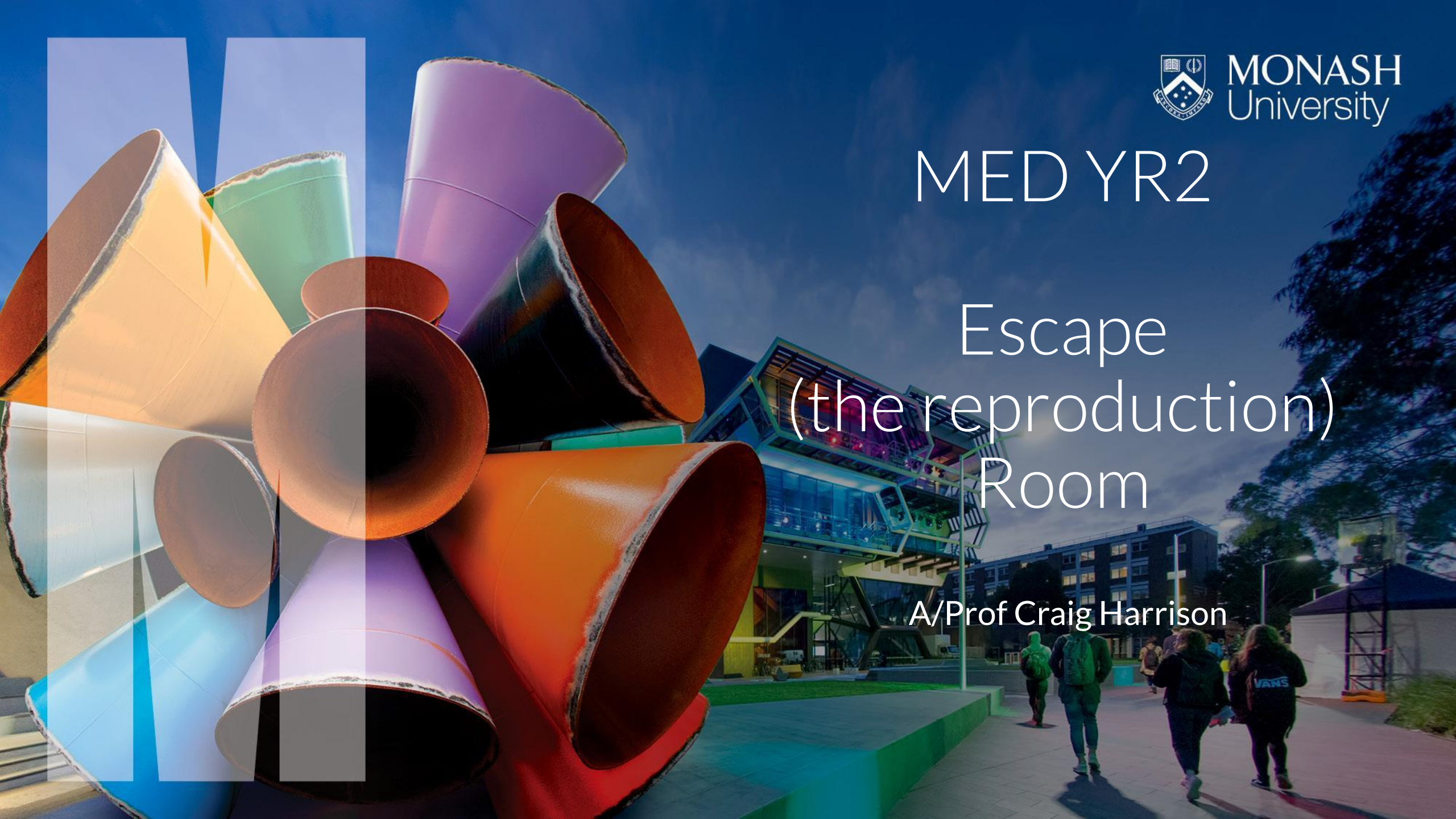


# MED YR2

## Escape (the reproduction) Room

A/Prof Craig Harrison



# THE ROYAL PROBLEM



# Notes from King Richard and Queen Barbara's Vlogs

	Queen Barbara says:
Video 1	
Video 2	
Video 3	
Video 4	

	King Richard says:
Video 1	
Video 2	
Video 3	
Video 4	

# Vlog entry 1 – Queen Barbara

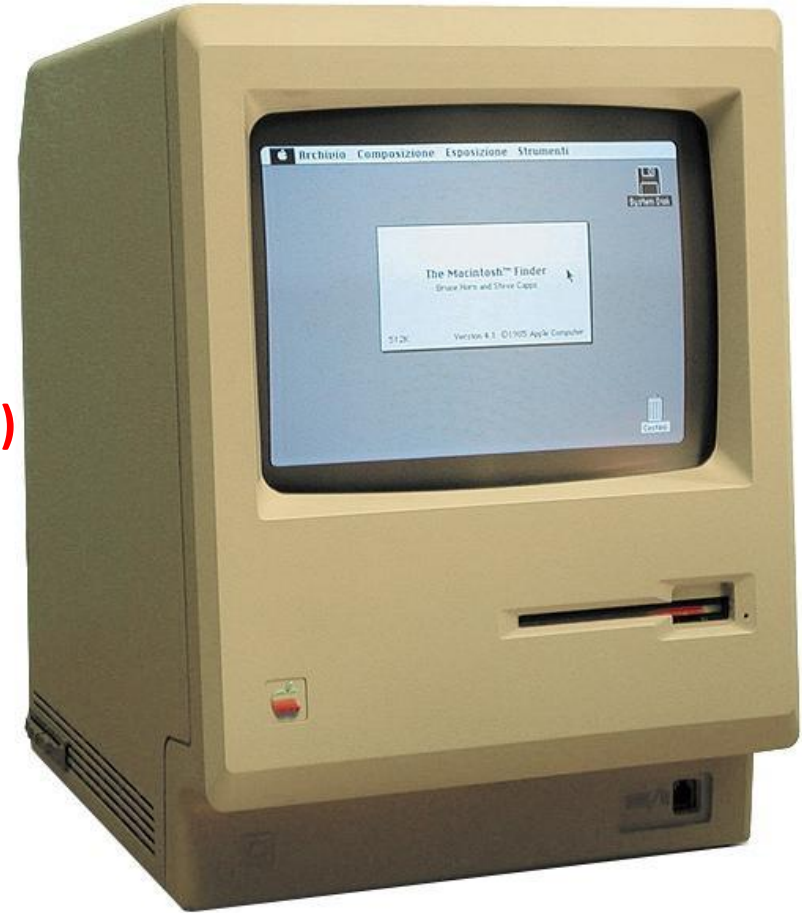


# ESCAPE ROOM - RULES

1. Each group selects a Head Scholar
2. Head Scholars from all groups assemble in one of the Apothecaries to collect activity 1
3. When told to do so, Head Scholars return to their tables and group commences activity. For most activities there are 2 copies, so everyone can assist in solving the puzzle.
  - 4a. Once you have determined the numerical/alphabetical code to unlock one of the Royal Vlogs, raise your hands
  - 4b. A Herald will swiftly (but safely) move to your table to confirm your answer and record your time (NB: You must show the Herald the completed activity + the code, i.e., you can't just guess the answer).
  - 4c. Wait patiently or heckle the teams around you who have yet to solve the puzzle
5. Time allowed for each activity will typically be 8-12 minutes. A 2-minute warning will be given. Groups that do not complete the activity will have the final stop-watch time entered in their records.
6. Everyone will watch the Royal Vlog entry and take note of the revealed medical history
7. Head Scholars return to the Apothecary to receive the next activity etc.



**NO**  
(unless indicated)



# HEAD SCHOLARS – GATHER AT THE APOTHECARY





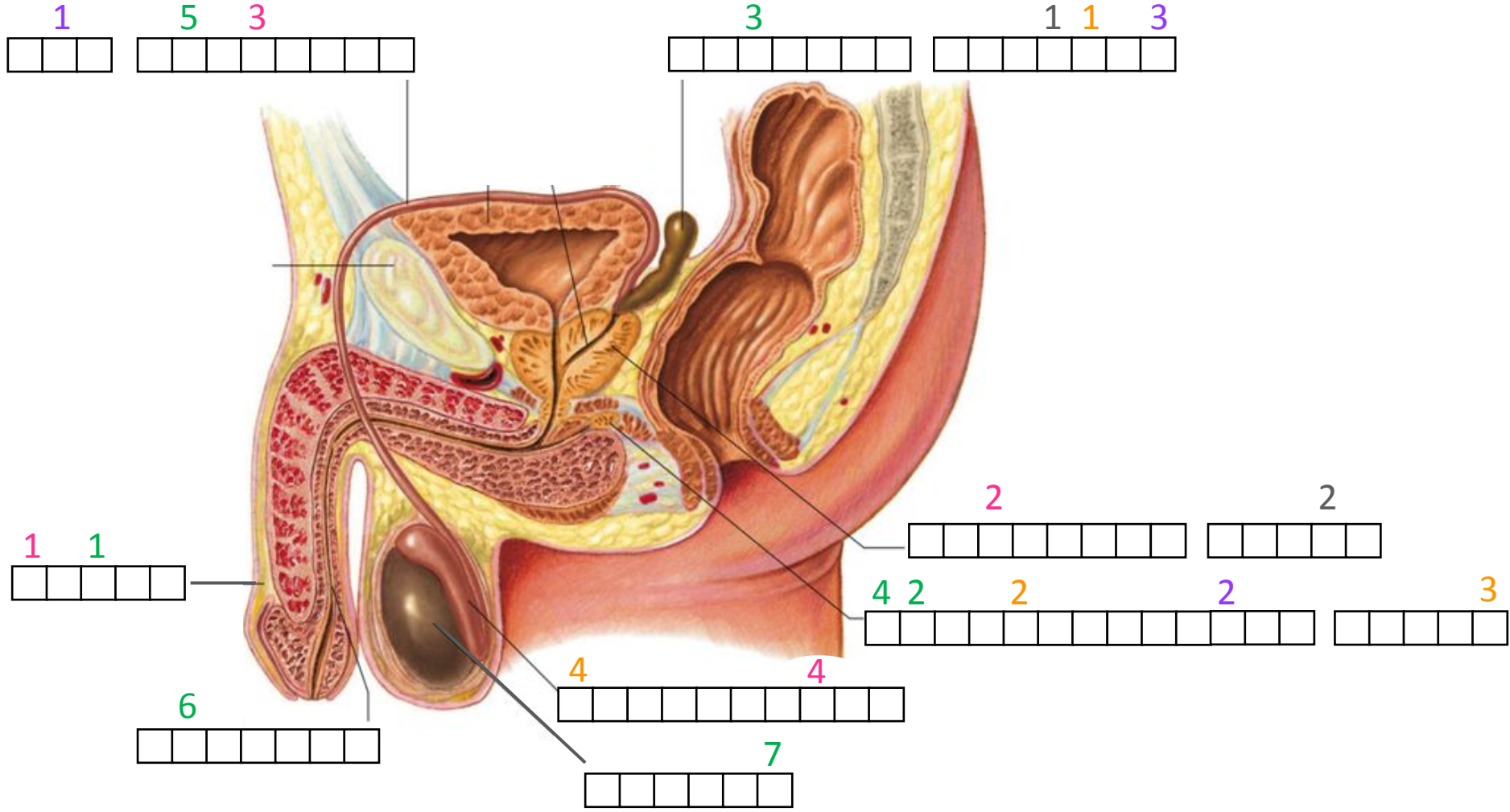
# ACTIVITY 1a

Label the male reproductive system

Answer Activity 1a before you attempt to solve Activity 1b

Memorise, then burn this parchment

(Disclaimer: This is just included for dramatic effect - please don't set fire to anything!)



