

## **Types of chromosomal abnormalities caused by chemotherapy cyclophosphamide in mice (*Mus musculus L.*)**

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**Received: -March, 4, 2022; Accepted: March. 31, 2022 ; Available Online March 31, 2022**

### **Abstract**

The current study was designed to study the genetic effects of *Mus musculus L.* on male and female laboratory mice. The study included the following: Cyclophosphamide's effects on chromosomal changes in bone marrow cells and testes, as well as a study of Cyclophosphamide's effects on the mitotic index of bone marrow cells and germ cells (testes). Cyclophosphamide dosing resulted in a (0.006mg/kg body weight) for 30 days . Chromosomal changes appear in bone marrow cells (chromatid gap, chromatid break, centromere gap, ring chromosomes, centromere break, deletion) within a statistically significant difference (0.004). Cyclophosphamide also led to the occurrence of chromosomal changes in testicular cells (chromatid gap, centromere break, centromere gap, ring chromosomes, polyploidy) at a statistically significant difference (0.046). The results of the study also showed that the activity of cyclophosphamide caused a significant decrease in the mitotic index of bone marrow cells at the duration of the dose . at a statistically significant difference (0.016). For calculating the mitotic factor of the germ cell (testes), the results showed a decrease in the dose while there were no significant differences ( $p \geq 0.05$ ).

**Keywords:** laboratory mice, Cyclophosphamide, mitotic index, Chromosomal changes.

## Introduction

Chemotherapy concepts :

Chemotherapy (chemo means the chemistry and therapy means the treatment) is a cancer treatment that uses anticancer drugs as part of the protocol. Chemotherapy may be given alone or in combination with other drugs to decrease clinical signs and prolong life. Chemotherapy is one of the major categories of drugs that are specifically for treating cancer and autoimmune diseases (1). Use of drugs, chemotherapy, hormonal therapy or targeted therapy systemically for the tumor by getting it into the blood flow to reach the cancer site, Chemotherapeutic agents are cytotoxic due to their interfering with cell division (mitosis), so they are used to treat cancer. Chemotherapy can cause cell stress or cell death. Many reports show that chemotherapy's side effects include damage to normal cells, particularly those that divide rapidly, such as bone marrow cells, hair follicles, and the digestive tract. The chemotherapy drugs are used for the treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, vasculitis, and systemic lupus erythematosus (2-3). Chemotherapy can cause side effects. The chemotherapy drugs kill the cancer cells and have side effects on the healthy normal

cells such as skin cells, blood cells, and stomach cells. The most common side effects of using chemotherapy drugs include feeling tired, hair loss, infections, mouth dryness, itchy skin, constipation, or diarrhea (4). Types of chromosomal abnormalities caused by chemotherapy consist of numerical and structural abnormalities. The numerical abnormalities involve aneuploidy and chromosome instability, produced by segregation errors of the chromosome within the mitosis stages. While the structural abnormalities are included the destruction of the genetic Abnormalities of the structural chromosome: deletion or amplification of the chromosome are the most common structural chromosome abnormalities, occurring in 88% of cancer samples. Theodor Boveri was the first to find that chromosomal abnormalities were associated with cancer(5). The chromosome abnormalities could regulate cellular division by changing the function of proteins and RNA(6 - 7). The proliferation of the tumor cells can affect the immune system and has been associated with chromosome abnormalities. The proliferation of the tumor cells can affect the immune system and has been associated with chromosome abnormalities(8 - 9).The deletion or amplification of some genes, or

chromosome rearrangements, forms the genome and influences tumor progression and prognosis(7,10). Numerical and structural chromosomal defects cause genomic instability (11). Anomalies of the numerical chromosome include chromosome instability and aneuploidy characterized by chromosome gain or loss (12). Nearly 90% of cancer cases show loss or gain of at least one chromosome (13). Abnormalities of the structural chromosome are caused by genetic material damage to varying degrees, ranging from deletions of the chromosome arm-level or amplifications to changes of many chromosomes(14). The structural chromosomal abnormalities include deletions, amplifications, and unbalanced translocations, while abnormalities of the structural chromosome include heterogeneity(15). The new studies showed that chromosome abnormalities could play a role in the cases of repeated fetal abortion (16). Studies about spermatozoa in humans are minimal, but many genetic reports on animals show the process's negative effects in humans, chemotherapy drugs and radiation are used together to treat cancer and cause a high percentage of mutations within the spermatogenesis after seven to fourteen days after administration of the chemotherapy drugs(14). The

