

## A comparative Study of Liver Regeneration After Partial Hepatectomy in Young and Adult Goat (*Caprus Hircus*)

Y. D. H. Al-Hameary\*, M. J. Eesa\*\* and R. M. A. Al-Harbawy\*\*

\*College of Veterinary Medicine\ University of Anbar

\*\*College of Veterinary Medicine\ University of Baghdad

### Abstract

The study was carried out to compare the regenerated ability of liver between young and adult goats after partial hepatectomy and evaluate the regeneration of these two different periods depend on histological study. Twelve healthy female goats were used. The animals were divided according to the age, six adult goat aged between 2 - 3 years, and six young goat aged between 2 - 3.5 months. Each group was subdivided into equal subgroups according to the time of laparoscopic biopsy postoperative at 21 days and 60 day. All the operations were performed under general anesthesia by Xylazine hydrochloride 0.1mg/kg B.W., Ketamine hydrochloride 4 mg/kg B. W. intramuscularly. The ventral abdominal was prepared for aseptic surgical technique. The animals were fixed at dorsal recumbency position. And under general anesthesia. Skin incision of about 13-15cm was created at parallel to the paracostal coast from the right side. Then liver was exposed and peripheral edge of its was holded by hand of assistant surgeon. About 5cm width and 4 cm depth was surrounded by horizontal interrupted. This area was cut using scissors. The histological outcome of these two groups indicated that the young goat has regenerated ability higher than adult goat of animals.

### دراسة مقارنة لتجدد الكبد بعد استئصاله جزئياً في الماعز اليافع والبالغ (المحلي)

يحيى دهش حسن الحميري\*، محمد جواد عيسى\*\* ورشا محمد علي سالم الحرباوي\*\*

\*كلية الطب البيطري/ جامعة الأنبار

\*\*كلية الطب البيطري/ جامعة بغداد

### الخلاصة

أجريت الدراسة لمقارنة قابلية تجدد الكبد في الماعز اليافع والبالغ بعد الاستئصال الجزئي وتقييم التجدد في فترتين مختلفتين اعتماداً على دراسة الكيمياء الحيوية، الدموية، المنظرية والنسجية. استخدمت اثني عشر من إناث الماعز. تم تقسيم الحيوانات حسب العمر، ستة معز بالغة تراوحت أعمارها بين 2 - 3 سنوات (المجموعة A)، وستة معز يافعة تراوحت أعمارها بين ما بين 2 - 3.5 أشهر (المجموعة B). تم تقسيم كل مجموعة إلى مجموعتين متساويتين ثانويتين وفقاً لأخذ الخزعة منضارياً لفترات 21 و 60 يوماً بعد العملية الجراحية. أجريت جميع العمليات تحت التخدير العام عن طريق حقن هيدروكلوريد زيلازين 0.1 مغ/كغم من وزن الجسم، الكيتامين هيدروكلوريد 4 مغ/كغم داخل العضل. تم عمل شق في الجلد حوالي 13-15 سم في القوس الموازي للأضلاع من الجانب الأيمن. ثم إخراج جزء من الكبد وتثبيت حافظته من قبل الجراح المساعد. أحيط جزء من حافة الكبد بمقدار 5 سم عرضاً و 4 سم عمقاً بخياطة الأفقي المتواز المتقطع وفصلت قطعة الكبد بواسطة. أظهرت النتائج النسجية لهاتين المجموعتين إلى أن قابلية تجدد الكبد في الماعز اليافع أسرع من البالغ.

### Introduction

The liver is the largest gland of the body, weighing about 1-1.5 kg. It is situated in the abdominal cavity beneath the diaphragm. The liver is the organ in which nutrients absorbed in the digestive tract are processed and stored for use by other parts of the body. It is thus an interface between the digestive system and the blood. Most of its blood (70- 80%) comes from the portal vein, arising from the stomach, intestines, and

spleen; the smaller percentage (20- 30%) is supplied by the hepatic artery. All the materials absorbed via the intestines reach the liver through the portal vein, except the complex lipids (chylomicrons), which are transported mainly by lymph vessels. The position of the liver in the circulatory system is optimal for gathering, transforming, and accumulating metabolites and for neutralizing and eliminating toxic substances. Elimination occurs in the bile, an exocrine secretion of the liver that is important for lipid digestion. The liver also has the very important function of producing plasma proteins, such as albumin, other carrier proteins, coagulation factors, and growth factors (1). Liver regeneration after the loss of hepatic tissue is a fundamental parameter of liver response to injury. Recognized as a phenomenon from mythological times, it is now defined as an orchestrated response induced by specific external stimuli and involving sequential changes in gene expression, growth factor production, and morphologic structure. Many growth factors and cytokines, most notably hepatocyte growth factor, epidermal growth factor, transforming growth factor, interleukin-6, tumor necrosis factor, insulin, and norepinephrine, appear to play important roles in this process (2, 3, 4). Injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process. This process can be broadly separated into regeneration and repair. Regeneration results in the complete restitution of lost or damaged tissue; repair may restore some original structures. In healthy tissues, healing, in the form of regeneration or repair, occurs after practically any insult that causes tissue destruction, and is essential for the survival of the organism. Regeneration refers to the proliferation of cells and tissues to replace lost structures, such as the growth of an amputated limb in amphibians (5).

## Materials and Methods

### Materials:

**Animals:** Twelve healthy female goats The animals were divided according to the age, six adult goat aged between 2 - 3 years, and weight (25-38 kg.) and six young goat aged between 2 - 3.5 months, and weight (10-15 kg. ). The animals were fasted 24 hour for food and 12 hours for water preoperatively. The treated animals were put under observation for 7 days postoperatively.

