Reproductive toxicity of cyto-static drugs and pharmacological ways to reduce it

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Intensity of reproductive dysfunction in women with cancer under different treatment regimens

Disease	Scheme	Status of reproductive function
Breast Cancer	CMF	amenorrhea in 88%
	FAC	amenorrhea in 55%
Hemoblastosis	COPP	amenorrhea
	EEACOPP	amenorrhea
	CHOP	amenorrhea
		in the majority of women
	ABVD	Violations in ovarian cycle are minimal
Ovarian cancer (after conserving surgery)	POMB/ACE	Does not result in sterilization

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* Mormor D. (1993). Fertile après traitements cytostatiques. *Contracept.-fertil.-sex.,* 21(10):739-43.

* Evain P.L. Bazonzelly M., Dusol F., Demaille M. (1986). *Chemiotherapia anticancereuse at fertilite cher la femime. Rev. Fr. gynecolog at obsted.*, 3:451-4.

* Howell S.G., Shalet S.M. (2001). Testicular function following chemoterapy. *Human Reprod. Update,* 7 (4):3369-3.

* Taksey Y, dissada N.K., Chayndhary U.B. (2003). Fertility after chemotherapy for testicular cancer. *Arch. Androl.*, 49(5):389-95.

Group and name of the drug, chemical structure	Main mechanism of anti-tumor action
PLATINUM COMPLEXES	
Cisplatin, Lachema AC, Austria	Form a cross-link between DNA molecules
Carboplatin, EBEWE Pharma, Austria	
ANTHRACYCLINE ANTIBIOTICS	
Doxorubicin, EBEWE Pharma, Austria	Intercalation between the base pairs of DNA
Epirubicin, Karlo Arba, Italy	
INHIBITORS TOPOIZOMERAZNOY ACTIVITY	
Etoposide, Teva Pharmaceutical Industries, Israel	Inhibition of topoisomerase II
TAXOIDS	
Paclitaxel, Dr Reddis, India	Stimulation of assembling of anomalous microtubules

The object of study is Wistar rats

The drugs were administered intravenously in a single MTD, because in clinics high-dose therapy is used

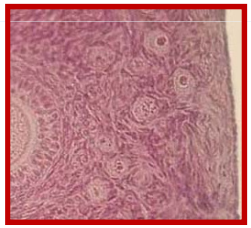
Methods of study

- ***morphological***

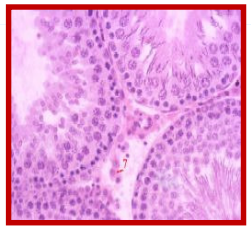
(using quantitative indicators characterizing extent of the damage)

- ***functional***

(fertility index, the index pregnancy, fetal death)



gonads



testes

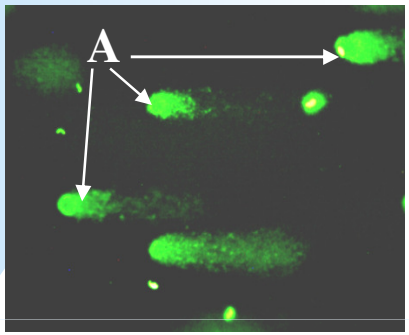
Research terms

The assessment of effects was performed 3 and 6 months after administration of cyto-static drugs

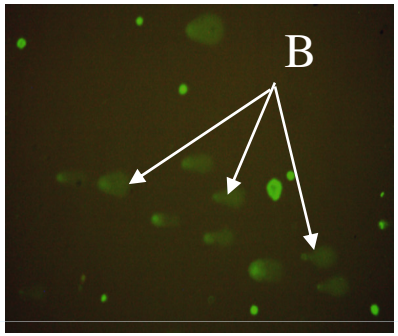
Early antiproliferative effects of cytotoxic drugs on gonads

On testicular tissue:

"DNA-comets" of mouse testis



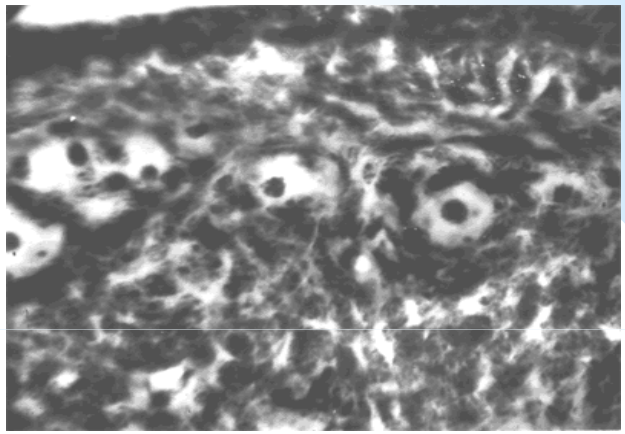
A – cells with DNA-damages



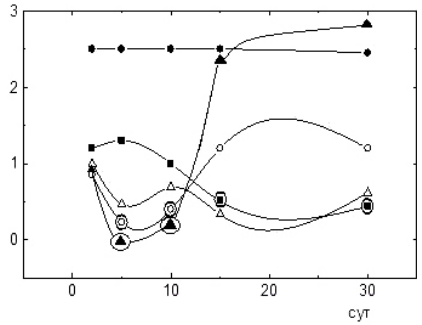
B – Apotopic "DNA-comets"

On ovarian tissue::

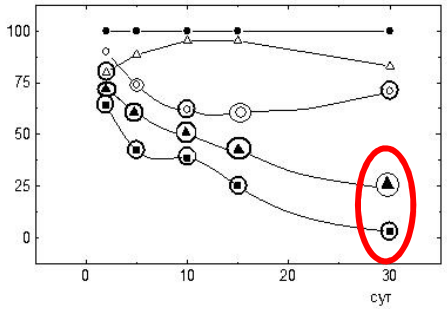
Death of follicular epithelium cells



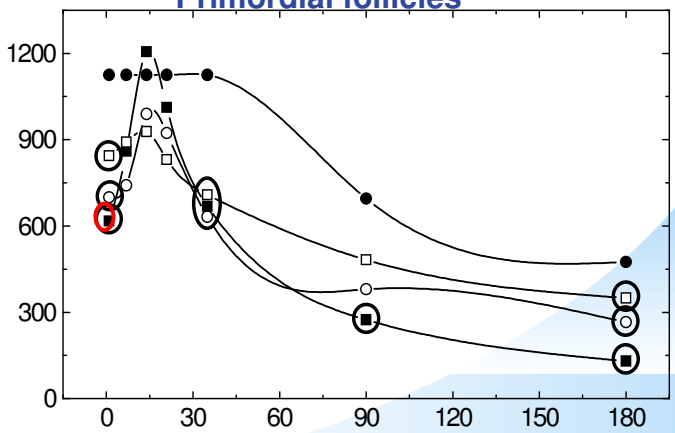
Tubules with the 12th stage of meiosis, %



