

# Microscopic Changes in Spleen and Testis of Male Albino Rats due to Exposure to Sodium Arsenate- an Experimental Study

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## ABSTRACT

**Background:** Arsenic is a recognized environmental toxicant with immunotoxic and gonadotoxic potential. The spleen and testis are particularly vulnerable, and early microscopic changes may precede grossly evident pathology. The present study aimed to assess the time- and dose-dependent effects of sodium arsenate exposure on the gross and microscopic features of the spleen and testes in male albino rats. **Methods:** Male albino rats were divided into control (Group A), moderate-dose (Group B), and high-dose (Group C) arsenic exposure groups. Animals were sacrificed at 4, 8, and 12 weeks for detailed gross and histopathological evaluation of spleen and testis. **Results:** At 12 weeks, Group A remained normal, Group B showed follicular depletion and marginal zone changes microscopically, and Group C displayed splenomegaly, congestion, discoloration, and microscopic red pulp expansion with follicular depletion. For testes, at 4 weeks all groups retained gross and microscopic integrity. At 8 weeks, Groups A and B were unremarkable, while Group C exhibited microscopic derangement despite normal gross appearance. By 12 weeks, Group A remained unchanged, Group B showed reduced size, altered consistency, decreased Leydig cell density, interstitial widening, and seminiferous vacuolization, and Group C demonstrated gross atrophy with vascular congestion, architectural disruption, basement membrane damage, interstitial widening, Leydig cell depletion, and loss of germinal stratification. **Conclusion:** Sodium arsenate induces progressive, dose- and time-dependent damage to the spleen and testes in male albino rats. Microscopic changes precede gross alterations, highlighting the need for histological assessment to detect early arsenic toxicity.

**KEY WORDS:** Arsenic, Spleen, Testis, Albino rats, Histopathology, Toxicity

## Introduction

Heavy metals are naturally associated with the earth's crust and, unlike many organic pollutants, cannot be degraded or destroyed. Their persistence, high toxicity, and bioaccumulative potential enable them to concentrate within organisms and undergo biomagnification through the food chain, making them some of the most severe biological poisons<sup>[1]</sup>. Among these metals, arsenic stands out as one of the most widespread environmental pollutants and a well-recognized human carcinogen, characterized by its complex metabolism and diverse toxic effects<sup>[2]</sup>. Arsenic contamination is a major global environmental concern due to the highly toxic and carcinogenic nature of trivalent arsenic ( $As^{3+}$ , arsenite), which poses serious

implications for the environment, agriculture, and human as well as animal health<sup>[3, 4]</sup>. Human exposure primarily occurs through two major pathways: natural geological sources and anthropogenic activities<sup>[5]</sup>. Among these, atmospheric air, contaminated drinking water, and food are the principal contributors to arsenic entry into the body<sup>[6]</sup>. Industrial applications have also played a significant role, as arsenic has historically been used in wood preservatives, insecticides, fungicides, paints, herbicides, and cotton desiccants. In addition, arsenic-based compounds were once incorporated into livestock feed for pigs and poultry to enhance meat color, increase feed efficiency, and promote growth. However, due to mounting evidence of arsenic's toxicity and associated health hazards, such practices have been increasingly restricted<sup>[7]</sup>. Arsenic exists predominantly in its inorganic forms arsenite ( $As^{3+}$ ) and arsenate ( $As^{5+}$ ) both of which are highly toxic to humans and terrestrial animals<sup>[8]</sup>. Among the various chemical forms of arsenic, sodium arsenate is one of the most commonly encountered inorganic salts, widely used in experimental models to study arsenic-induced toxicity. It is highly soluble, easily absorbed, and capable of inducing systemic toxic effects by generating oxidative stress, impairing cellular respiration, and altering enzymatic

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activities. Prolonged exposure to sodium arsenate has been shown to cause multi-organ damage and among the organs vulnerable to arsenic exposure, the spleen and testes deserve particular attention because of their central roles in immunity and reproduction

