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THE HISTOLOGICAL AND PHYSIOLOGICAL ASSESSMENT OF EFFECT LEAD ACETATE LONG TERM EXPOSURE ON LIVER OF ALBINO RAT AND TREATED WITH ATROPINE SULFATE

Shaymaa Abdalkader Mahdy[1]; Muneef Saab Ahmed[2]; Ayad Hameed Ebraheem[3]
Branch of oral diagnoses, college of dentistry ,university of Tikrit, Iraq[1]
Branch of Pharmaceuticals, Physiology and Chemistry, college of veterinary ,university of Tikrit, Iraq[2]
Branch of anatomy and histology, college of veterinary ,university of Tikrit, Iraq[3]

Abstract: The gall of this study is to assess the effects of long term exposure to lead acetate on histological architecture of liver in white rat. 24 animals were used in the experiment, which distributed to 4 groups, 1st group (G1) control group was injected intraperitonially by distilled water 1 ml/kg body weight for three month. 2nd group (G2) was injected intraperitonially by lead acetate 12 mg / kg body weight / 10 days for three month. 3rd (G3) was injected intraperitonially by lead acetate 12 mg / kg body weight / 10 days for three months and then injected intraperitonially by 0.2 ml Atropine sulfate for 5 days. 4th (G4) was injected intraperitonially by lead acetate 12 mg / kg body weight / 10 days for three months and then injected intraperitonially by 0.2 ml Atropine sulfate for 7 days. The histological results of G2 showed liver cells with vacuolar degeneration, pyknosis of a number of cell nuclei, and the disappearance of nuclei from other necrotic liver cells. Blood sinusoids were containing dark-colored kupffer cells., results of group G3 and G4, treated with lead acetate for three months and treated for 5 and 7 days respectively with the drug atropine sulfate, showed The presence of normal-shaped hepatic cells interconnected with other cells, including blood sinusoids containing kupffer cells. The central vein in the hepatic lobule showed decomposed blood with some white blood cells in its lumen. The central vein extended with blood sinusoids filled with enlarged kupffer cells. The hepatic cells were found in folded rows and appeared polygonal, and each cell had two nuclei. Physiological results showed of lactate dehydrogenase (LDH) and acid phosphatase (ACP) of all groups, as it was observed that there was a significant increase in the concentration of them at a significant level in G2 compared to the G1. While the results showed a significant lowering in their concentration in both G3 and G4 .
Conclusion: The results of this study revealed the occurrence of histological and physiological changes in the liver as a result of exposure to lead, and that the drug atropine sulfate played a positive role in the healing process.Key words: Cerebellum, lead acetate, histological changes
Key Words: Liver, Lead Acetate , Atropine Sulfate, Histological and Physiological Effects

Introduction:

Lead is found abundantly in the Earth's crust, with average concentrations of 10-20 mg/kg in the soil. The largest natural sources are volcanic activity and geochemical weathering (1). Volcanoes and related igneous activities redistribute harmful elements (arsenic, beryllium, cadmium, mercury, lead, radon, and uranium) on the Earth's surface. Through the processes of physical and chemical weathering, rocks break down to form the soil on which crops are raised, which constitute the food supply for human and animal consumption. Drinking water moves through rocks and soil as part of the hydrological cycle and

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in the process of leaching elements into the solution. Estimates indicate that natural emissions of lead amount to 19,000 tons. However, processes carried out by humans, such as painting, adding lead to gasoline, manufacturing batteries, etc., are important processes responsible for the environmental presence of lead (1).

Lead has been extracted and used as an industrial raw material for centuries and is considered by chemists to be the oldest metal (2). Its uses include applications in car batteries, sealants in the construction sector (e.g. chimney roofs), and various uses in electrical technology as well as electronic goods (e.g. Welding, glazing for television tubes), weights and bullets, hunting and other applications, and among other uses are the use of lead stabilizers in PVC.

Lead was used in large quantities as an additive to automobile fuel (gasoline) to reduce popping (Antiknock additive), the use of which has decreased due to its danger to the environment and public health, and due to the large quantities of lead emitted into the air resulting from the combustion of fuel, in heating and cooling devices for cars, as well as in the manufacture of metal cans used in food packaging (3).

The liver is the largest gland in the body. They are located in the upper three regions of the abdomen (4). Hepatocytes are arranged in hexagon-shaped lobules (classical lobules) about 2 mm long and 700 μm in diameter. These lobules are clearly defined by thin connective tissue elements (known as the portal tract) in animals such as the pig and the camel. However, due to the scarcity of connective tissue and the close arrangement of lobules in humans, the boundaries of classical lobules can only be approximated (5). Liver cells are involved in the breakdown of drugs, toxins and other proteins foreign to the body (xenobiotics). Many drugs and toxins are not hydrophilic, so they cannot be effectively eliminated from the circulation by the kidneys. The liver converts these substances into more soluble forms (4).

Materials and Methods:

The animal model which used in current study was Rattus norvegicus to observe the effect of lead acetate on cerebellum of the animals. lead acetate was obtained from Lead acetate was obtained from the chemical storeroom at the Department of biology /College of Education for Pure Sciences at Tikrit University. Experimental animals were obtained from Animal House / College of Veterinary Medicine of University of Tikrit and the experiment accomplished in there. 24 adult rat males of the above type were used in this experiment. Their weights were 250-270 g and their age about 10-14 weeks and distributed into four groups.

Lead acetate was use as a causative agent to induce the histological effects, the dose was 12mg/kg/10 days as intraperitoneal injection (6)

Experiment design: Experimental animals were distributed to 3 groups, each group contain 6 animals, As follows:

1. The first group (G1) control group was injected intraperitonealy by distilled water 1 ml/kg body weight for three months .
2. The second group (G2) was injected intraperitonealy by lead acetate 12 g / kg body weight / 10 days for three months (6).
3. The third group (G3) was injected intraperitonealy by lead acetate 12 g / kg body weight / 10 days

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for three months, and then treated by intraperitoneal injection of 0.2 ml/ day of atropine sulfate for 5 days (7).

4. The third group (G3) was injected intraperitonealy by lead acetate 12 g / kg body weight / 10 days for three months, and then treated by intraperitoneal injection of 0.2 ml/ day of atropine sulfate for 7 days (7).

Results:

Histological results: Control Group (G1): The liver tissue contained rows of hepatic cells stacked together, and each cell contained one or two spherical-shaped nuclei of dark pigment. Between the rows of cells were found the blood sinusoids, which contained a few kupffer cells. The hepatic lobule contained in its middle the central vein, into which the blood sinusoids opened.(Figure 1 and 2).