Number of normal spermatogonia, % of control

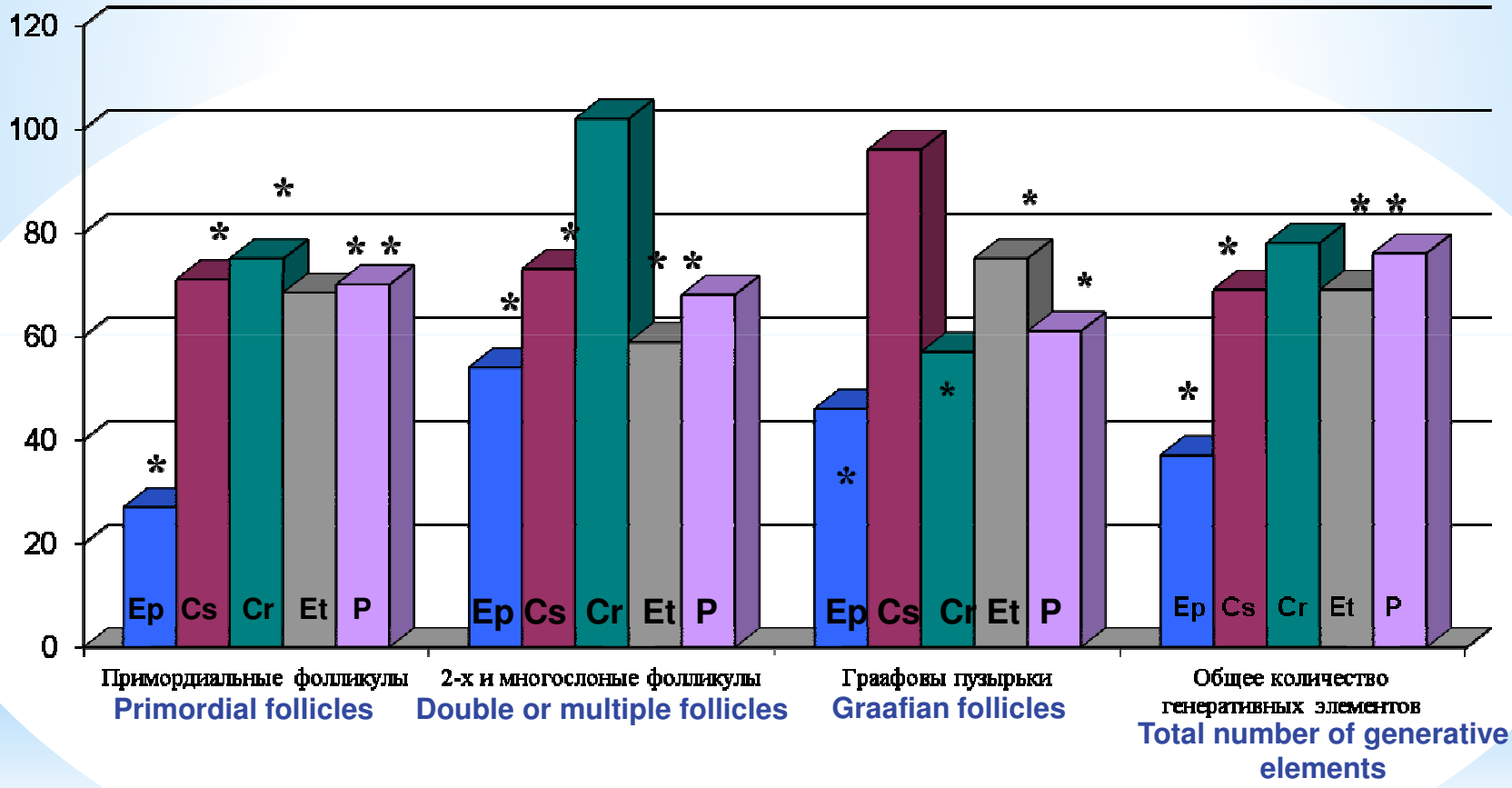


Primordial follicles



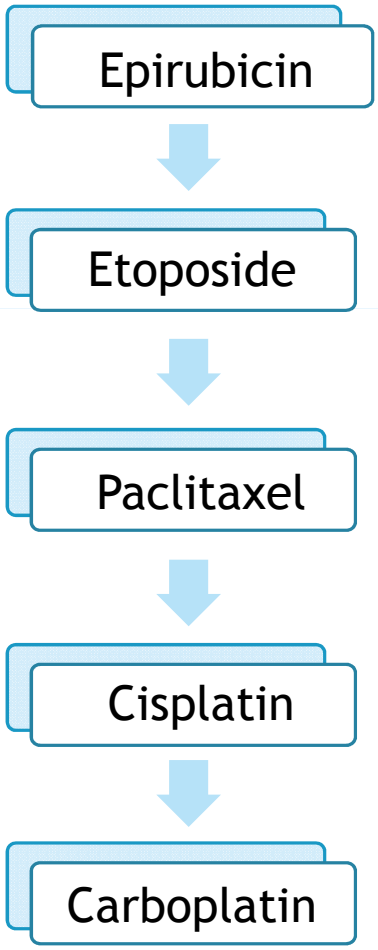
● Control ■ Epirubicin △ Etoposide □ Doxorubicin ○ Cisplatin ▲ Paclitaxel

Content of structural-functional elements of rats ovaries, 6 months after a single injection of anticancer drugs in the MTD (% of control)

