Estrogen insufficiency and the Metabolic Syndrome

- NIA workshop on
- Biology of the Perimenopause

- Evan Simpson, PhD

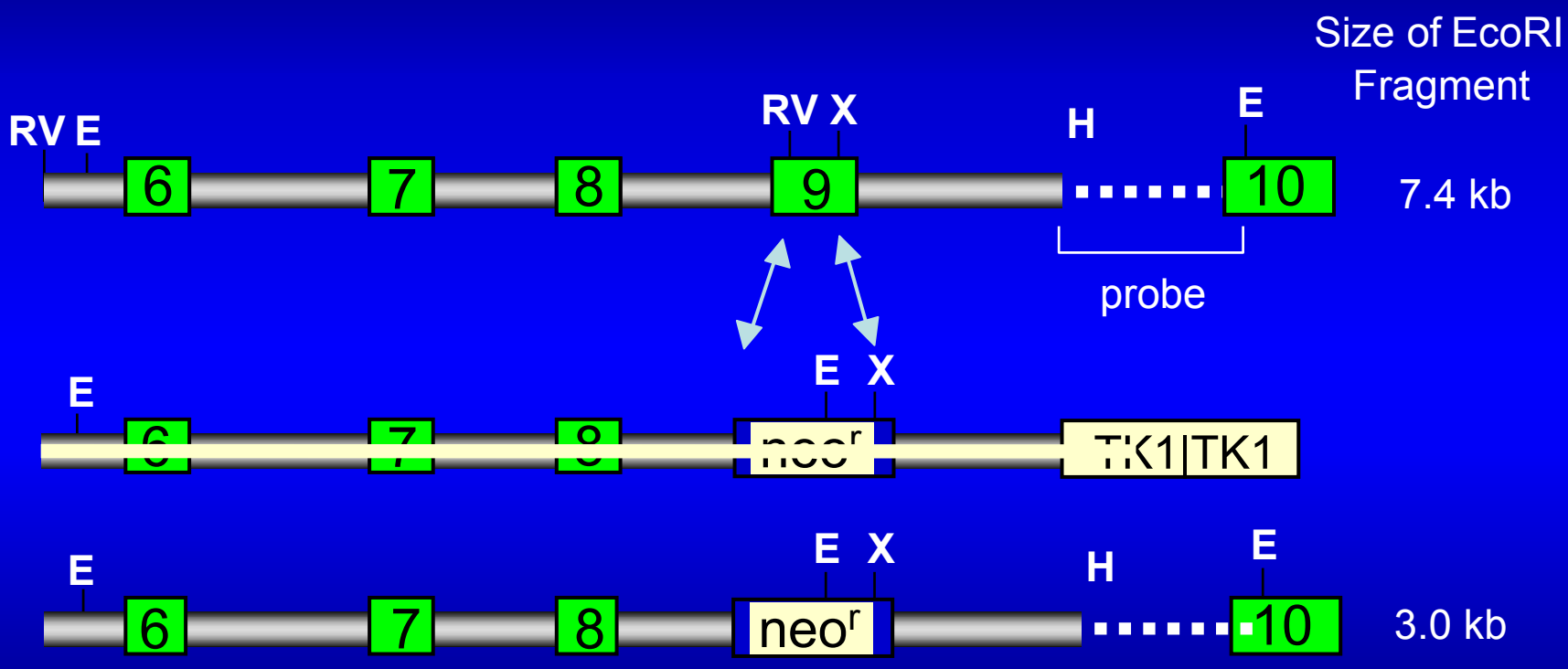
- Supported by the National Institute on Aging

Models of estrogen insufficiency have revealed new and unexpected roles for estrogens in both males and females.

These models include natural mutations in the aromatase gene, as well as mouse KOs of aromatase and the estrogen receptors.

Some of these roles apply equally to males and females and do not relate to reproduction, for example the bone, vascular and “Metabolic Syndrome” phenotypes.

