

# ***Progesterones and Breast Cancer***

***Endogenous and Exogenous  
Synthetic or Natural Bio-identical  
Progestins, Progestogens or  
Progestagens***

***“Act like progesterone”***

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# *Contraceptive and Menopausal Progestogens and Oestrogens*

- *W H O International Agency for Research  
in Cancer (IARC monograph, 2005)*
- **“Group 1 Carcinogen”**
- **Highest level** (dioxin, mycotoxins)
- **Direct Genotoxins**

# *Collaborative (51), MWS, WHI*

- xs Breast Ca      5 yr      10 yr      Study
- *Oestrogen HRT*      2      6      *Collab*
- 1.5      5      *MWS*
- *P plus O HRT*      6      19      *MWS*
- 6      18      *WHI*
- *Beral Lancet 2003*
- HRT Studies      (1.09 – 19)      2 – 8

# Contraceptive Breast Cancer Risks

- **OESTROGEN + PROGESTOGEN**
- Combined OCs (1.6 - 7.8) 2 - 5
- **By age 50 - Ever use  $\geq$  4yrs before FFTP 1.52**
- **Kahlenborn, 2006**
- Combined OCs + **Ethinyl oestradiol** 35 mcg 2
- >35 mcg 4
- **PROGESTOGEN only 1.6 - 6**
- (UK study, P mostly lactation 1 – 12 months)



# Breast cancer ↑↑ with *P* use

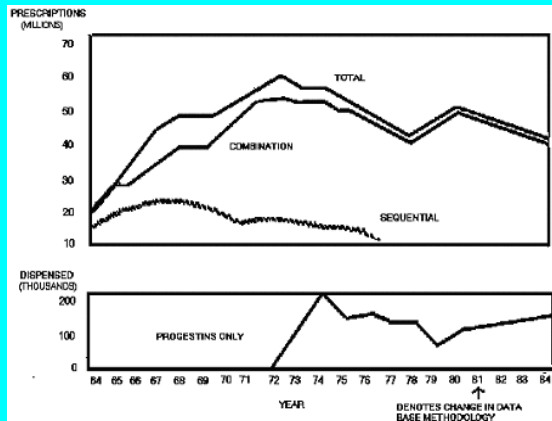


Fig 1.a. OC use in USA, 1964-84. [8]

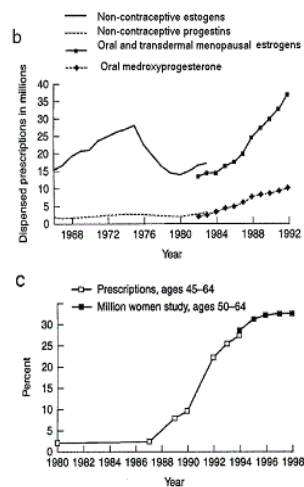
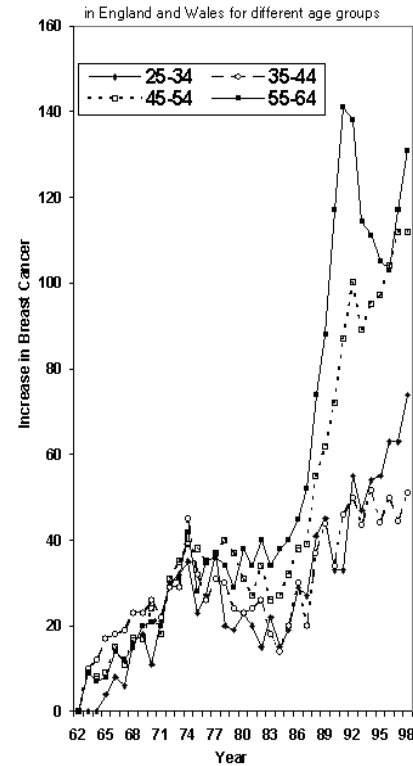


Fig 1b. Dispersed prescriptions (in millions) of HRT estrogens and progestins in the USA 1966-92.

Fig 1c. Estimated prevalence of HRT use in women aged 45-64 in England, 1980-98 [10]

Figure 2. Percentage increases from 1962 in annual breast cancer registration rates in England and Wales for different age groups



