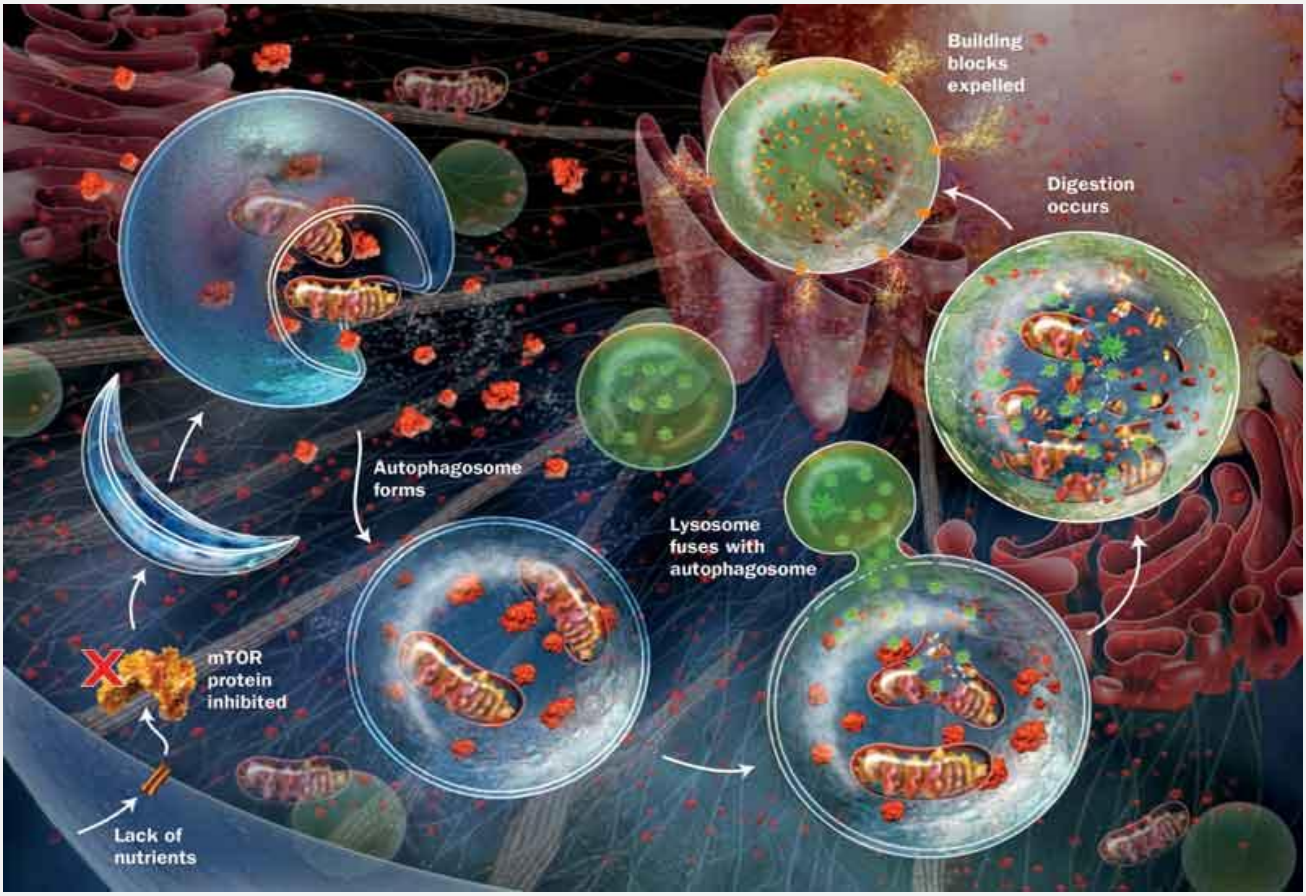
SYRIAN ARAB REPUBLIC

MINISTRY OF HIGHER EDUCATION

NATIONAL CENTER FOR THE DISTINGUISHED

Apoptosis and Cell Death



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Class: 12.

INTRODUCTION

CELLS ARE THE MAIN BUILD IN OUR BODIES, IN REAL, HUMAN BODY CONTAIN BILLIONS OF CELLS. THERE ARE MANY KINDS OF THIS CELLS WHICH DIFFER IN SHAPE, LOCATION AND IN FUNCTIONS, A LOT OF CELLS DOES NOT STILL ALIVE IN OUR BODIES TILL WE DIE BECAUSE CELLS COULD BE HURTLED OR FATIGUED . BECAUSE OF THE HUGE NUMBER OF CELLS EVERY MOMENTS, MANY CELLS DIE AND TOO MANY ARE CREATED. THEREFORE IT IS ESSENTIAL TO HAVE A MECHANISM TO CONTROL CELL DEATH, IN REAL THERE ARE TWO MAIN MECHANISMS TO DO THE JOB ARE CALLED: PROGRAMMED CELL DEATH AND NECROSIS SO, WHAT ARE NECROSIS AND APOPTOSIS? IN ADDITIONS WHAT IS DIFFERENT BETWEEN THE TWO? IS THERE ANY IMMUNE RESPONDS OF ANY OF THIS TWO MECHANISM? ALL THIS QUESTIONS WILL BE ANSWERED IN THE SEARCH BELOW.

