

# NUTRITIONAL SUPPORT SYSTEMS

**Nutritional Support systems or Life support** refers to the treatments and techniques performed in an emergency in order to support life after the failure of one or more vital organs. Healthcare providers and emergency medical technicians are generally certified to perform basic and advanced life support procedures; however, basic life support is sometimes provided at the scene of an emergency by family members before emergency services arrive. In the case of cardiac injuries, cardiopulmonary resuscitation is initiated by or family members 25% of the time. Basic life support techniques, such as performing CPR on a victim of cardiac arrest, can double or even triple that patient's chance of survival.

The purpose of basic life support is to save lives in a variety of situations that require immediate attention. These situations can include, but are not limited to, cardiac arrest, stroke, drowning, choking, accidental injuries, violence, severe allergic reactions, burns, hypothermia, birth complications, drug overdose, and alcohol intoxication. The most common emergency that requires BLS is cerebral hypoxia, a shortage of oxygen to the brain due to heart or respiratory failure. A victim of cerebral hypoxia may die within 8–10 minutes without basic life support procedures.

## TECHNIQUES

There are many techniques that may be used by clinicians to achieve the goal of sustaining life. These include:

- **Feeding tube**
- **Total parenteral nutrition**
- **Mechanical ventilation**
- **Heart/Lung bypass**
- **Urinary catheterization**
- **Dialysis**
- **Cardiopulmonary resuscitation**
- **Defibrillation**
- **Artificial pacemaker**
- **Life extension**
- **Life support system for human spaceflight**

These techniques are applied most commonly in the Emergency Department, Intensive Care Unit and, Operating Rooms.

The ultimate goals of life support depend on the specific patient situation. Typically, life support is used to sustain life while the underlying injury or illness is being treated or evaluated for prognosis. Life support techniques may also be used indefinitely if the underlying medical condition cannot be corrected, but a reasonable quality of life can still be expected.

## **1-Tube Feeding**

Tube feeding is a medical device used to provide nutrition to patients who cannot obtain nutrition by mouth, are unable to swallow safely, or need nutritional supplementation. The state of being fed by a feeding tube is called gavage, enteral feeding or tube feeding. Placement may be temporary for the treatment of acute conditions or lifelong in the case of chronic disabilities. A variety of feeding tubes are used in medical practice. They are usually made of polyurethane or silicone. The diameter of a feeding tube is measured in French units (each French unit equals 0.33 millimeters). They are classified by site of insertion and intended use.

There are dozens of conditions that may require tube feeding. The more common conditions that necessitate feeding tubes include prematurity, failure to thrive (or malnutrition), neurologic and neuromuscular disorders, inability to swallow, anatomical and post-surgical malformations of the mouth and esophagus, cancer, and digestive disorders.

## **Types**

The most common types of tubes include those placed through the nose, including nasogastric, naso-duodenal, and naso-jejunal tubes, and those placed directly into the abdomen, such as a gastrostomy, gastro-jejunostomy, or jejunostomy feeding tube.

## **Complications**

The nasogastric (NG) tube is meant to convey liquid food to the stomach. Thus, its tip must rest in the stomach. When inserted incorrectly, the tip may rest in the respiratory system instead of the stomach; in this case, the liquid food will enter the lungs, resulting in pneumonia and death, however this is a rarer complication.

Leakage of gastric contents (containing hydrochloric acid) around the tube into the abdominal (peritoneal) cavity results in peritonitis, a serious complication which will cause death if it is not properly treated. Septic shock is another possible complication. Minor leakage may cause irritation of the skin around the gastro-

stomy site or stoma. Barrier creams, to protect the skin from the corrosive acid, are generally recommended.

All feeding tubes will eventually need to be changed because of wear and tear.

### **Side Effects**

Some side effects may occur with tube feeding. Several complications only become evident when enteral nutritional support (ENS) is applied on a long-term basis. Medically fragile patients remain malnourished during the first year of life despite receiving ENS. Study shows that a majority of children receiving long-term enteral nutritional support are not provided with an adequate amount of energy for their age and showed a lack of appetite.

Failure to gain weight is mainly caused by an imbalance of beneficial variables and undesired adverse effect.

### **2-Parenteral nutrition**

**Parenteral nutrition (PN)** is feeding a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formulae that contain nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals. It is called **total parenteral nutrition (TPN)** or **total nutrient admixture (TNA)** when no significant nutrition is obtained by other routes. It may be called **peripheral parenteral nutrition (PPN)** when administered through vein access in a limb, rather than through a central vein.

### **Indications**

Total parenteral nutrition (TPN) is provided when the gastrointestinal tract is nonfunctional because of an interruption in its continuity (it is blocked, or has a leak - a fistula) or because its absorptive capacity is impaired. It has been used for comatose patients, although enteral feeding is usually preferable, and less prone to complications. Parenteral nutrition is used to prevent malnutrition in patients who are unable to obtain adequate nutrients by oral or enteral routes.

### **Gastrointestinal disorders**

TPN may be the only feasible option for providing nutrition to patients who do not have a functioning gastrointestinal tract or who have disorders requiring complete bowel rest, including bowel obstruction, short bowel syndrome, prolonged

diarrhea or ulcerative colitis, and certain pediatric GI disorders including congenital GI anomalies

### **Solutions Total parenteral nutrition**

Solutions for total parenteral nutrition may be customized to individual patient requirements, or standardized solutions may be used. The use of standardized parenteral nutrition solutions is cost effective and may provide better control of serum electrolytes. Ideally each patient is assessed individually before commencing on parenteral nutrition, and a team consisting of specialized doctors, nurses, clinical pharmacists and Registered Dietitians evaluate the patient's individual data and decide what PN formula to use and at what infusion rate.

For energy only, intravenous sugar solutions with dextrose or glucose are generally used. This is not considered to be parenteral nutrition as it does not prevent malnutrition when used on its own. Standardized solutions may also differ between developers. Following are some examples of what compositions they may have. The solution for normal patients may be given both centrally and peripherally.

