



Club de conseil génétique de **langue** française

# Conseil génétique chez les hommes exposés aux agents mutagènes

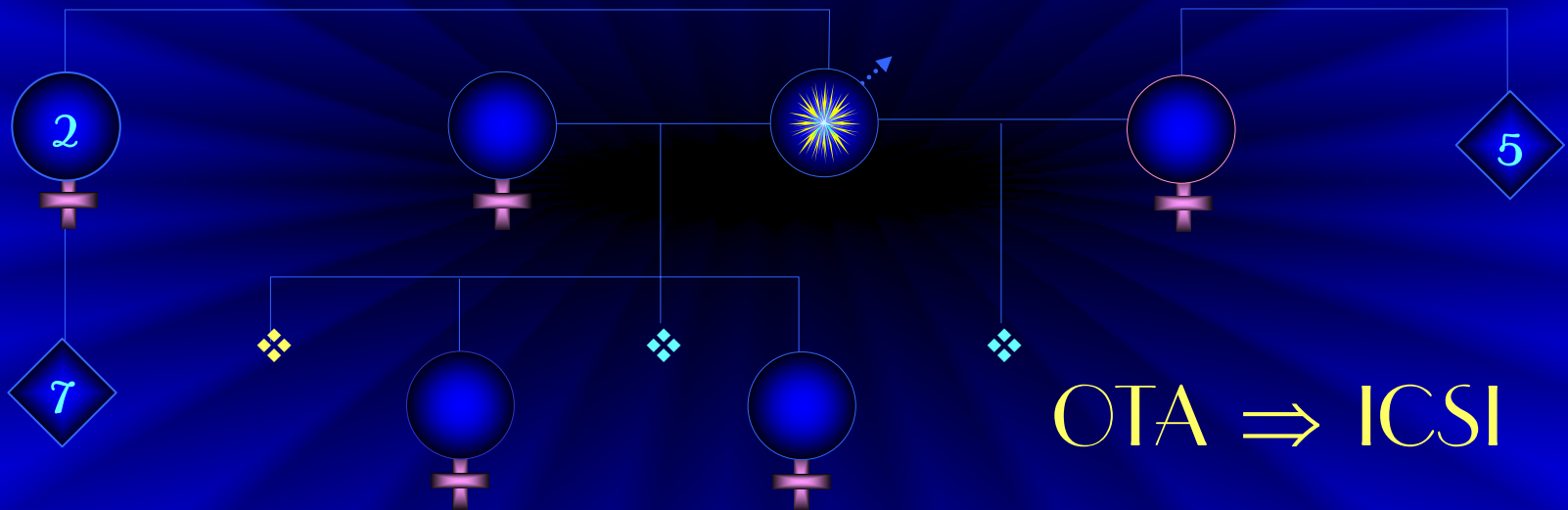
Professeur **Graziano Pescia**



AMS-MNS AMS-Pathologie Analyza BBR/LTC Immunosa



# E.B., fonctionnaire de police international



OTA  $\Rightarrow$  ICSI

 Mission au Kosovo



## Soldiers' sperm

Feb. 25 — When soldiers go off to battle, they're usually told to get their legal and financial affairs in order... that's the normal reality of war. Now there's a new twist in soldiers' preparations for the unthinkable: Some of the men who may fight and die in Iraq are leaving deposits at sperm banks before heading overseas.



**Le Monde.fr**

2 avril 2003

### LE CRI DES VÉTÉRANS

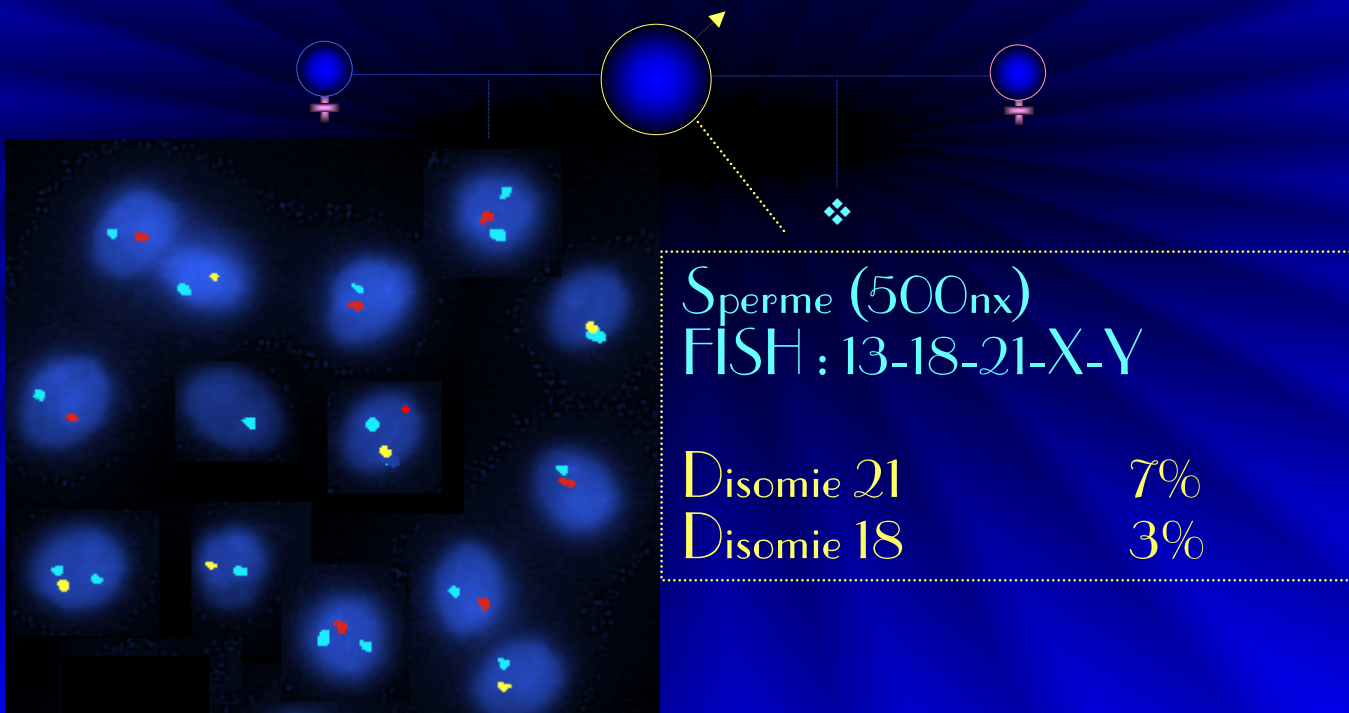
Sur les risques encourus aujourd'hui, il y a des indices qui ne trompent pas. On a aussi proposé aux hommes de faire congeler leur sperme.