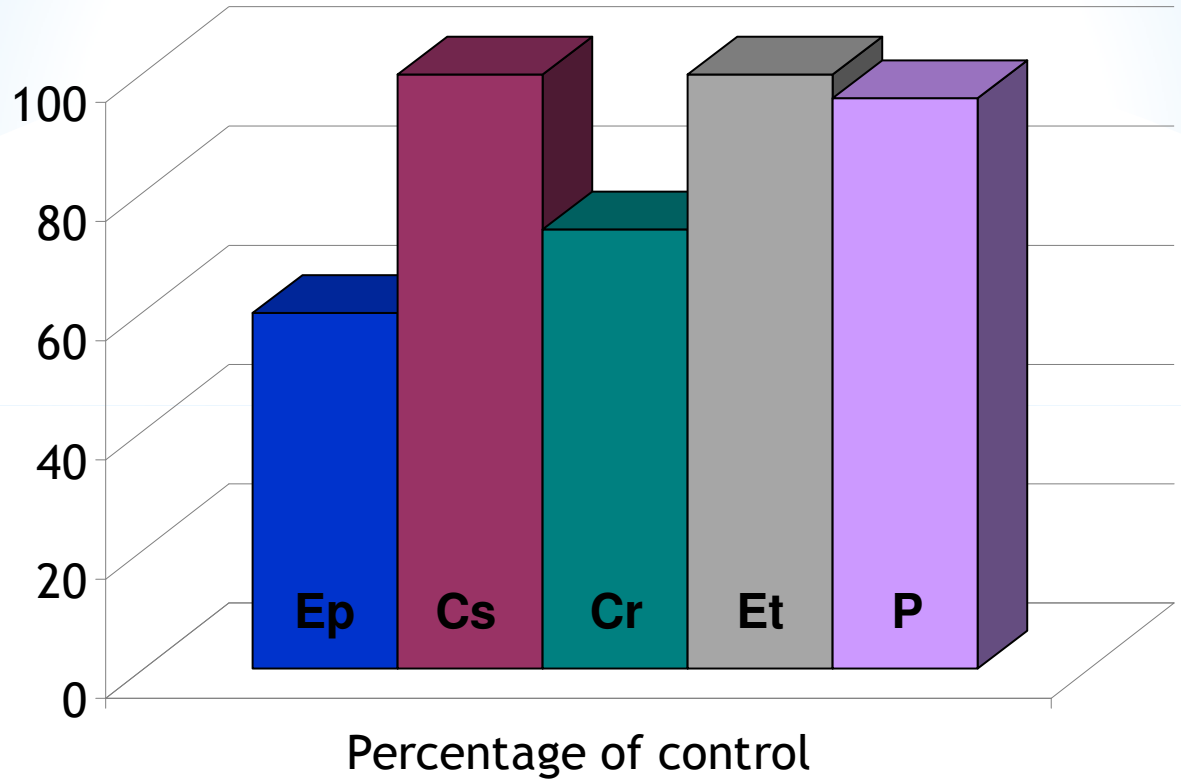


Ep – Epirubicin; Cs – Cisplatin; Cr – Carboplatin; Et – Etoposide; P – Paclitaxel

Intensity of long-term-late effects of cyto-static drugs on structural and functional elements of the rat ovary is decreased in the following order:

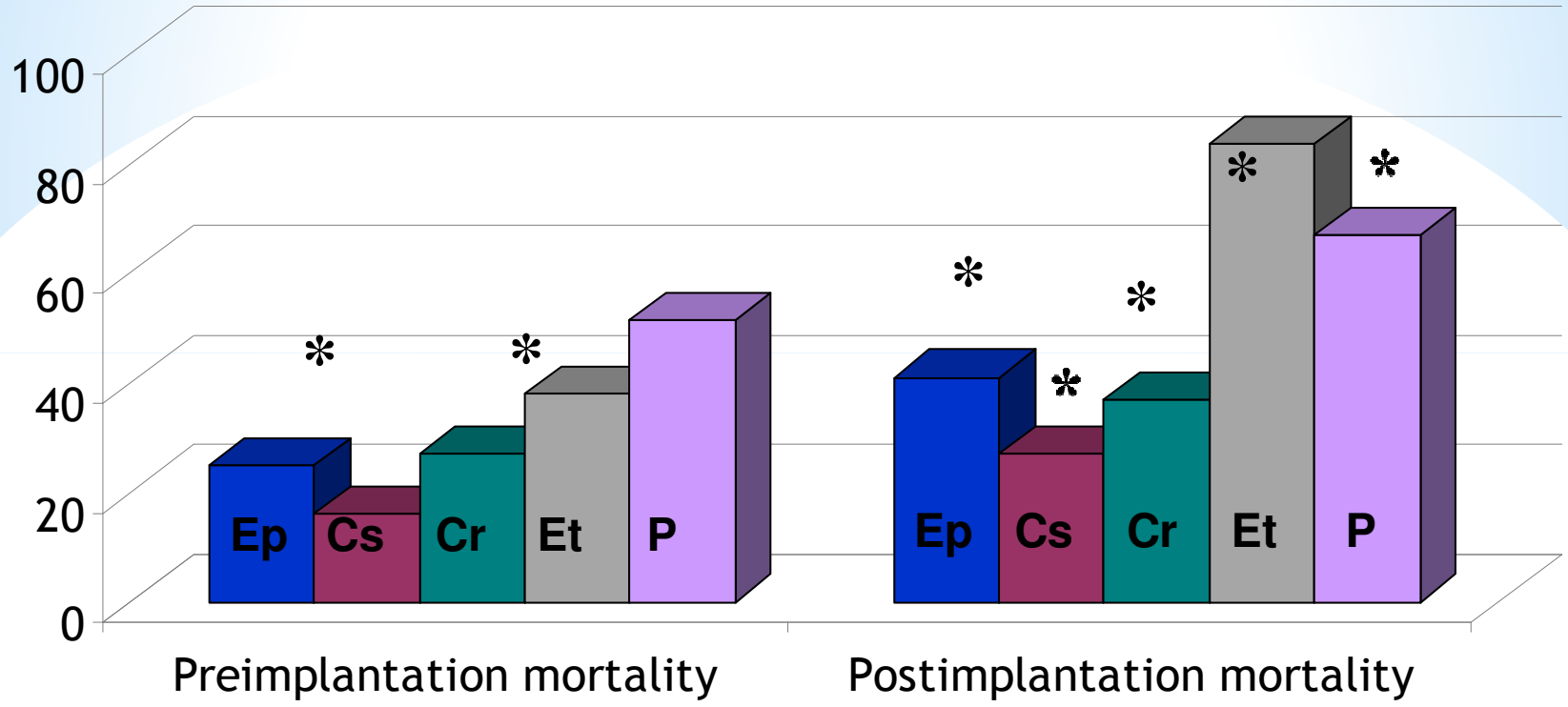


Efficiency of mating in female-rats in the long-term period after administration of cytotoxic drugs of different groups



