Key developments in research on reproductive endocrinology

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Arguably the most important risk factor for a shorter, unhealthier life ……….

*Increased risk of*

- Dying earlier
- Cardiovascular disease
- Kidney disease/hypertension
- Visceral obesity
- Most cancers
- Gastric ulcers
- Schizophrenia
- Autism spectrum disorders
The biggest question of all?

Why are we here? To serve others.
Why are we here?

Nature/evolution has shaped us for one purpose - To pass on our genes to the next generation -
Male preoccupation with sex
It starts at an early age

And the fascination never ends!!

RICHARD
When it comes to that sexual urge
Common sense is discarded in males

Bronze statue of a buffalo on a plinth

Randy
Male moose
When it comes to that sexual urge
Common sense is discarded in males
As Jeremy Clarkson commented

‘It should not surprise us that teenage boys are unable to keep their bedroom tidy or to have decent table manners, when all you are is a life support system for your testicles’
When to start puberty?
What says ‘Go’
When to start puberty?
What says ‘Go’

Reproduction requirements

**Female** (*to support pregnancy & lactation*)
- Bone and general physical development
- Energy stores/reserves

**Male** (*to support sperm production/sex drive*)
- Make sperm and be able to have sex
- (?fight off other interested males)

FOOD, FAT Stores, a functional reproductive system
The diverse influence of reproductive hormones

Reproductive/Sex hormones regulate or modulate:

• Body appearance (male or female)

• Body growth rates and final height (skeletal effects)

• Body composition (muscle and fat amounts and distribution)

• Brain development and organisation (male or female)

• Liver, kidney, lung and cardiovascular development/function

• The immune system

• Puberty, sex drive/function and fertility
Arguably the most important risk factor for a shorter, unhealthier life...........

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Welcome to the exclusive club of being a MALE
Why are we here?

Males and females have completely different roles in this process – hence we are ‘made’ differently so that we are fit for purpose.
Masculinisation of males
Is it the Y chromosome or is it androgens?

• Inactivating mutation of AR
• Phenotypically normal female
• Testes (abdominal) are present and hormonally functional
• Testosterone levels are elevated
• Fallopian tubes, uterus and top part of vagina missing
• Body fat distribution is female
• Brain is female
• Disease risk is female

XY
Male - female differences
Fat deposition is fundamentally different

This is thought to reflect sex differences in energy needs/utilisation (from an evolutionary perspective)
Male - female differences

Fat deposition is fundamentally different

Reduced testosterone

This is the main reason why men die earlier than women
Male - female differences
Differences in disease risks

Cancers
Relative risk in **males** versus **females**

- Lung
- Colorectal
- Stomach
- Liver
- Bladder
- Skin
- Thyroid
Masculinisation of males
How common are subtle disturbances of this?

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## Prevalence data for reproductive disorders in newborn or young adult males

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prevalence</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidism (undescended testis)</td>
<td>2-9%</td>
<td>Prospective EU studies</td>
</tr>
<tr>
<td>Hypospadias (Penis abnormality)</td>
<td>0.4-0.9%</td>
<td>Prospective EU studies</td>
</tr>
<tr>
<td>Low sperm counts</td>
<td>16-20%</td>
<td>Prospective EU studies</td>
</tr>
<tr>
<td>Testis germ cell cancer</td>
<td>0.45%</td>
<td>Registry data (reliable)</td>
</tr>
<tr>
<td>Low adult testosterone</td>
<td>~10%</td>
<td>Longitudinal birth cohorts</td>
</tr>
</tbody>
</table>

Environmental/lifestyle factors are implicated in the high/increasing prevalence of these disorders. What these factors are, is unknown.
The commonest reproductive disorders of the developing and young adult male

‘Testicular dysgenesis syndrome’

- Testicular dysgenesis syndrome
- Cryptorchidism
- Hypospadias
- Testis germ cell cancer
- Low sperm counts
- Low testosterone

Subnormal Testosterone production or action

Testosterone is an androgen (type of hormone)
The ‘masculinisation programming window’ (MPW)

Studies in rodents have identified that androgen exposure within the MPW is critical for determining normal reproductive development and ultimate reproductive organ size.

