secreted, or after the meal, as the alkaline duodenal contents reflux into the stomach. Symptoms of duodenal ulcers would manifest mostly before the meal — when acid (production stimulated by hunger) is passed into the duodenum. However, this is not a reliable sign in clinical practice.

Complications

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This article has been tagged since **June 2007**.

- Perforated ulcer (anterior. Surface) with sudden onset of the pain, a chemical peritonitis followed by bacterial peritonitis
- Posterior penetration (posterior. Surface), maybe to pancreas=>increased amylase-pain=>radiating to back, unrelated to meals.

- Hemorrhage (post. Surface), bleeding from Gasteroduodenal artery.
- Gastric Outlet Obstruction (Goo) which happens usually because of edema or scarring, most often occurs in the setting of duodenal or pyloric channel ulcers

Stress and ulcers

Despite the finding that a bacterial infection is the cause of ulcers in more than 75% of cases, bacterial infection does not appear to explain all ulcers and researchers continue to look at stress as a possible cause, or at least a complication in the development of ulcers.

An expert panel convened by the Academy of Behavioral Medicine research concluded that ulcers are not purely an infectious disease and that psychological factors do play a significant role.[2] Researchers are examining how stress might promote H. pylori infection. For example, Helicobacter pylori thrives in an acidic environment, and stress has been demonstrated to cause the production of excess stomach acid.

The discovery that Helicobacter pylori is a cause of peptic ulcer has tempted many to conclude that psychological factors are unimportant. But this is dichotomised thinking. There is solid evidence that psychological stress triggers many ulcers and impairs response to treatment, while helicobacter is inadequate as a monocausal explanation as most infected people do not develop ulcers. Psychological stress probably functions most often as a cofactor with H pylori. It may act by stimulating the production of gastric acid or by promoting behavior that causes a risk to health. Unravelling the aetiology of peptic ulcer will make an important contribution to the biopsychosocial model of disease.[3]

A study of peptic ulcer patients in a Thai hospital showed that chronic stress was strongly associated with an increased risk of peptic ulcer, and a combination of chronic stress and irregular mealtimes was a significant risk factor (PMID 12948263).

A study on mice showed that both long-term water-immersion-restraint stress and H. pylori infection were independently associated with the development of peptic ulcers (PMID 12465722).

Pathophysiology

Tobacco smoking, blood group, spices and other factors that were suspected to cause ulcers until late in the 20th century, are actually of relatively minor importance in the development of peptic ulcers.[4]

A major causative factor (60% of gastric and 90% of duodenal ulcers) is chronic inflammation due to Helicobacter pylori that colonizes (i.e. settles there after entering the body) the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion is increased. Gastrin, in turn, stimulates the production of gastric acid by parietal cells. The acid erodes the mucosa and causes the ulcer.

Another major cause is the use of NSAIDs (see above). The gastric mucosa protects itself from gastric acid with a layer of mucous, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (cox-1), which is essential for the production of these prostaglandins. Newer NSAIDs (celecoxib, rofecoxib) only inhibit cox-2, which is less essential in the gastric mucosa, and roughly halve the risk of NSAID-related gastric ulceration.

Glucocorticoids lead to atrophy of all epithelial tissues. Their role in ulcerogenesis is relatively small.

There is debate as to whether Stress in the psychological sense can influence the development of peptic ulcers (see Stress and ulcers). Burns and head trauma, however, can lead to "stress ulcers", and it is reported in many patients who are on mechanical ventilation.

Smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers through ischemia.

Overuse of Laxatives are also known to cause peptic ulcers.

A family history is often present in duodenal ulcers, especially when blood group O is also present. Inheritance appears to be unimportant in gastric ulcers.

Gastrinomas (Zollinger Ellison syndrome), rare gastrin-secreting tumors, cause multiple and difficult to heal ulcers.

Diagnosis

An esophagogastroduodenoscopy (EGD), a form of endoscopy, also known as a gastroscopy, is carried out on patients in whom a peptic ulcer is suspected. By direct visual identification, the location and severity of an ulcer can be described. Moreover, if no ulcer is present, EGD can often provide an alternative diagnosis.

The diagnosis of Helicobacter pylori can be by:

- Breath testing (does not require EGD);
- Direct culture from an EGD biopsy specimen;
- Direct detection of urease activity in a biopsy specimen;
- Measurement of antibody levels in blood (does not require EGD). It is still somewhat controversial whether a positive antibody without EGD is enough to warrant eradication therapy.

The possibility of other causes of ulcers, notably malignancy (gastric cancer) needs to be kept in mind. This is especially true in ulcers of the greater (large) curvature of the stomach; most are also a consequence of chronic H. pylori infection.

If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract (which always contains some air) to the peritoneal cavity (which normally never contains air). This leads to "free gas" within the peritoneal cavity. If the patient stands erect, as when having a chest X-ray, the gas will float to a position underneath the diaphragm. Therefore, gas in the peritoneal cavity, shown on an erect chest X-ray or supine lateral abdominal X-ray, is an omen of perforated peptic ulcer disease.

Treatment

Younger patients with ulcer-like symptoms are often treated with antacids or H2 antagonists before EGD is undertaken. Bismuth compounds may actually reduce or even clear organisms.

Patients who are taking nonsteroidal anti-inflammatories (NSAIDs) may also be prescribed a prostaglandin analogue (Misoprostol) in order to help prevent peptic ulcers, which may be a side-effect of the NSAIDs.

When H. pylori infection is present, the most effective treatments are combinations of 2 antibiotics (e.g. Erythromycin, Ampicillin, Amoxicillin, Tetracycline, Metronidazole) and 1 proton pump inhibitor (PPI). An effective combination would be Amoxicillin + Metronidazole + Pantoprazole (a PPI). In the absence of H. pylori, long-term higher dose PPIs are often used.

Treatment of H. pylori usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers. Recurrence of infection can occur and retreatment may be required, if necessary with other antibiotics. Since the widespread use of PPI's in the 1990s, surgical procedures (like "highly selective vagotomy") for uncomplicated peptic ulcers became obsolete.

Perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery or injection.

PANCREATITES

The most common cause of acute pancreatitis is gallstones. Excessive alcohol use is often cited as the second most common cause of acute pancreatitis, but this is technically incorrect, as these patients invariably have enough destruction to their pancreatic parenchyma to be considered to have chronic pancreatitis, so it is more correct to say that these patients present with acute flare-ups of their chronic pancreatitis rather than acute pancreatitis. Less common causes include hypertriglyceridemia (but not hypercholesterolemia) and only when triglyceride values exceed 1500 mg/dl (16 mmol/L), hypercalcemia, viral infection (e.g. mumps), trauma (to the abdomen or elsewhere in the body) including post-ERCP (i.e. Endoscopic Retrograde Cholangiopancreatography), vasculitis (i.e. inflammation of the small blood vessels within the pancreas), and autoimmune pancreatitis. Pregnancy can also cause pancreatitis, but in some cases the development of pancreatitis is probably just a reflection of the hypertriglyceridemia which often occurs in pregnant women. Pancreas divisum, a common congenital malformation of the pancreas may underlie some cases of recurrent pancreatitis.

Many medications have been reported to cause pancreatitis. Some of the more common ones include the AIDS drugs DDI and pentamidine, diuretics such as furosemide and hydrochlorothiazide, the chemotherapeutic agents L-asparaginase and azathioprine, and estrogen. Just as is the case with pregnancy associated pancreatitis, estrogen may lead to the disorder because of its effect to raise blood triglyceride levels.

Conditions that can lead to gut dysmotility predispose patients to pancreatitis. This includes the inherited neurovisceral porphyrias and related metabolic disorders. Alcohol, hormones and many drugs including statins are known porphyrinogenic agents. Physicians should be on alert concerning underlying porphyrias in patients presenting with pancreatitis and should investigate and eliminate any drugs that may be activating the disorders.

It is worth noting that pancreatic cancer is seldom the cause of pancreatitis.

Symptoms and Signs

Severe upper abdominal pain, with radiation through to the back, is the hallmark of pancreatitis. Nausea and vomiting are prominent symptoms. Findings on the physical exam will vary according to the severity of the pancreatitis, and whether or not it is associated with significant internal bleeding. The blood pressure may be high (when pain is prominent) or low (if internal bleeding or dehydration has occurred). Typically, both the heart and respiratory rates are elevated. Abdominal tenderness is usually found but may be less severe than expected given the patient's degree of abdominal pain. Bowel sounds may be reduced as a reflection of the reflex bowel paralysis (i.e. ileus) that may accompany any abdominal catastrophe.

Diagnosis

The diagnostic criteria for pancreatitis are "two of the following three features: 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase and/or lipase ≥3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan."[1]

Complications

Acute (early) complications of pancreatitis include shock, hypocalcemia (low blood calcium), high blood glucose, dehydration, and kidney failure (resulting from inadequate blood volume which, in turn, may result from a combination of fluid loss from vomiting, internal bleeding, or oozing of fluid from the circulation into the abdominal cavity in response to the pancreas inflammation). Respiratory complications are frequent and are major contributors to the mortality of pancreatitis. Some degree of pleural effusion is almost ubiquitous in pancreatitis. Some or all of the lungs may collapse (atelectasis) as a result of the shallow breathing which occurs because of the abdominal pain. Pneumonitis may occur as a result of pancreatic enzymes directly damaging the lung, or simply as a final common pathway response to any major insult to the body (i.e. ARDS or Acute Respiratory Distress Syndrome). Likewise, SIRS (Systemic inflammatory response syndrome) may ensue.

Infection of the inflamed pancreatic bed can occur at any time during the course of the disease. In fact, in cases of severe hemorrhagic pancreatitis, antibiotics should be given prophylactically.

Late complications of pancreatitis include recurrent pancreatitis and the development of pancreatic pseudocysts. A pancreatic pseudocyst is essentially a collection of pancreatic secretions which has been walled off by scar and inflammatory tissue. Pseudocysts may cause pain, may become infected, may rupture and hemorrhage, may press on and block structures such as the bile duct, thereby leading to jaundice, and may eve migrate around the abdomen.

Treatment

The treatment of pancreatitis will, of course, depend on the severity of the pancreatitis itself. Still, general principles apply and include 1. provision of pain relief (with meperidine, contrary to earlier pronouncements, being the agent of choice), 2. provision of adequate replacement fluids and salts (intravenously), 3. limitation of oral intake (with dietary fat restriction the most important point), and 4. monitoring and assessment for, and treatment of, the various complications listed above. When necrotizing pancreatitis ensues and the patient shows signs of infection it is imperative to start antibiotics such as Imipenem due to its high penetration of the drug in the pancreas.

Types

There are three forms of pancreatitis, which are different in causes and symptoms, and require different treatment:

- Acute pancreatitis: One-time occurrence
- Chronic pancreatitis: Persists even after the cause has been removed
- Hereditary pancreatitis: A genetic abnormality that renders trypsinogen active within the pancreas, which in turn leads to digestion of the pancreas from the inside.

Acute hepatic porphyrias, including acute intermittent porphyria, hereditary coproporphyria and variegate porphyria, are genetic disorders that can be linked to both acute and chronic pancreatitis. Acute pancreatitis has also occurred with erythropoietic protoporphyria

NEPHROLOGY

Nephritis

Nephritis is inflammation of the kidney. The word comes from the Greek *nephro-* meaning "of the kidney" and *-itis* meaning "inflammation". Nephritis is often caused by infections, toxins, and auto-immune diseases.

Subtypes

- glomerulonephritis is inflammation of the glomeruli. (Often when the term "nephritis" is used without qualification, this is the condition meant.)
- interstitial nephritis or tubulo-interstitial nephritis is inflammation is of the spaces between renal tubules.
- pyelonephritis is when a urinary tract infection has reached the pyelum (pelvis) of the kidney.
- Lupus nephritis is an inflammation of the kidney caused by systemic lupus erythematosus (SLE), a disease of the immune system.

Glomerulonephritis, also known as **glomerular nephritis** and abbreviated **GN'**, is a primary or secondary immune-mediated renal disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria (blood resp. protein in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute renal failure, or chronic renal failure. They are categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Diagnosing the pattern of GN is important because the outcome and treatment differs in different types. Primary causes are one which are intrinsic to the kidney, whilst secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis) or cancers.

Pyelonephritis is an ascending urinary tract infection that has reached the *pyelum* (pelvis) of the kidney (*nephros* in Greek). If the infection is severe, the term "**urosepsis**" is used interchangeably. It requires antibiotics as therapy. It is a form of nephritis. It can also be called *pyelitis*.

Pathology

Acute pyelonephritis is an, *exudative purulent localized inflammation* of kidney and renal pelvis. The renal parenchyma presents in the interstitium abscesses (suppurative necrosis), consisting in purulent exudate (pus): neutrophils, fibrin, cell debris and central germ colonies (hematoxylinophils). Tubules are damaged by exudate and may contain neutrophil casts. In the early stages, glomeruli and vessels are normal.[1] Gross pathology often reveals pathognomonic radiations of hemorrhage and suppuration through the renale pelvis to the renale cortex. Chronic infections can result in fibrosis and scarring.

Chronic pyelonephritis is often caused by Xanthogranulomatous pyelonephritis.

Causes

Ascending bacteria (such as E.coli) from lower urinary tract infections, mainly cystitis and prostatitis. true....

Signs and symptoms

It presents with high spiking fever, backache, vomiting, dysuria (painful voiding), rigors and often also with confusion. There may be renal angle tenderness on physical examination.

Diagnosis

Nitrite and leukocytes on a urine dipstick are often detected, which may be an indication for empirical treatment. Formal diagnosis is with culture of the urine and bloods.

In patients with recurrent ascending urinary tract infections, it may be necessary to exclude an anatomical abnormality, such as vesicoureteric reflux (urine from the bladder flowing back into the ureter).

Treatment

Treatment is with antibiotics, which are often administered intravenously to improve the effect. Trimethoprim (or co-trimoxazole) or nitrofurantoin are often used first-line, although in full-blown pyelonephritis amoxicillin (with or without clavulanic acid), gentamycin (with or without ampicillin), fluoroquinolones (eg. ciprofloxacin) or a third generation cephalosporins are often favoured.

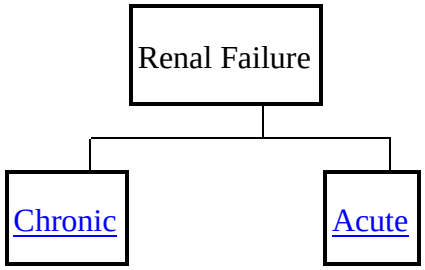
Renal failure or **kidney failure** is the condition in which the kidneys fail to function adequately.

Biochemically, it is typically detected by an elevated serum creatinine. In the science of physiology, renal failure is described as a decrease in the glomerular filtration rate

Classification

Renal failure can broadly be divided into two categories (see flowchart below): acute renal failure and chronic renal failure.

Renal failure classification



The type of renal failure (acute vs. chronic) is determined by the trend in the serum creatinine. Other factors which may help differentiate acute and chronic renal failure include the presence of anemia and the kidney size on ultrasound. Long-standing, i.e. chronic, renal failure generally leads to anemia and small kidney size.

Acute renal failure

Main article: Acute renal failure

Acute renal failure (ARF) is, as the name implies, a rapidly progressive loss of renal function, generally characterised by oliguria (decreased urine production, quantified as less than 400 mL per day in adults,[1] less than 0.5 mL/kg/h in children or less than 1 mL/kg/h in infants); body water and body fluids disturbances; and electrolyte derangement. An underlying cause must be identified to arrest the progress, and dialysis may be necessary to bridge the time gap required for treating these fundamental causes. ARF can result from a large number of causes.

Chronic renal failure

Main article: Chronic renal failure

Chronic renal failure (CRF) can either develop slowly and show few initial symptoms, be the long term result of irreversible acute disease or be part of a disease progression. There are many causes of CRF. The most common cause is diabetes mellitus. End-stage renal failure (ESRF) is the ultimate consequence, in which case dialysis is required unless a donor for a renal transplant is found.

Acute on chronic renal failure

Acute renal failure can be present on top of chronic renal failure. This is called acute-on-chronic renal failure (AoCRF). The acute part of AoCRF may be reversible and the aim of treatment, as with ARF, is to return the patient to their baseline renal function, which is typically measured by serum creatinine. AoCRF, like ARF, can be difficult to distinguish from chronic renal failure, if the patient has not been monitored by a physician and no baseline (i.e., past) blood work is available for comparison.

Use of the term *uremia*

Before the advancement of modern medicine, renal failure was often referred to as uremic poisoning. Uremia was the term used to describe the contamination of the blood with urine. Starting around 1847, this term was used to describe reduced urine output, now known as oliguria, that was thought to be caused by the urine mixing with the blood instead of being voided through the urethra.

HAEMATOLOGY

ANEMIA

Anemia (AmE) or **anæmia** (BrE), from the Greek (Ἀναιμία) meaning "without blood", is a deficiency of red blood cells (RBCs) and/or hemoglobin. This results in a reduced ability of blood to transfer oxygen to the tissues, causing tissue hypoxia. Since all human cells depend on oxygen for survival, varying degrees of anemia can have a wide range of clinical consequences. Hemoglobin (the oxygen-carrying protein in the red blood cells) has to be present to ensure adequate oxygenation of all body tissues and organs. The three main classes of anemia include excessive blood loss (acutely such as a hemorrhage or chronically through low-volume loss), excessive blood cell destruction (hemolysis) or deficient red blood cell production (ineffective hematopoiesis). In menstruating women, dietary iron deficiency is a common cause of deficient red blood cell production.

