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# ADVERSE EFFECTS OF NICKEL ON TESTICULAR EFFICIENCY OF MALE RABBITS

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## ABSTRACT

This study was designed to understand the role of nickel chloride ($NiCl_2$) on the testicular efficiency of male rabbits . Effects of low (200 µg / animal ) and high (1000 µg / animal) doses of $NiCl_2$ on the level of testosterone and estradiol -17ß hormones and on the blood picture of male rabbits were investigated . Thirty two mature male rabbits were divided into 4 groups. The first group was kept as control. $NiCl_2$ was orally administered to rabbits 5 times per week for 8 weeks. The low dose of Ni (200 µg/animal) was drenched to rabbits in the second group, while those in the third group received the higher dose (1000 µg / animal). The fourth group received 200 µg/animal of $NiCl_2$ along the period of the experiment (8 weeks), then left without Ni treatment for more 8 weeks to study the possible recovery. The results showed that low and high concentration of Ni induced a significant increase in White Blood Cells (WBCs) and blood platelets count. Testosterone level in both plasma and testicular tissues from rabbits in second and third groups was significantly decreased . However estradiol -17ß level was significantly increased in their plasma . The level of zinc (Zn) and copper (Cu) were significantly decreased in plasma and testicular tissues of animals in second and third groups, while the level of manganese (Mn) in their plasma and testicular tissues did not changed. The level of Ni in their plasma and testicular tissues showed a highly significant increase . Recovery period was quiet good that it allowed some parameters to regain nearly the control values . Fractionation of serum proteins showed only elevation in gamma globulins with low and high dose levels of nickel, while other types of globulins were not affected. Histological examination of the testis showed a partial degeneration of testicular elements and the severity of the effects increased with increasing the dose. It is concluded that, nickel administration may affect the reproductive efficiency of male rabbits through direct affection on testicular tissues or through disturbance of reproductive hormones levels.

## INTRODUCTION

World wide concern with regard to the potential health effects of Ni is clearly understandable, since Ni and its compounds are of great economic importance. They have numerous industrial uses, resulting in occupational exposure of large numbers of workers, and the risks associated with exposure to certain Ni compounds have been the subject of numerous studies [1-3].

Regarding the understanding of the fundamental mechanism of action of Ni as a carcinogen, important experimental evidence was presented showing that Ni, probably in the ionic form, cross the cell membrane and is deposited in the nucleus and in the nucleolus [4]. Physical and chemical structure relationships with regards to Ni carcinogenicity were considered and various indices of prediction of carcinogenicity (e.g. capability to stimulate erythropoiesis susceptibility to phagocytosis) was discussed[5] . The erythropoeitic stimulation correlates with carcinogenicity and both erythropoeisis and carcinogenecity are antagonized by manganese [1,2,6] . However, previous studies by Hamam et al[7] showed that manganese was unsuccessful in the treatment of nickel toxicity in female rabbits.

Data on the effects of Ni on male reproductive system are limited. Some investigators have reported the toxicity of Ni on the testes and spermatogenesis. Tubular damage and spermatozoal degeneration were observed in the testis following exposure to 60 mg Ni/Kg for 30 days [8]. A dose of 40 mg / Kg body weight did not affect the fertilizing capacity of spermatozoa or the ability of the fertilized egg to cleave but a dose of 56 mg Ni nitrate /Kg body weight yielded a significant proportion of uncleaved unfertilized eggs [9]. Although these data are suggestive of a possible direct testicular toxicity, it is not clear if Ni directly alters sperm function.

The present study determined the pathological and biochemical alterations produced in blood and testes after administration of 2 different doses of $NiCl_2$ in particular, of male rabbits. The possibility of recovery of Ni toxicity was also studied.

## MATERIALS AND METHODS

### Animals:

Thirty two mature male white Newzealand rabbits were used (Average weight is 2.5 kg). They were maintained in individual cages, given concentrated pellets of food and water *ad libitum*, reared in the animal house, National Research Center.