# ACTIVITY 1b

## Anatomy Poem

By Chamberlain Craigos



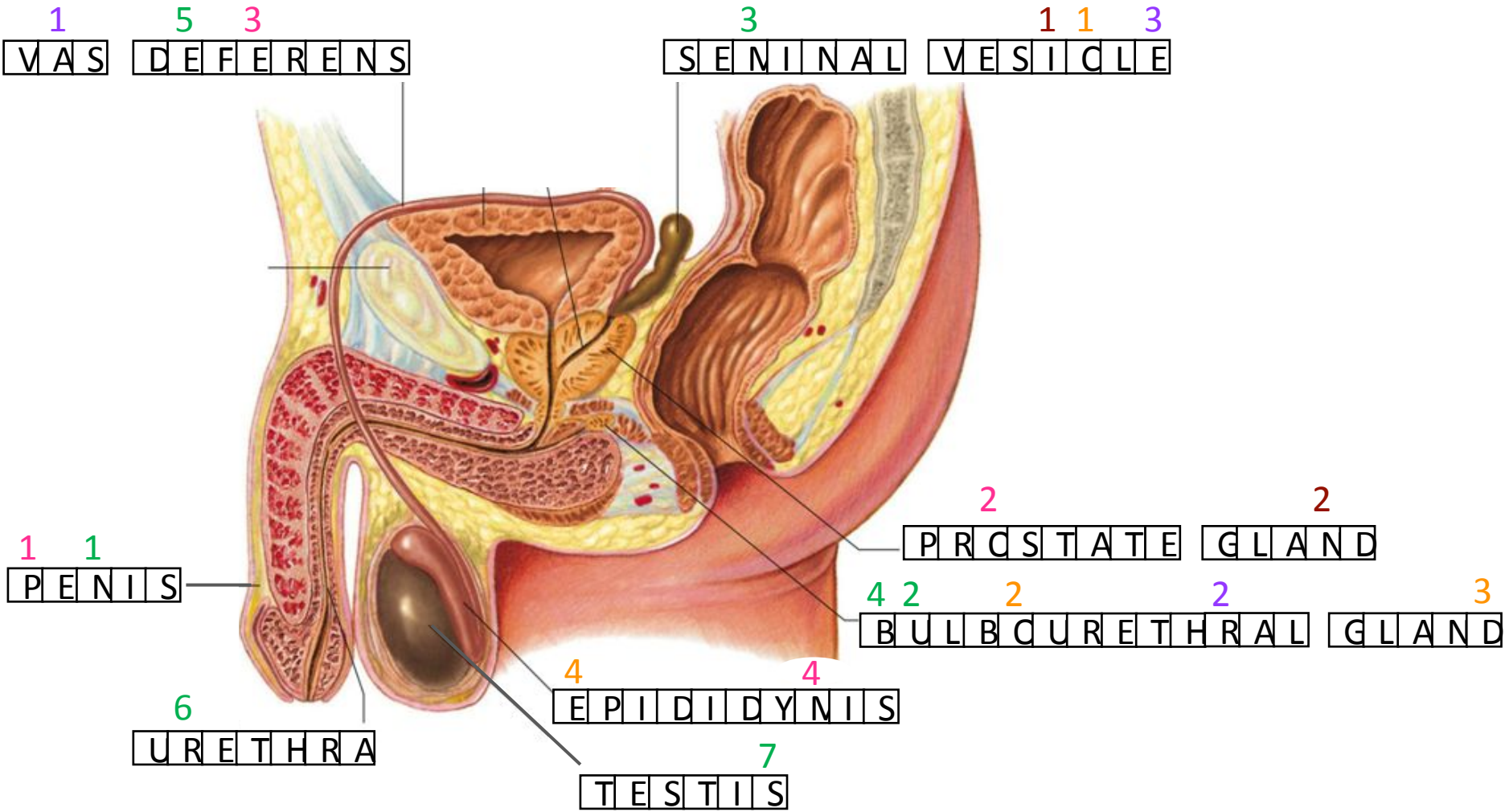
Scrotum is one sac of skin that hangs outside the body  
Parked within (this sac of skin) two organs known as testes  
Oh, why did evolution create a system quite so shoddy  
Now cremaster and dartos muscles must contract when it doth freeze

Guarding the testes further, two tunicas' vaginalis and albuginea  
Internal spermatic fascia should stop them getting broken  
Oh, why then does so much pain transmit these adventitia  
Spermatic cord encloses three arteries that supply the scrotum

Uniquely, the pampiniform venous veins cool the testes  
Mend the king's condition and you will be his bestie

Raise your hands when you have the code to unlock King  
Richard's first vlog entry

# ACTIVITY 1a -Answer



NUMBERS IN PCEM ARE CCDE

## ACTIVITY 1b -Answer

Scrotum is **one** sac of skin that hangs outside the body  
Parked within (this sac of skin) **two** organs known as testes  
Oh, why did evolution create a system quite so shoddy  
Now cremaster and dartos muscles must contract when it doth freeze



Guarding the testes further, **two** tunicas' vaginalis and albuginea  
Internal spermatic fascia should stop them getting broken  
Oh, why then does so much pain transmit these adventitia  
Spermatic cord encloses **three** arteries that supply the scrotum

Uniquely, the pampiniform venous veins cool the testes  
Mend the king's condition and you will be his bestie

1 2 2 3

Raise your hands when you have the code to unlock King  
Richard's first vlog entry

# ACTIVITY 1b -Answer

Scrotum is **one** sac of skin that hangs outside the body

Parked within (this sac of skin) **two** organs known as testes

Oh, why did evolution create a system quite so shoddy

Now cremaster and dartos muscles must contract when it doth freeze



Corpus  
spongiosum

Guarding the testes further, **two** tunicas' vaginalis and albuginea

Internal spermatic fascia should stop them getting broken

Oh, why then does so much pain transmit these adventitia

Spermatic cord encloses **three** arteries that supply the scrotum

Uniquely, the pampiniform venous veins cool the testes

Mend the king's condition and you will be his bestie

1 2 2 3

Raise your hands when you have the code to unlock King Richard's first vlog entry

# Vlog entry 1 – King Richard

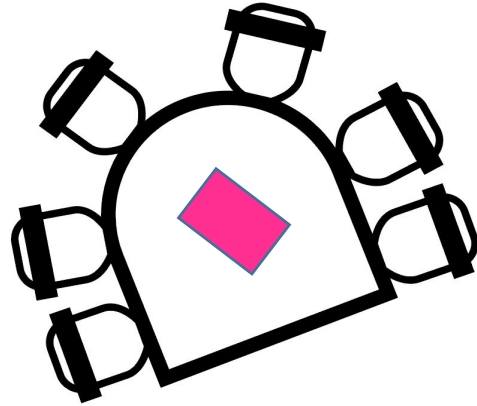


# HEAD SCHOLARS – GATHER AT THE APOTHECARY





## ACTIVITY 2



- The folder contains the 15 “events” in the hormonal control of the ovarian cycle. However, the “events” are in random order
- Align the 15 “events” in their correct order in a single column down the centre of your bench
- Raise your hand to call a Herald to check your order

- When students call you, quietly tell them to turn the bits of paper over.
- If the images of the owl, bee, windmill and radioactivity are correct, give them the time that they raised their hands.
- If images not correct, add 1 minute to their time!

C

In reproductive years, a cohort of preantral and early antral follicles are always present in the ovary

J

Hypothalamic GnRH stimulates production and release of LH and FSH by the anterior pituitary

O

FSH acts on granulosa cells and causes preantral and early antral follicles to enlarge and mature

A

LH acts on theca cells and stimulates production of androgens, which are converted to estrogen in granulosa cells

F

The rising estrogen levels exert negative feedback on the hypothalamus and pituitary

N

Inhibin, produced by granulosa cells, acts back on the pituitary to further reduce FSH levels

G

Only the dominant follicle survives this dip in FSH – the remaining growing follicles degenerate

B

The dominant follicle now responds to both FSH and LH – estrogen production rises



E

High circulating estrogen briefly exerts positive feedback on the hypothalamus and pituitary

L

The net result of high estrogen is the LH surge (due to increased production and release of L

K

The LH surge stimulates many events that lead to ovulation

D

LH surge also stimulates the reactions that convert granulosa/theca cells into the corpus luteum

H

The corpus luteum produces progesterone, estrogen and inhibin, which exert negative feedback – GnRH, FSH and LH levels are low

M

If no pregnancy, the corpus luteum degenerates and plasma estrogen and progesterone concentrations decrease

I

FSH and LH secretions begin to rise, and a new cycle begins



# Vlog entry 2 – Queen Barbara



# HEAD SCHOLARS – GATHER AT THE APOTHECARY

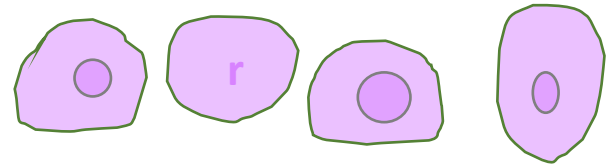




## ACTIVITY 3a

- Reconstruct the seminiferous epithelium and interstitial space.
- If reconstruction is correct, you will see some letters (from top to bottom)
- These letters are the password for the antique combination padlock, which are on the table near the Apothecary
- Open the lock to gain access to activity 3b

Basement membrane



Leydig cells



Round Spermatids

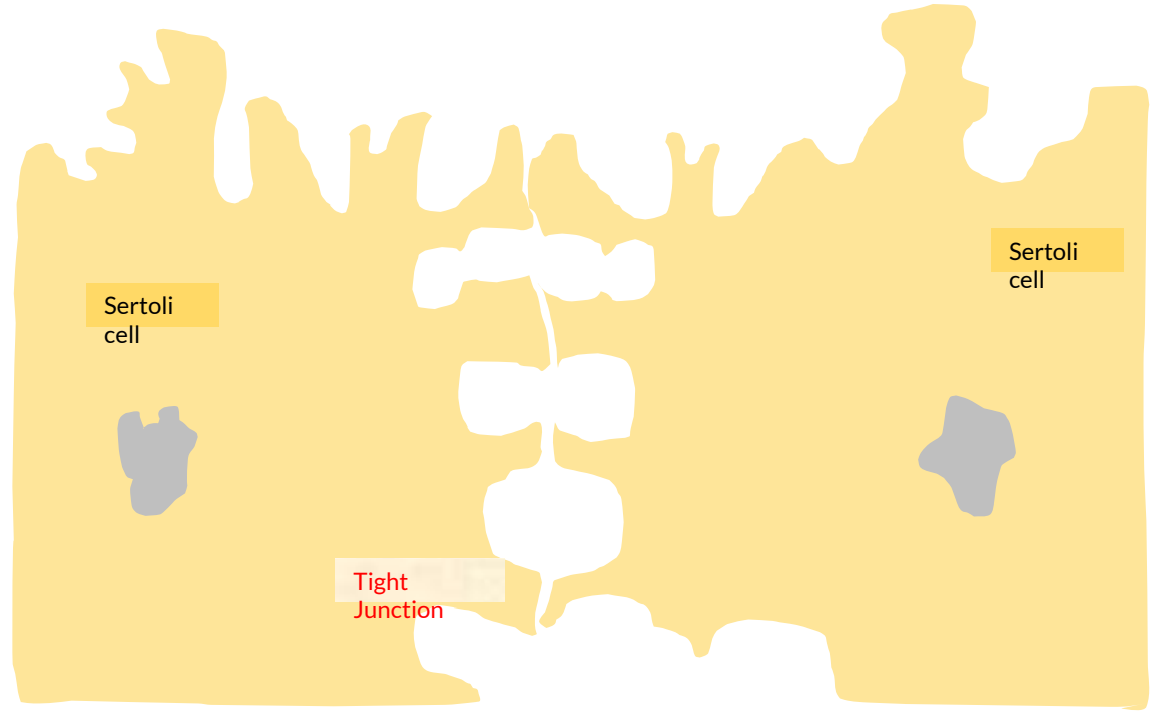
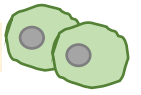


