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# Death: A Molecular Definition

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*Abstract:* This article tries to understand and define death scientifically. Today's scientific development of Cardiopulmonary Resuscitation and prompt defibrillation posed a challenge, rendering the previous definition inadequate. This general definition of death is now called "clinical death", and even after it occurs, breathing and heart beat may be restarted in some cases. Events which were causally linked to death in the past are now prevented from having an effect; even without a functioning heart and lungs, a person can be sustained with life-support devices. In addition to such extremes, a growing number of people would die quickly if their organ transplants or cardiac pacemakers failed. The author explains in detail the phenomenon of Apoptosis and describes scientifically the phenomenon of death.

*Keywords:* Apoptosis, brain death, Cell death, DNA, RNA.

Death is the full cessation of vital functions in the biological life. Generally death is defined as the cessation of heart beat (cardiac arrest) and of breathing. The development of Cardiopulmonary Resuscitation (CPR) and prompt defibrillation posed a challenge, rendering the previous definition inadequate. This general definition of death is now called "clinical death", and even after it occurs, breathing and heart beat may be restarted in some cases. Events which were causally linked to death in the past are now prevented from having an effect; even without a functioning heart and lungs, a person can be sustained with life-support devices. In addition to such extremes, a growing number of people would die quickly if their organ transplants or cardiac pacemakers failed.

Today, where a definition of the moment of death is required, doctors and coroners usually turn to "brain death" or "biological death": people are considered dead when the electrical activity in their brain ceases. It is presumed that a stoppage of electrical activity indicates the end of consciousness. However, suspension of consciousness must be permanent, and not transient, as occurs during sleep, and especially a coma. In the case of sleep, EEGs can easily tell the difference. Identifying the moment of death is important in cases of transplantation, as organs for transplant (the brain excluded) must be harvested as quickly as possible after the death of the body.

## Cell Death

Normal cellular function involves the production of free energy required for vital cellular metabolism, the production of enzymatic and structural protein, the maintenance of chemical and osmotic homeostasis of cell, and cell reproduction. During normal functions, cells require oxygen, phosphate, calcium, nutritional substrates, ATP - which is required as a source of free energy, intact cell membranes, and a steady-state activity that requires oxygen consumption. If any of these functions are interrupted, eventually it will lead to cell death.

The cell starts to multiply and proliferate to start a life. Initial division of the cells is influenced by environment and surrounding biochemicals which maintain the viable or conducive atmosphere for division. The changes in this immediate environment influence the cellular proliferation and also death. Every day cells divide and die to maintain the balance. The different biomolecules are distributed in the body maintaining a fine balance among themselves and their environment. The slightest alterations in these biomolecules lead to death in later stages. For e.g.; the alterations in deoxyribonucleic acid (DNA) with a consequence of synthesis of faulty proteins lead to accumulation of wrong molecules. These molecules accumulate causing dysfunction of the cellular machinery leading to cell death.

Ribonucleic acid (RNA) is the molecule that receives information (transcription) from DNA and converts this message to a protein sequence (translation). A change in RNA which is transcribed normally from the DNA, by a change in gene sequence will lead to death of the accurate message transfer, which is not noticed in the

initial stage. The abnormal protein synthesized, due to a sequence change leads to the production of non-functional protein. The accumulation of this abnormal protein in the cellular environment can lead to functional deterioration of cell and finally death of cell.

In every individual, cells die and are replaced everyday. As individuals grow old functional capability of this repair is reduced and death of the cells increases than proliferation leading to death of the tissue. The accumulated tissue death in an organ can lead to the functional arrest of the organ – that's the death of the organ. This is also supported by recent clinical research. If the deterioration of one organ is not cared for appropriately, the cumulative functional deterioration of a specific organ can affect the other organs and finally the death of an individual.

For every cell, there is a time to live and a time to die. There are two ways in which cells die:

- They are killed by injurious agents.
- They are induced to commit suicide.