# E.B., fonctionnaire de police international

Caryotype (30 métph) et FISH (200nx)

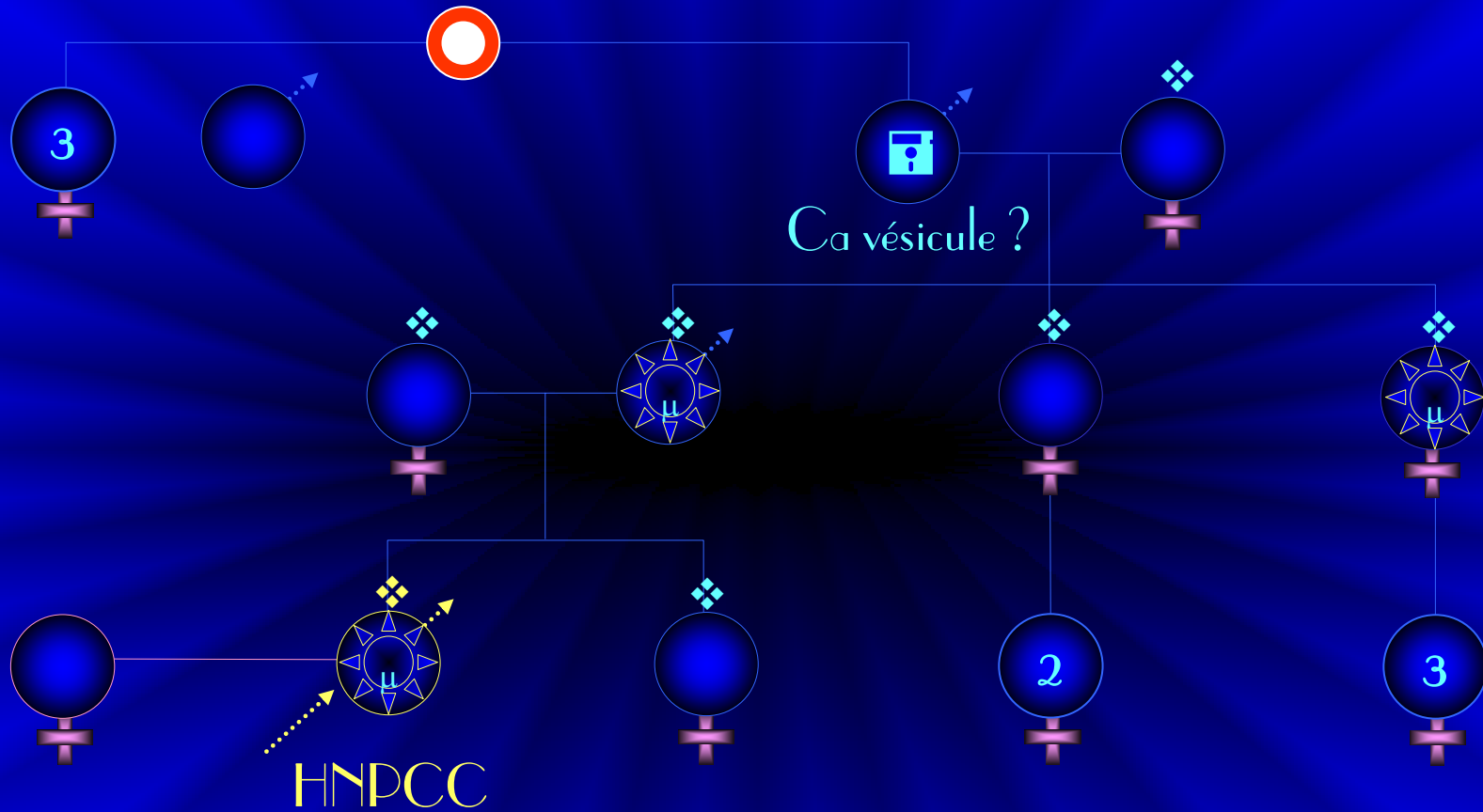
lymphocytaires : Normal  
Dél Y Négatif



# K.U, agriculteur



# Généalogie, ADN et diagnostic



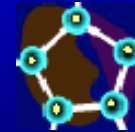
 ADN tumoral : instabilité des microsatellites  
ADN lymphocytaire :  $\mu$  *MSH2*



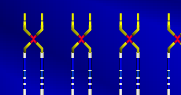
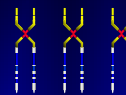
# Circonstances et types d'exposition

Circonstances

Types d'exposition



Professionnelles		
Accidentelles		
Médicales (1 jeune adulte/250 est survivant du Ca)		
Diagnostiques		
Thérapeutiques		



- \* Paternal occupations associated with birth defects were  
janitors, painters, printers,  
and occupations exposed to solvent;  
fire fighters or firemen;  
and occupations related to agriculture.
- \* Common weaknesses in most of these studies included  
inaccurate assessment of exposures,  
different classification systems,  
different inclusion criteria of birth defects,  
and low statistical power.
- \* Future studies could be focused on these specific,  
rather than general, occupational groups so that  
causative agents may be confirmed, thus  
enabling appropriate preventive measures to be taken

S-E Chia & L-M Shi, *Occup enviro Med*, 2002, 59, 149-155





# Cibles d'exposition (MMT)



Fœtus (effet tératogène)

Liquide séminal

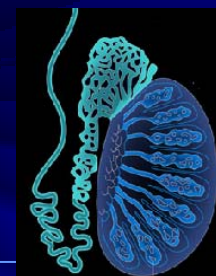
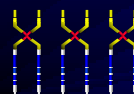
Habits souillés