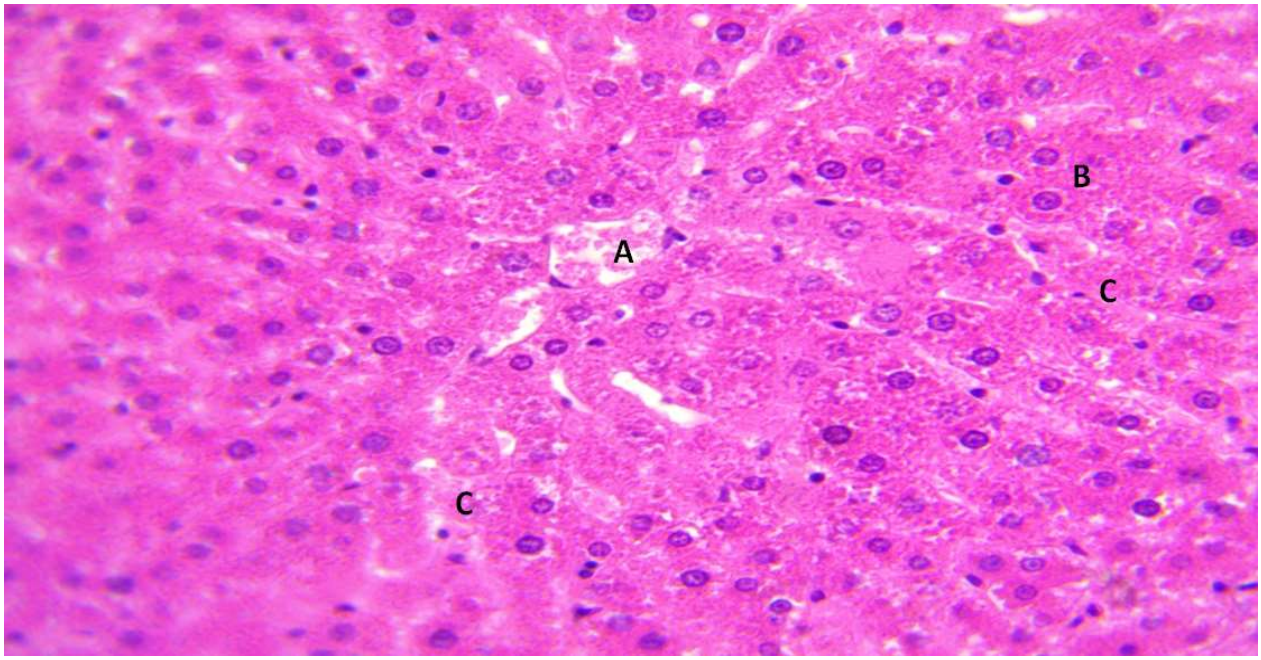

Figure 1 A cross-section of liver tissue of group G1, showing the central vein (A), rows of closely packed hepatocytes (B), and blood sinusoids containing Kupfer cells (C)..(H&E 400x).

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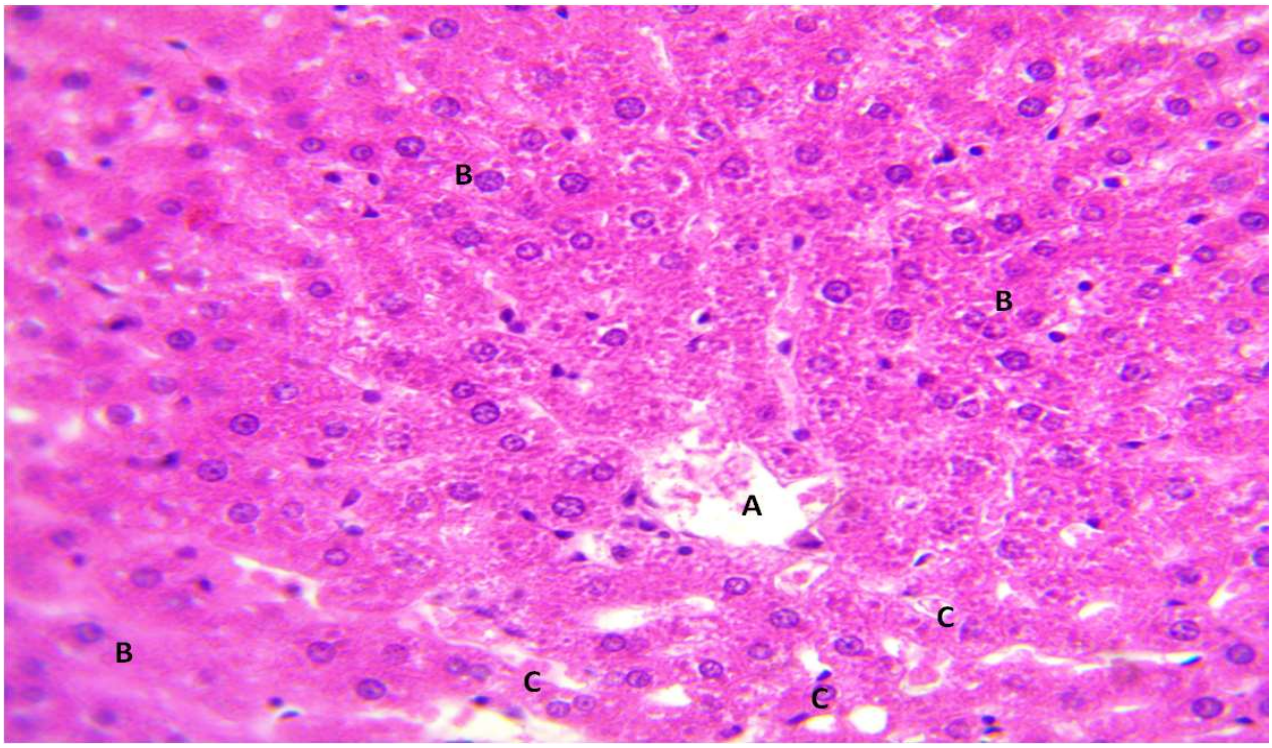

Figure 2 A cross-section of liver tissue of group G1, showing the central vein (A), rows of closely packed hepatocytes (B), and blood sinusoids containing Kupffer cells (C). (H&E 400x).

Lead Group (G2): As for the results of the histological examinations for group G2 and those treated with lead acetate for three months, these results showed liver cells with vacuolar degeneration, pyknosis of a number of cell nuclei, and the disappearance of nuclei from other necrotic liver cells. Blood sinusoids were found in the form of widespread pockets containing dark-colored kupffer cells. The liver capsule is united in the form of loose, loose connective tissue (Figure 3).