#### **Examples of total parenteral nutrition solutions**

<b>Substance</b>	<b>Normal patient</b>	<b>High stress</b>	<b>Fluid-restricted</b>
<a href="#"><u>Amino acids</u></a>	85 g	128 g	75 g
<a href="#"><u>Dextrose</u></a>	250 g	350 g	250 g
<a href="#"><u>Lipids</u></a>	100 g	100 g	50 g
<a href="#"><u>Na<sup>+</sup></u></a>	150 mEq	155 mEq	80 mEq
<a href="#"><u>K<sup>+</sup></u></a>	80 mEq	80 mEq	40 mEq
<a href="#"><u>Ca<sup>2+</sup></u></a>	360 mg	360 mg	180 mg
<a href="#"><u>Mg<sup>2+</sup></u></a>	240 mg	240 mg	120 mg
<a href="#"><u>Acetate</u></a>	72 mEq	226 mEq	134 mEq

<a href="#">Cl<sup>-</sup></a>	143 mEq	145 mEq	70 mEq
<a href="#">P</a>	310 mg	465 mg	233 mg
<a href="#">MVI-12</a>	10 mL	10 mL	10 mL
<a href="#">Trace elements</a>	5 mL	5 mL	5 mL

## Complications

TPN fully by-passes the GI tract and normal methods of nutrient absorption. Possible complications, which may be significant, are listed below.

### a-Infection

TPN requires a chronic IV access for the solution to run through, and the most common complication is infection of this catheter. Infection is a common cause of death in these patients, with a mortality rate of approximately 15% per infection, and death usually results from septic shocks.

### b-Blood clots

Chronic IV access leaves a foreign body in the vascular system, and blood clots on this IV line are common. Death can result from pulmonary embolism wherein a clot that starts on the IV line but breaks off goes into the lungs. Patients under long-term TPN will typically receive a periodic heparin flush to dissolve such clots before they become dangerous.

### c-Fatty liver and liver failure

Fatty liver is usually a more long term complication of TPN, though over a long enough course it is fairly common. The pathogenesis is due to using linoleic acid (an omega-6 fatty acid component of soybean oil) as a major source of calories. TPN-associated liver disease strikes up to 50% of patients within 5–7 years, correlated with a mortality rate of 2-50%. Onset of this liver disease is the major complication that leads TPN patients to requiring an intestinal transplant.

## **d-Hunger**

Because patients are being fed intravenously, the subject does not physically eat, resulting in intense hunger pangs. The brain uses signals from the mouth (taste and smell), the stomach/G.I. Tract (fullness) and blood (nutrient levels) to determine conscious feelings of hunger. In cases of TPN, the taste, smell and physical fullness requirements are not met, and so the patient experiences hunger, despite the fact that the body is being fully nourished. Patients who eat food despite the inability can experience a wide range of complications.

## **e-Cholecystitis**

Total parenteral nutrition increases the risk of acute cholecystitis due to complete disuse of gastrointestinal tract, which may result in bile stasis in the gallbladder. Other potential hepatobiliary dysfunctions include steatosis, steatohepatitis, cholestasis, and cholelithiasis. Six percent of patients on TPN longer than 3 weeks and 100% of patients on TPN longer than 13 weeks develop biliary sludge. The formation of sludge is the result of stasis due to lack of enteric stimulation and is not due to changes in bile composition. Gallbladder sludge disappears after 4 weeks of normal oral diet. Administration of exogenous cholecystikinin (CCK) or stimulation of endogenous CCK by periodic pulse of large amounts of amino acids have been shown to help prevent sludge formation. These therapies are not routinely recommended. Such complications are suggested to be the main reason for mortality in people requiring long-term total parenteral nutrition, such as in short bowel syndrome. In newborn infants with short bowel syndrome with less than 10% of expected intestinal length, thereby being dependent upon total parenteral nutrition, 5 year survival is approximately 20%.

## **f-Gut atrophy**

Infants who are sustained on TPN without food by mouth for prolonged periods are at risk for developing gut atrophy.

## **g-Other complications**

Other complications are either related to catheter insertion, or metabolic, including refeeding syndrome. Catheter complications include pneumothorax, accidental arterial puncture, and catheter-related sepsis. The complication rate at the time of insertion should be less than 5%. Catheter-related infections may be minimized by appropriate choice of catheter and insertion technique. Metabolic complications

include the refeeding syndrome characterised by hypokalemia, hypophosphatemia and hypomagnesemia. Hyperglycemia is common at the start of therapy, but can be treated with insulin added to the TPN solution. Hypoglycaemia is likely to occur with abrupt cessation of TPN. Liver dysfunction can be limited to a reversible cholestatic jaundice and to fatty infiltration (demonstrated by elevated transaminases). Severe hepatic dysfunction is a rare complication. Overall, patients receiving TPN have a higher rate of infectious complications. This can be related to hyperglycemia.

## **h-Special Complications in Pregnancy**

Pregnancy can cause major complications when trying to properly dose the nutrient mixture. Because all of the baby's nourishment comes from the mother's blood stream, the doctor must properly calculate the dosage of nutrients to meet both recipients' needs and have them in usable forms. Incorrect dosage can lead to many adverse, hard-to-guess effects, such as death, and varying degrees of deformation or other developmental problems.

It is recommended that parenteral nutrition administration begin after a period of natural nutrition so doctors can properly calculate the nutritional needs of the fetus. Otherwise, it should only be administered by a team of highly skilled doctors who can accurately assess the fetus' needs.

## **3-Mechanical ventilation**

In medicine, **mechanical ventilation** is a method to mechanically assist or replace spontaneous breathing. This may involve a machine called a ventilator or the breathing may be assisted by a registered nurse, physician, physician assistant, respiratory therapist, paramedic, or other suitable person compressing a bag or set of bellows. Mechanical ventilation is termed "invasive" if it involves any instrument penetrating through the mouth (such as an endotracheal tube) or the skin (such as a tracheostomy tube). There are two main modes of mechanical ventilation within the two divisions: positive pressure ventilation, where air (or another gas mix) is pushed into the trachea, and negative pressure ventilation, where air is, in essence, sucked into the lungs.

