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لم ترد بالأصل

HISTOPATHOLOGICAL AND ULTRASTRUCTURAL STUDY OF APOPTOIS IN NON-HODGKIN'S LYMPHOMAS

Thesis
Submitted in partial fulfillment of the requirements of the Master Degree in
Pathology

By

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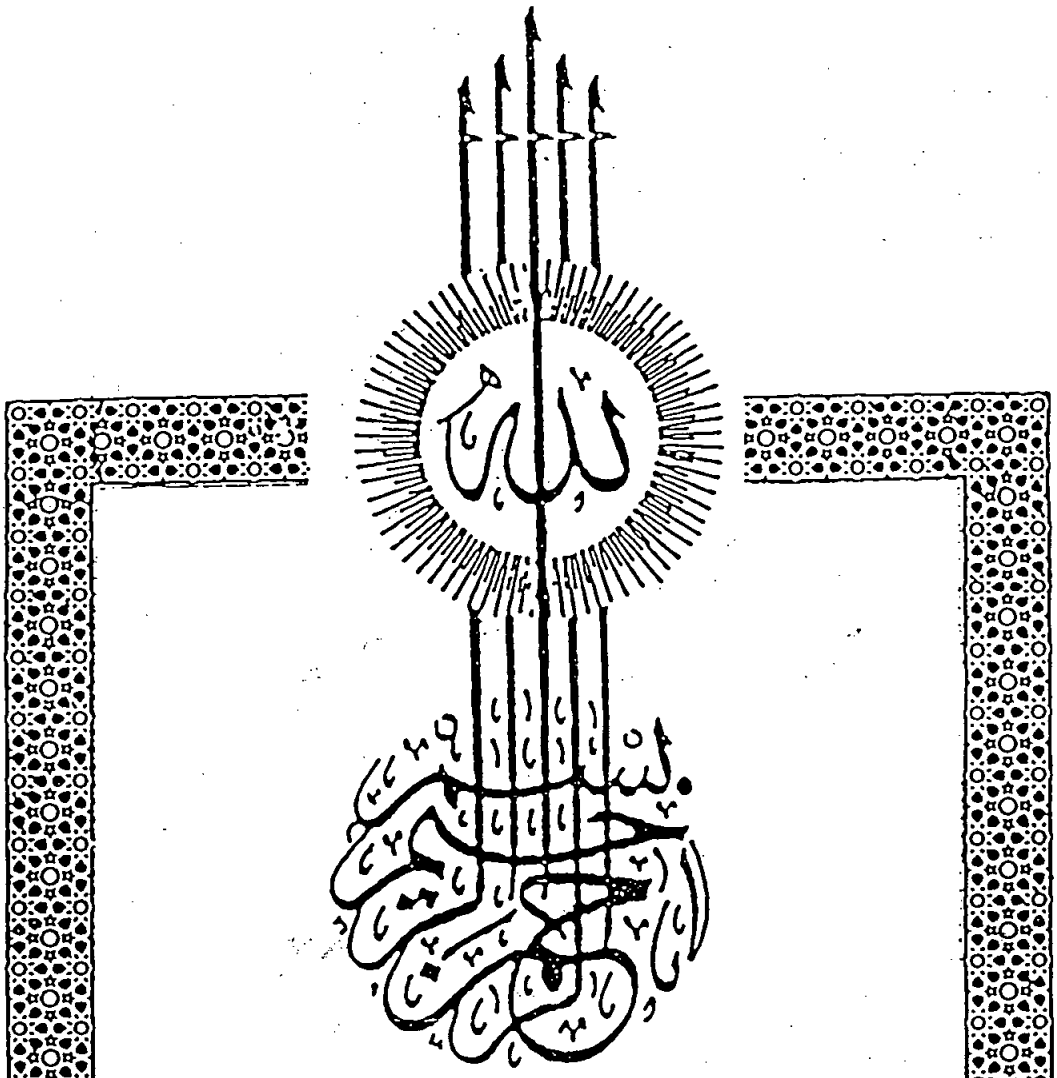

سبحانك

لا علم لنا إلا ما علمتنا

إنك أنت العليم الحكيم

صدق الله العظيم

(البقرة ٣٢)

إهداء

إلى روح والدى العظيم .....

الذى سأظل أفتقده طالما حييت

والذى علمنى وأدبنى وشجعنى على المزيد من التعلم

أعلم أنى لن أوفيك حقك مهما فعلت

لكن علك يا أبى ترضى بهديتى ...