Likewise, hepatic tissue cells were found in a compact mass with each other, with widespread vacuolar degeneration of the cytoplasm of these cells and thickening of some of their nuclei. There was a cluster of white blood cells in the form of a sheath around the branch of the small portal vein and the bile duct of the portal region (Figure 4).

The central vein contains decomposed blood clots with the presence of some red blood cells surrounded by a number of white blood cells. Around the central vein, liver cells were found to be excessive in size and closely packed together, and degenerated liver cells were found. The blood sinusoids also appeared narrow and contained a number of Cover cells (Figure 5).

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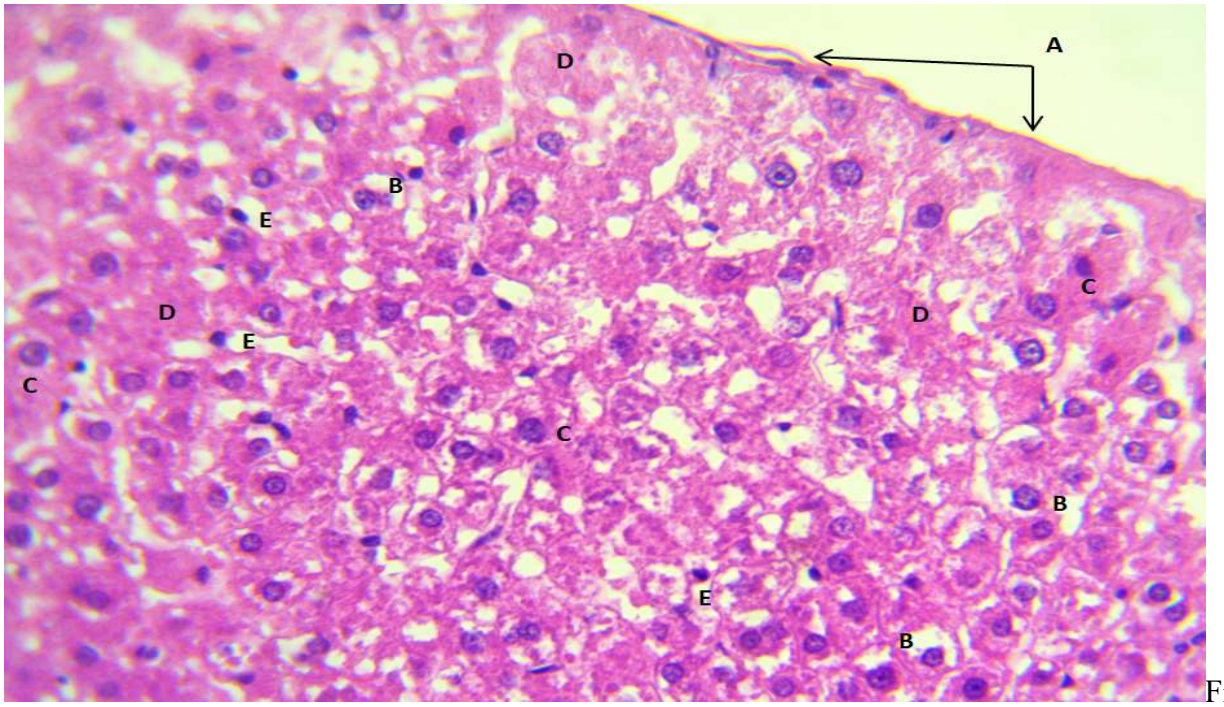

Figure 3 A section of a G2 liver showing a thin liver capsule (A), vacuolar degeneration of hepatocytes (B), thickening of cell nuclei (C), disappearance of cell nuclei (D), and blood sinuses containing Coffer cells (E) (H&E 400x).

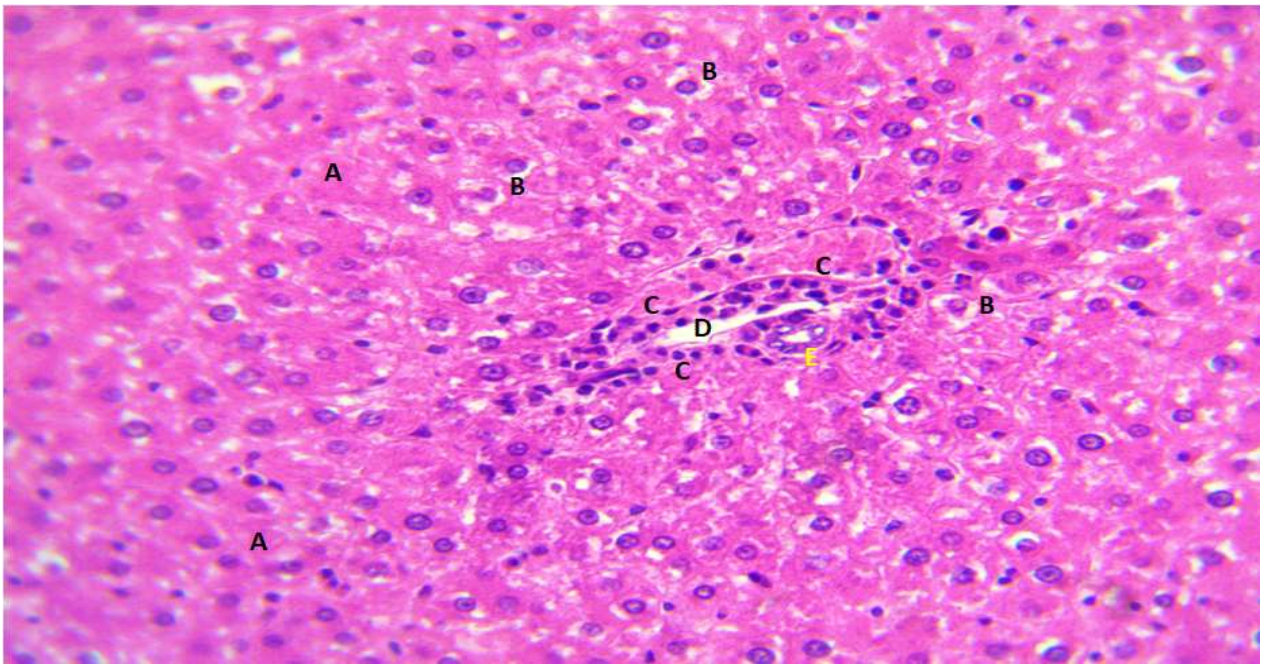

Figure 4 A cross-section of the liver of group G2 shows clumps of hepatocytes tightly packed together (A), vacuolar degeneration in the liver cells (B) with thickening of their nuclei and infiltration of white blood cells in a sheath (C) around the branches of the portal vein (D) and bole duct (E) (H&E 400).