## **Medical uses**

Mechanical ventilation is indicated when the patient's spontaneous ventilation is inadequate to maintain life. It is also indicated as prophylaxis for imminent

collapse of other physiologic functions, or ineffective gas exchange in the lungs. Because mechanical ventilation serves only to provide assistance for breathing and does not cure a disease, the patient's underlying condition should be correctable and should resolve over time. In addition, other factors must be taken into consideration because mechanical ventilation is not without its complications

Common medical indications for use include:

- Acute lung injury (including ARDS, trauma)
- Apnea with respiratory arrest, including cases from intoxication
- Acute severe asthma, requiring intubation
- Chronic obstructive pulmonary disease (COPD)
- Acute respiratory acidosis with partial pressure of carbon dioxide ( $p\text{CO}_2$ )  $> 50$  mmHg and  $\text{pH} < 7.25$ , which may be due to paralysis of the diaphragm due to Guillain-Barré syndrome, myasthenia gravis, motor neuron disease, spinal cord injury, or the effect of anaesthetic and muscle relaxant drugs
- Increased work of breathing as evidenced by significant tachypnea, retractions, and other physical signs of respiratory distress
- Hypoxemia with arterial partial pressure of oxygen ( $P\text{aO}_2$ )  $< 55$  mm Hg with supplemental fraction of inspired oxygen ( $F\text{iO}_2$ ) = 1.0
- Hypotension including sepsis, shock, congestive heart failure
- Neurological diseases such as muscular dystrophy and amyotrophic lateral sclerosis

### **Associated risk**

**Barotrauma** — Pulmonary barotrauma is a well-known complication of positive-pressure mechanical ventilation.<sup>1</sup> This includes pneumothorax, subcutaneous emphysema, pneumo-mediastinum, and pneumo-peritoneum.

**Ventilator-associated lung injury** — Ventilator-associated lung injury (VALI) refers to acute lung injury that occurs during mechanical ventilation. It is clinically indistinguishable from acute lung injury or acute respiratory distress syndrome (ALI/ARDS).

**Diaphragm** — Controlled mechanical ventilation may lead to a rapid type of disuse atrophy involving the diaphragmatic muscle fibers, which can develop within the first day of mechanical ventilation. This cause of atrophy in the



diaphragm is also a cause of atrophy in all respiratory related muscles during controlled mechanical ventilation.

**Motility of mucocilia in the airways** — Positive pressure ventilation appears to impair mucociliary motility in the airways. Bronchial mucus transport was frequently impaired and associated with retention of secretions and pneumonia.

## **Complications**

Mechanical ventilation is often a life-saving intervention, but carries potential complications including pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia. Other complications include diaphragm atrophy, decreased cardiac output, and oxygen toxicity. One of the primary complications that presents in patients mechanically ventilated is acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). ALI/ARDS are recognized as significant contributors to patient morbidity and mortality.

In many healthcare systems, prolonged ventilation as part of intensive care is a limited resource (in that there are only so many patients that can receive care at any given moment). It is used to support a single failing organ system (the lungs) and cannot reverse any underlying disease process (such as terminal cancer). For this reason, there can be (occasionally difficult) decisions to be made about whether it is suitable to commence someone on mechanical ventilation. Equally many ethical issues surround the decision to discontinue mechanical ventilation.

## **Mechanical ventilators Types**

Mechanical ventilators typically require power by a battery or a wall outlet (DC or AC) though some ventilators work on a pneumatic system not requiring power.

- **Transport ventilators** — these ventilators are small and more rugged, and can be powered pneumatically or via AC or DC power sources.
- **Intensive-care ventilators** — these ventilators are larger and usually run on AC power (though virtually all contain a battery to facilitate intra-facility transport and as a back-up in the event of a power failure). This style of ventilator often provides greater control of a wide variety of ventilation parameters (such as inspiratory rise time). Many ICU ventilators also incorporate graphics to provide visual feedback of each breath.
- **Neonatal ventilators** — designed with the preterm neonate in mind, these are a specialized subset of ICU ventilators that are designed to deliver the

smaller, more precise volumes and pressures required to ventilate these patients.

- **Positive airway pressure ventilators (PAP)** — these ventilators are specifically designed for non-invasive ventilation. This includes ventilators for use at home for treatment of chronic conditions such as sleep apnea or COPD.

Breaths can also be cycled when an alarm condition such as a high pressure limit has been reached, which is a primary strategy in pressure regulated volume control.

#### **4-Cardiopulmonary bypass**

**Cardiopulmonary bypass (CPB)** is a technique that temporarily takes over the function of the heart and lungs during surgery, maintaining the circulation of blood and the oxygen content of the body. The CPB pump itself is often referred to as a **heart–lung machine** or "the pump". Cardiopulmonary bypass pumps are operated by perfusionists. CPB is a form of extracorporeal circulation. Extracorporeal membrane oxygenation is generally used for longer-term treatment.

#### **Uses of cardiopulmonary bypass**

Cardiopulmonary bypass is commonly used in heart surgery because of the difficulty of operating on the beating heart. Operations requiring the opening of the chambers of the heart require the use of CPB to support the circulation during that period. The machine nourishes the blood cells and allows them to continue cellular respiration even through surgery.

CPB can be used for the induction of total body hypothermia, a state in which the body can be maintained for up to 45 minutes without perfusion (blood flow). If blood flow is stopped at normal body temperature, permanent brain damage normally occurs in three to four minutes — death may follow shortly afterward. Similarly, CPB can be used to rewarm individuals suffering from hypothermia.

Extracorporeal membrane oxygenation (ECMO) is a simplified form of CPB sometimes used as life-support for newborns with serious birth defects, or to oxygenate and maintain recipients for organ transplantation until new organs can be found.

CPB mechanically circulates and oxygenates blood for the body while bypassing the heart and lungs. It uses a heart–lung machine to maintain perfusion to other body organs and tissues while the surgeon works in a bloodless surgical field. The

surgeon places a cannula in right atrium, vena cava, or femoral vein to withdraw blood from the body. The cannula is connected to tubing filled with isotonic crystalloid solution. Venous blood that is removed from the body by the cannula is filtered, cooled or warmed, oxygenated, and then returned to the body. The cannula used to return oxygenated blood is usually inserted in the ascending aorta, but it may be inserted in the femoral artery. The patient is administered heparin to prevent clotting, and protamine sulfate is given after to reverse effects of heparin. During the procedure, hypothermia is maintained; body temperature is usually kept at 28 °C to 32 °C (82.4–89.6 °F). The blood is cooled during CPB and returned to the body. The cooled blood slows the body's basal metabolic rate, decreasing its demand for oxygen. Cooled blood usually has a higher viscosity, but the crystalloid solution used to prime the bypass tubing dilutes the blood.

### **Components of cardiopulmonary bypass**

Cardiopulmonary bypass consists of two main functional units, the pump and the oxygenator which remove oxygen-deprived blood from a patient's body and replace it with oxygen-rich blood through a series of tubes (hoses).

