Assiut Vet. Med. J. Vol. 47 No. 94, July 2002

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ULTRASONOGRAPHIC, CLINICAL AND BIOCHEMICAL FINDINGS OF DEXAMETHASONE INDUCED HEPATOPATHY IN DOGS

(With 2 Tables and 13 Figures)

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(Received at 21/4/2002)

صورة الأشعة فوق الصوتية والأكلينيكية والبيوكيميائية إعتلال الكبد نتيجة الأستخدام التجريبي لمركب الدكساميسازون في الكلاب

مدحت ناصف ناصف

لقد تم إحداث الإعتلال الكبدي بالأستيرويدات في خمسة من الكلاب الهجين وذلك بالحقن العضي اليومي لدواء الدكساميسازون بجرعة ٢٠٢ جرام لكل كيلو جرام من وزن جسم الحيوان لمدة ٤٢ يوماً. ثم تم تقييم الكلاب المعالجة بواسطة التحليل البيوكيمائي لسيرم الدم والتغيرات المرضية في نسيج الكبد والموجات فوق الصوتية ووظائف الكبد. ولقد أظهر الفحص البيوكيميائي وجود نقص معنوي متدرج في البورتين الكلي وزلال الدم. وعلى الجانب الأخر فقد كانت هناك زيادة معنوية في نشاط أنزيمات AST, ALT, ALP, GGT في سيرم الدم بعد المعالجة بالدكساميسازون ولقد ظلت هذه القيم مرتفعة لمدة ٦ أسابيع على الرغم من إنتهاء العلاج. ولقد أظهر الفحص بالموجات فوق الصوتية للكلاب المعالجة بالدكساميسازون وجود زيادة متقدمة في مخطط الصدى لنسيج الكبد بزيادة فترة العلاج ، وقد كانت الزيادة في مخطط الصوت لنسيج الكبد بؤرية في البداية ثم أصبحت منتشرة وخطيرة. وقد كانت التغيرات المرضية في نسيج الكبد نتائج الموجات فوق الصوتية والتي أظهرت وجود تنكس كبدي دهني أدى إلى زيادة في مخطط الصدى ثم أدت إلى موت النسيج في النهاية.

SUMMARY

Steroid hepatopathy was induced in 5 Mongrel dogs by a daily intramuscular injection of dexamethasone (2.2 mg/kg body weight) for 42 days. Dexamethasone treated dogs were evaluated by blood serum biochemical analysis, histopathogically by study of liver tissue changes, ultrasonographically and liver function tests. The examination revealed significant gradual decrease in blood serum total protein and albumin. On the other hand, serum enzyme activities including alanine

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) were significantly increased after dexamethasone treatment and inspite of treatment termination the values were still increasing after 6 weeks. The ultrasonographic features in dexamethasone treated dogs showed progressive increase in the liver tissue echogencity with increasing the duration of dexamethasone administration. Initially the increased echogencity was focal then become diffuse and severe. Histopathology confirmed the ultrasonographic findings revealed in the early stages, fatty degeneration which resulted into increased eachogenicity ended by tissue necrosis.

Key words:Ultrasonographic, Dexamethasone, Hepatopathy, Dogs.

INTRODUCTION

Liver acts as a biochemical cross roads for the body, it processes the raw materials, detoxifis the industrial wastes of the body, so it is affected by a wide range of diseases including viral and bacterial infections, degenerative changes neoplastic diseases and toxic insults (Rothuizen and Meyer, 2000). Drugs induced damage are one of the possibilities of liver diseases in dogs including corticosteroid hepatopathy (Canis and Felis 1995, O'Brien *et al.*, 1996, Syakalima *et al.*, 1997 and Rothuizen and Meyer 2000), carbon tetrachloride induced liver damage (Dimski, 1995, Turgut *et al.*, 1997 and Matwichuk *et al.*, 2000), amiodarone (antiarrhythmic) hepatopathy (Jacobs *et al.*, 2000) and tetracholorethylene anthilminthic hepatopathy (Youngbum and Myungcheol, 1999).

Glucocorticoids affect almost every cell of the body. They are used to treat a variety of conditions including allergies, autoimmune disease, some cancers, shocks and Addison's disease. These corticosteroid, when used correctly side effects can be kept minimum (Glaze *et al.*, 1988). The adverse effects are usually dose dependent and include panting, increase thirst and urination. By the long term, side effects include muscular weakness, diabetes mellitus, Cushing's disease and corticosteroid hepatopathy (Williams and Marks 1994 and Mansfield and Jones, 2000).