Anemia is the most common disorder of the blood. There are several kinds of anemia, produced by a variety of underlying causes. Anemia can be classified in a variety of ways, based on the morphology of RBCs, underlying etiologic mechanisms, and discernible clinical spectra, to mention a few.

There are two major approaches of classifying anemias, the "kinetic" approach which involves evaluating production, destruction and loss[1], and the "morphologic" approach which groups anemia by red blood cell size. The morphologic approach uses a quickly available and cheap lab test as its starting point (the MCV). On the other hand, focusing early on the question of production may allow the clinician more rapidly to expose cases where multiple causes of anemia coexist.

Signs and symptoms

Anemia goes undetected in many people, and symptoms can be vague. Most commonly, people with anemia report a feeling of weakness or fatigue, general malaise and sometimes a poor concentration. People with more severe anemia often report dyspnea (shortness of breath) on exertion. Very severe anemia prompts the body to compensate by increasing cardiac output, leading to palpitations and sweatiness, and to heart failure.

Pallor (pale skin, mucosal linings and nail beds) is often a useful diagnostic sign in moderate or severe anemia, but it is not always apparent. Other useful signs are cheilosis and koilonychia.

Diagnosis

Generally, clinicians request complete blood counts in the first batch of blood tests in the diagnosis of a suspected anemia. Apart from reporting the number of red blood cells and the hemoglobin level, the automatic counters also measure the size of the red blood cells by flow cytometry, which is an important tool in distinguishing between the causes of anemia. Examination of a stained blood smear using a microscope can also be helpful, and is sometimes a necessity in regions of the world where automated analysis is less accessible.

In modern counters, four parameters (RBC Count, hemoglobin concentration, MCV and RDW) are measured, allowing others (hematocrit, MCH and MCHC) to be calculated, and compared to values adjusted for age and sex. Some counters estimate hematocrit from direct measurements. For adult

men, a hemoglobin level less than 13.0 g/dl is diagnostic of anemia, and for adult women, the diagnostic threshold is below 12.0 g/dl.

Reticulocyte counts, and the "kinetic" approach to anemia, have become more common than in the past in the large medical centers of the United States and some other wealthy nations, in part because some automatic counters now have the capacity to include reticulocyte counts. A reticulocyte count is a quantitative measure of the bone marrow's production of new red blood cells. The reticulocyte production index is a calculation of the ratio between the level of anemia and the extent to which the reticulocyte count has risen in response. If the degree of anemia is significant, even a "normal" reticulocyte count actually may reflect an inadequate response.

If an automated count is not available, a reticulocyte count can be done manually following special staining of the blood film. In manual examination, activity of the bone marrow can also be gauged qualitatively by subtle changes in the numbers and the morphology of young RBCs by examination under a microscope. Newly formed RBCs are usually slightly larger than older RBCs and show polychromasia. Even where the source of blood loss is obvious, evaluation of erythropoiesis can help assess whether the bone marrow will be able to compensate for the loss, and at what rate.

When the cause is not obvious, clinicians use other tests: ESR, ferritin, serum iron, transferrin, RBC folate level, serum vitamin B12, hemoglobin electrophoresis, renal function tests (e.g. serum creatinine).

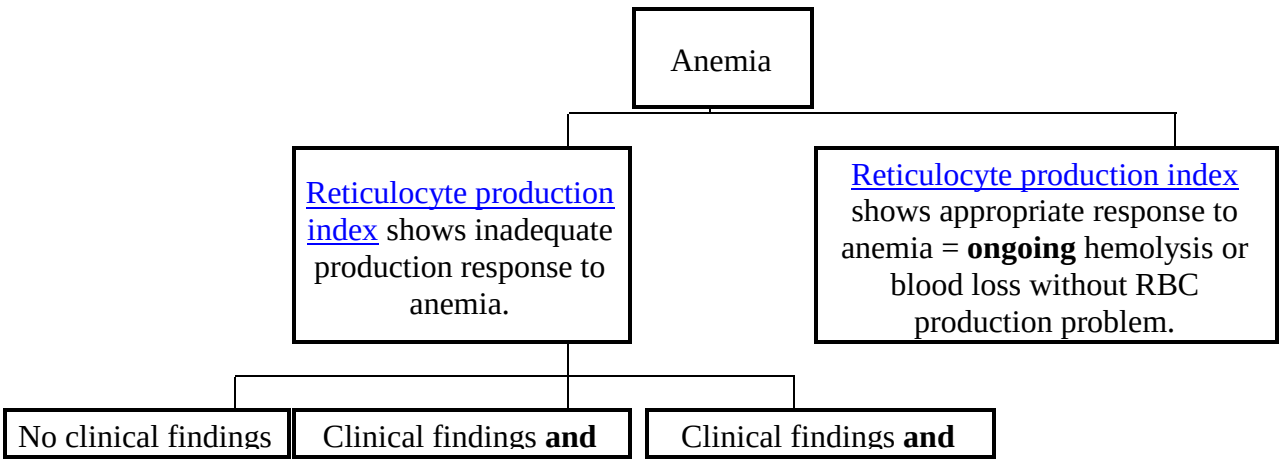
When the diagnosis remains difficult, a bone marrow examination allows direct examination of the precursors to red cells.

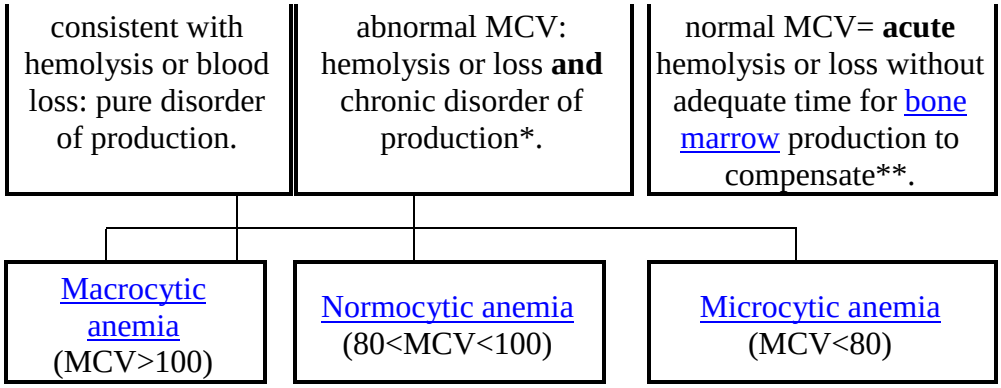
Classification

Production vs. destruction or loss

The "kinetic" approach to anemia yields what many argue is the most clinically relevant classification of anemia. This classification depends on evaluation of several hematological parameters, particularly the blood reticulocyte (precursor of mature RBCs) count. This then yields the classification of defects by decreased RBC production versus increased RBC destruction and/or loss. Clinical signs of loss or destruction include abnormal peripheral blood smear with signs of hemolysis; elevated LDH suggesting cell destruction; or clinical signs of bleeding, such as guiaic-positive stool, radiographic findings, or frank bleeding.

Here is a simplified schematic of this approach:



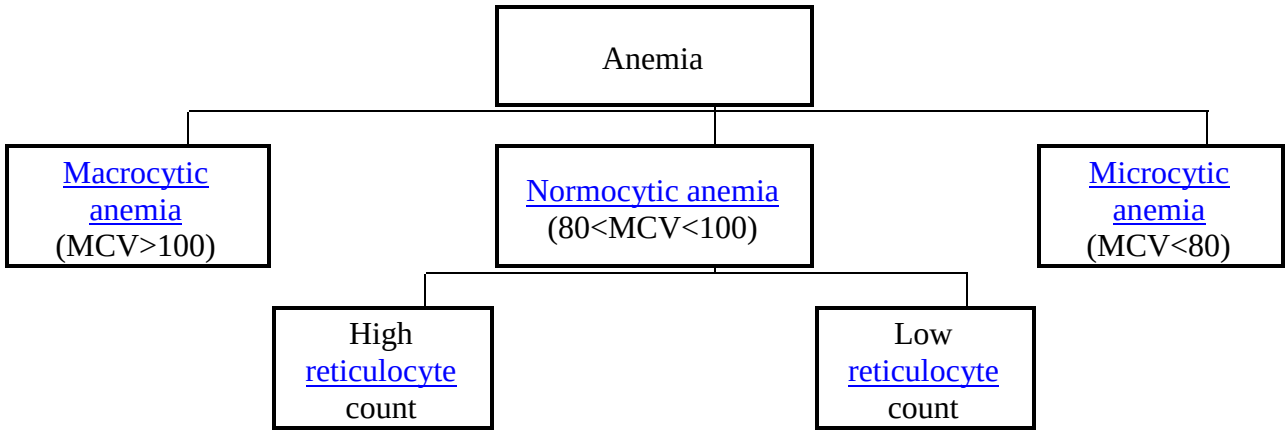


** For instance, sickle cell anemia with superimposed iron deficiency; chronic gastric bleeding with B12 and folate deficiency; and other instances of anemia with more than one cause. ** Confirm by repeating reticulocyte count: ongoing combination of low reticulocyte production index, normal MCV and hemolysis or loss may be seen in bone marrow failure or anemia of chronic disease, with superimposed or related hemolysis or blood loss.*

Red blood cell size

In the morphological approach, anemia is classified by the size of red blood cells; this is either done automatically or on microscopic examination of a peripheral blood smear. The size is reflected in the *mean corpuscular volume* (MCV). If the cells are smaller than normal (under 80 fl), the anemia is said to be *microcytic*; if they are normal size (80-100 fl), *normocytic*; and if they are larger than normal (over 100 fl), the anemia is classified as *macrocytic*. This scheme quickly exposes some of the most common causes of anemia; for instance, a microcytic anemia is often the result of iron deficiency. In clinical workup, the MCV will be one of the first pieces of information available; so even among clinicians who consider the "kinetic" approach more useful philosophically, morphology will remain an important element of classification and diagnosis.

Here is a schematic representation of how to consider anemia with MCV as the starting point:



Other characteristics visible on the peripheral smear may provide valuable clues about a more specific diagnosis; for example, abnormal white blood cells may point to a cause in the bone marrow.

Microcytic anemia

- Iron deficiency anemia is the most common type of anemia overall and it has many causes. RBCs often appear hypochromic (paler than usual) and microcytic (smaller than usual) when viewed with a microscope.
    - Iron deficiency anemia is caused by insufficient dietary intake or absorption of iron to replace losses from menstruation or losses due to diseases.[2] Iron is an essential part of hemoglobin, and low iron levels result in decreased incorporation of hemoglobin into red blood cells. In the United States, 20% of all women of childbearing age have iron deficiency anemia, compared with only 2% of adult men. The principal cause of iron deficiency anemia in premenopausal women is blood lost during menses. Studies have shown that iron deficiency without anemia causes poor school performance and lower IQ in teenage girls. Iron deficiency is the most prevalent deficiency state on a worldwide basis. Iron found in animal meats are more easily absorbed by the body than iron found in non-meat sources. In countries where animal meats are only occasionally available in the diet, iron deficiency anemia is six to eight times more prevalent than in North America and Europe. Iron deficiency is sometimes the cause of abnormal fissuring of the angular (corner) sections of the lips (angular cheilitis).
    - Iron deficiency anemia can also due to bleeding lesions of the gastrointestinal tract. Fecal occult blood testing, upper endoscopy and lower endoscopy should be performed to identify bleeding lesions. In men and post-menopausal women the chances are higher that bleeding from the gastrointestinal tract could be due to colon polyp or colorectal cancer.
    - Worldwide, the most common cause of iron deficiency anemia is parasitic infestation (hookworm, amebiasis, schistosomiasis and whipworm).[3]

A mnemonic commonly used to remember causes of microcytic anemia is ***TAILS***: ***T*** - Thalassemia, ***A*** - Anemia of chronic disease, ***I*** - Iron deficiency anemia, ***L*** - Lead toxicity associated anemia, ***S*** - Sideroblastic anemia.

Normocytic anemia

Normocytic anaemia is when the overall Hb levels are decreased, but the red blood cell size (MCV) remains normal. Causes include:

- Acute blood loss
- Anemia of chronic disease
- Aplastic anemia (bone marrow failure)
- Hemolytic anemia

Macrocytic anemia

- Megaloblastic anemia due to a deficiency of either vitamin B12 or folic acid (or both) due either to inadequate intake or insufficient absorption. Folate deficiency normally does not produce neurological symptoms, while B12 deficiency does. Megaloblastic anemia is the most common cause of macrocytic anemia.
- Pernicious anemia is an autoimmune condition directed against the parietal cells of the stomach. Parietal cells produce intrinsic factor, required to absorb vitamin B12 from food. Therefore, the destruction of the parietal cells causes a lack of intrinsic factor, leading to poor absorption of vitamin B12.
- Alcoholism

- Methotrexate, zidovudine, and other drugs that inhibit DNA replication. This is the most common etiology in nonalcoholic patients.

Macrocytic anemia can be further divided into "megaloblastic anemia" or "non-megaloblastic macrocytic anemia". The cause of megaloblastic anemia is primarily a failure of DNA synthesis with preserved RNA synthesis, which result in restricted cell division of the progenitor cells. The megaloblastic anemias often present with neutrophil hypersegmentation (6-10 lobes). The non-megaloblastic macrocytic anemias have different etiologies (i.e. there is unimpaired DNA globin synthesis,) which occur, for example in alcoholism.

In addition to the non-specific symptoms of anemia, specific symptoms of vitamin B12 deficiency include neuropathy, in particular balance difficulties from posterior column spinal cord pathology,[4] and having a smooth, red tongue, (glossitis). The treatment for vitamin B12-deficient macrocytic and pernicious anemias was first devised by William Murphy who bled dogs to make them anemic and then fed them various substances to see what (if anything) would make them healthy again. He discovered that ingesting large amounts of liver seemed to cure the disease. George Minot and George Whipple then set about to chemically isolate the curative substance and ultimately were able to isolate the vitamin B12 from the liver. All three shared the 1934 Nobel Prize in Medicine. [5]

Dimorphic anemia

When two causes of anemia act simultaneously, e.g., macrocytic hypochromic, due to hookworm infestation leading to deficiency of both iron and vitamin B12 or folic acid [6] or following a blood transfusion more than one abnormality of red cell indices may be seen. Evidence for multiple causes appears with an elevated RBC distribution width (RDW), which suggests a wider-than-normal range of red cell sizes.

Possible complications

Anemia diminishes the capability of individuals who are affected to perform physical activities. This is a result of one's muscles being forced to depend on anaerobic metabolism. The lack of iron associated with anemia can cause many complications, including hypoxemia, brittle or rigid fingernails, cold intolerance, impaired immune function, and possible behavioral disturbances in children.

Hypoxemia resulting from anemia can worsen the cardio-pulmonary status of patients with pre-existing chronic pulmonary disease. Brittle or rigid fingernails may be a result of abnormal thinness of nails due to insufficient iron supply. Cold intolerance occurs in one in five patients with iron deficiency anemia, and becomes visible through numbness and tingling. Impaired immune functioning leading to increased likelihood of sickness is another possible complication.

Anemia during pregnancy

Anemia affects 20% of all females of childbearing age in the United States. Because of the subtlety of the symptoms, women are often unaware that they have this disorder, as they attribute the symptoms to the stresses of their daily lives. Possible problems for the fetus include increased risk of growth retardation, prematurity, intrauterine death, rupture of the amnion and infection.

During pregnancy, women should be especially aware of the symptoms of anemia, as an adult female loses an average of two milligrams of iron daily. Therefore, she must intake a similar

quantity of iron in order to make up for this loss. Additionally, a woman loses approximately 500 milligrams of iron with each pregnancy, compared to a loss of 4-100 milligrams of iron with each period. Possible consequences for the mother include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and increased need for blood transfusion in the postpartum period.

Diet and anemia

Consumption of food rich in iron is essential to prevention of iron deficiency anemia.

The twenty richest sources of iron in descending order: Canned clams; Fortified dry cereals; Cooked oysters; Organ meats (liver, giblets); *Fortified instant cooked cereals; Soybeans, mature, cooked; Pumpkin and squash seed kernels, roasted; White beans; Blackstrap molasses, 1 Tbsp; Lentils, cooked; Spinach, cooked from fresh; Beef (chuck); Kidney beans; Sardines; Beef(rib); Chickpeas; Duck, meat only; Lamb shoulder; Prune juice.[7]

Certain foods have been found to interfere with iron absorption in the gastrointestinal tract, and these foods should be avoided in persons with established iron deficiency. They include tea, coffee, wheat bran, rhubarb, chocolate, red wine, and dairy products.[8]

Treatments for anemia

There are many different treatments for anemia and the treatment depends on severity and the cause.

Iron deficiency from nutritional causes is rare in non-menstruating adults (men and post-menopausal women). The diagnosis of iron deficiency mandates a search for potential sources of loss such as gastrointestinal bleeding from ulcers or colon cancer. Mild to moderate iron deficiency anemia is treated by iron supplementation with ferrous sulfate or ferrous gluconate. Vitamin C may aid in the body's ability to absorb iron.

Vitamin supplements given orally (folic acid) or subcutaneously vitamin b-12 will replace specific deficiencies.

In anemia of chronic disease, anemia associated with chemotherapy, or anemia associated with renal disease, some clinicians prescribe recombinant erythropoietin, epoetin alfa, to stimulate red cell production.

In severe cases of anemia, or with ongoing blood loss, a blood transfusion may be necessary.