antimetabolites, nucleoside analogues, and bleomycin have mutagenic effects on spermatogenesis several weeks after use (17). Chemotherapy causes cell division to be disrupted. The nucleus is a black glob in the middle of each live cell. The nucleus is the cell's command center. It is made up of chromosomes, which carry genes. Each time a cell divides into two to produce new cells, these genes must be replicated exactly. Chemotherapy causes the genes in the nucleus of cells to be damaged, Some medicines cause harm to cells when they divide. Some cells cause harm to the other cells as they duplicate all of their genes before splitting. Chemotherapy has a lower risk of harming cells that are dormant, such as most normal cells. At various phases of the procedure, a combination of chemotherapy medicines will induce cell destruction (18,19). The aim of the research is to Investigating the effects of cyclophosphamide treatment on chromosomal integrity in bone marrow and germ cells Calculating the mitotic index of bone marrow cells and germ cells (testes).

## **Materials and methods**

The experimental animals:

The animals were divided into two main groups: the first group consists of 12 mice

,6 males to weighed  $\pm 33$  gm and 6 females weighed  $\pm 25$  gm , at 8 weeks of age,, was the treated group to cyclophosphamide at a dose of 6 micg./kg body weight [Endoxan/ Germany ] for 30 days before mating, while the second group was the non-treated animals called the control group consists of 12 mice (6 males,6 females) , at 8 weeks of age, the males weighed  $\pm 33$  gm , the females weighed  $\pm 25$  gm. The mice were treated orally with gavage tube Cyclophosphamide (0.3cc) while the control animals were administered distilled water.

#### **Dissection of animals:**

Animals (males and females) were anesthetized by inhalation of chloroform, killed and dissected to collect the target tissues in the present study: bone marrow for males and females and sperm cells for male mice. Preparation of chromosomes from mouse bone marrow according to (20), preparation of chromosomes from spermatogonial cells according to (21). And then calculation of the mitotic coefficient of cells (mitotic index) according to (22).

#### **Statistical analysis**

To analyze the study data, SPSS software, version 24, was used. Quantitative data were presented in terms of mean $\pm$  standard

deviation, while qualitative data were presented in absolute numbers and percentages. Quantitative data were investigated for normality of distribution. To investigate the statistical significance of differences in quantitative data, student t-test was used; to investigate associations between qualitative data, Chi<sup>2</sup>test was used; and correlations between quantitative variables, Pearson's correlation test was used. A p-value of less than 0.05 was considered statistically significant.

## **Results**

### **The effect of cyclophosphamide on chromosomal changes in male and female somatic cells (bone marrow) in *Mus musculus L.***

As indicated in the table (1), structural chromosomal changes occurred, represented by the appearance of (chromatid gap, chromatid break, centromere gap, and ring-chromosomes) in the somatic cells (bone marrow) of male and female mice *Mus musculus L.*, as a result of treatment with cyclophosphamide in a dose (0.006 mg/kg body weight) for 30 days, compared with the group of control animals in Figure 1. As shown in Figures 2,3,4,5 ,The results showed that the two types of chromosomal