# ***Progesterone carcinogenesis***

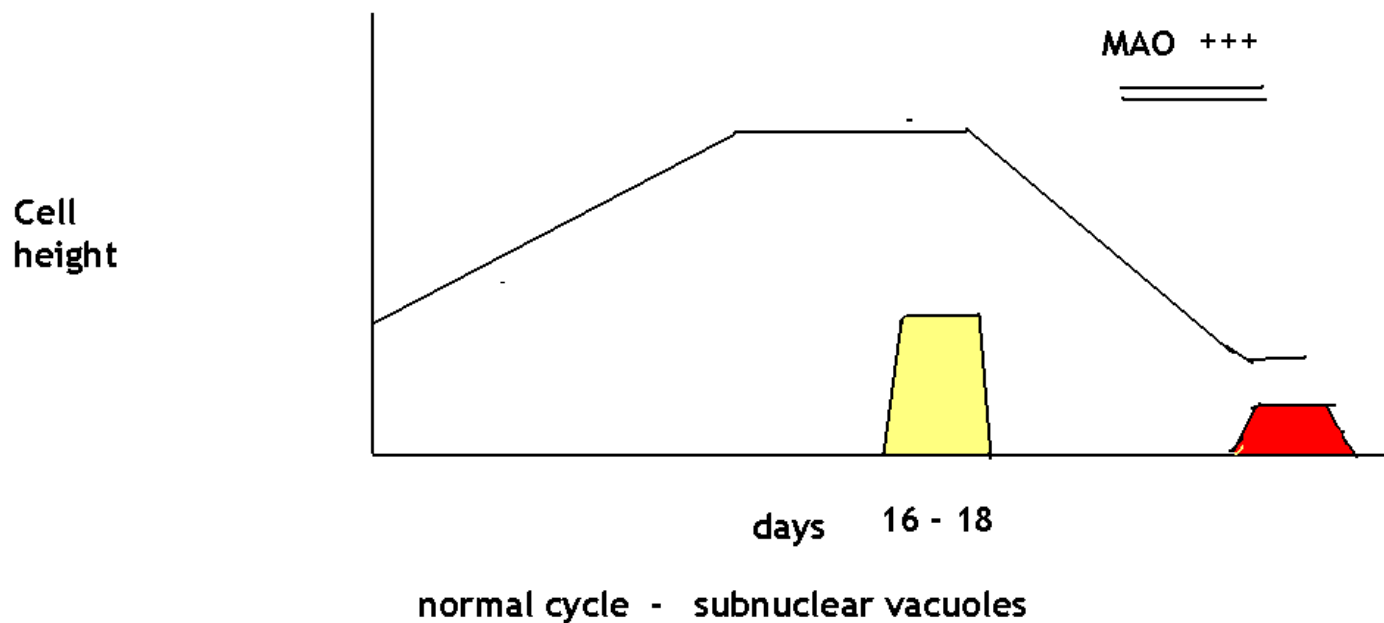
- Why does **Progesterone** cause – **3-4 x more breast cancers** than **Oestrogen**?
- **4 x more genes up or down regulated**
- **All tissues Carcinogenic Metabolites**
- **+ or - Progesterone Receptors**
- **Angiogenesis** ↑ ↑ **Immune diseases** ↑ ↑ (x9)

# ***Actions of Progesterone***

- ***↑ oestrogen priming***
- ***Subnuclear vacuoles***
- ***ESP Alkaline phosphatase*** ↓↓
- ***Acid phosphatase, SODase, COMT*** ↑↑
- ***LSP Monoamine oxidase*** ↑↑
- ***Immediate Angiogenesis*** ↑↑