Blood transfusions for anemia

Doctors attempt to avoid blood transfusion in general, but there are several instances where doctors are now more aggressive than in the past. For instance, the currently accepted Rivers protocol for early goal directed therapy for sepsis requires keeping the hematocrit above 30; this is based on evidence that even moderate anemia reduces survival [9]. The presumed physiological principle is that the reduction in oxygen delivery associated with anemia is especially dangerous to people who are already at risk for organ damage from lack of perfusion. There is controversy about what hematocrit or hemoglobin levels should be used as "triggers" for transfusion in other settings. Anemia also may be especially risky for people with acute coronary syndromes, again because

anemia hampers already impaired oxygen delivery to the heart.[10] However, the point at which this danger emerges in other settings is controversial and awaits further study. [11]

Finally, chronic anemia may result in behavioral disturbances in children as a direct result of impaired neurological development in infants, and reduced scholastic performance in children of school age. Behavioral disturbances may even surface as an attention deficit disorder.

HAEMOBLASTOSIS

Leukemia or **leukaemia** (see spelling differences) is a cancer of the blood or bone marrow and is characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes). It is part of the broad group of diseases called hematological neoplasms.

Symptoms

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system (white blood cells etc.) to start attacking other body cells.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea. All symptoms may also be attributable to other diseases; for diagnosis, blood tests and a bone marrow examination are required.

Some other related symptoms

- Fever, chills, night sweats and other flu-like symptoms
- Weakness and fatigue
- Loss of appetite and/or weight
- Swollen or bleeding gums
- Excess bleeding (from minor cut)
- Neurological symptoms (headache)
- Enlarged liver and spleen
- Easy Bruising
- Frequent Infection
- Bone Pain
- Joint Pain
- Swollen Tonsils

The word leukemia, which means 'white blood,' is derived from the disease's namesake high white blood cell counts that most leukemia patients have before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope. Frequently, these extra white blood cells are immature or dysfunctional. The excessive number of cells can also interfere with the normal function of other cells.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called aleukemia. The bone marrow still contains cancerous white blood cells, and they are disrupting the normal production of blood cells. However, they are staying in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.

Four major types

Leukemia is a broad term covering a spectrum of diseases.

Leukemia is clinically and pathologically split into its *acute* and *chronic* forms.

- *Acute leukemia* is characterized by the rapid proliferation of immature blood cells. This crowding makes the bone marrow unable to produce healthy blood cells. Acute forms of leukemia can occur in children and young adults. (In fact, it is a more common cause of death for children in the US than any other type of malignant disease). Immediate treatment is required in acute leukemias due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. However, CNS involvement is uncommon, though the disease occasionally causes cranial nerve palsies.

- *Chronic leukemia* is distinguished by the excessive build up of relatively mature, but still abnormal, blood cells. Typically taking months to years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy.

Furthermore, the diseases are classified according to the type of abnormal cell found most in the blood (lymphoid cells vs. myeloid cells).

Combining these two classifications provides a total of four main categories:

	Acute	**Chronic**
lymphocytic leukemia	Acute lymphocytic leukemia (also known as Acute Lymphoblastic Leukemia, or ALL) is the most common type of leukemia in young children. This disease also affects adults, especially those age 65 and older.	Chronic lymphocytic leukemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children.
myelogenous leukemia (or "myeloid")	Acute myelogenous leukemia (also known as Acute Myeloid Leukemia, or AML) occurs more commonly in adults than in children. This type of leukemia was previously called	Chronic myelogenous leukemia (CML) occurs mainly in adults. A very small number of children also

	"acute nonlymphocytic leukemia".	develop this disease.

The most common forms in adults are AML and CLL, whereas in children ALL is more prevalent.

Causes and risk factors

There is no single known cause for all of the different types of leukemia. The different leukemias likely have different causes, and very little is certain about what causes them. Researchers have strong suspicions about four possible causes:

- natural or artificial ionizing radiation
- certain kinds of chemicals
- some viruses
- genetic predispositions

Leukemia, like other cancers, result from somatic mutations in the DNA which activate oncogenes or deactivate tumor suppressor genes, and disrupt the regulation of cell death, differentiation or division. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenic substances and are likely to be influenced by genetic factors. Cohort and case-control studies have linked exposure to petrochemicals, such as benzene, and hair dyes to the development of some forms of leukemia.

Viruses have also been linked to some forms of leukemia. For example, certain cases of ALL are associated with viral infections by either the human immunodeficiency virus (HIV, responsible for AIDS) or human T-lymphotropic virus (HTLV-1 and -2, causing adult T-cell leukemia/lymphoma).

Fanconi anemia is also a risk factor for developing acute myelogenous leukemia.

Until the cause or causes of leukemia are found, there is no way to prevent the disease. Even when the causes become known, they may prove to be things which are not readily controllable, such as naturally occurring background radiation, and therefore not especially helpful for prevention purposes.

Treatment options for leukemia by type

Acute Myelogenous Leukemia (AML)

It is most common for adults; more men than women are affected. Many different chemotherapeutic plans are available for the treatment of AML. Overall, the strategy is to control bone marrow and systemic (whole-body) disease while offering specific treatment for the central nervous system (CNS), if involved. In general, most oncologists rely on combinations of drugs for the initial, induction phase of chemotherapy. Such combination chemotherapy usually offers the benefits of early remission (lessening of the disease) and a lower risk of disease resistance. Consolidation or "maintenance" treatments may be given to prevent disease recurrence once remission has been achieved. Consolidation treatment often entails a repetition of induction chemotherapy or the intensification chemotherapy with added drugs. By contrast, maintenance treatment involves drug doses that are lower than those administered during the induction phase.

In addition, specific treatment plans may be used, depending on the type of leukemia that has been diagnosed. Whatever the plan, it is important for the patient to understand the treatment that is being given and the decision-making process behind the choice.

Chronic Myelogenous Leukemia (CML)

The challenge of treating newly diagnosed CML is to determine the best overall strategy to control the disease. General strategies for management include a variety of options:

Leukapheresis, also known as a peripheral blood stem cell transplant, with stem cell cryopreservation (frozen storage) prior to any other treatment. The patient's blood is passed through a machine that removes the stem cells and then returns the blood to the patient. Leukapheresis usually takes 3 or 4 hours to complete. The stem cells may or may not be treated with drugs to kill any cancer cells. The stem cells then are stored until they are transplanted back into the patient.

Acute Lymphocytic Leukemia (ALL)

Proper management of ALL focuses on control of bone marrow and systemic (whole-body) disease as well as prevention of cancer at other sites, particularly the central nervous system (CNS). In general, ALL treatment is divided into several phases:

Induction chemotherapy to bring about remission - that is, leukemic cells are no longer found in bone marrow samples. For adult ALL, standard induction plans include prednisone, vincristine, and an anthracycline drug; other drug plans may include L-asparaginase or cyclophosphamide. For children with low-risk ALL, standard therapy usually consists of three drugs (prednisone, L-asparaginase, and vincristine) for the first month of treatment. High-risk children may receive these drugs plus an anthracycline such as daunorubicin.

Consolidation therapy (1-3 months in adults; 4-8 months in children) to eliminate any leukemia cells that are still "hiding" within the body. A combination of chemotherapeutic drugs is used to keep the remaining leukemia cells from developing resistance. Patients with low- to average-risk ALL receive therapy with antimetabolite drugs such as methotrexate and 6-mercaptopurine (6-MP). High-risk patients receive higher drug doses plus treatment with extra chemotherapeutic agents.

CNS prophylaxis (preventive therapy) to stop the cancer from spreading to the brain and nervous system. Standard prophylaxis may consist of:

1. Cranial (head) irradiation plus spinal tap or intrathecal (IT) delivery (into the space around the spinal cord and brain) of the drug methotrexate.
2. High-dose systemic and IT methotrexate, without cranial irradiation
3. IT chemotherapy.

Only children with T-cell leukemia, a high white blood cell count, or leukemia cells in the cerebrospinal fluid (CSF) need to receive cranial irradiation as well as IT therapy.

Chronic Lymphocytic Leukemia (CLL)

The unpleasant truth is that CLL is probably "incurable" by present treatments. But, fortunately, a large group of CLL patients do not require therapy. Studies suggest that people with Stage A CLL (that is, individuals who have fewer than three areas of enlarged lymphoid tissue) do not benefit from early treatment. They may, in fact, suffer drawbacks because of it. Therefore, most oncologists base CLL treatment upon both the stage and symptoms of the patient.

For example, in older patients (60+ years) who have low-risk early stage disease (Rai Stage 0) a conservative "watch and wait" approach may be taken.

By contrast, older individuals with CLL-related complications or more advanced disease (Rai Stage III or IV) may benefit from chemotherapy and treatment with a corticosteroid (e.g., prednisone, prednisolone).

Corticosteroids are first-line agents for people in whom the immune systems has been altered by CLL. CLL may cause autoimmune syndromes in which the patient's immune system attacks and destroys his or her own blood cells. When the red blood cells are affected, the condition is known as immunohemolytic anemia, characterized by decreased numbers of red blood cells, which may cause fatigue, dizziness, and shortness of breath. When the blood platelets are affected, it is called immune-mediated thrombocytopenia, in which a decreased numbers of platelets may lead to bleeding.

For younger patients who are experiencing symptoms, the physician may consider early chemotherapy, plus allogeneic or autologous bone marrow transplantation (alloBMT; autoBMT).

In general, the indications for treatment are:

- falling hemoglobin or platelet count
- progression to a later stage of disease
- painful, disease-related overgrowth of lymph nodes or spleen
- lymphocyte doubling time (an indicator of lymphocyte reproduction) of fewer than 12 months

HEMOCOAGULATION DESORDERS

Hemophilia

Genetic deficiencies and a rare autoimmune disorder may lower plasma clotting factor levels of coagulation factors needed for a normal clotting process. When a blood vessel is injured, a temporary scab does form, but the missing coagulation factors prevent fibrin formation which is necessary to maintain the blood clot. Therefore, there is no increase in bleeding time with hemophilia because platelets are intact, allowing the formation of these temporary hemostatic plugs (clots). However, "late" bleeding is affected, because these hemostatic plugs are not able to be maintained.

The bleeding with external injury is normal, but incidence of late re-bleeding and internal bleeding is increased, especially into muscles, joints, or bleeding into closed spaces. Major complications include hemarthrosis, hemorrhage, Gastrointestinal bleeding, and menorrhagia.

Causes

It is caused by a lack of clotting factors:

- Haemophilia A has a lack of the clotting Factor VIII. (Haemophilia A occurs in 90% of cases.)
- Haemophilia B has a lack of the clotting Factor IX.
- Haemophilia C has a lack of the clotting Factor XI.

Genetics structure

Females possess two X-chromosomes, whereas males have one X and one Y chromosome. Since the mutations causing the disease are recessive, a woman carrying the defect on one of her X-chromosomes may not be affected by it, as the equivalent allele on her other chromosome should express itself to produce the necessary clotting factors. However the Y-chromosome in men has no gene for factors VIII or IX. If the genes responsible for production of factor VIII or factor IX present on a male's X-chromosome is deficient there is no equivalent on the Y-chromosome, so the deficient gene is not masked by the dominant allele and he will develop the illness.

Differential Diagnosis

Hemophilia A can be mimimicked by von Willebrand Disease

- von Willebrand Disease type 2A, where decreased levels of von Willebrand Factor can lead to premature proteolysis of Factor VIII. In contrast to hemophilia, vWD type 2A is inherited in an autosomal dominant fashion.
- von Willebrand Disease type 2N, where von Willebrand Factor cannot bind Factor VIII
- von Willebrand Disease type 3, where lack of von Willebrand Factor causes premature proteolysis of Factor VIII. In contrast to hemophilia, vWD type 3 is inherited in an autosomal recessive fashion.

Treatment

Though there is no cure for haemophilia, it can be controlled with **regular injections** of the deficient clotting factor, i.e. factor VIII in haemophilia A or factor IX in haemophilia B. Some haemophiliacs develop antibodies (inhibitors) against the replacement factors given to them, so the amount of the factor has to be increased or non-human replacement products must be given, such as porcine factor VIII Troy.

If a patient becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be overcome with recombinant human factor VII (NovoSeven®), which is registered for this indication in many countries.

In western countries, common standards of care fall into one of two categories: prophylaxis or on-demand. Prophylaxis involves the infusion of clotting factor on a regular schedule in order to keep clotting levels sufficiently high to prevent spontaneous bleeding episodes. On-demand treatment involves treating bleeding episodes once they arise.

As a direct result of the contamination of the blood supply in the late 1970s and early/mid 1980s with viruses such as Hepatitis and HIV, new methods were developed in the production of clotting factor products. The initial response was to heat treat (pasteurize) plasma-derived factor concentrate, followed by the development of monoclonal factor concentrates which use a combination of heat treatment and affinity chromatography to inactivate any viral agents in the pooled plasma from which the factor concentrate is derived. The Lindsay Tribunal in Ireland investigated, among other things, the slow adoption of the new methods.

Since 1993 (Dr. Mary Nugent), recombinant factor products (which are typically cultured in Chinese hamster ovary (CHO) tissue culture cells and involve little, if any human plasma products) have become available and are widely used in wealthier western countries. While recombinant clotting factor products offer higher purity and safety, they are, like concentrate, extremely expensive, and not generally available in the developing world. In many cases, factor products of any sort are difficult to obtain in developing countries.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (**DIC**), also called **consumptive coagulopathy**, is a pathological process in the body where the blood starts to coagulate throughout the whole body. This depletes the body of its platelets and coagulation factors, and there is a paradoxically increased risk of hemorrhage. It occurs in critically ill patients, especially those with Gram-negative sepsis (particularly meningococcal sepsis) and acute promyelocytic leukemia

Causes

There are a variety of causes of DIC, all usually causing the release of chemicals into the blood that instigates the coagulation.

- Sepsis, particularly with gram-negative bacteria.
- Obstetric complications (most common cause), with chemicals from the uterus being released into the blood, or from amniotic fluid embolisms, and eclampsia can be causes. Another obstetric condition which can cause DIC is *abruptio placentae*.
- Tissue trauma such as burns, accidents, surgery or shock.
- Liver disease
- Incompatible blood transfusion reactions or massive blood transfusion (more than the total circulatory volume)
- Malignant cancers, or widespread tissue damage (e.g. burns), or hypersensitivity reactions all can produce the chemicals leading to a DIC.
- Viral hemorrhagic fevers bring about their frank effects, paradoxically, by causing DIC.
- Envenomation by some species of venomous snakes, such as those belonging to the genus Diagnosis

Although numerous blood tests are often performed on patients prone to DIC, the important measures are: full blood count (especially the platelet count), fibrin degradation products or D-dimer tests (markers of fibrinolysis), bleeding time and fibrinogen levels. Decreased platelets, elevated FDPs or D-dimers, prolonged bleeding time and decreased fibrinogen are markers of DIC.

Treatment

The underlying cause must be treated initially. Anticoagulants are only given when indicated (development of thrombotic renal complications) as patients with DIC are prone to bleeding. Platelets may be transfused if counts are very low, and fresh frozen plasma may be administered.

DIC results in lower fibrinogen (as it has all been converted to fibrin), and this can be tested for in the hospital lab. A more specific test is for "fibrin split products" (FSPs) or "fibrin degradation products" (FDPs) which are produced when fibrin undergoes degradation when blood clots are dissolved by fibrinolysis.

In some situations, infusion with antithrombin may be necessary. A new development is drotrecogin alfa (Xigris®), a recombinant activated protein C product. Activated Protein C (APC) deactivates clotting factors V and VIII, and the presumed mechanism of action of drotrecogin is the cessation of the intravascular coagulation. Due to its high cost, it is only used strictly on indication in intensive care patients.[1]

The prognosis for those with DIC, depending on its cause, is often grim, leading the initials to be known colloquially as "death is coming".[2]

HAEMATOLOGY

ANEMIA

Anemia (AmE) or **anæmia** (BrE), from the Greek (Ἀναιμία) meaning "without blood", is a deficiency of red blood cells (RBCs) and/or hemoglobin. This results in a reduced ability of blood to transfer oxygen to the tissues, causing tissue hypoxia. Since all human cells depend on oxygen for survival, varying degrees of anemia can have a wide range of clinical consequences. Hemoglobin (the oxygen-carrying protein in the red blood cells) has to be present to ensure adequate oxygenation of all body tissues and organs. The three main classes of anemia include excessive blood loss (acutely such as a hemorrhage or chronically through low-volume loss), excessive blood cell destruction (hemolysis) or deficient red blood cell production (ineffective hematopoiesis). In menstruating women, dietary iron deficiency is a common cause of deficient red blood cell production.

Anemia is the most common disorder of the blood. There are several kinds of anemia, produced by a variety of underlying causes. Anemia can be classified in a variety of ways, based on the morphology of RBCs, underlying etiologic mechanisms, and discernible clinical spectra, to mention a few.

There are two major approaches of classifying anemias, the "kinetic" approach which involves evaluating production, destruction and loss[1], and the "morphologic" approach which groups anemia by red blood cell size. The morphologic approach uses a quickly available and cheap lab test as its starting point (the MCV). On the other hand, focusing early on the question of production may allow the clinician more rapidly to expose cases where multiple causes of anemia coexist.

Signs and symptoms

Anemia goes undetected in many people, and symptoms can be vague. Most commonly, people with anemia report a feeling of weakness or fatigue, general malaise and sometimes a poor concentration. People with more severe anemia often report dyspnea (shortness of breath) on exertion. Very severe anemia prompts the body to compensate by increasing cardiac output, leading to palpitations and sweatiness, and to heart failure.

Pallor (pale skin, mucosal linings and nail beds) is often a useful diagnostic sign in moderate or severe anemia, but it is not always apparent. Other useful signs are cheilosis and koilonychia.

Diagnosis

Generally, clinicians request complete blood counts in the first batch of blood tests in the diagnosis of a suspected anemia. Apart from reporting the number of red blood cells and the hemoglobin level, the automatic counters also measure the size of the red blood cells by flow cytometry, which is an important tool in distinguishing between the causes of anemia. Examination of a stained blood smear using a microscope can also be helpful, and is sometimes a necessity in regions of the world where automated analysis is less accessible.