**Laparoscopic system:** The laparoscopic system used in this study was (Karl Storz Company, Germany).

**Anesthesia:** All the operations were performed under general anesthesia by a mixture of Xylazine hydrochloride 0.1mg/kg B.W. and Ketamine hydrochloride 4 mg/kg B.W. intramuscularly (6).

**Animals grouping:** The experimental animals were divided into two equal treated groups according to the age, adult goats (A) and young goats (B). Each group was subdivided into two equal subgroups according to the time of biopsy postoperative at 21 and 60 days.

The following parameters will be performed for each subgroups, which include.

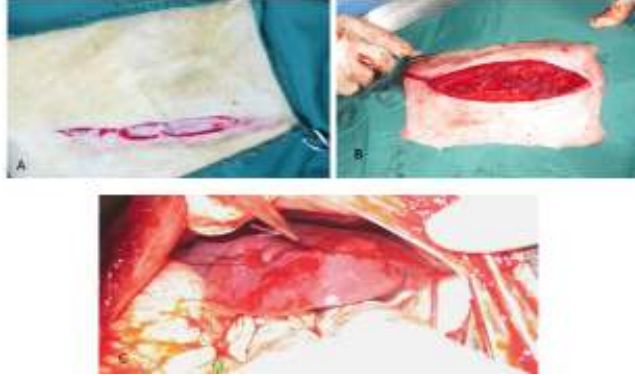
1. Peripheral segment of liver has been taken as procedure for induce partial hepatectomy was regard as a control in all subgroups.
2. Biopsy has been taken by laparoscopy at 21 days and 60 days postoperative for histopathological examination.

### Methods :

#### Surgical operation:

The ventral abdominal region from the xyphoid cartilage to the pubis, and laterally as far as the flanks was prepared for aseptic surgical technique. The animals were fixed at dorsal recumbency position. And under general anesthesia as mentioned above was used in order to control animals. Skin incision of about 13-15cm was created at parallel

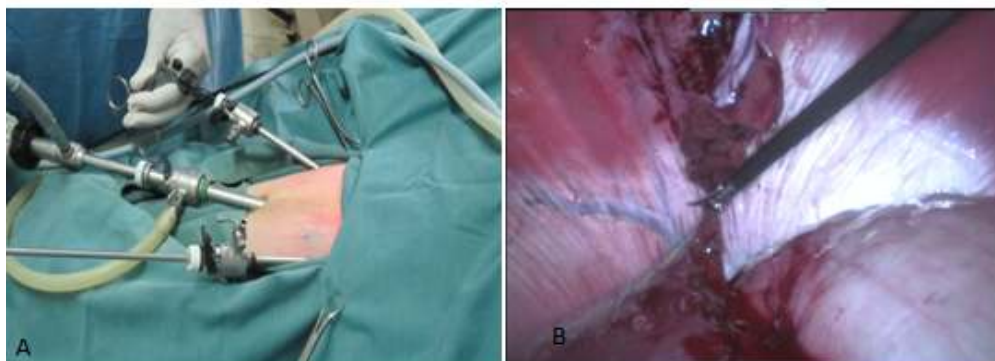
to the paracostal coast from the right side (Fig.1A). Muscle and subcutaneous tissue was sharply dissected (Fig.1B) and bleeding was stopped by crush of blood vessels or ligated use catgut (size 0). Then liver was exposed and peripheral edge of its was holded by hand of assistant surgeon. About 5 cm width and 4 cm depth was surrounded by horizontal interrupted matters overlap suture technique using polydioxinone (size 0) (Fig.1C). This area was cut using scissors. The abdominal wall was closed routinely.



**Fig. (1):** A- Inducing (13-15) cm skin incision about parallel to the costal arch from right side in adult goat. B-Subcutaneous tissue and muscles were sharply dissected in young goat. C-The excised part of liver was surrounded by horizontal interrupted matters suture pattern (arrows).

**Laparoscopic technique for taken biopsy:** Animals of both subgroups were prepared aseptically at the similar manner mentioned above. Skin incision about 1cm was created on umbilical area in order to insert port (10 mm) then connection with insufflators tube to facilitate pumping of abdominal cavity with  $\text{CO}_2$  at pressure (10-12 mmHg). Laparoscope 10 mm was inserted through this port. The abdominal organs, was explored to observe degree of healing of liver resected site, adhesion of its with adjacent organs and any abnormalities in between surgical site and others organs which may be occur. Also two ports (10 mm and 5mm) were inserted under vision, the first one near the xyphoid slightly to lift side and the second at the right side near the costal arch (Fig. 2A). The right port was used to inserted laparoscopic grasper forceps, while the left port used to inserted monopolar electrocautary. The biopsy was taken by grasping of surgical area and using monopolar electrocautary to cut it and coagulation at the same time. Biopsy was exteriorized through (10mm) port after expanding by scissor into about 2-2.5cm and the three skin incision closed routinely.

**Histopathological Examinations:** Biopsies about 1.5 square  $\text{cm}^2$  were taken laparoscopically at the 21<sup>st</sup> and 60<sup>th</sup> day postoperatively (Fig.2B). They were fixed in 10% neutral buffered formalin, then routinely processed and embedded in paraffin. The paraffin imbedded blocks were cut at (5) microns and stained by hematoxyline and eosin stain and Perodic Acid Schief stain (PAS) (7).



