

UNIVERSITY OF
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No going back: Biological perspectives on maternal/fetal identity



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About me...

- I study placental function
- Working out how the bits in placentas work, then work with engineers to computationally model how the bits work together
 - We are interested in identifying the essential characteristics sufficient to describe the function of the system
- How maternal environment affects placental function
 - Developmental Origins of Health and Disease
 - Evolutionary drivers of placental function

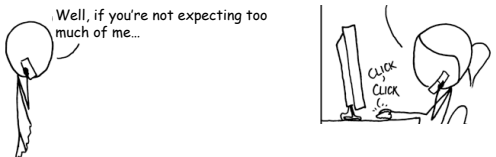
How I got here ...

Hello? Hello? Is that a scientist? I'm a philosopher and I'm looking for someone really, really, naïve!

Are you using naïve in an academic sense?

um, sure I guess, you can use it that way. Anyway, do you want to give a talk at my conference?

Well, if you're not expecting too much of me...



Artist's impression adapted from www.XKCD.com

What I'm going to talk about

- Maternal, placental & fetal similarity and difference
 - how are they related?
 - how are they connected?
- Maternal, placental & fetal communication
 - what sort of messages, why, over what timeframes?
 - what does this tell us about maternal fetal relationships?

Which brings us onto technical terms...

- You have thousands of years of accumulated philosophical tradition
- I have some quick and dirty definitions
 - they may not map to technical philosophical terms but at least that will be clear

Rohan's classification of identity

Biological identity

identity by unit

i.e. things or who

identity by description

i.e. the properties of things (genetic, immunological ...) or what

Social identity

→ I am

→ I am a...

→ You are a ...

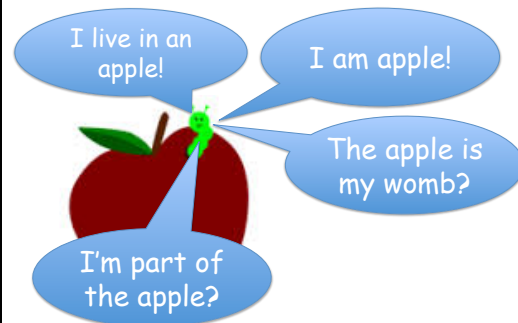


identical heads!

Biological levels

- Cells are made up of bits, we can identify the bits
- Cells
- Organisms (uni and multicellular)
- Super-organisms
 - Ants, bees, termites, (humans?)
- Species (hard to define!)
- Biosphere
 - parts of which don't, and can't, exist in isolation

Moths and butterfly babies..



Seeds are embryos



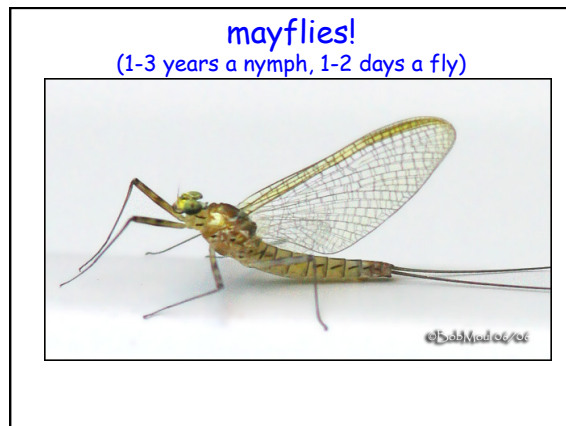
Gametes, genes and early cell development

Our story starts in the grandmother's womb

- Oocytes form when the mother is a fetus
 - Q: Does the grandmother communicate with the oocyte?
- 10-20 oocytes begin to mature each menstrual cycle
 - one or two of these will mature
 - the rest die (no sentimentality here)
- Sperm, formed in the adult
 - lots more mature and lots more die

Is this pollen part of the flower?





Are gametes the same as/part of the parent?