Spermatogonium

Primary Spermatocyte crosses blood-testis-barrier



Primary Spermatocyte

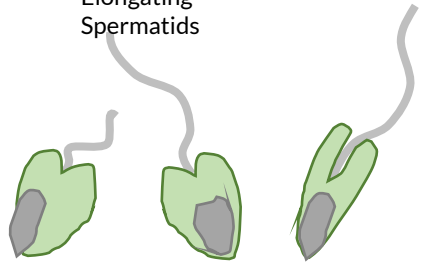


Sertoli cell

Sertoli cell

Tight Junction

Elongating Spermatids

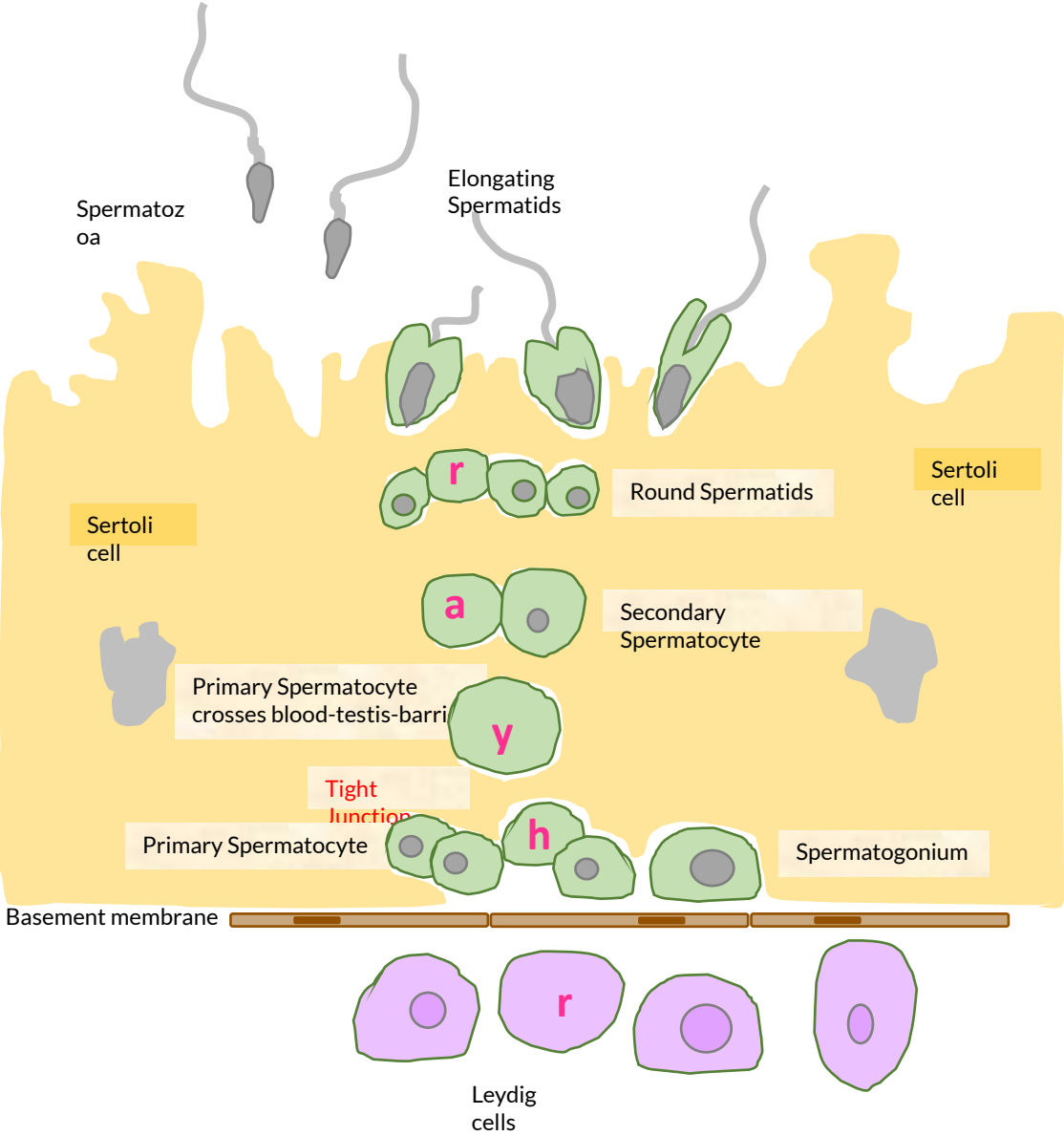


Spermatozoa



Secondary Spermatocyte

# ACTIVITY 3a -Answer



## ACTIVITY 3a

Prior to workshop, we will hole-punch activity 3b and slide 6 copies onto each of the vintage combination locks

Students turn the combination until they spell RAYHR between the triangles

Students remove 2 copies of activity 3b

Herald closes lock and spins the combinations

Repeat for next group



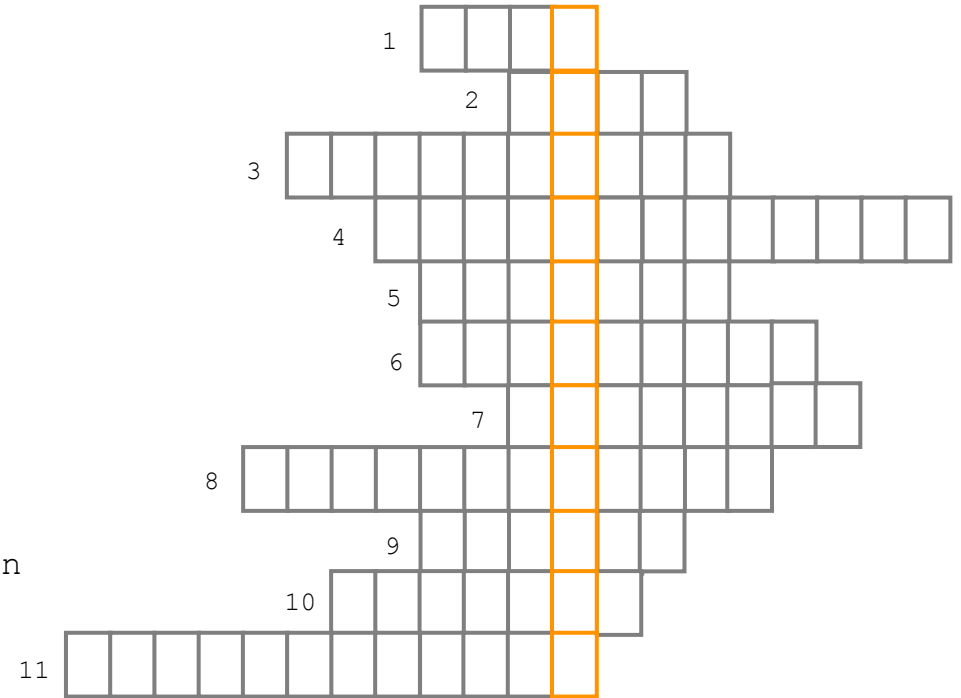
# ACTIVITY 3b

Spermatogenesis

Hidden Word

Answer the **Clues** in the following order (might help you guess the code word):

11. The site of sperm production within the testis is the ..... tubule
4. Hypothalamic hormone that drives FSH and LH production is ..... releasing hormone
7. Sperm structure that contains hydrolytic enzymes that enable penetration of egg
2. Region of sperm that contains the genetic material
5. Hormone produced by Sertoli cells that negatively feeds back to the pituitary to suppress FSH synthesis
10. Name of testicular cells that respond to FSH and support spermatogenesis
9. Number of stages in the spermatogenic cycle in humans
3. Stores and protects spermatozoa, while facilitating functional maturation
1. The region of sperm that propels it through the female reproductive tract
6. The mid-piece of sperm contains mitochondria that provide energy for the whip-like movements of the .....
8. A hormone produced by Leydig cells



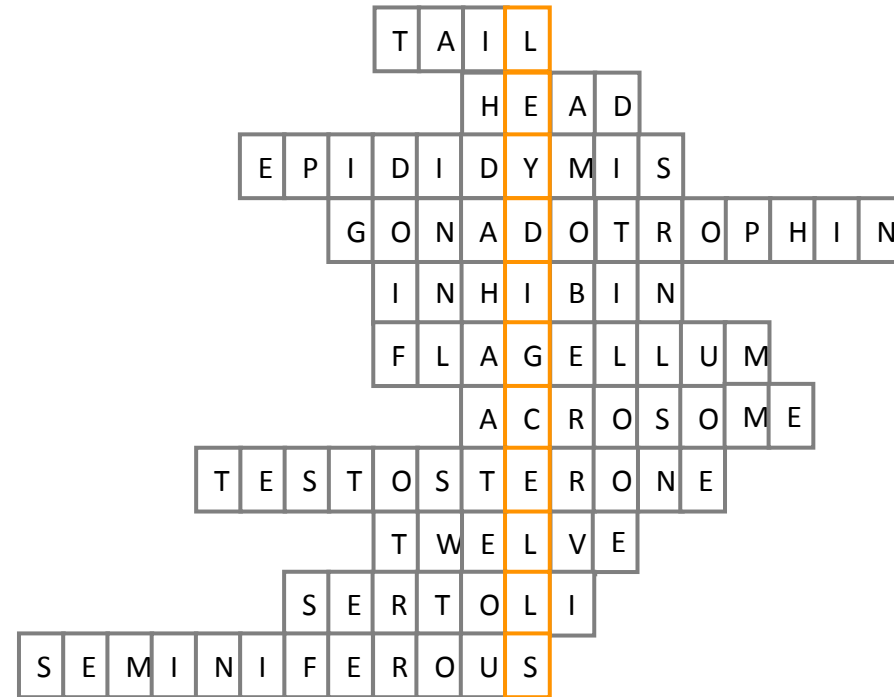
Transpose the code to unlock  
Ari's second vlog



Raise your hands when you have the answer

# ACTIVITY 3b

-Answer



Transpose the code to unlock Video

3

L E Y D I G C E L L S

# Vlog entry 2 – King Richard



# HEAD SCHOLARS – GATHER AT THE APOTHECARY





# ACTIVITY 4 – Escape Womb

Prepare your endometrium for potential implantation

Unfortunately, the steps involved are:

1. Jumbled
2. Encrypted

Once deciphered and unjumbled, add the step numbers in their correct order in the spaces provided on the uterine image

1. JCB GOLFQJVFOT GFETOV>OFEOO

2. LOFAGLJE BKLV >NGLWOOV JCB <>OF  
OO B<FOVLOOLO GV BJV>JFOO

3. FOCBAO OV>FETO JCB GFETOV>OFEOO

4. C<OL>FEOJL LJ<OF >NGLWOOV GFETOV>  
OFEOO FOLOTE>EF O>GFQVFOO GOLFQJVO  
V LOFAGLJE BKLV >NFOV

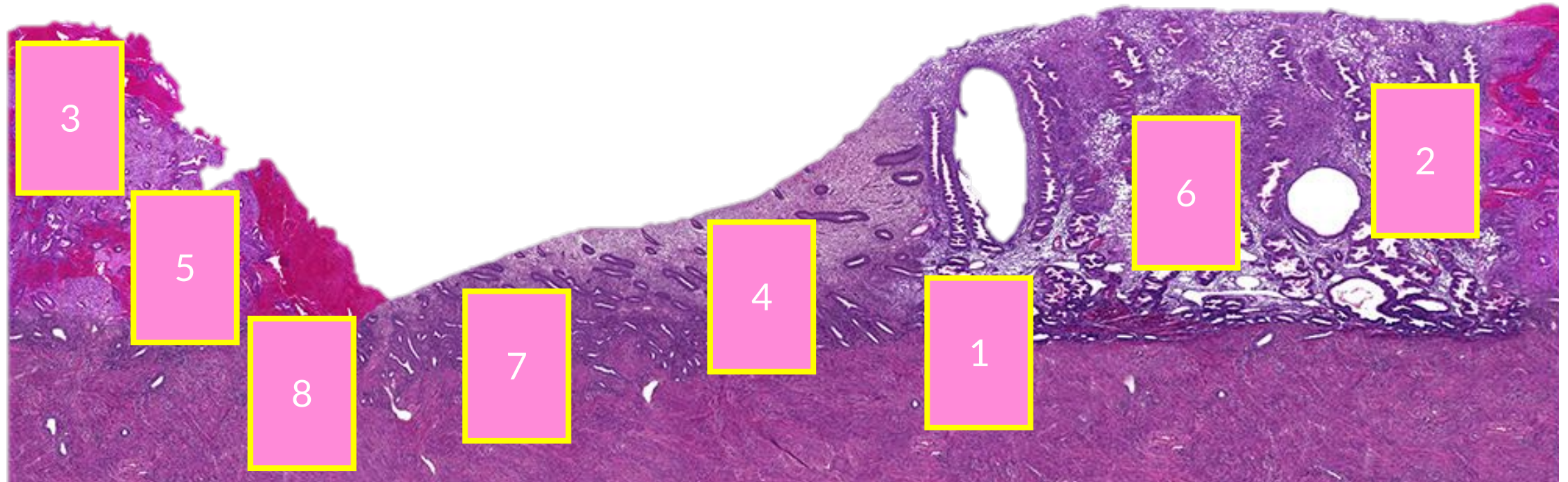
5. JCB GFQV>JGLJBOFOV

6. GLJNV OOLJFOT JF>OFQOV OLOOTJ>  
O JCB GL<LETOO GV VOLFO>CB

7. JCB GOLFQJVFOT OV>FETO

8. JLEEV C<OL>FEOJLGV LJ<OF >E VLE<T  
N ECC





NB: It's ok if 6 and 2 are in the opposite order

# Vlog entry 3 – Queen Barbara



# HEAD SCHOLARS – GATHER AT THE APOTHECARY





# ACTIVITY 5

## Case Study – Infertility in pesticide (DBCP) workers

(From: The National  
Academies of Sciences,  
Engineering and Medicine)

COMPARISON OF NON-VASECTOMISED DBCP WORKERS WITH VERY LOW (GROUP A) AND  
NORMAL (GROUP B) SPERM COUNTS

Group	Number of Subjects	Age (years)	Exposure (years)	Sperm count ( $10^6$ /ml)	FSH (mIU/ml)	LH (mIU/ml)	Testosterone (ng/dl)	Inhibin (pg/ml)
A	11	33*	8*	0.2**	9**	15	468	37**
B	11	27*	0.1*	93**	2.5**	14	459	216**

\*Difference between groups A and B significant at  $P < 0.01$

\*\*Difference between groups A and B significant at  $P < 0.001$

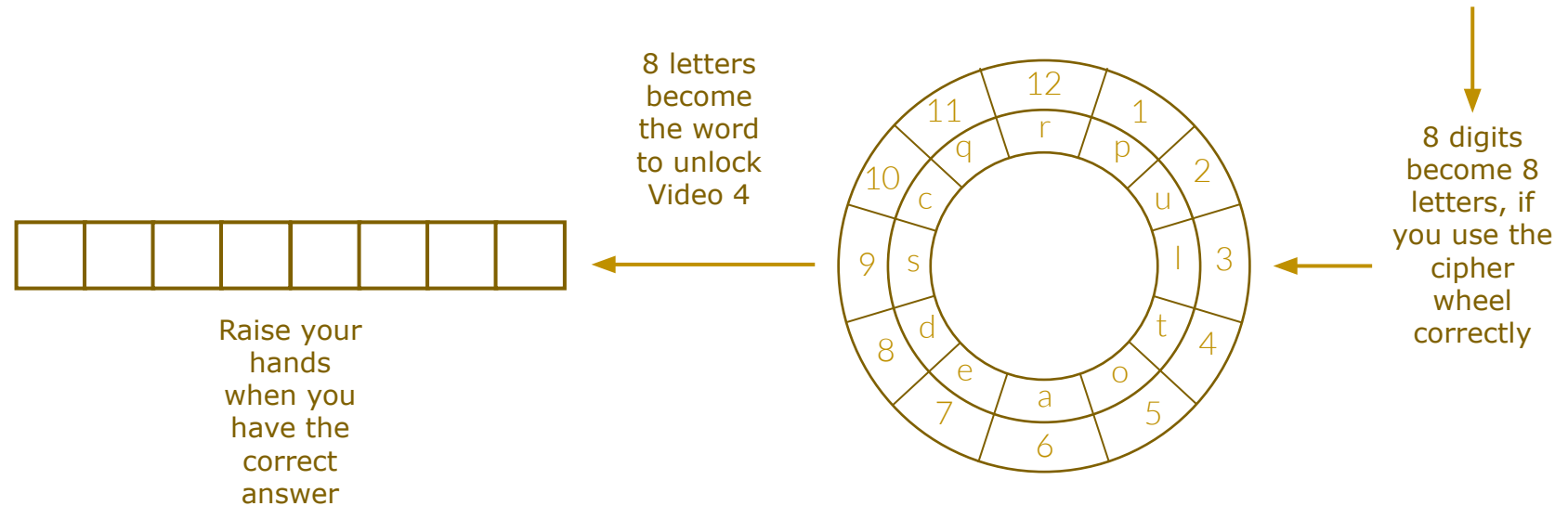
# ACTIVITY 5

## Case Study – Infertility in pesticide (DBCP) workers

(From: The National  
Academies of Sciences,  
Engineering and Medicine)

QUESTIONS RELATE TO DATA IN PREVIOUS TABLE

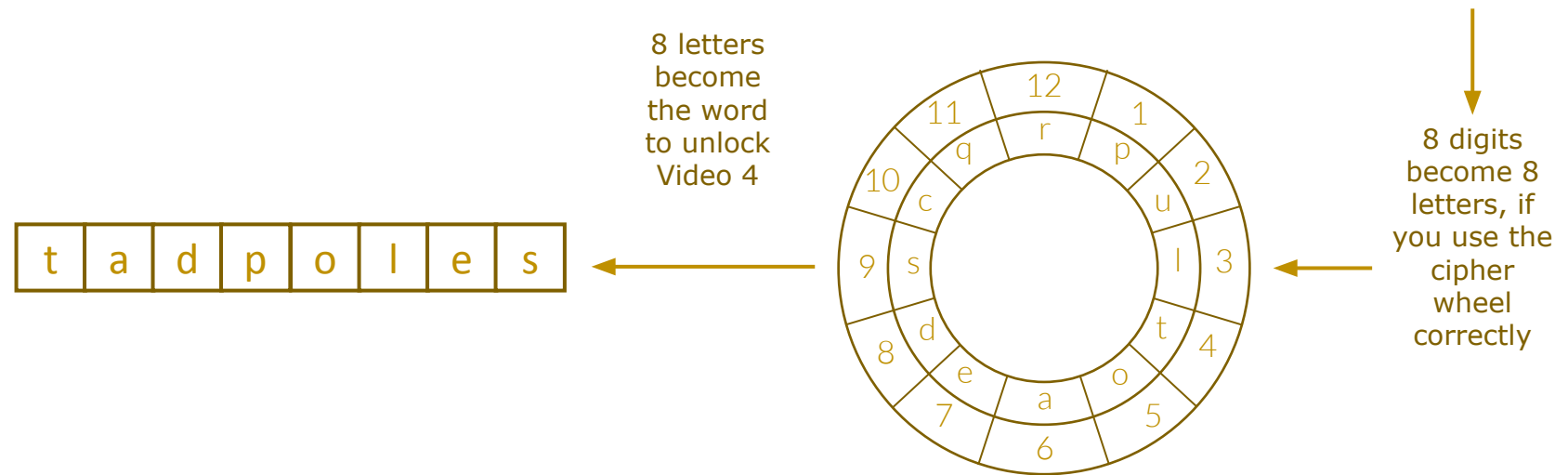
Hormone	Value in affected men (number only)
1. The levels of which hormone in affected men suggests DBCP does not damage Leydig cells?	
2. Normal levels of the above Leydig cell hormone ensure negative feedback to which pituitary hormone?	
3. The levels of which hormone in affected men suggests DBCP damages Sertoli cells?	
4. A loss of negative feedback from Sertoli cells affects which hormone's production?	