Diagnosis of liver diseases is based upon, clinical history, clinical signs, biochemical assays, radiography, ultrasonography and eventually

histopathological examination (Dimski, 1995, Thomas *et al.*, 1996 and Youngbum and Myungcheol, 1999).

The ultrasound provide a simple quantitative method of assessing liver in dog (Barr, 1992, Mwanza *et al.*, 1997 and Bhadwall *et al.*, 1999). Moreover, O'Brien *et al.* (1996) reported that, video signal method is a sensitive technique for detecting subacoustic changes in the liver of corticosteroid treated dogs. The goal of this study is to investigate, the ultrasonographic features together with some blood serum biochemical and histopathological findings in dogs experimentally intoxicated with dexamethasone as powerful long acting corticosteroid.

MATERIALS and METHODS

Experimental Animals:

Five clinically healthy Mongrel dogs (1 to 5 years old) have live body weight 11-25 kgs were experimentally used to establish the hepatic ultrasonographic features before and weekly after dexamethasone treatment to coincide with ultrasonographic and biochemical blood serum examination. Hepatopathy was experimentally induced by parenteral overdosing with dexamethasone* (2.2 mg/kg of body weight for 42 days) according to O'Brien *et al.* (1996).

Animal preparation for ultrasonographic examination:

The liver is usually ultrasonographically imaged from the cranioventral abdomen just caudal to the xiphoid and costal arch at right side. Generally the hair over the area of examination was clipped then thoroughly shaved before examination. Transmission coupling gel (Shaff Lab.) was applied to the area of examination.

Ultrasonographic examination:

Dogs were ultrasonically imaged in left lateral recumbency. The area of ultrasonographic examination was prepared as previously described. Ultrasonography was performed using computed real time ultrasound system by means of 5.0 and 7.0 convex and sector transducers (Acuson 128 P/10), power and gain were fixed at 50 DB and zero DB during the period of experiment to ensure that the changes were attributed to dexamethasone treatment. The transducer was positioned

* Produced by the Egyptian Co. for Chemicals and Pharmaceuticals (ADWIAA). Each ml contains: dexamethasone sodium phosphate 2 mg

between 9th and 11th intercostal space according to Bhadwal *et al.* (1999). All examinations were carried out in the Animal Medicine Department, Faculty of Veterinary Medicine, Kafr El-Sheikh, Tanta University.

Sampling:

A) Blood samples:

Five whole blood samples (without anticoagulant) were collected from each dog at 0, 7, 14, 28 and 42 days of dexamethasone treatment through recurrent tarsal vein puncture for preparation of non haemolysed serum samples. These blood serum samples used for estimation of aminotransferases (Retiman and Frankel 1957), alkaline phosphatase (Kind and King 1954) gamma glutamyl- transferase (Szasz, 1969), total protein (Josephson and Gyllensward 1957) and albumin (Doumas and Biggsm, 1972).

B) Liver tissue samples:

Liver tissue samples were obtained via laparotomy of dogs according to Garnier (2000). Liver samples were processed routinely for paraffin embedding, then the embedded tissues were sectioned and stained with haematoxylin and eosin (H and E) according to Bancroft *et al.* (1984).

Statistical analysis:

The obtained results were statistically analyzed for t test by means of software computer programme (Spsswin, 1995).

RESULTS

Prolonged overdosing of dogs with dexamethasone resulted in non specific liver intoxication symptoms. These included panting, polydipsia and polyuria, depression, prostration (Fig. 3), slightly icteric mucous membranes together with accelerated heart rate (135-170/m).

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP) before and after dexamethasone treatment were tabulated in Table (1) and Fig. (1). These enzymes showed gradual significant increase after dexamethasone treatment and the experiment was terminated after 6 weeks, when values were still increasing. On the other hand, serum total protein and albumin were gradually decreased (Table 2 and Fig. 2).

Table 1: Blood serum enzyme activities in dogs before and after dexamethasone treatment.