# ***Normal endometrial cycle***

- *2 days subnuclear vacuoles mid cycle*

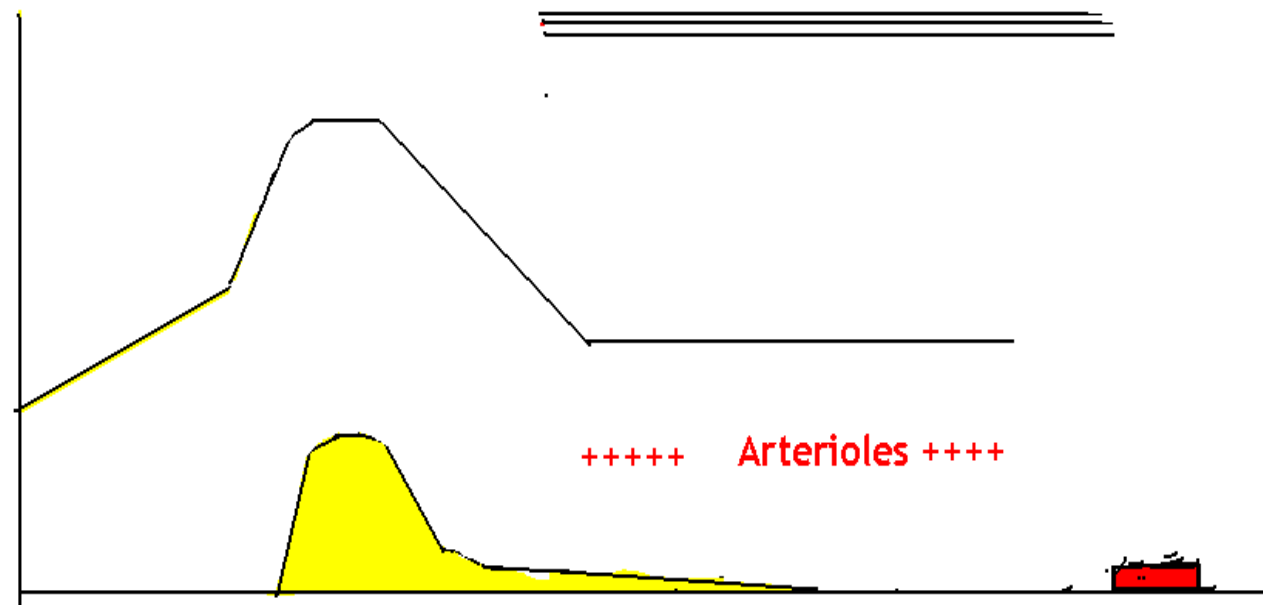


# ***P treated endometrium***



MONOAMINE OXIDASE ++++