The available evidence suggests that TDS disorders arise because of androgen deficiency in the MPW.

The human equivalent of the MPW is estimated to be within 8-14 weeks’ gestation.

The commonest reproductive disorders of the developing and young adult male

‘Testicular dysgenesis syndrome’

- Testicular dysgenesis syndrome
- Cryptorchidism
- Hypospadias
- Testis germ cell cancer
- Low sperm counts
- Low testosterone

Maternal Diet, Lifestyle, exposures

Subnormal Testosterone production or action

Cryptorchidism Hypospadias

Testosterone is an androgen (type of hormone)
Fetal programming of adult disease risk

Adult cardiovascular disease is inversely related to birth weight.

Deaths before age 65 from coronary heart disease

The picture is similar for blood pressure – the lower your birth weight the higher is your blood pressure.

The higher your birth weight the lower your adult blood pressure and the lower your risk of coronary heart disease.
Birth weight is positively associated with adult testosterone levels (independent of adult bodyweight)

Birth Weight in Relation to Sex Steroid Status and Body Composition in Young Healthy Male Siblings

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Context: Sex steroid concentrations have a strong genetic determination, but environmental factors and body composition play an important role. From studies in children with intrauterine growth restriction, low birth weight has been associated with altered gonadotropin concentrations.

Objective: We aim to investigate sex steroid concentrations in healthy young brothers in relation to birth weight (normal gestational age), body composition, and parental steroid concentrations.

Design and Setting: We conducted a cross-sectional, population-based sibling pair study with inclusion of parental data.

Participants: A total of 677 men (25–45 yr old) were included in this study, with 296 independent pairs of brothers and 122 fathers.

Main Outcomes: We measured testosterone, estradiol, leptin, adiponectin, IGF-I (immunoassays), and free steroid hormones (calculated) in relation to birth weight and changes in body composition (dual-energy x-ray absorptiometry).

Results: Birth weight was associated with serum testosterone (P = 0.0004) and SHBG (P = 0.0001), independent from weight, age, or fat mass, whereas no association with (free) estradiol, LH, or FSH was found. Paternal testosterone (P = 0.02), estradiol (P = 0.04), and SHBG (P = 0.0004) were associated with the respective sex steroid concentrations in the brothers. Weight increase (population rank) during life, was associated with lower testosterone (−15%; P < 0.001), independent from current weight and with higher free estradiol concentrations (+8%; P = 0.002), whereas weight decrease was associated with higher testosterone (+13%; P < 0.001).

Conclusion: Birth weight and paternal steroid concentrations are associated with testosterone concentrations, independent from adult weight. These findings support the concept of in utero programming across the range of birth weight. (*J Clin Endocrinol Metab* 95: 1587–1594, 2010)

Therefore, higher birth weight is associated with reduced risk of adult obesity and cardiovascular disease AND with higher blood testosterone levels (in men)
Disorders in men associated with lowered testosterone levels

- Cardiovascular disease
- Hypertension
- Visceral obesity
- Insulin resistance
- Type II diabetes
- Fatty liver disease
- Pro-inflammatory blood profile
- Erectile dysfunction

Early warning alert
Normal female development

Female development is about avoiding androgens

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- Phenotypically normal female
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Male - female differences

Fat deposition is fundamentally different

As intra-abdominal fat increases in men:
- Reduced testosterone
- Testosterone decreases*
- Insulin resistance increases*

*Both these changes lead to more fat deposition

In women, it operates in exactly the opposite direction
Polycystic ovary syndrome (PCOS)
Affects 7-15% of women

In animal models (monkeys, sheep), PCOS can be induced via increased androgen exposure in fetal life.

Some elements can be induced via increased androgen in adulthood.

PCOS Phenotype

Clinical  Hormonal  Ovarian  Metabolic
Polycystic ovary syndrome (PCOS)

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PCOS Phenotype

Clinical  Hormonal  Ovarian  Metabolic

Slide courtesy of Dr Colin Duncan
Effect of androgen (TP) exposure in adult female sheep and in females exposed in utero to androgens (PCOS*)

*PCOS = polycystic ovary syndrome (affects 7-15% of women of reproductive age)
Male versus female
Mirror images?