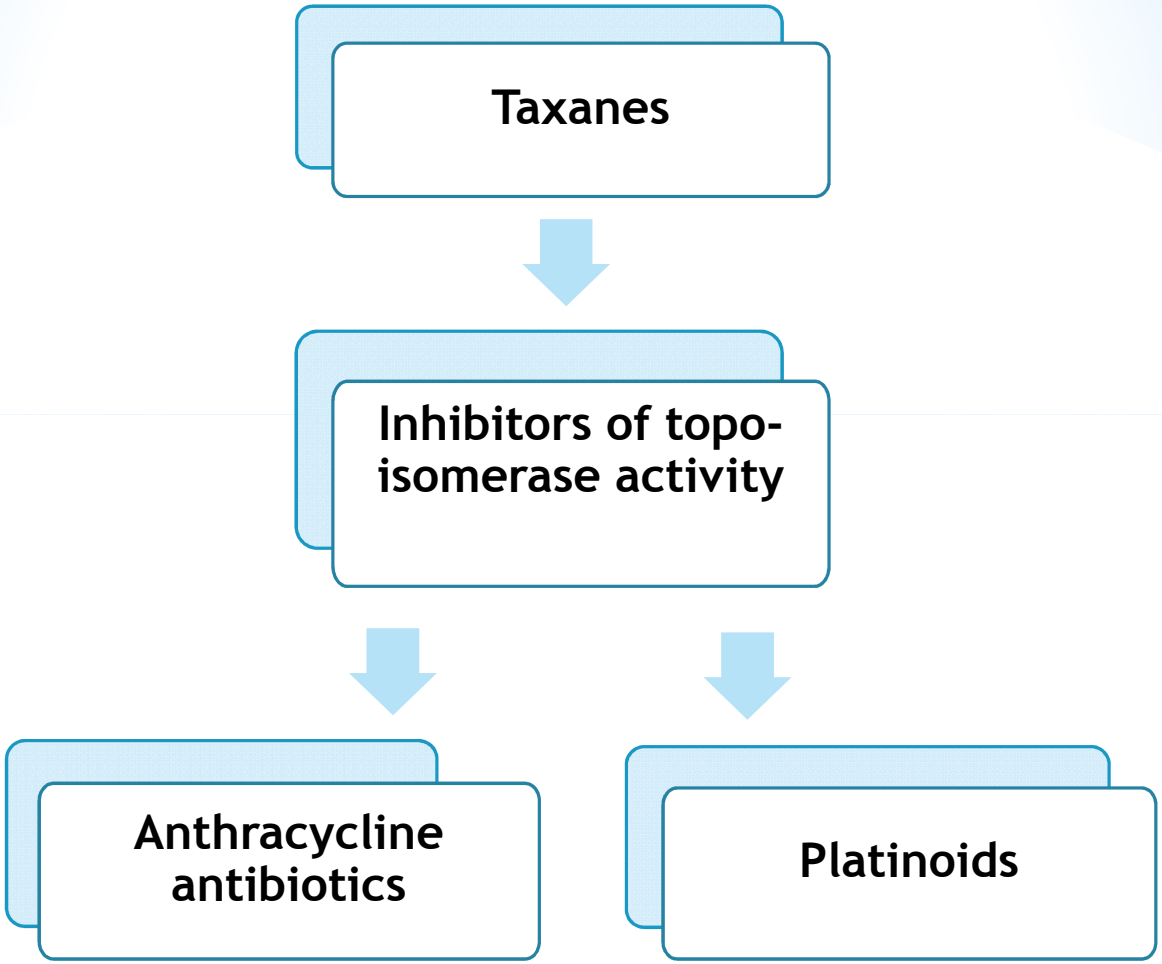
Ep – Epirubicin; Cs – Cisplatin; Cr – Carboplatin; Et – Etoposide; P – Paclitaxel

Embryonic mortality in female rats while the crossbreeding long-term period after administration of cito-static drugs of different groups (% of control)

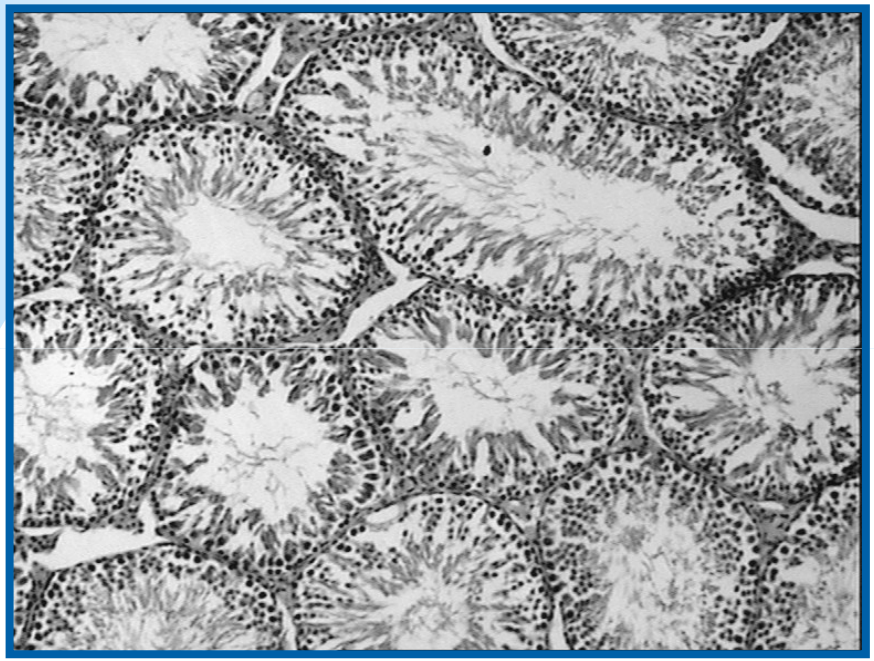


Ep – Epirubicin; Cs – Cisplatin; Cr – Carboplatin; Et – Etoposide; P – Paclitaxel

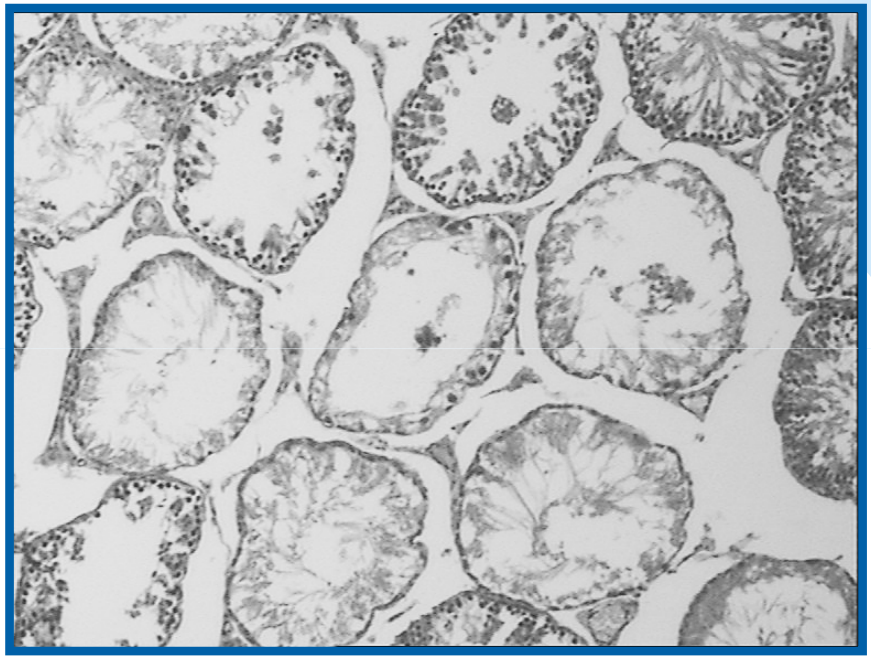
Toxic effect of drugs on embryonic mortality is decreased in the following order:



Morphological status of the testes of rats at 3 months after administration of Paclitaxel and Epirubicin

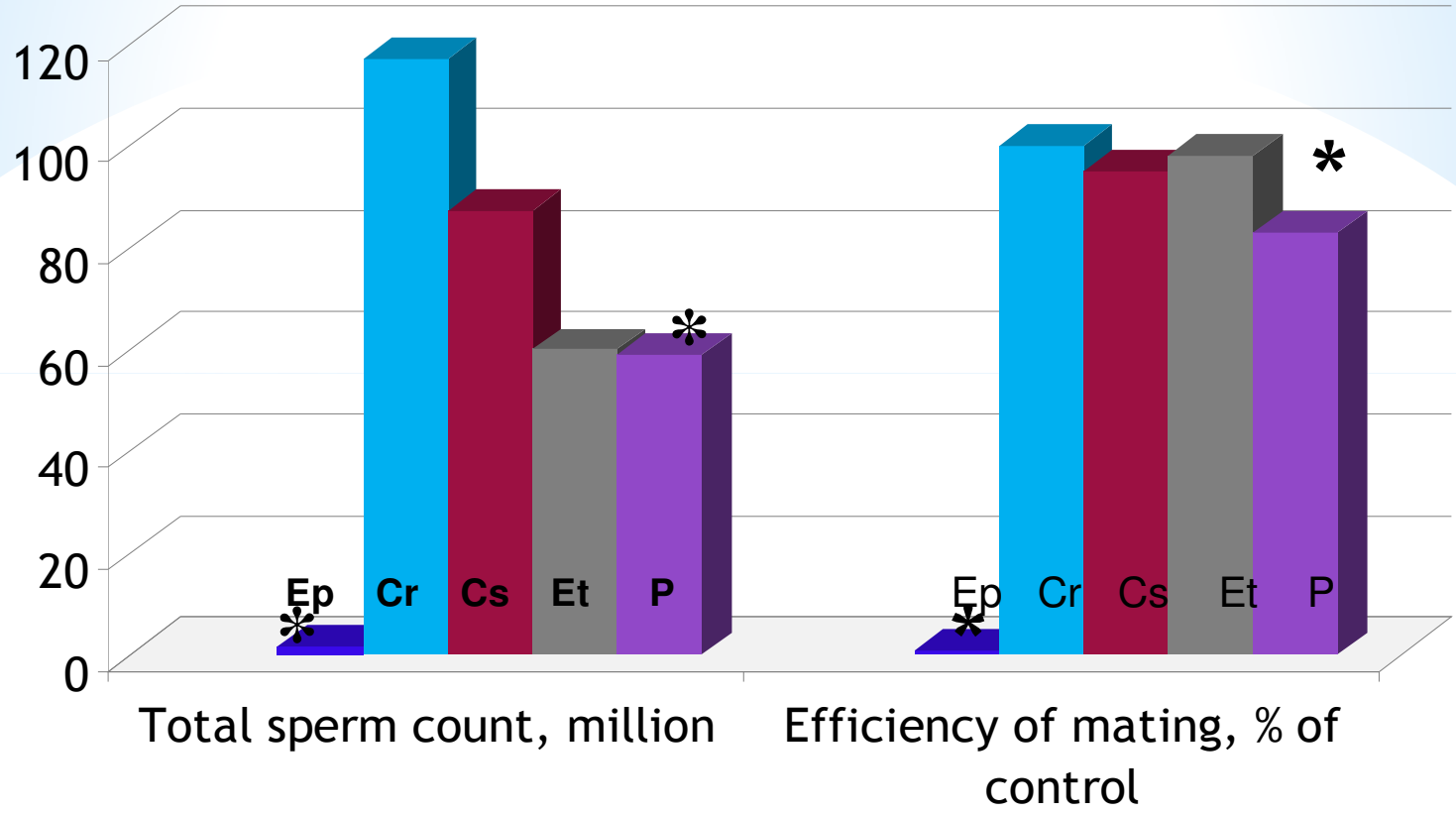


Intact rat testis, age 5.5 months, x160. Staining with hematoxylin and eosin.



Testis rats 3 months after administration of Paclitaxel and / or Epirubicin, x160. Thinning seminiferous epithelium. Staining with hematoxylin and eosin.

Sperm count, and efficiency of mating male rats at 3 months after administration of cyto-static drugs of different groups

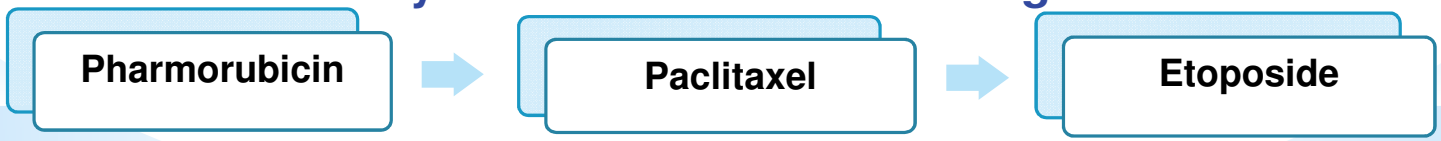


Ep – Epirubicin; Cs – Cisplatin; Cr – Carboplatin; Et – Etoposide; P – Paclitaxel

State of reproductive system of male rats long-term after administration of cyto-static drugs of different groups

Drug	Sexual instinct	Fertility	Level of (DLM) (characterizes the probability to save pregnancy)
Platidiam	Not disturbed	Not disturbed	Not increased
Carboplatin	Not disturbed	Not disturbed	Not increased
Pharmorubicin	Not disturbed	**Infertility, 100 %**	Not increased
Doxorubicin	Not disturbed	Not disturbed	Not increased
Etoposide	Not disturbed	Not disturbed	**Increased**
Paclitaxel	Not disturbed	**Infertility, 100 %**	**Increased**

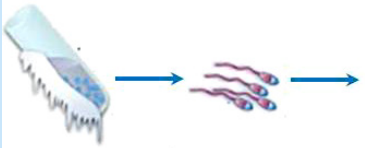
Toxicity decreases in the following order:



In platinum drugs toxicity was not found

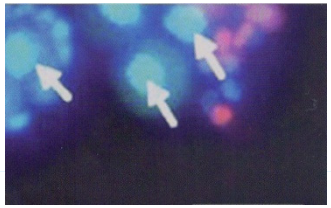
Possible ways to reduce the long-term consequences of the effect of cyto-static drugs on reproductive system by assisting reproductive technologies

- ***Cryopreservation of sperm***



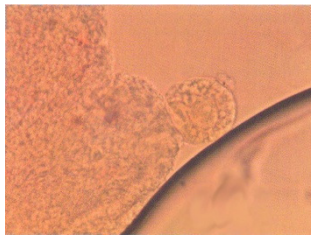
IVF
ISI

- ***Cryopreservation of oocytes***



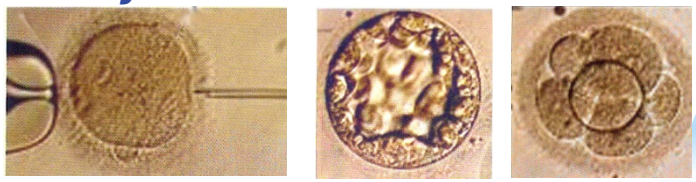
- ***Testis tissue biopsy***

- ***Cryopreservation of ovarian tissue***



- ***Differentiation of bone marrow stem cells into male germ cells***

- ***Cryopreservation of embryos***



Negative aspects of assisted reproductive technologies:

1. High cost
2. Inability to perform due to the need to start chemotherapy
3. high sensitivity of oocytes to freezing

Comments:
IVF - in vitro fertilization
ISI - Intracytoplasmic Sperm Injection
чССК - human spermatogonial stem cell

The effectiveness of drug therapy as the way to reduce the effects of cyto-static gonadotoxicity

❖ **Immunomodulators**

[*Carmely A., 2009*]

❖ **Gonadal-hormone products**

❖ **Stimulator of spermatogenesis (testosterone)**

Эффективность низкая
[*Delis J. et al., 1987*]

❖ **Hypothalamic regulators of pituitary function**

[*Bocker L. et al., 1990; Borovskaya T.G. et al., 2007*]

Drugs limiting apoptosis in oocytes (sfignozin monophosphate)

[*Tilly J.L. et al., 2004*]

❖ **Means of regenerative medicine**

[*Borovskya T.G., Dygai A.M., Zhdanov V.V., 2008*]

Widely used in clinic, highly effective

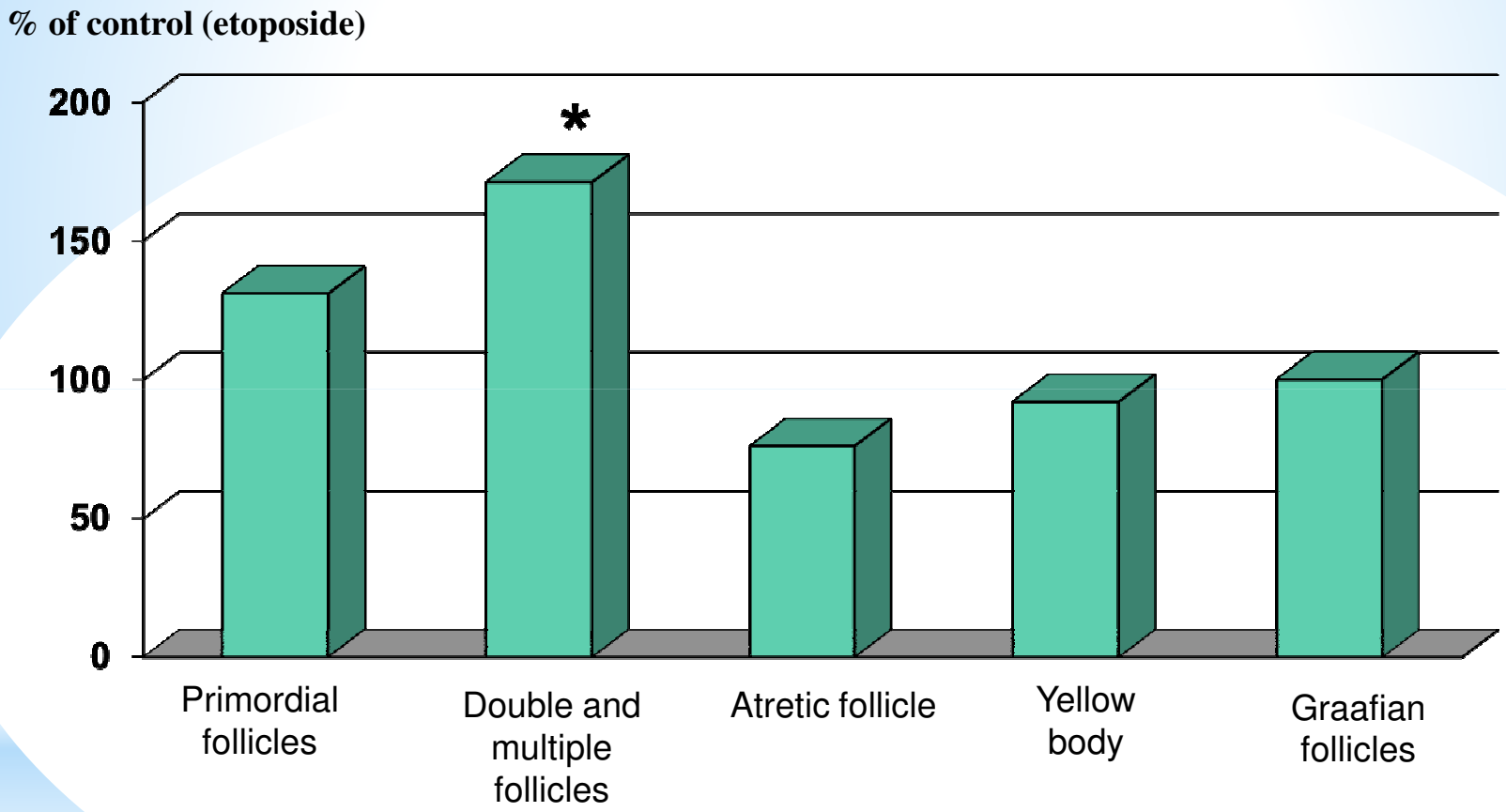
Low efficiency

Negative aspects:
1. High cost
2. Inability to perform due to the need to start chemotherapy

