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Histopathological and Hematological Effects of Dimethoate 40EC on Some Organs of Albino Mice

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Abstract. The study investigated the toxic effects of the pesticide Dimethoate 40EC on some blood constituents i.e. RBCs, and WBCs count, hemoglobin content, hematocrit value and blood plasma protein; and on the tissues of selected organs, i.e. liver, kidney, stomach and intestine of the Swiss albino mice. The doses administered were 16mg/kg and 4mg/kg of Dimethoate 40EC and were proportional to what is used in the field.

Treated mice showed significant decline in the hemoglobin and hematocrit (PCV) values compared to controls, but no effect was detected on the total plasma protein. Hepatocytes of treated mice showed histochemically marked depletion in glycogen concenrations compared with the controls.Histopathological changes observed in the liver were hepatocyte pycnosis, vacuolation, blood congestion and high lymphocytic infiltration around the central vein. Meanwhile, kidney showed some changes in the cortex at the glomeruli as swollen cellular lining of the Bowman capsule .

Moreover, both the stomach and intestine showed high intensity of lymphocytic infiltration, and some enlarged lymph nodes.

Keywords: Dimehoate, Histopathological, Hematological, Lymphocytic infiltration, Pycnosis.

Introduction

Pesticides are biologically active chemicals, which have been thoroughly tested for safety and usefulness before they are released for agricultural use. However, if misused, they may be harmful to humans, animals and the environment. [1].

Human exposure to pesticides is usually estimated by measuring levels in the environment such as air, food, water, etc., i.e. environmental monitoring. In some cases

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however, information on exposure might be obtained by the analysis of concentration of a specific pesticide in the human body, tissues, fluids that is to say biological monitoring, or might be done by designing experiments to study pesticide effects on non-target animals and to assess the risk in humans exposed to pesticides.

Also, pesticides have been implicated in various disorders and diseases including cancer, adverse reproductive outcomes, peripheral neuropathies, neurobehavior disorders, impaired immune functions and allergic sensitization reactions, particularly of the skin, cumulative inhibition of cholinesterase activity as a result of long-term low doses of exposure to organophosphorus compounds [2].

Organophosphorus insecticides are generally short-lived and tend not to accumulate in plant or animal tissues to any great extent. They are considered as anticholinestrase insecticides and the mechanism by which they elicit their toxicity is identified and is associated with the inhibition of nervous tissue [3-5] and other neurophysiological abnormalities [6].

Many studies have been carried on the toxicity of dimethoate on non-target animals and on humans. A study on the toxicological effects of dimethoate (the parameter investigated is serum and erythrocyte cholinesterase activity) in industrial workers in different phases of work formulating dimethoate products showed no significant difference before and after exposure [7].

Results from experiments on the effect of dimethoate on reproductive and endocrine function suggested that it could influence serum concentration of reproductive and metabolic hormones[8].

Administration of dimethoate to pregnant rats produced enzymatic changes associated with mild pathomorphological changes in liver and brain, but no teratogenic effects were observed [9]. Immunotoxic effects of chronic doses of dimethoate could be detected in three generations of out-breed Wistar rats [10]. Direct exposure of free living wood mice *Apodemus sylvaticus* to dimethoate demonstrated that it causes a maximum depression of 75% in brain acetylcholinestrase activity compared to non-exposed mice and decreased locomotory activity [11].

Dimethoate was also found to have an effect on protein and on the carbohydrate metabolism as well as transaminases in the liver tissue of the fish *Clarias balrachus* (Linn) and to make alteration in protein metabolism of the muscle tissue in the same fish [12]. Also, Poet *et al.* [13] studied the effect of two organophosphorous pesticide on the hepatic and intestinal metabolism in the rat and found that the metabolizing enzymes reponsible for both the bioactivation and detoxification are present in the small intestine at lower level than the liver but still significant. Also, Bulusu and Chakravartylndira [14] studied nucleic acid and protein propel in normal and malnourished rat liver on exposure to organophosphorous group of pesticides and found that were affected in both.

Few studies have been made on the histopathological effects of dimethoate [15-17]. The present study aimed to investigate the histopathological and hematological effects of the organophosphorous pesticide dimethoate that is extensively used in some agricultural areas in Saudi Arabia on some organs of laboratory animals.

2. Materials and Methods

2.1. Chemicals

Dimethoate 40 EC is an organophosphorus pesticide with a chemical formula

$$CH_3NHCOCH_2SP(OCH3)_2$$

It has a stomach action and a cholinesterase inhibitor. It is of low persistence in the soil, water and environment (half-lives of 4 to 16 days). Disappearance from open waters is possibly due to microbial action or chemical degradation as photolysis and evaporation [18]. Dimethoate was dissolved and diluted to the required doses using sunflower oil.