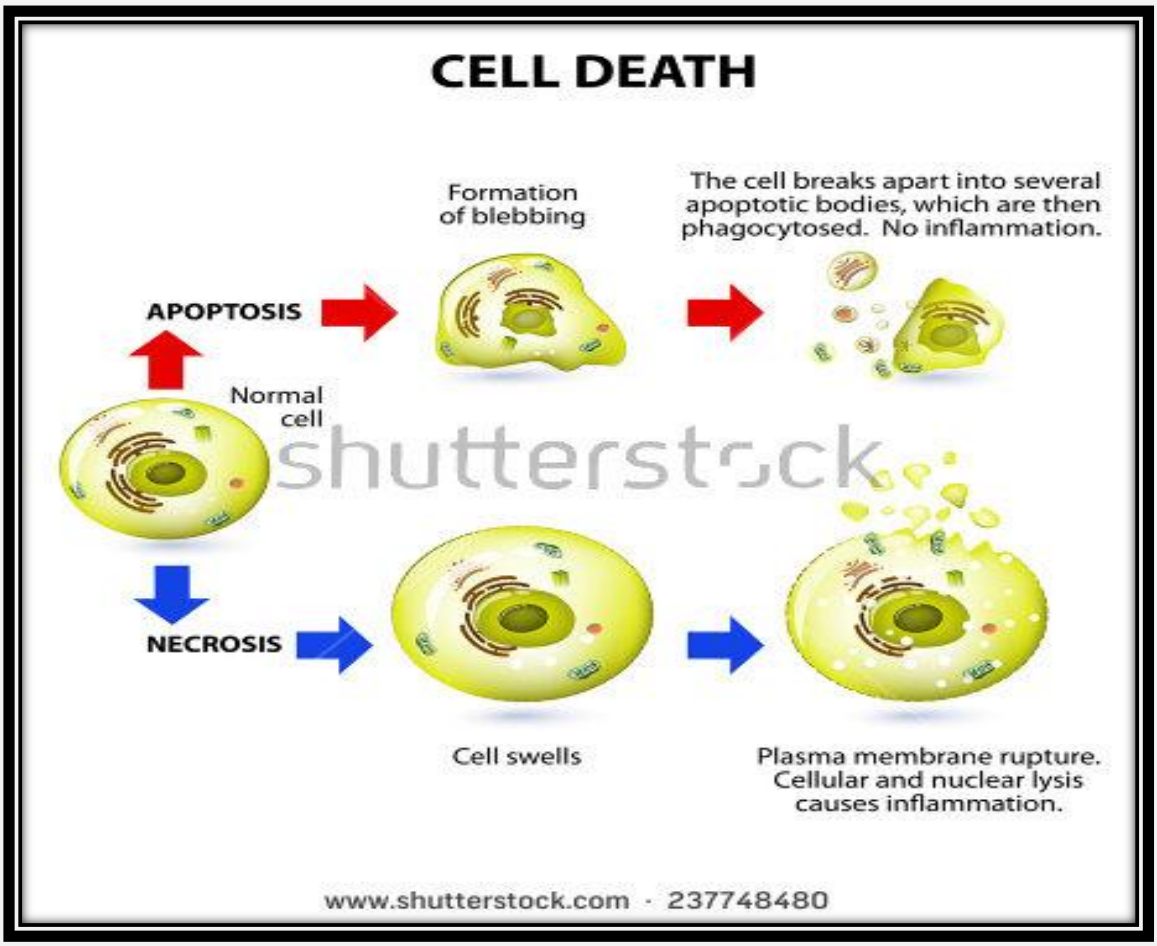

FIGURE NUMBER (2)

SEARCH INDEX:

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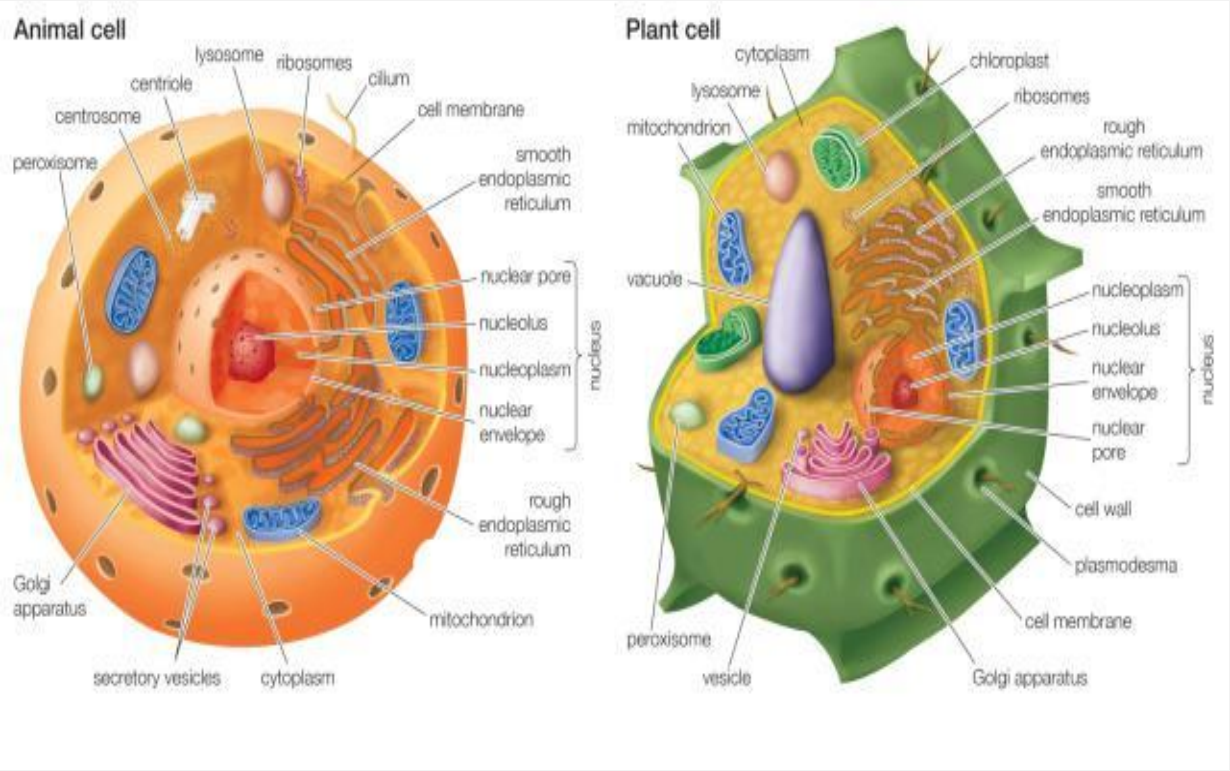
CHAPTER1: CELLS

1.1 WHAT IS CELLS?

CELLS ARE THE BASIC STRUCTURAL, FUNCTIONAL, AND BIOLOGICAL UNIT OF KNOWN LIVING ALL ORGANISMS. A CELL IS THE SMALLEST UNIT OF LIFE THAT CAN REPLICATE INDEPENDENTLY, AND CELLS ARE OFTEN CALLED THE "BUILDING BLOCKS OF LIFE".