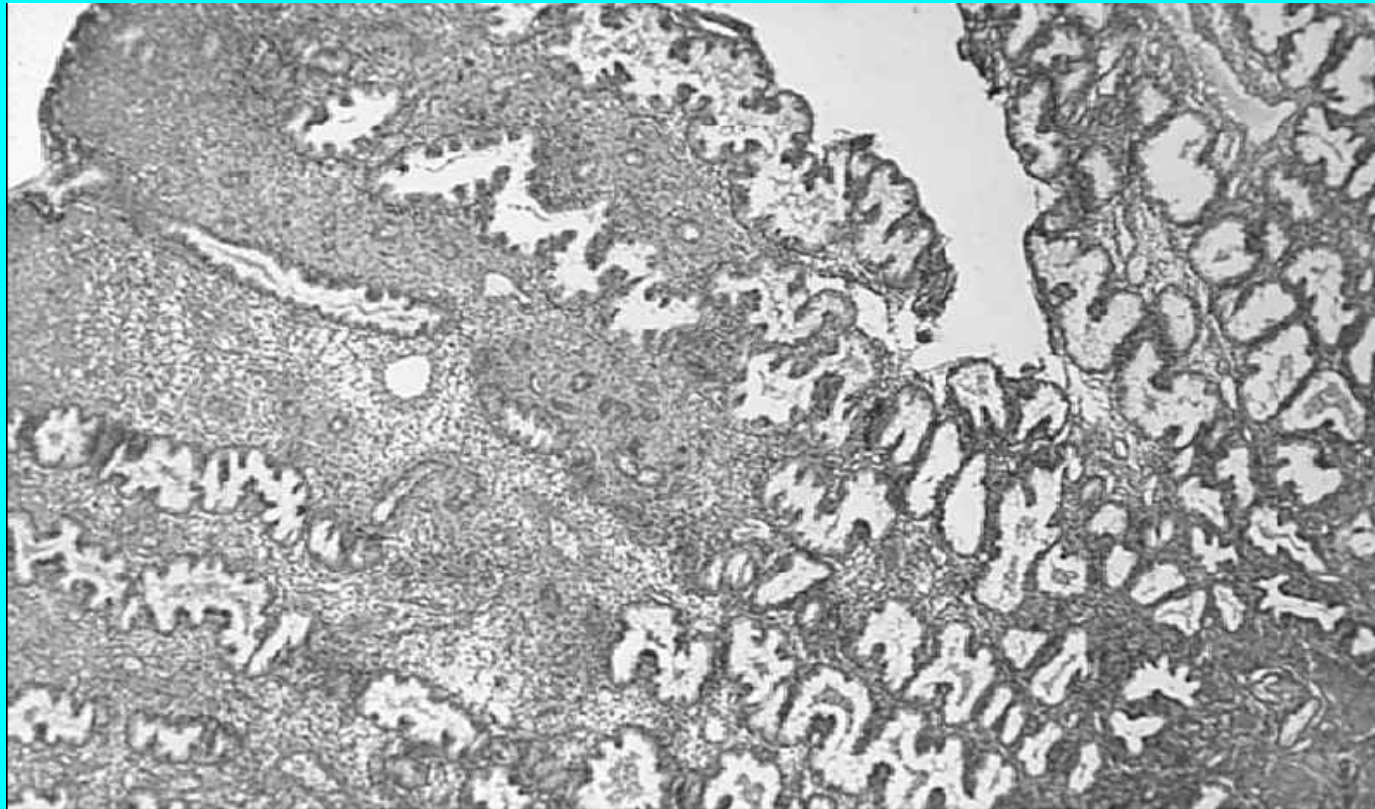
Cell  
Height



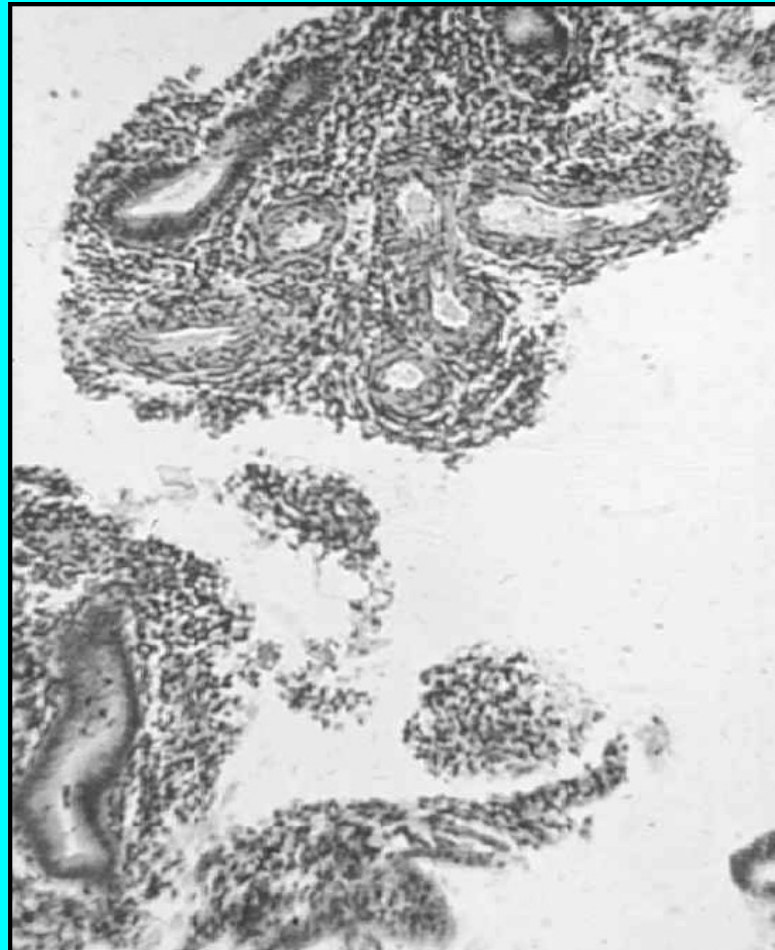
days 8 to 11

Dilated sinusoids ++++