2.2. Animals and dosing

Experiments were designed to examine the histopathological effects on the liver, intestine, stomach, and kidney and changes in some blood parameters of Swiss Albino mice following different routes of treatment with dimethoate.

A total of 90 adult male Swiss albino mice were used in the experiment. Animals were divided into three groups of 30 mice each. They were maintained in the animal house on daily observations and well fed by standard mouse chaw under good condition of ventilation, and at room temperature 25 to 30 ^{o}C.

Weight of mice was registered before the beginning of treatment and at the end. LD50 value for dimethoate has been reported to be 160mg/kg for mice [18] and was used in the present study.

2.3. Treatment schedule

The three groups of 30 mice each were treated according to the following schedule:

Group 1 was given 16mg/kg of dimethoate (1/10 LD50) intraperitonial once a week for four months.

Group 2 was given 4mg/kg of dimethoate (1/40 LD50) intraperitonial twice a week for four months.

Group 3 was given 4mg/kg of dimethoate orally twice a week for four months.

Two control groups of 30 mice each were kept all through the experiment. For each group, 15 mice were given the same dose of sunflower and the other 15 mice were given distilled water.

At the end of the treatment period, the mice were taken in batches dissected and liver, stomach, intestine and kidney were removed and fixed for histopathological investigations using 10% neutral formal saline. Tissues were processed by routine histological techniques, sectioned at 7um, stained with hematoxylin and eosin (H&E). Some parts of the livers were fixed by alcoholic Bouins and stained with best carmine for glycogen content. Finally, stained sections were examined under the light microscope and subsequently micrographs were taken.

Blood samples were collected from the heart of mice for hematological investigations. The parameters investigated were the hemoglobin content, the hematocrit value (PCV), blood cell count and total plasma protein.

2.4. Semiquantitative statistical analysis

Semiquantitative statistical analysis for the cumulative histopathological effects of the two doses on the four organs of albino mice were made using Mann-Whitney Rank Sum Test and Krushal-Wallis one way Analysis of Variance on Ranks and student t-test.

3. Results

3.1. Histopathological studies

Sections from the liver, stomach, intestine and kidney were prepared from both control and treated mice and were examined under the light microscope. The microscopic observations were reported for each organ and the intensity of changes were tabulated in Table 1, and are presented by the Figs. 1 to 4.

The **liver** sections from treated mice showed moderate changes when compared with those from the control mice (Fig. 1-a). These changes include the presence of more endothelial cells scattered among the hepatocytes and some vacuolation in the liver texture (Fig. 1-b). Only 10% of the sections from mice treated with 16mg/kg dimethoate showed rupture in some hepatocytes (Fig. 1-d). About 30% showed dense lymphocytic infiltration round the central vein and dark stained hepatocytic nuclei indicating cell pycnosis (Figs. 1.b & c). Some hepatocyes have shrinked nuclei (Fig. 1-d). About 15% of the sections from mice treated with 4mg/kg dimethoate orally showed dark stained hepatocytic nuclei and minor hepatocytic rupture with lymphocytic infiltrate.

Sections from the mice **liver**, which were fixed with alcoholic Bouins to examine the glycogen content showed high content in the controls (Fig. 2-a), while those from mice treated with dimethoate 4 mg/kg showed moderate glycogen content; and sections