**Fig.(2):** A- Inserting three ports, the center for telescope, the left for monopolar electrocautary and right for grasper. B-laparoscopic liver biopsy from (group, A) adult goats at 60<sup>th</sup> days posoperation.

## Results and Discussion

### Histopathological examination:

#### Histological examination At 21 day postoperative:

**Capsule:** Thickness of capsular layer in group A was ( $80.66 \pm 11.28 \mu\text{m}$ ) while in group B ( $79.33 \pm 9.82 \mu\text{m}$ ) (Fig.3A).

**Hepatocyte:** Revealed hypertrophy of the liver as a result of hepatocytes enlargement with increased size of the cytoplasm and the nuclei in which the average range of the cell diameter was ( $21.48 \pm 1.29 \mu\text{m}$ ) in group A, while in group B ( $18.13 \pm 2.84 \mu\text{m}$ ) (Table,1). The mitotic figure (binucleated cell) in group A fewer than group B. Hepatocytes having dark heterochromatic (mitosis) or euchromatic (protein synthesis) nuclei with bright or light eosinophilic cytoplasm (Fig.3B).

**Central vein:** The central vein showed congested contained hemolyzed RBCs and thrombosis, sometimes the central vein swelling and thickening in its wall as a result of edema could also be detected the diameter in adult was ( $161.4 \pm 36.27 \mu\text{m}$ ) while in young ( $129.96 \pm 18.04 \mu\text{m}$ ) (Table,2) (Fig. 3 C and D).

**Sinusoids:** Some hepatic sinusoids were narrow, absent or dilated. Others were congested. There were also newly formed blood sinusoids and blood capillaries (Fig.3B).

**Kupffer cells:** The hepatic macrophage (Kupffer cells), appears critical during regeneration of resected liver. The Kupffer cells increased in number and showed moderate hypertrophy, ( $10.5 \pm 3.3 \mu\text{m}$ ) in group A and ( $11 \pm 0.8 \mu\text{m}$ ) in group B (Table,1). In area of hemorrhage macrophage engulf dark brown pigment hemosidrine, macrophage aggregation filled with hemosidrine this phenomena less prominence in group A than group B (Fig.3B).

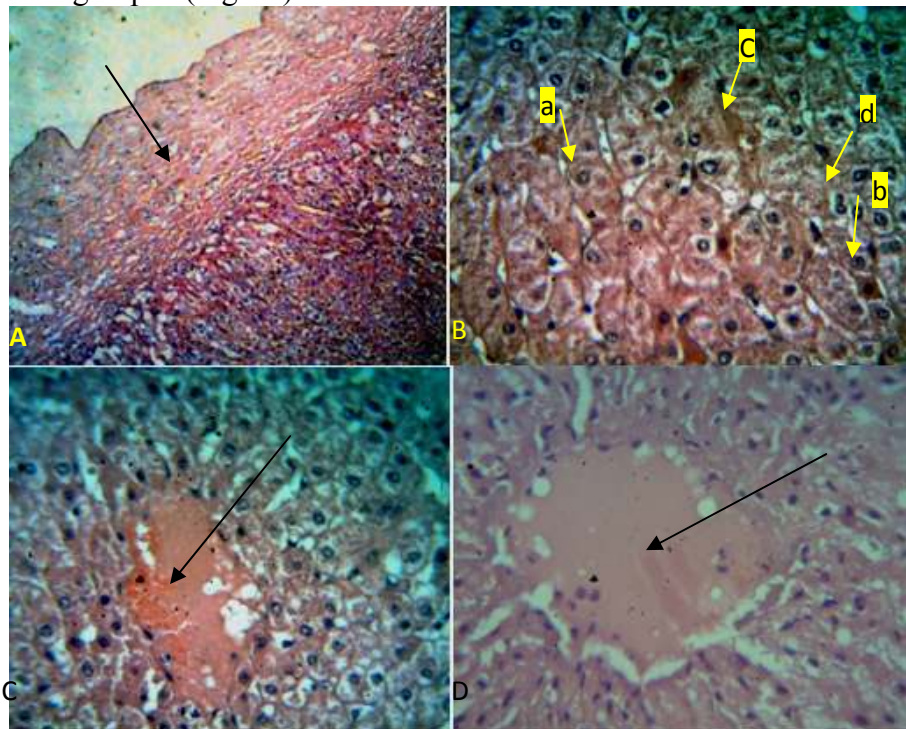


Fig. (3): A-capsule of young goat liver 400X H&E stain B- liver of adult goat at 21<sup>st</sup> day post operative shows a-hypertrophy hepatocyte b-Ito cell, c.congested sinusoid d.binucleated hepatocyte. 400X H&E stain C- liver of adult goat at 21<sup>st</sup> shows congested central vein. H&E stain 400X D-liver of young goat at 21<sup>st</sup> day shows; wide congested central vein contain hemolyzid red blood cells. H&E stain 400X.