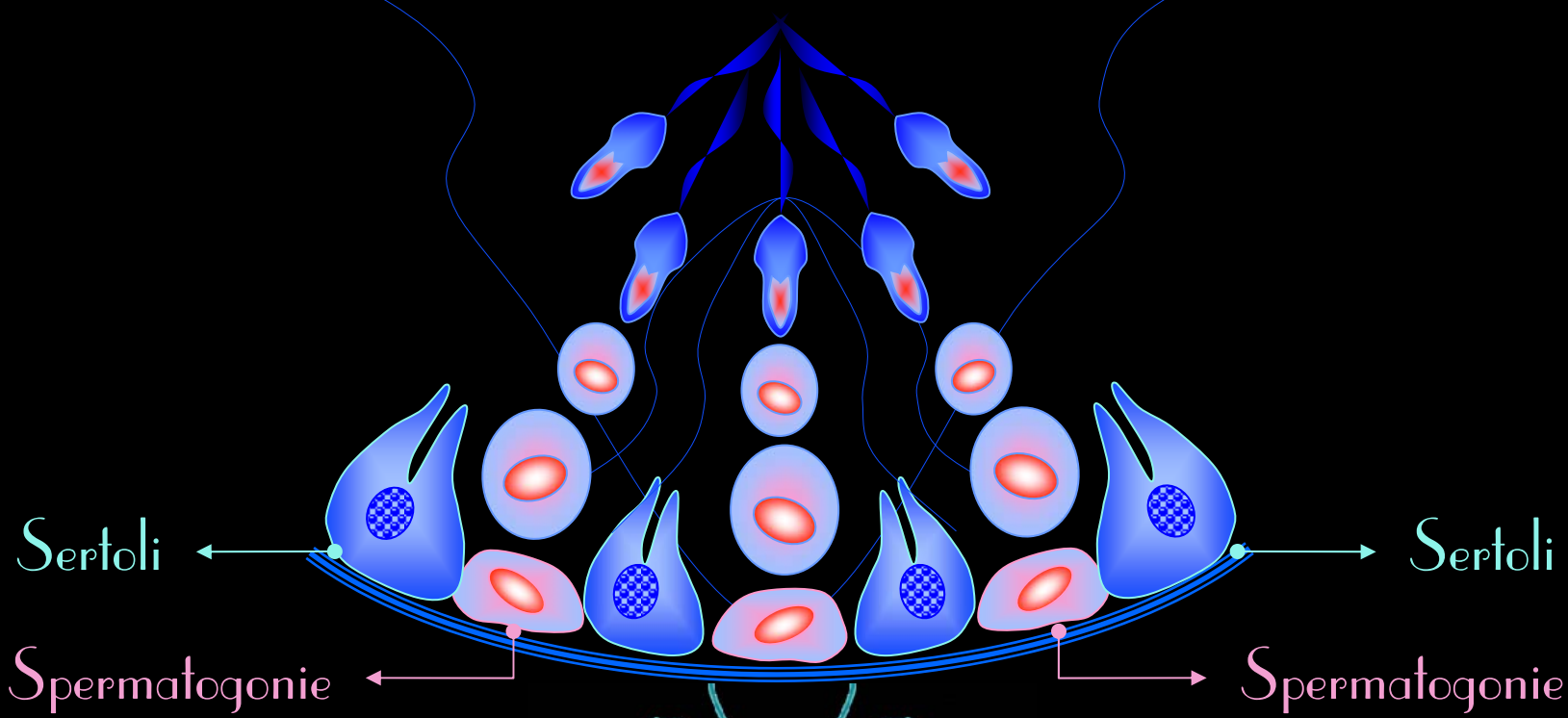
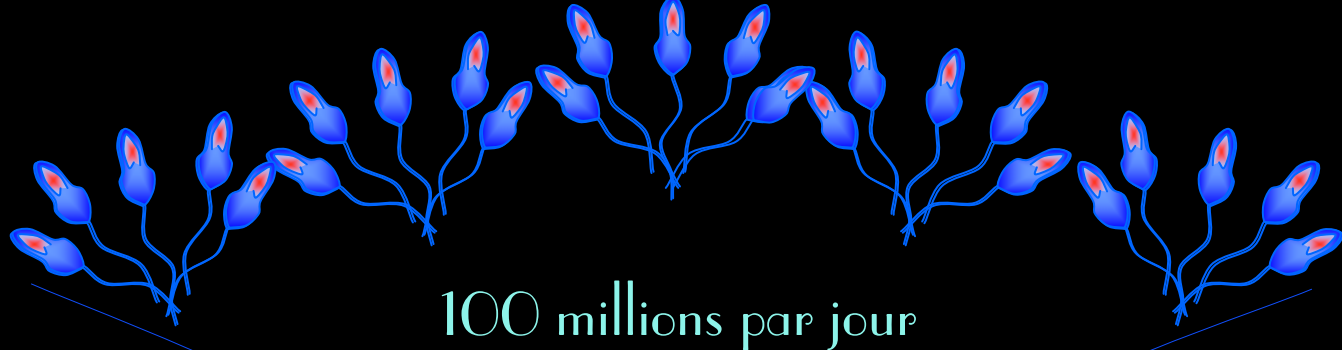
Testicules (effet mutagène)

Lignée germinale

Cellules de Sertoli

Cellules de Leydig





A handwritten signature in the bottom right corner of the image.