**Tubing-The components of the CPB circuit are interconnected by a series of tubes made of silicone rubber or PVC.**

### **Pumps**

#### ***Roller pump***

The pump console usually comprises several rotating motor-driven pumps that peristaltically "massage" tubing. This action gently propels the blood through the tubing. This is commonly referred to as a roller pump, or peristaltic pump.

#### ***Centrifugal pump***

Many CPB circuits now employ a centrifugal pump for the maintenance and control of blood flow during CPB. By altering the speed of revolution (RPM) of the pump head, blood flow is produced by centrifugal force. This type of pumping action is considered to be superior to the action of the roller pump by many because it is thought to produce less blood damage (Hemolysis, etc.).

## Oxygenator

The oxygenator is designed to transfer oxygen to infused blood and remove carbon dioxide from the venous blood. Cardiac surgery was made possible by CPB using bubble oxygenators, but membrane oxygenators have supplanted bubble oxygenators since the 1980s. The main reasons for this are that membrane oxygenators tend to filter out more micro bubbles, referred to as gaseous microemboli which is generally considered harmful to the patient <sup>[8]</sup> and reduce damage to blood cells, compared to bubble oxygenators.

Another type of oxygenator gaining favour recently is the heparin-coated blood oxygenator which is believed to produce less systemic inflammation and decrease the propensity for blood to clot in the CPB circuit.

## Cannulae

Multiple cannulae are sewn into the patient's body in a variety of locations, depending on the type of surgery. A venous cannula removes oxygen deprived blood from a patient's body. An arterial cannula infuses oxygen-rich blood into the arterial system. A cardioplegia cannula delivers a cardioplegia solution to cause the heart to stop beating.

Some commonly used cannulation sites:

<b>Venous</b>	<b>Arterial</b>	<b>Cardioplegia</b>
<a href="#">Right atrium</a>	Proximal <a href="#">aorta</a> , distal to the <a href="#">cross-clamp</a>	Proximal <a href="#">aorta</a> , proximal to the <a href="#">cross-clamp</a>
<a href="#">Vena cavae</a>	<a href="#">Femoral artery</a>	<a href="#">Coronary sinus</a> (retrograde delivery)
<a href="#">Femoral vein</a>	<a href="#">Axillary artery</a>	Coronary ostia
	Distal <a href="#">aorta</a>	Bypass grafts (during <a href="#">CABG</a> )
	Apex of the <a href="#">heart</a>	

## **Complications**

CPB is not benign and there are a number of associated problems:

- Postperfusion syndrome (also known as "pumphead")
- Hemolysis
- Capillary leak syndrome
- Clotting of blood in the circuit – can block the circuit (particularly the oxygenator) or send a clot into the patient.
- Air embolism
- Leakage – a patient can rapidly exsanguinate (lose blood perfusion of tissues) if a line becomes disconnected.
- 1.5% of patients that undergo CPB are at risk of developing Acute Respiratory Distress Syndrome.

As a consequence, CPB is only used during the several hours a cardiac surgery may take. Most oxygenators come with a manufacturer's recommendation that they are only used for a maximum of 6 hours, although they are sometimes used for up to 10 hours, with care being taken to ensure they do not clot off and stop working. For longer periods than this, an ECMO (extracorporeal membrane oxygenation) is used, which can be in operation for up to 31 days – such as in this Taiwanese case, for 16 days, after which the patient received a heart transplant.

CPB may contribute to immediate cognitive decline. The heart-lung blood circulation system and the connection surgery itself release a variety of debris into the bloodstream, including bits of blood cells, tubing, and plaque. For example, when surgeons clamp and connect the aorta to tubing, resulting emboli may block blood flow and cause mini strokes. Other heart surgery factors related to mental damage may be events of hypoxia, high or low body temperature, abnormal blood pressure, irregular heart rhythms, and fever after surgery.

## **6-Urinary catheterization**

In **urinary catheterization** a latex, polyurethane, or silicone tube known as a urinary catheter is inserted into a patient's bladder via the urethra. Catheterization allows the patient's urine to drain freely from the bladder for collection. It may be used to inject liquids used for treatment or diagnosis of bladder conditions. A clinician, often a nurse, usually performs the procedure, but self-catheterization is

also possible. The catheter may be a permanent one (indwelling catheter), or an intermittent catheter removed after each catheterization.

### **Preventing infection**

Everyday care of catheter and drainage bag is important to reduce the risk of infection.<sup>[10]</sup> Such precautions include:

- Cleansing the urethral area (area where catheter exits body) and the catheter itself.
- Disconnecting drainage bag from catheter only with clean hands
- Disconnecting drainage bag as seldom as possible.
- Keeping drainage bag connector as clean as possible and cleansing the drainage bag periodically.
- Use of a thin catheter where possible to reduce risk of harming the urethra during insertion.
- Drinking sufficient liquid to produce at least two liters of urine daily
- Sexual activity is very high risk for urinary infections, especially for catheterized women.

There is no clear evidence that any one catheter type or insertion technique is superior to another in preventing infection.

Recent developments in the field of the temporary prostatic stent have been viewed as a possible alternative to indwelling catheterization and the infections associated with their use.

### **7-Dialysis**

In medicine, **dialysis** (from Greek **dialusis**, "διάλυσις", meaning *dissolution*, **dia**, meaning *through*, and **lysis**, meaning *loosening or splitting*) is a process for removing waste and excess water from the blood and is used primarily as an artificial replacement for lost kidney function in people with kidney failure.<sup>[1]</sup> Dialysis may be used for those with an acute disturbance in kidney function (acute kidney injury, previously acute renal failure) or progressive but chronically worsening kidney function—a state known as chronic kidney disease stage 5 (previously chronic renal failure or end-stage renal disease). The latter form may develop over months or years, but in contrast to acute kidney injury is not usually reversible and dialysis is regarded as a "holding measure" until a kidney transplant can be performed or sometimes as the only supportive measure in those for whom a transplant would be inappropriate.