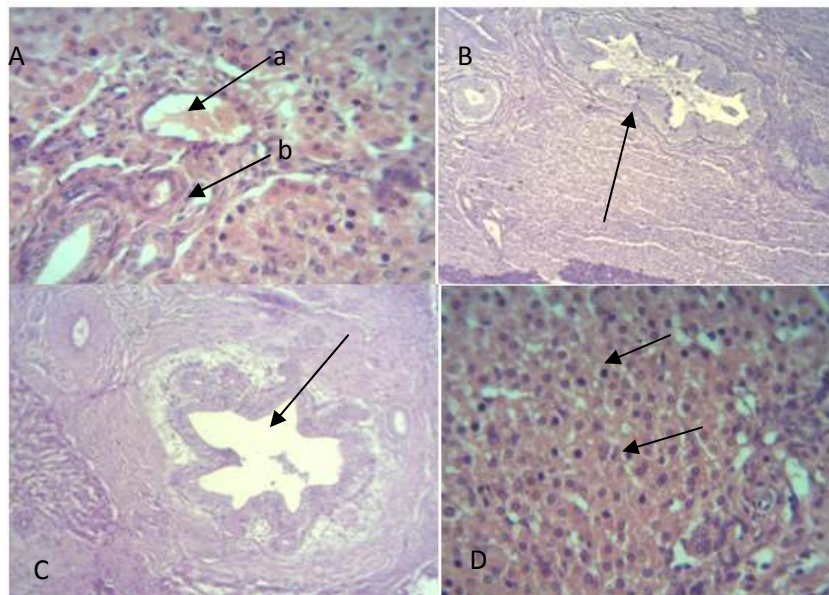
**Portal area (portal triad):** The portal area showed different changes including: newly formed bile duct with immature hepatic artery and congested portal vein (Fig.4A).

Edema in the portal area was seen, with congestion of the hepatic artery. Proliferation of the fibroblast and angioblast was noticed in the portal area and result in formation of newly formed blood capillary. The increase in size of hepatic artery comparable with zero time in group A ( $60.4 \pm 10.62 \mu\text{m}$ ) less than group B ( $52.16 \pm 4.15 \mu\text{m}$ ) (Table,2).

**Bile duct:** Enlargement of the bile duct was evident due to high proliferation epithelial cell, thickness of it wall in group A ( $120.38 \pm 16.8 \mu\text{m}$ ) and in group B ( $125.5 \pm 24.73 \mu\text{m}$ ) (Table,2). Number of fold also have been seen in the inner surface of the duct (7-8 fold) in group B, while in group A mild hyperplasia or degree of cellular hypertrophy was smaller than young in its epithelial lining and less number of fold (5-6) in number (Fig.4 B and C).

**Ito cells (Hepatic stellate cells, perisinusoidal cell, lipocyte):** They are spindle-shaped with oval or elongated nuclei and located in the space between the hepatocytes and sinusoidal endothelial cells (Fig.3B). One major characteristic of ito cells in normal liver is have cytoplasmic droplets which contain vitamin-A primarily in the form of retinylesters.

**Oval cell ( Hepatic stem cell ):** Liver stem (progenitor) cells, known as oval cells. The oval cells are morphologically characterized by circumscribe round to oval cell with dark nucleus and clear cytoplasm with small cellular size ( $9.7 \mu\text{m}$ ) in young while in adult ( $11.13 \mu\text{m}$ ), high nuclear/ cytoplasm volume ratio appear during liver regeneration (Fig.4D).



**Fig.(4):** A-liver of adult goat at 21 day shows; a- portal vein b-newly formed bile duct. H&E stain 400X. B-liver of young goat at 21<sup>st</sup> day shows bile duct with proliferation of epithelial cell and thickness of wall also number of fold formed in the inner surface duct near the regenerated area. PAS stain 100X. C-liver of adult goat at 60<sup>th</sup> day postoperative shows bile duct with mild proliferation of epithelial cell and thickness of wall also number of fold formed in the inner surface of duct less than young a-number of apoptotic cell. PAS stain 100X. D-liver of young goat at 21 day shows oval cell proliferation H&E. stain 400X

**Histological examination At 60 day postoperative:** On day 60, the regenerative liver showed a regular liver histology with a regular hepatocellular structure, regular hepatic cord and the signs of regeneration in the liver were pronounced. Hepatic histology consists of lobules larger in size than before regeneration (Fig.5A).

**Capsule:** The capsule be converted into the regular shape and size. The capsule consist of strands of collagen and elastic fibers with fibroblast proliferation. The thickness of capsule in group A ( $29 \pm 10.39 \mu\text{m}$ ) while in group B ( $26.3 \pm 10.39 \mu\text{m}$ ) (Fig.5B) (Table,1).

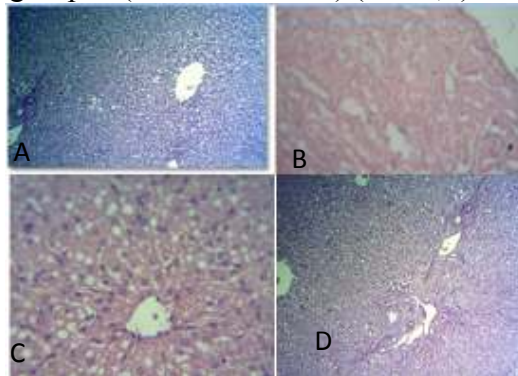
**Hepatocyte:** The small hepatocyte clumps become rearranged into the typical hepatocyte plates seen in group B more than group A. Hepatocytes were hypertrophied and reached ( $19.46 \pm 1.19 \mu\text{m}$ ) group A and ( $15.33 \pm 1.4 \mu\text{m}$ ) in group (B) and became arranged in plates or cord consisting of one or two cell layer (Fig.5C) (Table,1).

**Central vein:** Swelling and thickening in the central vein were evident less than at 21 day transformed into the usual characters and dimension in group A ( $131.66 \pm 32.72 \mu\text{m}$ ) while in group B ( $66.33 \pm 7.99 \mu\text{m}$ ) (Fig.5C) (Table, 2).