Enzyme	Before treatment	1st week after treatment	2nd week after treatment	4th week after treatment	6th weeks after treatment
AST	4.0 ± 0.12 a	6.33 ± 0.33 b	8.33 ± 0.33 c	10.0 ± 0.58 d	18.0 ± 0.58 e
ALT	4.0 ± 0.17 a	8.33 ± 0.33 b	9.66 ± 0.33 c	11.50 ± 0.50 d	18.33 ± 1.68 e
ALP	7.0 ± 0.0a	12.0 ± 1.35 b	14.33 ± 0.88 c	15.0 ± 2.0 c	18.33 ± 1.45 c
GGT	3.67 ± 0.88 a	7.33 ± 1.20 b	11.0 ± 1.15 c	14.67 ± 0.88 d	20.33 ± 1.33 e

Table 2: Blood serum total protein, albumin, globulin and albumin: globulin ratio in dogs before and after dexamethasone treatment.

Parameter	Before treatment	1st week after treatment	2nd week after treatment	4th week after treatment	6th k after tment
Total protein	6.10 ± 0.2 c	5.90 ± 0.0c	5.33 ± 0.13b	5.40 ± 0.0b	4.70.15a
Albumin	3.87 ± 0.03c	3.60 ± 0.10 bc	3.27 ± 0.12 ab	3.0 ± 0.0 a	3.00.28 a
Globulin	2.23 ± 0.23	2.17 ± 0.03	2.07 ± 0.03	2.40 ± 0.0	2.(0.12
Albumin: globulin ratio	1.77 ± 0.18	1.66 ± 0.02	1.58 ± 0.06	1.25 ± 0.0	1.50.13

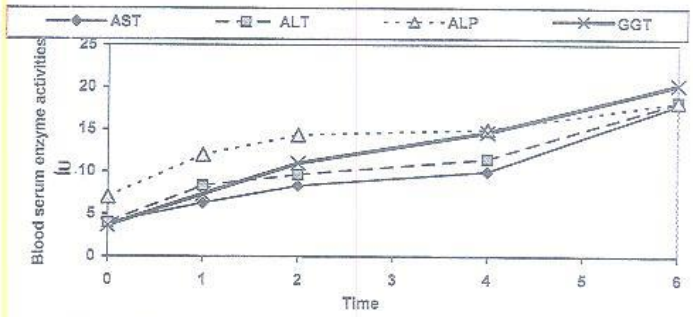

Fig. 1: Blood serum enzyme activities in dogs before and after dexamethasone treatment.

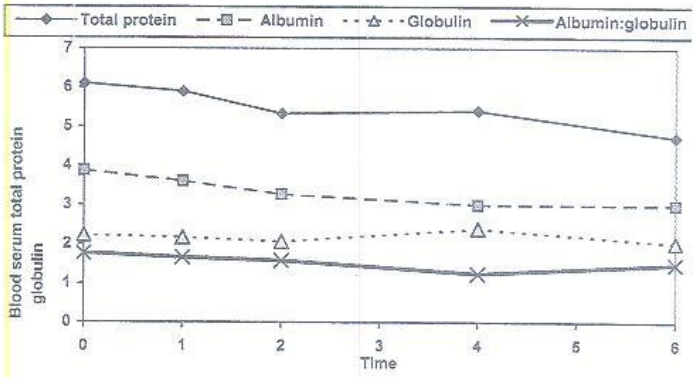

Fig. 2: Blood serum total protein, albumin, globulin and albumin: globulin ratio in dogs before and after examethasone treatment.

The ultrasonographic and histopathological features of normal liver and affected liver after dexamethasone treatment were shown at Figures from 3 to 13.

DISCUSSION

The present study showed that dog seem abnormally sensitive to corticosteroid drugs and developed typical lesions in the liver after multiple dose therapy. This observation was previously recorded by Cornelius and Bjorling 1992 and Rothuizen and Meyer (2000). Moreover, Williams and Mark (1994) recorded that, dexamethasone and betamethasone are the powerhouses of steroids and they are thirty to thirty-five times powerful than cortisol in their effect on the body. The adverse side effects of prolonged overdosing with dexamethasone included, panting, polyuria, thirst and polydipsia, depression, and severe weakness together with slightly icteric mucous membranes. These results were similar to those noticed by Chapman *et al.* (1993), Dimski (1995) and Rothuizen and Meyer (2000). This could be attributed to that, increased water consumption and urination are two of the most common side effects of corticosteroids usage in pets as it increase the activity of glomeruli which are the filtration units of the kidney and this cause the animal to excrete higher levels of urine and this loss stimulates thirst in an attempt to compensate lost fluid. These action may increase water consumption and urination to the point that, the animal can control neither one. Moreover, such signs can be observed within hours after initiating steroid therapy if the initial doses were to high for the individual to tolerate and can continue for several weeks after long acting dexamethasone treatment (Williams and Marks, 1994). They also, attributed muscular weakness to the alteration of animal's metabolism of protein where it can easily lead to muscular weakness or atrophy and with consistent and long term use, this sign become quite apparent and the abdominal muscles may become weaken, causing the animal to have a sagging or pendulous abdomen.