The kidneys have important roles in maintaining health. When healthy, the kidneys maintain the body's internal equilibrium of water and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, sulfate). The acidic metabolism end-products that the body cannot get rid of via respiration are also excreted through the kidneys. The kidneys also function as a part of the endocrine system, producing erythropoietin, calcitriol and renin. Erythropoietin is involved in the production of red blood cells and calcitriol plays a role in bone formation. Dialysis is an imperfect treatment to replace kidney function because it does not correct the compromised endocrine functions of the kidney. Dialysis treatments replace some of these functions through diffusion (waste removal) and ultrafiltration (fluid removal).<sup>[4]</sup>

## **Principle**

Dialysis works on the principles of the diffusion of solutes and ultrafiltration of fluid across a semi-permeable membrane. Diffusion is a property of substances in water; substances in water tend to move from an area of high concentration to an area of low concentration. Blood flows by one side of a semi-permeable membrane, and a dialysate, or special dialysis fluid, flows by the opposite side. A semipermeable membrane is a thin layer of material that contains holes of various sizes, or pores. Smaller solutes and fluid pass through the membrane, but the membrane blocks the passage of larger substances (for example, red blood cells, large proteins). This replicates the filtering process that takes place in the kidneys, when the blood enters the kidneys and the larger substances are separated from the smaller ones in the glomerulus.

The two main types of dialysis, hemodialysis and peritoneal dialysis, remove wastes and excess water from the blood in different ways.<sup>[2]</sup> Hemodialysis removes wastes and water by circulating blood outside the body through an external filter, called a dialyzer, that contains a semipermeable membrane. The blood flows in one direction and the dialysate flows in the opposite. The counter-current flow of the blood and dialysate maximizes the concentration gradient of solutes between the blood and dialysate, which helps to remove more urea and creatinine from the blood. The concentrations of solutes (for example potassium, phosphorus, and urea) are undesirably high in the blood, but low or absent in the dialysis solution, and constant replacement of the dialysate ensures that the concentration of undesired solutes is kept low on this side of the membrane. The dialysis solution has levels of minerals like potassium and calcium that are similar to their natural concentration in healthy blood. For another solute, bicarbonate, dialysis solution level is set at a slightly higher level than in normal blood, to encourage diffusion of

bicarbonate into the blood, to act as a pH buffer to neutralize the metabolic acidosis that is often present in these patients. The levels of the components of dialysate are typically prescribed by a nephrologist according to the needs of the individual patient.

In peritoneal dialysis, wastes and water are removed from the blood inside the body using the peritoneum as a natural semipermeable membrane. Wastes and excess water move from the blood, across the peritoneal membrane, and into a special dialysis solution, called dialysate, in the abdominal cavity.

## **Types**

There are two types of dialysis: hemodialysis and peritoneal dialysis

## **Starting indications**

The decision to initiate dialysis in patients with kidney failure depends on several factors. These can be divided into acute or chronic indications.

- Indications for dialysis in the patient with acute kidney injury are summarized with the vowel acronym of "AEIOU":
  1. Acidemia from metabolic acidosis in situations in which correction with sodium bicarbonate is impractical or may result in fluid overload.
  2. Electrolyte abnormality, such as severe hyperkalemia, especially when combined with AKI.
  3. Intoxication, that is, acute poisoning with a dialyzable substance. These substances can be represented by the mnemonic SLIME: salicylic acid, lithium, isopropanol, magnesium-containing laxatives, and ethylene glycol.
  4. Overload of fluid not expected to respond to treatment with diuretics
  5. Uremia complications, such as pericarditis, encephalopathy, or gastrointestinal bleeding.

## **Dialyzable substances**

### **Substances**

- Ethylene glycol
- Procainamide
- Methanol
- Isopropyl alcohol



- Barbiturates
- Lithium
- Bromide
- Sotalol
- Chloral hydrate
- Ethanol
- Acetone, Atenolol
- Theophylline
- Salicylates

## **8-Cardiopulmonary resuscitation**

Cardiopulmonary resuscitation, commonly known as CPR, is an emergency procedure performed in an effort to manually preserve intact brain function until further measures are taken to restore spontaneous blood circulation and breathing in a person who is in cardiac arrest. It is indicated in those who are unresponsive with no breathing or abnormal breathing, for example, agonal respirations.

According to the International Liaison Committee on Resuscitation guidelines, CPR involves chest compressions for adults between 5 cm (2.0 in) and 6 cm (2.4 in) deep and at a rate of at least 100 to 120 per minute. The rescuer may also provide breaths by either exhaling into the subject's mouth or nose or using a device that pushes air into the subject's lungs. This process of externally providing ventilation is termed artificial respiration. Current recommendations place emphasis on high-quality chest compressions over artificial respiration; a simplified CPR method involving chest compressions only is recommended for untrained rescuers. In children only doing compressions may result in worse outcomes.

CPR alone is unlikely to restart the heart. Its main purpose is to restore partial flow of oxygenated blood to the brain and heart. The objective is to delay tissue death and to extend the brief window of opportunity for a successful resuscitation without permanent brain damage. Administration of an electric shock to the subject's heart, termed defibrillation, is usually needed in order to restore a viable or "perfusing" heart rhythm. Defibrillation is effective only for certain heart rhythms, namely ventricular fibrillation or pulseless ventricular tachycardia, rather than asystole or pulseless electrical activity. CPR may succeed in inducing a heart rhythm that may be shockable. In general, CPR is continued until the patient has a return of spontaneous circulation (ROSC) or is declared dead, or until there is no rescuer physically able to continue (CPR can be found exhausting).

## **Medical uses**

CPR is indicated for any person unresponsive with no breathing or breathing only in occasional agonal gasps, as it is most likely that they are in cardiac arrest. If a person still has a pulse but is not breathing (respiratory arrest) artificial respirations may be more appropriate, but, due to the difficulty people have in accurately assessing the presence or absence of a pulse, CPR guidelines recommend that lay persons should not be instructed to check the pulse, while giving healthcare professionals the option to check a pulse. In those with cardiac arrest due to trauma, CPR is considered futile but still recommended. Correcting the underlying cause such as a pneumothorax or pericardial tamponade may help.

CPR serves as the foundation of successful cardiopulmonary resuscitation, preserving the body for defibrillation and advanced life support. Even in the case of a "non-shockable" rhythm, such as Pulseless Electrical Activity (PEA) where defibrillation is not indicated, effective CPR is no less important. Used alone, CPR will result in few complete recoveries, though the outcome without CPR is almost uniformly fatal.