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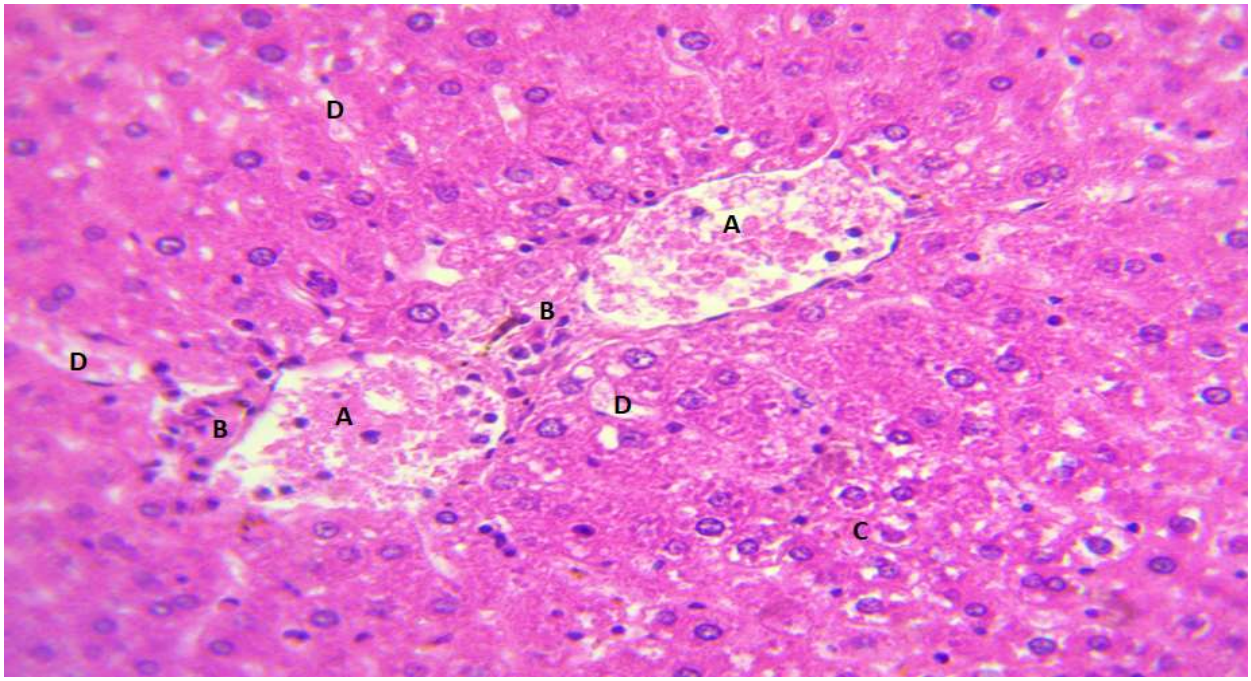

Figure 5 A section of the liver of group G2 showing the central vein with blood clots (A), white blood cells around the central vein (B), degenerated hepatocytes (C), constricted blood sinusoids with Cover cells and red blood cells (D) (H&E 400).

Lead with Atropine 5 Days Group (G3): The histological results of group G3, treated with lead acetate for three months and treated for five days with the drug atropine sulfate, showed a number of changes in the liver tissue, as the liver tissue contained degeneration of numbers of hepatocytes, and in some of those cells there were degenerated nuclei, and the disappearance of the nuclei of other hepatocytes. As for the portal region, it was surrounded by several inflammatory cells of white blood cells surrounding the bile ducts, the branch of the hepatic artery, the branch of the portal vein, and the lymphatic vessel. The presence of normal-shaped hepatic cells interconnected with other cells, including blood sinusoids containing kupffer cells (Figure 6). The presence of vacuolar degeneration of the liver cells (balloon degeneration) appeared, the cytoplasm of the cells contained decomposition and disappearance of a number of nuclei, the blood sinusoids were found in the form of pockets containing kupffer cells, and the periphery of the liver was surrounded by a thin capsule of connective tissue (Photo 7).

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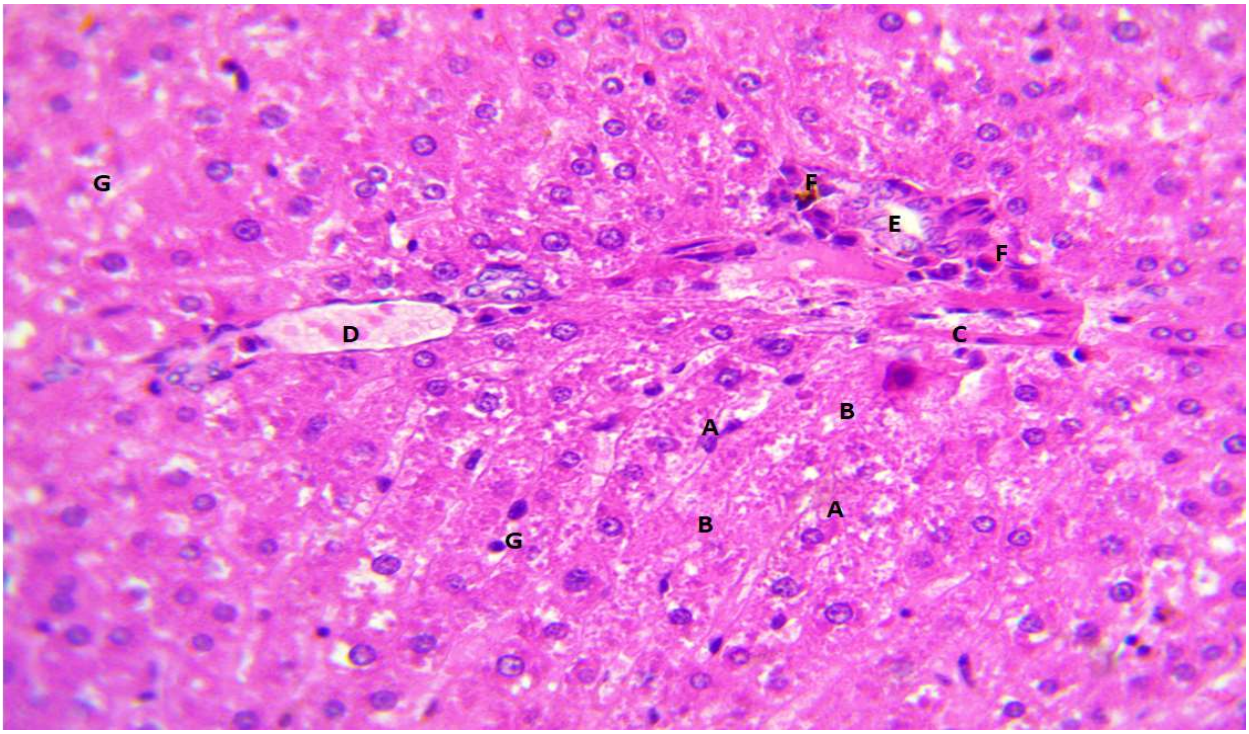

Figure 6 A section of the liver of group G3 showing degeneration of hepatocytes (A), disappearance of the nuclei of some cells (B), blood-congested portal vein branch (C), endovascular vessel (D), bile duct (E), infiltration of white blood cells. (F), kupffer cells (G) in hemosinusoids (H&E 400x).