Départs : tous les 16 jours

Durée 74 jours

## Spermatogonie Ad

Arrêt à : ⚠ ← R

Sp~gonie Ap

⚠ ← R

Sp~gonie B

⚠ ← R

Sp~cyte I

⚠ ← Mé I + R

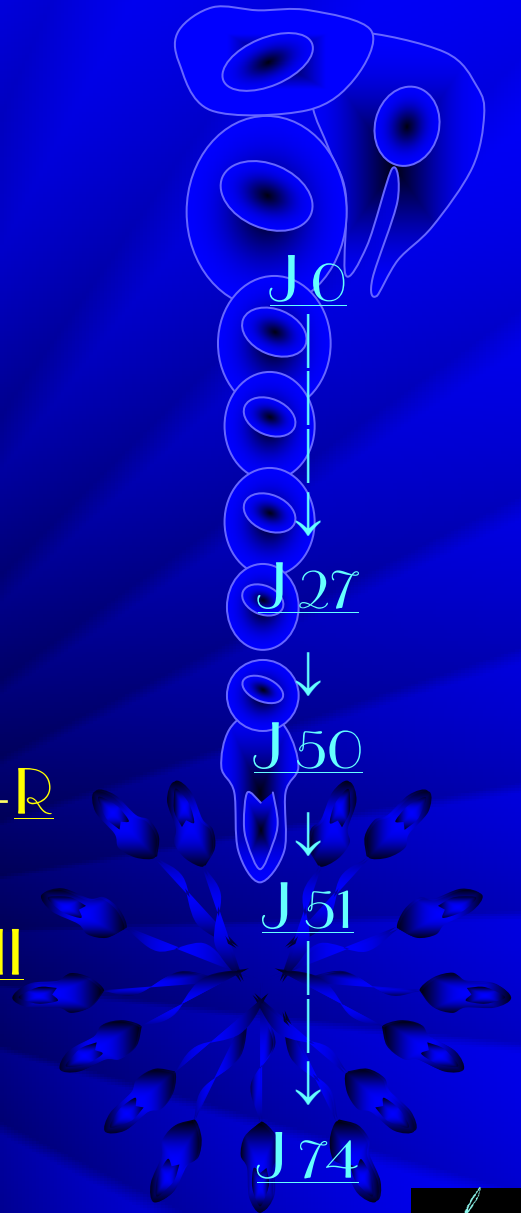
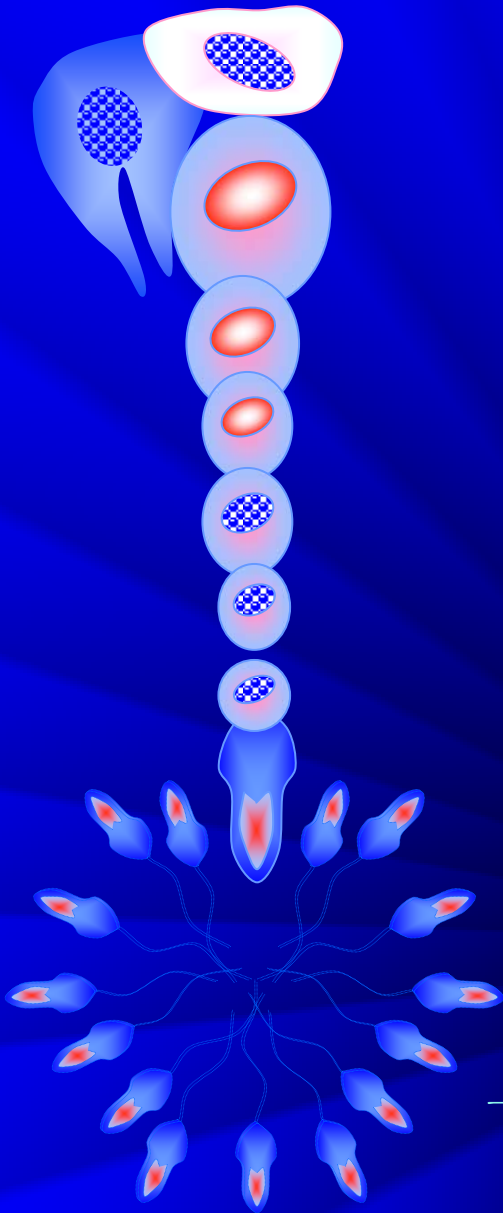
Sp~cyte II

⚠ ← Mé II

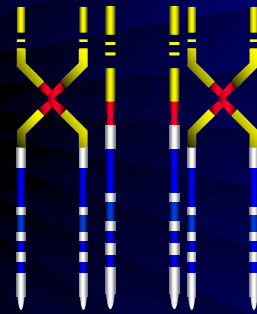
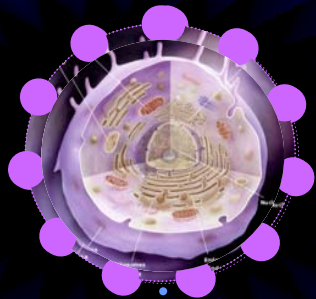
Spermatide

Terminus

Spermatozoïde

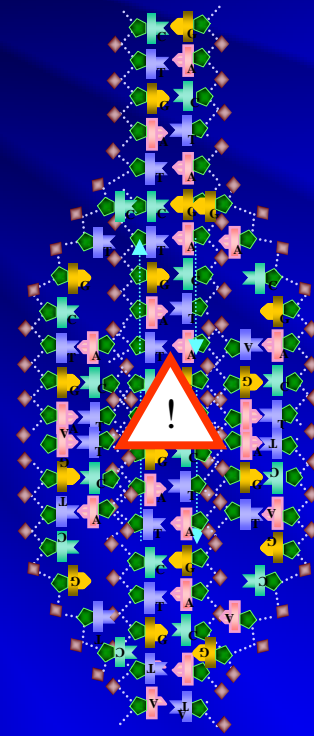
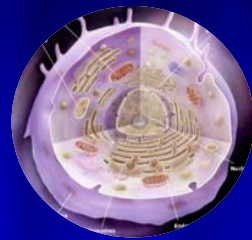