**Sinusoids:** The hepatic sinusoids were swollen and others congested (Fig.5C). There were also newly formed blood sinusoids.

**Kupffer cell:** The Kupffer cell have irregular shape with eccentric dark nuclei and cytoplasm contain debris. Kupffer cell showed hypertrophy less than at 21 day in group A ( $8.6 \pm 2.61 \mu\text{m}$ ) and in group B ( $7.7 \pm 1.18 \mu\text{m}$ ) (Fig.5C) (Table,1).

**Portal area:** The newly formed portal area in group B and A has standard organization more than at 21 day (Fig.5D). The portal area showed edema, congestion and proliferation of the fibroblasts and angioblast less than at 21 day. Enlargement of hepatic artery less than at 21 day which returned to the level nearly to the zero time, in group A ( $46.33 \pm 3.98 \mu\text{m}$ ) and in group B ( $27.66 \pm 5.68 \mu\text{m}$ ) (Table,2).



**Fig. (5):** A- liver of adult goat at 60 day show liver lobule and hepatic cord. 100x PAS stain B- liver of adult goat at 60 day show thickness of liver capsule (arrow). 100x H&E stain C-liver of young goat at 60 day shows a- hypertrophy hepatocyte demonstrate deferent stages of mitosis with regular hepatic cord. b-central vein. C-Kupffer cells. d-sinusoid. 400x H&E stain D-liver of adult goat at 60 day shows portal area a- bile duct, b- portal vein, c-hepatic artery branch. 100x PAS stain

**Bile duct:** Bile duct lined by high cuboidal epithelial, surrounded by thick layer of connective tissue, accumulation of apoptotic exfoliated cell in lumen of duct in young more than adult. Swelling of the bile duct was seen as a result of hypertrophy and hyperplasia in its epithelial lining less than at 21 day diameters of group A ( $59 \pm 6.01 \mu\text{m}$ ) while in group B ( $39.31 \pm 8.25 \mu\text{m}$ ) and epithelial thickening of duct in group A ( $6.21 \pm 1.34 \mu\text{m}$ ) while in group B ( $6.5 \pm 1.37 \mu\text{m}$ ) (Fig.6 A and B) (Table, 2).

**Omentun facilities regeneration:** Histological examination at the omental fusion. At the site of fusion there was a wide and compact band of interlying tissue between the omentum and the growing edge of the liver (Fig.6C). On one side of the interlying tissue lay the liver tissue. Liver grew to fill the wound and continued to grow.

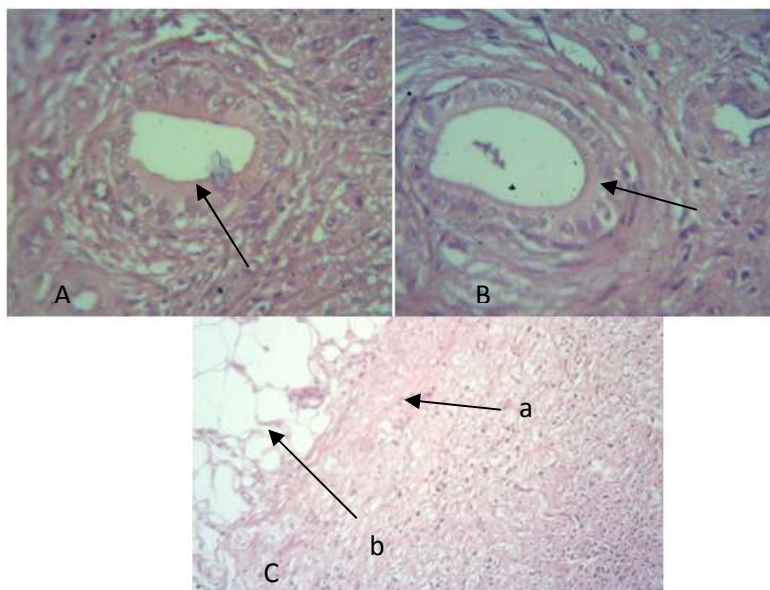


Fig. (6) A- liver of young goat at 60<sup>th</sup> day shows bile duct epithelial proliferation. (arrow)X400 H&E stain B- liver of adult goat at 60<sup>th</sup> day shows bile duct epithelial proliferation (arrow). X400 H&E stain C- liver of adult goat at 21<sup>st</sup> day post operative shows, a- granulation tissue.b-omentum. 100X H&E stain.

Table (1) Show histological parameter (um) of capsule, hepatocyte and Kupffer cell in group A (adult) and group B (young)

| Histological Periods  | Capsule adult um  | Capsule young um  | Hepatocytes adult um | Hepatocytes young um | Kupffer cell young um | Kupffer cell adult um |
|-----------------------|-------------------|-------------------|----------------------|----------------------|-----------------------|-----------------------|
| Zero time             | 12.66± 2.45<br>bA | 8.5±3.19<br>bA    | 16.48± 4.74<br>bA    | 11.9± 1.42<br>cB     | 4.93± 1.05<br>bA      | 5.16± 1.07<br>bA      |
| 21 day post operative | 80.66±11.28<br>aA | 79.33±9.82<br>aA  | 21.48± 1.29<br>aA    | 18.13± 2.84<br>bB    | 11± 0.8<br>aA         | 10.5± 3.3<br>aA       |
| 60 day post operative | 29± 17.39<br>bB   | 26.3± 10.39<br>aA | 19.46 ± 1.19<br>aA   | 15.33±1.4<br>bB      | 7.9±1.18<br>aA        | 8.6± 2.61<br>aA       |

Small different letters denoted that a significant difference between period ( $P<0.05$ ).