The Aromatase Knockout (ArKO) Mouse



Fisher et al (1998) PNAS 95:6965-6970

Aromatase KO (ArKO) mouse: percent adipose tissue

	10 weeks	*1 year*
Females		
ArKO	17.6 ± 4.4 (5)*	64.3 ± 11.0 (19)*
WT	4.9 ± 1.0 (5)	42.1 ± 6.7 (9)
Males		
ArKO	15.2 ± 2.3 (5)*	40.3 ± 3.8 (13)*
WT	7.3 ± 1.7 (5)	29.5 ± 3.7 (16)

Mean ± S.E.M. (n) * indicates at least $p<0.05$ compared to WT.

ArKO mice develop insulin resistance

	Insulin (mU/L)	*Glucose (mmol/L)*
ArKO		
4 months old	5.98 ± 1.00 (3)	N.D.
1 year old	38.67 ± 11.18 (5)*	8.52 ± 1.56 (3)
WT		
4 months old	5.26 ± 0.75 (4)	N.D.
1 year old	13.82 ± 3.82 (4)	8.61 ± 2.02 (3)

Serum leptin levels

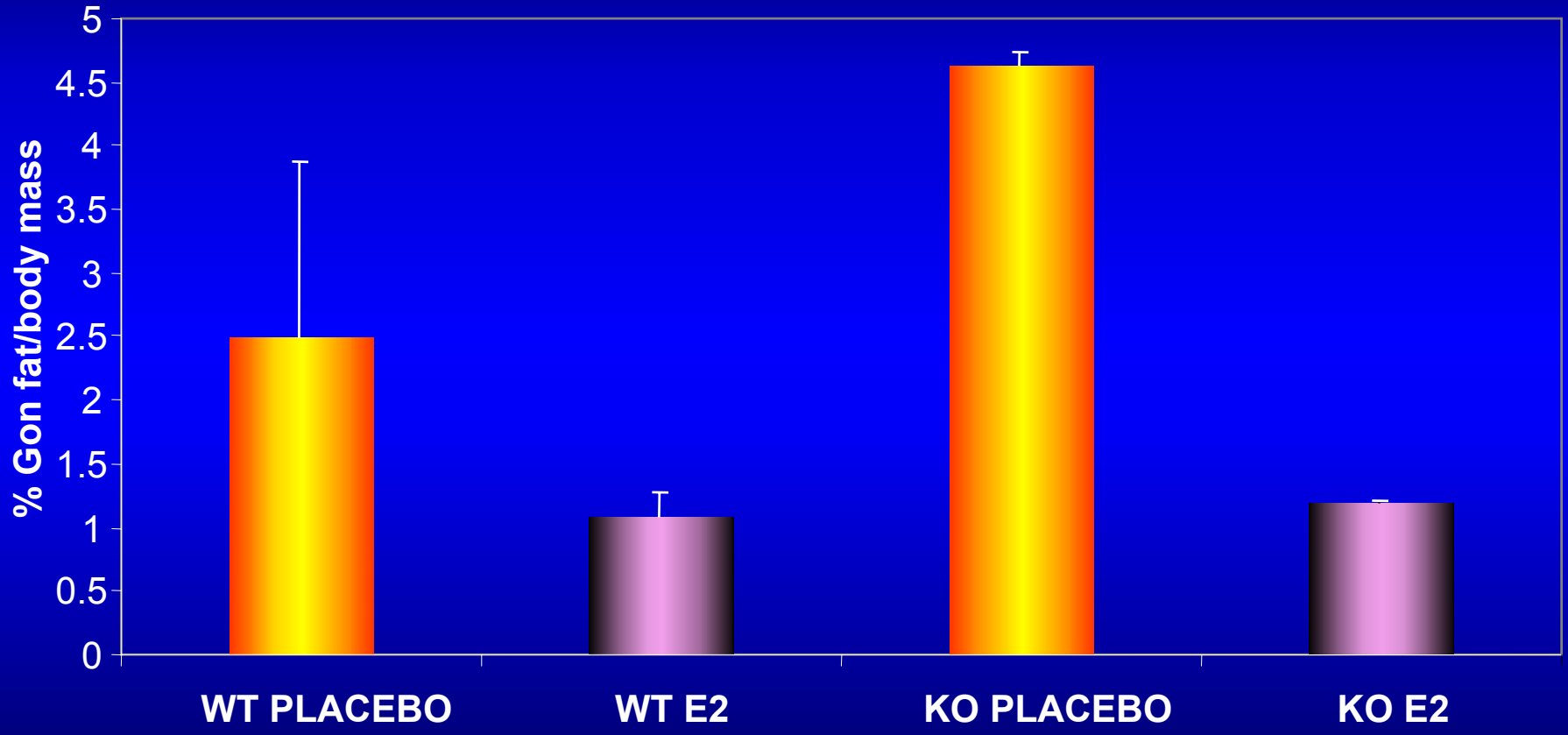
mean ± SEM (ng/ml)