### Experimental Design :

Male rabbits were randomly divided into 4 groups, each of 8 animals . The first group was left as control,

the second group was drenched a low dose of nickel chloride (200 µg/animal). While the third group was treated with high dose of nickel chloride (1000 µg/animal). The animals were treated five times per week for 8 successive weeks. The fourth group was drenched low dose of nickel chloride (200 µg/animal) for 8 weeks (five times per week) then left without treatment for another 8 weeks to study the possible recovery.

**Blood samples:**

Blood samples were collected during decapitation of rabbits in 3 tubes containing either EDTA disodium salt (for haematological examination), heparin (for separation of plasma) or whole blood (to separate blood serum for electrophoresis). Aliquots of blood were collected freshly on EDTA for haematological studies (RBCs, WBCs counts, Hb%, HCT, MCV and platelets count) using Cell Counter Serono Diagnostic 190 T. Blood plasma was collected in heparinized tubes, and kept at -20.C, until analyzed for hormonal assay, trace and heavy metals.

**Testicular Homogenization:**

One testis from each animal was immediately dissected out from surrounding tissues, weighed and homogenized using polytran homogenizer, diluted with normal saline 0.9 % NaCl (w/v), the homogenate was filtered to remove the connective tissues, then centrifuged at 3000 rpm/30 min., in cooling centrifuge (5 °C). Testosterone and estradiol concentrations were determined in the homogenate.

**Hormonal Assay:**

Testosterone and estradiol-17ß were determined in the plasma and testicular homogenate using radioimmunoassay technique according to Abraham[10] and Allen and Redshaw[11]. The triiodothyronin ($T_3$) was determined according to the methods of Eastman et al [12] and Thyroxine ($T_4$) was measured in the plasma using RIA technique according to the method of Chopra [13].

**Electrophoresis:**

Electrophoretic patterns were performed using polyacrylamide gel electrophoresis[14,15]. Nickel, manganese, zinc and copper were determined in the plasma and testicular tissues after wet weight digestion by using atomic absorption spectrophotometry [16].

**Histopathological Examination:**

The other testis was prepared for histopathological examination using the technique of [17].

**Statistical analysis :** statistical analysis of the obtained data was made according to Snedecor and Cochran[18], using Student's "t" test.

## RESULTS

**Effect of Nickel on Blood Picture :**

As shown in Table (1), oral administration of nickel chloride resulted in a significant increase in W.B.Cs and platelets counts with the low and high doses of nickel. The counts of W.B.Cs and platelets returned to nearly their normal levels after 8 weeks recovery period. However, R.B.Cs count, Hb%, HCT and MCV values did not significantly changed.

**Effect of nickel on some hormonal profiles:**

The results in Table (2) showed that the level of plasma estradiol-17ß was significantly increased with both low and high doses of nickel. However, non significant changes were recorded after recovery. Unfortunately, the levels of estradiol-17ß in the testicular extract was out of he curve.

A highly significant decrease in the testosterone level was observed in both plasma and testicular tissues following low and high doses of nickel compared with the control value. No significant changes were observed after recovery. The levels of triiodothyronin ($T_3$) and thyroxine ($T_4$) were not significantly affected as shown in table (2).

**Effect of Nickel on Protein Fractions :**

As shown in table (3), a significant decrease ($P<0.05$) in α-globulins was observed only in low dose-treated group, while ß-globulins did not show any significant changes. However, a significant increase in γ-globulins was observed in all treated groups. On the other hand nickel didn't affect the albumin levels in all groups.

**Levels of Ni, Mn, Zn and Cu in the plasma and testicular tissues :**

As shown in Table (4), Ni in both doses is responsible for increasing the Ni levels in the rabbit plasma, but after the recovery, the plasma Ni level returned nearly to the control levels. While in the testes, it was observed that even after recovery, Ni level was still higher than the control group.

On the other hand, Mn did't show any significant changes in both plasma and testicular tissues. Zinc de-

creased significantly in plasma and testes of both Ni-treated groups.

Copper also, decreased significantly in plasma of both Ni treated groups and only in the testicular tissues of animals that received low dose of Ni, but there was a significant increase in Cu level in the testes of high dosed animals. Regarding Cu, both low and high doses of Ni resulted in a highly significant increase ($P<0.01$) in Cu concentration in both plasma and testicular tissues, while after the recovery period, its level returned nearly to the control level.