The present investigation revealed that, all studied enzymes increased significantly in dexamethasone treated dogs. During the experiment, serum enzymes including AST, ALT, CGT and ALP reached their peak levels at 42 days after treatment. These findings are in agreement with those reported by Dillon *et al.* (1983), Cornelius and Bjorling (1992), Rutgers *et al.* (1995), Sevelius (1995) and Rothuizen and Meyer (2000). Williams and Marks (1994) mentioned that dogs

treated with glucocorticoids especially dexamethasone often have increased liver enzymes arising from corticosteroid hepatopathy.

Serum ALT is liver specific enzyme in dogs and cats and cell damage cause elevation of this enzyme due to leakage, moreover, the elevation of this enzyme suggested to be positively correlated with the number of cell damage, but not the severity. Also, AST and ALT elevation should parallel each other in liver diseases (Hall, 1985; Sutherland, 1989; Hadley *et al.*, 1990 and Rothuizen and Meyer, 2000). Also, Hoffmann and Dorner (1975) and Kidney and Jackson (1988) suggested that, corticosteroid induced hepatopathy in dogs is characterized by abnormal morphology and increase in serum ALT, GGT and liver alkaline phosphatase (LALP) and by the appearance of unusual isoenzyme of alkaline phosphatase known as the corticosteroid induced alkaline phosphatase (CALP). Moreover, Syakalima *et al.* (1998) and Meyer and Twedt (2000) reported that, steroid hepatopathy is the most common cause of increase serum ALP in dogs, but it seldom occur in cat. Kuhlenschmidt *et al.* (1990) and Syakalima *et al.* (1997) supported this view where they reported that ALP increased in all dogs with corticosteroid hepatopathy and the monitoring this enzyme has greater significancy in assessing the level of hepatocellular damage.

Serum total protein, albumin and albumin: globulin ratio were gradually decreased in dogs with corticosteroid hepatopathy, but globulin revealed insignificant changes. These results were in agreement with Sevelius and Anderson (1995) and Mwanza *et al.* (1997). These findings could be contributed to the liver damage as this organ play a major role in the synthesis of albumin and most globulins, so the hepatic diseases leading to hypoproteinemia and hypoalbuminemia which may be associated with ascites.

Increased serum enzyme activities paralled with the liver damage demonstrated histopathologically in dexamethasone treated dogs and the histopathological examination revealed small sharp outlined clear vacuoles within the cytoplasm of hepatocytes indicating early or mild fatty changes (Fig. 9) in addition to the scattered eosinophylic droplets in the cytoplasm of hepatocytes surrounded with holes indicating cell necrosis (Fig. 10). These results were in agreement with those of Glaze *et al.* (1988) Kuhlenschmidt *et al.* (1991), Rutgers *et al.* (1995), Voros *et al.* (1997) and Altug and Agaoglu (2000).

Ultrasonography proved to be an efficient tool for assessment of liver size in dogs (Barr, 1992 and Mwanza *et al.*, 1997). As diffuse liver

diseases in animals are common due to multifactorial agents, steroid hepatopathy was used as a mode of diffuse liver disease to demonstrate the ultrasonographic findings in such affection. In the present study, there were progressive increase in the liver tissue echogenicity with the increased the duration of dexamethasone administration. Initially the increased echogenicity was focal, then became diffuse and severe. Gall bladder was slightly dilated. O'Brien *et al.* (1996) found that echogenicity was increased during experimental period and approximately similar to the spleen on day 10 and greater than spleen on day 14. The present ultrasonographic findings coincided with that described by Dimski (1995) and Syakalima *et* al.(1998).