	Females	*Males*
4 months		
ArKO	8.18 ± 0.78 (5)*	8.79 ± 1.83 (6)*
Wildtype	2.92 ± 0.68 (5)	3.81 ± 1.00 (7)
1 year		
ArKO	19.86 ± 4.90 (6)*	8.47 ± 1.85 (7)*
Wildtype	6.19 ± 2.33 (4)†	4.89 ± 0.72 (8)

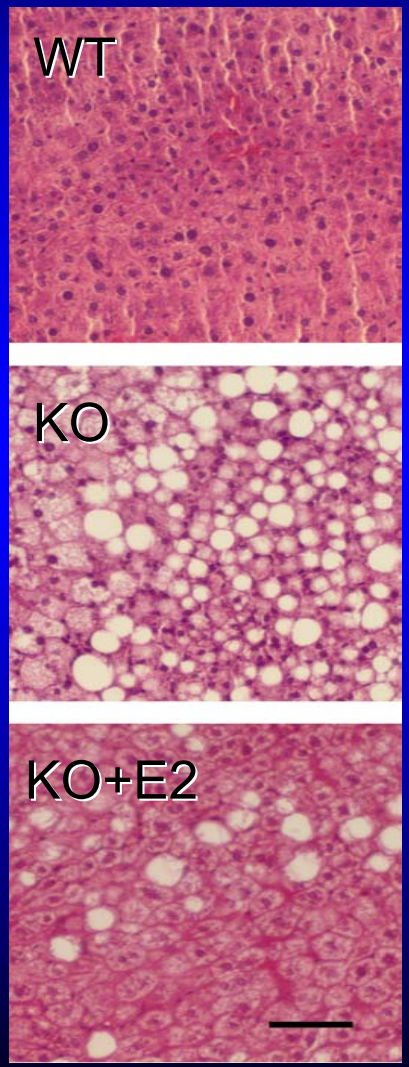
* indicates at least $p<0.05$ compared to age-matched WT mice.

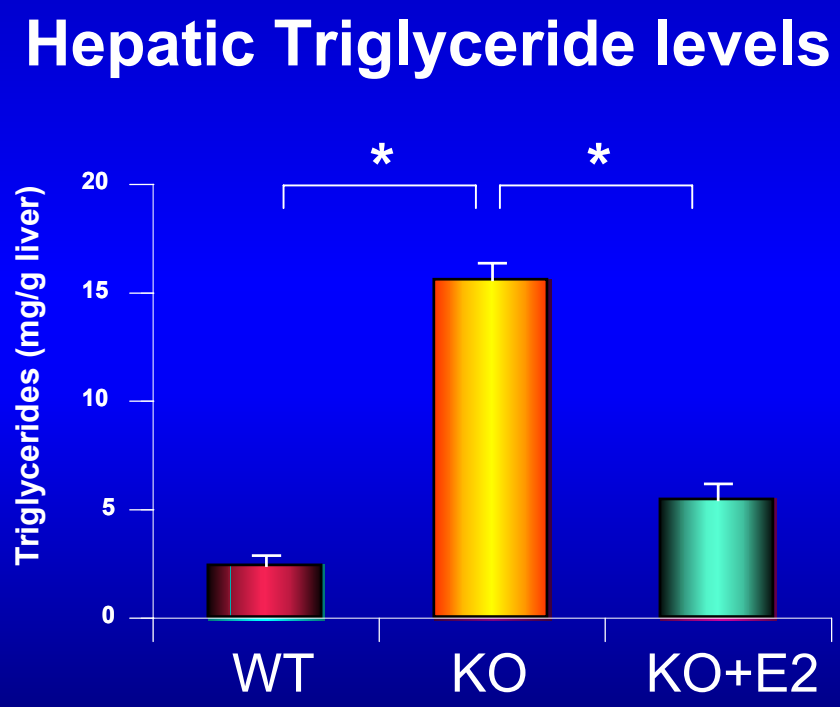
† indicates at least $p<0.05$ compared to 4-month old, genotype- and sex-matched mice.