**Histopathological examination of the testes:**

Administration of low dose of nickel chloride caused a partial degeneration of testicular elements (Fig. 1) and the severity of the effects increased with increasing the dose. High dose of nickel chloride produced a wide spread damage in the germinal elements of rabbit testes and complete arrest of spermatogenesis (Fig. 2). The degenerative changes caused by the high dose included pronounced shrinkage in the diameter of the seminiferous tubules, and germinal elements became reduced to only 1-2 cell layers. Spermatogenic impairment was evident by general reduction in the size of the nucleus and appearance of vacuoles in the cytoplasm of the germinal cells. The number of decapitated spermatozoa increased with the increase in the dose. The tubular lumina were either devoid of spermatozoa or contained debris. Except the Sertoli cells, a few spermatogonia and primary spermatocytes, all other cells lost their identities and became mostly vacuolated. Many damaged cells were clumped together near or inside the tubular lumen, forming many giant multinucleated cells. Spermatogenesis and interstitial tissues restored nearly their normal picture after the recovery period (Fig. 3).

## DISCUSSION

The blood picture in the present study revealed a highly significant elevation in WBCs counts in both nickel treated groups. This result coincides with Sunderman et al. [4] who reported that the chronic exposure to nickel compounds primarily affect the immune system.

The significant increase in the platelets count in both nickel treated groups may be due to the increased thrombocytopoesis or decreased zinc levels or decreased plasma volume [19].

The present study showed that nickel administration resulted in a dose related suppression of plasma and testicular testosterone levels and spermatogenesis. The mechanism of the toxic action of nickel appeared to be a disruption of the hypothalamus control of the pituitary

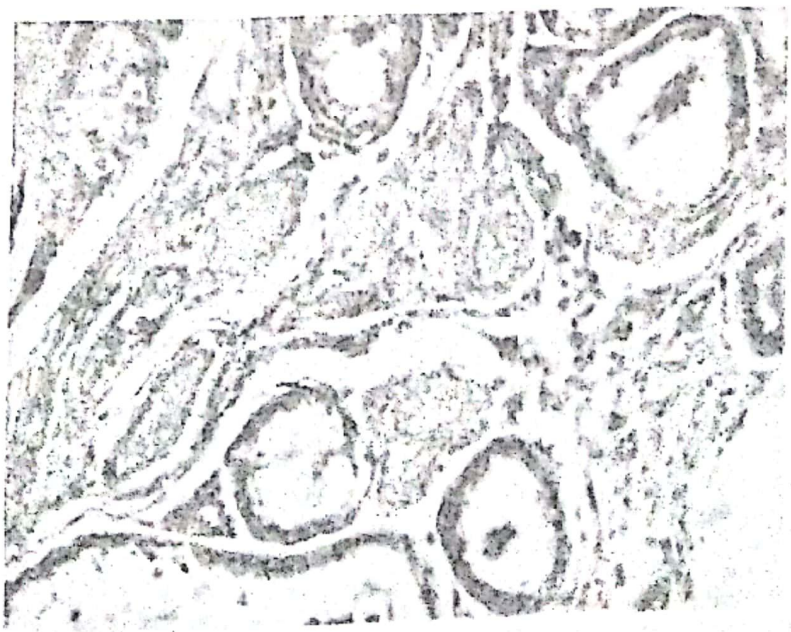

Fig. (1): Testis of rabbits that received low dose of nickel chloride, showing partial arrest of spermatogenesis, partial degeneration, vacuolation and pyknosis of the germinal cells in some seminiferous tubules (H & E stain).