In modern counters, four parameters (RBC Count, hemoglobin concentration, MCV and RDW) are measured, allowing others (hematocrit, MCH and MCHC) to be calculated, and compared to values adjusted for age and sex. Some counters estimate hematocrit from direct measurements. For adult men, a hemoglobin level less than 13.0 g/dl is diagnostic of anemia, and for adult women, the diagnostic threshold is below 12.0 g/dl.

Reticulocyte counts, and the "kinetic" approach to anemia, have become more common than in the past in the large medical centers of the United States and some other wealthy nations, in part because some automatic counters now have the capacity to include reticulocyte counts. A reticulocyte count is a quantitative measure of the bone marrow's production of new red blood cells. The reticulocyte production index is a calculation of the ratio between the level of anemia and the extent to which the reticulocyte count has risen in response. If the degree of anemia is significant, even a "normal" reticulocyte count actually may reflect an inadequate response.

If an automated count is not available, a reticulocyte count can be done manually following special staining of the blood film. In manual examination, activity of the bone marrow can also be gauged qualitatively by subtle changes in the numbers and the morphology of young RBCs by examination under a microscope. Newly formed RBCs are usually slightly larger than older RBCs and show polychromasia. Even where the source of blood loss is obvious, evaluation of erythropoiesis can help assess whether the bone marrow will be able to compensate for the loss, and at what rate.

When the cause is not obvious, clinicians use other tests: ESR, ferritin, serum iron, transferrin, RBC folate level, serum vitamin B12, hemoglobin electrophoresis, renal function tests (e.g. serum creatinine).

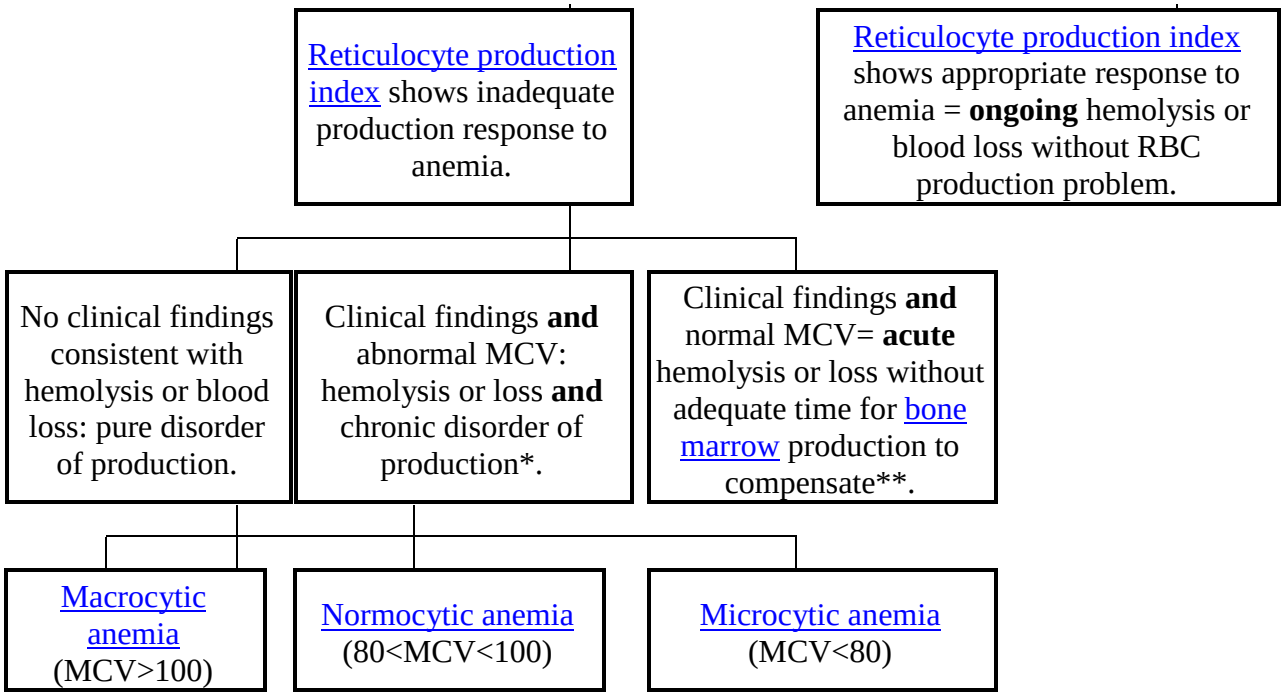
When the diagnosis remains difficult, a bone marrow examination allows direct examination of the precursors to red cells.

Classification

Production vs. destruction or loss

The "kinetic" approach to anemia yields what many argue is the most clinically relevant classification of anemia. This classification depends on evaluation of several hematological parameters, particularly the blood reticulocyte (precursor of mature RBCs) count. This then yields the classification of defects by decreased RBC production versus increased RBC destruction and/or loss. Clinical signs of loss or destruction include abnormal peripheral blood smear with signs of hemolysis; elevated LDH suggesting cell destruction; or clinical signs of bleeding, such as guiaic-positive stool, radiographic findings, or frank bleeding.

Here is a simplified schematic of this approach:

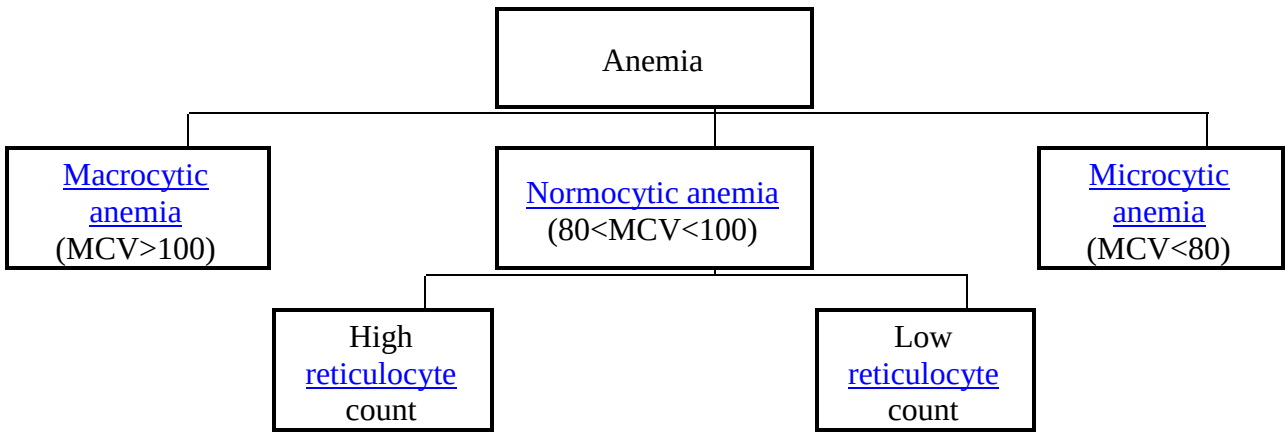


** For instance, sickle cell anemia with superimposed iron deficiency; chronic gastric bleeding with B12 and folate deficiency; and other instances of anemia with more than one cause. ** Confirm by repeating reticulocyte count: ongoing combination of low reticulocyte production index, normal MCV and hemolysis or loss may be seen in bone marrow failure or anemia of chronic disease, with superimposed or related hemolysis or blood loss.*

Red blood cell size

In the morphological approach, anemia is classified by the size of red blood cells; this is either done automatically or on microscopic examination of a peripheral blood smear. The size is reflected in the *mean corpuscular volume* (MCV). If the cells are smaller than normal (under 80 fl), the anemia is said to be *microcytic*; if they are normal size (80-100 fl), *normocytic*; and if they are larger than normal (over 100 fl), the anemia is classified as *macrocytic*. This scheme quickly exposes some of the most common causes of anemia; for instance, a microcytic anemia is often the result of iron deficiency. In clinical workup, the MCV will be one of the first pieces of information available; so even among clinicians who consider the "kinetic" approach more useful philosophically, morphology will remain an important element of classification and diagnosis.

Here is a schematic representation of how to consider anemia with MCV as the starting point:



Other characteristics visible on the peripheral smear may provide valuable clues about a more specific diagnosis; for example, abnormal white blood cells may point to a cause in the bone marrow.

Microcytic anemia

- Iron deficiency anemia is the most common type of anemia overall and it has many causes. RBCs often appear hypochromic (paler than usual) and microcytic (smaller than usual) when viewed with a microscope.
  - Iron deficiency anemia is caused by insufficient dietary intake or absorption of iron to replace losses from menstruation or losses due to diseases.[2] Iron is an essential part of hemoglobin, and low iron levels result in decreased incorporation of hemoglobin into red blood cells. In the United States, 20% of all women of childbearing age have iron deficiency anemia, compared with only 2% of adult men. The principal cause of iron deficiency anemia in premenopausal women is blood lost during menses. Studies have shown that iron deficiency without anemia causes poor school performance and lower IQ in teenage girls. Iron deficiency is the most prevalent deficiency state on a worldwide basis. Iron found in animal meats are more easily absorbed by the body than iron found in non-meat sources. In countries where animal meats are only occasionally available in the diet, iron deficiency anemia is six to eight times more prevalent than in North America and Europe. Iron deficiency is sometimes the cause of abnormal fissuring of the angular (corner) sections of the lips (angular cheilitis).
  - Iron deficiency anemia can also due to bleeding lesions of the gastrointestinal tract. Fecal occult blood testing, upper endoscopy and lower endoscopy should be performed to identify bleeding lesions. In men and post-menopausal women the chances are higher that bleeding from the gastrointestinal tract could be due to colon polyp or colorectal cancer.
  - Worldwide, the most common cause of iron deficiency anemia is parasitic infestation (hookworm, amebiasis, schistosomiasis and whipworm).[3]

A mnemonic commonly used to remember causes of microcytic anemia is ***TAILS***: ***T*** - Thalassemia, ***A*** - Anemia of chronic disease, ***I*** - Iron deficiency anemia, ***L*** - Lead toxicity associated anemia, ***S*** - Sideroblastic anemia.

Normocytic anemia

Normocytic anaemia is when the overall Hb levels are decreased, but the red blood cell size (MCV) remains normal. Causes include:

- Acute blood loss
- Anemia of chronic disease
- Aplastic anemia (bone marrow failure)
- Hemolytic anemia

Macrocytic anemia

- Megaloblastic anemia due to a deficiency of either vitamin B12 or folic acid (or both) due either to inadequate intake or insufficient absorption. Folate deficiency normally does not produce neurological symptoms, while B12 deficiency does. Megaloblastic anemia is the most common cause of macrocytic anemia.

- Pernicious anemia is an autoimmune condition directed against the parietal cells of the stomach. Parietal cells produce intrinsic factor, required to absorb vitamin B12 from food. Therefore, the destruction of the parietal cells causes a lack of intrinsic factor, leading to poor absorption of vitamin B12.
- Alcoholism
- Methotrexate, zidovudine, and other drugs that inhibit DNA replication. This is the most common etiology in nonalcoholic patients.

Macrocytic anemia can be further divided into "megaloblastic anemia" or "non-megaloblastic macrocytic anemia". The cause of megaloblastic anemia is primarily a failure of DNA synthesis with preserved RNA synthesis, which result in restricted cell division of the progenitor cells. The megaloblastic anemias often present with neutrophil hypersegmentation (6-10 lobes). The non-megaloblastic macrocytic anemias have different etiologies (i.e. there is unimpaired DNA globin synthesis,) which occur, for example in alcoholism.

In addition to the non-specific symptoms of anemia, specific symptoms of vitamin B12 deficiency include neuropathy, in particular balance difficulties from posterior column spinal cord pathology,[4] and having a smooth, red tongue, (glossitis). The treatment for vitamin B12-deficient macrocytic and pernicious anemias was first devised by William Murphy who bled dogs to make them anemic and then fed them various substances to see what (if anything) would make them healthy again. He discovered that ingesting large amounts of liver seemed to cure the disease. George Minot and George Whipple then set about to chemically isolate the curative substance and ultimately were able to isolate the vitamin B12 from the liver. All three shared the 1934 Nobel Prize in Medicine. [5]

Dimorphic anemia

When two causes of anemia act simultaneously, e.g., macrocytic hypochromic, due to hookworm infestation leading to deficiency of both iron and vitamin B12 or folic acid [6] or following a blood transfusion more than one abnormality of red cell indices may be seen. Evidence for multiple causes appears with an elevated RBC distribution width (RDW), which suggests a wider-than-normal range of red cell sizes.

Possible complications

Anemia diminishes the capability of individuals who are affected to perform physical activities. This is a result of one's muscles being forced to depend on anaerobic metabolism. The lack of iron associated with anemia can cause many complications, including hypoxemia, brittle or rigid fingernails, cold intolerance, impaired immune function, and possible behavioral disturbances in children.

Hypoxemia resulting from anemia can worsen the cardio-pulmonary status of patients with pre-existing chronic pulmonary disease. Brittle or rigid fingernails may be a result of abnormal thinness of nails due to insufficient iron supply. Cold intolerance occurs in one in five patients with iron deficiency anemia, and becomes visible through numbness and tingling. Impaired immune functioning leading to increased likelihood of sickness is another possible complication.

Anemia during pregnancy

Anemia affects 20% of all females of childbearing age in the United States. Because of the subtlety of the symptoms, women are often unaware that they have this disorder, as they attribute the

symptoms to the stresses of their daily lives. Possible problems for the fetus include increased risk of growth retardation, prematurity, intrauterine death, rupture of the amnion and infection.

During pregnancy, women should be especially aware of the symptoms of anemia, as an adult female loses an average of two milligrams of iron daily. Therefore, she must intake a similar quantity of iron in order to make up for this loss. Additionally, a woman loses approximately 500 milligrams of iron with each pregnancy, compared to a loss of 4-100 milligrams of iron with each period. Possible consequences for the mother include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and increased need for blood transfusion in the postpartum period.

Diet and anemia

Consumption of food rich in iron is essential to prevention of iron deficiency anemia.

The twenty richest sources of iron in descending order: Canned clams; Fortified dry cereals; Cooked oysters; Organ meats (liver, giblets); *Fortified instant cooked cereals; Soybeans, mature, cooked; Pumpkin and squash seed kernels, roasted; White beans; Blackstrap molasses, 1 Tbsp; Lentils, cooked; Spinach, cooked from fresh; Beef (chuck); Kidney beans; Sardines; Beef(rib); Chickpeas; Duck, meat only; Lamb shoulder; Prune juice.[7]

Certain foods have been found to interfere with iron absorption in the gastrointestinal tract, and these foods should be avoided in persons with established iron deficiency. They include tea, coffee, wheat bran, rhubarb, chocolate, red wine, and dairy products.[8]

Treatments for anemia

There are many different treatments for anemia and the treatment depends on severity and the cause.

Iron deficiency from nutritional causes is rare in non-menstruating adults (men and post-menopausal women). The diagnosis of iron deficiency mandates a search for potential sources of loss such as gastrointestinal bleeding from ulcers or colon cancer. Mild to moderate iron deficiency anemia is treated by iron supplementation with ferrous sulfate or ferrous gluconate. Vitamin C may aid in the body's ability to absorb iron.

Vitamin supplements given orally (folic acid) or subcutaneously vitamin b-12 will replace specific deficiencies.

In anemia of chronic disease, anemia associated with chemotherapy, or anemia associated with renal disease, some clinicians prescribe recombinant erythropoietin, epoetin alfa, to stimulate red cell production.

In severe cases of anemia, or with ongoing blood loss, a blood transfusion may be necessary.

Blood transfusions for anemia

Doctors attempt to avoid blood transfusion in general, but there are several instances where doctors are now more aggressive than in the past. For instance, the currently accepted Rivers protocol for early goal directed therapy for sepsis requires keeping the hematocrit above 30; this is based on evidence that even moderate anemia reduces survival [9]. The presumed physiological principle is

that the reduction in oxygen delivery associated with anemia is especially dangerous to people who are already at risk for organ damage from lack of perfusion. There is controversy about what hematocrit or hemoglobin levels should be used as "triggers" for transfusion in other settings. Anemia also may be especially risky for people with acute coronary syndromes, again because anemia hampers already impaired oxygen delivery to the heart.[10] However, the point at which this danger emerges in other settings is controversial and awaits further study. [11]

Finally, chronic anemia may result in behavioral disturbances in children as a direct result of impaired neurological development in infants, and reduced scholastic performance in children of school age. Behavioral disturbances may even surface as an attention deficit disorder.

HAEMOBLASTOSIS

Leukemia or **leukaemia** (see spelling differences) is a cancer of the blood or bone marrow and is characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes). It is part of the broad group of diseases called hematological neoplasms.

Symptoms

Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may become bruised, bleed excessively, or develop pinprick bleeds (petechiae).

White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the patient's immune system (white blood cells etc.) to start attacking other body cells.

Finally, the red blood cell deficiency leads to anemia, which may cause dyspnea. All symptoms may also be attributable to other diseases; for diagnosis, blood tests and a bone marrow examination are required.

Some other related symptoms

- Fever, chills, night sweats and other flu-like symptoms
- Weakness and fatigue
- Loss of appetite and/or weight
- Swollen or bleeding gums
- Excess bleeding (from minor cut)
- Neurological symptoms (headache)
- Enlarged liver and spleen
- Easy Bruising
- Frequent Infection
- Bone Pain
- Joint Pain
- Swollen Tonsils

The word leukemia, which means 'white blood,' is derived from the disease's namesake high white blood cell counts that most leukemia patients have before treatment. The high number of white blood cells are apparent when a blood sample is viewed under a microscope. Frequently, these extra white blood cells are immature or dysfunctional. The excessive number of cells can also interfere with the normal function of other cells.