Capital different letters denoted that significant differences between young and adult ( $P<0.05$ ).

## Discussion

Increase of capsule thickness comparable to control in young higher than adult due to proliferation of fibroblast in young more than adult. Hypertrophy of the liver as a result of hepatocytes enlargement. The mitotic figure (binucleated cell) in group A fewer than group B. This statement in concurrence with (8) who mention that there was unexpected increase in both size of the liver cells (hypertrophy) and active cell division and multiplication (hyperplasia) subsequent of hepatic resection in dog. The central vein was congested contained hemolyzed RBCs and thrombosis, sometimes the central vein swelling. This result differ with (9) who stated that, regeneration of hepatocytes which form pseudo lobule composed of aggregation of hepatocytes with dark nuclei and without central vein. The absent or narrow sinusoid due to hypertrophy crowded hepatocytes in proliferating area while dilated sinusoid also can be seen in resected area to increase blood supply in support of regeneration area to promote healing processes. This result have the same opinion with (9) who mention that the in regenerating liver showed vacuolar degeneration with dilated sinusoid. During regeneration macrophages migrate to the site of injury where they phagocytes post apoptotic debris. The macrophage engulf hemosidrine in group B more than group A so that the end of inflammation stage and beginning of regeneration stage in group B faster. Furthermore Kupffer cells generate numerous enzymes and cytokines which are responsible for the

destruction of matrix but perhaps more importantly are implicated in the recruitment of other secondary cell types, which can have a pro-fibrotic or pro-resolution phenotype this result in agreement with (10, 11), whom stated that during hepatocellular damage which results in hepatic progenitor cell (HPC) activation macrophages are known to migrate to these regenerative sites and as such may act to stimulate or influence the hepatic progenitor cell, certainly in models of other tissue injury macrophages are critical for the mobilization of progenitor cells and are needed for the correct restoration of the epithelial architecture. In the present investigation there was newly formed bile duct, hyperplasia in the epithelial lining of the bile ducts this result agreed with (12) after partial hepatectomy in dog. This result have the same opinion with (13) who mention that after Cholecystectomy and laparoscopic liver biopsy in dog that severe congestion and dilation of the blood vessels at portal area and central vein with edema. The bile duct in group A lined with low columnar and rate of proliferation around duct less than group B the later lined by high columnar. Mitosis process lead to increase of the bile duct diameter and epithelial height. This increase in size was to cover the over function happening on the duct. Each mitosis was accompanied by apoptosis to control on the stability between the divided cells and dead cell otherwise cancer may occur the number of apoptotic cell in group A less than group B. This result is confirmed with (13) who mention that the hyperplasia of epithelial cells in mucosa layers of bile ducts as finger projections with accumulations of exudates in the lumen of the bile ducts because over function triggers the cellular growth. The Presence of myofibroblasts indicated, there is sever destruction and these cells attempt to contract the affected area due to their active as smooth muscle cells. They lose retinoids and become very proliferative, fibrogenic and contractile in regeneration area to assist in reduce incision distance to encourage remedial processes. Ito cells can recruit inflammatory cells through expression of adhesion molecules, secretion of chemokines and cytokines and hence play regulatory roles in liver inflammation. This finding be of the same opinion with (14, 15) who mention that vitamin A necessary growth, regeneration of the tissue and cell development throughout the life. The activation of hepatic stellate cells involve the trans differentiation from a quiescent state into myofibroblast-like cells with the appearance of smooth muscle  $\alpha$ -actin and loss of vitamin A storage. And this end result disagreement with (9, 16) whom mentioned that the Presence of myofibroblasts in granulation tissue which originated from mature fibroblasts. Oval cells appeared inside the portal fields around the triads at 21day in group A less than group (Fig.22 and 36). They proliferated in the portal fields and then infiltrated the liver lobules. This result in conformity with (17) who suggested that the Oval cells can be recognized in the liver tissue parenchyma by their characteristic morphology: they have scant cytoplasm, the most part of their volume consists of the nucleus, and the cell size (10  $\mu$ m) and it main function, recruited to generate the hepatic lineages of the hepatocytes and biliary cells. (18) also mention that oval cells able to differentiate in adult hepatocytes and biliary cells (cholangiocytes) (cells of bile duct) and they possess the self-renewal capability to proliferate and propagate. Hence, the oval cells could represent a second compartment involved in the liver regeneration when the insult of the organ is too massive and proliferation of hepatocytes is not sufficient. My result is incongruity with (19) who believed that the clear cell have relationship with water metabolism. Also disagree with (20) whom define regeneration as the ability of liver to restore lost or damaged tissues by reactivating already differentiated cells to start dividing again and not mention the stem cell. The thickness of capsule of capsule less than at 21 day, in young returned to the point close to the zero time due to healing evolution and cellular augmentation in young faster than adult. The mitotic index was at 21day more than 60 day in both