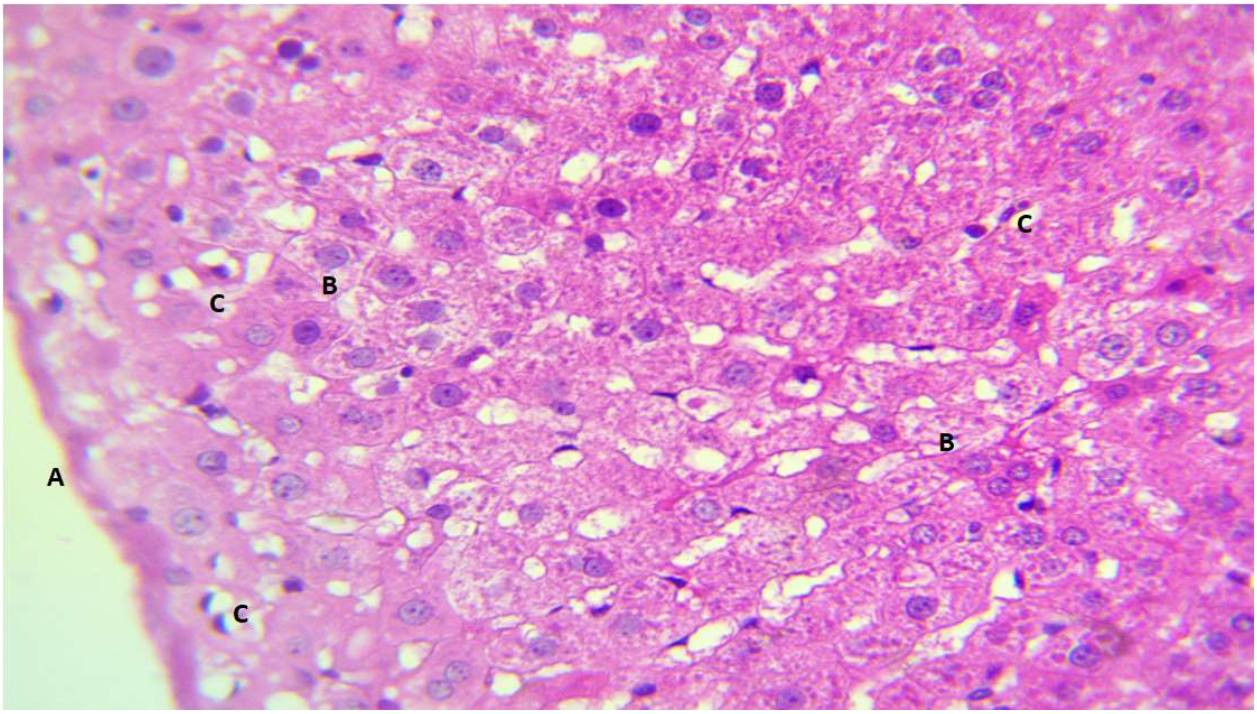

Figure 7 A section of a G3 liver showing a thin liver capsule (A), balloon degeneration of hepatocytes (B) with thickening of the nuclei, blood sinusoids containing kupffer cells (C) (H&E 400x).

Lead with Atropine 7 Days Group (G4): The results of histological examinations for group G4, which

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were treated with lead acetate for three months and the drug atropine sulfate for seven days, showed a number of changes in the liver tissue. These changes were represented by the liver tissue containing focal clusters of white blood cells between the hepatocytes, some of which showed degeneration, the rest of the cell rows. They appeared normal, surrounded by blood sinusoids containing kupffer cells (Figure 8).

The central vein in the hepatic lobule showed decomposed blood with some white blood cells in its lumen. The central vein extended with blood sinusoids filled with enlarged kupffer cells. The hepatic cells were found in folded rows and appeared polygonal, and each cell had two nuclei (Figure 9).