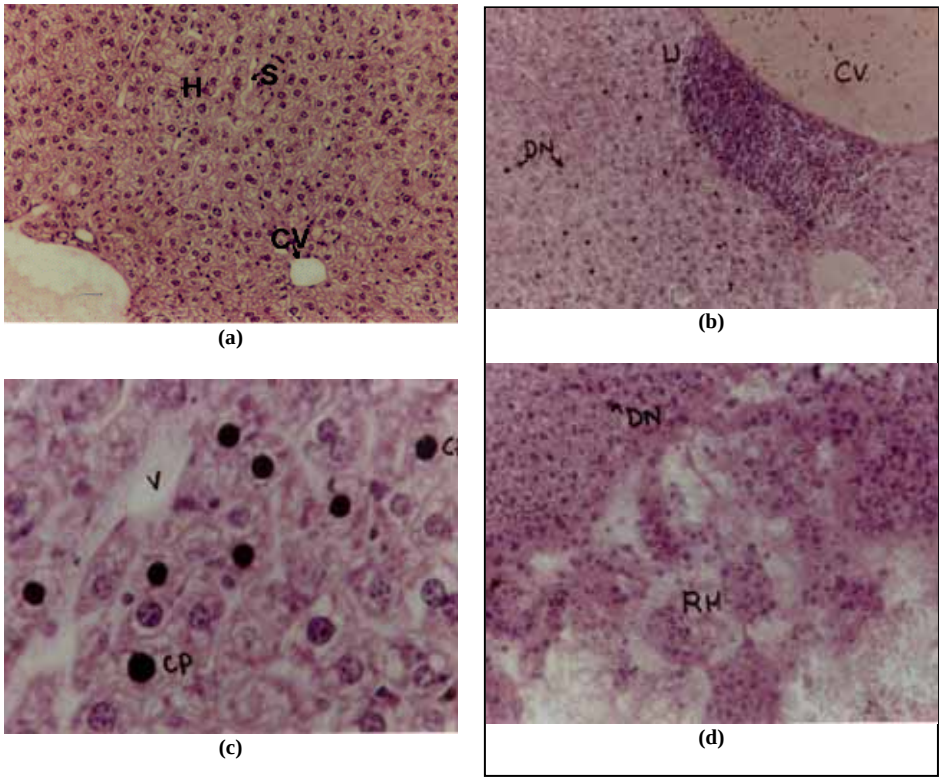
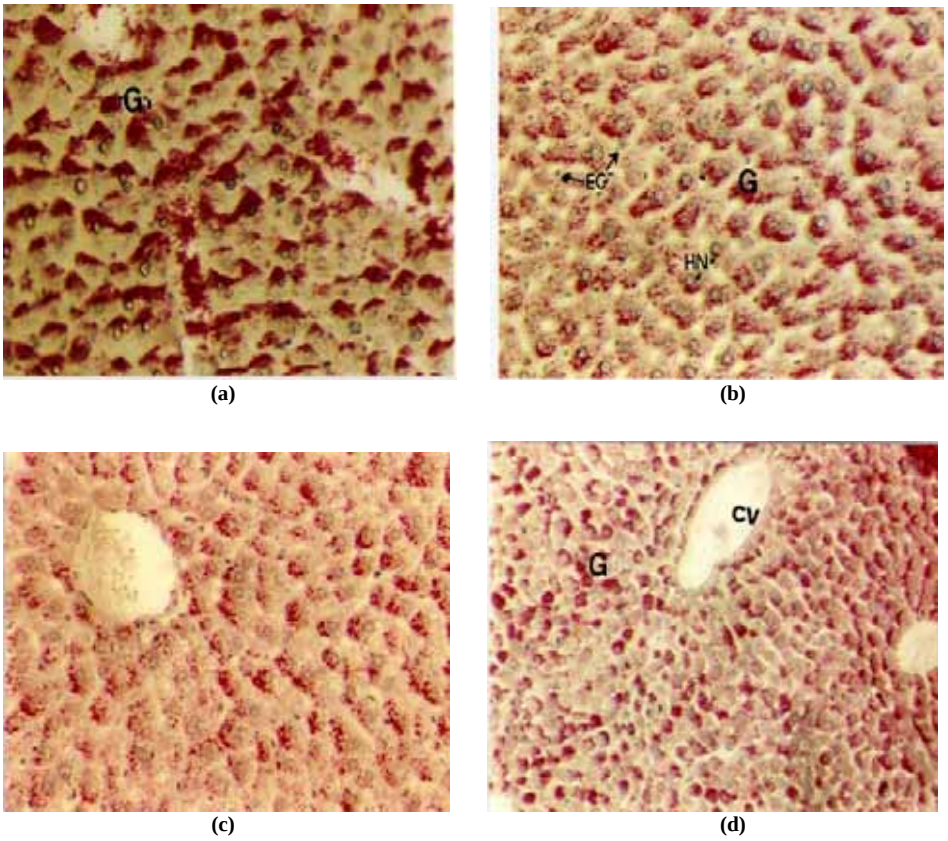


Fig. 1. (a) Shows control liver section; (b-d) sections through the liver from mice treated with 16mg/kg (b) shows some lymphocytic infiltration (LI) beside the central vien (CV) and some cells show dead nuclei (DN) ; (c) liver section shows some cell pycnosis; vacuolation (V); (d) shows some ruptured hepatocytes (RH).

from mice treated with 16 mg/kg showed some parts devoid of glycogen (Fig. 2-b & d) similar to those liver sections subjected to digestion by diastase for 20 minutes (Fig. 2-c) .