subgroup. The (Table, 3) shows that there was a striking decrease in their numbers in all age of the regenerating livers. In area far away from resected area showed normal structure of the hepatocytes with dark basophilic in their nuclei and some of cells have more nuclei. The present study found the regenerating capability in the young higher than adult this confined by the high mitotic or binucleated hepatocyte in young. This result in consistent with (21) in his study on the kidney of the rabbit he found the compensatory hyperplasia and hypertrophy in young higher and faster. All process of regeneration are in coincide with (5,22) who mention that after liver injure increased hepatocyte metabolic activity occurs, which is a signal for the liver cells to proliferate. Hepatocyte proliferation start soon after the damage of liver proliferate to restore normal hepatic mass and hepatic functional capacity. After partial hepatectomy necrosis occur, the cellular contents are released uncontrolled into the cell's environment resulting in damage of surrounding cells and strong inflammatory response of the neighboring tissue this resulted in atrophy, centrilobular necrosis, cytoplasmic fat deposits in hepatocytes, even greater proportion of binucleate cells undergoing mitotic division. Binucleated cell division will be found that the percentage of cells in mitosis in adult less than young. The dilation in central vein were evident. This result in agree with (23, 24) who mention that the activated Kupffer cell secrete Tumor Necrosis Factor (TNF) and others cytokines which contribute in vasodilatation. The capillaries of the small hepatocyte clumps change into true hepatic sinusoids surrounded by very scant matrix and lined by fenestrated endothelial cells and Kupffer cells. Also these extension in the circulation for the production of enough blood supply to the newly formed area resulted from the regeneration. This result have the same opinion with (8,13) who mention that after partial hepatectomy dogs the sinusoid became very dilated or expand.

In this study there were hypertrophy and hyperplasia of the Kupffer's cells, this result agreed with (25) who mention that in injured livers, activated Kupffer cells secrete cytokines and growth factors that induce the growth of hepatocytes, stellate cells and the migration of inflammatory cells. Moreover, they are more phagocytic than are their normal states and have impaired capacity to remove endotoxins. Enlargement of hepatic artery less than at 21 day which returned to the level nearly to the zero time. This findings coincide with (26) whom said that the liver regeneration occurred rapidly after liver resection and hepatocyte proliferation starts in the areas of the lobules surrounding the portal area and proceeds to the pericentral areas followed by the biliary ductular cells, then the Kupffer cells, and finally the endothelial cells. Accumulation of apoptotic exfoliated cell in lumen of duct. The number of apoptotic cell in young more than adult. This finding have the same view with (27,28) who mention that cell death is often divided into two different processes, necrosis and apoptosis. However, features characteristic of both necrotic and apoptotic cell death can occur in the same tissue and even in the same cell simultaneously. Necrosis results from metabolic disruption with energy depletion (loss of adenosine triphosphate, ATP), mitochondrial and cellular swelling and activation of degradative enzymes. This leads to cell lysis followed by loss of cell constituents in its surroundings. Therefore, necrosis is accompanied by inflammation. In contrast, apoptotic cell death is ATP-dependent and develops more orderly (programmed cell death) following a cascade of events. Apoptosis is characterized by DNA condensation, nuclear fragmentation, plasma membrane blebbing and cell shrinkage. Eventually, the apoptotic cell breaks into small membrane-surrounded fragments (apoptotic bodies) which are cleared by surrounding cells. All these events are tightly controlled and well organized. The omentum plays an important role in bringing about growth and regeneration of the resected liver. This end result have the same opinion with (29, 30) who mention that the omentum has been called the

“policeman of the abdomen” because after traumatic injury it migrates to the injured site, adheres to the wound, and promotes healing processes. In present study the regeneration process was generally completed at 60 day. This result opposed with (31) who mention that the duration of regeneration is relatively short: 7-10 days in rats and 3-6 months in humans, while it takes only 2 or 3 weeks to achieve a normal functional level. The regenerated ability in the liver of young and adult goat similar to finding of (32) whom noticed that during regeneration, not only hyperplasia (increase in the number of cells) occurs. Injury also implies hypertrophy, when the level of amino acids, proteins and triglycerides increases. Liver regeneration is a unique biological process in which partial organ loss can be compensated by a coordinated proliferation of remaining viable liver cells. In present work the regenerative capacity in young faster than adult and this result be of the same opinion with (33) who noticed that the agents that is compromised in old animals and in elderly humans. (i) The rate of liver regeneration, rather than the regenerative capacity, is diminished in the elderly.(ii) The induction of hepatocyte proliferation factors and the expression of cell cycle genes is inhibited in the elderly.(iii) The repression of cell proliferation and cell cycle gene inhibitors is compromised in the elderly.

### References

1. Junqueira, L. C. & Carneiro, J. 2005. Basic histology. Text and atlas. 11<sup>th</sup> ed. By Appleton and Lange. PP. 316- 333.
2. Michalopoulos, G. K. & DeFrances, M. C. 1997. Liver regeneration. *Sci.*, 276:60-66.
3. Bird, T. G.; Lorenzini, S. & Forbes, S. J. 2008. Activation of stem cells in hepatic diseases. *Cell Tissue Res.*, 331: 283-300.
4. Van Hul, N. K.; Barca-Quinones, J.; Sempoux, C.; Horsmans, Y. & Leclercq, I. A. 2009. Relation between liver progenitor cell expansion and extracellular matrix deposition in a CDE-induced murine model of chronic liver injury. *Hepato.*, 49: 1625-1635.
5. Michalopoulos, G. K. 2010. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am. J. Pathol.*, 176:2-13.
6. Hikasa, Y.; Hokushin, S.; Takase, K. & Ogasawara, S. 2002. Cardiopulmonary, hematological, serum biochemical and behavioral effects of sevoflurane compared with isoflurane or halothane in spontaneously ventilating goats. *Small Rumin. Res.*, 43 (2):167-178. (Abstract).
7. Luna, L. G. 1968. Manual of histological staining methods. Armed forces institute of pathology. 3<sup>rd</sup> ed. New York. Mac Graw. Hill Bock Company. PP. 38-76.
8. Mahmoud, H. E. 2003. Surgical evaluation of the liver functions post partial hepaticectomy in dogs. Ph.D. Thesis, Fac. of Vet. Med., Alex. Univ.
9. Ajeel, A. A. 2010. A comparative Study of Laparoscopic Partial Hepatectomy in Sheep With Different Techniques. Ph.D. Thesis, Vet Medicine/ Baghdad University. Baghdad Iraq.
10. Fausto, N.; Campbell, J. S. & Riehle, K. J. 2006. Liver regeneration. *Hepato.*, 43: S45-S53.
11. Henderson, N. C. & Iredale, J. P. 2007. Liver fibrosis: cellular mechanisms of progression and resolution. *Clin. Sci.*, (Lond) 112: 265-280.
12. Abdalla, O. A.; Mohamed, A. A.; Seham, A. H. & Mohamed, T. A. 2009. Histological and Clinicopathological Studies Following Partial Hepatectomy in Dogs. *J. Vet. Anat.*, 2 (1):17- 34.
13. Al-Badrany, M. S. 2006. Cholecystectomy and liver biopsy achievement by laparoscopy in dogs. Ph.D. Thesis. Collage of Vet. Medicine. University of Mousel.
14. Friedman, S. L. 2000. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. *J. Biol. Chem.*, 275:2247-2250.
15. Ganog, W. F. 2005. Review of medical physiology. 22ed. Lange.