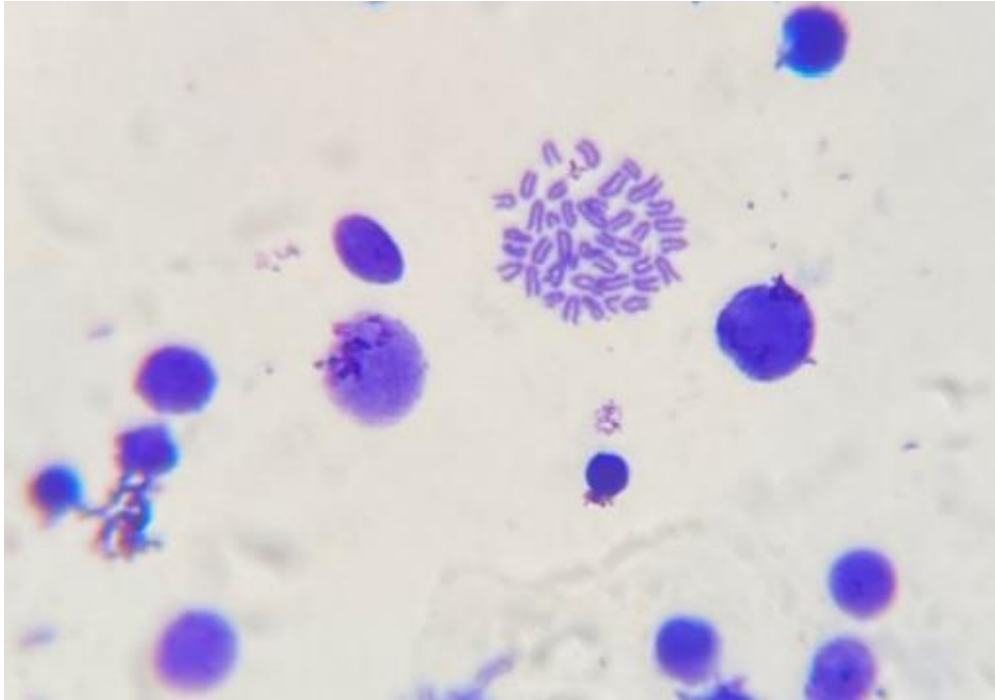
changes, chromatid gap and chromatid breakage, are the most common types of chromosomal changes, while ring-chromosomes are less common in bone marrow cells, and the statistical analysis showed that their incidence is greater in females than in males . Statistical analysis and comparison between the treated groups and the control group showed a significant increase in the percentage of chromosomal abnormalities of laboratory animals treated with cyclophosphamide at a dose of 0.006

mg/kg body weight for 30 days, with a statistically significant difference ( $p \leq 0.05$ ) Table (2). The statistical analysis did not show a significant difference when comparing by sex (male and female) in the percentage of chromosomal abnormalities in the bone marrow of experimental animals treated with cyclophosphamide for treatment groups.

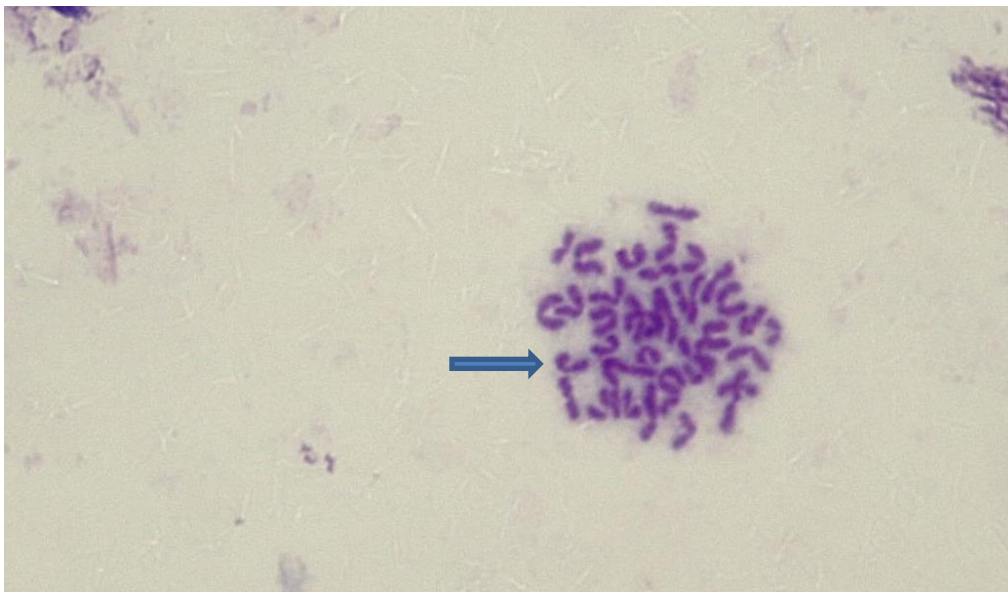
**Table 1: The percentage types of chromosomal changes in bone marrow cells of the male and female mice treated by cyclophosphamide N=12**

type of chromosomal	chromatid gap %	chromatid break %	centromere break %	Polyploidy %	centromere gap %	ring chromosome %	Deletion %
<b>Treatment control (Male)</b>	66.7	0.0	0.00	0.00	0.00	0.00	0.00
<b>control (Female)</b>	66.7	33.3	0.00	0.00	0.00	0.00	0.00
<b>Treatment (Male &amp; Female)</b>	66.7 a	66.7 a	0.00	0.00	50.0	33.3 b	0.00
<b>Treatment (Male)</b>	33.3	33.3	0.00	0.00	33.3	33.3	0.00
<b>Treatment (Female)</b>	100.0 a	100.0 a	0.00	0.00	66.7	33.3 b	0.00