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APOPTOSIS

Over the past three decades two fundamentally different forms of cell death apoptosis and necrosis have been defined in terms of morphology, biochemistry and incidence (Cumming et al, 1997).

It was the first time to draw attention to apoptosis when John Kerr, Andrew Wyllie and Sir Alastair Currie (1972) have described it in details including morphology by light and electron microscope (Fuster et al, 1992).

From the historical point of view, the phenomenon of apoptosis was known before 1972 when John Kerr have referred to it, but the phenomenon was known under different items *e.g.* Councilman bodies in viral hepatitis, Civatte bodies in the epidermis, tingible bodies in macrophages of reactive lymph nodes, karyolytic bodies in the gut crypts, and in melanosis coli where large number of apoptotic bodies are formed over times forming lipofuscin pigment (Walker et al, 1988).

In a refining work of atrophy Kerr (1965) ligated portal vein branches to the left and medium lobes of rat liver, these lobes shrank to one sixth of their original weight in 8 days and the other lobes simultaneously underwent hyperplasia, the total weight of the liver

remains approximately constant. In the atrophying lobes patches of confluent necrosis occurred around terminal hepatic venules, whereas periportal parenchyma sustained by blood from hepatic artery, survived. Individual hepatocytes outside the zone of necrosis, in the absence of inflammation, gave rise to small round cytoplasmic masses, some containing pyknotic chromatin, a manifestation of cell death distinctly different form necrosis, which Kerr named shrinkage necrosis, which was another old name for the phenomenon of apoptosis (Kerr, 1965).

Apoptosis is now defined as genetically determined biologically meaningful *active* process that plays a role opposite of mitosis in tissue size regulation (Kerr et al, 1995).

It is an active process in contrast to necrosis requiring ongoing protein synthesis. The term is derived from a Greek word used for the dropping off of leaves from trees. This term is very meaningful because apoptosis affects single cells in the midst of living tissue. The noxious agent is not so violent to cause cell death but triggers a suicide program (Alison and Sarraf, 1995).

The net result is that the apoptotic cells show various morphological features as margination of the DNA as crescent, decrease cell volume, with retained integrity of the apoptotic cell membrane, then

convolution of the cells, fragmentation of the nucleus, formation of membrane bound apoptotic bodies and phagocytosis of their fragments without inflammation. In contrast, necrosis is accidental cell death as a response to severe and sudden injury which result in massive and contiguous cell deaths. The dying cells have their chromatin marginated as small aggregates and smear pattern of DNA electrophoresis. The morphological changes include, increase in cell volume, swelling of the organelles which results at the end in cell rupture which results from damage of cell membrane integrity leading to disturbance in cellular homeostasis, swelling and rupture with release of cellular contents with resulting intense inflammation (Ueda and Shah, 1994).

Microscopically, the apoptotic cells appear as shrunken cells with deeply eosinophilic cytoplasm (Alison and Sarraf, 1995), but in cells containing abundant ribosomes such as pancreatic acinar cells, the cytoplasm may be basophilic (Cumming et al, 1997). Their nuclei appear pyknotic, and the cells are surrounded with haloes of unstained tissue apparent at low power examination. The apoptotic cells rapidly fragment to apoptotic bodies which are rapidly phagocytosed by macrophages, the haloes around apoptotic bodies may be unstained tissue or heterophagic vacuoles (Alison and Sarraf, 1995). Phagocytosis of apoptosis bodies does not induce macrophages to start an inflammatory response (Meagher et al, 1992). Apoptotic bodies vary

considerably in size, the smallest being undetectable by light microscope unless they contain at least one basophilic nuclear fragment. The characteristic well defined crescentic clumps of chromatin seen in apoptotic nuclei and nuclear fragments ultrastructurally, are hardly seen in 5-µm paraffin sections or smears instead the chromatin appears as uniformly dense, basophilic masses. Larger, discrete apoptotic bodies have long been recognized in normal and pathological states in a variety of tissues under other names, as formerly mentioned (Walker et al, 1988).

Ultrastructurally, in tissues, apoptosis affects cells asynchronously in the absences of inflammatory changes. The earliest event observed is the condensation of chromatin to form sharply circumscribed, uniformly dense, crescentic masses that abut the nuclear envelope (Wyllie, 1987).

Nucleolar changes include the dispersal of peripheral nucleolar chromatin to form aggregates of osmiophilic granules in the center of the nucleus; the protein fibrillar core forms a compact granular mass usually closely opposed to the inner surface of the condensed nuclear chromatin (Wyllie, 1987).

Simultaneously with the nuclear changes apoptotic cells detach from neighboring cells, their desmosomes breakdown and specialized