Sections through the **stomach** from control mice showed normal structure. Sections from stomach treated with 16mg/kg dimethoate showed moderate lymphocytic infiltration and some small granular masses between the gastric glands in the mucosal region of the stomach (Fig. 3-a). About 20% of the examined sections showed some vacuolation in the mucosal region (Fig. 3-b). Sections from the **intestine** of mice treated with dimethoate 16mg/kg showed no rupture in the structure but about 20% showed high lymphocytic infiltration inside the villi when compared with those from the control (Figs. 3-c & d). Also, animals treated orally by 4mg/kg twice a week showed high intensity of lymphocytes and enlarged lymph nodes (Fig. 3-e & f). Sections from mice treated with 4mg/kg dimethoate twice a week intraperitoneally did not show significant difference from those treated with 16mg/kg once a week.

Sections from the **kidneys** of mice treated with dimethoate as well as those from the controls were also examined (Figs. 4-a, b & c). The main changes in the sections from kidney of mice treated with 16mg/kg dimethoate were some blood congestion in between the tubules and only about 4% showed fibrous tissue and tubule rupture (Fig. 4-b). The glomeruli showed various structures of which some seemed swollen with congested blood, others were shrinked . Also, most of the Bowman's capsules round the glomeruli seemed to be lined with swollen cells which look like cubiodal cells that is showing hypoplasia (Fig. 4-c) instead of normal liner squamous cells as in the control sections (Fig. 4-a).



(a) **(b)**

(c) **(d)**

Fig. 2. (a) Section through the liver of control mouse showing the intensity of glycogen. (b) Section through the liver of mouse treated with 16mg/kg dimethoate. (c) Control mouse liver section treated with diastase. (d) Section through the liver of mouse treated with 4mg/kg dimethoate twice a week.