Cellule souche



Réplication

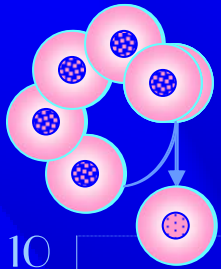
Division



Différentiation

Mort

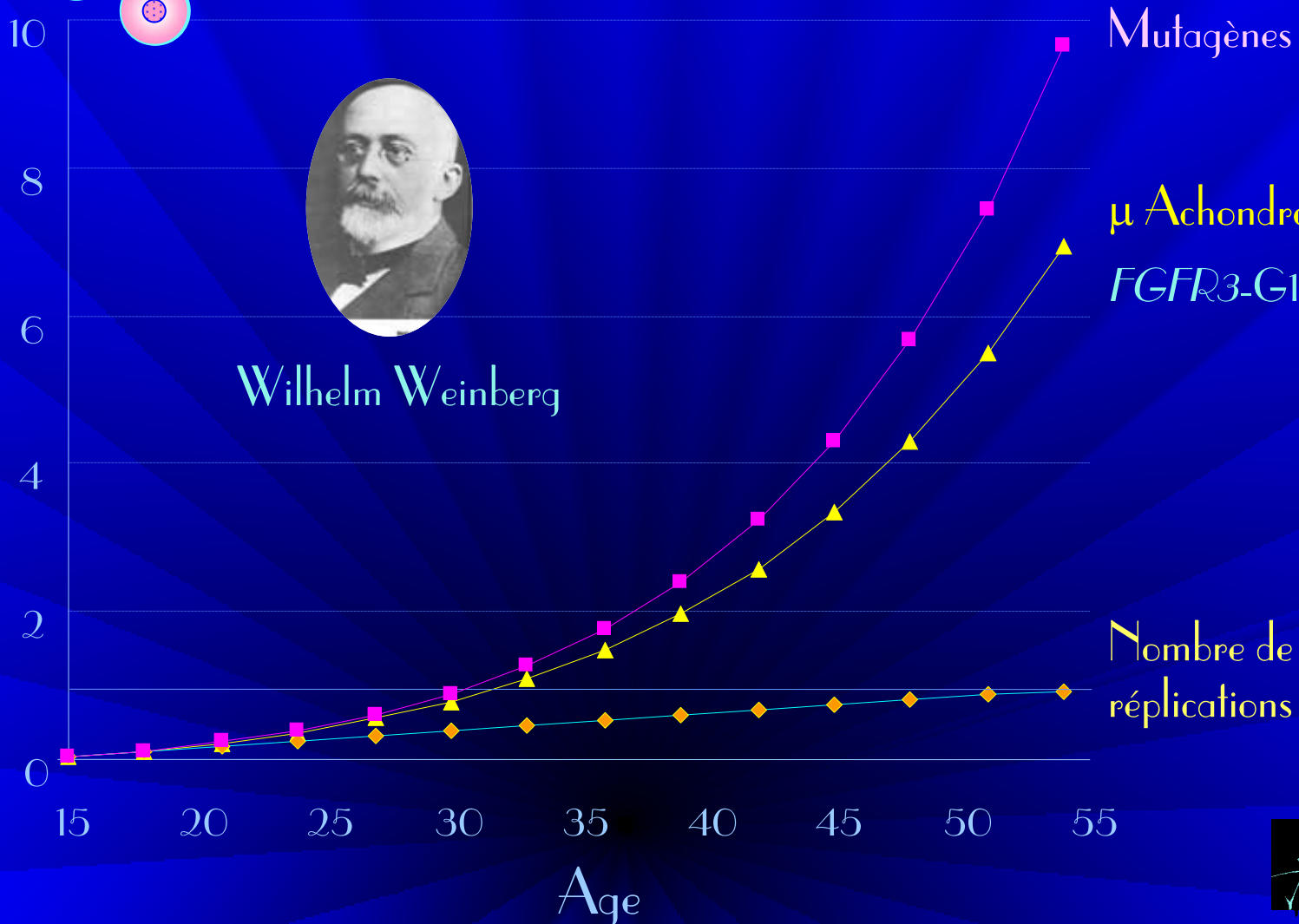




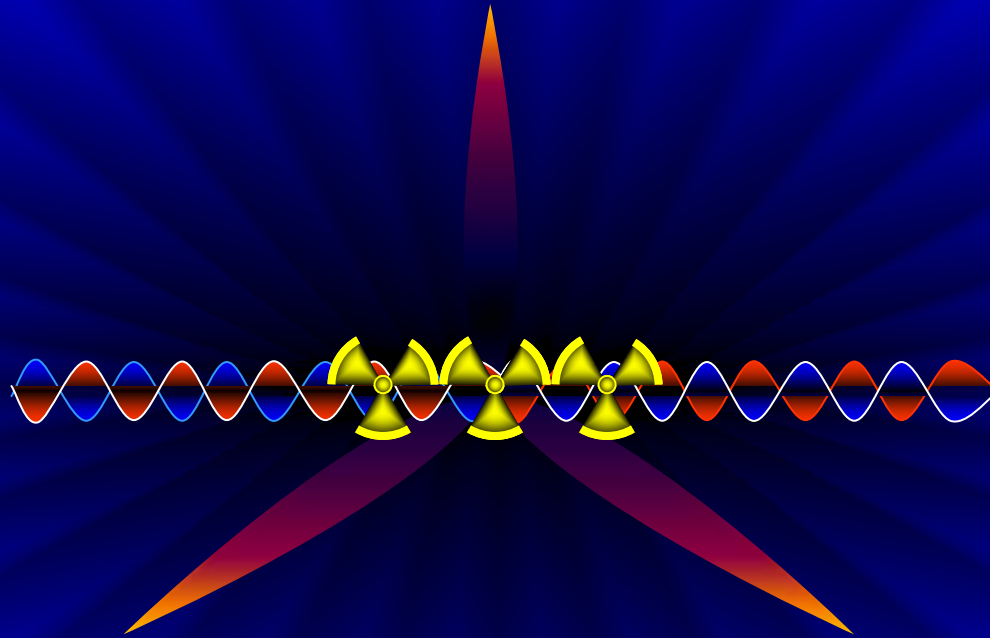
$$\text{Nombre de réplifications de l'ADN} = 30 + (A - A_p) * 23 + 5$$