## **Complications**

While CPR is a last resort intervention, without which a person without a pulse will all but certainly die, the physical nature of how CPR is performed does lead to complications that may need to be rectified. Common complications due to CPR are rib fractures, sternal fractures, bleeding in the anterior mediastinum, heart contusion, hemopericardium,<sup>1</sup> upper airway complications, damage to the abdominal viscera - lacerations of the liver and spleen, fat emboli, pulmonary complications - pneumothorax, hemothorax, lung contusions.

The most common injuries sustained from CPR are rib fractures.

Where CPR is performed in error by a bystander, on a patient not in cardiac arrest, only around 2% suffer injury as a result (although 12% experienced discomfort).

## **Pathophysiology**

CPR is used on people in cardiac arrest in order to oxygenate the blood and maintain a cardiac output to keep vital organs alive. Blood circulation and oxygenation are required to transport oxygen to the tissues. The physiology of CPR involves generating a pressure gradient between the arterial and venous vascular beds; CPR achieves this via multiple mechanisms. The brain may sustain damage

after blood flow has been stopped for about four minutes and irreversible damage after about seven minutes. Typically if blood flow ceases for one to two hours, then body cells die. Therefore, in general CPR is effective only if performed within seven minutes of the stoppage of blood flow. The heart also rapidly loses the ability to maintain a normal rhythm. Low body temperatures, as sometimes seen in near-drowning, prolong the time the brain survives. Following cardiac arrest, effective CPR enables enough oxygen to reach the brain to delay brain stem death, and allows the heart to remain responsive to defibrillation attempts.

## **8-Defibrillation**

**Defibrillation** is a common treatment for life-threatening cardiac dysrhythmias and ventricular fibrillation. Defibrillation consists of delivering a therapeutic dose of electrical current to the heart with a device called a **defibrillator**. This depolarizes a critical mass of the heart muscle, terminates the dysrhythmia and allows normal sinus rhythm to be re-established by the body's natural pacemaker, in the sinoatrial node of the heart.

Defibrillators can be external, transvenous, or implanted (implantable cardioverter-defibrillator), depending on the type of device used or needed. Some external units, known as automated external defibrillators (AEDs), automate the diagnosis of treatable rhythms, meaning that lay responders or bystanders are able to use them successfully with little or no training at all.

### **Medical uses**

In a study of CPR and defibrillation for cardiac arrest under ideal conditions, survival with normal neurological function occurred in 38%. Assuming survival without defibrillation to be zero, this is equivalent to saving the life of 2 out of 5 people using defibrillation. Furthermore, when considering only those with a heart rhythm correctable by defibrillation (ventricular fibrillation), survival rate was 59%, equivalent to saving 3 out of 5. Survival rates from cardiac arrest was less, however, in more common circumstances seen outside of the study, including among ill hospitalized persons, people without access to immediate (<4-5 minutes) CPR, and for those whose arrest is not witnessed.

## **9-Artificial cardiac pacemaker**

A pacemaker (or **artificial pacemaker**, so as not to be confused with the heart's natural pacemaker) is a medical device which uses electrical impulses, delivered by electrodes contracting the heart muscles, to regulate the beating of the heart.

The primary purpose of a pacemaker is to maintain an adequate heart rate, either because the heart's natural pacemaker is not fast enough, or because there is a block in the heart's electrical conduction system. Modern pacemakers are externally programmable and allow a cardiologist to select the optimum pacing modes for individual patients. Some combine a pacemaker and defibrillator in a single implantable device. Others have multiple electrodes stimulating differing positions within the heart to improve synchronisation of the lower chambers (ventricles) of the heart.

### **Basic function**

Modern pacemakers usually have multiple functions. The most basic form monitors the heart's native electrical rhythm. When the pacemaker does not detect a heartbeat within a normal beat-to-beat time period, it will stimulate the ventricle of the heart with a short low voltage pulse. This sensing and stimulating activity continues on a beat by beat basis.

Since a pacemaker uses batteries, the device itself will need replacement as the batteries lose power. Device replacement is usually a simpler procedure than the original insertion as it does not normally require leads to be implanted. The typical replacement requires a surgery in which an incision is made to remove the existing device, the leads are removed from the existing device, the leads are attached to the new device, and the new device is inserted into the patient's

### ***Lifestyle considerations***

A patient's lifestyle is usually not modified to any great degree after insertion of a pacemaker. There are a few activities that are unwise such as full contact sports and activities that involve intense magnetic fields.

Any kind of an activity that involves intense magnetic fields should be avoided. This includes activities such as arc welding possibly, with certain types of equipment, or maintaining heavy equipment that may generate intense magnetic fields (such as a magnetic resonance imaging (MRI) machine).

However, in February 2011 the FDA approved a new pacemaker device called the Revo MRI SureScan which is the first to be labeled conditional for MRI use.

A 2008 U.S. study has found that the magnets in some headphones included with portable music players, when placed within an inch of pacemakers, may cause interference.

## Complications

A possible complication of dual-chamber artificial pacemakers is 'pacemaker-mediated tachycardia' (PMT), a form of reentrant tachycardia. In PMT, the artificial pacemaker forms the anterograde (atrium to ventricle) limb of the circuit and the atrioventricular (AV) node forms the retrograde limb (ventricle to atrium) of the circuit. Treatment of PMT typically involves reprogramming the pacemaker.

Another possible complication is "pacemaker-tracked tachycardia," where a supraventricular tachycardia is tracked by the pacemaker and produces beats from a ventricular lead. This is becoming exceedingly rare as newer devices are often programmed to recognize supraventricular tachycardia and switch to non-tracking modes.

Sometimes the leads, which are small diameter wires, from the pacemaker to the implantation site in the heart muscle will need to be removed. The most common reason for lead removal is infection however over time leads can degrade due to a number of reasons such as lead flexing. Changes to programming of the pacemaker may overcome lead degradation to some extent. However a patient who has several pacemaker replacements over a decade or two in which the leads were reused may require a lead replacement surgery.

Lead replacement may be done in one of two ways. Insert a new set of leads without removing the current leads (not recommended as it provides additional obstruction to blood flow and heart valve function) or remove the current leads and then insert replacements. The lead removal technique will vary depending on the surgeon's estimation of the probability that simple traction will suffice to more complex procedures. Leads can normally be disconnected from the pacemaker easily which is why device replacement usually entails simple surgery to access the device and replace it by simply unhooking the leads from the device to replace and hooking the leads to the new device. The possible complications, such as perforation of the heart wall, come from removing the lead{s} from the patient's body.