# ACTIVITY 5 - Answer

QUESTIONS RELATE TO DATA IN PREVIOUS TABLE

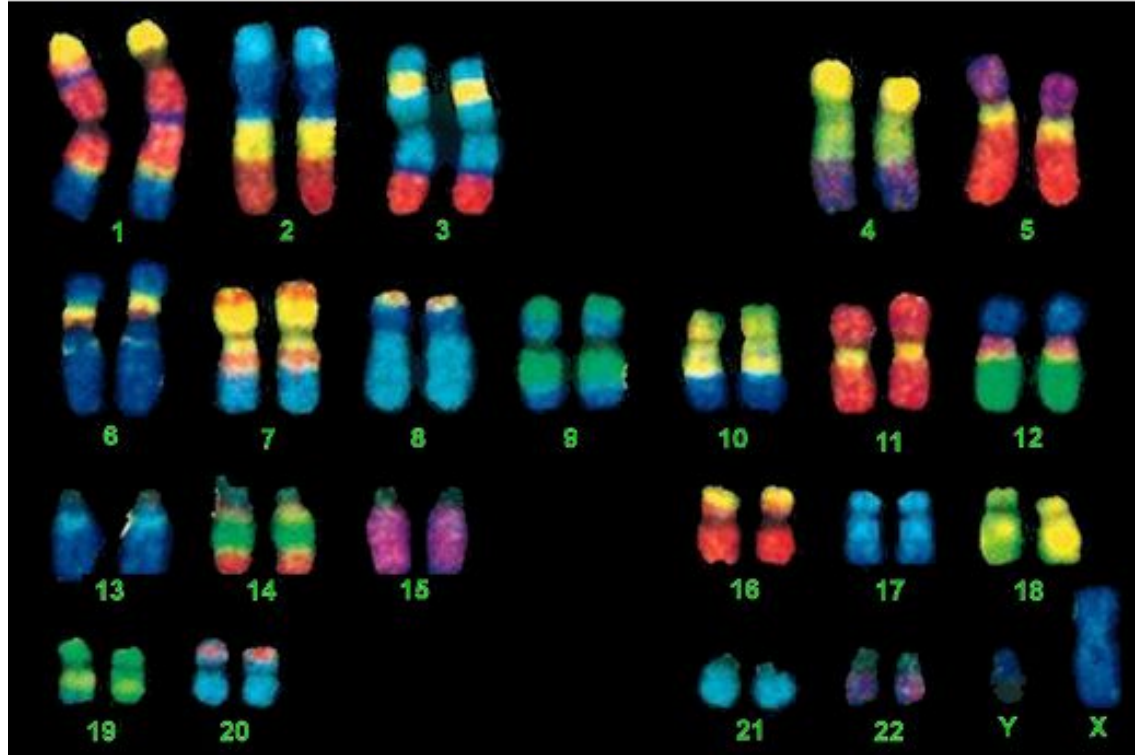
	Hormone	Value in affected men (number only)
1. The levels of which hormone in affected men suggests DBCP does not damage Leydig cells?	Testosterone	468
2. Normal levels of the above Leydig cell hormone ensure negative feedback to which pituitary hormone?	LH	15
3. The levels of which hormone in affected men suggests DBCP damages Sertoli cells?	Inhibin	37
4. A loss of negative feedback from Sertoli cells affects which hormone's production?	FSH	9



# Vlog entry 3 – King Richard



Richard seemed proud of his karyotype – maybe it's important?



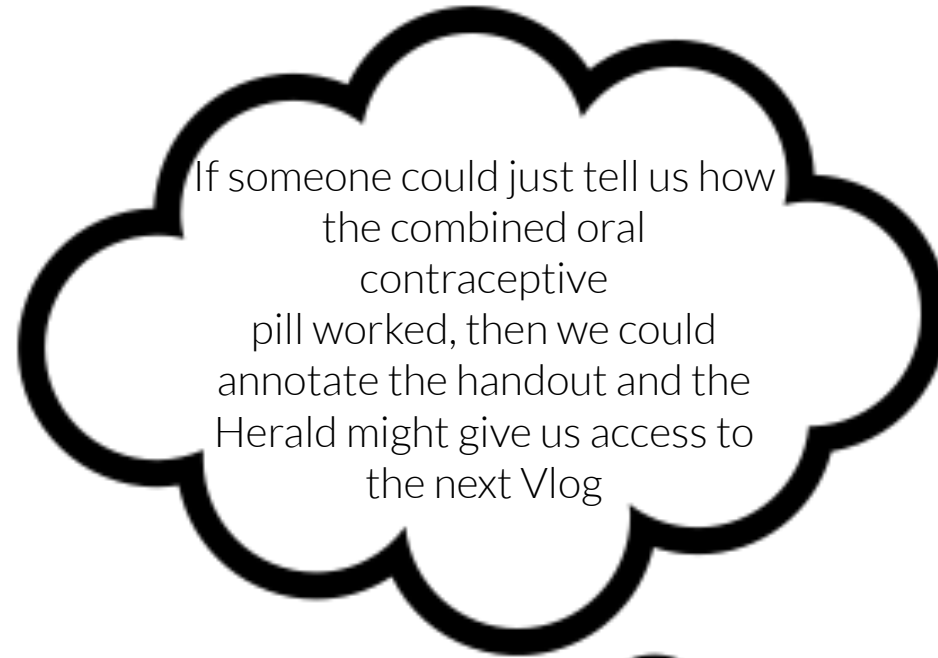
(Hand out with activity 6 folder)

# HEAD SCHOLARS – GATHER AT THE APOTHECARY





# ACTIVITY 6



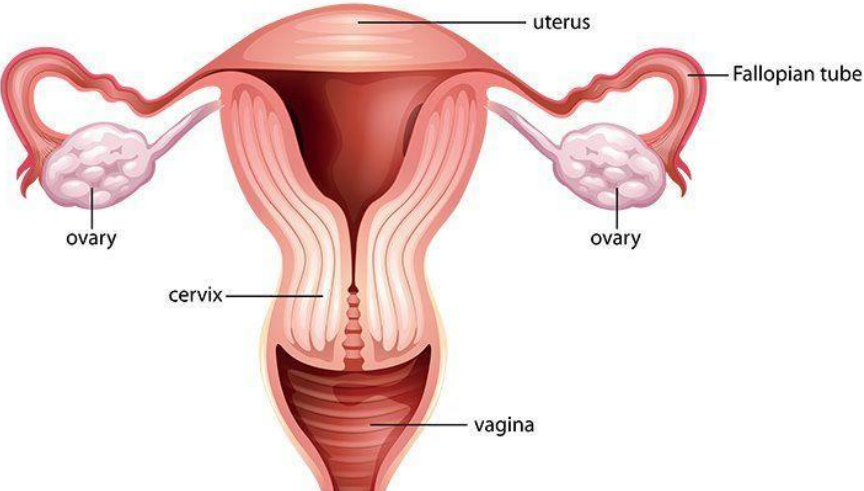
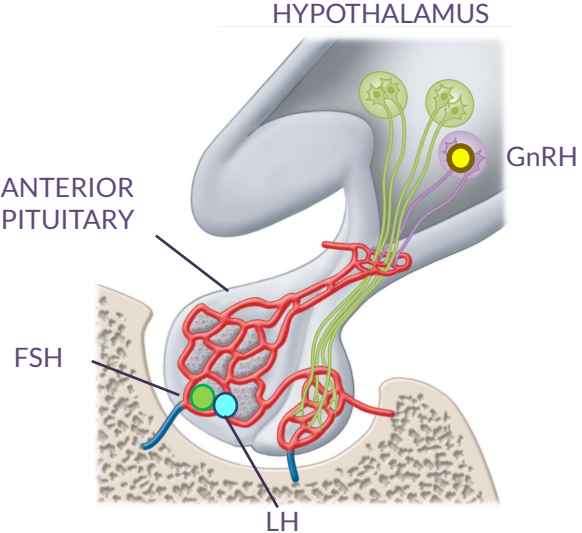
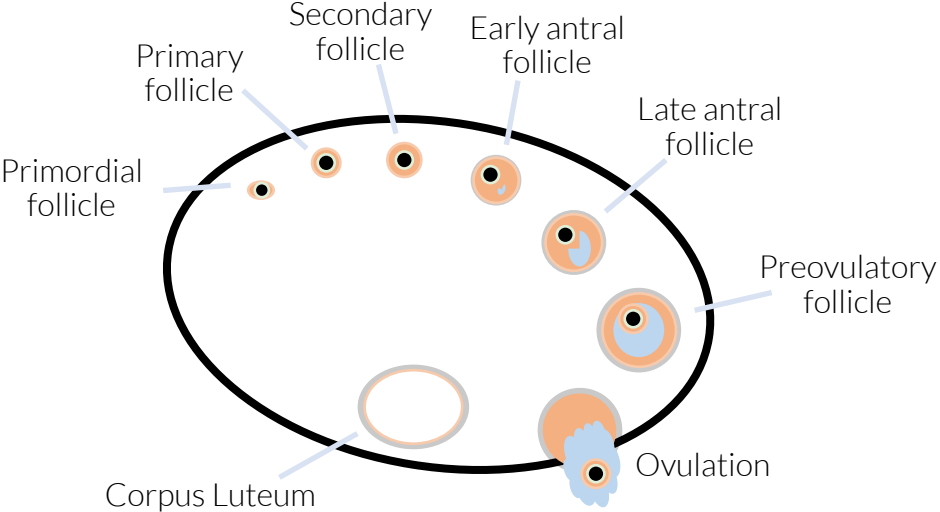
If someone could just tell us how  
the combined oral  
contraceptive  
pill worked, then we could  
annotate the handout and the  
Herald might give us access to  
the next Vlog



# ACTIVITY 6

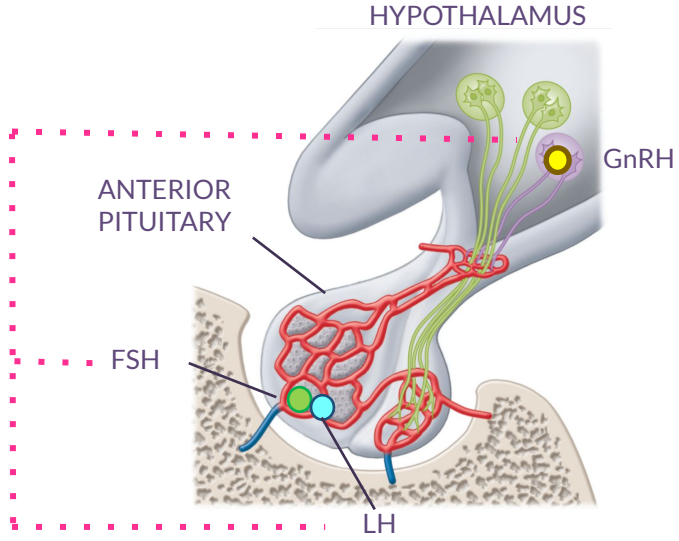
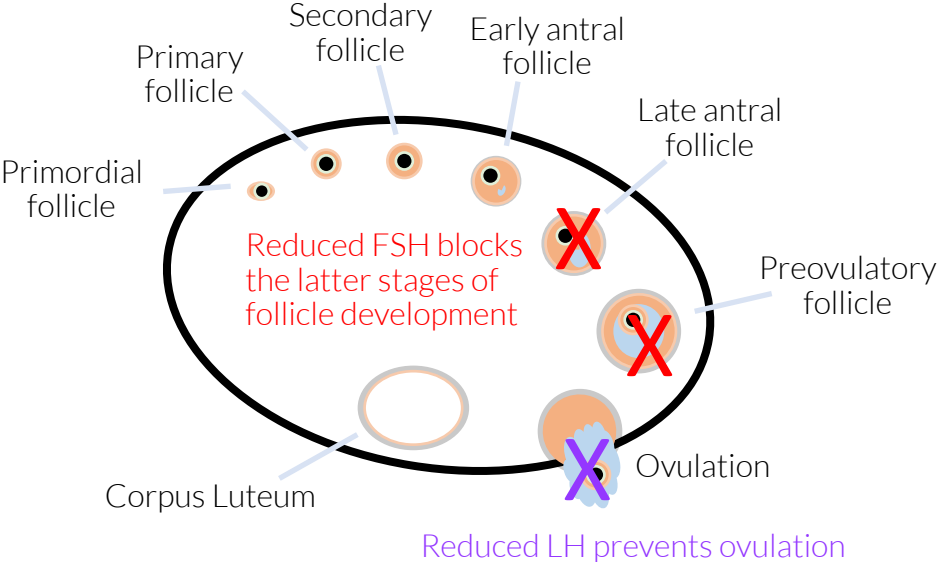
Indicate on this handout how the pill affects the normal physiological regulation of the menstrual cycle.