Female Gonadal Fat



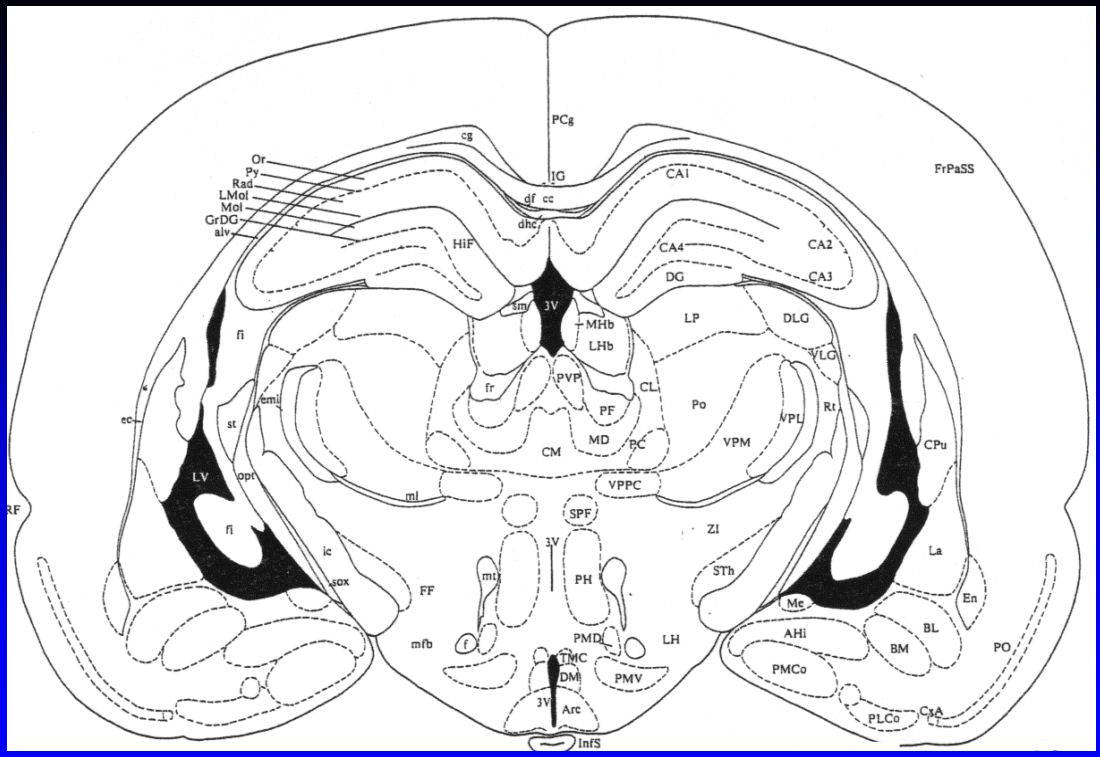
Estrogen replacement reverses hepatic steatosis in male ArKO mice