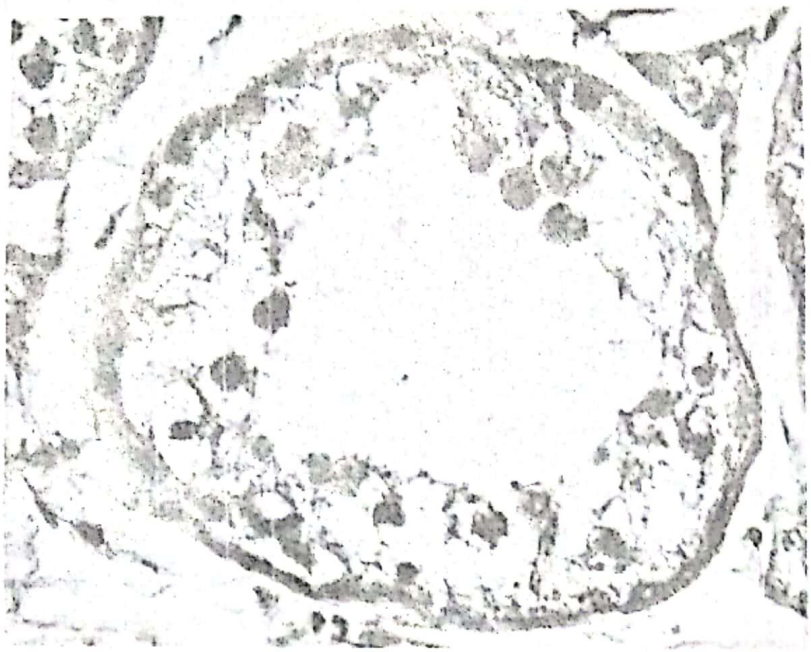

**Fig (2)**: Testis of rabbits received high dose of nickel chloride, showing degenerative changes including shrinkage in the diameter of the seminiferous tubules, vacuolation and pyknosis of some primary spermatocytes. Tubular lumina were either devoid of spermatozoa or contained debris (H & E stain).

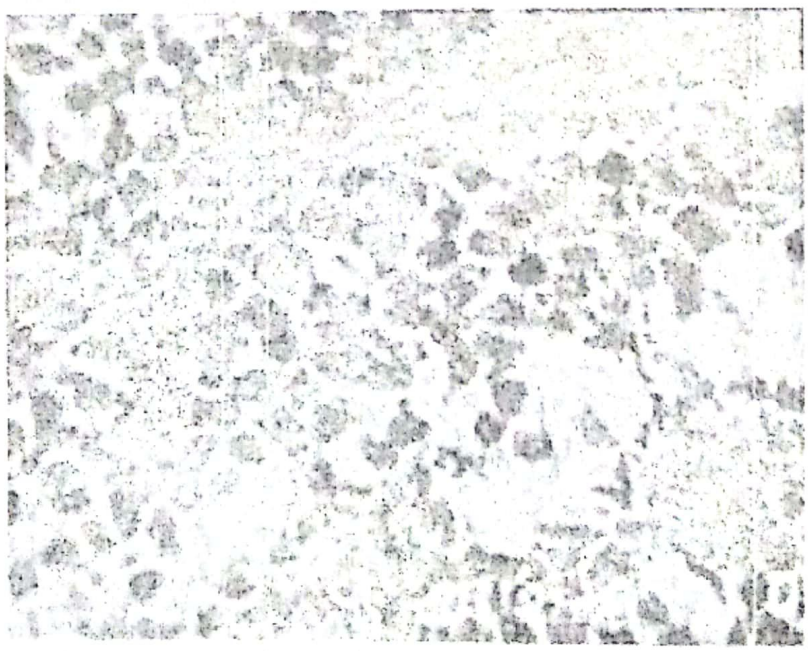

**Fig. (3)**: Rabbit testis after the recovery period, showing active spermatogenesis, nearly normal testicular composition (H & E stain).

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**Table (1): Blood picture of male rabbits after oral administration of low and high doses of nickel for 8 weeks. (Mean ± S.E.)** n = 8

| Variables | Control | LD Ni (200 µg nickel / animal) | HD Ni (1000 µg nickel / animal) | Recovery |
|---|---|---|---|---|
| RBCs x $10^2$ /$mm^3$ | 6.344 ± 0.29 | 5.85 ± 0.15 | 5.31 ± 0.64 | 6.06 ± 0.3 |
| Hb gm % | 14.56 ± 0.37 | 15.1 ± 1.91 | 14.52 ± 0.93 | 1.51 ± 0.19 |
| WBCs x $10^3$ /$mm^3$ | 8.29 ± 0.33 | 13.86 ± 1.83* | 14.43 ± 1.77** | 8.56 ± 0.19 |
| HCT | 42.78 ± 0.85 | 41.58 ± 5.31 | 41.13 ± 0.55 | 43.2 ± 1.83 |
| MCV | 67.88 ± 2.77 | 69.5 ± 0.29 | 68.2 ± 1.07 | 69.75 ± 1.93 |
| Platelets x $10^3$/$mm^3$ | 271 ± 29.77 | 606.2 ± 79.3** | 660.4±75.68*** | 360 ± 10.61 |