16. Cullen, J. M. & Maclachlan, N. J. 2001. Liver, biliary system and exocrine pancreas. In: Carlton, W. W. and Zachary, J. F. Thomson's Special Veterinary Pathology. 3<sup>rd</sup> ed. Mosby, Chapter 2, P.81.
17. Alison, M. R.; Golding, M. & Sarraf, C. E. 1996. Liver damage in the rat induces hepatocyte stem cells from biliary epithelial cells. Gastroenterol., 110: 1182-1190.
18. Alison, M. R.; Poulson, R.; Forbes, S. & Wright, N. A. 2002. An introduction to stem cells. J. Pathol., 197:419-423.
19. Breazile, J. E. 1971. Textbook of veterinary physiology. Lea and Febiger, Philadelphia, USA. PP. 214-308.
20. Alkhalani, M. A. G. 2010. A comparative Study between Complete and Subtotal Laparoscopic Cholecystectomy in Goats in induced Cholecystitis, Ph.D. Thesis, Vet Medicine/ Baghdad University. Baghdad Iraq.
21. Al-Khuzae, B. A. J. 2012. Histological, Anatomical, Biochemical, study of unilateral nephrectomy in young and adult indigenous rabbit (*Oryctolagus Cuniculus*). Ph.D. Thesis, Vet Medicine/ Baghdad University. Baghdad Iraq.
22. Kluger, Y.; Rabau, M.; Rub, R.; Weinbroum, A.; Chaushu, G. & Avraham, R. 1999. Comparative study of wound healing in young and adult rats. J. Trauma, 47(2): 261- 264.
23. He, Q.; Kim, J. & Sharma, R. P. 2005. Fumonisin B1 hepatotoxicity in mice is attenuated by depletion of Kupffer cells by gadolinium chloride. Toxicol., 207: 137-147.
24. Kresse, M.; Latta, M.; Kunstle, G.; Riehle, H. M.; van Rooijen, N.; Hentze, H.; Tiegs, G.; Biburger, M.; Lucas, R. & Wendel, A. 2005. Kupffer cell expressed membrane-bound TNF mediates melphalan hepatotoxicity via activation of both TNF receptors. J. Immunol., 175: 4076-4083.
25. Decker, K. 1998. The response of liver macrophages to inflammatory stimulation. Keio J. Med., 47: 1-9.
26. Zappa, M.; Dondero, F.; Sibert, A.; Vullierme, M.; Belghiti, J. & Vilgrain, V. 2009. Liver regeneration at day 7 after right hepatectomy: global and segmental volumetric analysis by using CT. RSNA. Transplant Proc., 32: 249-251.
27. Brown, S. 2002. Apoptosis disables CD31-mediated cell detachment from phagocytes promoting binding and engulfment. Nature, 418: 200-203.
28. Canbay, A.; Friedman, S. & Gores, G. J. 2004. Apoptosis: the nexus of liver injury and fibrosis. Hepatol., 39:273-278.
29. Liebermann, M. D. 2000. The greater omentum. Anatomy, embryology, and surgical applications. Surg. Clin. North Am., 80: 275-293.
30. Litbarg, N. O.; Gudehithlu, K. P.; Sethupathi, P.; Arruda, J. A.; Dunea, G. & Singh, A. K. 2007. Activated omentum becomes rich in factors that promote healing and tissue regeneration. Int. J. Artif. Organs, 30: 95-99.
31. Court, F. G.; Wemyss-Holden, S. A.; Dennison, A. R. & Maddern, G. J. 2002. The mystery of liver regeneration. Br. J. Surg., 89: 1089-1095.
32. Minuk, G. Y. 2003. Hepatic regeneration: if it ain't broke, don't fix it. Can. J. Gastroenterol., 17: 418-424.
33. Juan, M. S.; Alvaro, N.; Rub, C.; Isidora, R.; Patricia, A. M.; Gustavo, F.; Amparo, V.; Sebasti, R.; Pedro Cillero, J. M. & Javier, B. 2012. Impact of Age on Liver Regeneration Response to Injury After Partial Hepatectomy in a Rat Model. J. Surgical Res., accepted for publication November 17,2011.