IT IS THE SMALLEST COMMON DENOMINATOR OF LIFE. SOME CELLS ARE ORGANISMS UNTO THEMSELVES; OTHERS ARE PART OF MULTICELLULAR ORGANISMS. ALL CELLS ARE MADE FROM THE SAME MAJOR CLASSES OF ORGANIC MOLECULES: NUCLEIC ACIDS, PROTEINS, CARBOHYDRATES, AND LIPIDS. IN ADDITION, CELLS CAN BE PLACED IN TWO MAJOR CATEGORIES AS A RESULT OF ANCIENT EVOLUTIONARY EVENTS: PROKARYOTES, WITH THEIR CYTOPLASMIC GENOMES, AND EUKARYOTES, WITH THEIR NUCLEAR-ENCASED GENOMES AND OTHER MEMBRANE-BOUND ORGANELLES. THOUGH THEY ARE SMALL, CELLS HAVE EVOLVED INTO A VAST VARIETY OF SHAPES AND SIZES. TOGETHER THEY FORM TISSUES THAT THEMSELVES FORM ORGANS, AND EVENTUALLY ENTIRE ORGANISMS.[1]

FIGURE NUMBER (3)



1.2 Cells Theory:

Theory in biology that includes one or both of the statements that the cell is the fundamental structural and functional unit of living matter and that the organism is composed of autonomous cells with its properties being the sum of those of its cells.

There are three main points to the cell theory:

- The cell is the basic unit of life.
- All living things are composed of one or more cells.
- All cells come from pre-existing cells.[1]

1.3 Types of cells:

Multicellular organisms contain a vast array of highly specialized cells. Plants contain root cells, leaf cells, and stem cells. Humans have skin cells, nerve cells, and sex cells. Each kind of cell is structured to perform a highly specialized function. Often, examining a cell's structure reveals much about its function in the organism.

however, can also exist as single-celled organisms. The organisms called protists, for instance, are single-celled organisms. Examples of protists include the microscopic organism called Paramecium and the single-celled alga called Chlamydomonas.

Two types of cells are recognized in living things: prokaryotes and eukaryotes. The word prokaryote literally means "before the nucleus." As the name suggests, prokaryotes are cells that have no distinct nucleus. Most prokaryotic organisms are single-celled, such as bacteria and algae.

the term eukaryote means, "true nucleus." eukaryotes have a distinct nucleus and distinct organelles. the organelle is a small structure that performs a specific set of functions within the eukaryotic cell. these membranes hold organelles together. in addition to their lack of a nucleus, prokaryotes also lack these distinct organelles.

1.4 The structure of cells:

The basic structure of all cells, whether prokaryote and eukaryote, is the same. All cells have an outer covering called a plasma membrane. The plasma membrane holds the cell together and permits the passage of substances into and out of the cell. With a few minor exceptions, plasma membranes are the same in prokaryotes and eukaryotes. The interior of both kinds of cells is called the cytoplasm. Within the cytoplasm of eukaryotes are embedded the cellular organelles. As noted above, the cytoplasm of prokaryotes contains no organelles.[2]

1.5 Cells organelles:

NUCLEUS:

The nucleus is the control center of the cell. The nucleolus is the site where parts of ribosomes are manufactured. Surrounding the nucleus is a double membrane called the nuclear envelope. The nuclear envelope is covered with tiny openings called nuclear pores.

The nucleus directs all cellular activities by controlling the synthesis of proteins.

Golgi apparatus:

The Golgi body is named for its discoverer. It is one of the most unusually shaped organelles. Surrounding the Golgi body are numerous small membrane-bounded vesicles (particles). The function of the Golgi body and its vesicles is to sort, modify, and package large molecules that are secreted by the cell or used within the cell for various functions.

Mitochondria:

The mitochondria are the power plants of cells. Each sausage-shaped mitochondrion is covered by an outer membrane. The inner membrane of a mitochondrion is folded into compartments called cristae. The matrix, or inner space created by the cristae, contains the enzymes necessary for the many chemical reactions that eventually transform food molecules into energy.[3]

Vesicles:

Vesicles are small, spherical particles that contain various kinds of molecules. Some vesicles are used to transport molecules from the endoplasmic reticulum to the Golgi body and from the Golgi body to various destinations.[4]

SPECIAL KINDS OF VESICLES PERFORM OTHER FUNCTIONS AS WELL. LYSOSOMES ARE VESICLES THAT CONTAIN ENZYMES INVOLVED IN CELLULAR DIGESTION.

ENDOPLASMIC RETICULUM:

ENDOPLASMIC RETICULUM CONSISTS OF FLATTENED SHEETS, AND TUBES OF MEMBRANE THAT COVER THE ENTIRE EXPANSE OF A EUKARYOTIC CELL'S CYTOPLASM. A MAJOR FUNCTION OF ENDOPLASMIC RETICULUM IS TO TRANSPORT MATERIALS THROUGHOUT THE CELL. TWO KINDS OF ENDOPLASMIC RETICULUM CAN BE IDENTIFIED IN A CELL. ONE TYPE IS CALLED ROUGH ENDOPLASMIC RETICULUM AND THE OTHER ARE CALLED SMOOTH ENDOPLASMIC RETICULUM.[4]

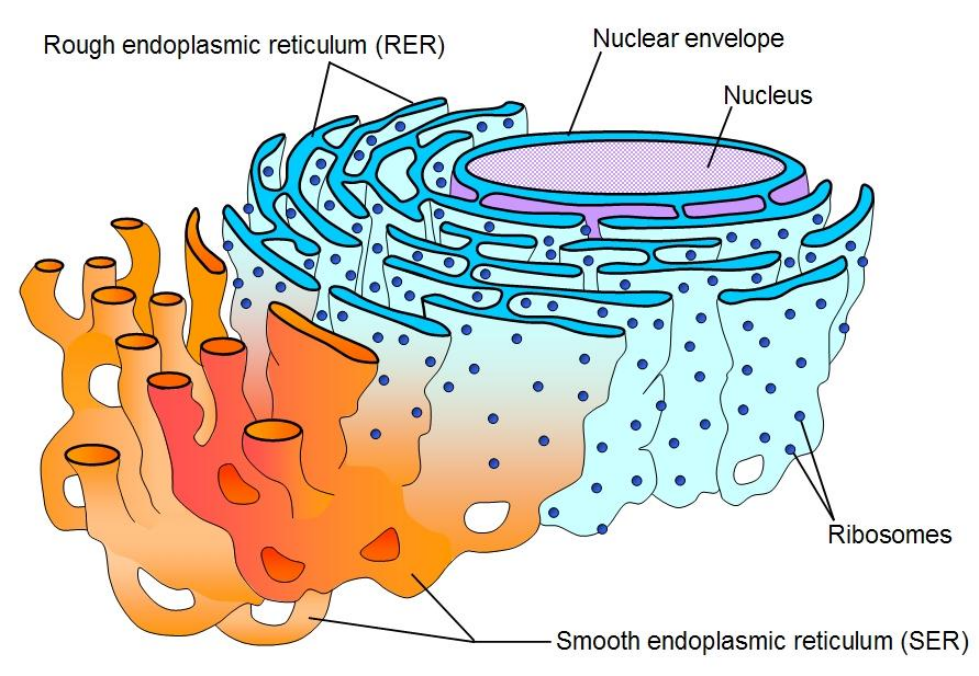


FIGURE NUMBER (4)