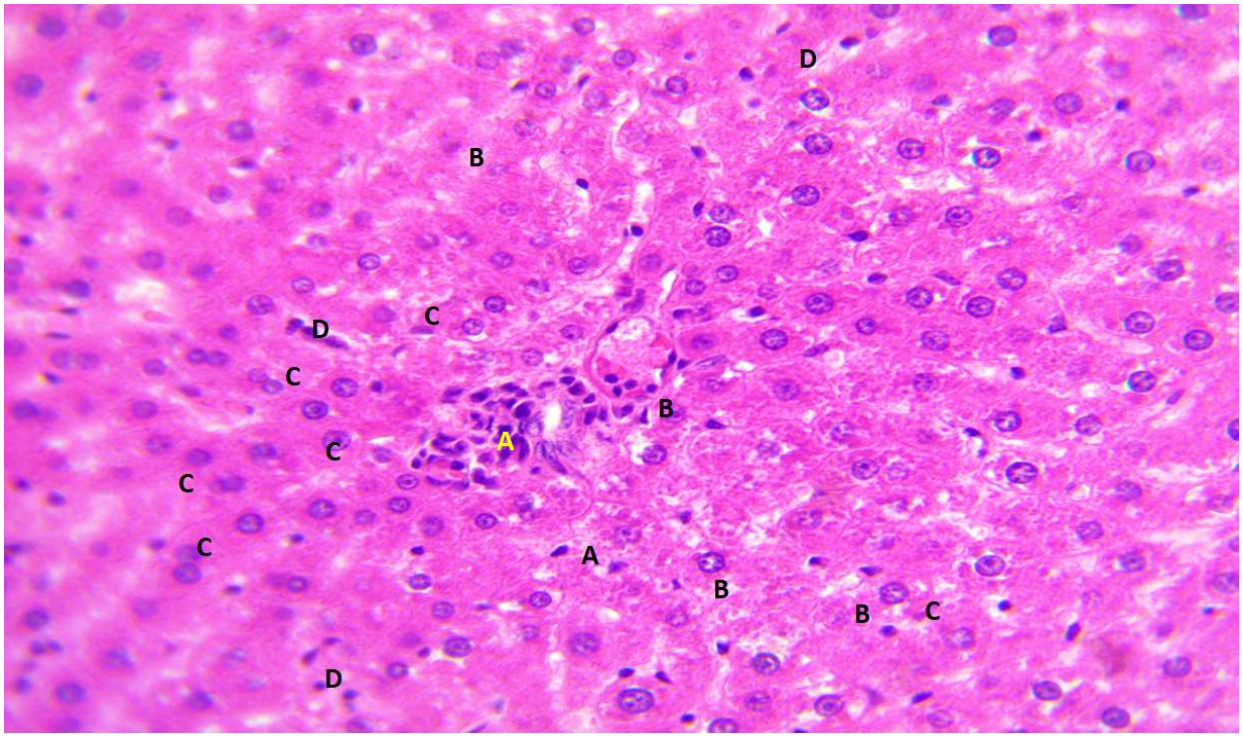

Figure 8 A section of a G4 liver showing focal clusters of white blood cells around hepatocytes (A), hepatocyte degeneration (B), normal hepatocytes (C), and kupffer cells in the blood sinusoids (D) (H&E 400x).

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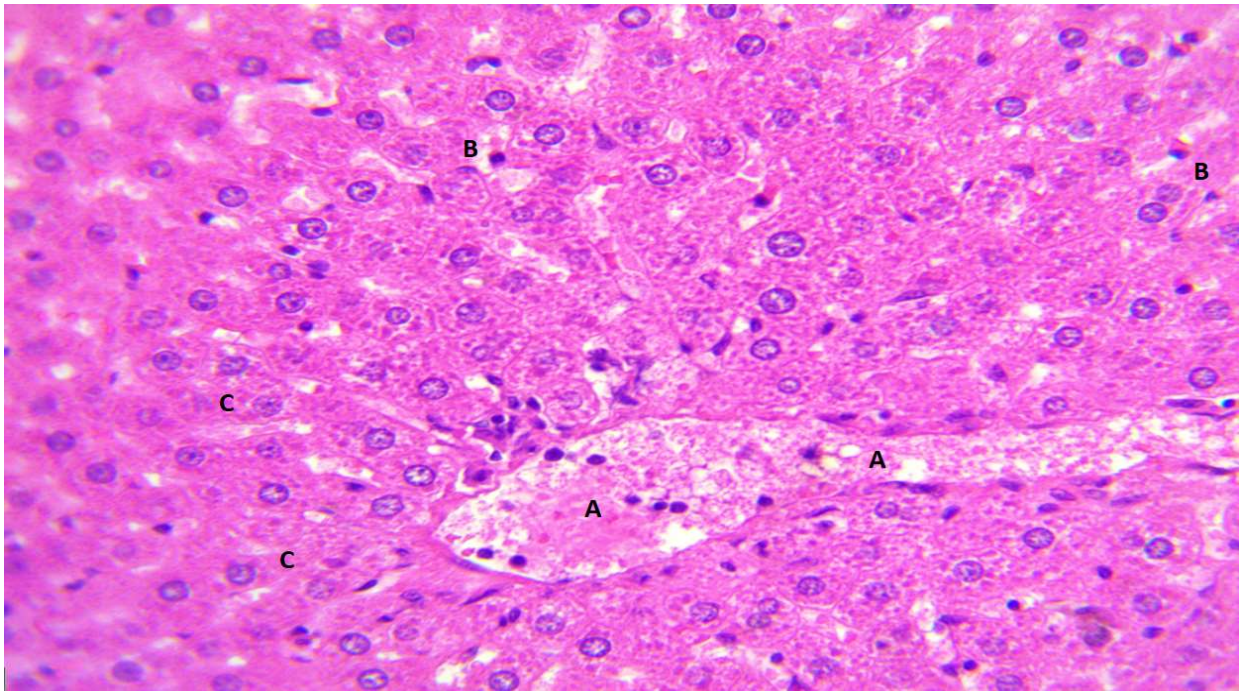

Figure 9 A section of the liver of group G4 shows the presence of hemolysis in the central vein with white blood cells in its lumen (A), enlarged Coffer cells (B) in the lumen of the blood sinusoids, rows of hepatocytes (C) (H&E 400x.

Physiological Results: Diagram (1), it showed the results of lactate dehydrogenase (LDH) of all groups, as it was observed that there was a significant increase in the concentration of the enzyme at a significant level ($p \leq 0.05$) for the group treated with lead acetate (G2), compared to the control group (G1) which was (13.310 ± 0.564) ng/ml, while it was (35.400 ± 4.131) ng/ml for the group treated with lead acetate for three months (G2), while the result was in the group treated with lead acetate for three months and then treated with atropine sulfate for a period Five days (G3) (16.244 ± 0.856) ng/ml, which did not show significant differences from the control group. As for the result of the group treated with lead acetate for three months and treated with atropine sulfate for seven days (G4), it was (14. 873±0.157)ng/ml. It also did not show significant differences from the control group.

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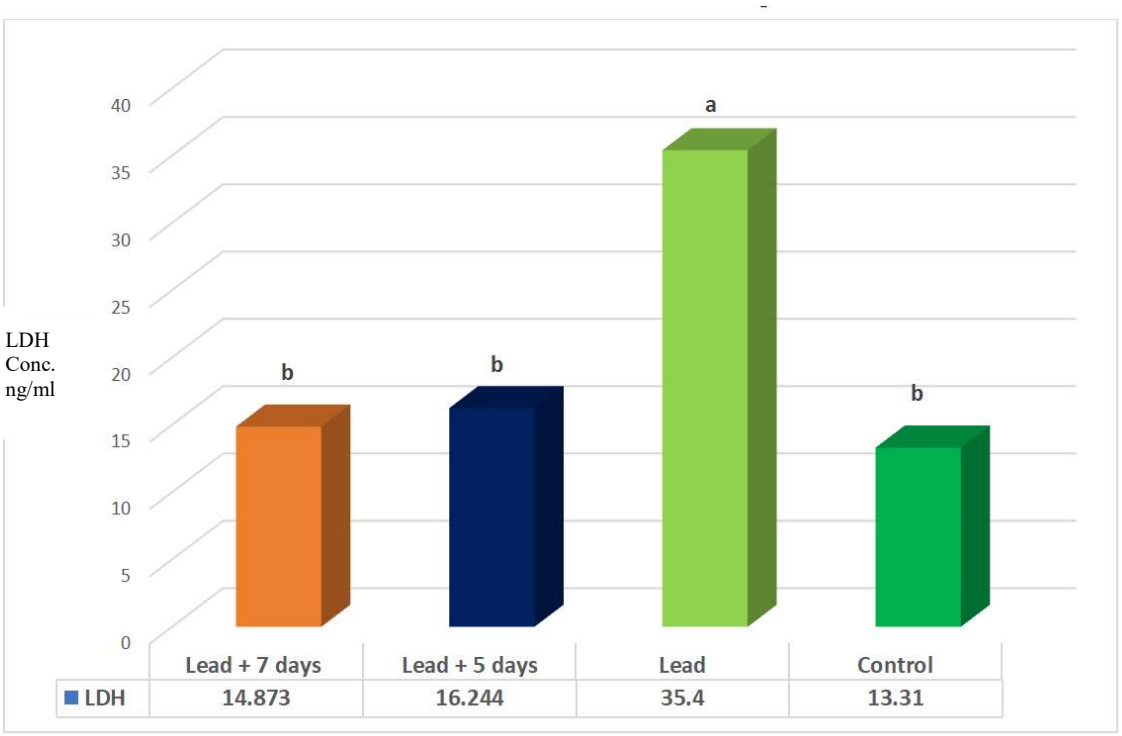