The other end of a pacemaker lead is actually implanted into the heart muscle. In addition leads that have been implanted for a decade or two will usually have attachments to the patient's body at various places in the pathway from device to heart muscle since the human body tends to incorporate foreign devices into tissue. In some cases such as a device that has been inserted for a short amount of time, removal may involve simple traction to pull the lead from the body. Removal in

other cases is typically done with a cutting device which threads over the lead and is moved down the lead to remove any organic attachments with tiny cutting lasers or similar device.

Pacemaker lead malposition in various locations has been described in the literature. Depending on the location of the pacer lead and symptoms treatment varies.<sup>[57]</sup>

Another possible complication called twiddler's syndrome occurs when a patient manipulates the pacemaker and causes the leads to be removed from their intended location and causes possible stimulation of other nerves.

## **10-Life extension**

**Life extension science**, also known as **anti-aging medicine**, **indefinite life extension**, **experimental gerontology**, and **biomedical gerontology**, is the study of slowing down or reversing the processes of aging to extend both the maximum and average lifespan. Some researchers in this area, and "life extensionists", "immortalists" or "longevists" (those who wish to achieve longer lives themselves), believe that future breakthroughs in tissue rejuvenation, stem cells, regenerative medicine, molecular repair, gene therapy, pharmaceuticals, and organ replacement (such as with artificial organs or xenotransplantations) will eventually enable humans to have indefinite lifespans (agerasia) through complete rejuvenation to a healthy youthful condition.

The sale of putative anti-aging products such as nutrition, physical fitness, skin care, hormone replacements, vitamins, supplements and herbs is a lucrative global industry, with the US market generating about \$50 billion of revenue each year.<sup>[2]</sup> Some medical experts state that the use of such products has not been proven to affect the aging process and many claims regarding the efficacy of these marketed products have been roundly criticized by medical experts, including the American Medical Association.

However, it has not been shown that the goal of indefinite human lifespans itself is necessarily not feasible; some animals such as hydra, planarian flatworms, and certain sponges, corals, and jellyfish do not die of old age and exhibit potential immortality. The ethical ramifications of life extension are debated by bioethicists.

## **Current strategies and issues**

### **Diets and supplements**

Much life extension research focuses on nutrition—diets or supplements—as a means to extend lifespan, although few of these have been systematically tested for significant longevity effects. The many diets promoted by anti-aging advocates are often contradictory. A dietary pattern with some support from scientific research is caloric restriction.

Preliminary studies of caloric restriction on humans using surrogate measurements have provided evidence that caloric restriction may have powerful protective effect against secondary aging in humans. Caloric restriction in humans may reduce the risk of developing Type 2 diabetes and atherosclerosis.

The free-radical theory of aging suggests that antioxidant supplements, such as vitamin C, vitamin E, Q<sub>10</sub>, lipoic acid, carnosine, and N-acetylcysteine, might extend human life. However, combined evidence from several clinical trials suggest that  $\beta$ -carotene supplements and high doses of vitamin E increase mortality rates. Resveratrol is a sirtuin stimulant that has been shown to extend life in animal models, but the effect of resveratrol on lifespan in humans is unclear as of 2011.

There are many traditional herbs purportedly used to extend the health-span, including a Chinese tea called Jiaogulan (*Gynostemma pentaphyllum*), dubbed "China's Immortality Herb." Ayurveda, the traditional Indian system of medicine, describes a class of longevity herbs called rasayanas, including *Bacopa monnieri*, *Ocimum sanctum*, *Curcuma longa*, *Centella asiatica*, *Phyllanthus emblica*, *Withania somnifera* and many others.

### **Hormone treatments**

The anti-aging industry offers several hormone therapies. Some of these have been criticized for possible dangers to the patient and a lack of proven effect. For example, the American Medical Association has been critical of some anti-aging hormone therapies.

Although some recent clinical studies have shown that low-dose growth hormone (GH) treatment for adults with GH deficiency changes the body composition by increasing muscle mass, decreasing fat mass, increasing bone density and muscle strength, improves cardiovascular parameters (i.e. decrease of LDL cholesterol),

and affects the quality of life without significant side effects, the evidence for use of growth hormone as an anti-aging therapy is mixed and based on animal studies. There are mixed reports that GH or IGF-1 signaling modulates the aging process in humans and about whether the direction of its effect is positive or negative.

## **Proposed strategies**

### **Caloric restriction**

The best-characterized anti-aging therapy was, and still is, CR. In some studies caloric restriction has been shown to extend the life of mice, yeast, and rhesus monkeys significantly. However, a more recent study has shown that in contrast, caloric restriction has not improved the survival rate in rhesus monkeys. Long-term human trials of CR are now being done. It is the hope of the anti-aging researchers that resveratrol, found in grapes, or pterostilbene, a more bio-available substance, found in blueberries, as well as rapamycin, a biotic substance discovered on Easter Island, may act as CR mimetics to increase the life span of humans.

More recent work reveals that the effects long attributed to caloric restriction may be obtained by restriction of protein alone, and specifically of just the sulfur-containing amino acids cysteine and methionine. Current research is into the metabolic pathways affected by variation in availability of products of these amino acids.

### **Anti-aging drugs**

There are a number of chemicals intended to slow the aging process currently being studied in animal models. One type of research is related to the observed effects a caloric restriction (CR) diet, which has been shown to extend lifespan in some animals. Based on that research, there have been attempts to develop drugs that will have the same effect on the aging process as a caloric restriction diet, which are known as Caloric restriction mimetic drugs. Some drugs that are already approved for other uses have been studied for possible longevity effects on laboratory animals because of a possible CR-mimic effect; they include rapamycin, metformin and other geroprotectors. Resveratrol and pterostilbene are dietary supplements that have also been studied in this context.

Other attempts to create anti-aging drugs have taken different research paths. One notable direction of research has been research into the possibility of using the enzyme telomerase in order to counter the process of telomere shortening.



However, there are potential dangers in this, since some research has also linked telomerase to cancer and to tumor growth and formation. In addition, some preparations, called senolytics are designed to effectively deplete senescent cells, that poisoning an organism by their secretions.