Histopathology confirmed the ultrasonographic findings. In the early stages where fatty degeneration resulted in increased echogencity and eventually ended by tissue necrosis.

Finally it is concluded that, hepatic ultrasonography is a reliable and relatively sensitive method for monitoring liver diseases, but the diagnosis can be improved using liver function tests and histopathological examination of hepatic tissue spacimen.

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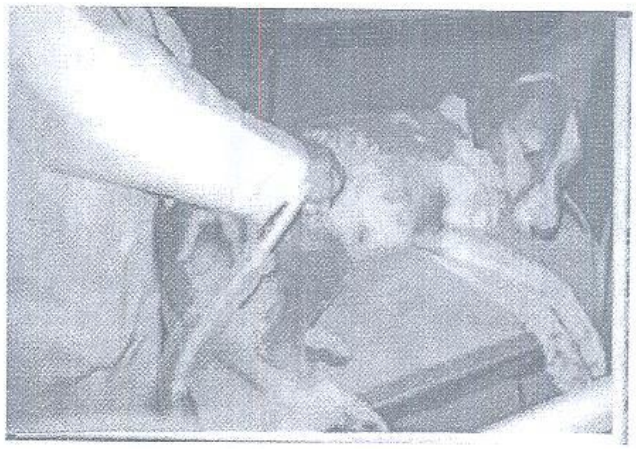

Fig. 3: Ultrasonographic examination of dog liver.

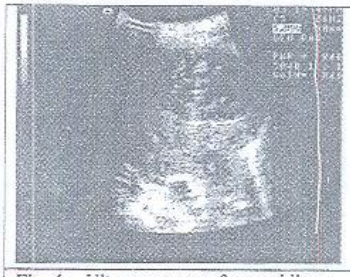

Fig. 4: Ultrasonogram of normal liver of dog and its relation to the right kidney.
L = Liver tissue C = Caudal vena cava
K = right kidney
Notice liver tissue is echogenic than renal tissue

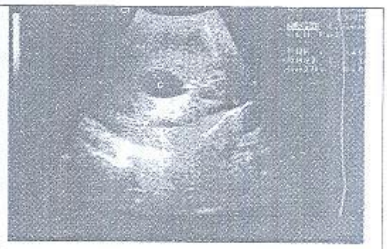

Fig. 5: Ultrasonogram of normal liver (preadminstration of dexamethasone)
G = Gasses of the intestine
P = Portal vein.
Notice liver tissue is uniformly echogenic (L)

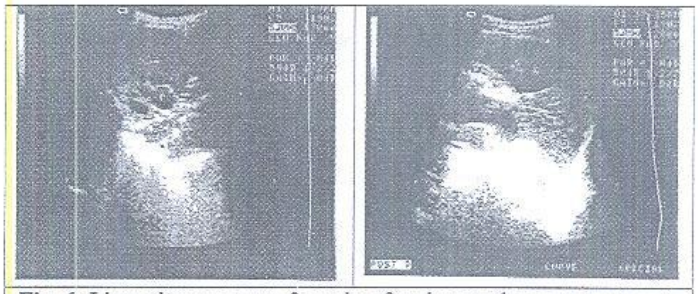

Fig. 6: Liver ultrasonogram 2 weeks after dexamethasone treatment. Notice uniformly increased echogenicity with dilation of gall bladder.

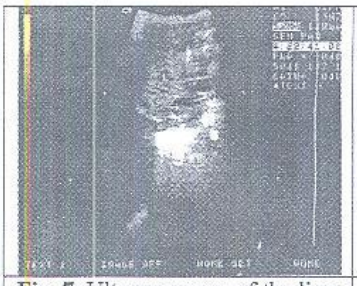

Fig. 7: Ultrasonogram of the liver 3 weeks after dexamethasone treatment. Notice increased echogenicity with the presence of focal area of necrosis

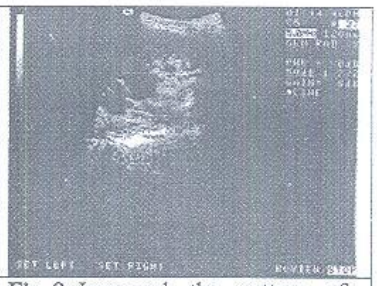

Fig. 8: Increased the pattern of echogenicity and uniformly 4 weeks after dexamethasone treatment.