Some leukemia patients do not have high white blood cell counts visible during a regular blood count. This less-common condition is called aleukemia. The bone marrow still contains cancerous white blood cells, and they are disrupting the normal production of blood cells. However, they are staying in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For an aleukemic patient, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.

Four major types

Leukemia is a broad term covering a spectrum of diseases.

Leukemia is clinically and pathologically split into its *acute* and *chronic* forms.

- *Acute leukemia* is characterized by the rapid proliferation of immature blood cells. This crowding makes the bone marrow unable to produce healthy blood cells. Acute forms of leukemia can occur in children and young adults. (In fact, it is a more common cause of death for children in the US than any other type of malignant disease). Immediate treatment is required in acute leukemias due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. However, CNS involvement is uncommon, though the disease occasionally causes cranial nerve palsies.

- *Chronic leukemia* is distinguished by the excessive build up of relatively mature, but still abnormal, blood cells. Typically taking months to years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy.

Furthermore, the diseases are classified according to the type of abnormal cell found most in the blood (lymphoid cells vs. myeloid cells).

Combining these two classifications provides a total of four main categories:

	Acute	**Chronic**
lymphocytic leukemia	Acute lymphocytic leukemia (also known as Acute Lymphoblastic Leukemia, or ALL) is the most common type of leukemia in young children. This disease also affects adults,	Chronic lymphocytic leukemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it

	especially those age 65 and older.	almost never affects children.
myelogenous leukemia (or "myeloid")	Acute myelogenous leukemia (also known as Acute Myeloid Leukemia, or AML) occurs more commonly in adults than in children. This type of leukemia was previously called "acute nonlymphocytic leukemia".	Chronic myelogenous leukemia (CML) occurs mainly in adults. A very small number of children also develop this disease.

The most common forms in adults are AML and CLL, whereas in children ALL is more prevalent.

Causes and risk factors

There is no single known cause for all of the different types of leukemia. The different leukemias likely have different causes, and very little is certain about what causes them. Researchers have strong suspicions about four possible causes:

- natural or artificial ionizing radiation
- certain kinds of chemicals
- some viruses
- genetic predispositions

Leukemia, like other cancers, result from somatic mutations in the DNA which activate oncogenes or deactivate tumor suppressor genes, and disrupt the regulation of cell death, differentiation or division. These mutations may occur spontaneously or as a result of exposure to radiation or carcinogenic substances and are likely to be influenced by genetic factors. Cohort and case-control studies have linked exposure to petrochemicals, such as benzene, and hair dyes to the development of some forms of leukemia.

Viruses have also been linked to some forms of leukemia. For example, certain cases of ALL are associated with viral infections by either the human immunodeficiency virus (HIV, responsible for AIDS) or human T-lymphotropic virus (HTLV-1 and -2, causing adult T-cell leukemia/lymphoma).

Fanconi anemia is also a risk factor for developing acute myelogenous leukemia.

Until the cause or causes of leukemia are found, there is no way to prevent the disease. Even when the causes become known, they may prove to be things which are not readily controllable, such as naturally occurring background radiation, and therefore not especially helpful for prevention purposes.

Treatment options for leukemia by type

Acute Myelogenous Leukemia (AML)

It is most common for adults; more men than women are affected. Many different chemotherapeutic plans are available for the treatment of AML. Overall, the strategy is to control bone marrow and systemic (whole-body) disease while offering specific treatment for the central nervous system (CNS), if involved. In general, most oncologists rely on combinations of drugs for the initial, induction phase of chemotherapy. Such combination chemotherapy usually offers the benefits of early remission (lessening of the disease) and a lower risk of disease resistance. Consolidation or

"maintenance" treatments may be given to prevent disease recurrence once remission has been achieved. Consolidation treatment often entails a repetition of induction chemotherapy or the intensification chemotherapy with added drugs. By contrast, maintenance treatment involves drug doses that are lower than those administered during the induction phase.

In addition, specific treatment plans may be used, depending on the type of leukemia that has been diagnosed. Whatever the plan, it is important for the patient to understand the treatment that is being given and the decision-making process behind the choice.

Chronic Myelogenous Leukemia (CML)

The challenge of treating newly diagnosed CML is to determine the best overall strategy to control the disease. General strategies for management include a variety of options:

Leukapheresis, also known as a peripheral blood stem cell transplant, with stem cell cryopreservation (frozen storage) prior to any other treatment. The patient's blood is passed through a machine that removes the stem cells and then returns the blood to the patient. Leukapheresis usually takes 3 or 4 hours to complete. The stem cells may or may not be treated with drugs to kill any cancer cells. The stem cells then are stored until they are transplanted back into the patient.

Acute Lymphocytic Leukemia (ALL)

Proper management of ALL focuses on control of bone marrow and systemic (whole-body) disease as well as prevention of cancer at other sites, particularly the central nervous system (CNS). In general, ALL treatment is divided into several phases:

Induction chemotherapy to bring about remission - that is, leukemic cells are no longer found in bone marrow samples. For adult ALL, standard induction plans include prednisone, vincristine, and an anthracycline drug; other drug plans may include L-asparaginase or cyclophosphamide. For children with low-risk ALL, standard therapy usually consists of three drugs (prednisone, L-asparaginase, and vincristine) for the first month of treatment. High-risk children may receive these drugs plus an anthracycline such as daunorubicin.

Consolidation therapy (1-3 months in adults; 4-8 months in children) to eliminate any leukemia cells that are still "hiding" within the body. A combination of chemotherapeutic drugs is used to keep the remaining leukemia cells from developing resistance. Patients with low- to average-risk ALL receive therapy with antimetabolite drugs such as methotrexate and 6-mercaptopurine (6-MP). High-risk patients receive higher drug doses plus treatment with extra chemotherapeutic agents.

CNS prophylaxis (preventive therapy) to stop the cancer from spreading to the brain and nervous system. Standard prophylaxis may consist of:

4. Cranial (head) irradiation plus spinal tap or intrathecal (IT) delivery (into the space around the spinal cord and brain) of the drug methotrexate.
5. High-dose systemic and IT methotrexate, without cranial irradiation
6. IT chemotherapy.

Only children with T-cell leukemia, a high white blood cell count, or leukemia cells in the cerebrospinal fluid (CSF) need to receive cranial irradiation as well as IT therapy.

Chronic Lymphocytic Leukemia (CLL)

The unpleasant truth is that CLL is probably "incurable" by present treatments. But, fortunately, a large group of CLL patients do not require therapy. Studies suggest that people with Stage A CLL (that is, individuals who have fewer than three areas of enlarged lymphoid tissue) do not benefit from early treatment. They may, in fact, suffer drawbacks because of it. Therefore, most oncologists base CLL treatment upon both the stage and symptoms of the patient.

For example, in older patients (60+ years) who have low-risk early stage disease (Rai Stage 0) a conservative "watch and wait" approach may be taken.

By contrast, older individuals with CLL-related complications or more advanced disease (Rai Stage III or IV) may benefit from chemotherapy and treatment with a corticosteroid (e.g., prednisone, prednisolone).

Corticosteroids are first-line agents for people in whom the immune systems has been altered by CLL. CLL may cause autoimmune syndromes in which the patient's immune system attacks and destroys his or her own blood cells. When the red blood cells are affected, the condition is known as immunohemolytic anemia, characterized by decreased numbers of red blood cells, which may cause fatigue, dizziness, and shortness of breath. When the blood platelets are affected, it is called immune-mediated thrombocytopenia, in which a decreased numbers of platelets may lead to bleeding.

For younger patients who are experiencing symptoms, the physician may consider early chemotherapy, plus allogeneic or autologous bone marrow transplantation (alloBMT; autoBMT).

In general, the indications for treatment are:

- falling hemoglobin or platelet count
- progression to a later stage of disease
- painful, disease-related overgrowth of lymph nodes or spleen
- lymphocyte doubling time (an indicator of lymphocyte reproduction) of fewer than 12 months

HEMOCOAGULATION DESORDERS

Hemophilia

Genetic deficiencies and a rare autoimmune disorder may lower plasma clotting factor levels of coagulation factors needed for a normal clotting process. When a blood vessel is injured, a temporary scab does form, but the missing coagulation factors prevent fibrin formation which is necessary to maintain the blood clot. Therefore, there is no increase in bleeding time with hemophilia because platelets are intact, allowing the formation of these temporary hemostatic plugs (clots). However, "late" bleeding is affected, because these hemostatic plugs are not able to be maintained.

The bleeding with external injury is normal, but incidence of late re-bleeding and internal bleeding is increased, especially into muscles, joints, or bleeding into closed spaces. Major complications include hemarthrosis, hemorrhage, Gastrointestinal bleeding, and menorrhagia.

Causes

It is caused by a lack of clotting factors:

- Haemophilia A has a lack of the clotting Factor VIII. (Haemophilia A occurs in 90% of cases.)
- Haemophilia B has a lack of the clotting Factor IX.
- Haemophilia C has a lack of the clotting Factor XI.

Genetics structure

Females possess two X-chromosomes, whereas males have one X and one Y chromosome. Since the mutations causing the disease are recessive, a woman carrying the defect on one of her X-chromosomes may not be affected by it, as the equivalent allele on her other chromosome should express itself to produce the necessary clotting factors. However the Y-chromosome in men has no gene for factors VIII or IX. If the genes responsible for production of factor VIII or factor IX present on a male's X-chromosome is deficient there is no equivalent on the Y-chromosome, so the deficient gene is not masked by the dominant allele and he will develop the illness.

Differential Diagnosis

Hemophilia A can be mimimicked by von Willebrand Disease

- von Willebrand Disease type 2A, where decreased levels of von Willebrand Factor can lead to premature proteolysis of Factor VIII. In contrast to hemophilia, vWD type 2A is inherited in an autosomal dominant fashion.
- von Willebrand Disease type 2N, where von Willebrand Factor cannot bind Factor VIII
- von Willebrand Disease type 3, where lack of von Willebrand Factor causes premature proteolysis of Factor VIII. In contrast to hemophilia, vWD type 3 is inherited in an autosomal recessive fashion.

Treatment

Though there is no cure for haemophilia, it can be controlled with **regular injections** of the deficient clotting factor, i.e. factor VIII in haemophilia A or factor IX in haemophilia B. Some haemophiliacs develop antibodies (inhibitors) against the replacement factors given to them, so the amount of the factor has to be increased or non-human replacement products must be given, such as porcine factor VIII Troy.

If a patient becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be overcome with recombinant human factor VII (NovoSeven®), which is registered for this indication in many countries.

In western countries, common standards of care fall into one of two categories: prophylaxis or on-demand. Prophylaxis involves the infusion of clotting factor on a regular schedule in order to keep clotting levels sufficiently high to prevent spontaneous bleeding episodes. On-demand treatment involves treating bleeding episodes once they arise.

As a direct result of the contamination of the blood supply in the late 1970s and early/mid 1980s with viruses such as Hepatitis and HIV, new methods were developed in the production of clotting

factor products. The initial response was to heat treat (pasteurize) plasma-derived factor concentrate, followed by the development of monoclonal factor concentrates which use a combination of heat treatment and affinity chromatography to inactivate any viral agents in the pooled plasma from which the factor concentrate is derived. The Lindsay Tribunal in Ireland investigated, among other things, the slow adoption of the new methods.

Since 1993 (Dr. Mary Nugent), recombinant factor products (which are typically cultured in Chinese hamster ovary (CHO) tissue culture cells and involve little, if any human plasma products) have become available and are widely used in wealthier western countries. While recombinant clotting factor products offer higher purity and safety, they are, like concentrate, extremely expensive, and not generally available in the developing world. In many cases, factor products of any sort are difficult to obtain in developing countries.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (**DIC**), also called **consumptive coagulopathy**, is a pathological process in the body where the blood starts to coagulate throughout the whole body. This depletes the body of its platelets and coagulation factors, and there is a paradoxically increased risk of hemorrhage. It occurs in critically ill patients, especially those with Gram-negative sepsis (particularly meningococcal sepsis) and acute promyelocytic leukemia

Causes

There are a variety of causes of DIC, all usually causing the release of chemicals into the blood that instigates the coagulation.

- Sepsis, particularly with gram-negative bacteria.
- Obstetric complications (most common cause), with chemicals from the uterus being released into the blood, or from amniotic fluid embolisms, and eclampsia can be causes. Another obstetric condition which can cause DIC is *abruptio placentae*.
- Tissue trauma such as burns, accidents, surgery or shock.
- Liver disease
- Incompatible blood transfusion reactions or massive blood transfusion (more than the total circulatory volume)
- Malignant cancers, or widespread tissue damage (e.g. burns), or hypersensitivity reactions all can produce the chemicals leading to a DIC.
- Viral hemorrhagic fevers bring about their frank effects, paradoxically, by causing DIC.
- Envenomation by some species of venomous snakes, such as those belonging to the genus Diagnosis

Although numerous blood tests are often performed on patients prone to DIC, the important measures are: full blood count (especially the platelet count), fibrin degradation products or D-dimer tests (markers of fibrinolysis), bleeding time and fibrinogen levels. Decreased platelets, elevated FDPs or D-dimers, prolonged bleeding time and decreased fibrinogen are markers of DIC.

Treatment

The underlying cause must be treated initially. Anticoagulants are only given when indicated (development of thrombotic renal complications) as patients with DIC are prone to bleeding. Platelets may be transfused if counts are very low, and fresh frozen plasma may be administered.

DIC results in lower fibrinogen (as it has all been converted to fibrin), and this can be tested for in the hospital lab. A more specific test is for "fibrin split products" (FSPs) or "fibrin degradation products" (FDPs) which are produced when fibrin undergoes degradation when blood clots are dissolved by fibrinolysis.

In some situations, infusion with antithrombin may be necessary. A new development is drotrecogin alfa (Xigris®), a recombinant activated protein C product. Activated Protein C (APC) deactivates clotting factors V and VIII, and the presumed mechanism of action of drotrecogin is the cessation of the intravascular coagulation. Due to its high cost, it is only used strictly on indication in intensive care patients.[1]

The prognosis for those with DIC, depending on its cause, is often grim, leading the initials to be known colloquially as "death is coming".[2]

ENDOCRINOLOGY

Diabetes mellitus

Diabetes mellitus (IPA pronunciation: is a metabolic disorder characterized by hyperglycemia (high blood sugar) and other signs, as distinct from a single illness or condition. The World Health Organization recognizes three main forms of diabetes: *type 1*, *type 2*, and *gestational diabetes* (occurring during pregnancy), which have similar signs, symptoms, and consequences, but different causes and population distributions. Ultimately, all forms are due to the beta cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycemia. Type 1 is usually due to autoimmune destruction of the pancreatic beta cells which produce insulin. Type 2 is characterized by tissue-wide insulin resistance and varies widely; it sometimes progresses to loss of beta cell function. Gestational diabetes is similar to type 2 diabetes, in that it involves insulin resistance; the hormones of pregnancy cause insulin resistance in those women genetically predisposed to developing this condition.

Types 1 and 2 are incurable chronic conditions, but have been treatable since insulin became medically available in 1921, and today are usually managed with a combination of dietary treatment, tablets (in type 2) and, frequently, insulin supplementation. Gestational diabetes typically resolves with delivery.

Diabetes can cause many complications. Acute complications (hypoglycemia, ketoacidosis or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease (doubled risk), chronic renal failure (diabetic nephropathy is the main cause of dialysis in developed world adults), retinal damage (which can lead to blindness and is the most significant cause of adult blindness in the non-elderly in the

developed world), nerve damage (of several kinds), and microvascular damage, which may cause erectile dysfunction (impotence) and poor healing. Poor healing of wounds, particularly of the feet, can lead to gangrene which can require amputation — the leading cause of non-traumatic amputation in adults in the developed world. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and keeping a healthy body weight), may improve the risk profile of most aforementioned complications.

Type 1 diabetes mellitus

Main article: Diabetes mellitus type 1

Type 1 diabetes mellitus—formerly known as insulin-dependent diabetes (IDDM), childhood diabetes or also known as juvenile diabetes, is characterized by loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency of insulin. It should be noted that there is no known preventative measure that can be taken against type 1 diabetes. Most people affected by type 1 diabetes are otherwise healthy and of a healthy weight when onset occurs. Diet and exercise cannot reverse or prevent type 1 diabetes. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. This type comprises up to 10% of total cases in North America and Europe, though this varies by geographical location. This type of diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of cases of diabetes affecting children.

The main cause of beta cell loss leading to type 1 diabetes is a T-cell mediated autoimmune attack.[2] The principal treatment of type 1 diabetes, even from the earliest stages, is replacement of insulin. Without insulin, ketosis and diabetic ketoacidosis can develop and coma or death will result.

Currently, type 1 diabetes can be treated only with insulin, with careful monitoring of blood glucose levels using blood testing monitors. Emphasis is also placed on lifestyle adjustments (diet and exercise). Apart from the common subcutaneous injections, it is also possible to deliver insulin by a pump, which allows continuous infusion of insulin 24 hours a day at preset levels and the ability to program doses (a bolus) of insulin as needed at meal times. An inhaled form of insulin, Exubera, was approved by the FDA in January 2006.[12]

Type 1 treatment must be continued indefinitely. Treatment does not impair normal activities, if sufficient awareness, appropriate care, and discipline in testing and medication is taken. The average glucose level for the type 1 patient should be as close to normal (80–120 mg/dl, 4–6 mmol/l) as possible. Some physicians suggest up to 140–150 mg/dl (7-7.5 mmol/l) for those having trouble with lower values, such as frequent hypoglycemic events. Values above 200 mg/dl (10 mmol/l) are often accompanied by discomfort and frequent urination leading to dehydration. Values above 300 mg/dl (15 mmol/l) usually require immediate treatment and may lead to ketoacidosis. Low levels of blood glucose, called hypoglycemia, may lead to seizures or episodes of unconsciousness.