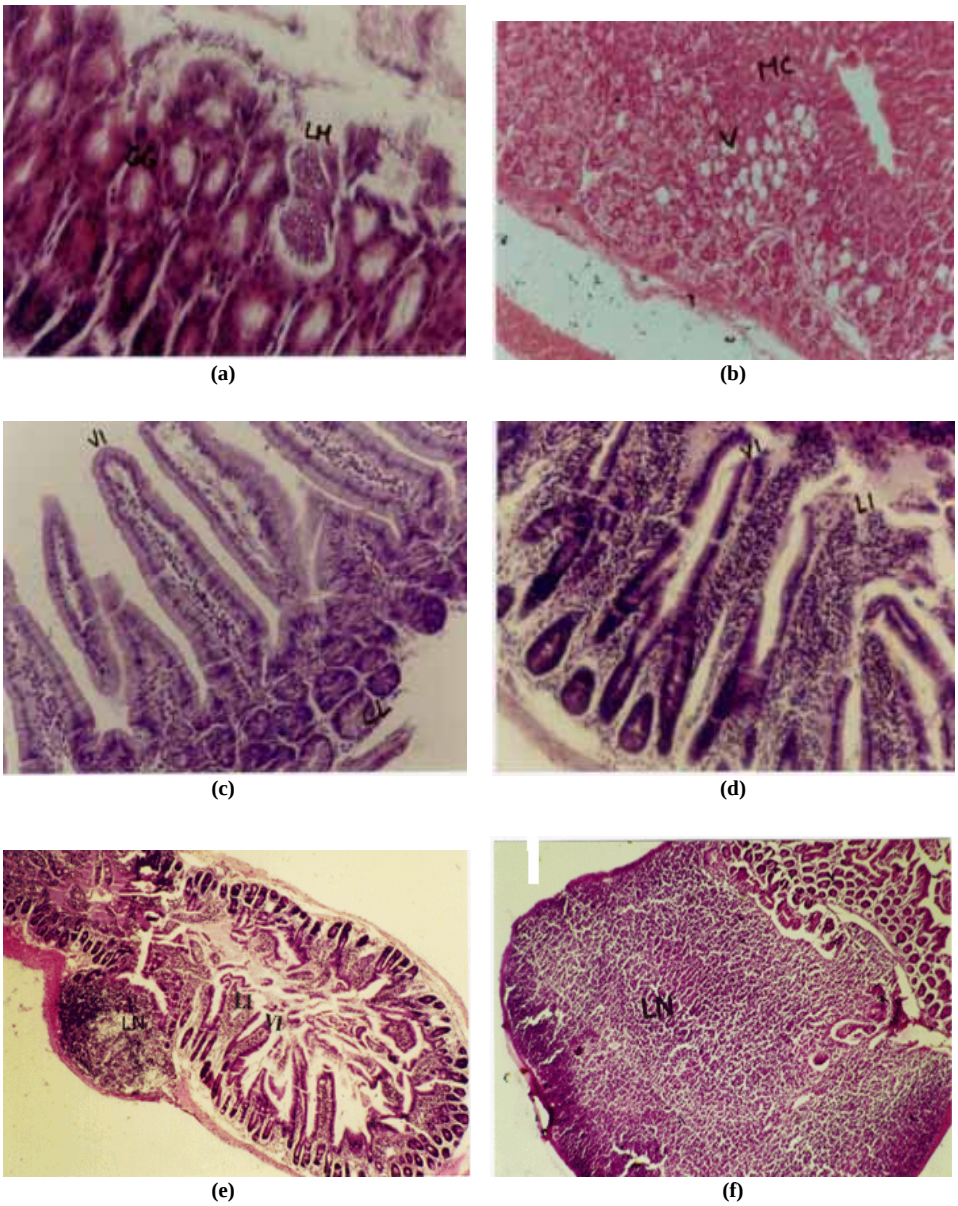
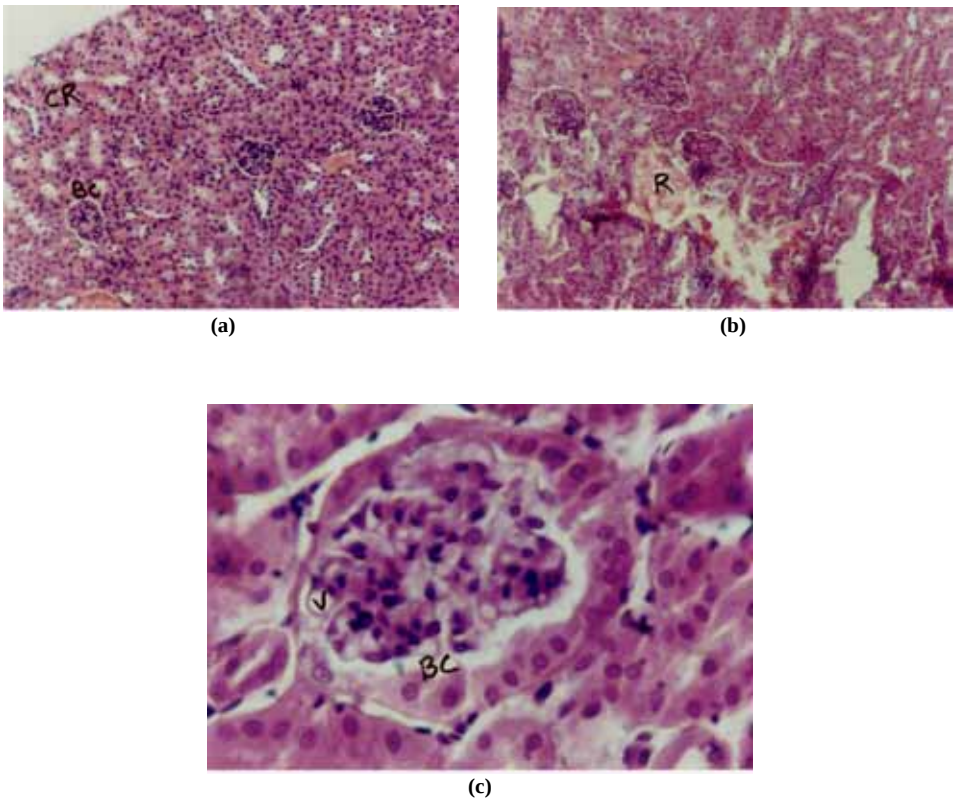


Fig. 3. (a) and (b) show sections from the stomach of mice treated with 16 mg/kg dimethoate showing lymphocytic infiltration (Li) between mucosal cells (MC) and vacoulation (V). (c) shows section through the intestine from control mice showing villi (VI). (d) shows intestine section from mice treated with 16 mg/kg dimethoate showing high lymphocytic infiltration (LI). (e) and (f) show enlarged lymph node in the intestinal wall.



(a) **(b)**

(c)

Fig. 4. Section through the kidney from albino mice treated with 16mg/kg of dimethoate (b) showing rupture (R) compared with section from control mice (a). (c) magnified section showing hypoplasia in cells of Bowman's capsule (BC) and vacuolation (V) in the glomerulus.

Semiquantitative statistical analysis

The main histopathological changes observed from microscopic investigations of the four selected organs were presented in Table 1 and included: lymphocytic infiltration, vacuolation, cell rupture, nuclear death or pycnosis and swollen cells.