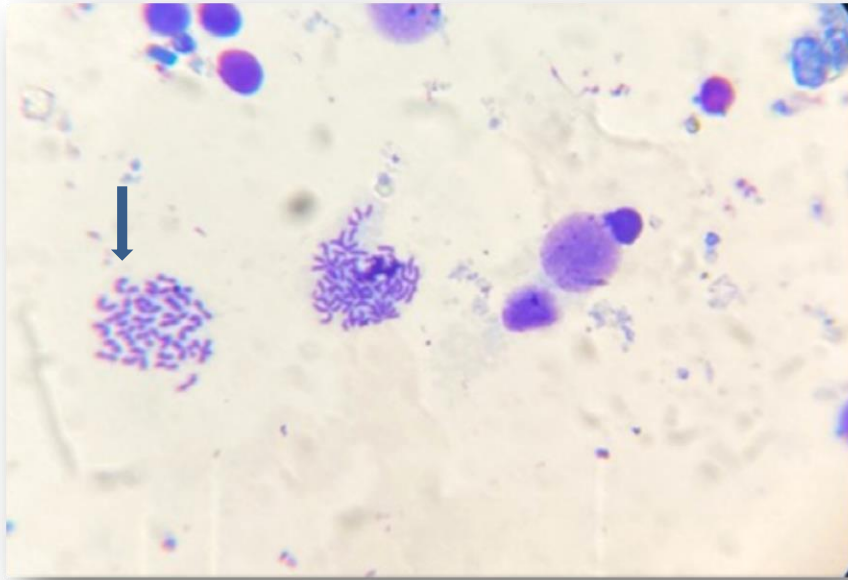
Significant differences at the ( $p \geq 0.05$ ) level are denoted by values in tiny letters. \*\* Highest value(a),less value(b),



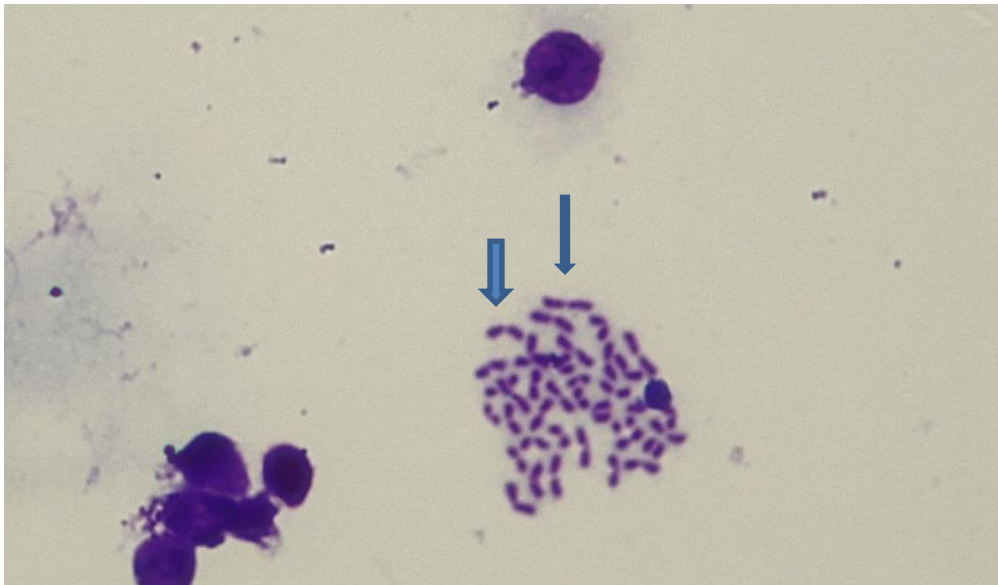
**Fig. 1:Normal chromosomes in bone marrow cells of mice from the control group, using Giemsa stain (1000x).**