Wilhelm Weinberg



Génétiques

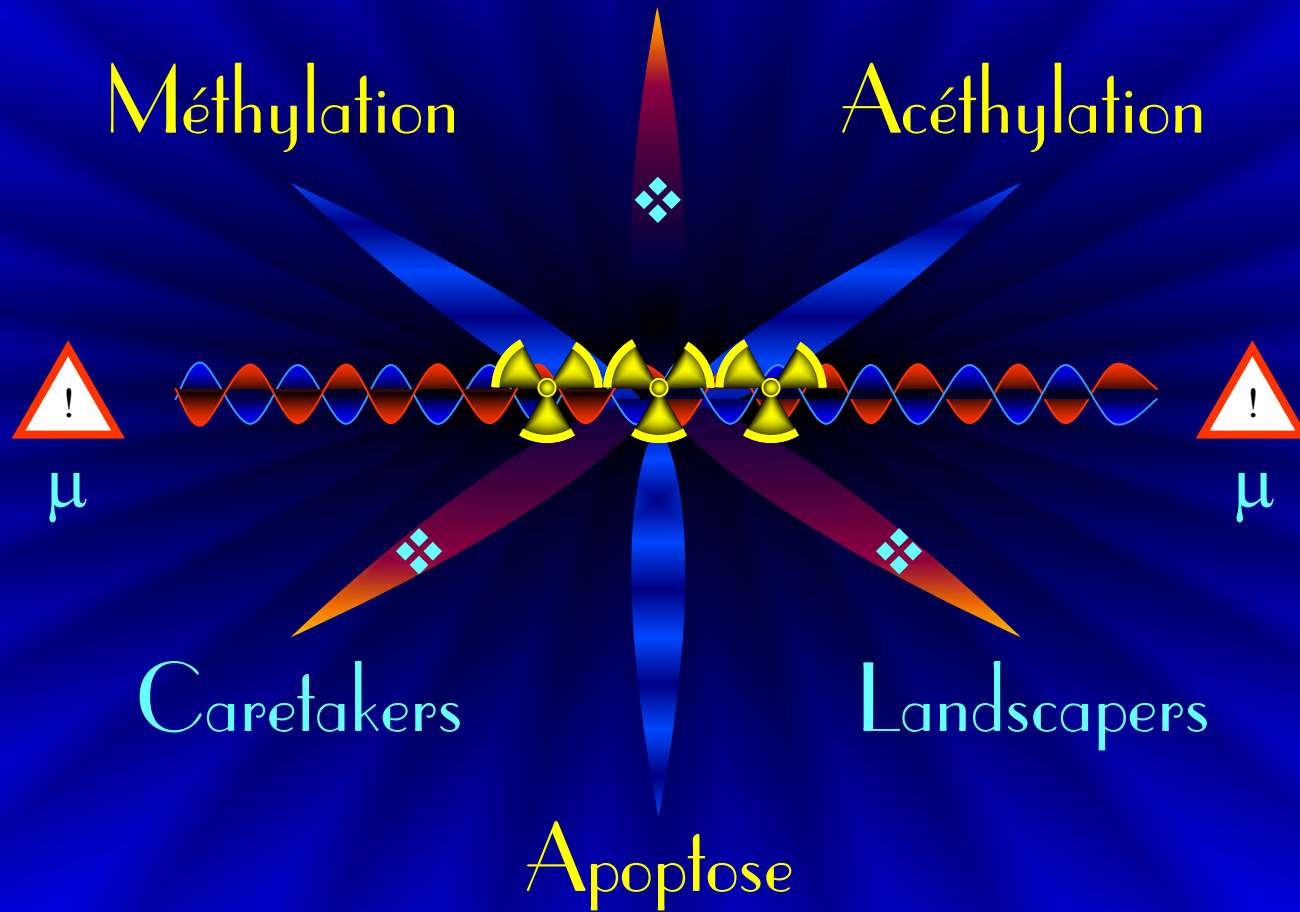


Épigénétiques

Environnement



# Gatekeepers



## Modifications



de la forme  
de l'expression  
du trafic + signalétique

des protéines sans mutation  
≈ **TÉRATOGENÈSE**

Modifications de  
la structure  
la fonction  
des protéines par mutation  
≈ **MUTAGENÈSE**



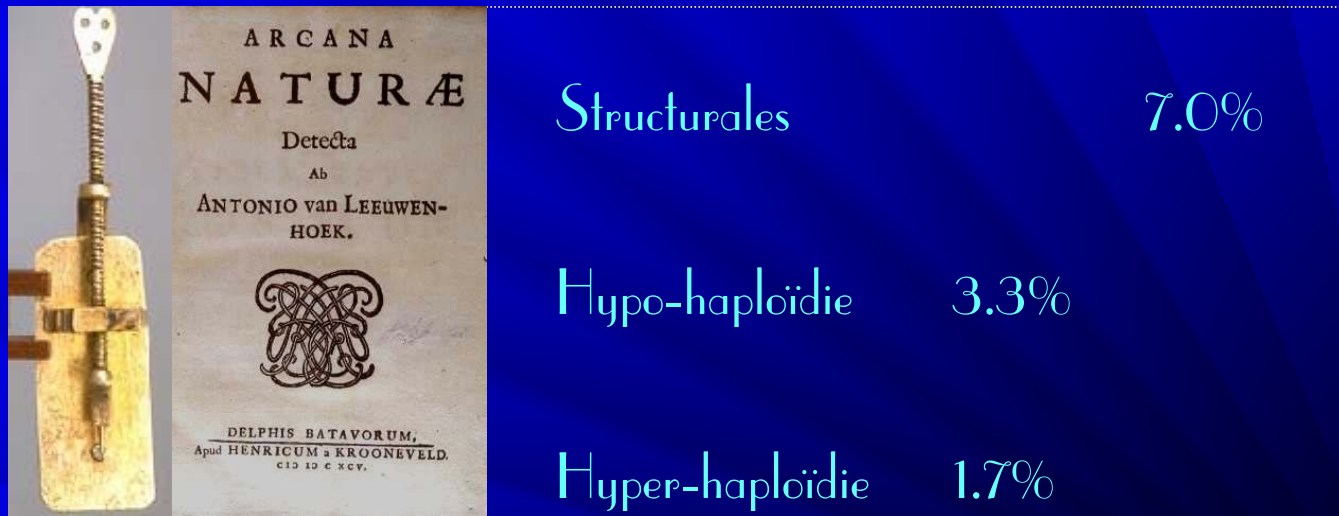
## Modifications

de l'expression  
des gènes sans mutation  
(méthylation CpG)  
≈ **EPIGÉNÉTIQUES**



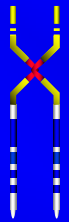


# Anomalies chromosomiques dans les spermatozoïdes de sujets normaux (17'998 spermatozoïdes)

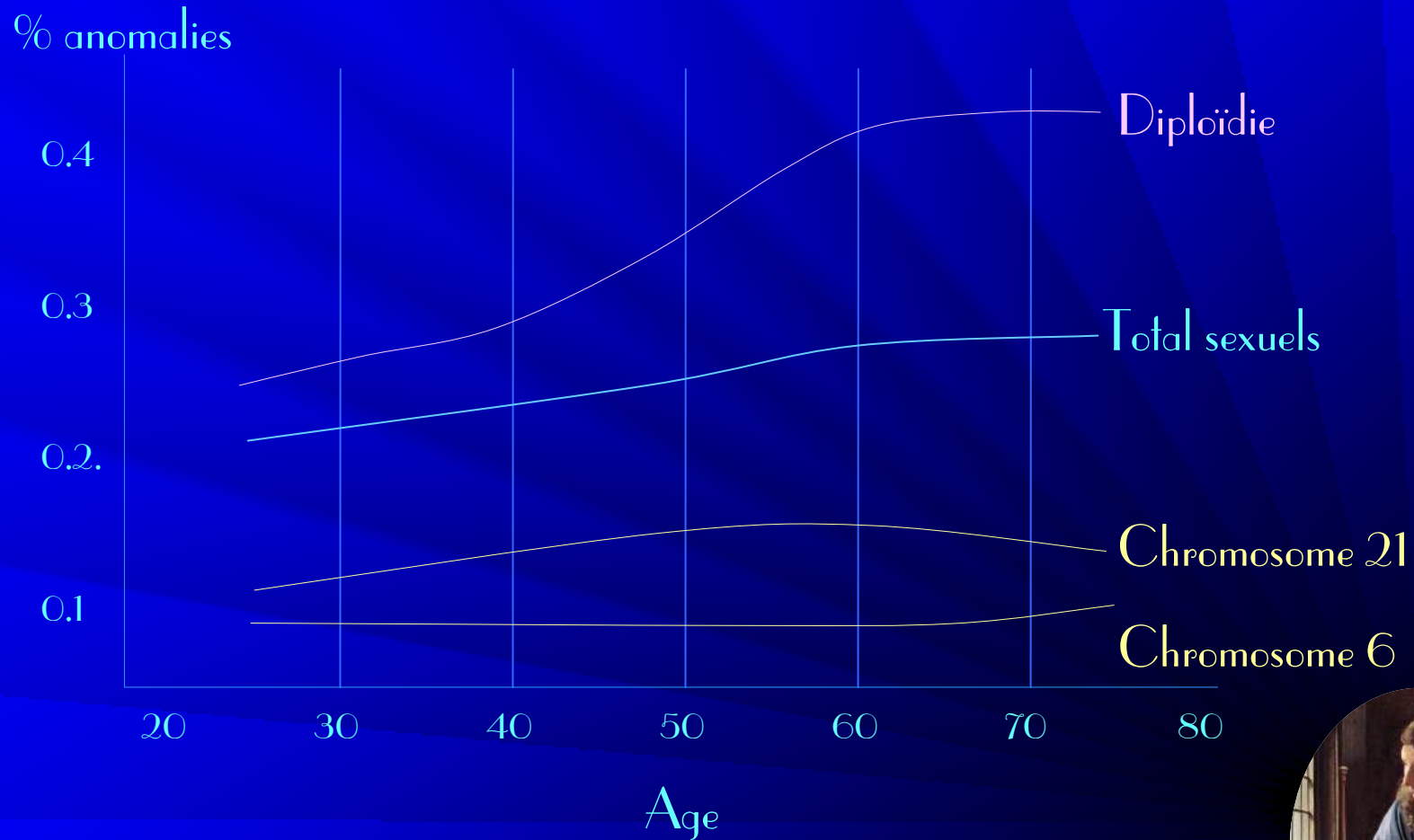
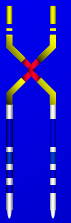