The comparisons of the effects were made between the different doses, of the pesticide; the different organs with control and between the different organs, and the route of dosing using Mann-Whiteney Rank Sum Test and Krushal-Wallis one way Analysis of Variance on Ranks. Comparison between the two concentrations given to the three groups showed no significant difference for all organs. But, the cumulative effects seem considerable, comparing the three groups with the control group high statistical difference was obtained ($P \leq 0.001$). The histopathological changes were found to be significantly higher in the liver ($P \leq 0.001$) and other organ ($P=0.019$) after treatment with the higher dose when compared with the control.

When comparing the effects on the liver with those on the kidney for the same concentration of the pesticide, the former proved to be more affected. The changes in the kidney, the difference in the medial values among the treated groups and the control group were found to be greater than would be expected by chance and statistically significant difference was observed between the three (P=0.009). No statistcal difference could be observed between the median values of histopathological changes in stomach and intestine at the second dose level used ($P \leq 0.322$).

Table 1. Showing the main types of histopathological changes detected after treatment with the two doses of dimethoate. and the percenage of the affected animals

Organ	Histopathlogical change	% of animals treated with dimethoate (both conc.) in which the effect was detected	% of control animals affected	Significance
Liver	Lymphocytic infiltration	30 %	14 %	*
	Cell rupture	10 %	0	*
	Nuclear death (pycnosis)	15 %	0	*
	Vacuolation	42 %	9%	**
Kidney	Blood congestion	36 %	9 %	*
	Tubule rupture	8 %	0	*
	Swollen capsule lining	29 %	0	*
	Yellowish secretion	15 %	9%	*
				*
Stomach	Lymphocytic infiltration	41%	13 %	*
	1- Vacuolation	21 %	8%	*
	2- Mucosal region rupture	12.5%	0	*
Intestine	1- Lymphocytic infiltration	51 %	17 %	*
	2- Rupture in villi	14 %	0	*
	3- Eosinophilic granules	19 %	،8%	*

*=P<0.05
**=P<0.01

3.2. Hematological studies

The blood parameters investigated were hemoglobin content, hematocrit value (PCV), blood cell counts and the total plasma protein. The results were statistically analyzed using student t-test and tabulated in Tables 2 and 3.

The hemoglobin content and hematocrit values showed significant decline in those mice treated with 16mg/kg dimethoate ($P \leq 0.05$) when compared with control values and were highly significant in those mice treated twice a week with 4mg/kg dimethoate ($P \leq 0.001$). The plasma protein was investigated both quantitatively and qualitatively. The total plasma protein content showed no significant difference between the mice treated with both doses of the pesticide and those from the two control groups .

The electrophoretic investigation showed no significant difference between the differential bands of the plasma proteins in treated and control mice (Fig. 5). The fractions that appeared clearly were albumin, alpha-, beta- and gamma- globulins. The blood cell counts from control and treated mice are tabulated in Table 3. The red blood cell (RBC) counts in mice treated with each of the dimethoate concentrations showed no significant difference from those of the controls ($P \geq 0.05$).

The differential count of white blood cells (WBC) was also investigated. The total white blood cell (WBC) count showed variable values, but were found not significant. In the differential count of the white blood cells from those mice treated with 16mg/kg, the values of neutrophils and lymphocytes showed significant difference ($P \leq 0.05$) compared with those from those controls. The values of monocytes, eosinophils and basophils in mice treated with 16mg/kg or 4mg/kg showed no significant difference.

Table 2. Some hematological values from mice treated with different concentrations of dimethoate compared with those from the controls

Parameter / Route	Control sunflower oil	Control distill water	Dimethoate 16mg/kg (D1)	Dimethoate 4mg/kg (D2)	Dimethoate 4mg/kg (Do)
	Intraperitonial	Orally	intraperitonial	Intraperitonial	Orally
Hb gm/100ml	13.38±1.96	12.93+2.13	11.17±2.11*	9.55±1.59**	10.05±1.67**
PCV %	41.0 ±2.86	40.45+3.14	37.86±4.98*	35.4±3.68**	36.67±4.71**
Total Plasma Protein	50.64±6.22	50.64+6.22	54.0 ±23.22	52.02±12.8	52.08±22.21

* = significant (P= 0.05).
** = highly significant (0.001).