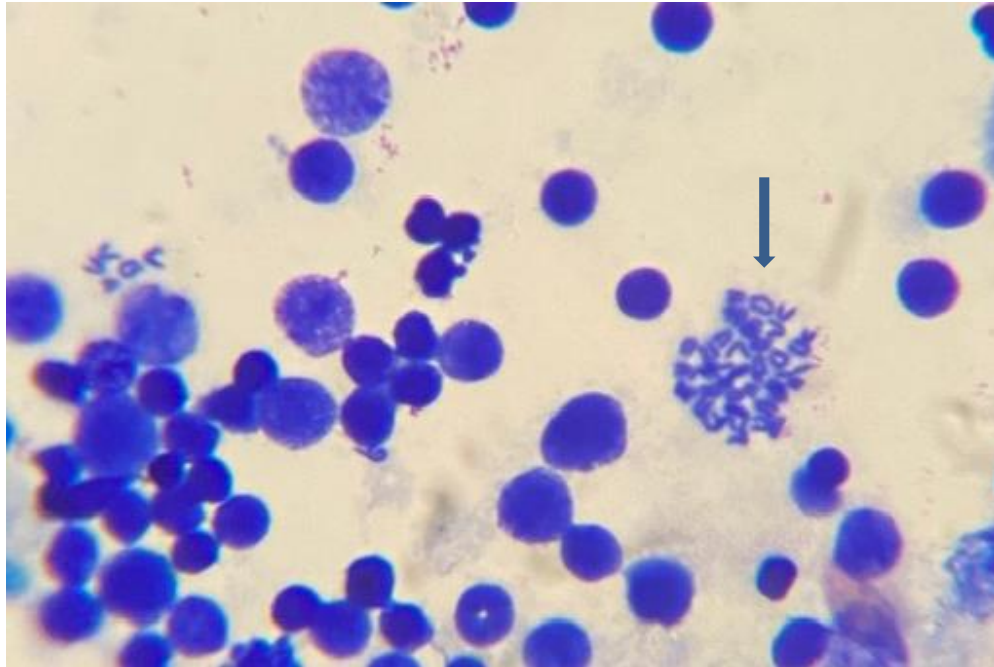
**Fig.2 :Chromatid gap, In bone marrow cells from mice of the treated group, using Giemsa stain (1000x).**



**Fig.3: Chromatid break, In bone marrow cells from mice of the treated group, using Giemsa stain (1000x).**



**Fig.4:Centromere gap In bone marrow cells from mice of the treated group, using Giemsa stain (1000x).**



**Fig. 5: Ring-chromosomes, In bone marrow cells from mice of the treated group, using Giemsa stain (1000x).**

**Table 2: The percentage of chromosome abnormalities in bone marrow cells and germ cells (testis) of *Mus musculus L.* laboratory mice treated with cyclophosphamide N=12  $p \leq 0.05$**

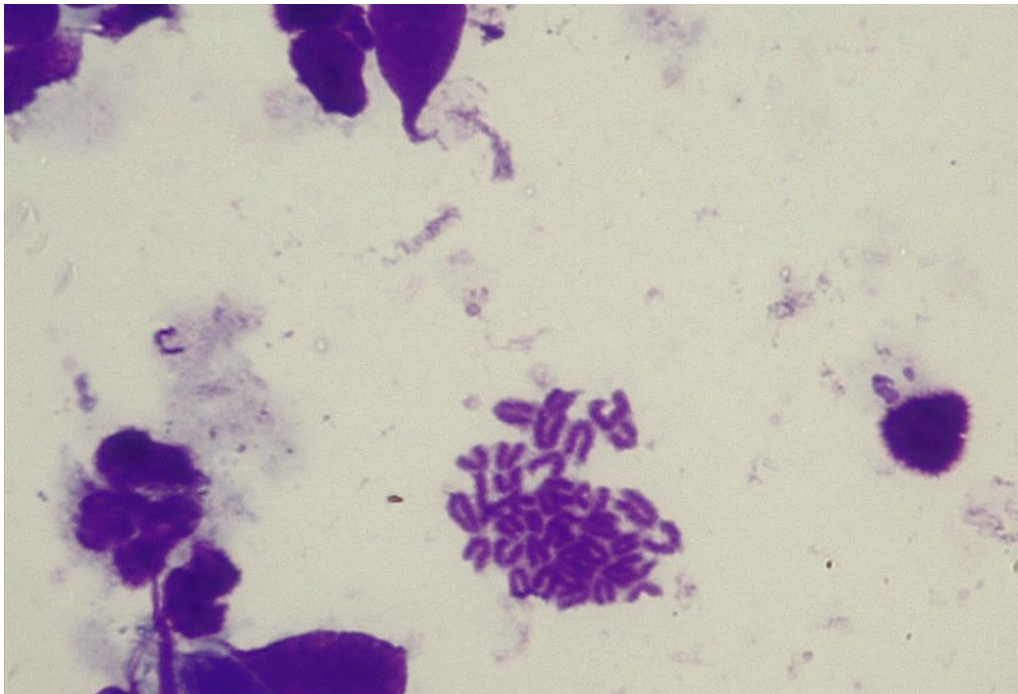
<b>Treatment</b>	<b>(bone marrow) (male and female )</b>	<b>(bone marrow) (male)</b>	<b>(bone marrow) (female)</b>	<b>germ cells (testes) (male)</b>
<b>Control animal group</b>	<b>12.02±10.18</b>	<b>12.93±11.55</b>	<b>11.10±11.1</b>	<b>7.87±6.85</b>
<b>Treatment group</b>	<b>43.48±13.33</b>	<b>38.87±9.64</b>	<b>48.10±16.96</b>	<b>37.77±3.87</b>