* P < 0.05 ** P < 0.01 *** P < 0.001 LD = low dose HD = High dose

**Table (2): Hormonal levels in plasma and testicular tissues of male rabbits given low and high doses of nickel for 8 weeks. (Mean ± S.E.)** n = 8

| Variables | Control | 200 µg nickel / animal) | 1000 µg nickel / animal | Recovery |
|---|---|---|---|---|
| Testosterone | | | | |
| Plasma (ng/ml) | 3.8 ± 0.74 | 0.78 ± 0.48** | 0.3 ± 0.04** | 1.44 ± 0.79 |
| Testis (pg/ml) | 259.9 ± 7.9 | 99.8 ± 4.13*** | 67.6 ± 9.45*** | 229.72 ± 12.98 |
| Estradiol - 17ß | | | | |
| Plasma (ng/ml) | 50.4 ± 6.24 | 139.00 ± 4.81*** | 181.71 ± 15.51*** | 97.43 ± 23.11 |
| Testis (pg/ml) | -------- | -------- | -------- | -------- |
| $T_3$ (ng /ml) | 176.66 ± 6.74 | 163.33 ± 17.28 | 138.33 ± 18.78 | 167.11 ± 14.81 |
| $T_4$ (ng /ml) | 3.26 ± 0.26 | 3.4 ± 0.14 | 2.68 ± 0.49 | 2.86 ± 0.49 |

** P < 0.01 *** P < 0.001

**Table (3): Serum protein fractionation of male rabbits treated with low and high doses of nickel for 8 weeks and after recovery. (Mean ± ( S.E.)** n = 8

| Dose | Globulins | | | Albumin gm/L |
|---|---|---|---|---|
| | Alpha (α) gm/L | Beta (β) gm/L | Camma (γ) gm/L | |
| Control | 14.90 ± 3.4 | 10.01 ± 3.05 | 3.63± 0.63 | 12.28 ± 2.84 |
| 200 µg nickel / animal | 6.94 ± 1.60 | 8.21 ± 1.29 | 8.69 ± 2.16* | 19.27 ± 5.42 |
| 1000 µg nickel / animal | 11.87 ± 3.92 | 8.75 ± 3.06 | 9.87 ± 2.76* | 11.98 ± 2.76 |
| Recovery | 10.8 ± 3.5 | 6.30 ± 1.86 | 12.25 ± 3.56* | 16.15 ± 3.16 |

* P < 0.05

**Table (4): Concentration of Nickel, manganese, zinc and copper in both plasma and testicular tissues of male rabbits treated with low and high doses of nickel for 8 weeks. (Mean ±S.E.) n = 8**

| Treatment | Levels of minerals (µmol /L) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Plasma | | | | Testicular tissues | | | |
| | Ni | Mn | Zn | Cu | Ni | Mn | Zn | Cu |
| Control | 0.10 ± 0.004** | 48.81 ± 12.24 | 24.39 ± 1.25 | 35.91 ± 1.65 | 13.14 ± 1.52 | 2.96 ± 0.35 | 704.42 ± 34.47 | 40.32 ± 0.87 |
| 200 µg nickel / animal | 0.18 ±0.007** | 59.07 ±7.36 | 18.55 ± 0.79** | 25.21 ± 1.67** | 17.16 ± 0.81** | 3.02 ± 0.09 | 500.18 ± 13.58** | 33.41 ± 1.12** |
| 1000 µg nickel / animal | 0.51± 0.97** | 33.16 ±.09 | 15.24 ± 0.87** | 22.99 ± 2.87** | 33.49 ± 1.60** | 2.12 ± 0.21 | 345.01 ± 27.64** | 27.16 ± 2.04** |
| After recovery | 0.095± 0.006 | 29.95 ±0.88 | 24.78 ±0.49 | 29.77 ± 1.89 | 21.60 ± 1.70** | 2.71 ± 0.32 | 465.51 ± 52.14** | 37.41 ± 0.99 |