Type 2 diabetes mellitus

Main article: Diabetes mellitus type 2

Type 2 diabetes mellitus—previously known as adult-onset diabetes, maturity-onset diabetes, or non-insulin-dependent diabetes mellitus (NIDDM)—is due to a combination of defective insulin secretion and *insulin resistance* or *reduced insulin sensitivity* (defective responsiveness of tissues to insulin), which almost certainly involves the insulin receptor in cell membranes. In the early stage the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage hyperglycemia can be reversed by a variety of measures and

medications that improve insulin sensitivity or reduce glucose production by the liver, but as the disease progresses the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary. There are numerous theories as to the exact cause and mechanism for this resistance, but central obesity (fat concentrated around the waist in relation to abdominal organs, and not subcutaneous fat, it seems) is known to predispose individuals for insulin resistance, possibly due to its secretion of adipokines (a group of hormones) that impair glucose tolerance. Abdominal fat is especially active hormonally. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes.[13] Other factors include aging (about 20% of elderly patients are diabetic in North America) and family history (type 2 is much more common in those with close relatives who have had it), although in the last decade it has increasingly begun to affect children and adolescents[*citation needed*], likely in connection with the greatly increased childhood obesity[*citation needed*] seen in recent decades in some places.

Type 2 diabetes may go unnoticed for years in a patient before diagnosis, as visible symptoms are typically mild or non-existent, usually without ketoacidotic episodes, and can be sporadic as well. However, severe long-term complications can result from unnoticed type 2 diabetes, including renal failure due to diabetic nephropathy, vascular disease (including coronary artery disease), vision damage due to diabetic retinopathy, loss of sensation or pain due to diabetes neuropathy, liver damage from non-alcoholic steatohepatitis, etc.

Type 2 diabetes is usually first treated by attempts to change physical activity (generally an increase is desired), the diet (generally to decrease carbohydrate intake), and weight loss. These can restore insulin sensitivity, even when the weight loss is modest, for example, around 5 kg (10 to 15 lb), most especially when it is in abdominal fat deposits. Some type 2 diabetics can achieve satisfactory glucose control, sometimes for years, as a result. However, the underlying tendency to insulin resistance is not lost, and so attention to diet, exercise, and weight loss must continue. The usual next step, if necessary, is treatment with oral antidiabetic drugs. As insulin production is initially only moderately impaired in type 2 diabetics, oral medication (often used in various combinations) can still be used to improve insulin production (e.g., sulfonylureas), to regulate inappropriate release of glucose by the liver (and attenuate insulin resistance to some extent (e.g., metformin), and to substantially attenuate insulin resistance (e.g., thiazolidinediones). According to one study, overweight patients treated with metformin compared with diet alone, had relative risk reductions of 32% for any diabetes endpoint, 42% for diabetes related death and 36% for all cause mortality and stroke.[14] When oral medications fail (cessation of beta cell insulin secretion is not uncommon amongst Type 2s), insulin therapy will be necessary to maintain normal or near normal glucose levels. A disciplined regimen of blood glucose checks is recommended, most particularly and necessarily when taking medications.

Gestational diabetes

Main article: Gestational diabetes

Gestational diabetes also involves a combination of inadequate insulin secretion and responsiveness, resembling type 2 diabetes in several respects. It develops during pregnancy and may improve or disappear after delivery. Even though it may be transient, gestational diabetes may damage the health of the fetus or mother, and about 20%–50% of women with gestational diabetes develop type 2 diabetes later in life.

Gestational diabetes mellitus (GDM) occurs in about 2%–5% of all pregnancies. It is temporary and fully treatable but, if untreated, may cause problems with the pregnancy, including macrosomia (high birth weight), fetal malformation and congenital heart disease. It requires careful medical supervision during the pregnancy.

Fetal/neonatal risks associated with GDM include congenital anomalies such as cardiac, central nervous system, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental profusion due to vascular impairment. Induction may be indicated with decreased placental function. Cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

Other types

There are several rare causes of diabetes mellitus that do not fit into type 1, type 2, or gestational diabetes:

- Genetic defects in beta cells (autosomal or mitochondrial)
- Genetically-related insulin resistance, with or without lipodystrophy (abnormal body fat deposition)
- Diseases of the pancreas (e.g. chronic pancreatitis, cystic fibrosis)
- Hormonal defects
- Chemicals or drugs

The tenth version of the International Statistical Classification of Diseases (ICD-10) contained a diagnostic entity named "malnutrition-related diabetes mellitus" (MRDM or MMDM, ICD-10 code E12). A subsequent WHO 1999 working group recommended that MRDM be deprecated, and proposed a new taxonomy for alternative forms of diabetes.[1] Classifications of non-type 1, non-type 2, non-gestational diabetes remains controversial.

Genetics

Both type 1 and type 2 diabetes are at least partly inherited. Type 1 diabetes appears to be triggered by some (mainly viral) infections, or in a less common group, by stress or environmental exposure (such as exposure to certain chemicals or drugs). There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 diabetes mellitus seems to require an environmental trigger. A small proportion of people with type 1 diabetes carry a mutated gene that causes maturity onset diabetes of the young (MODY).

Wolfram's syndrome - Wolfram's syndrome is an autosomal recessive neurodegenerative disorder that first becomes evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD.[15]

There is a stronger inheritance pattern for type 2 diabetes. Those with first-degree relatives with type 2 have a much higher risk of developing type 2, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of diabetes. Candidate genes include *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), which encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7–like 2), which regulates proglucagon gene expression and thus the production of glucagon-like peptide-1.[2]

Another risk factor is obesity, particularly central obesity (i.e., that in and around abdominal organs), which is found in approximately 85% of North American patients diagnosed with this type, so some experts believe that inheriting a tendency toward obesity also contributes.

Diagnosis

Signs and symptoms

The classical triad of diabetes symptoms is polyuria (frequent urination), polydipsia (increased thirst and consequent increased fluid intake), polyphagia (increased appetite). Weight loss may occur. These symptoms may develop quite fast in type 1, particularly in children (weeks or months) but may be subtle or completely absent—as well as developing much more slowly—in type 2. In type 1 there may also be weight loss (despite normal or increased eating) and irreducible fatigue. These symptoms may also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.

When the glucose concentration in the blood is high (i.e., above the "renal threshold"), reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and thus inhibits the resorption of water by the kidney, resulting in an increased urine production (polyuria) and an increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells, causing dehydration and increased thirst.

Prolonged high blood glucose causes glucose absorption and so leads to changes in the shape of the lenses of the eyes, leading to vision changes. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change whereas type 2 is generally more gradual, but should still be suspected.

Patients (usually with type 1 diabetes) may also present with diabetic ketoacidosis (DKA), an extreme state of metabolic dysregulation eventually characterized by the smell of acetone on the patient's breath, Kussmaul breathing (a rapid, deep breathing), polyuria, nausea, vomiting and abdominal pain, and any of many altered states of consciousness or arousal (e.g., hostility and mania or, equally, confusion and lethargy). In severe DKA, coma (unconsciousness) may follow, progressing to death. In any form, DKA is a medical emergency and requires expert attention.

A rarer, but equally severe, possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes, and is mainly the result of dehydration due to loss of body water. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to the water loss.

Diagnostic approach

The diagnosis of type 1 diabetes, and many cases of type 2, is usually prompted by recent-onset symptoms of excessive urination (*polyuria*) and excessive thirst (*polydipsia*), often accompanied by weight loss. These symptoms typically worsen over days to weeks; about 25% of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in other ways. The most common are (1) ordinary health screening, (2) detection of hyperglycemia when a doctor is investigating a complication of longstanding, though unrecognized, diabetes, and (3) new signs and symptoms due to the diabetes, such as vision changes or unexplainable fatigue.

1. Diabetes screening is recommended for many people at various stages of life, and for those with any of several risk factors. The screening test varies according to circumstances and local policy, and may be a random blood glucose test, a fasting blood glucose test, a blood glucose test two hours after 75 g of glucose, or an even more formal glucose tolerance test. Many healthcare providers recommend universal screening for adults at age 40 or 50, and

often periodically thereafter. Earlier screening is typically recommended for those with risk factors such as obesity, family history of diabetes, high-risk ethnicity (Mestizo, Native American, African American, Pacific Island, and South Asian ancestry).
2. Many medical conditions are associated with diabetes and warrant screening. A partial list includes: high blood pressure, elevated cholesterol levels, coronary artery disease, past gestational diabetes, polycystic ovary syndrome, chronic pancreatitis, fatty liver, hemochromatosis, cystic fibrosis, several mitochondrial neuropathies and myopathies, myotonic dystrophy, Friedreich's ataxia, some of the inherited forms of neonatal hyperinsulinism, etc. The risk of diabetes is higher with chronic use of several medications, including high-dose glucocorticoids, some chemotherapy agents (especially L-asparaginase), as well as some of the antipsychotics and mood stabilizers (especially phenothiazines and some atypical antipsychotics).
3. Diabetes is often detected when a person suffers a problem frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

Diagnostic criteria

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:[1]

- fasting plasma glucose level at or above 126 mg/dL (7.0 mmol/l).
- plasma glucose at or above 200 mg/dL or 11.1 mmol/l two hours after a 75 g oral glucose load as in a glucose tolerance test.
- random plasma glucose at or above 200 mg/dL or 11.1 mmol/l.

A positive result should be confirmed by another of the above-listed methods on a different day, unless there is no doubt as to the presence of significantly-elevated glucose levels. Most physicians prefer measuring a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which can take two hours to complete. By current definition, two fasting glucose measurements above 126 mg/dL or 7.0 mmol/l is considered diagnostic for diabetes mellitus.

Patients with fasting sugars between 6.1 and 7.0 mmol/l (ie, 110 and 125 mg/dL) are considered to have "impaired fasting glycemia" and patients with plasma glucose at or above 140mg/dL or 7.8 mmol/l two hours after a 75 g oral glucose load are considered to have "impaired glucose tolerance". "Prediabetes" is either impaired fasting glucose or impaired glucose tolerance; the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

While not used for diagnosis, an elevated level of glucose irreversibly bound to hemoglobin (termed glycosylated hemoglobin or *HbA1c*) of 6.0% or higher (the 2003 revised U.S. standard) is considered abnormal by most labs; HbA1c is primarily used as a treatment-tracking test reflecting average blood glucose levels over the preceding 90 days (approximately). However, some physicians may order this test at the time of diagnosis to track changes over time. The current recommended goal for HbA1c in patients with diabetes is <7.0%, which as defined as "good glycemic control", although some guidelines are stricter (<6.5%). People with diabetes who have HbA1c levels within this range have a significantly lower incidence of complications from diabetes, including retinopathy and diabetic nephropathy.[16]

Complications

The complications of diabetes are far less common and less severe in people who have well-controlled blood sugar levels.[17][18] In fact, the better the control, the lower the risk of complications. Hence, patient education, understanding, and participation is vital. Healthcare professionals treating diabetes also often attempt to address health issues that may accelerate the deleterious effects of diabetes. These include smoking (stopping), elevated cholesterol levels (control or reduction with diet, exercise or medication), obesity (even modest weight loss can be beneficial), high blood pressure (exercise or medication if needed), and lack of regular exercise.

Acute complications

Main articles: Diabetic ketoacidosis , Nonketotic hyperosmolar coma , Hypoglycemia , and Diabetic coma

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute, dangerous complication and is always a *medical emergency*. Lack of insulin causes the liver to turn fat into ketone bodies, a fuel mainly for the brain. Large concentration of ketone bodies in the blood decreases the blood's pH, leading to most of the symptoms of DKA. On presentation at hospital, the patient in DKA is typically dehydrated and breathing both fast and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy (dulled or reduced level of alertness or consciousness) may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and death. Prompt proper treatment usually results in full recovery, though death can result from inadequate treatment, delayed treatment or from a variety of complications. Ketoacidosis occurs in type 1 and type 2 but is much more common in type 1.

Nonketotic hyperosmolar coma

While not generally progressing to coma, this *hyperosmolar nonketotic state* (HNS) is another acute problem associated with diabetes mellitus. It has many symptoms in common with DKA, but an entirely different cause, and requires different treatment. In anyone with very high blood glucose levels (usually considered to be above 300 mg/dl (16 mmol/l)), water will be osmotically drawn out of cells into the blood. The kidneys will also be "dumping" glucose into the urine, resulting in concomitant loss of water, and causing an increase in blood osmolality. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually result in very high serum osmolality (i.e. dehydration). The body's cells will become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common, and dangerous. This combination of changes, especially if prolonged, will result in symptoms of lethargy (dulled or reduced level of alertness or consciousness) and may progress to coma. As with DKA urgent medical treatment is necessary, especially volume replacement. This is the 'diabetic coma' which more commonly occurs in type 2 diabetics.

Hypoglycemia

Hypoglycemia, or abnormally low blood glucose, is a complication of several diabetes treatments. It may develop if the glucose intake does not cover the treatment. The patient may become agitated, sweaty, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings similar to dread and immobilized panic. Consciousness can be altered, or even lost, in extreme cases, leading to coma and/or seizures, or even brain damage and death. In patients with diabetes, this can be caused by several factors, such as too much or incorrectly timed insulin, too much exercise or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (actually an insufficient amount of glucose-producing carbohydrates in food). In most cases, hypoglycemia is treated with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with the opposite effects of insulin) or an intravenous infusion of glucose is used for

treatment, but usually only if the person is unconscious. In hospital, intravenous dextrose is often used.

Amputation

Persons with poorly controlled diabetes often heal slowly, even from small cuts, abrasions, blisters, or separated callus (corns). The underlying cause of this healing problem is impaired circulation, which in diabetics is usually adequate to support normal tissue function but which may be inadequate for the additional circulation required to support tissue healing. In such cases, the damage, if unnoticed, left untreated, or failing to heal, can result in an infection. The resulting infection, in extreme cases, can necessitate to amputation.

Chronic complications

Vascular disease

Chronic elevation of blood glucose level leads to damage of blood vessels. In diabetes, the resulting problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries).

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

- *Diabetic retinopathy*, growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.
- *Diabetic neuropathy*, abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. When combined with damaged blood vessels this can lead to *diabetic foot* (see below). Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy.
- *Diabetic nephropathy*, damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world.

Macrovascular disease

Macrovascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor:

- Coronary artery disease, leading to angina or myocardial infarction ("heart attack")
- Stroke (mainly the ischemic type)
- Peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.
- Diabetic myonecrosis ('muscle wasting')

Diabetic foot, often due to a combination of neuropathy and arterial disease, may cause skin ulcer and infection and, in serious cases, necrosis and gangrene. It is the most common cause of adult amputation, usually of toes and or feet, in the developed world.

Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions.[19]

Treatment and management

Main article: Diabetes management

Diabetes mellitus is currently a chronic disease, without a cure, and medical emphasis must necessarily be on managing/avoiding possible short-term as well as long-term diabetes-related problems. There is an exceptionally important role for patient education, dietetic support, sensible exercise, self glucose monitoring, with the goal of keeping both short-term blood glucose levels, and long term levels as well, within acceptable bounds. Careful control is needed to reduce the risk of long term complications. This can be achieved with combinations of diet, exercise and weight loss (type 2), various oral diabetic drugs (type 2 only), and insulin use (type 1 and increasingly for type 2 not responding to oral medication). In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications should be undertaken to control blood pressure[20] and cholesterol by exercising more, smoking cessation, consuming an appropriate diet, wearing diabetic socks, and if necessary, taking any of several drugs to reduce pressure.

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care of a patient in a team approach. Optometrists, podiatrists/chiropodists, dietitians, physiotherapists, clinical nurse specialists (eg, Certified Diabetes Educators), or nurse practitioners may jointly provide multidisciplinary expertise. In countries where patients must provide their own health care, the impact of out-of-pocket costs of diabetic care can be high. In addition to the medications and supplies needed, patients are often advised to receive regular consultation from a physician (eg, at least every three months).

Hyperthyroidism

Causes

Hyperthyroidism is the result of excess thyroid hormone production, causing an overactive metabolism and increased speed of all the body's processes.

Thyroid hormone generally controls the pace of all of the processes in the body. This pace is called your metabolism. If there is too much thyroid hormone, every function of the body tends to speed up. The thyroid gland regulates the body temperature by secreting two hormones that control how quickly the body burns calories and energy. If the thyroid produces too much hormone, the condition is called hyperthyroidism, but if too little is produced the result is hypothyroidism.

Major causes in humans are:

- Graves' disease (the most common etiology with 70-80%)
- Toxic thyroid adenoma
- Toxic multinodular goitre

- AIDS

Other causes of hyperthyroxinemia (high blood levels of thyroid hormones) are not to be confused with true hyperthyroidism and include subacute and other forms of thyroiditis (inflammation) and struma ovarii (a teratoma). Thyrotoxicosis (symptoms caused by hyperthyroxinemia) can occur in both hyperthyroidism and thyroiditis. When it causes acutely increased metabolism, it is sometimes called "thyroid storm", a life-threatening event characterized by tachycardia, hypertension, and fever.

Excess thyroid hormone from pills can also cause hyperthyroidism. Amiodarone, a heart medication, can sometimes cause hyperthyroidism. Hamburger toxicosis is a condition that occurs sporadically and is associated with ground beef contaminated with thyroid hormone.