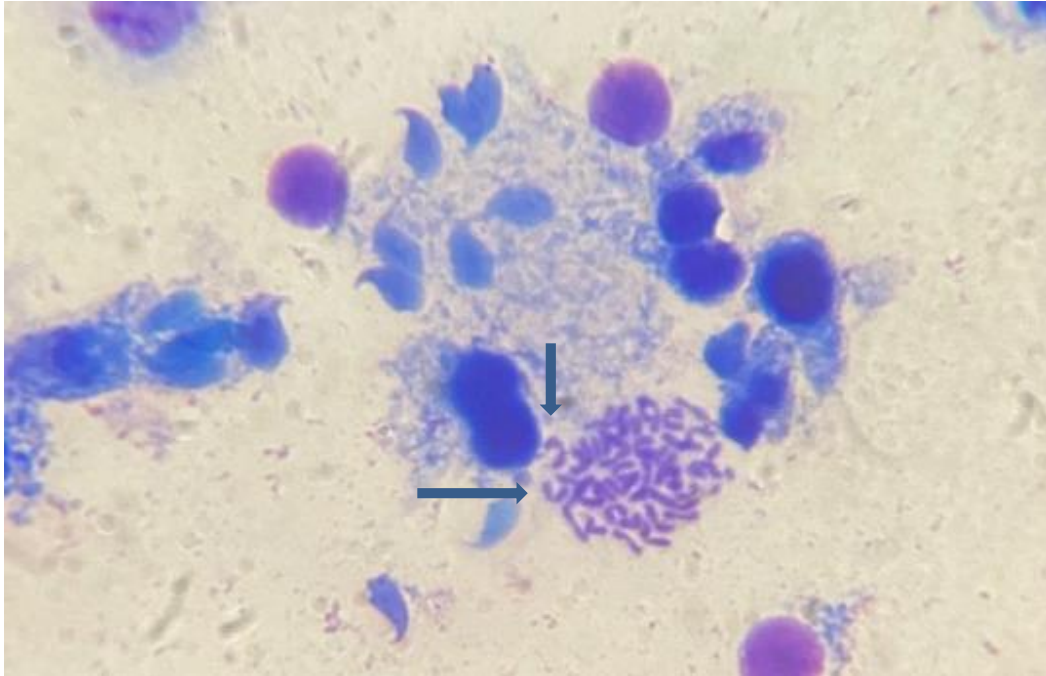
**Effect of cyclophosphamide on  
chromosomal changes of germ cell (Testes  
) of male *Mus musculus L.***

Table 3 shows the presence of chromosomal changes represented by the appearance of chromosomal types (centromere gap and