# ***Normal Late Secretory***

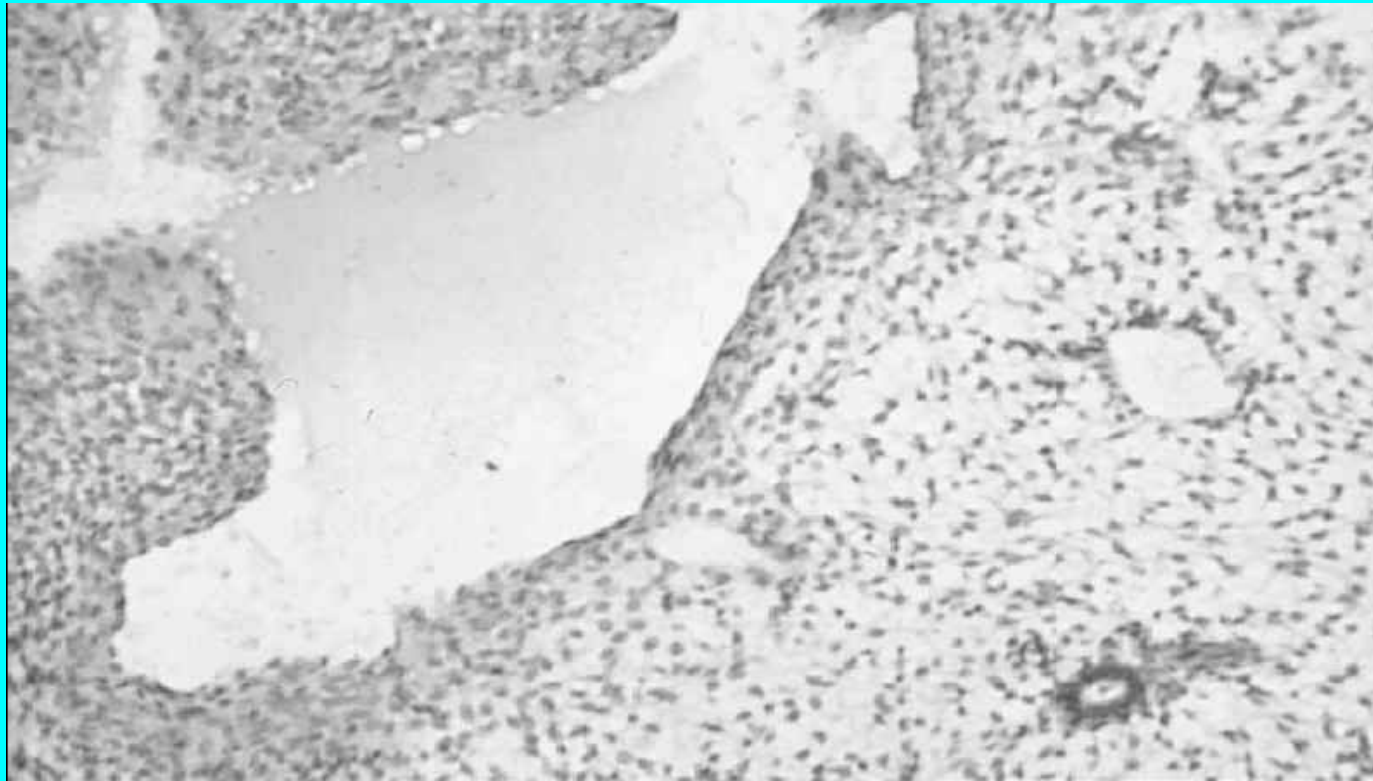


***Progestogenic ++ arterioles ++***



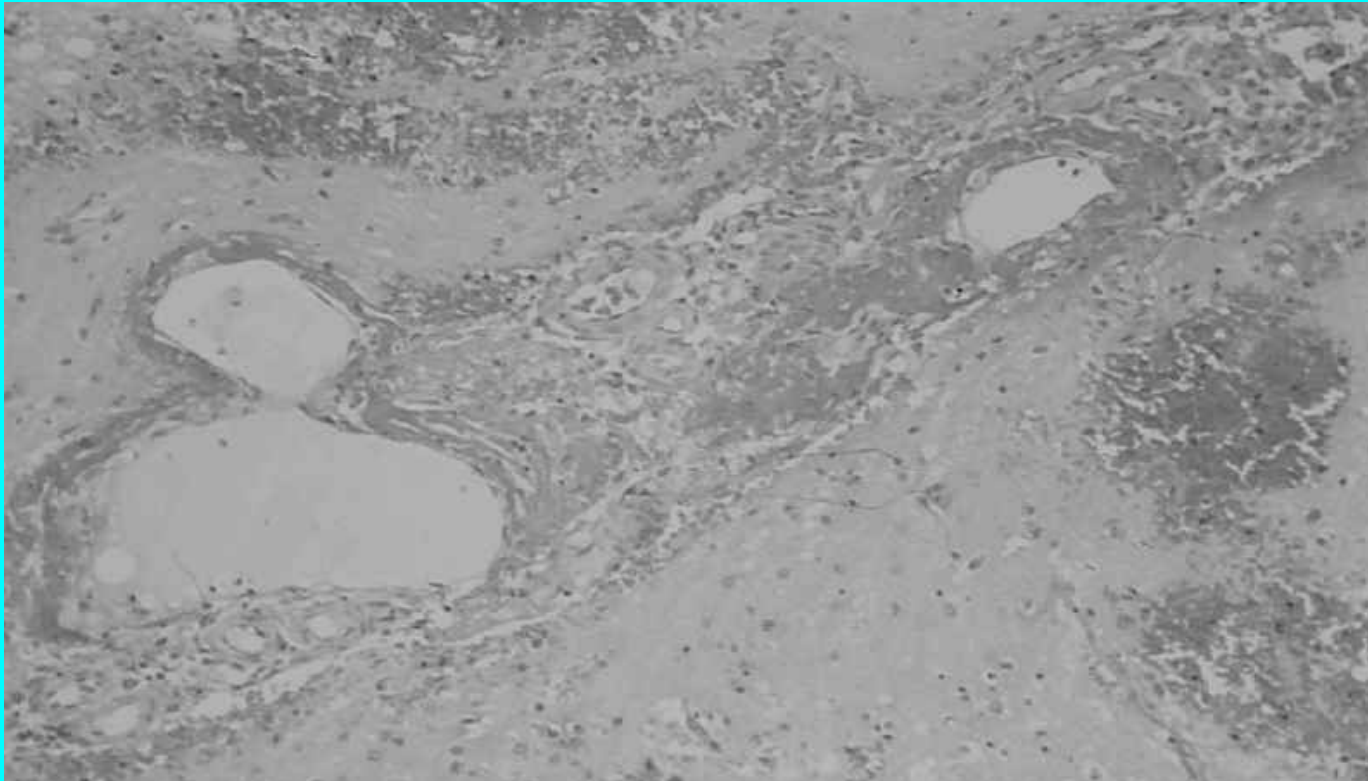