** P < 0.01

hormone secretion and in turn spermatogenesis. The possibility of nickel toxicity is directed at the hypothalamic-pituitary axis, as nickel has been reported to be localized within the pituitary and the hypothalamus and to inhibit LH secretion [20,21]. The suppressive effect of nickel chloride on the testosterone level may be also due to a direct damage of Leydig cells or due to reduction of LH receptors concentration on Leydig cells[22] with subsequent inhibition of testicular responsiveness to gonadotrophins and inhibition of 17ß -hydroxylase activity in Leydig cells. Another possibility is that nickel reduces the capacity for testosterone production in Leydig cells by reduction in P450 17ß and P450 mRNA as well as by decreased availability of cholesterol[23].

Signs of inflammation which is manifested by increased lymphocytes and macrophages were detected in the present study. Testicular macrophages produce interleukin and tumour necrosis factor, both of these cytokines have shown to cause reduction in P450 and P450 17ß in Leydig cells accompanied by inhibition of LH [23]. A critical level of testosterone is necessary for sperm to achieve full fertilizing potential [24]. Testosterone and FSH are the main regulators of spermatogenesis [25] . Interference with spermatogenesis secondary to a disruption of the signals between the hypothalamus-pituitary and testis is well established [26]. The present study showed that nickel administration decreased testosterone production and spermatogenesis after 56 days of treatment. Since spermatogenesis in male rabbits takes 48-51 days, so the 56 days exposure period in this study covered the an entire cycle of spermatogenesis. Arrest of spermatogenesis and decrease in spermatocyte and spermatids in nickel treated groups were consistent with a disruption of normal androgenic control of the testes [27].

The significant increase of estradiol-17ß (E2) in the plasma may be due to the effect of heavy metals on metabolic and enzymatic activity [28] or due to Sertoli cells factors which acts in a paracrine fashion on Leydig cells to stimulate the clearance rate of already formed E2 leading to its accumulation and subsequent elevation of its plasma levels. Leydig cells also express cytochrome P450 aromatase which catalyzes the aromatization of testosterone to estradiol [29].

However, the levels of T3 and T4 were slightly decreased in treated groups especially with the high dose of Ni (1000 µg / animal) . These results disagree with those reported by Lestrovoi et al. [30] who stated that oral administration of nickel chloride (0.5 - 5 mg / kg per day) for 2 -4 weeks to rats significantly decreased iodine uptake by the thyroid. This discrepancy may be due to dose and species difference.

Concerning fractionation of serum total proteins, the significant increases in γ-globulins may be due to the effect on the immune system. The chronic effects of

exposure to nickel compounds primarily affect the immune system and the rate of synthesis and volume of distribution of many plasma proteins [31], this may explain the significant increase in γ-globulins after treatment and as a defensive mechanism in the period of recovery.

The present study showed that zinc concentration in both plasma and testes was significantly reduced. Zinc is necessary for a normal spermatogenesis process. In zinc deficient rabbits, most germ cells were degenerated and only spermatogonia and some spermatocyte remained. After zinc administration, there is a synchronous reinitiation of spermatogenesis starting from the remaining spermatogonia[32].

The present data suggest that the significantly low zinc level in plasma and testes induced by nickel administration may be in part related to the loss of germ cells or loss of testosterone levels as previously indicated [33]. The exact mechanism by which zinc deficiency or inadequate zinc levels modified nickel toxicity cannot be determined from the present study. It appeared that zinc deficiency increases microsomal P450 mediated metabolic activation and thus toxicity activity. Zinc deficiency however, increase the distribution of nickel to the testes and assuming that higher concentration of the nickel as shown in the present study, would lead to more lesions .

It also appears that zinc deficiency can reduce concentration of the nickel binding protein, metallothionein, in some tissues [34]. Thus, it appears that alterations in essential metals, Zn or Cu or Mn metabolism are of primary mechanistic importance in the process of metabolism or nickel toxicity, although this is clear in both tissue and metal specificity.