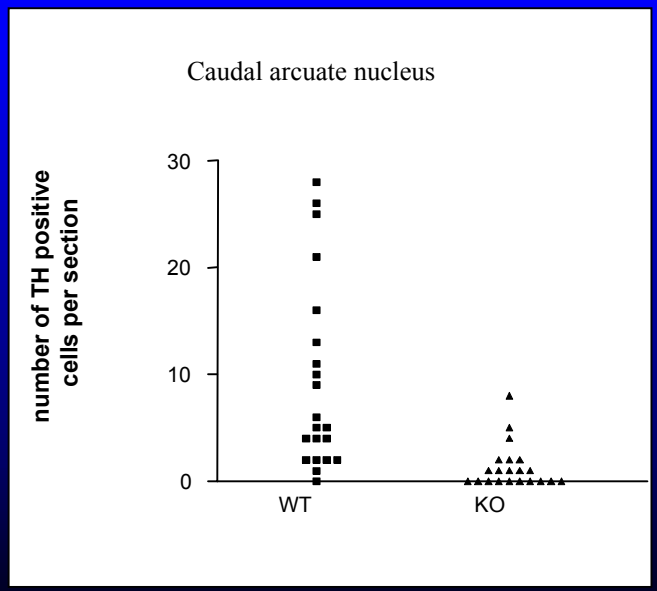


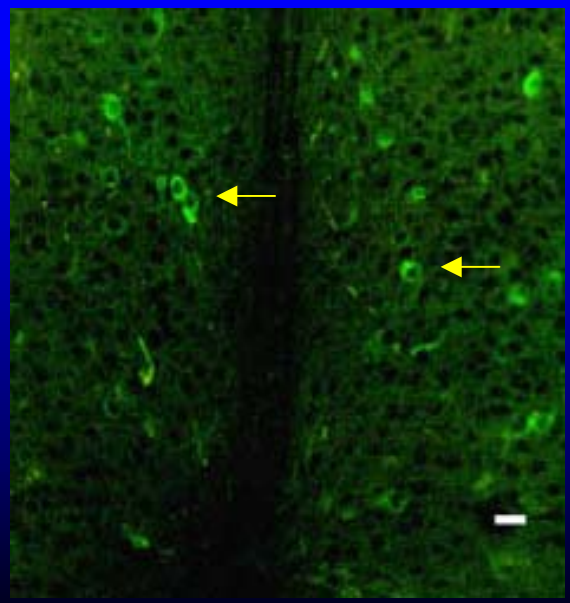


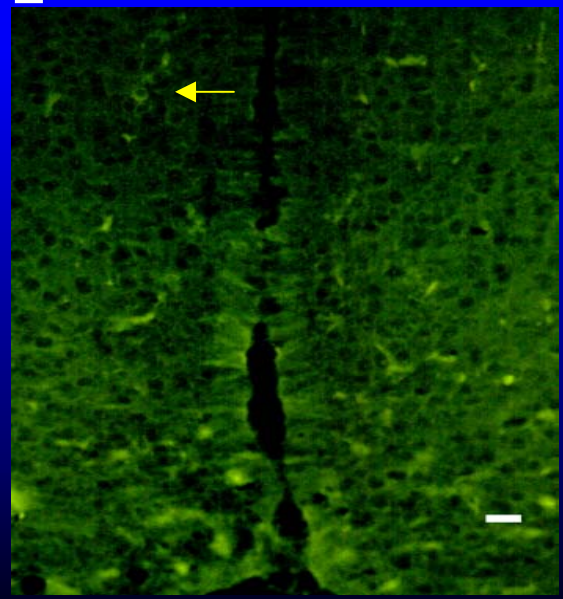
1 yo Male ArKO arcuate nucleus

Tyrosine hydroxylase postive cells ↓

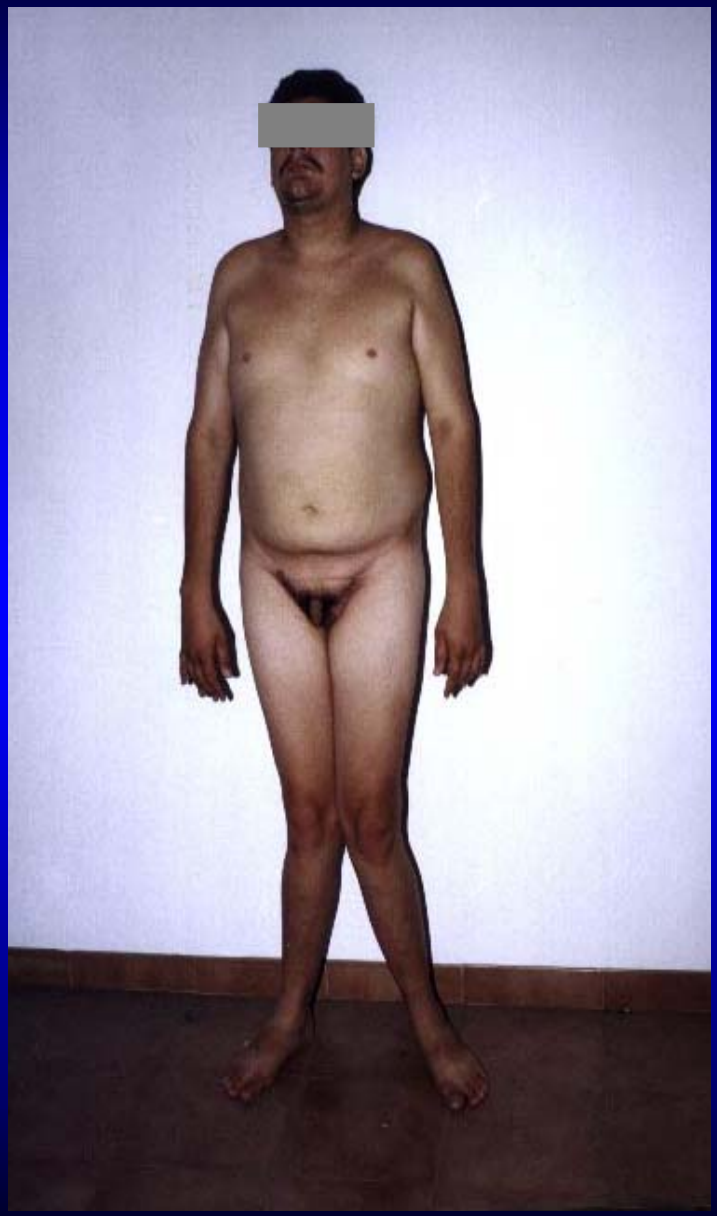








Argentinian man with aromatase deficiency