# ***Dilated sinusoid - thrombosis***

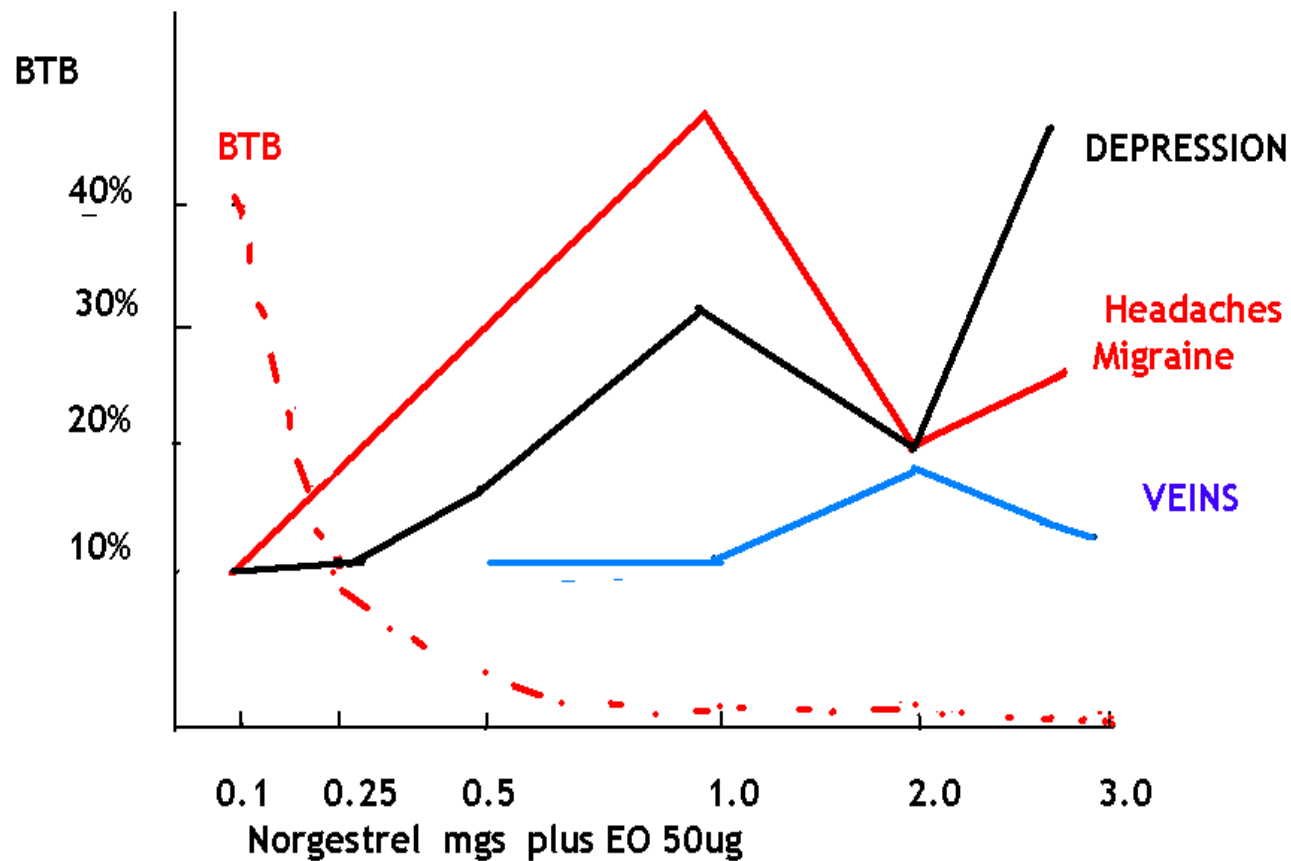




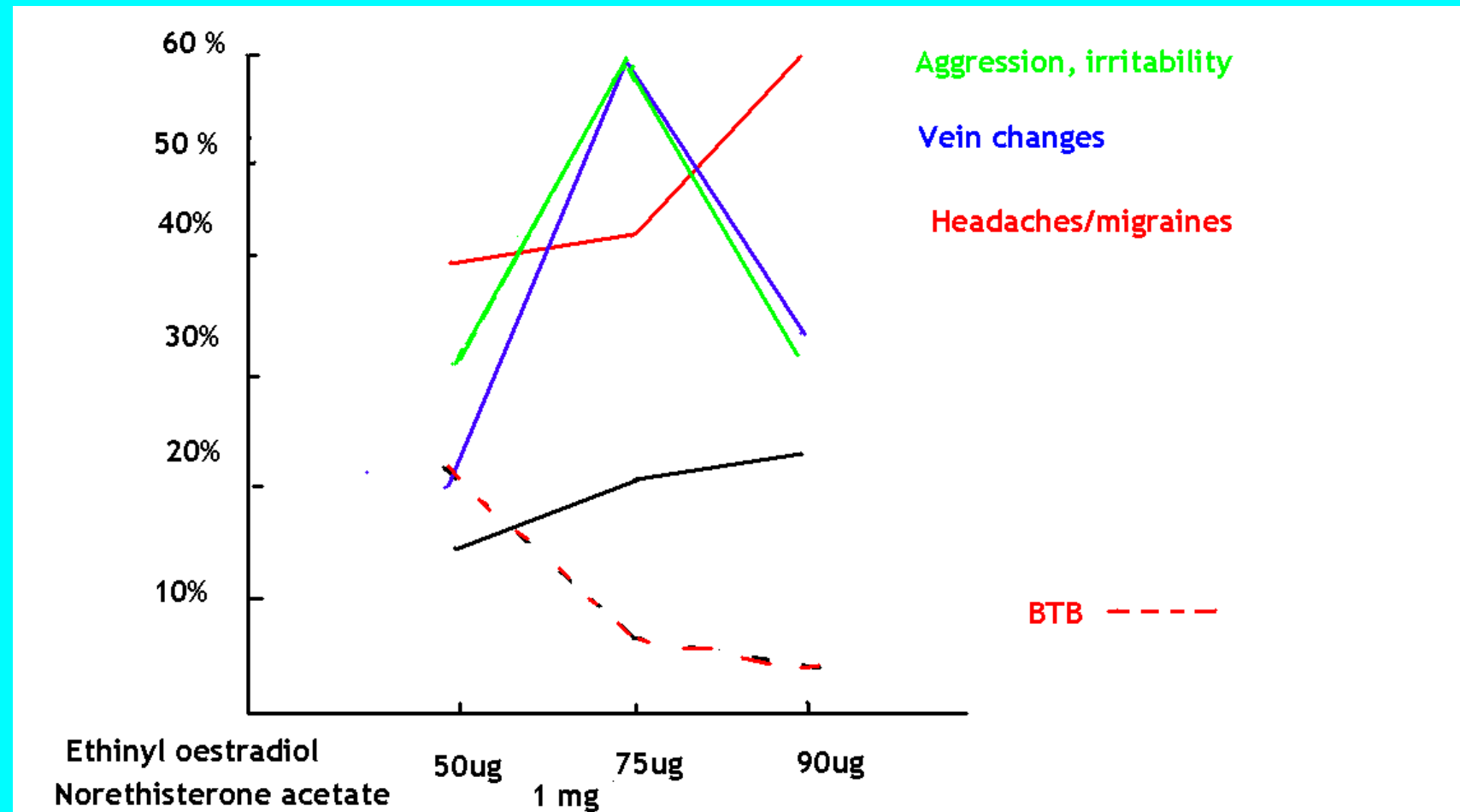
# *Thrombosed cerebral vessels* *– 5 yrs OC*