## Death by injury

Cells may be damaged by injury such as mechanical damage or by exposure to toxic chemicals. The dying cells undergo a characteristic series of changes - They and their organelles like mitochondria swell because the ability of the plasma membrane to control the passage of ions and water is disrupted. Then the cell contents leak out, leading to inflammation of surrounding tissues.

## Death by suicide

Cells that are induced to commit suicide undergo the following processes:

- shrink;
- develop bubble-like blebs on their surface;
- have the chromatin (DNA and chromosomal protein) in their nucleus degraded;
- mitochondria break down with the release of cytochrome C;
- break into small, membrane-wrapped, fragments.

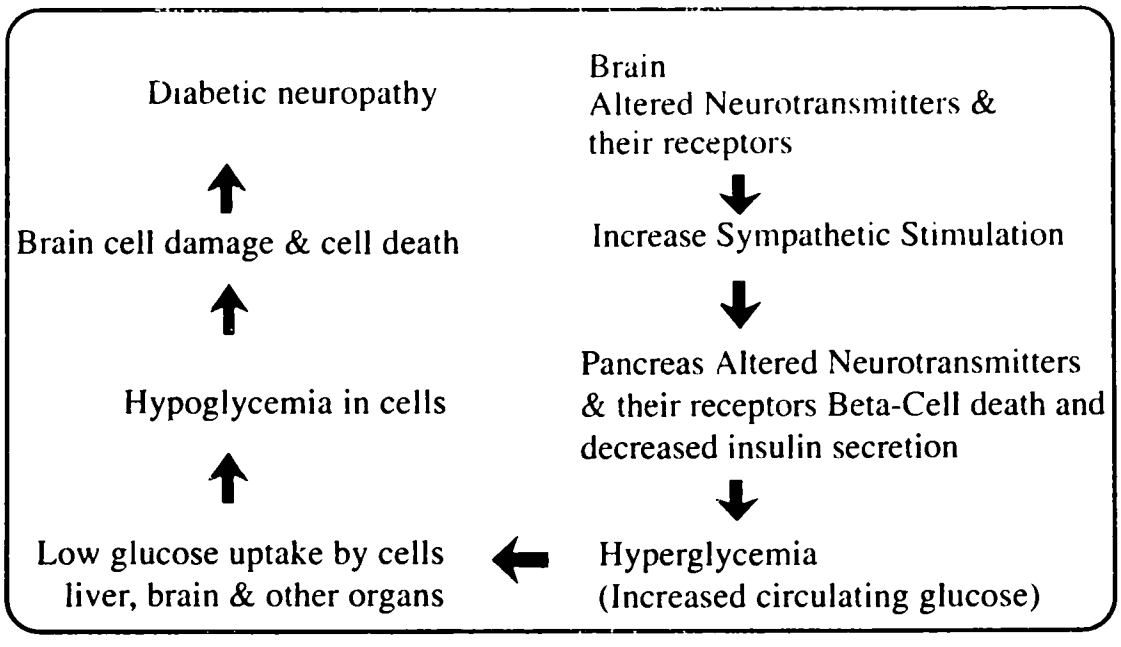



**Fig 1: Brain function and diabetic neuropathy**

- phospholipid phosphatidylserine, which is normally hidden within the plasma membrane, is exposed on the surface.
- bound receptors on phagocytic cells like macrophages and dendritic cells then engulf the cell fragments.
- phagocytic cells secrete cytokines inhibiting inflammation

The pattern of events in death by suicide is so orderly that the process is often called programmed cell death. The cellular machinery of programmed cell death turns out to be as intrinsic to the cell as mitosis. Programmed cell death is also called apoptosis.

## The Mechanisms of Apoptosis

There are 3 different mechanisms by which a cell undergoes apoptosis.

- Generated by signals arising within the cell;
- Triggered by death activators binding to receptors at the cell surface: eg: TNF-alpha, Lymphotoxin, Fas ligand
- Triggered by reactive oxygen species.