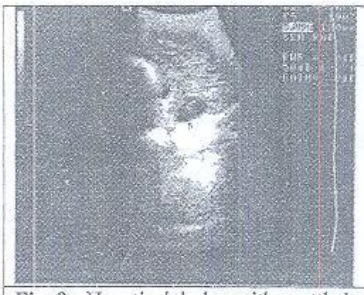

Fig. 9: Hepatic lobules with mottled appearance with increased echogenicity compared to previously mentioned changes 5th week after dexamethasone treatment

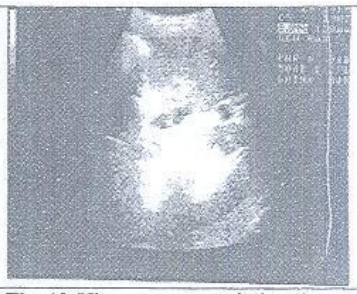

Fig. 10: Ultrasonogram of the liver 6 weeks after dexamethasone treatment showing focal area of fibrosis represented by focal echogenic areas.

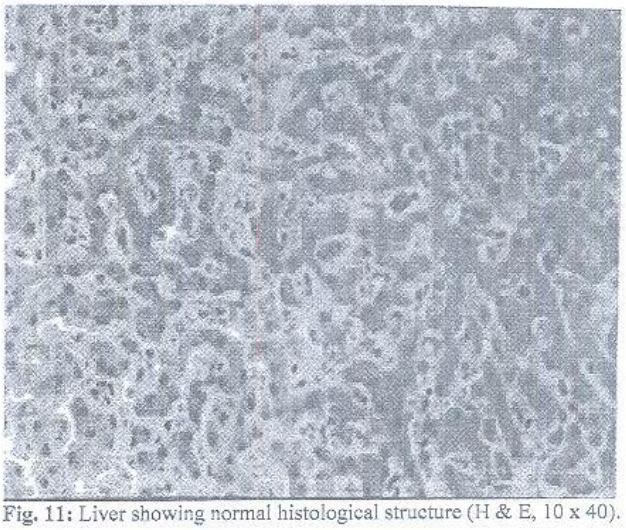

Fig. 11: Liver showing normal histological structure (H & E, 10 x 40).

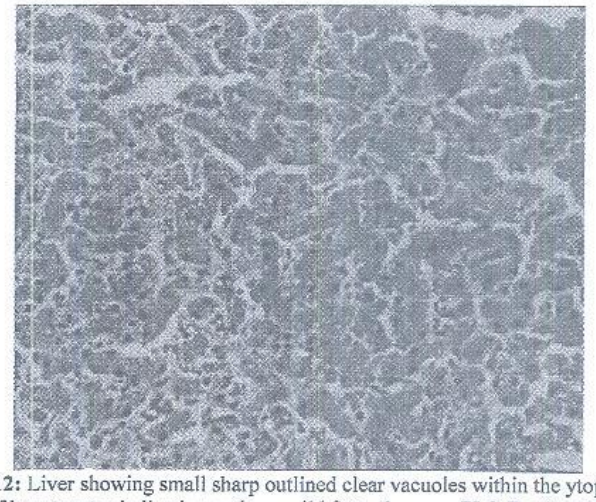

Fig. 12: Liver showing small sharp outlined clear vacuoles within the ytoplasm of hepatocytes indicating early or mild fatty changes (H & E, 10 x 40).

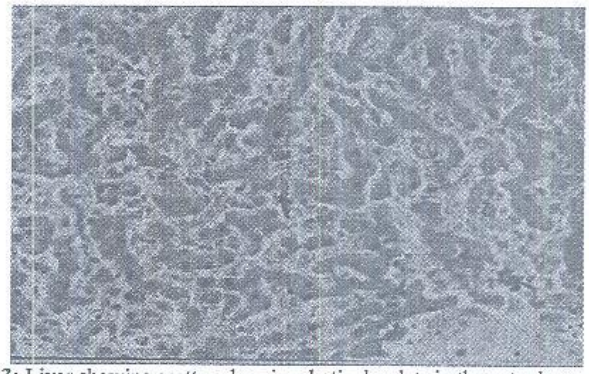

Fig. 13: Liver showing scattered eosinophytic droplets in the cytoplasm of hepatocytes surrounded with holes indicating cell necrosis (H & E, 10 x 40).