Signs and symptoms

Major clinical weight loss (often accompanied by a ravenous appetite), intolerance to heat, fatigue, weakness, hyperactivity, irritability, apathy, depression, polyuria, and sweating. Additionally, patients may present with a variety of symptoms such as palpitations and arrhythmias (notably atrial fibrillation), shortness of breath (dyspnea), loss of libido, nausea, vomiting, and diarrhea. In the elderly, these classical symptoms may not be present and they may present only with fatigue and weight loss leading to apathetic hyperthyroidism.

Neurological manifestations are tremor, chorea, myopathy, and periodic paralysis. Stroke of cardioembolic origin due to coexisting atrial fibrillation may be mentioned as one of the most serious complications of hyperthyroidism.

As to other autoimmune disorders related with thyrotoxicosis, an association between thyroid disease and myasthenia gravis has been well recognized. The thyroid disease, in this condition, is often an autoimmune one and approximately 5% of patients with myasthenia gravis also have hyperthyroidism. Myasthenia gravis rarely improves after thyroid treatment and the relationship between the two entities is as yet unknown. Some very rare neurological manifestations that are reported to be dubiously associated with thyrotoxicosis are pseudotumor cerebri, amyotrophic lateral sclerosis and a Guillain-Barré-like syndrome.

Minor ocular signs, which may be present in any type of hyperthyroidism, are eyelid retraction ("stare") and lid-lag. These "fear-like" eye-signs result from thyroid hormone's exacerbation of the action of norepinephrine. In hyperthyroid *stare* (Dalrymple sign) the eyelids are retracted upward more than normal (the normal position is at the superior corneoscleral limbus, where the "white" of the eye begins at the upper border of the iris). In lid-lag (von Graefe's sign), when the patient tracks an object downward with their eyes, the eyelid fails to follow the downward moving iris, and the same type of upper globe exposure which is seen with lid retraction occurs, temporarily. These signs disappear with treatment of the hyperthyroidism, or treatment by certain anti-adrenergic drugs.

Neither of these ocular signs should be confused with exopthalmos (protrusion of the eyeball) which occurs in one thyroid-related disease (Graves' disease), but which is not caused by the hyperthyroid state in that disease, and is unrelated to it. Exopthalmos when present may exacerbate these signs, however.[1]

Diagnosis

A diagnosis is suspected through blood tests, by measuring the level of thyroid-stimulating hormone (TSH) in the blood. A low TSH (the job of TSH taken over by thyroid-stimulating immunoglobulin [TSI] that act like TSH) indicates increased levels of T4 and/or T3 in the blood. Measuring specific antibodies, such as anti-TSH-receptor antibodies in Graves' disease, may contribute to the diagnosis. In all patients with hyperthyroxinemia, scintigraphy is required in order to distinguish true hyperthyroidism from thyroiditis.

Treatment

The major and generally accepted modalities for treatment of hyperthyroidism in humans are:

Surgery

Surgery (to remove the whole thyroid or a part of it) is not extensively used because most common forms of hyperthyroidism are quite effectively treated by the radioactive iodine method. However, some Graves' disease patients who cannot tolerate medicines for one reason or another or patients who refuse radioiodine opt for surgical intervention. Also, some surgeons believe that radioiodine treatment is unsafe in patients with unusually large gland, or those whose eyes have begun to bulge from their sockets, claiming that the massive dose of iodine needed will only exacerbate the patient's symptoms. The procedure is quite safe - some surgeons even perform partial thyroidectomies on an out-patient basis.

Radioiodine

In Iodine-131 (Radioiodine) Radioisotope Therapy, radioactive iodine is given orally (either by pill or liquid) on a one-time basis to destroy the function of a hyperactive gland. The iodine given for ablative treatment is different from the iodine used in a scan. Radioactive iodine is given after a routine iodine scan, and uptake of the iodine is determined to confirm hyperthyroidism. The radioactive iodine is picked up by the active cells in the thyroid and destroys them. Since iodine is only picked up by thyroid cells, the destruction is local, and there are no widespread side effects with this therapy. Radioactive iodine ablation has been safely used for over 50 years, and the only major reasons for not using it are pregnancy and breast-feeding.

Often, due to the difficulty of picking the correct dose, the treatment results in an opposite condition - hypothyroidism. However, that is usually easily treated by the administration of levothyroxine, which is a pure synthetic form of T4.

Thyrostatics

Thyrostatics are drugs that inhibit the production of thyroid hormones, such as methimazole (Tapazole®) or PTU (propylthiouracil). Thyrostatics are believed to work by inhibiting the iodination of thyroglobulin by thyroperoxidase.

If too high a dose is used in pharmacological treatment, patients can develop symptoms of hypothyroidism. Hypothyroidism is also a very common result of surgery or radiation treatment as it is difficult to gauge how much of the thyroid gland should be removed. Supplementation with levothyroxine may be required in these cases.

Beta-blockers

Beta-blockers do not treat, but rather mask, common symptoms of hyperthyroidism such as palpitations, trembling, and anxiety. Metoprolol is most frequently used to augment treatment for hyperthyroid patients.

Hypothyroidism

is the disease state in humans and animals caused by insufficient production of thyroid hormone by the thyroid gland. It affects about 5% of the United Kingdom population over 60 years of age. As of 2006, more than 1% of the United Kingdom population were receiving T_4 (Thyroxine) replacement therapy for hypothyroidism.[1]

Causes

There are several distinct causes for chronic hypothyroidism. Historically and, still, in many developing countries iodine deficiency is the most common cause of hypothyroidism world-wide. In present day developed countries, however, hypothyroidism is mostly caused by a lack of the thyroid gland or a deficiency of hormones from either the hypothalamus or the pituitary.

Hypothyroidism can also result from sporadic inheritance, sometimes autosomal recessive. It is a relatively common disease in purebred domestic dogs as well, and can have a hereditary basis in dogs.[*citation needed*]

Symptoms

The ability of Hypothyroidism to mimic a number of medical conditions originates in the vast functions of the thyroid hormones, which are absent in this case. The functions of thyroid hormones include modulation of carbohydrate, protein and fat metabolism, vitamin utilization, mitochondrial function, digestive process, muscle and nerve activity, blood flow, oxygen utilization, hormone secretion and sexual and reproductive health[6] to mention some. Thus, when the thyroid hormone content gets out of balance, systems covering the whole body are affected, and that's why hypothyroidism can look like other diseases.

Conversely, sometimes other conditions can be mistaken for Hypothyroidism.

Adults

In adults, hypothyroidism is associated with the following symptoms:[4]

[Early symptoms

[7]

- Poor muscle tone (muscle hypotonia)
- Fatigue (physical)
- Cold intolerance, increased sensitivity to cold
- Constipation

- Weight gain
- Depression (especially in the elderly)
- Muscle cramps and joint pain
- Thin, Brittle fingernails
- Thin, brittle hair
- Paleness

[Late symptoms

[7]

- Slowed speech and a hoarse, breaking voice. Deepening of the voice can also be noticed.
- Dry puffy skin, especially on the face
- Thinning of the outer third of the eyebrows
- Abnormal menstrual cycles (Specifically Menorrhagia)

Severity

The severity of hypothyroidism varies widely. Some have few overt symptoms, others with moderate symptoms can be mistaken for having other diseases and states. Advanced hypothyroidism may cause severe complications including cardiovasular and psychiatric myxedema.

Diagnostic testing

To diagnose primary hypothyroidism, many doctors simply measure the amount of Thyroid-stimulating hormone (TSH) being produced. High levels of TSH indicate that the thyroid is not producing sufficient levels of Thyroid hormone (mainly as thyroxine (T4) and smaller amounts of triiodothyronine (fT3)). However, measuring just TSH fails to diagnose secondary and tertiary forms of hypothyroidism, thus leading to the following suggested minimum blood testing:

- thyroid-stimulating hormone (TSH)
- free triiodothyronine (fT3)
- free levothyroxine (fT4)
- total T3
- total T4

Additionally, the following measurements may be needed:

- antithyroid antibodies - for evidence of autoimmune diseases that may be damaging the thyroid gland
- serum cholesterol - which may be elevated in hypothyroidism
- prolactin - as a widely available test of pituitary function

Treatment

A doctor can perform blood tests to see if a patient suffers from hypothyroidism. Both synthetic and animal-derived thyroid tablets are available and can be prescribed for patients in need of additional thyroid hormone. Thyroid hormone is usually taken daily, and doctors can monitor blood levels to

help assure proper dosaging. The American Thyroid Association cautions against taking herbal remedies, and warns that taking too much iodine can actually worsen both hypothyroidism and hyperthyroidism.[4]

A great deal of debate has emerged between treatment with T_4 (Thyroxin) monotherapy versus T_4 - T_3 (Thyroxine-Triiodothyronine) combination therapy. In July 2006 an evaluation of 11 published randomized clinical trials was published concluding no benefit to treatment with the T_4 - T_3 combination therapy over the T_4 monotherapy.[1]

HYPERPARATHYROIDISM

In cases of primary, tertiary and quintary hyperparathyroidism increased PTH consequently leads to increased serum calcium (hypercalcemia) due to:

1. increased bone resorption, allowing flow of calcium from bone to blood
2. reduced renal clearance of calcium
3. increased intestinal calcium absorption

By contrast, in secondary and quartary hyperparathyroidism effectiveness of PTH is reduced. Alkaline phosphatase levels are elevated in all types of hyperparathyroidism.

In primary hyperparathyroidism, serum phosphorus levels are abnormally low as a result of decreased renal tubular phosphorus reabsorption. This contrasts with secondary hyperparathyroidism, in which serum phosphorus levels are generally elevated because of renal disease.

Etiology

- Primary hyperparathyroidism results from a dysfunction in the parathyroid glands themselves, with oversecretion of PTH.
  - The most common cause is a benign parathyroid adenoma that loses its sensitivity to circulating calcium levels. Usually, only one of the four parathyroid glands is affected.
  - A less common cause is from multiple endocrine neoplasia (MEN).

- Secondary hyperparathyroidism is due to resistance to the actions of PTH, usually due to chronic renal failure. The bone disease in secondary parathyroidism along with renal failure is termed renal osteodystrophy.

- Tertiary, quartary and quintary hyperparathyroidism are rare forms that are caused by long lasting disorders of the calcium feedback control system.

Signs and symptoms

Many patients presenting with hyperparathyroidism will have no signs or symptoms, with diagnosis being made on further investigation after a coincidental finding of hypercalcemia. It is, however, reported that many patients will report that they feel better after treatment for hyperparathyroidism. Of those patient that do present with symptoms, they are commonly associated with the effects of an increased level of calcium.

Since calcium is responsible for the electrical conduction within our nervous system, high blood calcium levels have a direct effect on the nervous system. Thus, most of the symptoms of parathyroid disease are "neurological" in origin. The most common symptom is fatigue and tiredness. Other very common symptoms are lack of energy, memory problems, depression, problems with concentration, and problems sleeping. Other manifestations of hyperparathyroidism usually involve the kidney (stones) and the skeletal system (bone pain due to the development of osteoporosis).

The symptoms of hyperparathyroidism can be classically remembered by the rhyme "moans" (complaints of not feeling well), "groans" (abdominal pain, GERD), "stones" (kidney), "bones" (bone pain), and "psychiatric overtones" (lethargy, fatigue, depression, memory problems).

Almost all patients with hyperparathyroidism will develop osteoporosis. If untreated, this osteoporosis can be extreme. Unfortunately, medicines are usually not useful for treating the osteoporosis associated with hyperparathyroidism until the parathyroid tumor is removed. Osteoporosis associated with hyperparathyroidism is caused by the high parathyroid hormone that is secreted by the overactive parathyroid gland(s). This excess parathyroid hormone (PTH) acts directly on the bones to remove calcium from the bones. Thus, the high calcium in the blood comes from the bones. Removing the offending parathyroid gland will usually cause a significant improvement in the osteoporosis, often reversing this process back to normal bone density over several years.

Other symptoms include: headaches, gastroesophageal reflux, decreased sex drive, thinning hair, hypertension, and heart palpitations which are often due to bouts of atrial fibrillation.

Almost all patients will have symptoms if their calcium is high and the right questions are asked. Removing the parathyroid tumor which is causing the excess parathyroid hormone will eliminate the symptoms in most patients within several days or weeks. Often it is life-changing when the parathyroid tumor is removed.

Diagnosis

The gold standard of diagnosis is the PTH immunoassay. Once an elevated PTH has been confirmed, goal of diagnosis is to determine whether the hyperparathyroidism is primary or secondary in origin by obtaining a serum calcium level:

Tertiary hyperparathyroidism has a high PTH and a high serum calcium. It is differentiated from primary hyperparathyroidism by a history of chronic kidney failure and secondary hyperparathyroidism.

Treatment

Treatment is first and foremost directed at hypercalcemia, if symptomatic patients are sent for surgery to remove the parathyroid tumor (parathyroid adenoma). (see hypercalcemia) Most experts now believe that almost all patients with hyperparathyroidism should be evaluated for surgery. Watching and waiting has been falling out of vogue since it is being realized that the disease will rarely stay the same. It will almost always progress as the tumor grows.

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Addison's disease

(also known as **chronic adrenal insufficiency**, **hypocortisolism** or **hypocorticism**) is a rare endocrine disorder in which the adrenal gland produces insufficient amounts of steroid hormones (glucocorticoids and often mineralocorticoids). It may develop in children as well as adults, and may occur as the result of a large number of underlying causes. The condition is named after Dr Thomas Addison, the British physician who first described the condition in his 1855 *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*. The adjective "Addisonian" is used for features of the condition, as well as patients with Addison's disease.[1]

The condition is generally diagnosed with blood tests, medical imaging and additional investigations.[1] Treatment is with replacement of the hormones (oral hydrocortisone and

fludrocortisone). If the disease is caused by an underlying problem, this is addressed. Regular follow-up and monitoring for other health problems is necessary.[1]

Symptoms

The symptoms of Addison's disease develop insidiously, and it may take some time to be recognised. The most common symptoms are fatigue, muscle weakness, vomiting, diarrhoea, headache, sweating, changes in mood and personality and joint and muscle pains. Some have marked cravings for salty foods due to the urinary losses of sodium.[1]

Clinical signs

On examination, the following may be noticed:[1]

- Low blood pressure that falls further when standing (orthostatic hypotension)
- Darkening (hyperpigmentation) of the skin, including areas not exposed to the sun; characteristic sites are skin creases (e.g. of the hands) and the inside of the cheek (buccal mucosa).
- Signs of conditions that often occur together with Addison's: goitre and vitiligo

Addisonian crisis

An "Addisonian crisis" is a constellation of symptoms that indicate severe adrenal insufficiency. This may be the result of either previously undiagnosed Addison's disease, a disease process suddenly affecting adrenal function (such as adrenal haemorrhage, or in a patient with known Addison's disease who has suffered an intercurrent problem (e.g. infection, trauma). Additionally, this situation may develop in those on long-term oral glucocorticoids who have suddenly ceased taking their medication.

Untreated, an Addisonian crisis can be fatal. It is a medical emergency, usually requiring hospitalization. Characteristic symptoms are:[*citation needed*]

- Sudden penetrating pain in the legs, lower back or abdomen
- Severe vomiting and diarrhea, resulting in dehydration
- Low blood pressure
- Loss of consciousness/Syncope
- Hypoglycemia
- Confusion, psychosis
- Convulsions

Diagnosis

Features suggesting diagnosis

Routine investigations may show:[1]

- Hypoglycemia, low blood sugar (worse in children)
- Hyponatraemia (low blood sodium levels)
- Hyperkalemia (raised blood potassium levels), due to loss of production of the hormone aldosterone

- Eosinophilia and lymphocytosis (increased number of eosinophils or lymphocytes, two types of white blood cells)

Treatment

Maintenance treatment

Treatment for Addison's disease involves replacing the missing cortisol (usually in the form of hydrocortisone tablets) in a dosing regimen that mimics the physiological concentrations of cortisol. Treatment must usually be continued for life. In addition, many patients require fludrocortisone as replacement for the missing aldosterone. Caution must be exercised when the person with Addison's disease becomes unwell, has surgery or becomes pregnant. Medication may need to be increased during times of stress, infection, or injury.

Addisonian crisis

Treatment for an acute attack, an Addisonian crisis, usually involves intravenous (into blood veins) injections of:

- Cortisone (cortisol)
- Saline solution (basically a salt water, same clear IV bag as used to treat dehydration)
- Glucose

Hyperaldosteronism, also **aldosteronism**, is a medical condition where too much aldosterone is produced by the adrenal glands, which can lead to lowered levels of potassium in blood.

Symptoms

It can be asymptomatic, but the following symptoms can be present

- Fatigue
- Headache
- High blood pressure
- Hypokalemia
- Intermittent or temporary paralysis
- Muscle spasms
- Muscle weakness
- Numbness
- Polyuria
- Polydipsia
- Tingling

Cushing's syndrome

(also called **hypercortisolism** or **hyperadrenocorticism**) is a rare endocrine disorder caused by high levels of cortisol in the blood. Cortisol is released from the adrenal gland in response to ACTH being released from the pituitary gland. High levels of cortisol can also be induced by the administration of drugs. **Cushings disease**, or more properly termed ***secondary***

hyperadrenocorticism, is very similar to Cushing's syndrome in that all physiologic manifestations of the conditions are the same. Both diseases are characterized by elevated levels of cortisol in the blood, but the cause of elevated cortisol differs between the diseases. Cushing's disease specifically refers to a tumor in the pituitary gland that stimulates excessive release of cortisol from the adrenal gland by releasing large amounts of ACTH. It was discovered by American physician, surgeon and endocrinologist Harvey Cushing (1869-1939) and reported by him in 1932.