# *Norgestrel Dose Effects*



# ↑↑ Aggression ↑ Vascular



# *Types of Progestogens*

- *Androgenic* *Pregnanes*
- *Estranes* *Gonanes*
- OCs    10        13        *MPA - depot*
- HRT    13        5        *MPA in* USA
- *MPA* and *MA* (banned UK 1970s)
- *Breast cancer small or large doses*

# Progestogen Potency

## ANDROGENIC

- Estrane
- Norethisterone 1
- N Acetate 1.2

## PROGESTOGENIC

Gonane

Pregnane

- dl-Norgestrel 2.6
- MPA 0.3
- MA 0.4

- Micronised x 2 potency -

## Oral Progesterone

- Levonorgestrel 5.3
- Norgestimate 1.3
- Desogestrel 9
- Gestodene 12.6

# ***Actions of Progesterone***

- ***Blocks FSH and LH - prevents ovulation***
- ***Switches immune balance T1 → T2***
- ***Antibody production***      ↓↓
- ***Symptoms – increased - decreased***
- ***Immune diseases - PMS, SLE***

# *Genetics and Epigenetics*

- *Epigenetics – changes in gene function*
- Koa 2002    *12,686 genes implantation window*
- *1 in 25 genes activated*
- *Progesterone 4 x genes cf Oestrogen*

# *Progesterone –activated genes*

- *377 up regulated*
- *156 down regulated*
- **Striking Regulation of *Secretory Proteins***
- **Water and Ion Channels**
- *Signalling Molecules*
- **Immune Modulators**
- **Endometrial Development**
- **Embryonic Interactions.**



# ***P upregulated genes***

- ***cholesterol trafficking and transport***
- ***apolipoprotein E 100-fold***
- ***prostaglandin (PG) biosynthesis (PLA2) and action (PGE2 receptor)***
- ***proteoglycan synthesis (glucuronyltransferase), secretory proteins (glycodelin, mammaglobin, Dickkopf-1 - a Wnt inhibitor), IGF binding protein and TGF-beta superfamilies, signal transduction, extracellular matrix components (osteopontin, laminin)***
- ***neurotransmitter synthesis -MAO, receptors***