## **Nanotechnology**

Future advances in nanomedicine could give rise to life extension through the repair of many processes thought to be responsible for aging. K. Eric Drexler, one of the founders of nanotechnology, postulated cell repair machines, including ones operating within cells and utilizing as yet hypothetical molecular computers, in his 1986 book *Engines of Creation*. Raymond Kurzweil, a futurist and transhumanist, stated in his book *The Singularity Is Near* that he believes that advanced medical nanorobotics could completely remedy the effects of aging by 2030.

## **Cloning and body part replacement**

Some life extensionists suggest that therapeutic cloning and stem cell research could one day provide a way to generate cells, body parts, or even entire bodies (generally referred to as reproductive cloning) that would be genetically identical to a prospective patient. Recently, the US Department of Defense initiated a program to research the possibility of growing human body parts on mice. Complex biological structures, such as mammalian joints and limbs, have not yet been replicated. Dog and primate brain transplantation experiments were conducted in the mid-20th century but failed due to rejection and the inability to restore nerve connections. As of 2006, the implantation of bio-engineered bladders grown from patients' own cells has proven to be a viable treatment for bladder disease. Proponents of body part replacement and cloning contend that the required biotechnologies are likely to appear earlier than other life-extension technologies.

The use of human stem cells, particularly embryonic stem cells, is controversial. Opponents' objections generally are based on interpretations of religious teachings or ethical considerations. Proponents of stem cell research point out that cells are routinely formed and destroyed in a variety of contexts. Use of stem cells taken from the umbilical cord or parts of the adult body may not provoke controversy.

The controversies over cloning are similar, except general public opinion in most countries stands in opposition to reproductive cloning. Some proponents of therapeutic cloning predict the production of whole bodies, lacking consciousness, for eventual brain transplantation.

## Cyborgs

Replacement of biological (susceptible to diseases) organs with mechanical ones could extend life. This is the goal of 2045 Initiative.

## Cryonics

For cryonicists (advocates of cryopreservation), storing the body at low temperatures after death may provide an "ambulance" into a future in which advanced medical technologies may allow resuscitation and repair. They speculate cryogenic temperatures will minimize changes in biological tissue for many years, giving the medical community ample time to cure all disease, rejuvenate the aged and repair any damage that is caused by the cryopreservation process.

Many cryonicists do not believe that legal death is "real death" because stoppage of heartbeat and breathing—the usual medical criteria for legal death—occur before biological death of cells and tissues of the body. Even at room temperature, cells may take hours to die and days to decompose. Although neurological damage occurs within 4–6 minutes of cardiac arrest, the irreversible neurodegenerative processes do not manifest for hours. Cryonicists state that rapid cooling and cardio-pulmonary support applied immediately after certification of death can preserve cells and tissues for long-term preservation at cryogenic temperatures. People, particularly children, have survived up to an hour without heartbeat after submersion in ice water. In one case, full recovery was reported after 45 minutes underwater. To facilitate rapid preservation of cells and tissue, cryonics "standby teams" are available to wait by the bedside of patients who are to be cryopreserved to apply cooling and cardio-pulmonary support as soon as possible after declaration of death.

No mammal has been successfully cryopreserved and brought back to life, with the exception of frozen human embryos. Resuscitation of a postembryonic human from cryonics is not possible with current science. Some scientists still support the idea based on their expectations of the capabilities of future science.

## 11-Life support system in Human Space lift

In human spaceflight, a **life support system** is a group of devices that allow a human being to survive in space. US government space agency NASA, and private spaceflight companies use the term **environmental control and life support system** or the acronym **ECLSS** when describing these systems for their human

spaceflight missions. The life support system may supply air, water and food. It must also maintain the correct body temperature, an acceptable pressure on the body and deal with the body's waste products. Shielding against harmful external influences such as radiation and micro-meteorites may also be necessary. Components of the life support system are life-critical, and are designed and constructed using safety engineering techniques.

### **Human physiological and metabolic needs**

A crewmember of typical size requires approximately 5 kg or 11.0231 lb(total) of food, water, and oxygen per day to perform the standard activities on a space mission, and outputs a similar amount in the form of waste solids, waste liquids, and carbon dioxide. The mass breakdown of these metabolic parameters is as follows: 0.84 kg of oxygen, 0.62 kg of food, and 3.52 kg of water consumed, converted through the body's physiological processes to 0.11 kg of solid wastes, 3.87 kg of liquid wastes, and 1.00 kg of carbon dioxide produced. These levels can vary due to activity level, specific to mission assignment, but will correlate to the principles of mass balance. Actual water use during space missions is typically double the specified values mainly due to non-biological use (i.e. personal cleanliness). Additionally, the volume and variety of waste products varies with mission duration to include hair, finger nails, skin flaking, and other biological wastes in missions exceeding one week in length. Other environmental considerations such as radiation, gravity, noise, vibration, and lighting also factor into human physiological response in space, though not with the more immediate effect that the metabolic parameters have.

### **Atmosphere-**

Space life support systems maintain atmospheres composed, at a minimum, of oxygen, water vapor and carbon dioxide. The partial pressure of each component gas adds to the overall barometric pressure.

By reducing or omitting diluents (constituents other than oxygen, e.g., nitrogen and argon) the total pressure can be lowered to a minimum of 21 kPa, the partial pressure of oxygen in the Earth's atmosphere at sea level. This can lighten spacecraft structures, reduce leaks and simplify the life support system.

However, the elimination of diluent gases substantially increases fire risks, especially in ground operations when for structural reasons the total cabin pressure must exceed the external atmospheric pressure; see Apollo 1. Furthermore, oxygen toxicity becomes a factor at high oxygen concentrations. For this reason, most

modern crewed spacecraft use conventional air (nitrogen/oxygen) atmospheres and use pure oxygen only in pressure suits during extravehicular activity where acceptable suit flexibility mandates the lowest inflation pressure possible.

### **Water-**

Water is consumed by crew members for drinking, cleaning activities, EVA thermal control, and emergency uses. It must be stored, used, and reclaimed (from waste water) efficiently since no on-site sources currently exist for the environments reached in the course of human space exploration.

### **Food**

Life support systems could include a plant cultivation system which allows food to be grown within buildings and/or vessels. However, no such system has flown in space as yet. Such a system could be designed so that it reuses most (otherwise lost) nutrients. This is done, for example, by composting toilets which reintegrate waste material (excrement) back into the system, allowing the nutrients to be taken up by the food crops. The food coming from the crops is then consumed again by the system's users and the cycle continues.