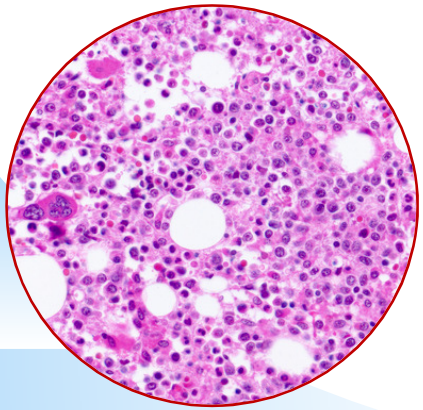
❖ **Antioxidants**

[*Kolomietz O.L. et al., 2001; Borovskaya T.G. et al., 2003*]

Number of structural and functional elements of rats ovaries, 6 months after combined administration of Etoposide and Buserelin

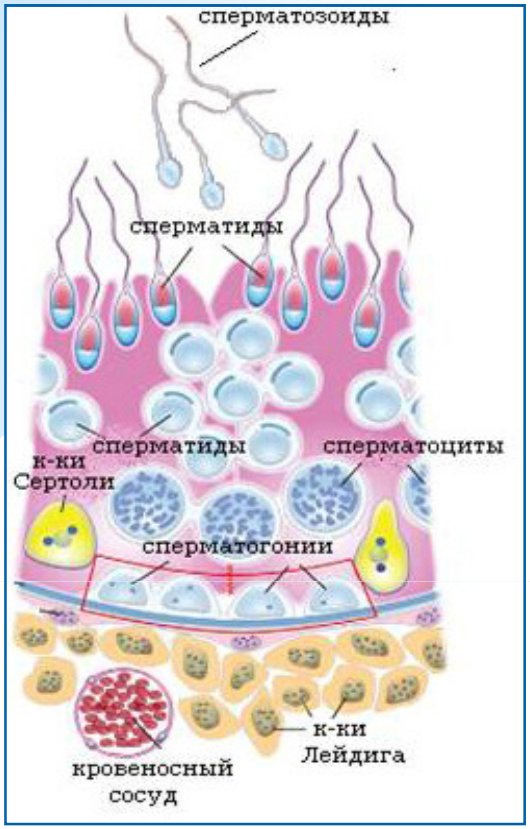


Recent years, the new information about the properties of pluripotent progenitor cells of the body was obtained. The possibility of mobilizing the internal mechanisms of "deep reserve" – bone marrow stem cells and their following homing into the damaged tissue and activation of regional stem cells by various cytokines is shown.

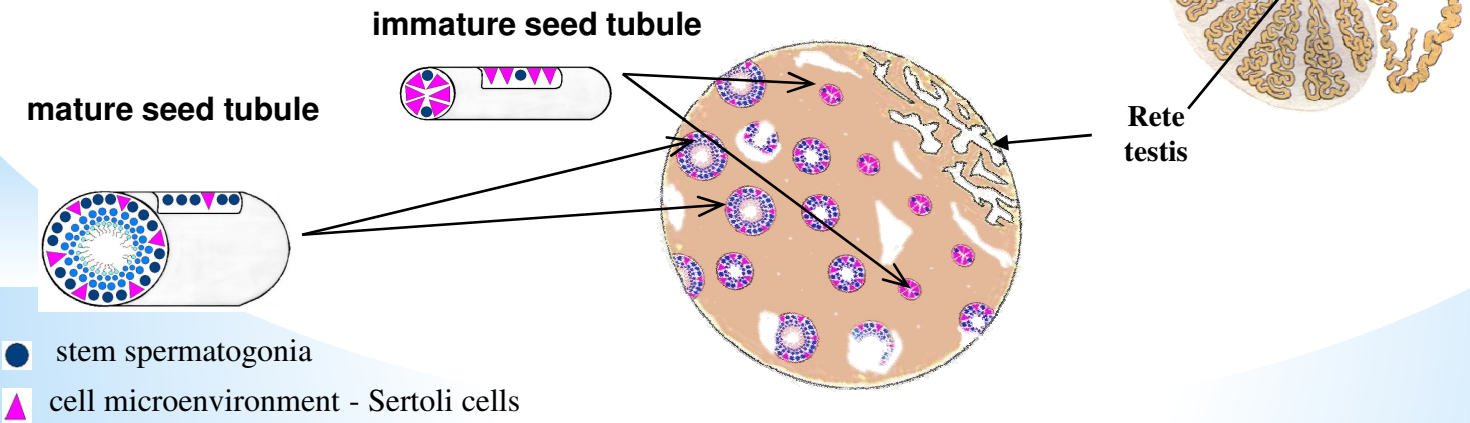


A.M. Dygai, V.V. Zhdanov et al.
2006, 2010, 2011

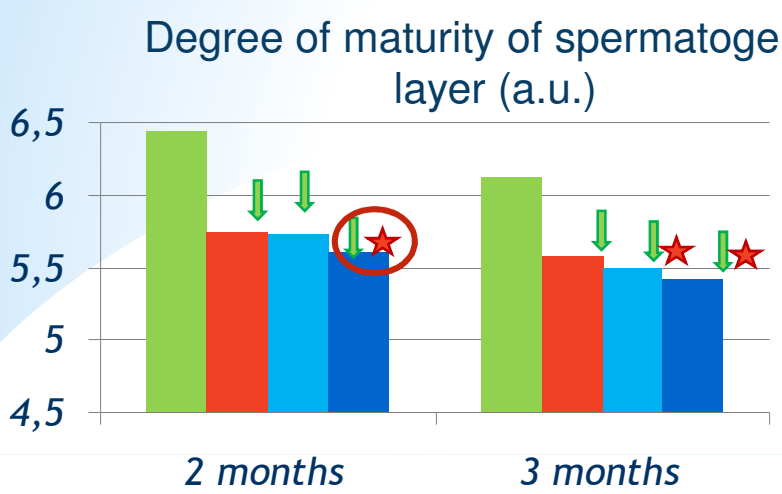
Reparative regeneration of testicular tissue after administration of Paclitaxel