The spleen is one of the most important lymphoid organs, functioning as a filter for blood, regulating both innate and adaptive immune responses, and maintaining immune surveillance. Its unique histoarchitecture, composed of red pulp and white pulp, makes it highly susceptible to systemic toxins and inflammatory mediators<sup>[9]</sup>. Arsenic exposure has been reported to cause significant splenic alterations, including congestion, expansion of red pulp chambers, and depletion of lymphoid follicles, which may lead to impaired immune competence, increased vulnerability to infections, and deranged hematopoietic regulation<sup>[10, 11]</sup>. The testis, on the other hand, is a vital organ for male fertility, responsible for spermatogenesis and androgen synthesis. Arsenic exposure has been strongly associated with male reproductive toxicity, disrupting germ cell proliferation and differentiation, impairing Leydig and Sertoli cell function, and inducing structural degeneration of seminiferous tubules. Histopathological changes such as vascular congestion, widening of interstitial spaces, depletion of Leydig cells, vacuolization of tubules, and reduced stratification of germinal epithelium are commonly observed<sup>[12, 13]</sup>. Such alterations not only impair spermatogenesis and reduce fertility potential but may also contribute to long-term endocrine dysfunction. Rodent models, particularly male albino rats, serve as reliable systems for assessing such toxicological effects due to their physiological and pathological resemblance to humans. Evaluating spleen and testis at sequential intervals provides critical information into the temporal progression of arsenic-induced injury. In this context, the present study aimed to observe the gross and microscopic changes in the spleen and testes of male albino rats following sodium arsenic exposure at 4, 8, and 12 weeks, thereby clarifying the dose- and time-dependent relationship between arsenic toxicity, immunological compromise, and reproductive impairment.

## Material And Methods

The present experimental study was carried out in the Postgraduate Department of Anatomy in collaboration with the Postgraduate Department of Pathology, Government Medical College, Srinagar, over a period of 18 months, of which one year was dedicated to experimental work and data collection and six months to compilation, analysis, and report writing. The study was performed on male Wistar albino rats, which were procured from the Central Animal House of Government Medical College, Srinagar. A total of eighteen healthy adult male albino rats, weighing between 180 and 200 grams, were selected for the study. Inclusion criteria

comprised apparently healthy animals within the specified weight range, while those showing lethargy, poor feeding, weight loss, generalized hair loss, diarrhea, or reduced activity were excluded. Ethical approval for the use of experimental animals was obtained from the Institutional Animal Ethical Committee (IAEC/Pharma/MC/19), and all procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

The animals were housed in polypropylene cages of dimensions 44 × 28.6 × 30 cm<sup>3</sup>, lined with dust-free husk as bedding, and maintained under standard laboratory conditions with controlled temperature (18–29°C), humidity (30–70%), and a 12-hour light and 12-hour dark cycle. They were provided with a standard rodent diet and water ad libitum. The rats were acclimatized for one week prior to the start of the experiment, and the principles of Replacement, Reduction, and Refinement (3Rs) were strictly followed.

## Experimental Design:

The rats were divided into three groups of six animals each.

- **Group A (Control):** Received only standard diet and tap water.
- **Group B (Low dose):** Received 50 ppm sodium arsenate (50 mg/L in drinking water) in addition to standard diet.
- **Group C (High dose):** Received 100 ppm sodium arsenate (100 mg/L in drinking water) in addition to standard diet.

The arsenic solutions were prepared fresh each time. Animals were observed daily for any physical or behavioral changes. Sacrifices were carried out at predetermined time intervals of 4, 8, and 12 weeks under chloroform anesthesia, following CPCSEA guidelines.

After sacrifice, dissection was carried out in a designated dissection room under aseptic conditions. Gross examination included assessment of the general appearance, body weight, skin condition, physical activity, and presence of any external lesions or discharges. Following sterilization of the ventral surface with 70% ethanol, a midline incision was made from the lower jaw to the pubic symphysis to access the thoraco-abdominal cavity. Gross observations of the liver, spleen, kidneys, and testes were made, after which the spleen and testes were dissected out, rinsed in normal saline, and fixed in 10% neutral buffered formalin for histopathological evaluation.