When finished, briefly explain mechanism to herald.

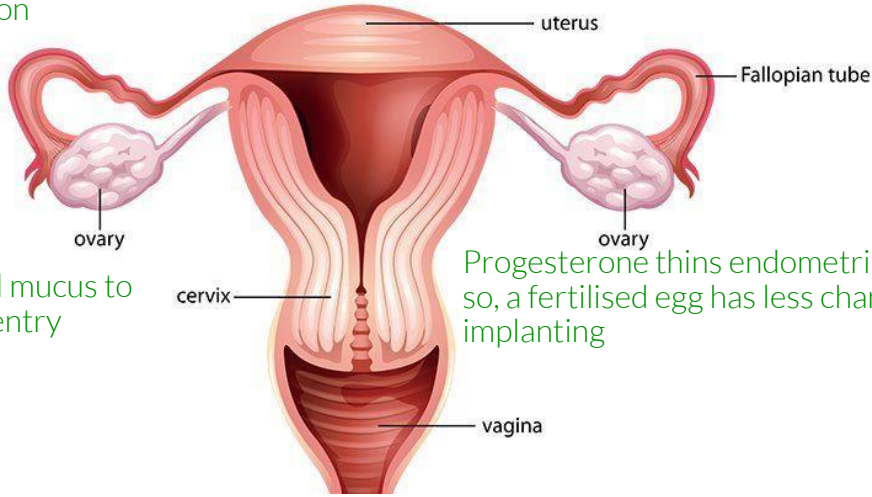


# ACTIVITY 6

Indicate on this handout how the pill affects the normal physiological regulation of the menstrual cycle



Progesterone slows tubal motility, which may interfere with fertilisation



Progesterone causes cervical mucus to thicken and prevents sperm entry

Progesterone thins endometrial lining, so, a fertilised egg has less chance of implanting

NEGATIVE FEEDBACK



# ACTIVITY 6

THE CODE IS THERE, SOMEWHERE .....



# ACTIVITY 6

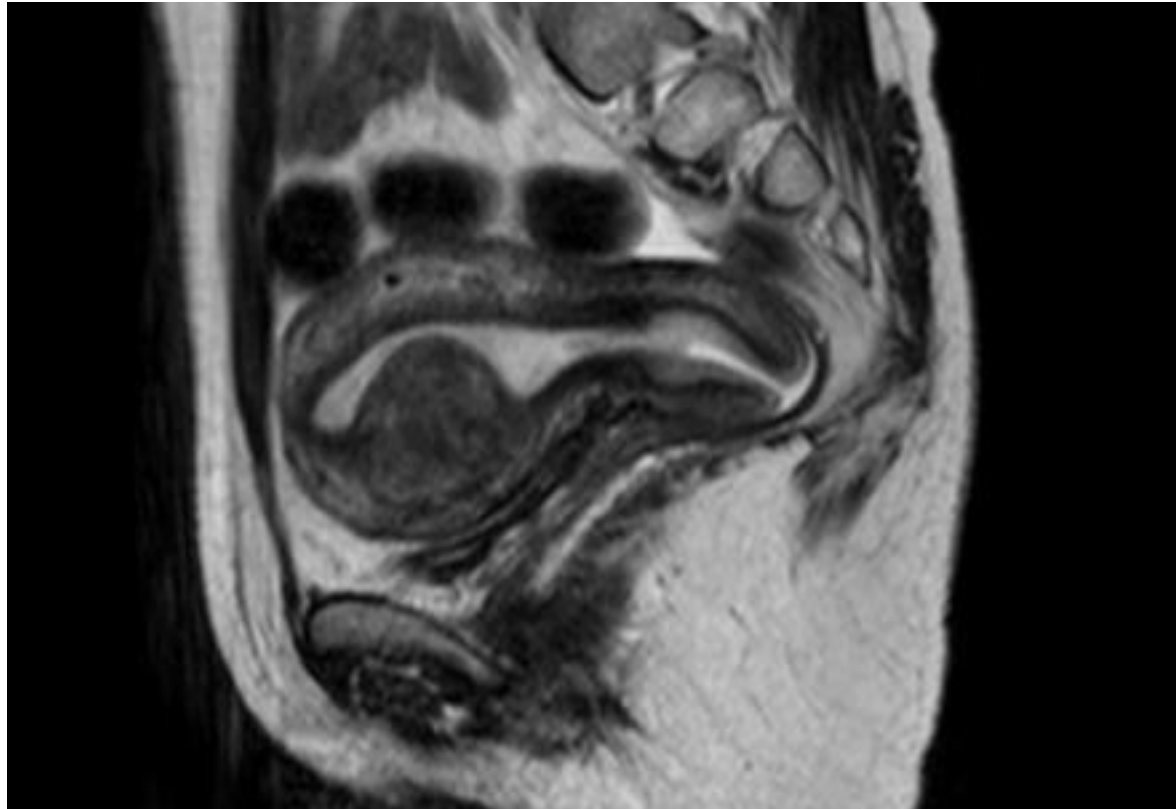
THIS MIGHT HELP?



# Vlog entry 4 – Queen Barbara



Barb seemed unsure about what her MRI scan showed  
(maybe it's worth a second look?)



(Hand out with activity 7 folder)

# HEAD SCHOLARS – GATHER AT THE APOTHECARY





PICTURE  
START

# ACTIVITY 7

A male contraceptive pill?

1. Watch the Video
2. Read through the 5 facts and jot down on your tables how WIN-18446 blocks spermatogenesis
3. Once you have the mechanism sorted, call a herald who will provide you with the activity to gain access to King Richard's final Vlog entry
4. Once you have the code word, call the Herald back



# ACTIVITY 7

## Fact #1 (Excerpt from Bloomberg Businessweek (3-8-17) by Emily Anthes)

The trouble began, as it so often does, with a bottle of Chivas Regal. Back in the 1950s, scientists at Sterling Drug, a now-defunct pharmaceutical company, synthesized a class of chemicals that made male rats temporarily infertile. They thought they might be onto something big: the first-ever birth control pill—for men. After identifying several promising compounds, including one known as WIN 18,446, a trio of researchers began testing them on a ready population, inmates at the Oregon State Penitentiary.

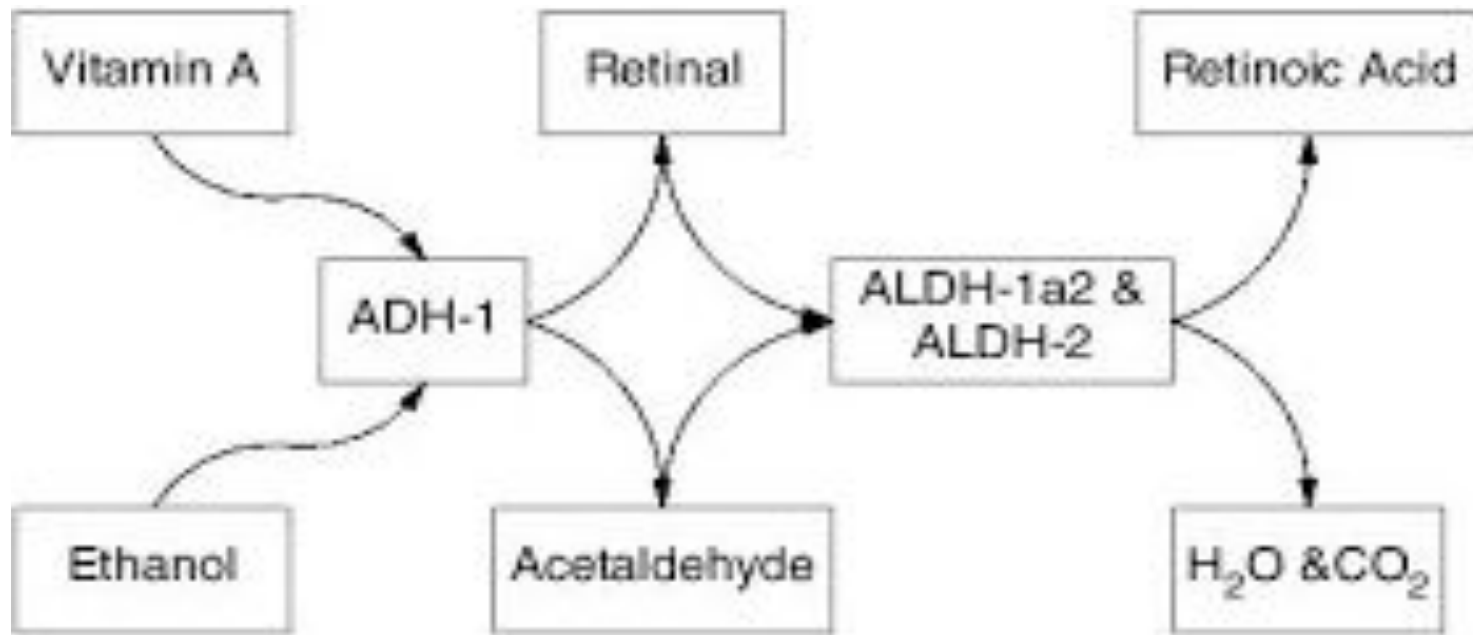
The results were astonishing. Within 12 weeks, the inmates' sperm counts had plummeted. When the men stopped taking the drugs, sperm production returned to normal. Better yet, they experienced few side effects.

Then one of the participants drank some contraband Scotch and became unusually, violently ill. He confessed his transgression to the researchers, and follow-up studies confirmed his account: WIN 18,446 didn't mix well with booze. Men who combined the two reported heart palpitations, sweating, nausea, and vomiting.

The research was quietly abandoned ...

# ACTIVITY 7

Fact #2 (Proceedings of the Australian Physiological Society 43:17-24)



# ACTIVITY 7

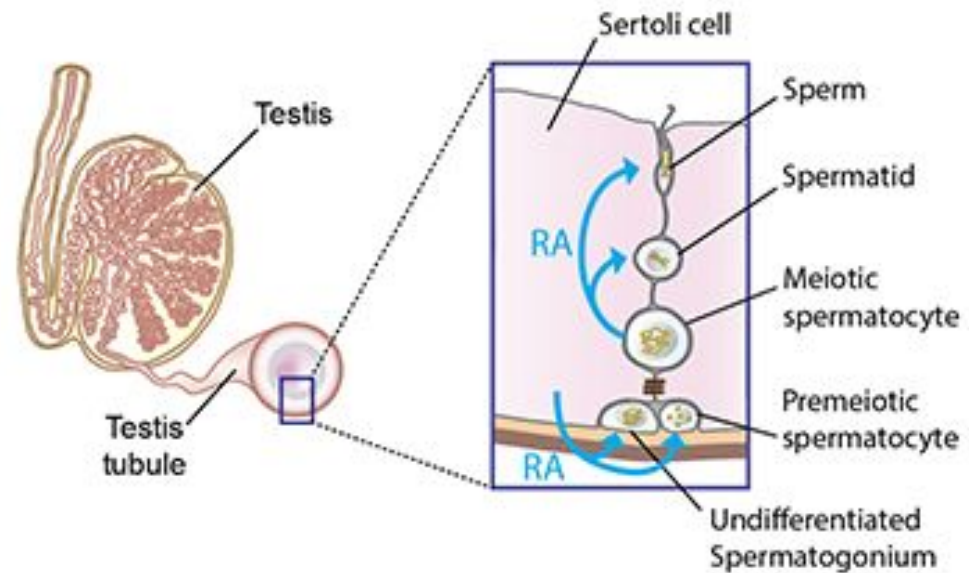
## Fact #3 (Excerpt from Bloomberg Businessweek (3-8-17) by Emily Anthes)

Antabuse (disulfiram) is prescribed to patients who struggle with alcohol addiction. The drug blocks most forms of the enzyme acetaldehyde dehydrogenase (ALDH), which helps the body metabolize alcohol; drinking while taking disulfiram leads to an extremely unpleasant, and occasionally fatal, constellation of hangover-like symptoms.