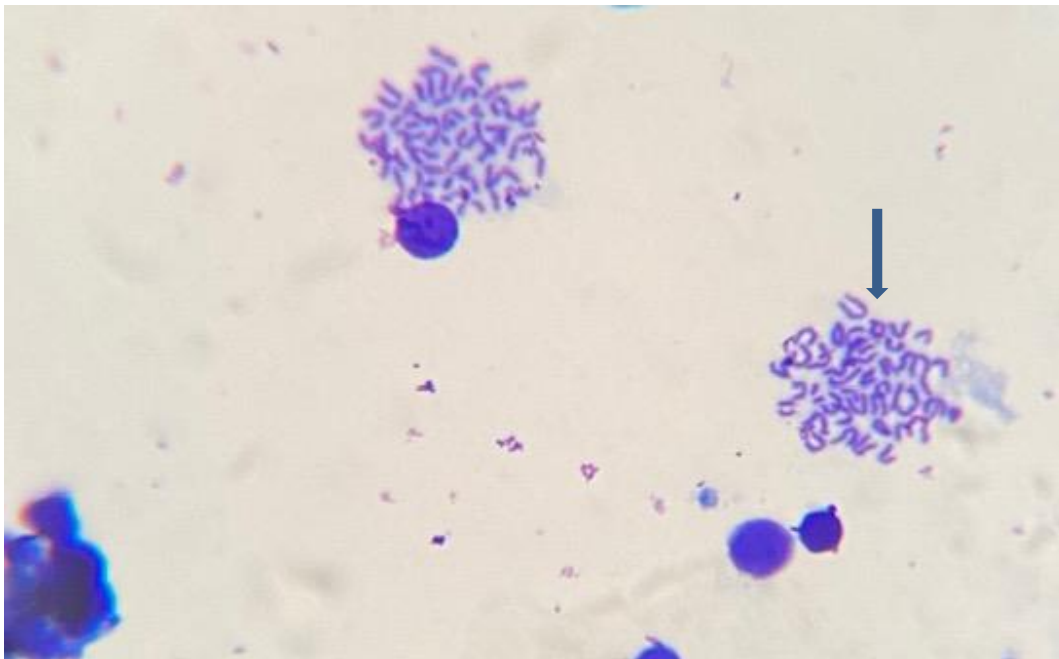
ring chromosome) in the treatment group in comparison with the control animal group (Figure 6), as shown in (Figures 7 and 8) . The results showed that the type of chromosomal change (centromere gap) is the most common type of chromosomal change in the germ cell, while the ring chromosome was the lowest type.



**Fig. 6:Normal chromosomes in the germ cell (testes) of male mice from the control group, using Giemsa stain (1000x).**



**Fig.7: Centromere gap chromosomes in the germ cell (testes) of male mice from the treated group, using Giemsa stain (1000x).**



**Fig. 8:, Ring chromosome chromosomes in the germ cell (testes) of male mice from the treated group, using Giemsa stain (1000x).**

As well as showing statistical analysis and comparison of the treated groups with the control group showed a significant increase in the percentage of chromosomal

abnormalities in the testicular cells of laboratory animals treated with cyclophosphamide, with a statistically significant difference ( $p \leq 0.05$ ) Table 3.

**Table 3: The percentage types of chromosome changes in the germ cells (testes) of male laboratory mice (*Mus musculus L.*) treated by cyclophosphamide N=12**

type of chromosomal	chromatid gap %	centromere break %	centromere gap %	ring chromosome %	Polyploidy %
<b>Treatment</b>					
<b>Parents control</b>	0.0	25.0	0.0	0.0	33.3
<b>Parents treatment</b>	0.0	0.0	50.0 a	40.0 b	0.0

\*\* Highest value(a),less value(b), Significant differences at the ( $p \geq 0.05$ ) level are denoted by values in tiny letters.

**Effect of cyclophosphamide on calculating the mitotic index of somatic cells (bone marrow) of males and females *Mus musculus L.***

It was observed in the current study that there was a significant and clear decrease in the division of bone marrow cells. The result of the treatment of males and females of the *Mus musculus L.* with cyclophosphamide (0.006 mg/kg body weight for a period of 30 days) was compared with a group of control animals. The statistical analysis did not show a significant difference between males

and females when compared with control animals ( $P \geq 0.05$ ). Table 4.

**The effect of cyclophosphamide on the mitotic index of the germ cells (testes) of the males *Mus musculus L.***

In the current study, there was a decrease in the mitotic coefficient of germ cells (testes) as a result of treatment with cyclophosphamide in the compared with a group of control animals ( $p \geq 0.05$ ) (Table 4).