For microscopic analysis, tissue specimens were cut into approximately 5 mm thick pieces and placed in tissue capsules labeled with organ name and group number. These were fixed in 10% formalin for 7–10 days, washed

in tap water, and subjected to dehydration through ascending grades of alcohol (50%, 70%, 90%, and absolute alcohol), followed by clearing in two changes of xylene. Paraffin wax embedding was carried out at 58–60°C, with tissues left overnight for complete impregnation, and blocks were prepared using L-blocks. Sections of 6–8 µm thickness were obtained using a rotary microtome, floated in a warm water bath to remove wrinkles, and mounted on slides coated with egg albumin.

The mounted sections were stained using Harris’s Hematoxylin and Eosin. Hematoxylin imparted a blue to black coloration to nuclei, while eosin stained the cytoplasm pink and red blood cells bright red. Following dehydration through graded alcohols, clearing in xylene, and mounting in DPX, the slides were examined under a light microscope, and representative photomicrographs were taken for documentation. Gross and microscopic changes in the spleen and testes were systematically recorded for each group at 4, 8, and 12 weeks, enabling assessment of the dose- and time-dependent effects of sodium arsenate exposure on these organs.

## Results

**Table 1: Gross and Microscopic Changes in Spleen after Arsenic Exposure**

Time Point	Group A (Control)	Group B (Moderate Exposure)	Group C (High Exposure)
4 weeks	Gross: Normal size, texture, color. Microscopy: Normal splenic architecture.	Gross: Normal. Microscopy: Normal.	Gross: Normal. Microscopy: Altered level of compartments.
8 weeks	Gross: Normal size, texture, color. Microscopy: Preserved architecture.	Gross: Normal. Microscopy: No significant change.	Gross: Normal. Microscopy: Increased red pulp chamber.
12 weeks	Gross: Normal size, texture, color. Microscopy: No change.	Gross: Normal. Microscopy: Depletion in size & number of lymphoid follicles; marginal zone noted.	Gross: Enlarged, congested, discolored. Microscopy: Increased red pulp chamber, decreased lymphoid follicle density around central arteriole.

At 4 weeks, the spleen in Group A and Group B showed no gross or microscopic alterations, with preserved

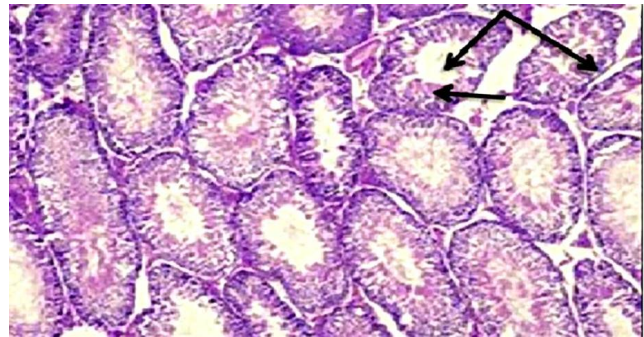
architecture. In Group C, the spleen appeared grossly normal, but microscopic examination revealed altered compartmental organization. At 8 weeks, the spleen in Group A remained normal in gross and microscopic appearance. Similarly, Group B did not show any significant changes. In Group C, while the gross morphology was preserved, microscopic evaluation demonstrated an increase in the red pulp chambers. At 12 weeks, the spleen in Group A continued to maintain normal size, texture, and histological integrity. In Group B, the spleen was grossly unremarkable but microscopically revealed depletion in the size and number of lymphoid follicles along with marginal zone changes. In Group C, the spleen was enlarged, congested, and discolored on gross examination, with histology showing expansion of red pulp chambers and decreased density of lymphoid follicles surrounding the central arteriole [Table. 1], [Fig. 1] & [Fig. 2].