Guttenbach et al, Hum Genet 1997 100:1-21





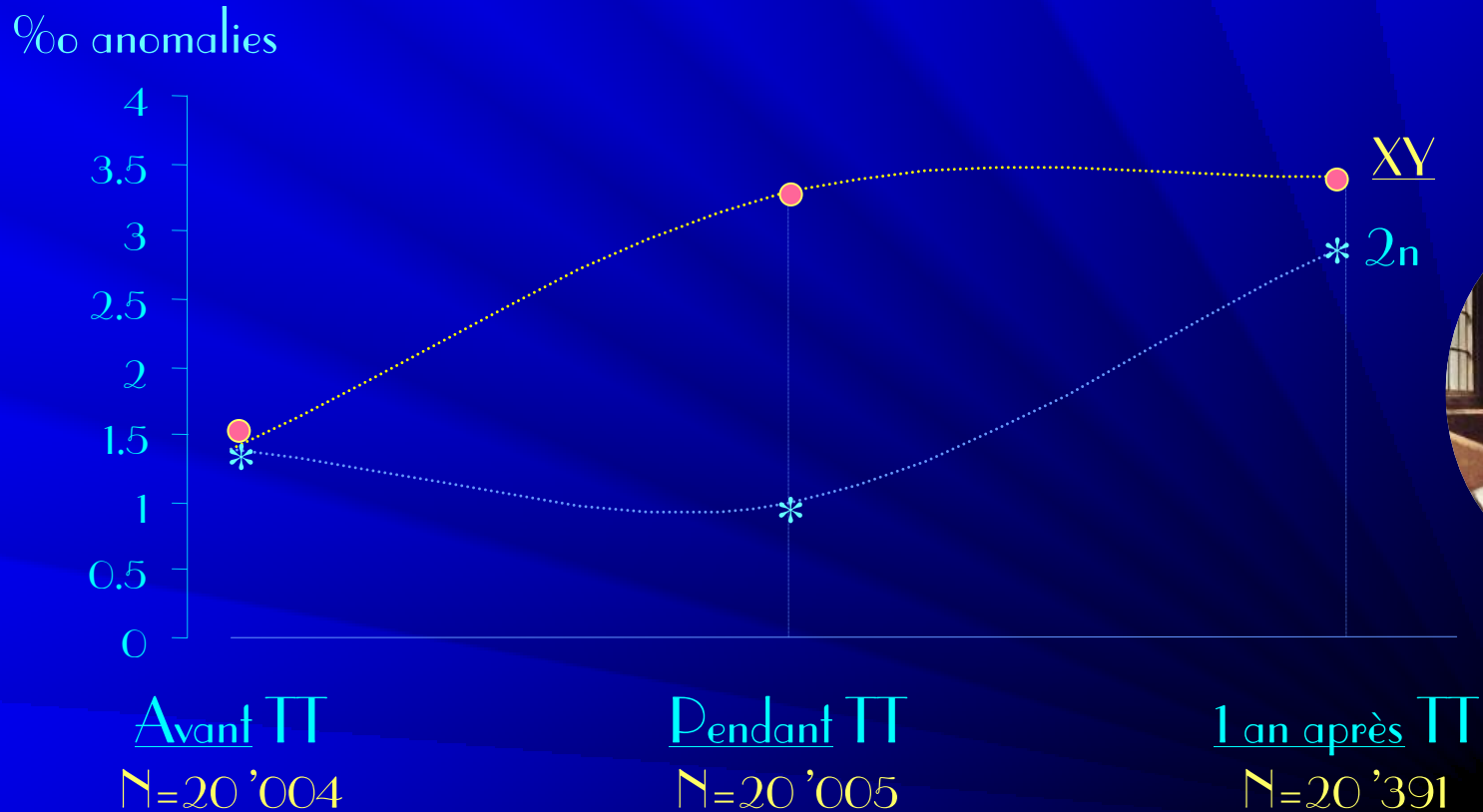
# Anomalies chromosomiques dans les spermatozoïdes de sujets normaux en fonction de l'âge



Bosch M et al, Europ J Hum Genet (2001) 9, 533

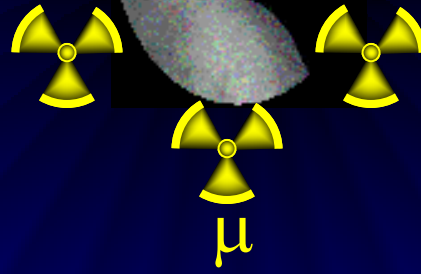


# Anomalies chromosomiques des spermatozoïdes chez les patients sous chimiothérapie



Martin R, Chromosoma (1998) 107, 523





↓ Fitness



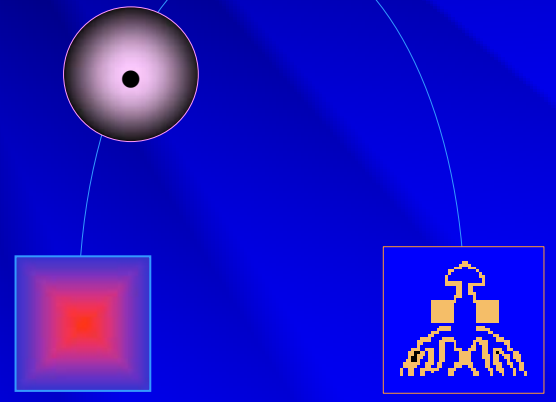
$\mu$  R-D-Polygéniques

Biologique

$\Psi$ -sociale

- Stérilité
- Mort fœtale
- Malformations
- Sex-ratio
- Cancer

↓ Nuptialité



# Fertilité chez les survivants



Taux général :