**Table 4: Cyclophosphamide's effect rate on calculating the mitotic index of somatic cells in bone marrow (males and females) and germ cells (testes) in males *Mus musculus L.* N=12**

Treatment	mitotic index	mitotic index	mitotic index	mitotic index of	mitotic index
		of bone marrow (male and female)	of bone marrow (male)	bone marrow (female)	of testes (male)
Control animal group (parents)		9.28±3.46	10.33±3.91	8.23±3.36	8.20±3.03
Treatment		3.75±2.83	2.6±0.66	4.90±3.95	6.77±1.54

p≤0.05

## Discussion

### Effect of cyclophosphamide on chromosomal changes in somatic cells (bone marrow) and germ cells (testis) in *Mus musculus L.*

The results of the current study showed the emergence of chromosomal abnormalities of the type (chromatid gap, chromatid break, centromere gap, and ring-chromosomes) in the bone marrow cells of male and female mice, *Mus musculus L.*, as a result of treatment with cyclophosphamide, at a dose (0.006mg/kg body weight for 30 days. These results are in agreement with (23-24-25),

who noticed the cyclophosphamide has been extensively tested to induce DNA damage, chromosome aberrations, and gene mutations due to its high chemical reactivity. They induce cellular damage in several ways, which can lead to many of pathological conditions, including cancer. And this is in agreement with what was reported by those who reported that cyclophosphamide is a strong inducer of chromosome aberrations,(26-29). (23,24,30,31,32) showed that cyclophosphamide is a potent mutagen. Although a powerful chemotherapeutic drug, it produces dose-dependent gene activity, leading to the development of many clinical

diseases such as cancer gene mutations, chromosomal abnormalities, sister chromatid exchanges, and other genotoxic activities.

With regard to the sex cells (testes), the results of the current study showed the appearance of chromosomal abnormalities and an increase in the percentage of chromosomal abnormalities by a statistically significant difference ( $p \leq 0.05$ ), in the treatment group compared with the control group. These results are in agreement with what was reported, in mice where cyclophosphamide has been linked to increased DNA damage (33,34). In male germ cells, chronic cyclophosphamide treatment reduced the expression profile of genes involved in DNA repair, post-translational modification, and antioxidant defense (35,36). Cyclophosphamide largely caused chromosomal aneuploidy in germ cells before meiosis, as well as a rise in the frequency of numerical chromosomal abnormalities in germ cells at various stages.

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أنواع تشوهات الكروموسومات التي يسببها العلاج الكيميائي سيكلوفوسفاميد في الفئران

(*Mus musculus L.*)

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**الخلاصة:** صممت الدراسة الحالية لدراسة التأثيرات الجينية لـ *Mus musculus L.* على ذكور وإناث فئران التجارب. حيث شملت الدراسة: تأثيرات سيكلوفوسفاميد على التغيرات الكروموسومية في خلايا نخاع العظم والخصيتين ، وكذلك دراسة تأثير سيكلوفوسفاميد على المؤشر الانقسامي لخلايا نخاع العظم والخلايا الجرثومية (الخصيتين). نتج عن جرعة سيكلوفوسفاميد (0.006 ملجم / كجم من وزن الجسم) لمدة 30 يوماً. التغيرات الكروموسومية في خلايا نخاع العظم (فجوة كروماتيد ، كسر كروماتيد ، فجوة مركزية ، كروموسومات حلقيية ، كسر مركزي ، حذف) ضمن فرق معنوي و باحتمالية (0.004). أدى سيكلوفوسفاميد أيضاً إلى حدوث تغيرات صبغية في خلايا الخصية (فجوة كروماتيد ، كسر مركزي ، فجوة مركزية ، كروموسومات حلقيية ، تعدد الصبغيات) بفارق معنوي و باحتمالية (0.046). كما أوضحت نتائج الدراسة بأن سيكلوفوسفاميد تسبب في انخفاض معنوي في مؤشر الانقسام الخيطي لخلايا نخاع العظم عند المجموعة بفارق معنوي و باحتمالية (0.016). وعند حساب العامل الانقسامي للخلية الجرثومية (الخصيتين) أظهرت النتائج انخفاضاً في المجموعة بينما لم تكن هناك فروق معنوية. ( $p \geq 0.05$ ) وقد أظهرت الدراسة الحالية لدراسة ان سيكلوفوسفاميد لا يسبب تشوهات خلقية أو موت الجنين عند إعطائه لحيوانات المختبر *Mus musculus L.*