Diagram (1) shows the effect of lead acetate and the drug atropine sulfate on the enzyme lactate dehydrogenase within the third main group . Different letters on the bars mean there are significant differences at a significant level ($p \leq 0.05$).

Diagram (2), showed the results of acid phosphatase (ACP) of all groups, as it was observed that there was a significant increase in the concentration of the acid phosphatase enzyme at a significant level ($p \leq 0.05$) for the groups treated with lead acetate and the drug atropine sulfate compared to the control group. (G1), which was (6.353 ± 0.624) ng/ml, while it was (13.440 ± 0.775) ng/ml for the group treated with lead acetate for three months (G2), while the result was in the group treated with lead acetate for three months and then treated with atropine. Sulfite for five days (G3) (10.794 ± 0.128) ng/ml, while the result of the group treated with lead acetate for three months and treated with atropine sulfate for seven days (G4) was (8.560 ± 0.675) ng/ml.

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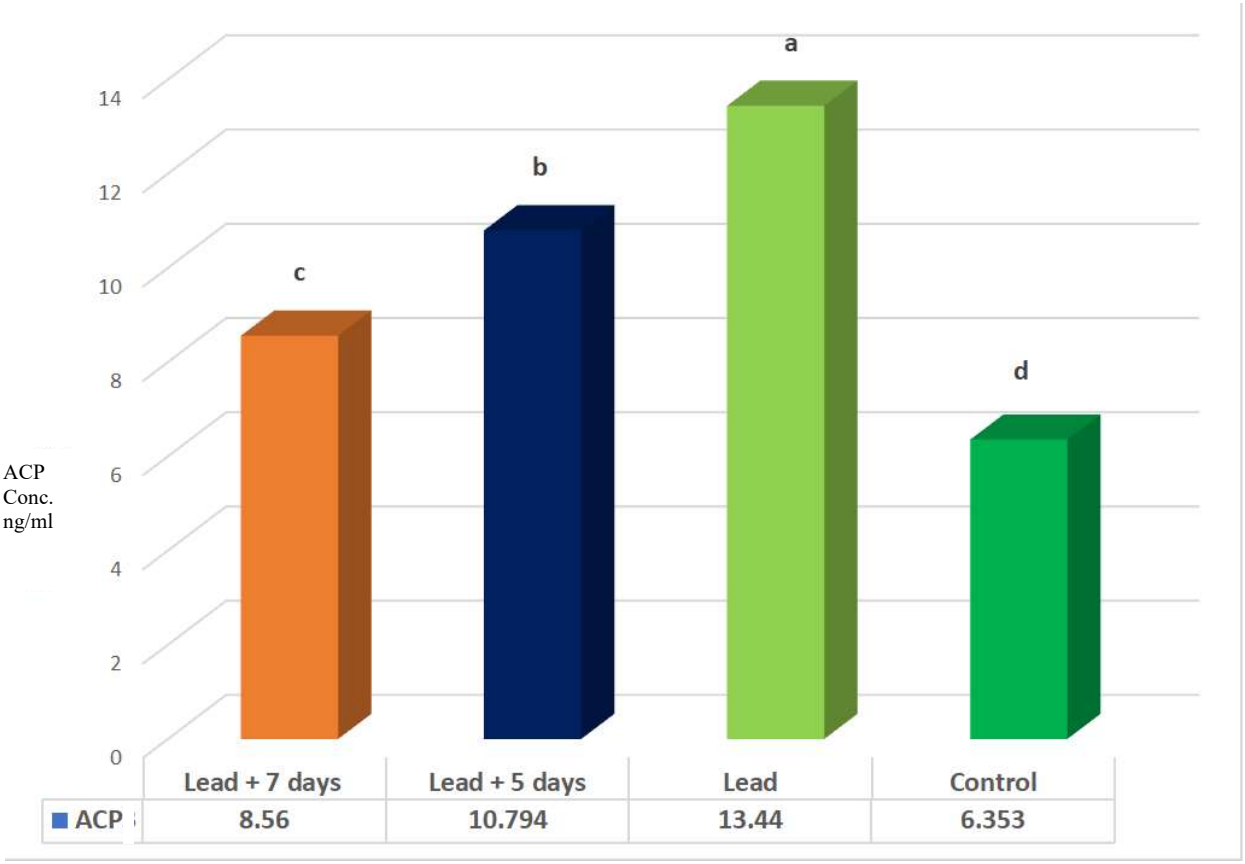

Figure (4-12) shows the effect of lead acetate and the drug atropine sulfate on the acid phosphatase enzyme within the third main group Different letters on the bars mean there are significant differences at a significant level ($p \leq 0.05$).

Discussion

Histology: Previous results agreed with a number of studies, where it was observed that necrosis of liver cells occurred due to chronic exposure to lead, which indicates the oxidative stress placed on these cells through glutathione depletion, and that lymphocyte infiltration and sinusoidal blood suffocation are considered indicators of liver damage (8). Lymphocyte infiltration showed evidence of irritation and inflammation with hypersensitivity to lead, which characterizes the role of neutrophils and mononuclear cells in cytotoxicity in the liver, in addition to central vein congestion (9).

Haouas and his group (8) stated that hepatotoxicity appears in the form of cell vacuolation, which is a cellular defense mechanism against harmful substances to separate these substances into vacuoles and thus prevent them from interfering with the metabolism of those cells, or it may be a result of disturbances in lipids and their metabolism, or it may be caused by a disturbance. Oxidative phosphorylation in mitochondria inhibits the production of ATP, thus causing the failure of the sodium pump that depends on it in the cell membrane, which leads to the accumulation of sodium inside the cells and thus the entry of water into the various cellular parts, which causes swelling of the cells. This appeared in the form of vacuolar degeneration in the cytoplasm of some hepatic cells in the study. current.