The present data showed that inadequate Zn or Cu levels, will enhance accumulation of nickel in the testes, this may have a very important role in increased toxicity of nickel, particularly since a fairly low critical concentration seems to be necessary for nickel induced testicular lesions to occur. Thus metal-metal interactions, specifically interactions with essential elements (Zn, Cu) are clearly a key aspect of metallic toxicity of nickel and a mechanism which contributes to enhanced nickel induced testicular toxicity.

The present study suggested that short term exposure to nickel chloride at the tested concentrations (200 and 1000 ug / animal) did not permanently affect reproduction in male rabbits. Reinitiation of spermatogenesis was detected following recovery period corresponding to one cycle of the seminiferous epithelium. So, these doses of nickel produced a reversible testicular lesions.

Finally we concluded that Ni in both tested doses affected the reproductive efficiency of male rabbits through different ways either directly through its effect on the testicular tissues or indirectly through its effect on male reproductive hormones.

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## التأثيرات العكسية للنيكل على كفاءة الخصية فى ذكور الأرنب

**أسامه عبد الحميد على - ماجده محمد التهامى - جمال عبد الدايم على**

**قسم التكاثر الحيوانى والتلقيح الصناعى - المركز القومى للبحوث - الدقى - الجيزة**

أجريت هذه الدراسة على عدد ٣٢ من ذكور الأرانب النيوزيلاندية البالغه وقد تم تقسيمها الى أربعة مجموعات بواقع ٨ أرانب لكل مجموعة . اعتبرت المجموعة الأولى كمجموعة ضابطة أما المجموعة الثانية والثالثة فقد تم تجريعهما كلوريد النيكل بالفم بجرعات منخفضه (٢٠٠ ميكروجرام / حيوان) وعالية (١٠٠٠ ميكروجرام / حيوان) على التوالى يوميا لمدة ٥ أيام أسبوعيا . وقد تم التجريع على مدار ٨ أسابيع متصلة . أما المجموعة الرابعة فقد تم تجريعها بالجرعة المنخفضة من كلوريد النيكل مثل المجموعة الثانية ثم تركت لمدة ٨ أسابيع أخرى بدون تجريع (فترة نقاهة) وذلك للمساعدة على التخلص من النيكل . وقد أظهرت نتائج الدراسة أن النيكل بجرعتيه المنخفضة والعالية قد أدى الى زيادة عدد الكرات الدموية البيضاء والصفائح الدموية . وبتقدير مستوى بعض الهرمونات وجد أن هناك نقص معنوى فى مستوى هرمون التستوستيرون فى بلازما الدم وأيضا فى أنسجة الخصية فى المجموعتين الثانية والثالثة . بينما كانت هناك زيادة معنوية فى مستوى هرمون الاستراديول فى بلازما الدم وأنسجة الخصية لنفس هاتين المجموعتين . ومن ناحية أخرى لم يكن هناك تأثير معنوى على مستوى هرمون الترای أيودوثيرونين ($T_3$) والثيروكسين ($T_4$) . وبالنسبة لمستوى بعض العناصر وجد أن هناك إنخفاض معنوى فى مستوى الزنك والنحاس بينما كان هناك زيادة معنوية فى مستوى النيكل وذلك فى كل من البلازما وأنسجة الخصية للمجموعتين الثانية والثالثة . بالنسبة للفصل الكهربائى للبروتينات وجد أن هناك زيادة معنوية فى مستوى الجاما جلوبيولين فى كل المجموعات المعالجة . وبالنسبة للفحص الهستوباثولوچى للخصية وجد تهتك فى بعض أنسجتها ويزداد التأثير مع زيادة الجرعة . وقد أظهرت الدراسة أن فترة النقاهه كانت ذات فائدة فى إعطاء الفرصة لجسم الحيوان للتخلص من النيكل الزائد حيث أظهرت النتائج أن هناك تحسن فى القراءات المختلفة بالنسبة لحيوانات المجموعة الرابعة مقارنة بالمجموعة الضابطة .

ويستخلص من هذه النتائج أن أى من جرعات النيكل المنخفضة أو العالية قد تؤثر على التكاثر والنشاط الجنسى فى الأرانب إما بطريقة مباشرة على نسيج الخصية أو بطريقة غير مباشرة عن طريق تأثيرها على بعض الهرمونات والمعادن.