## Why should there be apoptosis?

A cell undergoing apoptosis serves mainly two functions, *viz.* programmed cell death is as needed for proper development as mitosis. This can be understood by citing the following examples - The resorption of the tadpole tail at the time of its metamorphosis into a frog occurs by apoptosis, the formation of the fingers and toes of the fetus requires the removal of the tissue between them, the sloughing off of the inner lining of the uterus (the endometrium) at the start of menstruation occurs by apoptosis, the formation of the proper synapses between neurons in the brain requires that surplus cells be eliminated by apoptosis. Programmed cell death is also needed to destroy cells that represent a threat to the integrity of the organism. Examples: Cells infected with viruses - one of the methods by which cytotoxic T lymphocytes (CTLs) kill virus-infected cells is by inducing apoptosis. As cell-mediated immune responses wane, the effector cells of the immune system must be removed to prevent them from attacking its own cells. CTLs induce apoptosis in each other and even in themselves. Defects in the apoptotic machinery are associated with autoimmune diseases such as lupus erythematosus and rheumatoid arthritis. Damage to cell genome can cause a cell to disrupt proper embryonic development leading to birth defects or the cell to become cancerous.

Cells respond to DNA damage by increasing their production of p53. p53 is a potent inducer of apoptosis. The mutations in the p53 gene, producing a defective protein, are so often found in cancer cells. Radiation and chemicals used in cancer therapy induce apoptosis in cancer cells.

## What makes a cell decide to undergo apoptosis?

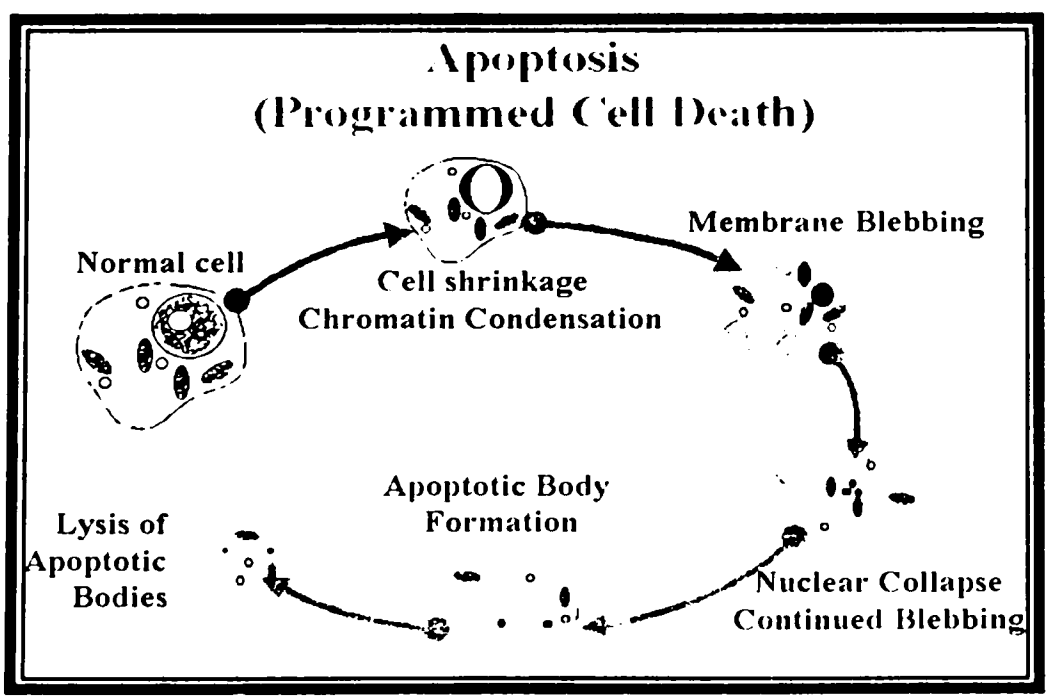
There is a fine balance between the withdrawal of positive signals; that is, signals needed for continued survival, and the receipt of negative signals. The cell death or continued survival depends on which way this balance tilts.