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As stated Rateb and Kamal (9) that hepatotoxins resulting from lead exposure work to stimulate the secretion of proinflammatory cytokines such as TNF and IL-1 by Cover cells, as well as recruiting endothelial cells and stellate cells present within the liver tissue to participate in this inflammatory response by producing some Types of cytokines and chemokines to attract circulating immune cells, which increases the amplification of the inflammatory response, and the chemokine released by Cover cells also plays an important role in inflammatory responses as a mediator for the maturation and activation of white blood cells, which explains the increase in the number of Cover cells and their number is directly proportional to the increase in the dosing period, as well as the increase Infiltration of inflammatory and macrophage cells in liver tissue.

Hepatotoxicity caused by lead leads to oxidative stress, inflammation, and liver dysfunction, and the potential effect of atropine sulfate on liver function is less clear, as cholinergic innervation plays a role in regulating hepatic blood flow and metabolism, and atropine sulfate's antagonism to muscarinic receptors can affect these. Operations that may alter liver function and response to damage caused by lead (10).

The potential pathways through which atropine sulfate may act in the liver to mitigate lead toxicity are not entirely clear, and it is possible that modulation of muscarinic receptors in these organs may affect blood flow, metabolism, and perhaps even the removal of lead itself. However, the direct effect of atropine sulfate on The response of these organs to lead poisoning requires further research (11).

The properties of chelation in treatment are mainly due to its ability to form a chelating complex with lead ions to remove them from the body without causing harm. The process of removing toxins by chelation not only cleanses the body, but also strengthens the immune system to fight various diseases in addition to correcting hepatic and renal insufficiency resulting from toxicity. Lead (12).

The results of the current study in confirming the positive role of repair using chelating agents against damage resulting from exposure to lead agreed with what was mentioned (13; 12).

The drug atropine sulfate contains a sulfate group, which is one of the chelating agents (14). Chelation therapy works by binding lead present in the blood and soft tissues such as the brain, liver, and kidneys, and forming a chelator-metal complex, which is non-toxic and has the ability to dissolve in fats, so it can pass through cell membranes and thus can be excreted through urine and bile (10). .

Oxidative stress can be considered one of the main contributing mechanisms to metal toxicity, and it has become logical to include chelation therapy using chelating agents capable of getting rid of heavy metals, especially lead, which has a high affinity for the sulfur group found in the drug atropine sulfate, to restore the affected biochemical variables to their normal state (15).

Therefore, the use of the compound atropine sulfate has shown promising results when used in treating the toxic and harmful effects resulting from lead on the soft tissues of laboratory animals, as it appears that chelation therapy is the most important and basic clinical treatment in all cases of metal poisoning, and that the process of removing a heavy metal is in fact a process. Binding ions or ligand molecules to a central metal atom or ion through a noncyclic or ring-like coordination bond. A ligand is a molecule or ion that contains two or more atoms and can easily donate two electrons to form a covalent bond (16).

Although mercury and lead ions have a higher affinity for the sulfur group and nitrogen group compared to the bonds of the oxygen group, the opposite is the case for calcium atoms. In addition, these

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differences that occur in the presence of affinity are the basic principle in determining the use of the chelating agent. Rezq et al. (17) This is consistent with the results of the current study in reducing the damage resulting from exposure to lead.

Physiology: Lead toxicity to the liver led to a breakdown in its cells and an increase in both the enzymes acid phosphatase (ACP) and lactate dehydrogenase (LDH), which indicates an attempt by the liver to adapt to resist lead toxicity. It can be inferred from the increase in their concentrations in the blood serum (extracellularly) to The presence of functional impairment as well as damage to the cells of these tissues, as lead poisoning led to an increase in the formation of free radicals and active oxygen species. Lead poisoning led to the destruction of liver cell membranes and mitochondrial membranes as a result of oxidative stress and the occurrence of lipid peroxidation, as well as the leakage of these liver enzymes. Its level in blood serum increased. This increase was explained by the concentrations of the two enzymes as a result of the effect of lead on membrane proteins, especially the sulfhydryl (SH) group, which led to a change in the permeability of liver cell membranes, which led to the leakage of these enzymes into the blood (6).

Firoozihahak (18) also confirmed that lead can lead to high levels of the enzyme (LDH) in the blood as a result of lead's ability to cause oxidative attack to change the integrity of the membrane and thus cause a disruption in cell membranes, leading to the enzyme leaking into the blood serum, or it can Lead interferes with heme synthesis, causing hemolysis and the release of hemoglobin, which contains the enzyme (LDH), and ultimately the level of this enzyme in the blood increases.

The drug atropine sulfate contains a sulfate group, which is one of the chelating agents (Altoé et al., 2021). Chelation therapy works by binding lead present in the blood and soft tissues such as the brain, liver, and kidneys to form a chelator-metal complex, which is non-toxic and has the ability to dissolve in fats and thus can pass through cell membranes and thus be excreted through urine and bile (19).

Oxidative stress can be considered one of the main contributing mechanisms to metal toxicity, and it has become logical to include chelation therapy using chelating agents capable of getting rid of heavy metals, especially lead, which has a high affinity for the sulfur group found in the drug atropine sulfate, to restore the affected biochemical variables to their normal state (15).

From what was mentioned above, it can be concluded that the drug atropine sulfate works in two mechanisms. The first is that the atropine part acts as an inhibitor of the action of muscarinic receptors, as it binds to them and prevents them from completing the process of stimulating acetylcholine, and then reduces the resulting nervous activity by reducing the release of acetylcholine (ACH) resulting from lead poisoning. Thus, atropine sulfate helps restore a more balanced environment for neurotransmitters. Neuroinflammation, oxidative stress, and neuronal damage can thus be reduced, as atropine sulfate exerts neuroprotective effects directly or by modifying the neurotransmitter imbalance resulting from the initial exposure. for lead (14). The other mechanism is related to the fact that the sulfate molecule can be considered a chelating agent, as it binds directly to lead to form a stable compound that is easy to excrete through the kidneys and bile duct. Thus, the main pathogen is eliminated, which leads to the end of all side effects that occurred due to the presence of lead in the tissues. Different body types, in addition to liberating self-repair mechanisms and restoring the work of enzymes necessary to catalyze structural reactions in all damaged cells and tissues (19). This explains the return of the levels of these two enzymes (ACP and LDH) to levels close to what they were in the

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control group.

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