85%



Dose (cGy)

- 10-30 Oligozoospermie transitoire
- 50-100 Azoospermie réversible (3-17 mois)
- 200-300 Azoospermie définitive

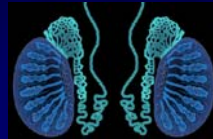




1'227 patients  
2'323 grossesses



↓ Fitness



Biologique

Vivants	69%
Mort-nés	1%
F. couches	13%
Avortements	13%
Inconnus	4%

Stérilité
Mort foetale
Malformations
Sex-ratio
Cancer

↓ 15%
ns
ns
↓
=



Green D et al,  
J Clin Oncol 21:716, 2003





# Risques pour les enfants des survivants

SURVIVANTS



436

912

CONTRÔLES

One Fewer Worry  
for Survivors of Childhood  
Cancer

468

1021

2.5%

TAUX DE MALFORMATIONS (NS)

3.3%

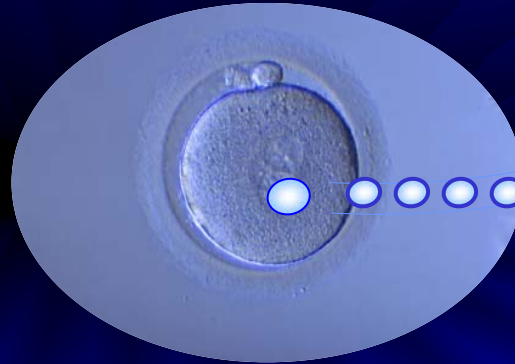


# Fertility options



Cryoconservation

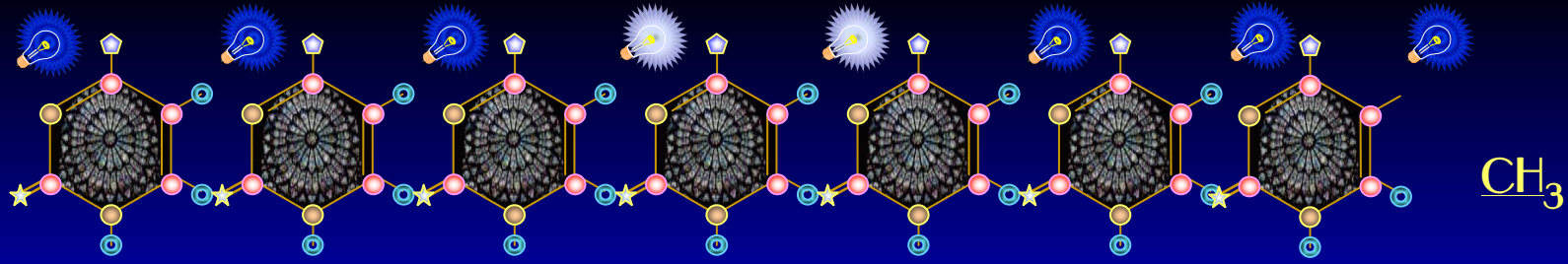
ICSI



Preservation of fertility in children treated for cancer  
*Wallace W, Thomson AB J. Arch Dis Child 2003, 88: 493,*

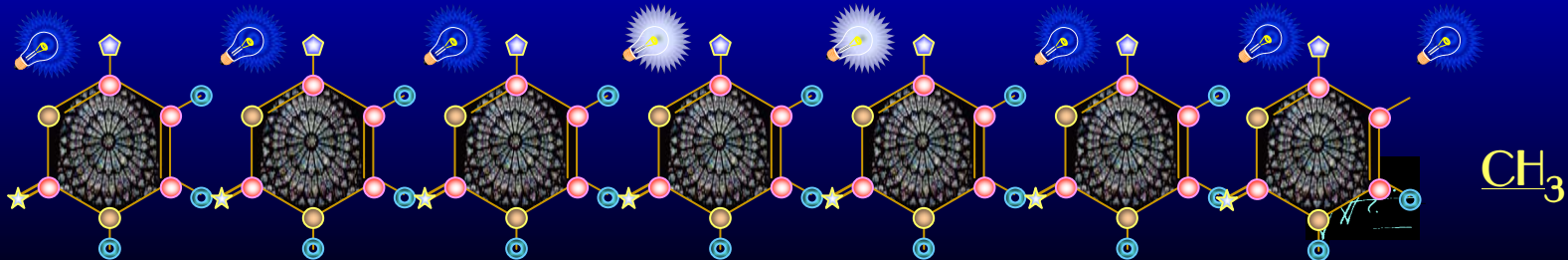
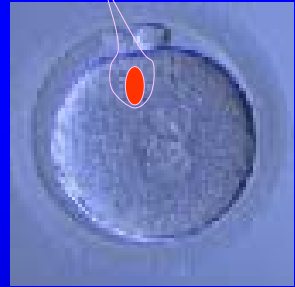






Maternal methylation imprints are established during or after fertilization

El-Maari et al, Nat Genet, 2001, 27, 341



# Anomalies de l'empreinte et ICSI



3 cas de AS

Cox et al, Am J Hum Genet, 71, 162, 2002

Ostavik et al, Am J Hum Genet, 72, 218, 2003



6 cas de BWS Maher et al, J Med Genet, 40, 62, 2003



# Malformations congénitales et ICSI



Sutcliffe AG et al, Lancet, 357, 2080, 2001

UK : 208 enfants

pas de ≠

Hansen M et al, N Engl J Med, 346, 725, 2002

Australie 301 enfants (26) 2x↑

Sutcliffe AG et al, Fertility Sterility, 79, 512, 2003

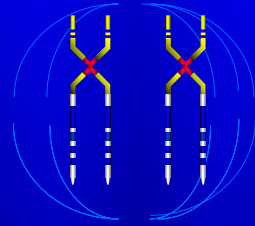
Australie 89 enfants

pas de ≠





# Conseil génétique



Risque général n'est pas significativement augmenté

Situations particulières

- \* Cancer héréditaires
- \* Cryoconservation
  - \* ICSI
- \* FISH du sperme ?
  - \* Enfants



Merci