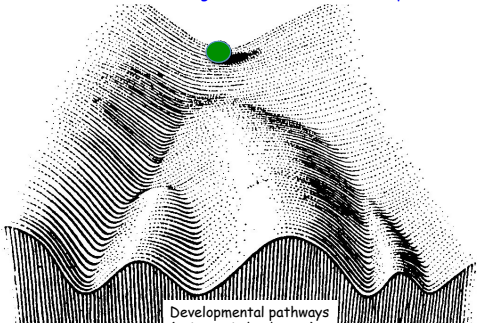
- Were part of the parent while developing
- At maturity physically distinct and separate
 - In body cavities but, once mature, outside the body
 - Can equally live in a test tube or a bees leg
- Contain a lot of the same information (e.g. DNA)
 - but in a different package
 - 'purpose' is to transmit this information (communication)

Inside vs outside the body

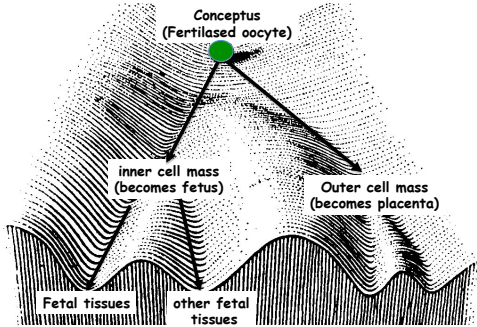
- The body has to protect itself from the outside world
- It's first line of defence is a layer of epithelial cells
 - these line the surface of the body and the body cavities
 - separate self from non-self
- From this perspective the GI tract and reproductive tract are outside the body



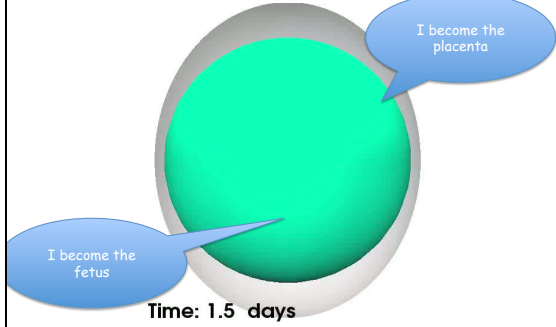
Cell development
all cell types are derived from the embryo
differentiate through a series of forks in the path



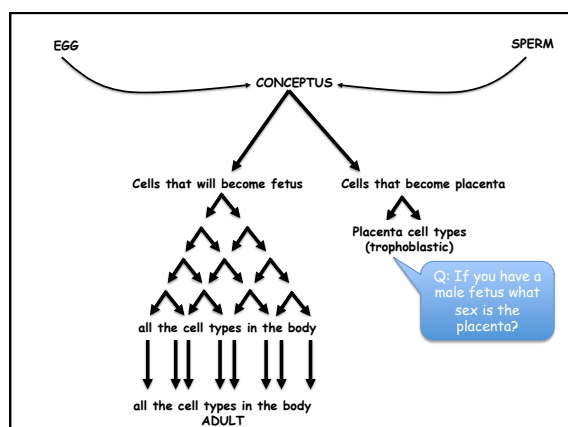
Cell development



Early development



Time: 1.5 days



Cell type is determined by which genes are expressed

- All cells have all genes
 - genes are a set of instructions "do this"
- But not all genes are expressed
 - as cells differentiate blocks of genes are turned off
- It's like library stacks

which genes can be read determines cell type (epigenetics)



If a stack gets closed then it can't be opened again, a fork in the developmental pathway

Genetic inheritance

- You inherit one physical genome from your parents
 - you then copy the information in these each cell division
 - at implantation few embryonic cells will have any actual physical parental DNA
- What you really inherit is the information
 - "this worked in the past" (+ some mutation)
 - "these are the uterine passwords"
- Clones all the genetic information
 - but there are other forms of information!