PLASMA MEMBRANE:

THE PLASMA MEMBRANE OF THE CELL IS OFTEN DESCRIBED AS SELECTIVELY PERMEABLE. THAT TERM MEANS THAT SOME SUBSTANCES ARE ABLE TO PASS THROUGH THE MEMBRANE BUT OTHERS ARE NOT. FOR EXAMPLE, THE PRODUCTS FORMED BY THE BREAKDOWN OF FOODS ARE ALLOWED TO PASS INTO A CELL, AND THE WASTE PRODUCTS FORMED WITHIN THE CELL ARE ALLOWED TO PASS OUT OF THE CELL.

THERE ARE MORE ORGANELLES IN THE CELL SUCH AS:

- AUTOPHAGOSOME.
- LYSOSOME.
- ENDOSOME.
- PHAGOSOME.

CHAPTER 2: CELL DEATH

2.1 WHAT IS CELL DEATH?

CELL DEATH IS THE EVENT OF A BIOLOGICAL CELL CEASING TO CARRY OUT ITS FUNCTIONS. THIS MAY BE THE RESULT OF THE NATURAL PROCESS OF OLD CELLS DYING AND BEING REPLACED BY NEW ONES, OR MAY RESULT FROM SUCH FACTORS AS DISEASE, LOCALIZED INJURY, OR THE DEATH OF THE ORGANISM OF WHICH THE CELLS ARE PART. KINDS OF CELL DEATH INCLUDE: PROGRAMMED CELL DEATH, NECROSIS...

IN ADDITION IT IS ALSO TERMINATES NORMAL CELLULAR FUNCTIONS, INCLUDING RESPIRATION, METABOLISM, GROWTH AND PROLIFERATION. CELL DEATH CAN BE NON-PROGRAMMED, FOR EXAMPLE AS THE RESULT OF ACCIDENTAL INJURY OR TRAUMA, OR PROGRAMMED. TYPES OF PROGRAMMED CELL DEATH INCLUDE ANOIKIS, APOPTOSIS, AUTOPHAGY, NECROSIS, NECROPTOSIS AND PYROPTOSIS. [5]

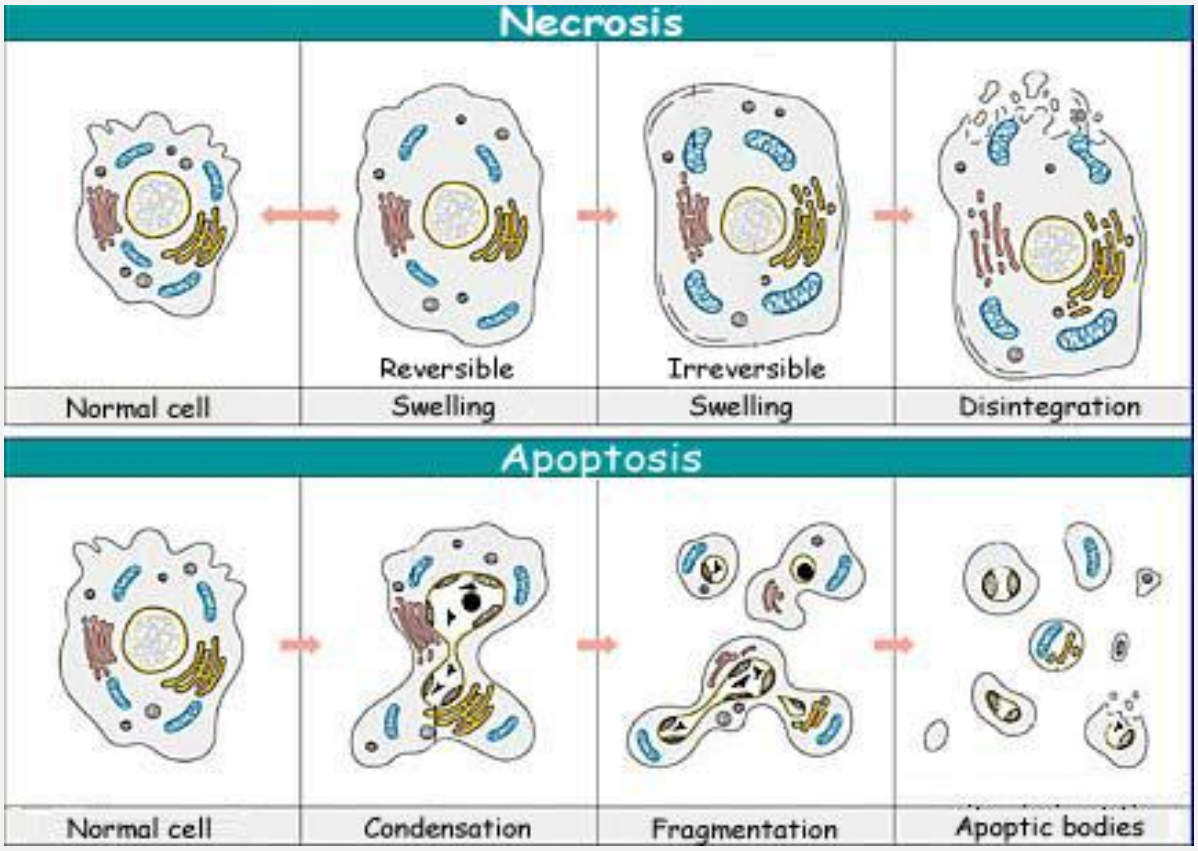


FIGURE NUMBER (5)