The continued survival of most cells requires that they receive continuous stimulation from other cells and, for many, continued adhesion to the surface on which they are growing. Some examples of positive signals are growth factors for neurons and Interleukin-2 (IL-2), an essential factor for the mitosis of lymphocytes.

The negative signals are increased levels of oxidants within the cell, damage to DNA by these oxidants or other agents like ultraviolet light, x-rays and chemotherapeutic drugs, accumulation of proteins that failed to fold properly into their proper tertiary structure and molecules that bind to specific receptors on the cell surface and signal the cell to begin apoptosis. These death activators include: Tumor necrosis factor-alpha (TNF-á ) that binds to the TNF receptor; Lymphotoxin (TNF-â ) that also binds to the TNF receptor and Fas ligand (FasL), a molecule that binds to a cell-surface receptor named Fas (CD95).

## When to establish that the brain is dead?

Certifying doctors must ascertain that there is no evidence of brain function over a period of time, the loss of function is not a result of drugs, hypothermia (low temperature), hypoglycaemia (low blood sugar) or hyponatraemia (low blood sodium). The person has sustained a brain injury sufficient to account for the irreversible loss



of brain function - often this is done by CT scan. There are no reflex functions associated with coughing, gagging, eye movement, blinking, or dilation of the pupils. The person makes no attempt to breathe when disconnected from the respirator for several minutes. During the previous test, the carbon dioxide level of the blood has risen above the point at which breathing is normally stimulated.

## Physiological changes leading up to death

The basic events leading to death involve the brain ceasing to supply information vital for controlling ventilation, heart rhythm, and/or vasodilation and vasoconstriction. The lung is unable to supply oxygen to exchange with the blood stream. The heart and blood vessels are unable to maintain adequate circulation of blood to vital tissues. In the cerebrovascular system, hemorrhage, pump failure, and decreased carbondioxide leads to decreased $PCO_2$ leading to Cheyne-Stokes respiration.

Problems in the central nervous system that may lead to death include infection, blood vessel disruption, malignant tumors, or metabolic changes such as renal failure, hepatic failure, and pancreatic failure. Early signs of decompensation in the central nervous system include sluggish pupils that are non-reactive to stimuli, and that are dilated and fixed (this is also an effect of certain drugs). Confusion and the inability to orient oneself may also be signs of decompensation. Later signs include lethargy, decreased ability to perform simple cognitive functions, and attention only by tactile, auditory, or visual stimuli. The very late signs include stupor or sleep, withdrawal of purposeless involvement to stimuli without wakefulness or arousal, or loss of bowel control. Other general signs include being in a semi-comatose state (movement occurs only with pain), or in a deep coma (unresponsive to all stimuli).

In the respiratory system, problems that may lead to death include the lack of pulmonary blood flow, chronic obstructive pulmonary disease (COPD), infections, and cancer metastasis.

## Changes after death

The physiological consequences of death for the human body follow a recognized sequence through early changes into bloating, decay, changes after decay and finally skeletal remains.

Soon after death (15–120 minutes depending on various factors), the body begins to cool (algor mortis), becomes pallid (pallor mortis), and internal sphincter muscles relax, leading to the release of urine, feces, and stomach contents if the body is moved. The blood moves to pool in the lowest parts of the body, livor mortis, within 30 minutes and then begins to coagulate. During this, the body becomes distended and skin colour progressively changes from green to purple and finally to black. The body experiences muscle stiffening (rigor mortis). During this process, the muscles gradually become hard due to decreased ATP and lactic acidosis within muscle fibrils which peaks at around 12 hours after death and is gone in another 24 (depending on temperature) as enzymes begin to break down the tissues. Within a day, the body starts to show signs of decomposition (decay), both autolytic changes and from 'attacking' organisms—bacteria, fungi, insects, mammalian scavengers, etc. Internally, the body structures begin to collapse, the skin loses integration with the underlying tissues, and bacterial action creates gases which cause bloating and swelling. The rate of decay is enormously variable and depends on numerous factors. Thus, a body may be reduced to skeletal remains in days, though it is possible under certain conditions for remains to stay largely intact for many years.

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