Signs and symptoms

Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs (central obesity), a round face often referred to as a "moon face", excess sweating, telangiectasia (dilation of capillaries), thinning of the skin (which causes easy bruising) and other mucous membranes, purple or red striae (also caused by thinning of the skin) on the trunk, buttocks, arms, legs or breasts, proximal muscle weakness (hips, shoulders), and hirsutism (facial male-pattern hair growth). A common sign is the growth of fat pads along the collar bone and on the back of the neck (known as a buffalo hump). The excess cortisol may also affect other endocrine systems and cause, for example, reduced libido, impotence, amenorrhoea and infertility. Patients frequently suffer various psychological disturbances, ranging from euphoria to frank psychosis. Depression and anxiety, including panic attacks, are common.

Other signs include persistent hypertension (due to the aldosterone-like effects) and insulin resistance, leading to hyperglycemia (high blood sugars) which can lead to diabetes mellitus. Untreated Cushing's syndrome can lead to heart disease and increased mortality. Cushing's syndrome due to excess ACTH may also result in hyperpigmentation of the skin, due to its ability to stimulate melanocyte receptors.

Diagnosis

When Cushing's is suspected, a dexamethasone suppression test (administration of dexamethasone and frequent determination of cortisol and ACTH levels) and 24-hour urinary measurement for cortisol have equal detection rates (Raff & Findling 2003). Dexamethasone is a glucocorticoid and simulates the effects of cortisol, including negative feedback on the pituitary gland. When dexamethasone is administered and a blood sample is tested, high cortisol would be indicative of Cushing's syndrome because there is an ectopic source of cortisol or ACTH (eg: adrenal adenoma) that is not inhibited by the dexamethasone. A low cortisol reading would be indicative of Cushing's disease because the dexamethasone inhibited the pituitary adenoma so that its' output of ACTH decreased, resulting in decreased cortisol levels. A novel approach, recently cleared by the US FDA, is sampling cortisol in saliva over 24 hours, which may be equally sensitive, as late night levels of salivary cortisol are high in Cushingoid patients. Other pituitary hormones may need to be determined, and performing physical examination directed for any visual field defect may be necessary if a pituitary lesion is suspected (which may compress the optic chiasm causing typical bitemporal hemianopia).

When these tests are positive, CT scanning of the adrenal gland and MRI of the pituitary gland are performed to detect the presence of an adrenal or pituitary adenoma. These should be performed when other tests are positive, to decrease likelihood of incidentalomas (incidental discovery of harmless lesions in both organs). Scintigraphy of the adrenal gland with iodocholesterol scan is occasionally necessary. Very rarely, determining the cortisol levels in various veins in the body by venous catheterisation working towards the pituitary (petrosal sinus sampling) is necessary.

Pheochromocytoma

A **phaeochromocytoma** (**pheochromocytoma** in the US) is a neuroendocrine tumor of the medulla of the adrenal glands originating in the chromaffin cells, which secretes excessive amounts of catecholamines, usually adrenaline and noradrenaline (epinephrine and norepinephrine in the US). Extra-adrenal paragangliomas (often described as extra-adrenal pheochromocytomas) are closely related, though less common, tumors that originate in the ganglia of the sympathetic nervous system and are named based upon the primary anatomical site of origin.

Diagnosis

The diagnosis can be established by measuring catecholamines and metanephrines in plasma or through a 24-hour urine collection. Care should be taken to rule out other causes of adrenergic (adrenalin-like) excess like hypoglycemia, stress, exercise, and drugs affecting the catecholamines like methyldopa, dopamine agonists, or ganglion blocking antihypertensives. Various foodstuffs (e.g. vanilla ice cream) can also affect the levels of urinary metanephrine and VMA (vanillyl mandelic acid). Imaging by computed tomography or a T2 weighted MRI of the head, neck, and chest, and abdomen can help localize the tumor. Tumors can also be located using Iodine-131 meta-iodobenzylguanidine (I131 MIBG) imaging.

One diagnostic test used in the past for a pheochromocytoma is to administer clonidine, a centrally-acting alpha-2 agonist used to treat high blood pressure. Clonidine mimics catecholamines in the brain, causing it to reduce the activity of the sympathetic nerves controlling the adrenal medulla. A healthy adrenal medulla will respond to the Clonidine suppression test by reducing catecholamine production; the lack of a response is evidence of pheochromocytoma.

Another test is for the clinician to press gently on the adrenal gland. A pheochromocytoma will often release a burst of catecholamines, with the associated signs and symptoms quickly following. This method is not recommended because of possible complications arising from a potentially massive release of catecholamines.

Pheochromocytomas occur most often during young-adult to mid-adult life. Less than 10% of pheochromocytomas are malignant (cancerous), bilateral or pediatric.

These tumors can form a pattern with other endocrine gland cancers which is labeled multiple endocrine neoplasia (MEN). Pheochromocytoma may occur in patients with MEN 2 and MEN 3. VHL (Von Hippel Lindau) patients may also develop these tumors.

Patients experiencing symptoms associated with pheochromocytoma should be aware that it is rare. However, it often goes undiagnosed until autopsy; therefore patients might wisely choose to take steps to provide a physician with important clues, such as recording whether blood pressure changes significantly during episodes of apparent anxiety.

Acromegaly

Acromegaly (from Greek *akros* "extreme" or "extremities" and *megalos* "large" - extremities enlargement) is a hormonal disorder that results when the pituitary gland produces excess growth

hormone (hGH). Most commonly it is a benign hGH producing tumor derived from a distinct type of cells (somatotrophs) and called **pituitary adenoma**.

Acromegaly most commonly affects middle-aged adults and can result in serious illness and premature death. Because of its insidious pathogenesis and slow progression, the disease is hard to diagnose in the early stages and is frequently missed for many years.

Symptoms

Features that result from high level of hGH or expanding tumor include:

- Soft tissue swelling of the hands and feet
- Brow and lower jaw protrusion
- Enlarging hands
- Enlarging feet
- Arthritis and carpal tunnel syndrome
- Teeth spacing increase
- Macroglossia [enlarged tongue]
- Heart failure
- Compression of the optic chiasm leading to loss of vision in the outer visual fields (typically bitemporal hemianopia)
- Headache
- Diabetes mellitus
- Hypertension
- Increased palmar sweating and sebum production over the face (seborrhea) are clinical indicators of active growth hormone (GH) producing pituitary tumours. These symptoms can also be used to monitor the activity of the tumour after surgery although biochemical monitoring is confirmatory.

Causes

Pituitary adenoma

In over 90 percent of acromegaly patients, the overproduction of GH is caused by a benign tumor of the pituitary gland, called an adenoma. These tumors produce excess GH and, as they expand, compress surrounding brain tissues, such as the optic nerves. This expansion causes the headaches and visual disturbances that are often symptoms of acromegaly. In addition, compression of the surrounding normal pituitary tissue can alter production of other hormones, leading to changes in menstruation and breast discharge in women and impotence in men because of reduced testosterone production.

There is a marked variation in rates of GH production and the aggressiveness of the tumor. Some adenomas grow slowly and symptoms of GH excess are often not noticed for many years. Other adenomas grow rapidly and invade surrounding brain areas or the sinuses, which are located near the pituitary. In general, younger patients tend to have more aggressive tumors.

Most pituitary tumors arise spontaneously and are not genetically inherited. Many pituitary tumors arise from a genetic alteration in a single pituitary cell which leads to increased cell division and tumor formation. This genetic change, or mutation, is not present at birth, but is acquired during life. The mutation occurs in a gene that regulates the transmission of chemical signals within pituitary cells; it permanently switches on the signal that tells the cell to divide and secrete GH. The

events within the cell that cause disordered pituitary cell growth and GH oversecretion currently are the subject of intensive research.

Other tumors

In a few patients, acromegaly is caused not by pituitary tumors but by tumors of the pancreas, lungs, and adrenal glands. These tumors also lead to an excess of GH, either because they produce GH themselves or, more frequently, because they produce GHRH, the hormone that stimulates the pituitary to make GH. In these patients, the excess GHRH can be measured in the blood and establishes that the cause of the acromegaly is not due to a pituitary defect. When these non-pituitary tumors are surgically removed, GH levels fall and the symptoms of acromegaly improve.

In patients with GHRH-producing, non-pituitary tumors, the pituitary still may be enlarged and may be mistaken for a tumor. Therefore, it is important that physicians carefully analyze all "pituitary tumors" removed from patients with acromegaly in order not to overlook the possibility that a tumor elsewhere in the body is causing the disorder.

Diagnosis

If acromegaly is suspected, medical imaging and medical laboratory investigations are generally used together to confirm or rule out the presence of this condition.

Hormonal

IGF1 provides the most sensitive and useful lab test for the diagnosis of acromegaly. A single value of the Growth hormone (GH) is not useful in view of its pulsatality (levels in the blood vary greatly even in healthy individuals). GH levels taken 2 hours after a 75 gram glucose tolerance test are helpful in the diagnosis: GH levels are suppressed below 1 µg/L in normal people, and levels higher than this cutoff are confirmatory of acromegaly.

Other pituitary hormones have to be assessed to address the secretory effects of the tumour as well as the mass effect of the tumor on the normal pituitary gland. They include TSH (thyroid stimulating hormone), gonadotropic hormones (FSH,LH), ACTH (adrenocorticotropic hormone), prolactin.

Radiological

An MRI of the brain focussing on the sella turcica after gadolinium administration allows for clear delineation of the pituitary and the hypothalamus and the location of the tumour.Treatment

The goals of treatment are to reduce GH production to normal levels, to relieve the pressure that the growing pituitary tumor exerts on the surrounding brain areas, to preserve normal pituitary function, and to reverse or ameliorate the symptoms of acromegaly. Currently, treatment options include surgical removal of the tumor, drug therapy, and radiation therapy of the pituitary.

Surgery

Surgery is a rapid and effective treatment, of which there are two alternative methods. The first method, a procedure known as **transsphenoidal surgery**, involves the surgeon reaching the pituitary through an incision in the nose and, with special tools, removing the tumor tissue. The second method is the removal of the tumor via a craniotomy, during which a *bone flap* is removed

from the patient's skull to allow access to the tumor from the front and side. Once the tumor has been removed, the section of bone is replaced. Transsphenoidal surgery is a less invasive procedure with a shorter recovery time than a craniotomy, yet the likelihood of successfully removing the entire tumor is lower. Consequently, transsphenoidal surgery is often used as a first option, with craniotomy and other treatments being used to remove any remaining tumor.

These procedures promptly relieve the pressure on the surrounding brain regions and lead to a lowering of GH levels. If the surgery is successful, facial appearance and soft tissue swelling improve within a few days. Surgery is most successful in patients with blood GH levels below 40 ng/ml before the operation and with pituitary tumors no larger than 10 mm in diameter. Success depends on the skill and experience of the surgeon. The success rate also depends on what level of GH is defined as a cure. The best measure of surgical success is normalization of GH and IGF-1 levels. Ideally, GH should be less than 2 ng/ml after an oral glucose load. A review of GH levels in 1,360 patients worldwide immediately after surgery revealed that 60 percent had random GH levels below 5 ng/ml. Complications of surgery may include cerebrospinal fluid leaks, meningitis, or damage to the surrounding normal pituitary tissue, requiring lifelong pituitary hormone replacement.

Even when surgery is successful and hormone levels return to normal, patients must be carefully monitored for years for possible recurrence. More commonly, hormone levels may improve, but not return completely to normal. These patients may then require additional treatment, usually with medications.

Drug therapy

Two medications currently are used to treat acromegaly. These drugs reduce both GH secretion and tumor size. Medical therapy is sometimes used to shrink large tumors before surgery. Bromocriptine (Parlodel) in divided doses of about 20 mg daily reduces GH secretion from some pituitary tumors. Side effects include gastrointestinal upset, nausea, vomiting, light-headedness when standing, and nasal congestion. These side effects can be reduced or eliminated if medication is started at a very low dose at bedtime, taken with food, and gradually increased to the full therapeutic dose. Because bromocriptine can be taken orally, it is an attractive choice as primary drug or in combination with other treatments. However, bromocriptine lowers GH and IGF-1 levels and reduces tumor size in less than half of patients with acromegaly. Some patients report improvement in their symptoms although their GH and IGF-1 levels still are elevated.

The second medication used to treat acromegaly is octreotide (Sandostatin) and lanreotide (Somatulin). Both are synthetic forms of a brain hormone, somatostatin, that stops GH production. The long-acting forms of these drugs must be injected every 2 to 4 weeks for effective treatment. Most patients with acromegaly respond to this medication. In many patients, GH levels fall within one hour and headaches improve within minutes after the injection. Several studies have shown that octreotide and lanreotide are effective for long-term treatment. Octreotide and lanreotide have also been used successfully to treat patients with acromegaly caused by non-pituitary tumors.

Because octreotide inhibits gastrointestinal and pancreatic function, long-term use causes digestive problems such as loose stools, nausea, and gas in one third of patients. In addition, approximately 25 percent of patients develop gallstones, which are usually asymptomatic. In rare cases, octreotide treatment can cause diabetes. On the other hand, scientists have found that in some acromegaly patients who already have diabetes, octreotide can reduce the need for insulin and improve blood sugar control.

The latest development in the medical treatment of acromegaly is the use of growth hormone receptor antagonists. The only available member of this family is pegvisomant (Somavert). By blocking the action of the endogenous growth hormone molecules, this compound is able to control disease activity of acromegaly in virtually all patients. Pegvisomant has to be administered subcutaneously by daily injections. Combinations of long-acting somatostatin analogues and weekly injections of pegvisomant seem to be equally effective as daily injections of pegvisomant.

Radiation therapy

Radiation therapy has been used both as a primary treatment and combined with surgery or drugs. It is usually reserved for patients who have tumor remaining after surgery. These patients often also receive medication to lower GH levels. Radiation therapy is given in divided doses over four to six weeks. This treatment lowers GH levels by about 50 percent over 2 to 5 years. Patients monitored for more than 5 years show significant further improvement. Radiation therapy causes a gradual loss of production of other pituitary hormones with time. Loss of vision and brain injury, which have been reported, are very rare complications of radiation treatments.

No single treatment is effective for all patients. Treatment should be individualized depending on patient characteristics, such as age and tumor size. If the tumor has not yet invaded surrounding brain tissues, removal of the pituitary adenoma by an experienced neurosurgeon is usually the first choice. After surgery, a patient must be monitored for a long time for increasing GH levels. If surgery does not normalize hormone levels or a relapse occurs, a doctor will usually begin additional drug therapy. The first choice should be bromocriptine because it is easy to administer; octreotide is the second alternative. With both medications, long-term therapy is necessary because their withdrawal can lead to rising GH levels and tumor re-expansion. Radiation therapy is generally used for patients whose tumors are not completely removed by surgery; for patients who are not good candidates for surgery because of other health problems; and for patients who do not respond adequately to surgery and medication.

Diabetes insipidus

Diabetes insipidus (**DI**) is a disease characterized by excretion of large amounts of severely diluted urine, which cannot be reduced when fluid intake is reduced. It denotes inability of the kidney to concentrate urine. DI is caused by a deficiency of antidiuretic hormone (ADH), also known as vasopressin, or by an insensitivity of the kidneys to that hormone.

Signs and symptoms

Excessive urination and extreme thirst (especially for cold water) are typical for DI. Symptoms of diabetes insipidus are quite similar to those of untreated diabetes mellitus, with the distinction that the urine is not sweet and there is no hyperglycemia (elevated blood glucose). Blurred vision is a rarity.

The extreme urination continues throughout the day and the night. In children, DI can interfere with appetite, eating, weight gain, and growth as well. They may present with fever, vomiting, or diarrhea. Adults with untreated DI may remain healthy for decades as long as enough water is drunk to offset the urinary losses. However, there is a continuous risk of dehydration.

Diagnosis

In order to distinguish DI from other causes of excess urination, blood glucose, bicarbonate and calcium need to be tested. Electrolytes can show substantial derangement; hypernatremia (excess sodium levels) are common in severe cases. Urinalysis shows low electrolyte levels, and measurement of urine osmolarity (or specific gravity) is generally low.

A *fluid deprivation test* helps determine whether DI is caused by:

1. excessive intake of fluid
2. a defect in ADH production
3. a defect in the kidneys' response to ADH

This test measures changes in body weight, urine output, and urine composition when fluids are withheld. Sometimes measuring blood levels of ADH during this test is also necessary.

To distinguish between the main forms, desmopressin stimulation is also used; desmopressin can be taken by injection, a nasal spray, or a tablet. While taking desmopressin, a patient should drink fluids or water only when thirsty and not at other times, as this can lead to sudden fluid accumulation in central nervous system. If desmopressin reduces urine output and increases osmolarity, the pituitary production of ADH is deficient, and the kidney responds normally. If the DI is due to renal pathology, desmopressin does not change either urine output or osmolarity.

If central DI is suspected, testing of other hormones of the pituitary, as well as magnetic resonance imaging (MRI), is necessary to discover if a disease process (such as a prolactinoma, or histiocytosis, syphilis, tuberculosis or other tumor or granuloma) is affecting pituitary function.

Habit drinking (in its severest form termed psychogenic polydipsia) is the most common imitator of diabetes insipidus at all ages. While many adult cases in the medical literature are associated with mental disorders, most patients with habit polydipsia have no other detectable disease. The distinction is made during the water deprivation test, as some degree of urinary concentration above isosmolar is eventually obtained before the patient becomes dehydrated.

Treatment

Central DI and gestational DI respond to desmopressin. In dipsogenic DI, desmopressin is not usually an option.

Desmopressin will be ineffective in nephrogenic DI. Instead, the diuretic hydrochlorothiazide (HCT or HCTZ) or indomethacin can improve NDI; HCT is sometimes combined with amiloride to prevent hypokalemia. Again, adequate hydration is importantant for patients with DI, as they may become dehydrated easily.