2.2 Programmed cell death AND NECROSIS.

2.2.1 PROGRAMMED CELL DEATH (APOPTOSIS):

THE TERM APOPTOSIS WAS PROPOSED BY KERR AND COLLEAGUES IN 1972 TO DESCRIBE A SPECIFIC MORPHOLOGICAL PATTERN OF CELL DEATH OBSERVED AS CELLS WERE ELIMINATED DURING EMBRYONIC DEVELOPMENT, NORMAL CELL TURNOVER IN HEALTHY ADULT TISSUE, AND ATROPHY UPON HORMONE WITHDRAWAL. THE MORPHOLOGY ASSOCIATED WITH THIS PHENOMENON WAS CHARACTERIZED BY NUCLEAR AND CYTOPLASMIC CONDENSATION AND CELLULAR FRAGMENTATION INTO MEMBRANE-BOUND FRAGMENTS. THESE FRAGMENTS OR APOPTOTIC BODIES WERE TAKEN UP BY OTHER CELLS AND DEGRADED WITHIN PHAGOSOME. THE AUTHORS SUGGESTED THAT THE DELETION OF CELLS WITH LITTLE TISSUE DISRUPTION AND NO INFLAMMATION ALLOWS REUTILIZATION OF CELLULAR COMPONENTS. THE MORPHOLOGICAL CHARACTERISTICS OF APOPTOSIS WERE PROPOSED TO RESULT FROM A GENERAL MECHANISM OF CONTROLLED CELL DELETION, WHICH PLAYS A COMPLEMENTARY ROLE TO MITOSIS AND CYTOKINESIS IN MAINTAINING STABLE CELL POPULATIONS WITHIN TISSUES.[6]

THE WORD APOPTOSIS WAS USED IN GREEK TO DENOTE A "FALLING OFF," AS LEAVES FROM A TREE. THE TERM CONNOTES A CONTROLLED PHYSIOLOGIC PROCESS OF REMOVING INDIVIDUAL COMPONENTS OF AN ORGANISM WITHOUT DESTRUCTION OR DAMAGE TO THE ORGANISM.

WE SHOULD KNOW THAT CELL DEATH RESULTING FROM INTRINSIC CELLULAR PROCESSES SHOULD BE CONSIDERED DISTINCTLY DIFFERENT FROM CELL DEATH CAUSED BY SEVERE ENVIRONMENTAL PERTURBATIONS. THE LATTER PROCESS WAS ASSOCIATED WITH THE MORPHOLOGY OF COAGULATION NECROSIS WHICH "IS PROBABLY THE RESULT OF AN IRREVERSIBLE DISTURBANCE OF CELLULAR HOMEOSTATIC MECHANISMS"

THE MAIN STEPS AT APOPTOSIS:

- SHRINK.
- DEVELOP BUBBLE-BLEBS IN THEIR SURFACE.
- CHROMATIN IN THEIR NUCLEUS IS DEGRADED.
- CYTOCHROME IS RELEASED FROM THE MITOCHONDRIA.
- BREAK INTO SMALL MEMBRANE WRAPPED FRAGMENT.
- PHOSPHOLIPIDS ARE EXPOSED TO SURFACE.
- PHOSPHOLIPIDS IS BOUND BY RECEPTORS ON PHAGOCYTIC CELLS.
- THE PHAGOCYTIC CELLS RELEASE CYTOKINES THAT INHIBIT INFLAMMATION.**[7]**

Necrosis:

Necrosis (from the Greek "death, the stage of dying, the act of killing" from "dead") is a form of cell injury which results in the premature death of cells in living tissue by autolysis.

Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma, which result in the unregulated digestion of cell components. In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death.

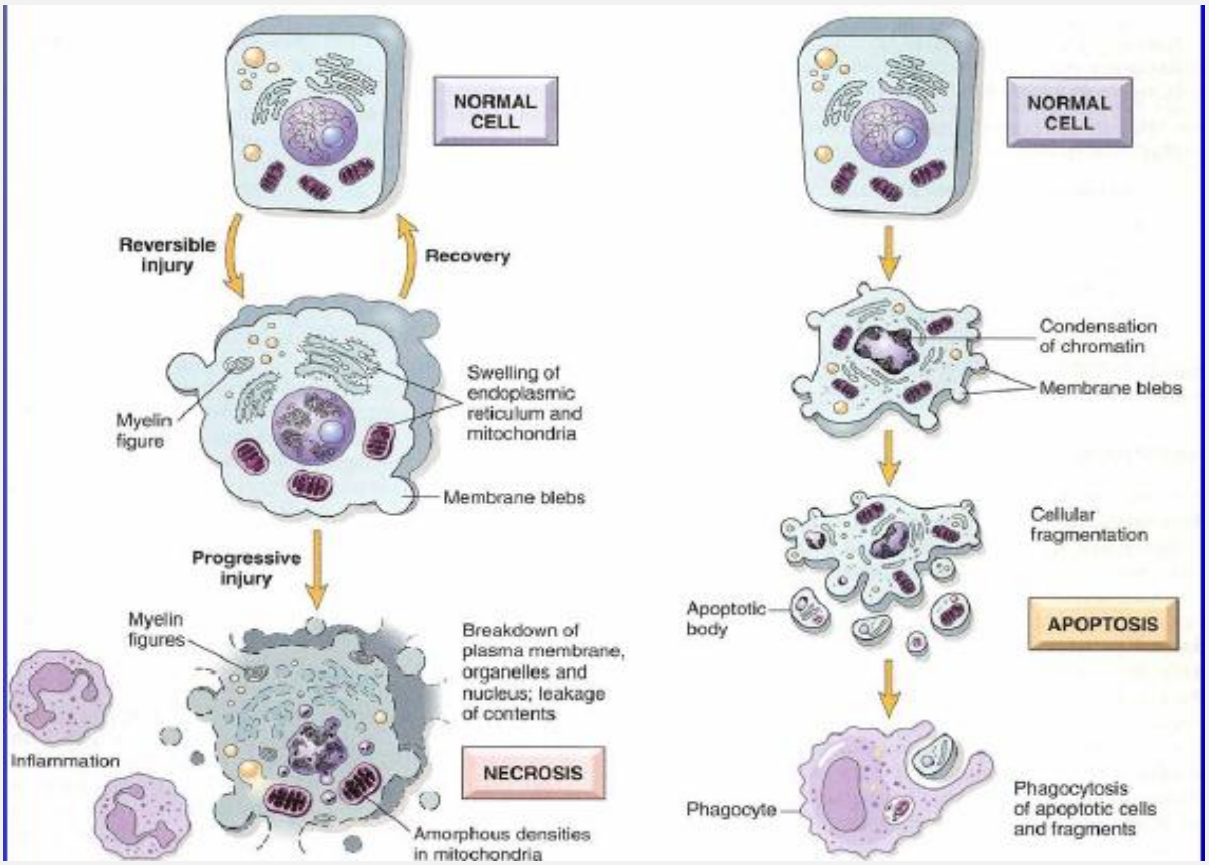
While apoptosis often provides beneficial effects to the organism, necrosis is usually detrimental and can be fatal. Cellular death due to necrosis does not follow the apoptotic signal transduction pathway, but rather various receptors are activated, and result in the loss of cell membrane integrity and an uncontrolled release of products of cell death into the extracellular space.