**Table 2: Gross and Microscopic Changes in Testis after Arsenic Exposure**

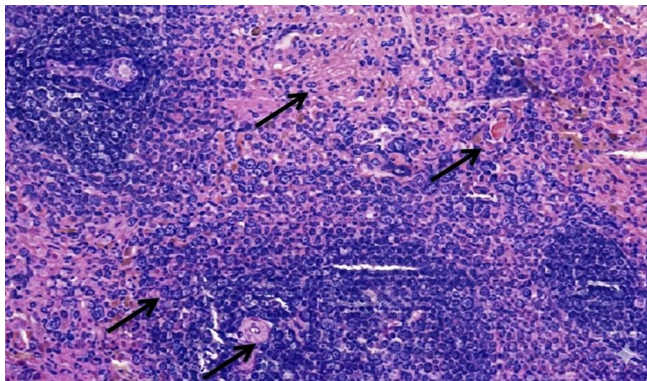
Time Point	Group A (Control)	Group B (Moderate Exposure)	Group C (High Exposure)
4 weeks	Gross: Normal size, texture, color. Microscopy: Preserved histological architecture.	Gross: Normal. Microscopy: Basic architecture preserved.	Gross: Normal. Microscopy: Preserved architecture.
8 weeks	Gross: Ovoid, whitish-blue, within normal limits. Microscopy: No significant change.	Gross: Normal. Microscopy: Basic architecture preserved.	Gross: Normal. Microscopy: Deranged histoarchitecture.
12 weeks	Gross: Normal. Microscopy: No significant changes.	Gross: Reduced size, altered consistency. Microscopy: Decreased Leydig cell density, widening of interstitial spaces, vacuolization of tubules.	Gross: Atrophy observed. Microscopy: Vascular congestion, deranged architecture, basement membrane disruption, interstitial widening, Leydig cell depletion, reduced stratification of spermatozoa.

At 4 weeks, the testes in Group A and Group B appeared grossly normal with preserved histoarchitecture. In Group C, the gross features were also within normal limits, and microscopic examination demonstrated intact histological structure. At 8 weeks, the testes in Group A

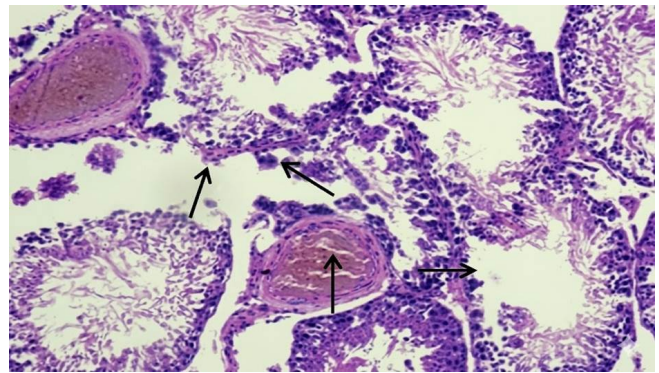
showed normal gross appearance and preserved histology. In Group B, the gross size, weight, and color remained normal, and the basic architecture was retained. In Group C, while the testes appeared grossly normal, histological analysis revealed deranged architecture. At 12 weeks, the testes in Group A did not exhibit any significant gross or microscopic alterations. In Group B, a reduction in testicular size and altered consistency were noted grossly, while histology showed decreased Leydig cell density, widening of interstitial spaces, and vacuolization of seminiferous tubules. In Group C, the testes exhibited gross atrophy, and microscopic examination revealed vascular congestion, architectural disruption, basement membrane damage, widening of interstitial spaces, depletion of Leydig cells, and reduced stratification of germinal epithelium [Table. 2], [Fig. 3] & [Fig. 4].



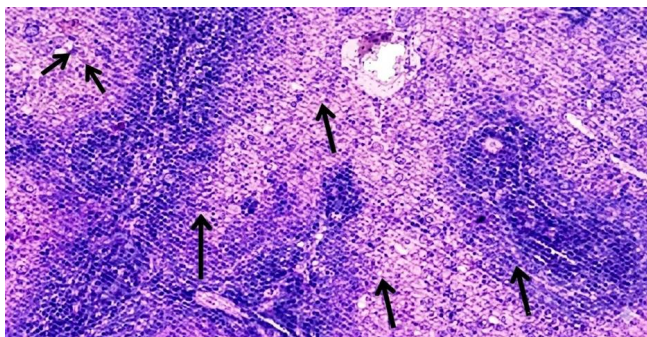
**Fig. 3: Microphotograph of the Testis from Group C at the end of 8 Weeks Showing deranged architecture of seminiferous tubules with distortion and increase in interstitial space. (Stain: H&E Magnification: 40x)**



**Fig. 1: Microphotograph of the Spleen from Group A at the end of 4 Weeks showing lymphoid follicles along with central artery surrounded by red pulp. (Stain: H&E Magnification: 40x)**