Table 3. The values of RBC count and WBC differential count of mice treated with different concentrations of dimethoate compared with those from controls

Parameter	**Control distill water**	**Control sunflower oil**	**Dimethoate 16mg/kg (D1)**	**Dimethoate 4mg/kg (D2)**	**Dimethoate 4mg/kg (Do)**
Route	**Orally**	**Intraperitonial**	**Intraperitonial**	**Intraperitonial**	**Orally**
RBC	7. 41+0.32	7. 39±0.41	7.82±1.22	7.88±0.96	7.73+1.06
WBC					
$X10^9/L$	3.63+ 0.34	3.54±1.52	4.11±1.91	4.54±2.94	4.52±1.75
NE %	3.92+ 0.35	3.88±2.47	20.72±16.8 *	5.6±4.35	8.56±13.72
LY %	81.43+ 15.4	86.84±18.05	69.13±24.1 *	79.85±24.1	83.05±16.19
MO %	1.68+ 0.96	1. 50±1.46	0..91±1.61	2.64±2.86	3.96±4.30
EO %	0.23+ 0.05	0.12±0.08	6.11±10.7*	9.00±27.3*	0.34±0.23
BA %	1.25+ 0.75	1.00±1.52	3.11±8.24	2.90±5.67	4.09±10.25

*= significant ($p \leq 0.05$)
NE= Neutrophils LY= Lymphocytes MO= Monocytes EO= Eosinophils BA= Basophils

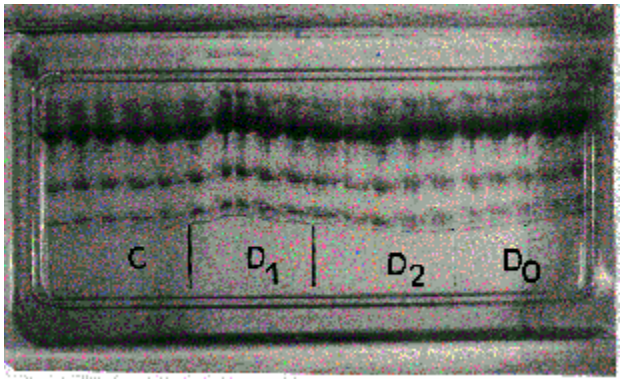


Fig. 1. A consistant pattern of separation of plasma protein from control mice (C) and treated mice with different concentration of dimethoate (D1=16mg/kg, D2=4mg/kg i.p and Do=4mg/kg given orally).

4. Discussion

Many studies concerning the effect of dimethoate on the inhibition of the enzyme acetylcholinestrase have been reported positive with acute doses and different delayed symptoms were seen to happen from repeated or prolonged exposures [16]. Histopatholgical and hematological effects of dimethoate on albino mice have been studied. The results obtained showed mild to severe effects on the organs investigated.

The histopathological changes investigated in the selected organs reflected some significant effects with variable intensities. The liver seemed to be mostly affected by all doses of the pesticides. The changes reported were mostly hepatocytic vacuolation, intercellular vacuolation and infiltration of lymphocytes around the central veins. To a lesser extent were nuclear death or pycnosis and hepatocytic rupture, as the liver is the most active mammalian organ in xenobiotic metabolism and contains a larger variety of enzymes for this action. Accordingly, its role in metabolic conversions is its susceptibility to chemical injury [19]. Many chemicals were found to cause hepatic necrosis and lipid accumulation or steatosis.

Similar studies showed the synergistic toxic effect of an organophosphate pesticide Dimecron and a carbamate fungicide Cuman L on the histology of liver and brain, that reported the histopathological changes like the destruction of hepatocytes and extrusion of nuclei [15].

Another investigation on the histological changes in the liver were done by Abd Rabou [20] which showed fatty change and hypertrophy in hepatic cells, amyloid – like structure and distintension of sinusoids. In this study, the fatty change is rarely detected though the doses administered were dissolved in light oil.

The lymphocytic infiltration showed various intensities with the treated mice. This indicates signs of irritability, inflammation and hypersensitivity to the chemical used. The dense lymphocytic infiltrate is confined to portal tracts and where there was no erosion of hepatic architecture, this abnormally progress rarely to cirrhosis [21]. The lymphoctic infltration observed in some control mice might be due to hygenic reason other than the chemical effects. Livers from mice treated with higher doses of the pesticide showed hepatocytic nuclear death or cell pycnosis. Similar findings were reported on the effect of carbofuran on fish by Singh *et al.* [22], which showed liver cytoplasmolysis, nuclear pycnosis and necrosis leading to disintegration of hepatocytes. Another study by Peris and Kalaiarasi [17] on the histopathological responses of catfish to chronic and acute toxicity of an organophosphate pesticide stated that the histopathological changes revealed that defense reactions occur in the fish to resist the pesticide.

However, the architectural alterations of the liver including cord disarray, hypertrophy and disintegration of hepatocytes showing different sizes of nuclei, lymphocytic infiltration, in addition to sinusoidal blood congestion and hemorrhage were all evidence of liver damage. These were evoked by many investigators using various chemicals and toxicants with different animals including fishes [17, 20, 21, 23] and many others. The kidney is an organ sensitive to external factors, which might induce histopathological change as well as functional deficit. Anatomically, the cortex of the kidney has more functional structures than the medulla and mainly nephrons. Most chemicals and toxins carried in the blood stream will have a great chance to influence cortical rather than medullary function. Furthermore, the maintenance of normal function of the kidney requires delivery of large amounts of fluids, electrolytes, metabolic substrate and oxygen to the kidney .