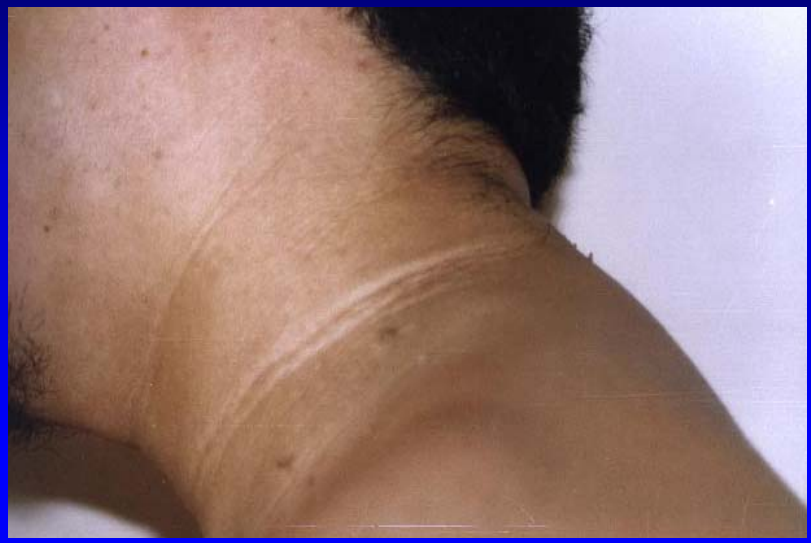
***genu valgum*,**
central obesity

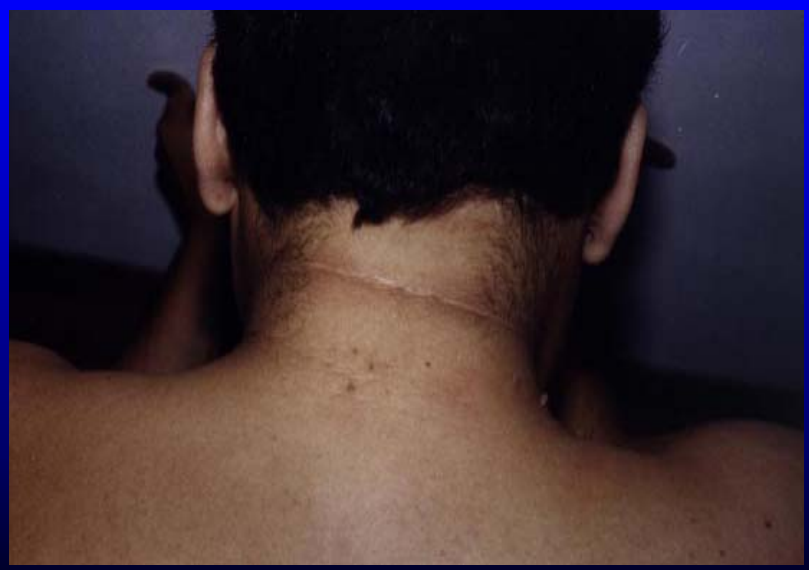
From: Maffei et al. JCEM 2004

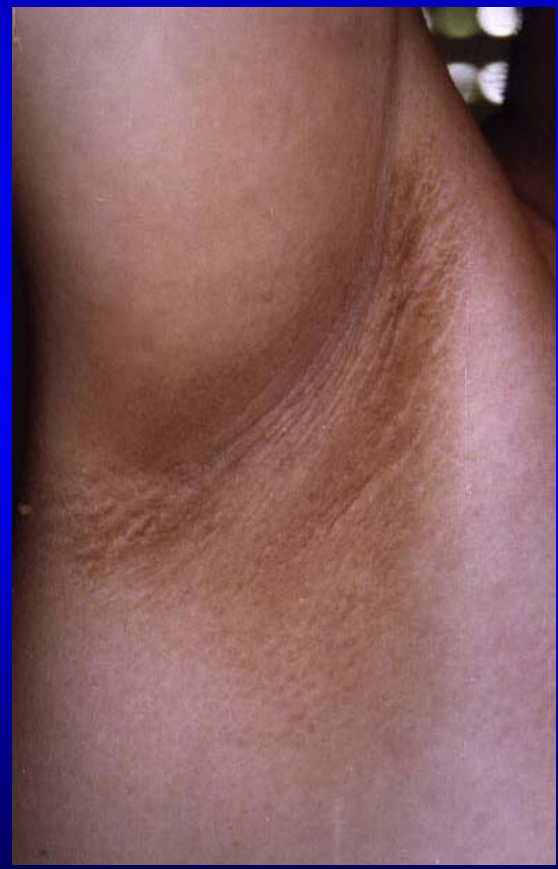
Metabolic and liver function parameters

	before E treatment	after E treatment
Metabolic parameters:		
Total cholesterol (mg/dl)	177	110
LDL cholesterol	107	66
HDL cholesterol	31	41
Triglycerides	199	106
Glucose (70-110mg/dl)	180	144
Insulin (5-30μU/ml)	94	53
Fructosamine (μmol/L)	406	315
Liver function parameters:		
GPT (<37U/L)	195	70
GOT (<40U/L)	108	45
γ-GT (<11-50U/L)	153	42