**Fig. 4: Microphotograph of the testis from Group C at the end of 12 Weeks Showing congestion of vessels, deranged architecture, basement membrane disruption, widening of interstitial spaces, depletion of Leydig cells and decreased stratification of spermatogonia. (Stain: H&E Magnification: 100x)**



**Fig. 2: Microphotograph of the Spleen from Group C at the end of 12 Weeks Showing increased in the Red pulp chamber and decreased density of lymphoid follicles surrounding central arteriole Stain: (H&E Magnification: 40x)**

## Discussion

The present study demonstrated a clear time- and dose-dependent pattern of arsenic-induced splenic alterations in male albino rats. At 4 weeks, Group A and Group B showed preserved gross and microscopic architecture, whereas Group C already exhibited microscopic disorganization of splenic compartments despite a grossly normal appearance. By 8 weeks, Group C displayed expansion of red pulp chambers on histology, while the gross morphology remained unchanged. At 12 weeks, Group B revealed depletion in the size and number of lymphoid follicles along with marginal zone changes, whereas Group C exhibited gross enlargement, congestion, and discoloration, with histological evidence of red pulp expansion and reduced density of lymphoid follicles surrounding the central arteriole. These observations highlight that arsenic toxicity in the spleen progresses in a sequential manner, where microscopic changes precede gross alterations, and severity increases

with both dose and duration. Our findings are consistent with the work of Yan *et al.*, who reported that chronic arsenic exposure induces a time-dependent modulation of splenic inflammation and immunosuppression, characterized by early inflammatory changes followed by histological disorganization and functional decline<sup>[14]</sup>. Similarly, Barai *et al.*, demonstrated splenic enlargement and red pulp disruption in mice exposed to arsenic, with the changes becoming more pronounced with prolonged exposure<sup>[15]</sup>. In agreement with our findings, Soria *et al.*, also observed that arsenic bioaccumulation in the spleen leads to enzymatic disturbances, oxidative stress, and depletion of lymphoid elements, thereby explaining the follicular atrophy and marginal zone alterations evident in our Group B and Group C rats at later time points<sup>[16]</sup>. The expansion of red pulp and depletion of lymphoid follicles seen in our high-dose group at 12 weeks parallels the histopathological findings described by Al-Forkan M *et al.* and Burchiel *et al.*, who emphasized that arsenic exposure adversely affects splenic immune parameters, including lymphoid tissue integrity and extramedullary hematopoiesis<sup>[17, 18]</sup>. Mechanistically, oxidative stress and apoptosis of splenocytes have been suggested as the primary drivers of arsenic-induced injury. In this regard, Yan *et al.* (2020), Zhao *et al.* and Soria *et al.*, highlighted that chronic arsenic exposure disrupts redox balance and triggers lymphocyte apoptosis, leading to progressive immune dysfunction and structural disintegration of splenic tissue<sup>[14, 15, 19]</sup>. Furthermore, the dose-dependent nature of our findings, with milder alterations in Group B compared to the severe changes in Group C, aligns with the observations of Yokohira *et al.* (2008), who reported that both the severity and onset of arsenic-induced tissue injury are closely related to the administered dose<sup>[20]</sup>. This dose-time interaction explains why follicular depletion was confined to Group B only at the 12-week interval, while Group C manifested gross splenomegaly and severe microscopic derangements. In nutshell, our study corroborates existing literature that arsenic exposure produces progressive, dose-dependent splenic toxicity. The sequential pattern observed ranging from early compartmental disorganization to follicular depletion and red pulp expansion suggests that the spleen is highly sensitive to arsenic-induced oxidative and immunotoxic stress. These findings also emphasize the importance of microscopic evaluation for detecting early changes, which may precede overt gross abnormalities.