# ACTIVITY 7

## Fact #4 (Endo et al PNAS 2017 doi:10.1073/pnas.1710837114)

“Authors show that retinoic acid (RA), a derivative of vitamin A, is required for differentiation and meiosis during spermatogenesis.



# ACTIVITY 7

Fact #5 (Excerpt from Bloomberg Businessweek (3-8-17) by Emily Anthes)

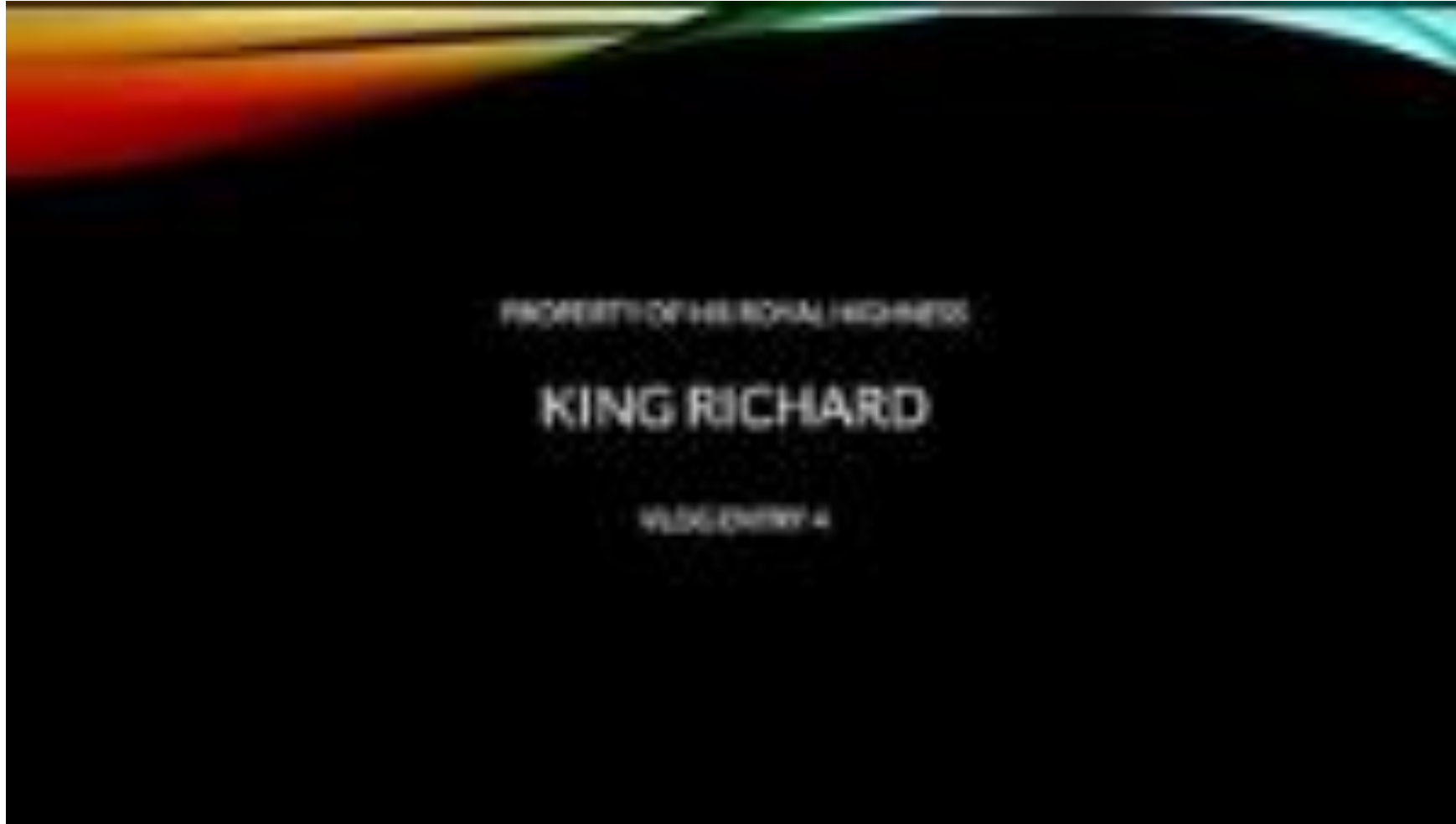
There are almost 20 different forms of ALDH; the liver relies primarily on ALDH2 to metabolize alcohol, while the testes use ALDH1A2 to make retinoic acid.

## ACTIVITY 7

WIN-18,446 failed as a male contraceptive because it \_\_\_\_\_ multiple forms of the enzyme acetaldehyde dehydrogenase

<https://mywordle.strivemath.com/?word=ohziwio>

# Vlog entry 4 – King Richard



## Notes from King Richard and Queen Barbara's Vlogs

	Queen Barbara says:
<b>Video 1</b>	"My doctor said that my anti-müllerian hormone levels were high for someone my age (which is 38, in case you were wondering)"
<b>Video 2</b>	"There was a gonorrhoea outbreak in the palace last September. Luckily, I managed to avoid that!"
<b>Video 3</b>	"Recently, my hormone levels were LH=4.1 IU/L; FSH=4.3 IU/L and T=1.2 nmol/L. Make of those values what you will"
<b>Video 4</b>	"My mother had uterine fibroids, so my doctor sent me for an MRI. I received this image but unfortunately, my doctor had parted ways with her head by the time it arrived. I haven't been able to fill the role since."

	King Richard says:
<b>Video 1</b>	"I've never had elective surgery in my life"
<b>Video 2</b>	"I saw a Urologist once. He said that my little swimmers looked great and moved really well. He also said that my scrotal temperature was higher than any other man. I wasn't surprised"
<b>Video 3</b>	"I have always been fascinated with genetics. I even had my own chromosomes karyotyped. The image was so nice that I hung it in the throne room"
<b>Video 4</b>	"I have Trypanophobia"

# HEAD SCHOLARS – GATHER AT THE APOTHECARY



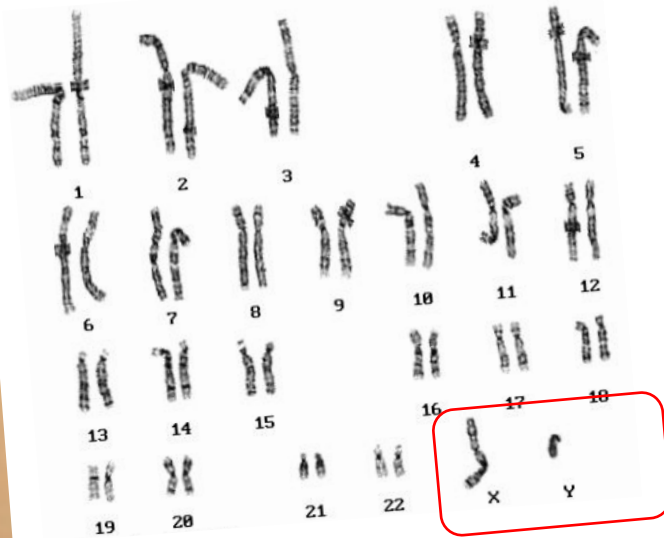


# Potential causes of Richard's infertility

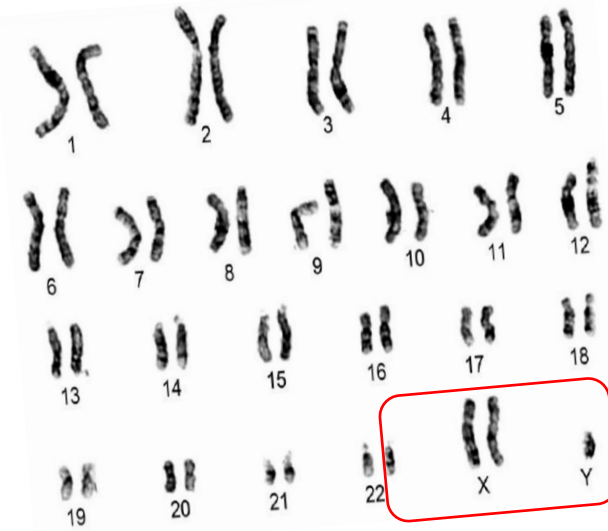


# Potential causes of Richard's infertility

**Klinefelter syndrome** has an estimated frequency of 1 in 600 in the general population. Affected individuals typically have small, firm testes with hyalinization of seminiferous tubules and consequent spermatogenic failure (>90% of men have azoospermia and the remaining men have severe oligospermia)



Normal Male  
Karyotype



Klinefelter's  
Karyotype

# Potential causes of Richard's infertility



## Anabolic steroids making musclemen infertile, say doctors

Bodybuilders destroying their chance of becoming fathers in their quest to bulk up, specialists report



▲ 'These patients walk through the door looking like Arnold Schwarzenegger in his younger days,' said Dr Allan Pacey. Schwarzenegger - pictured in 1977 - has said he took steroids when they were legal. Photograph: Everett Collection/Rex Features

Growing numbers of men are becoming infertile because they take anabolic steroids in their quest for a muscular body, doctors have warned.