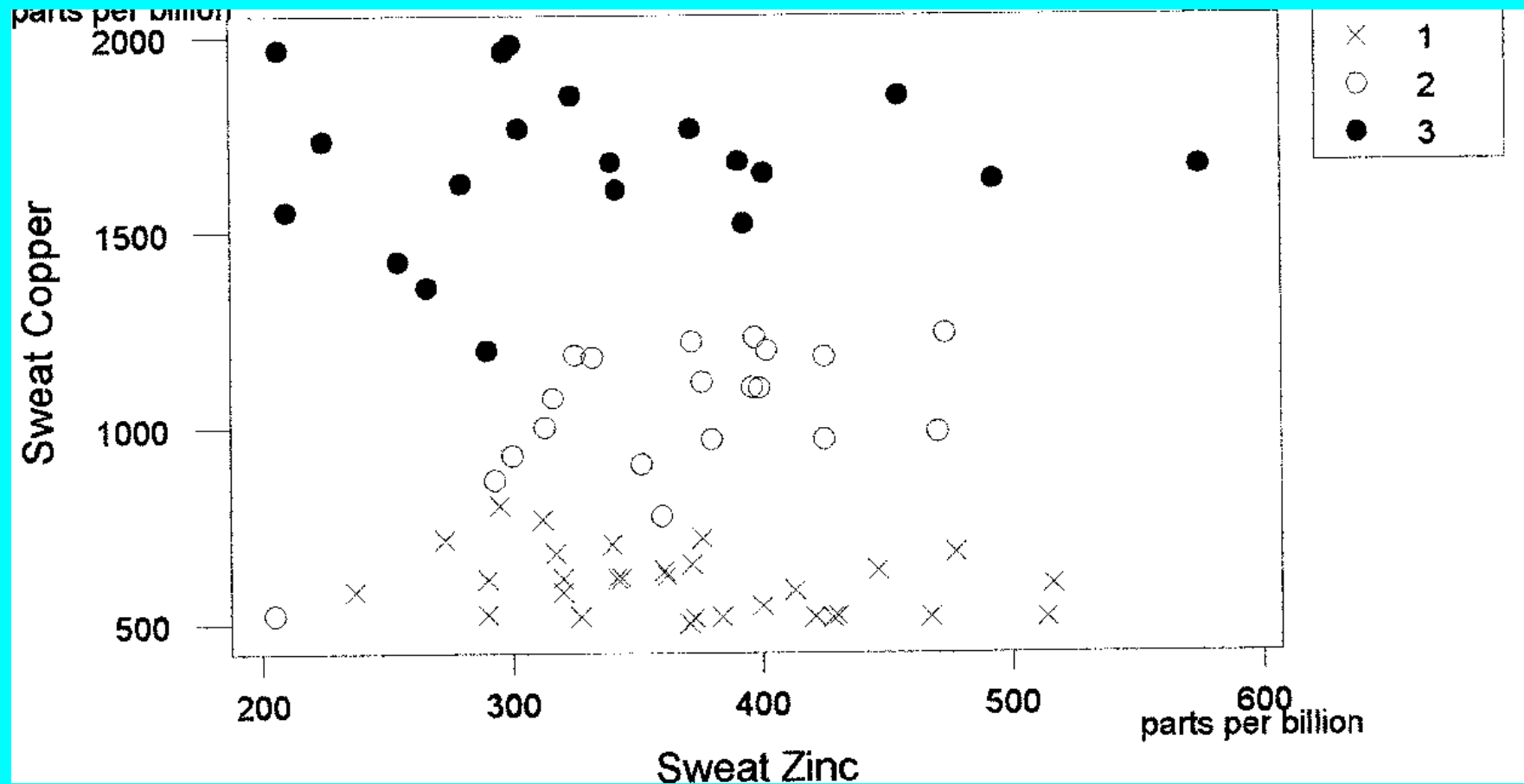
## ***P down regulated genes***

- ***Intestinal Trefoil Factor (ITF) - 50-fold***
- matrilysin, members of the G protein-coupled receptor signaling pathway, frizzled-related protein (FrpHE, a Wnt antagonist)
- ***Transcription Factors, TGF-beta signaling pathway members***
- ***Immune Modulators (major histocompatibility complex class II subunits) and other cellular functions***

# ***P up regulated genes***

- Numerous ***Immune Modulators***
- ***Detoxification genes***  
***Metallothioneins***
- ***Genes involved in water and ion transport - K(+) ion channel***
- ***Genes corresponding to IGFBP-1, glycodeclin, CPE1-R, Dkk-1, mammaglobin, and ApoD.***

↑↑ *Cu/Zn ratios in sweat* (serum and hair)  
in *treated* women - parts per billion at Biolab



# ***RCGP OC Study Vascular***

- **1974 DVTHROMBOSIS /PE 5.66**
- **Heart disease 5.2**
- **Cerebrovascular 4.1**
- **1981 Vascular 4.2**
- **non smoker 1.6 - 4.6**
- **smoker 3.4 - 7.4**
- **1983 AMI +Toxaemia history 41.0**
- **1999 Cerebrovascular +10 years 2.7**

# ***RCGP OC Study - Cancers***

- **Breast cancer** age 25-29 **2.53**
- **Breast cancer** age 30-34 **3.33**
- **Breast** + 10 yrs **10.17**
- **Breast** 8-9 yrs later **15.8**
- ***Breast cancer deaths 154*** 5- 9 yrs later ***1.5***
- ***Lung cancer*** **75** 1.3 + 10 yrs ***1.6***
- ***Liver cancer*** **5** ***5.0***

# ***RCGP OC Study***

- ***Cervical cancer 2 - 3 Deaths > 10yrs 5.3***
- ***Pruritis, vaginitis, 2***
- ***Trichomonas, leukorrhoea, cervicitis 1.6***
- ***Ex OC Irregular bleeding 1.55***
- ***Fibroids 2.5***
- ***Post Pill amenorrhoea - infertility 3.2***
- ***Abortions 13.3% → 30.61%***

# ***RCGP OC STUDY***

***NOT “ALL CLEAR”***

***Over 60 conditions increased  
immune diseases, infections and allergies***

***SERIOUS IMMUNE  
DYSFUNCTION***



# ***Walnut Creek OC Study***

- ***Cervical cancer*** ***x12***
- ***Ovarian retention cysts***
- ***Severe acute iron deficiency anaemia***
- ***Fibroids (vascular)***
- ***Adenomyosis (endometriosis)***
- ***Hysterectomies < age 40 6.3% x2.5***
- ***All Significantly Increased* → HRT “use” ++**

# ***Endocrine-disrupting chemicals***

- Over **70** years of animal research
- **Hormones organise the brain**
- **Peri-natally - critical timing**
- **Modify sexuality, perception and learning**
- **Endogenous - twins - risk taking – aggression**
- **Aromatase inhibitors , pesticides, fungicides**
- **Crews and McLachlan 2006**

# *Fertility and pregnancy hormonal “treatments”*

- *Genital organ malformations infertility treatment*
- *HR 2.32* Zhu JL, Danish national birth cohort. *BMJ*, 2006
- *Progesterone /progestogens*
- *4 weeks before to 14 weeks after conception*
- *HYPOSPADIAS OR 3.7* Carmichael 2005

# ***Effects of P on development***

- ***Most pregnancy **Progesterone** use now***
- ***↑ Cancers in children, DES breast, vaginal***
- ***Testicular Leukaemia Neuroblastomas***
- ***Brain Development ↓ Stress coping***  
***↑ Mental illness***                      ***↑ Autism x4***
- ***Sexual Orientation - Organ Abnormalities***
- ***Immune Dysfunction ↑ Allergies***

# ***Progesterone carcinogenesis***

- *A Preventable Epidemic ?*
- *WHI, MWS and WISDOM HRT trials terminated early*
- *but very young OC use*
- *off prescription very high doses ECs*
- *depot MPA* still vigorously promoted

# Ellen Grant on line

- [www.tandf.co.uk/journals](http://www.tandf.co.uk/journals)
- [J Nutr Environ Med June 1998](#)
- [www.bmj.com](http://www.bmj.com) Search - [Grant, E](#)  
Articles and Rapid Responses
- NCBI [www.pubmed.gov](http://www.pubmed.gov) - [grant ec](#)