The main changes reported in this study were blood congestion in the glomeruli and proximal tubule swollen Bowman capsule lining with minor tubule rupture and yellowish secretion between the tubules. However, most toxins appeared to have their primary site of action on the proximal tubules and glomeruli because most of the blood flow to the kidney is delivered to the cortex, predominantly to the proximal tubules. The swelling of the tubules and lining of Bowman's capsule seemed to be related to disturbances of the ionic milieu of the cells caused by toxic agents. Other toxic effects might be attributed to hypoxia.

The change seen in the glomeruli include membranous change, the peripheral loops are thickened due to basement membrane expansions and crescentric florid proliferation of cells including macrophages lining and the Bowman's capsule often compressing the glomerulus. Recognition of these changes, clinical implication, if this crescentic proliferation is in >80% of glomeruli, this condition is said to be cresentric nephritis associated with the chemical conditions of rapidly progressive glomerulu-nephritis and lead to poor prognosis for renal function. [24]. The kidney tubules were mostly swollen, the damage was restricted to the proximal tubular cells, while those of the distal being

spared. The pathological changes seen in the intestine of the treated mice were mostly the infiltration of lymphocytes. This might be attributed to hypersensitivity reaction as a response of inflammation.

The infiltration of lymphocytes and cell lining proliferation in the intestine have been reported by many investigators [20, 22], noticed accumulation of lymphocytes in the intestine of Nubian goats previously treated with Sevin as an indication of inflammation. Also, the appearance of eosinophilic bodies at the base of the villi may indicate hypersensitivity due to the toxicant reaction. The stomach showed minor effects compared with the liver and intestine. The lymphocytic infiltrations seen in the mucosal region seem to be due to some inflammatory effect or defensive in case of those mice treated orally. No rupture in the stomach texture was observed with these pesticides, although many investigations have shown mucosal cell rupture or excessive mucus secretion.

The hematological changes were mainly in the hemoglobin, hematocrit and the glycogen, which seems to be due to malabsorption of nutrients or the hyperactivity of the animal. Similarly, Thangavel *et al.* [15] reported similar results when exposing the fish *Sarotherodon mossambicius* to dimecron. While Singh *et al.* [22] showed that another organophosphate insecticide – Formothion gave a significant increase in the total erythrocyte count and hemoglobin content in fish. The plasma protein did not show any significant difference between the treated mice and the control. The results of a qualitative study of electrophoretic pattern of fish *C. punctatus* have provided a preliminary evidence that dimethoate may interfere with the distribution of serum proteins [25].

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التأثيرات المرضية لمبيد الديمثويت (40EC) على بعض قياسات الدم وبعض أعضاء الفئران السويسرية البيضاء

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ملخص البحث. شملت الدراسة مدى تأثير إحدى المبيدات الفسفوعضوية: ديمثويت 40 EC على بعض قياسات الدم وأنسجة الكبد والكلى والمعدة والأمعاء في فئران التجارب باستخدام الجرعات ١٠/١ و٤٠/١ من الجرعات تحت المميتة ولمدة أربعة شهور.

أظهرت النتائج بعض التغيرات في مكونات الدم للفئران المعالجة بالمبيد حيث انخفضت نسبة كل من الهيموجلوبين والهيماتوكريت في كل المجموعات مقارنة بالمجموعة الضابطة، بينما لم يحدث أي تغير على البروتينات الكلية لبلازما الدم أو للعدد الكلي لخلايا الدم البيضاء.

كما أظهرت الدراسة انخفاضا ملحوظا في نسبة الجلايكوجين في الخلايا الكبدية للفئران المعاملة بالمبيد عند مقارنتها مع المجموعة الضابطة. وقد شملت التغيرات النسيجية في الكبد زيادة في عدد الخلايا الليمفاوية خاصة في منطقة الوريد الأوسط وموت بعض الخلايا مما أدى إلى تهتك النسيج وظهور بعض الفجوات في النسيج الكبدي.

كما ظهرت بعض التغيرات في الكلى خاصة في جدار محفظة بومان التي أظهرت انتفاخا في الخلايا الجدارية، كما لوحظ في المعدة والأمعاء زيادة ملحوظة في عدد الخلايا الليمفاوية مع تضخم في بعض الغدد الليمفاوية.