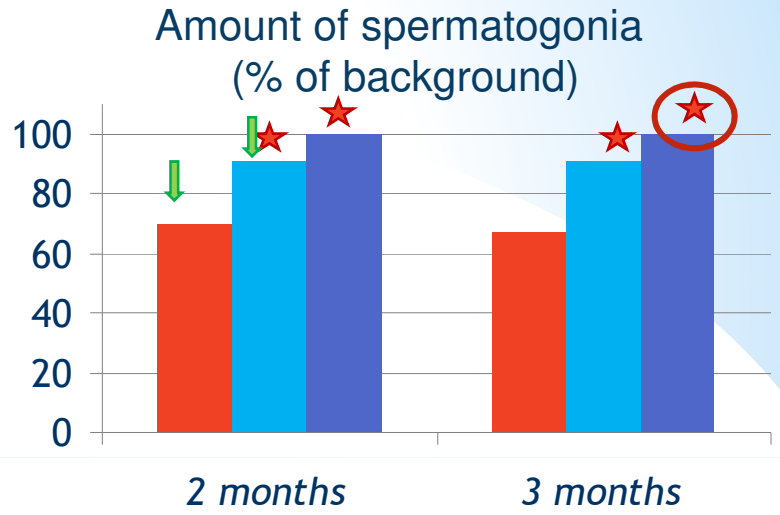


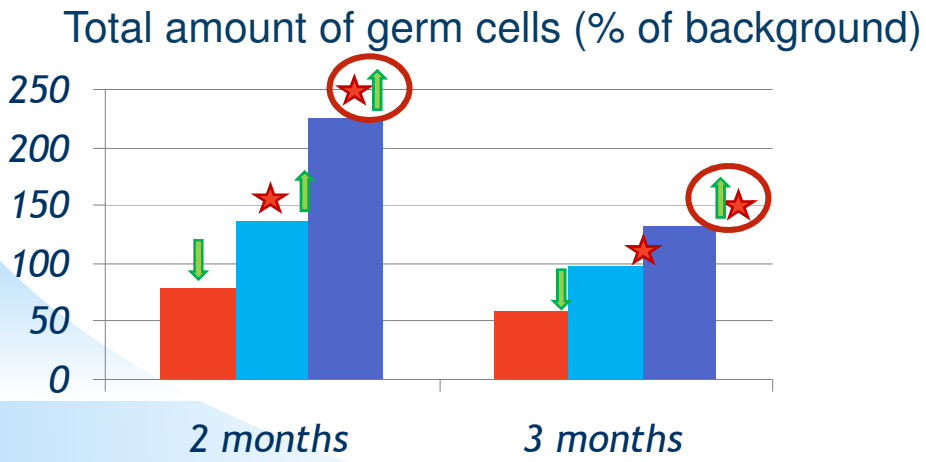
Restoring of spermatogonia goes under upgrading of spermatogenic layer



Status of spermatogenesis in rats late after combined administration of paclitaxel with G-CSF and pegylated G-CSF





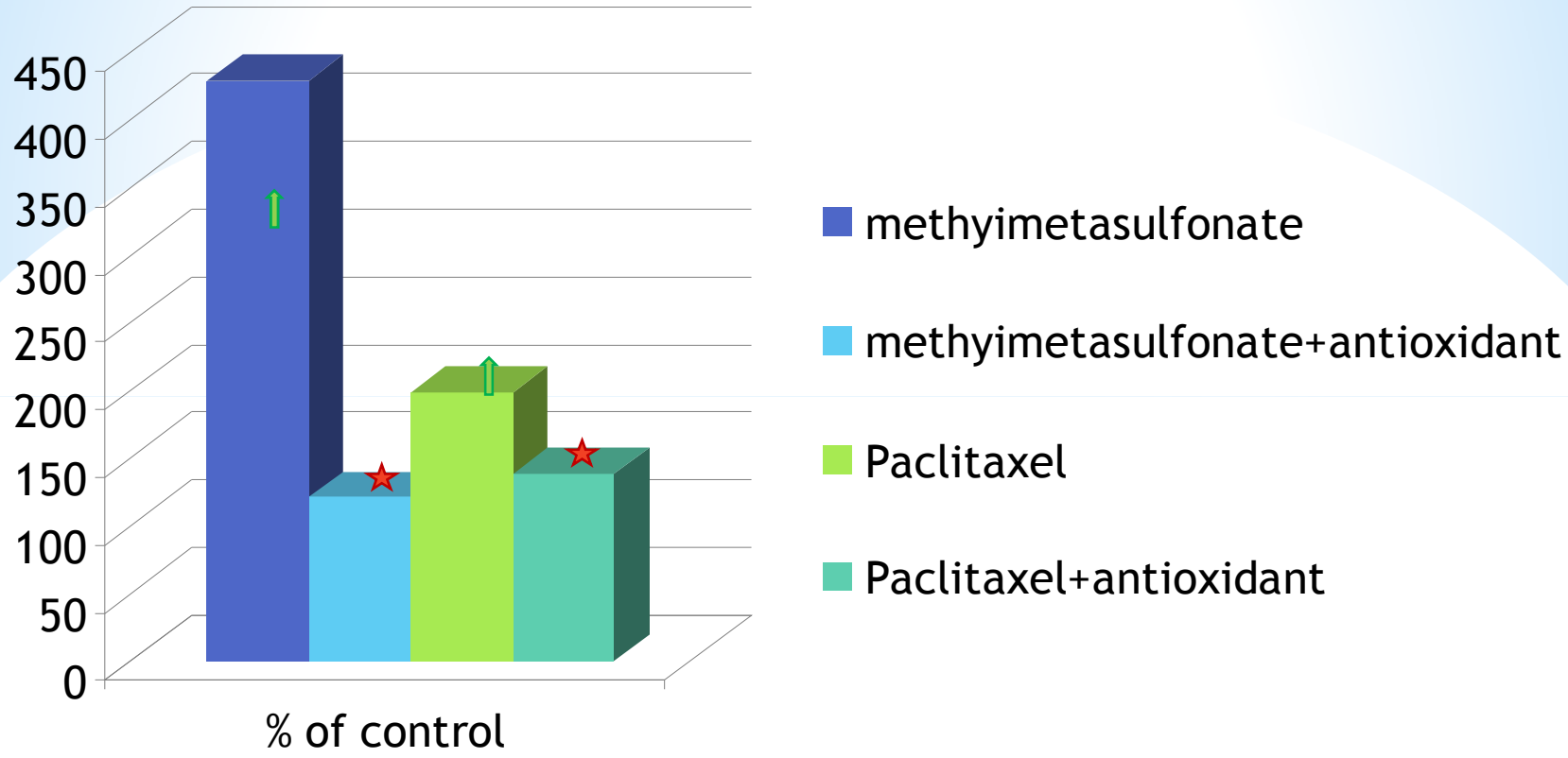


background
Paclitaxel (control)
Paclitaxel + G-CSF
Paclitaxel + pegylated G-CSF

– differences are significant compared to the background

– differences are significant compared to the control

Effect of antioxidant from the group of sterically hindered phenols to the level of DNA comets in the testes of mice treated with methyl-meta-sulphonate or paclitaxel



⇧ – differences are significant compared to the background

★ – differences are significant compared to corresponding control

Thank you for attention!