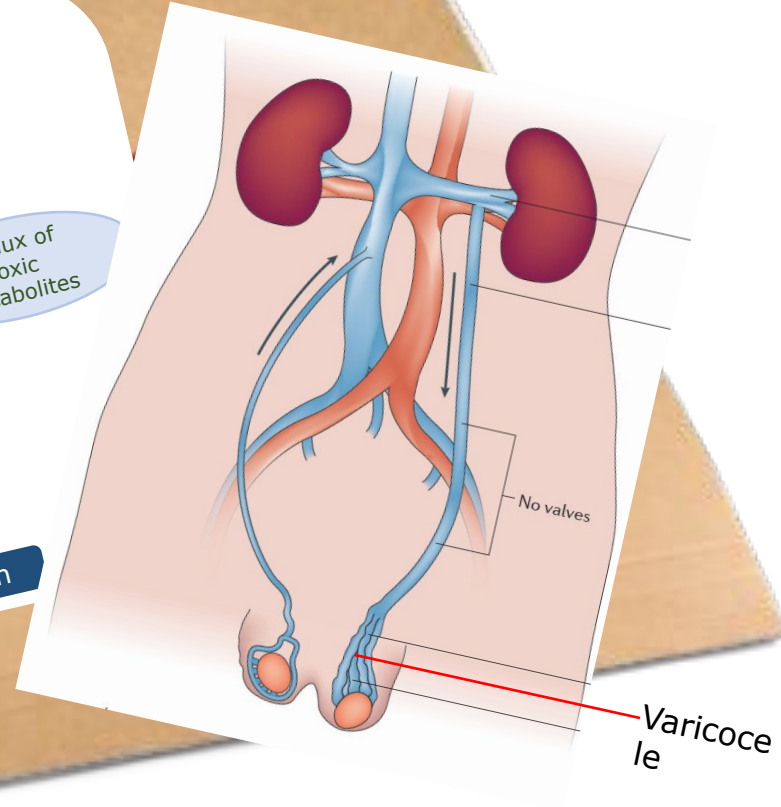
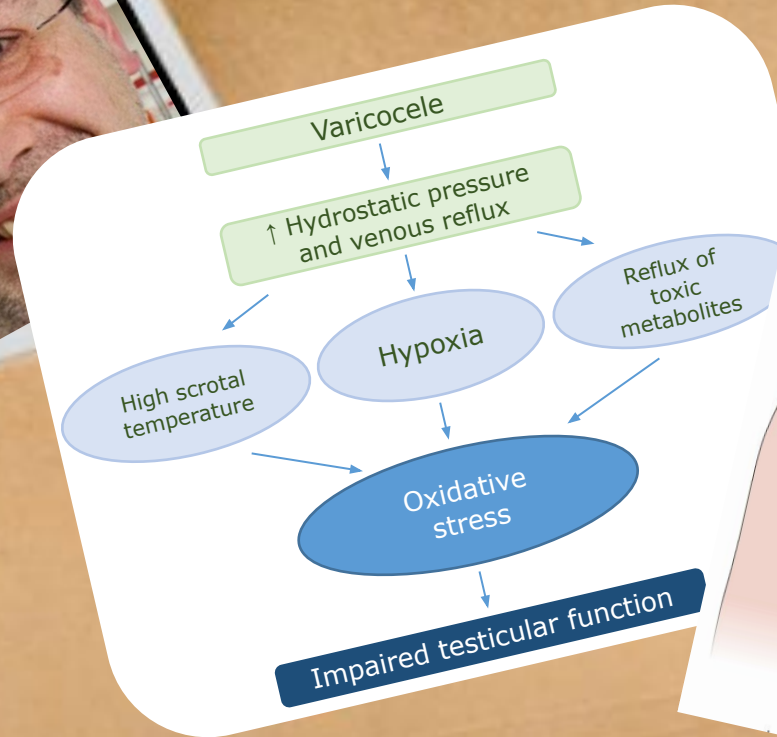
Urologists are seeing more and more men whose difficulty in becoming a father is linked to consumption of the muscle-boosting drugs.

Steve Payne, a consultant urologist at the Manchester Royal Infirmary and a council member of the British Association of Urological Surgeons, said: "Many fit young men who believe they are at the peak of physical perfection don't believe it could be their fault when their wives or girlfriends find it difficult to become pregnant."

# Potential causes of Richard's infertility



# Potential causes of Richard's infertility



# Potential causes of Richard's infertility



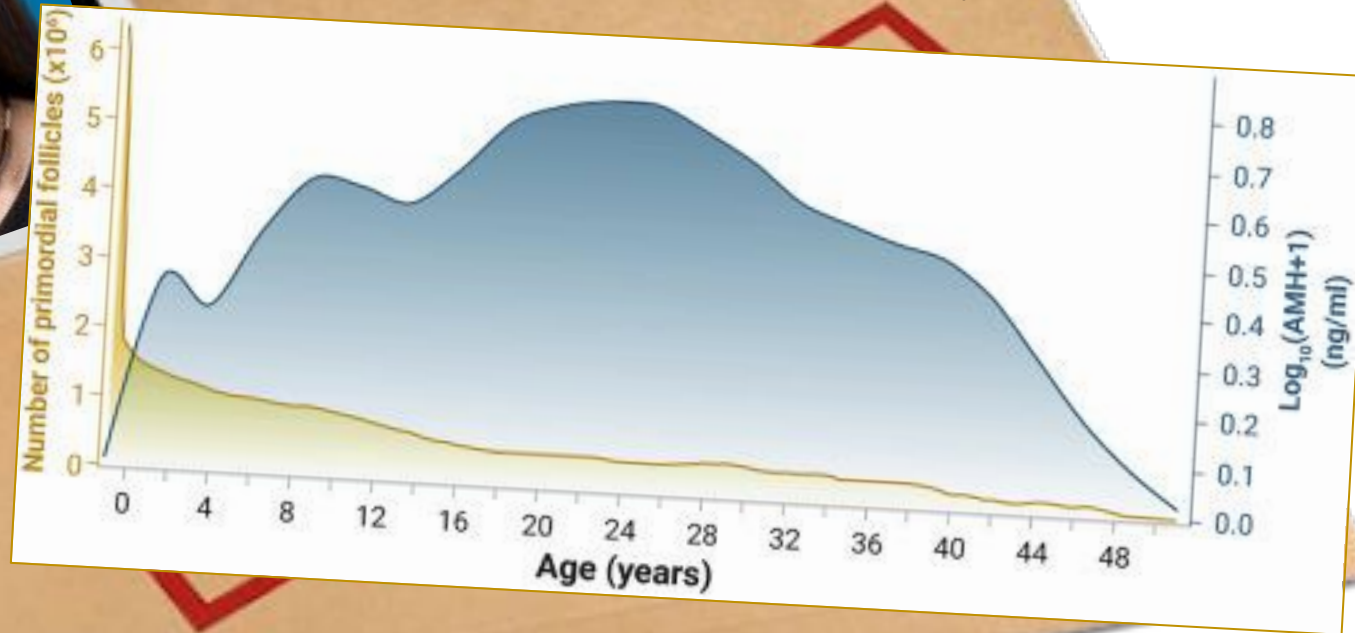
# Potential causes of Barbara's infertility



# Potential causes of Barbara's infertility



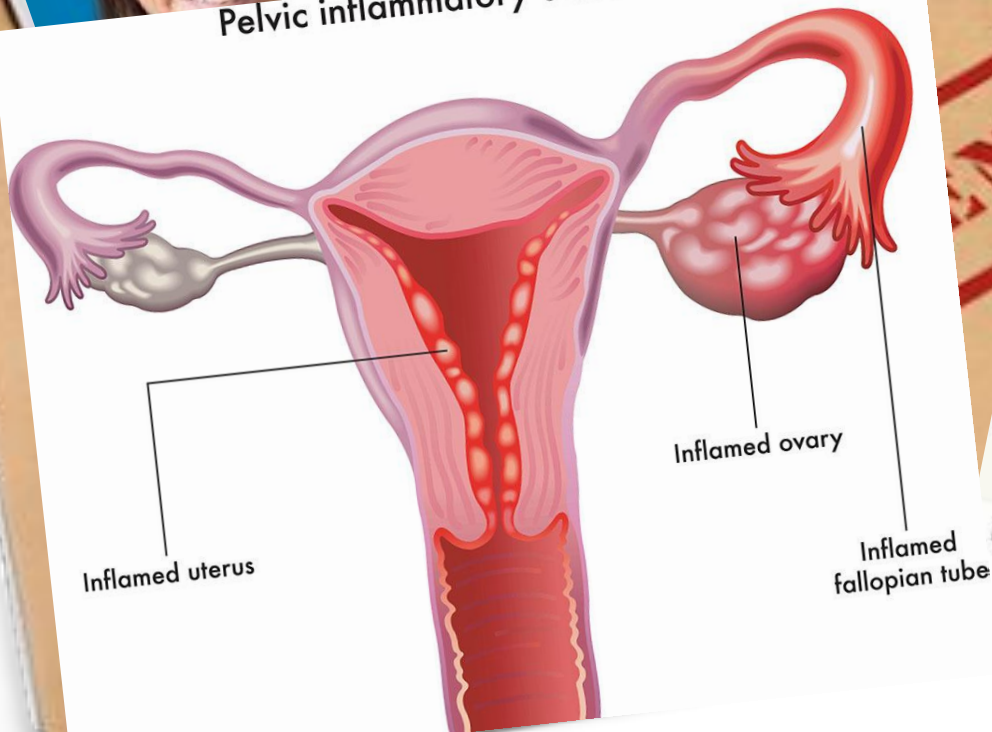
Premature menopause occurs in ~1% of women before the age of 40



# Potential causes of Barbara's infertility



Pelvic inflammatory diseases



## PELVIC INFLAMMATORY DISEASE

- Bacterial Infection
- Caused by untreated bacterial infections, like chlamydia or gonorrhea.
- May cause permanent scarring of reproductive organs
- Curable

Untreated  
P.I.D. may  
cause infertility

Condoms and Dental Dams offer excellent protection against Chlamydia and Gonorrhea \* Free Safer Sex Supplies

# Potential causes of Barbara's infertility



# Potential causes of Barbara's infertility



Variable	Controls (n = 168)	PCOS (n = 175)	P value
Age (years)	29.8±7.4 (15–52)	28.4±6.5 (16–47)	NS
BMI (kg/m <sup>2</sup> )	25.5±7.1 (17–51)	30.0±7.9 (18–58)	<0.001
LH (U/l) <sup>1</sup>	3.8±3.1 (0.5–15.0)	12.3±8.9 (0.4–6.9)	<0.05
FSH (U/l) <sup>1</sup>	4.1±2.5 (0.6–21.5)	4.9±1.8 (0.6–11.5)	<0.001
LH-to-FSH ratio <sup>1</sup>	1.0±0.5 (0.2–2.9)	2.5±1.8 (0.2–17.3)	NS
Testosterone (nmol/l) <sup>1</sup>	6.7±5.9 (2.5–33.3)	2.6±1.2 (0.4–9.0)	<0.001
Estradiol (ng/dl) <sup>1</sup>	8.5±4.9 (0.5–16.1)	6.3±4.4 (2.5–29.0)	<0.001
Progesterone (µg/l) <sup>1</sup>	2.4±1.3 (1.0–7.1)	1.0±0.8 (0.4–4.6)	NS
HOMA-IR (mU·mmol/l)	12.4±4.4 (5–26)	4.7±4.1 (0.5–19.6)	<0.001
Thyroid volume (ml)	6.5	14.8±11.2 (4–125)	NS
Hypoechoic US (%)	1.4±0.6 (0.5–3.4)	42.3	<0.001
TSH (mU/l)	14.9±2.4 (10–23)	2.0±1.0 (0.4–6.2)	<0.001
Free throxine (pmol/l)	10±18 (0–98)	14.1±2.5 (9–24)	<0.001
TPO antibodies (U/l)	4±17 (0–123)	123±328 (0–2860)	<0.001
TG antibodies (U/l)		113±312 (0–2770)	<0.001

BMI, body mass index; HOMA-IR, HOMA-insulin resistance; US, ultrasound; NS, not significant.  
<sup>1</sup> Subjects on contraceptives or antianandrogens were excluded.

# FINAL DIAGNOSIS

- NINE choices:
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  - (2) Premature/early menopause
  - (3) Anabolic steroid use
  - (4) Pelvic inflammatory disease
  - (5) Vasectomy
  - (6) Uterine fibroids
  - (7) Varicocele
  - (8) Polycystic ovary syndrome (PCOS)
  - (9) Abnormal sperm morphology and motility

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Call your Herald to confirm and enter your final time

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