This initiates in the surrounding tissue an inflammatory response, which prevents nearby phagocytes from locating and eliminating the dead cells by phagocytosis. For this reason, it is often necessary to remove necrotic tissue surgically, a procedure known as debridement. Untreated necrosis results in a build-up of decomposing dead tissue and cell debris at or near the site of the cell death. A classic example is gangrene.[8]

	Apoptosis	**Necrosis**
Natural	yes	Caused by factors external to the cells or tissue, such as infection
Effects	Usually beneficial. Only abnormal when cellular processes that keep the body in balance cause too many cell deaths or too few.	Always detrimental
Process	Membrane bleb Bing, shrinkage of cell, nuclear collapse (nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation), apoptotic body formation. Then, engulf by white blood cells.	Membrane disruption, respiratory poisons and hypoxia, which cause ATP depletion, metabolic collapse, cell swelling and rupture leading to inflammation.

SYMPTOMS	USUALLY NO NOTICEABLE SYMPTOMS RELATED TO THE PROCESS.	INFLAMMATION, DECREASING BLOOD FLOW AT AFFECTED SITE, TISSUE DEATH (GANGRENE).
CAUSES	SELF-GENERATED SIGNALS IN A CELL. GENERALLY NATURAL PART OF LIFE, THE CONTINUATION OF THE CELLULAR CYCLE INITIATED BY MITOSIS.	BACTERIAL OR FUNGAL INFECTIONS, DENATURED PROTEINS THAT IMPEDE CIRCULATION, FUNGAL AND MYCOBACTERIAL INFECTIONS, PANCREATITIS, DEPOSITS OF ANTIGENS AND ANTIBODIES COMBINED WITH FIBRIN.
Medical Treatment	Very rarely needs treatment.	ALWAYS REQUIRES MEDICAL TREATMENT. UNTREATED NECROSIS IS DANGEROUS AND CAN LEAD TO DEATH.

Figure number (6)



CHAPTER 3: NECROSIS: MECHANISM AND IMMUNE RESPONSE

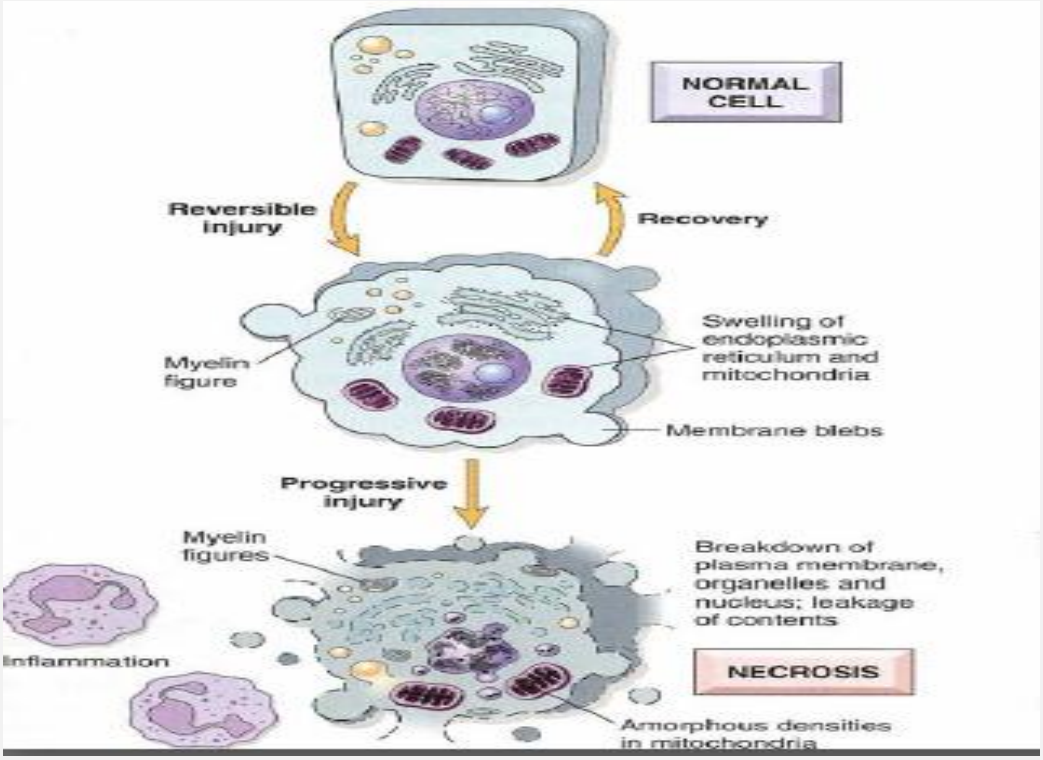
3.1 NECROSIS MECHANISM:

IN THE FIGURE BELOW SCHEMATIC, DIAGRAM THE EVENTS THAT OCCUR IN CELLS UNDERGOING DEATH BY NECROSIS.

FIRST, WE SEE IN NECROSIS AN IRREGULAR CONDENSATION OF CHROMATIN, SWELLING OF THE MITOCHONDRIA AND BREAKDOWN OF MEMBRANES AND RIBOSOMES. THE CELL IS EVENTUALLY DISRUPTED, RELEASING ITS CONTENTS AND INDUCING AN INFLAMMATORY REACTION.