- In adult men, disease risks associated with *subnormal* T levels (CVD, obesity, type 2 diabetes, liver disease) are associated with *supranormal* T levels in women.

- In many instances androgens and oestrogens have different or opposite cell-specific effects in males versus females.

- Many aspects of our sex-biased behaviour can be viewed as being ‘opposites’.
Negative feedback!
Impacts of obesity and ‘Western’ diet on fertility

- Ovulation
- Fertilisation
- Implantation
- Embryo & fetal development
- Sperm number/quality
- Testosterone levels
- Erectile function
Human disorders positively associated with dietary effects

**Adults**
- Obesity, waist circumference ✔
- Prediabetes & Type 2 diabetes ✔
- Cardiovascular disease ✔
- Impaired liver function, steatosis ✔
  - Altered oocyte development ✔
  - IVF outcome/success ✔
  - PCOS ✔
  - Reduced adult male testosterone ✔
  - Male libido/sexual function ✔
  - Semen Quality ✔
  - Mammary gland development/breast cancer ✔

**Fetus/Babies/Children**
- Reduced fetal growth/birth outcomes ✔
- Reduced anogenital distance ✔
- Thyroid hormone levels ✔
- Childhood obesity ✔
- Kidney disease ✔
- Behavioural disorders ✔
- CpG methylation (girls) ?✔

✔ Association and/or causal evidence for dietary induction
A jump outside of the conventional
Out of our comfort zone
Why are we here?

Reproduction

Reproduction also offers us a unique opportunity to change future generations for the better – make them better adapted (Darwin)
The pivotal role of reproduction

• Reproduction offers the opportunity to produce offspring that are better adapted to the prevailing environment (than their parents)

• According to natural selection, sexual reproduction offers a random way of changing the offspring in the hope that it may be better adapted to the prevailing environment. This seems awfully risky!
Genetic inheritance
DNA pattern of offspring is different from parents

Twin studies suggest that 40-70% of obesity is inherited, yet so far genetic explanations can only account for <5% of obesity
The pivotal role of reproduction

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• But it could, in theory, be achieved by epigenetic adaptations – does this occur?
Epigenetics
Regulating how genes work
Male - female differences
Fat deposition is fundamentally different

Reduced testosterone

This is the main reason why men die earlier than women.
Adverse phenotype in adult male rats
Visceral adiposity and insulin resistance

Visceral adiposity

\[ p < 0.001 \]

Plasma Leptin

\[ p < 0.001 \]

What caused this?

Primary hypogonadism

Tom Chambers et al – unpublished data
Male - female differences

Visceral adiposity

Over-consumption of calories is what makes us fat

But the rats that I showed you ate a normal control diet
The only intervention was in the diet of the male rats’ *grandfathers*

For 14 weeks (from weaning onwards) the ‘grandfathers’ were fed a high fat diet that caused ~10% increase in bodyweight

The resulting ‘effects’ in the grandsons is presumed to be the result of epigenetic changes induced in the grandfathers to their sperm (or to their seminal plasma)
The pivotal role of reproduction
Sperm as a genetic and epigenetic memory transfer

So it appears that sperm (and/or seminal plasma) are transferring epigenetic information that may modify the function of (DNA in) the resulting offspring.

Thus, you are influenced both genetically and epigenetically by your grandfather (and grandmother).

Do these grandparental effects provide evidence of attempts to (epigenetically) better adapt the grandchildren to their environment?
Epigenetic remodelling of germ cells in both sexes occurs during early fetal life

In all mammals, including humans, the germ cell epigenome is remodelled in fetal life.

For example, DNA methylation is ‘wiped clean’ early on and is then reinstated later in gestation.

Histone methylation also changes dramatically.

These changes provide an opportunity for modifications to ‘adapt’ the fetus better to the perceived environment (via the mother).
Male - female differences

Visceral adiposity

Over-consumption of calories is what makes us fat

Reduced testosterone

But it may also affect your children and/or your grandchildren
Thank you for your attention.