In the present study, the testes showed no gross or microscopic abnormality at 4 weeks across all groups. By 8 weeks, the high-dose group (Group C) already exhibited microscopic derangement despite preserved gross appearance, and by 12 weeks both moderate (Group B) and high (Group C) exposure produced progressive pathology, reduced testicular size and altered consistency in Group B and frank atrophy with extensive histological damage in Group C. This time- and dose-

dependent progression, in which early microscopic changes precede later gross atrophy, has been consistently described in experimental models of inorganic arsenic toxicity. Jana *et al.* observed that arsenic exposure in adult rats led to germ-cell degeneration and impaired androgen production, emphasizing that microscopic tubular injury can precede gross testicular shrinkage<sup>[21]</sup>. Similarly, Kaushal *et al.*, in their study on postnatal sodium arsenate exposure, reported vacuolization of seminiferous tubules, perturbation of Sertoli and Leydig cells, and impaired spermatogenesis, findings closely comparable to the vacuolization, interstitial widening, and loss of germinal stratification documented in the present 12-week high-dose group<sup>[22]</sup>. Histopathological hallmarks recorded in our 12-week specimens, vacuolization of seminiferous epithelium, widening of interstitial spaces, depletion of Leydig cells, basement membrane disruption, and loss of orderly germinal stratification have been repeatedly described across sodium-arsenite studies. For instance, Ahmad I *et al.*, reported a significant decrease in seminiferous tubular diameter, thickening of basement membrane, early arrest of spermatogenesis, damaged Leydig cells, and overall testicular atrophy following high-dose arsenic exposure, while Pachnanda *et al.*, documented dose-dependent destruction of testicular histoarchitecture, including complete arrest of spermatogenesis, disfigured seminiferous tubules, absence of spermatids in tubular lumens, distortion of germinal epithelium, interstitial edema, and damage to Sertoli and Leydig cells, which is akin to our study<sup>[23, 24]</sup>. These observations reinforce the reproducibility of testicular lesions in arsenic toxicity models. Mechanistic studies provide information into these pathological alterations. Aitken R *et al.* demonstrated that arsenic induces oxidative stress in testicular tissue, depleting antioxidants and increasing lipid peroxidation, which in turn triggers mitochondrial dysfunction and apoptosis in germ cells<sup>[25]</sup>. Additional work by Yilmaz B *et al.* showed that arsenic disrupts Leydig cell function and reduces testosterone synthesis, while exposing testicular tissue to apoptotic and degenerative changes<sup>[26]</sup>. These findings explain the Leydig cell depletion, interstitial widening, and architectural collapse observed in our 12-week moderate- and high-dose groups. Furthermore, Sun H *et al.*, reviewed arsenic's interference with the hypothalamic pituitary gonadal axis, adding another mechanistic layer to explain the reproductive decline<sup>[27]</sup>. The temporal dissociation between early microscopic injury and later gross atrophy observed in this study is supported by previous work. For example, Singh *et al.* reported that histological abnormalities such as germinal epithelial vacuolization and spermatogenic arrest appear before significant reductions in testicular weight or gross atrophy become apparent<sup>[28]</sup>. This observation highlights that reliance solely on gross morphology may underestimate the extent of early arsenic-induced reproductive toxicity.

The observed splenic/ testicular alterations can be reasonably attributed to sodium arsenate exposure, as other potential contributory factors were carefully minimized. All animals were age-matched, maintained under identical housing, dietary, and environmental conditions, and were free from clinical illness or stress-related exclusion criteria. The absence of comparable splenic/ testicular changes in the control group across all time points further excludes handling stress, nutritional deficiency, infection, or procedural artifacts as causes, thereby strengthening the causal association between arsenic exposure and the documented splenic histopathological changes.

## Conclusion

The present study demonstrated that arsenic exposure produces progressive alterations in both the spleen and testes of male albino rats, with microscopic changes often preceding gross abnormalities. In the spleen, early exposure was associated with subtle histological changes, while prolonged exposure led to congestion, discoloration, and architectural disruption, suggesting impaired immune function. Similarly, the testes exhibited a sequence of changes beginning with preserved gross morphology but early microscopic vacuolization and disorganization of seminiferous tubules. With extended exposure, these changes progressed to reduced testicular size, loss of Leydig cells, depletion of germinal epithelium, vascular congestion, and gross atrophy. The findings indicated that arsenic has both immunotoxic and gonadotoxic effects, which intensify with longer durations of exposure. Importantly, the study underscored that microscopic alterations appear much earlier than visible gross changes, making histopathological evaluation critical for detecting early organ damage induced by arsenic toxicity.

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