NECROSIS IS WHOLESALE UNREGULATED CELL DEATH CAUSED BY LACK OF NUTRIENTS OR INFECTION. FOR EXAMPLE, THE FAILURE OF THE BLOOD SUPPLY TO AN ORGAN DUE TO THROMBOSIS WILL CAUSE MASSIVE CELL DEATH DUE TO LACK OF OXYGEN (ISCHEMIA). A LARGE AREA OF CELL DEATH CAUSED BY ISCHEMIA IS CALLED AN INFARCTION. ANOTHER KIND OF CELL NECROSIS IS SEEN IN SEVERE VIRAL INFECTIONS WITH CYTOPATHIC VIRUSES (E.G. POLIO). THEREFORE, NECROSIS IS AN UNCONTROLLED PROCESS AND THE DYING CELLS RELEASE THEIR CONTENTS. AREAS OF NECROSIS ARE CHARACTERISED BY INFILTRATION WITH INFLAMMATORY CELLS; MACROPHAGES AND NEUTROPHILS ENTER THE AREA OVER A NUMBER OF DAYS AND WEEKS IN ORDER TO CLEAR THE DEAD CELLS AND ASSOCIATED CELLULAR DEBRIS. SUCH LARGE AREAS OF CELL LOSS AND INFLAMMATION ARE FREQUENTLY EASILY SEEN IN PATHOLOGICAL SPECIMENS, EVEN WITHOUT MICROSCOPIC EXAMINATION.

FIGURE NUMBER (7)



3.2 IMMUNE RESPONSE OF NECROSIS:

EVERY MOMENT WE LIVE, CELLS IN OUR BODIES ARE DYING. ONE TYPE OF CELL DEATH ACTIVATES AN IMMUNE RESPONSE WHILE ANOTHER TYPE DOES NOT.

"CELLS DIE IN TWO GENERAL WAYS: APOPTOSIS, OR PROGRAMMED CELL DEATH, AND NECROSIS, WHICH RESULTS FROM INJURIES AND INFECTIONS," IN GENERAL, IT DON'T WANT THE IMMUNE SYSTEM TO RESPOND TO APOPTOSIS, BUT WE DO WANT AN IMMUNE RESPONSE FOLLOWING NECROSIS BECAUSE NECROTIC DEATH CAN BE A SIGN OF INFECTION. NECROTIC CELLS RELEASE COMPONENTS TO STIMULATE THE IMMUNE SYSTEM.

APOPTOSIS NORMALLY IS A HEALTHY PROCESS THAT OCCURS ALL THE TIME, SO IT SHOULD NOT ACTIVATE AN IMMUNE RESPONSE, APOPTOSIS IS AN ORDERLY DEATH THAT OCCURS DURING DEVELOPMENT AND TISSUE TURNOVER, AND IT IS AN IMPORTANT PROCESS THAT ALLOWS US TO REPLACE OLD; WE DON'T NEED THE IMMUNE SYSTEM PAYING ATTENTION AS OUR CELLS DIE THROUGH APOPTOSIS. WHEN IT DOES REACT TO APOPTOSIS, WE CAN DEVELOP AUTOIMMUNITY, AS IN DIABETES, ARTHRITIS AND OTHER AUTOIMMUNE DISEASES IN WHICH THE IMMUNE SYSTEM WILL ATTACK THE 'SELF.'"

WHETHER THEY WERE APOPTOTIC OR NECROTIC, DYING CELLS WERE RELEASING THE PROTEIN, BUT THE CELLS THAT WERE UNDERGOING APOPTOSIS STILL WERE NOT STIMULATING THE IMMUNE SYSTEM.

FURTHER EXPERIMENTS SHOWED THAT WHEN THEY DIE, APOPTOTIC CELLS ALSO PRODUCE FREE RADICALS, AND THOSE REACTIVE OXYGEN FREE RADICALS MODIFY HMGB1 TO PREVENT IT FROM STIMULATING THE IMMUNE SYSTEM. IN NECROSIS, NO FREE RADICALS ARE PRODUCED, SO HMGB1 BOTH SIGNALS AND STIMULATES AN IMMUNE SYSTEM RESPONSE.[8]

FREE RADICALS HAVE BEEN THOUGHT TO BE BAD FOR US, BUT IN THE CASE OF CELL DEATH, THEY HAVE THE BENEFICIAL EFFECT OF PREVENTING THE IMMUNE SYSTEM FROM ATTACKING AND DESTROYING HEALTHY CELLS. THE FINDING MAY HAVE IMPORTANT IMPLICATIONS, BOTH FOR SOME AUTOIMMUNE PROCESSES AND FOR CANCER TREATMENT. IN ADDITION, IT IS POSSIBLE TO USE HMGB1 TO STOKE UP THE IMMUNE SYSTEM IN RESPONSE TO CANCER.

EVERY MOMENT WE LIVE, CELLS IN OUR BODIES ARE DYING. ONE TYPE OF CELL DEATH ACTIVATES AN IMMUNE RESPONSE WHILE ANOTHER TYPE DOES NOT.

NECROSIS IS ACCOMPANIED IN ITS EARLY STAGES BY INFLAMMATION, AS COMPONENTS (INCLUDING CELL STRUCTURES, CYTOPLASM, AND DNA/RNA) OF THE RUPTURED OR DAMAGED CELLS ARE RELEASED. TO AN ORGANISM, THIS UNREGULATED FLOW OF PROTEINS, CHEMICALS, AND GENETIC MATERIAL TRIGGERS EMERGENCY RESPONSES, SUCH AS INFLAMMATION TO PROTECT SURROUNDING TISSUES, AS WELL AS AN INCREASE IN WHITE BLOOD CELLS, MACROPHAGES, AND T CELL PRODUCTION TO FIGHT OFF INFECTION. THESE REACTIONS ARE OFTEN ACCOMPANIED BY A METABOLIC BOOST AND FEVER, WHICH CAN LEAD TO FATIGUE AND AN OVERALL WEAKENED IMMUNE SYSTEM.

IF LEFT UNTREATED, NECROTIC TISSUES WILL LOSE VASCULARITY, MEANING THEY WILL LOSE BLOOD FLOW, AND THUS START DYING. WHEN THIS HAPPENS, THE NECROSIS IS CALLED GANGRENE, A CONDITION WHERE TISSUE ULTIMATELY DIES AND MUST BE REMOVED TO STOP NECROSIS FROM EXPANDING.