acanthosis nigricans

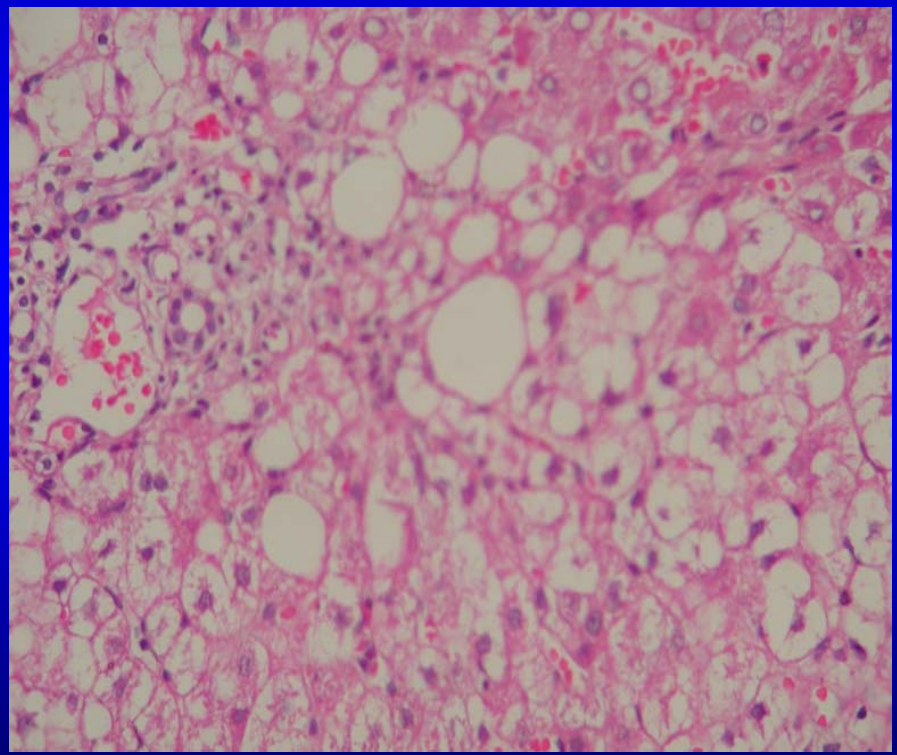




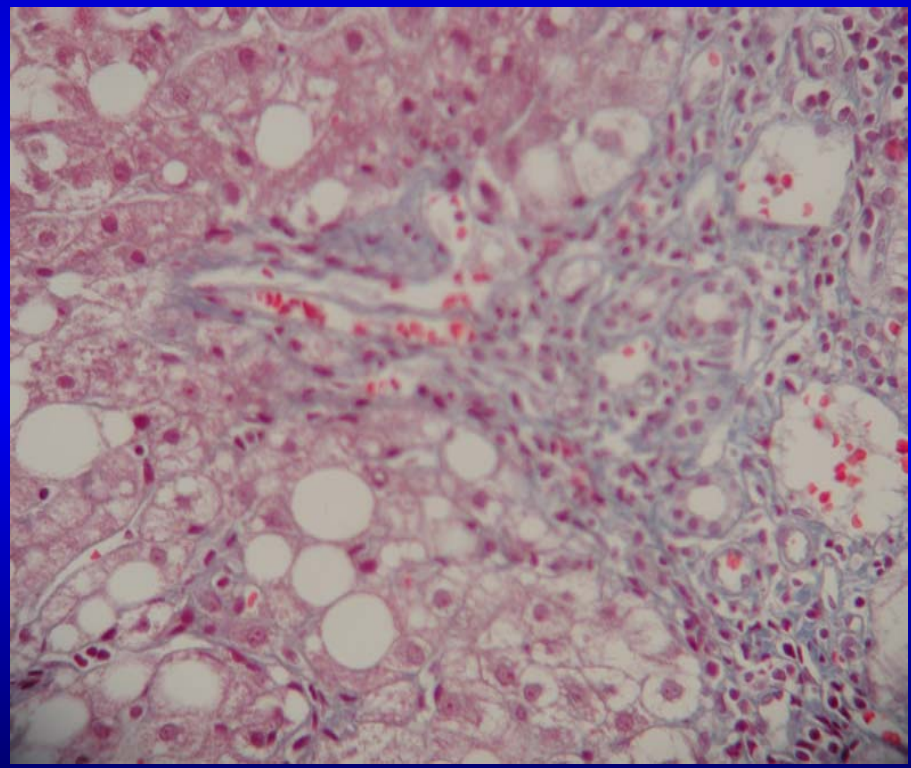


Liver

Macro and microsteatosis



Portal vein fibrosis and steatosis.



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Summary of metabolic effects of estrogens

- Estrogens have important roles to play in both males and females; many of these roles are unrelated to reproduction
- Peripheral estrogen synthesis is the most important source of estrogen influencing target tissues in postmenopausal women and men – circulating levels reflect rather than direct, estrogen action in these sites.
- Lack of estrogen results in the development of a Metabolic Syndrome in mice and men.
- This results in a sexually dimorphic partitioning of lipid such that in males, there is pronounced hepatic steatosis which is not seen in females
- Estrogen administration results in a prompt reversal of these symptoms

Summary of metabolic effects of estrogens (contd.)

Estrogen must be considered to be another hormone synthesized in adipose which acts to regulate lipid homeostasis, along with leptin, adiponectin, resistin and cortisol.

Issues

- Loss of estrogens at the Perimenopause – use of HRT
- Long-term use of aromatase inhibitors e.g. as adjuvant therapy for breast cancer, or else in the chemoprevention setting
- Polymorphisms in the aromatase gene as a genetic cause of susceptibility to the Metabolic Symptom?