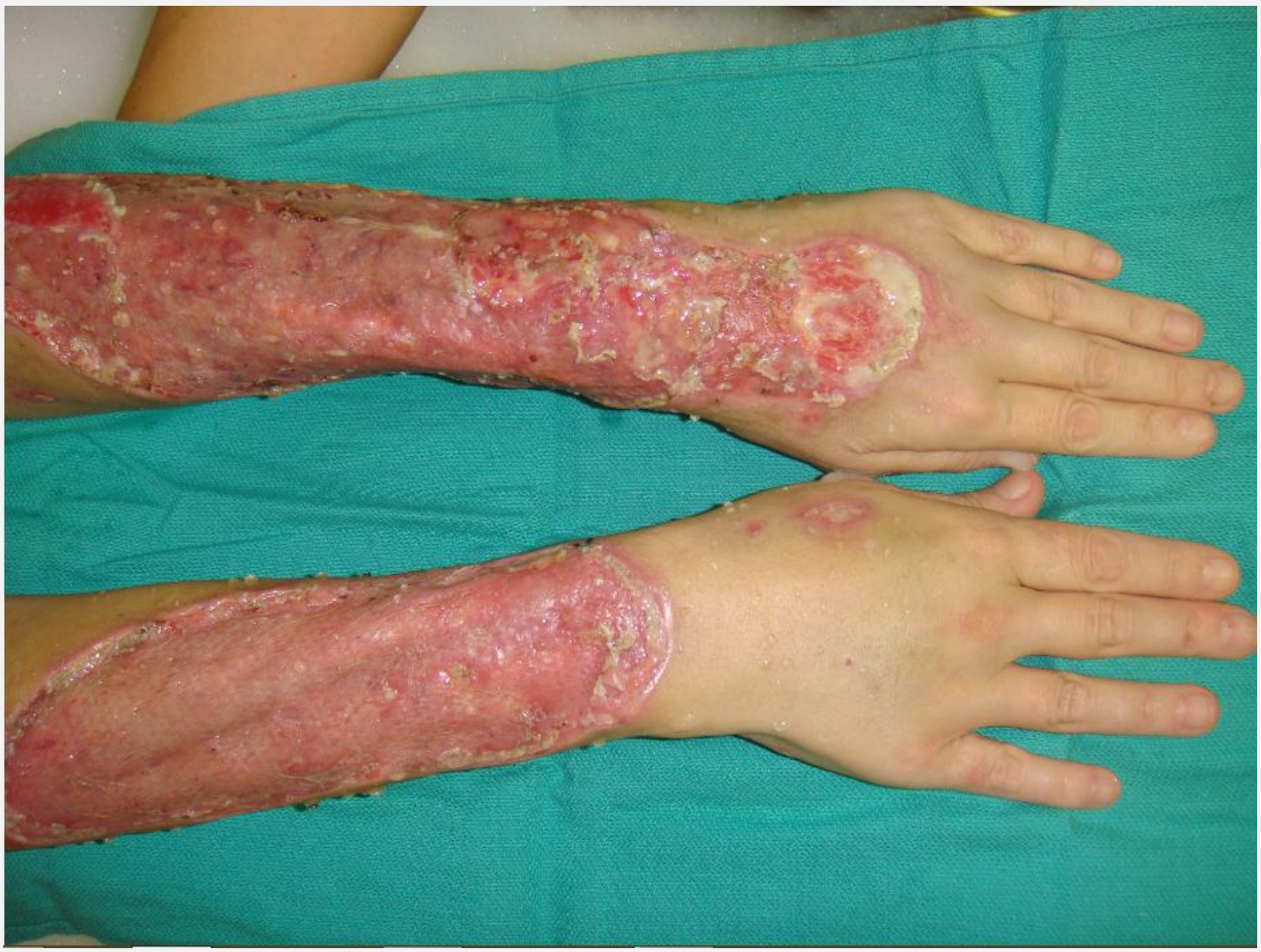


PHOTO NUMBER (8): HAND INFECTED IN NECROSIS

AS WE SAW, THE INFECTION OF NECROSIS IS A VERY DANGEROUS SO, IT SHOULD BE IMPORTANT TO FIND TREATMENTS FOR THIS INFECTION.

3.3 Common treatments of necrosis.

- **Antibiotics/NSAIDs**:

These fight the infectious and inflammatory nature of necrosis and are often the first line of defense against its damage. In extreme cases, immune suppressing drugs may be prescribed to reduce the inflammatory response.

- **Debridement:**

Removal of the dead tissue, from simple cleaning of the area to surgery, including amputation. Fly larvae (maggots) are also used quite effectively in some forms of debridement.

- **Antioxidants:**

May be used to treat internal necrotic tissues, most often related to ischemia.

Results:

- There are two main mechanisms for cell death (apoptosis and necrosis).
- These two mechanisms differ from each other in terms of cause, steps and effect.
- Apoptosis is controlled and safe; therefore, There are no complications to this process.
- Necrosis is very dangerous and it is not controlled, it also create A bad immune response.
- It produces immune responses as a result of cell damage and exit of contents.
- Necrosis will not stop easily and it continues expansion and can cause death if not treated.

CONCLUSION:

THIS SEARCH HAS DISCUSSED THE SUBJECT OF SELL DEATH, THE MAJORITY OF BODY CELLS RENEWESD FROM TIME TO TIME. IT REQUIRES THE DEATH OF SOME OF THEM AND THE REBUILDING OF NEW CELL INSTEAD. THESE CELLS AS WE NOTICED, DIES IN TWO DIFFERENT WAYS, FIRST, THE PROGRAMMED CELL DEATH WHICH IS THE BEST WAY TO CELL DEATH FOR BEING CONTROLLED, HARMLESS TO BODY, AND CONDUCT ACCORDING TO SPECIFIC STEP.

AS FOR DEATH NECROSIS, IT USUALLY HAPPENS ACCORDING TO EITHER EXTERNAL FACTORS OR SERIOUS INJURY IN THE CELL. THIS SERIOUS INJURY CAUSE THE CELL CORROSION IN ADDITION TO THE OUT OF SOME ORGANELLES OF IT.

THIS REQUIRES IMMUNE RESPONSE TO THESE OBJECTS, THIS KIND OF CELL DEATH IS CONSIDERED VERY DANGEROUS AND HARMFUL TO THE BODY , THE NECROSIS CONTINUES TO EXPAND AND MANY CAUSE THE DEATH BECAUSE OF THE FAILURE TO PROVIDE TREATMENT .

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