Genetic similarity provides the information for a successful pregnancy

- Genetic similarity means the fetus has the right codes to communicate with the womb
- The embryo must send the right signals at the right time
 - the womb is a machine, and responds mechanistically to signals it is genetically programmed to receive
 - A cuckoo organism could theoretically simulate the right signals

Oocyte and sperm gain a new identity at conception

- No longer the oocyte, no longer the sperm
 - a new unit essentially different from either
- Conception occurs in the fallopian tubes
 - in a body cavity
 - but outside the body
- Then the embryo implants in the womb

Maternal, placental and fetal connectedness

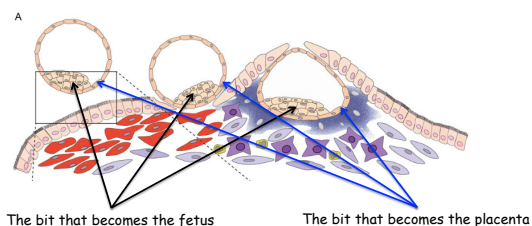


Implantation

- The embryo lives free for a week or so
- Then implants in the endometrium
 - Just deep enough to access the maternal blood
 - The endometrium is the cell layer lost each month during menstruation

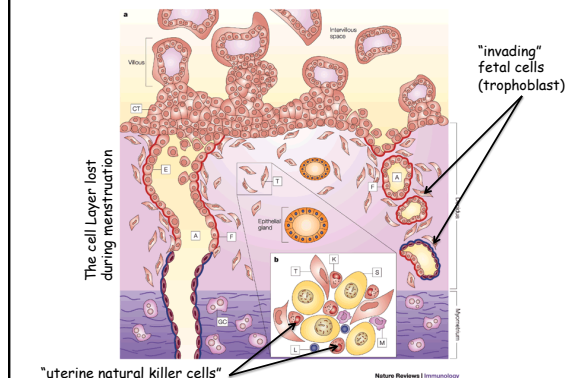
Implantation

- The embryo "invades" the uterine wall



If the process had been called "connection" would we think about it differently?

Placental cells "invade" the uterine decidua



What's the point of these "invading cells"

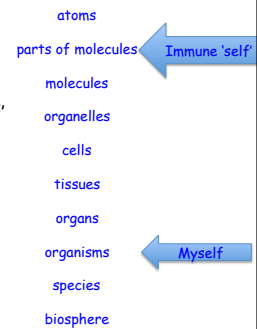
- They help remodel maternal blood vessels to support the pregnancy
 - These cells carry information needed to do this
 - But the maternal cells have the same information
- Perhaps being able to invade and remodel proves the fetuses identity?
 - not "invasion" but a calling card?
- Maternal "uterine natural killer cells" are also necessary for remodelling
 - part of the immune system
 - massively over simplified but somewhat like lock and key?
- Placental biology is vastly different across species
 - One hypothesis is that rapid evolution of placental design is driven by parasites, so proving identity important

Why doesn't the maternal immune system recognise the placenta as non-self?

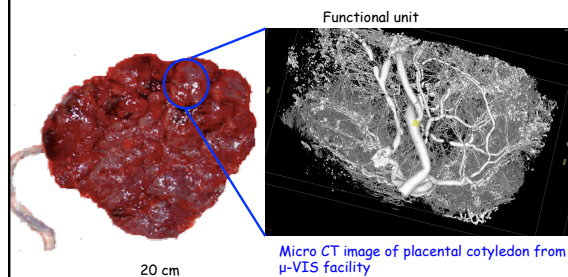
- The fetus is immunologically distinct (unless cloned)
 - Normally would be recognised as non self
 - Fetal tissue implanted in the mother would be rejected
 - Rhesus incompatibility is a major cause of fetal death
- "Uterine Natural Killer Cells" and other mechanisms help prevent rejection
- I spoke an expert last month who said the explanation is "complex and multifactorial"
 - which means we can't fully explain it
 - it's important to remember that science isn't finished yet

What does immune self recognition mean?

- The immune system recognises bits of non-self molecules
 - it doesn't recognise 'self'
 - it doesn't recognise most non-self



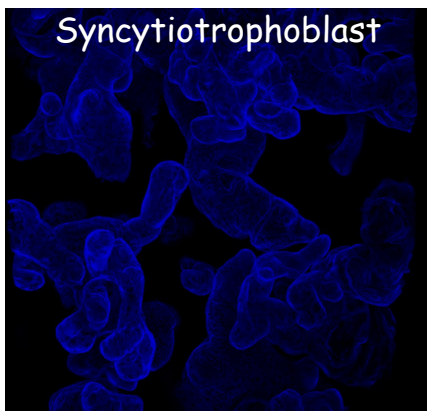
The human placenta



Placental function is dependent on its structure

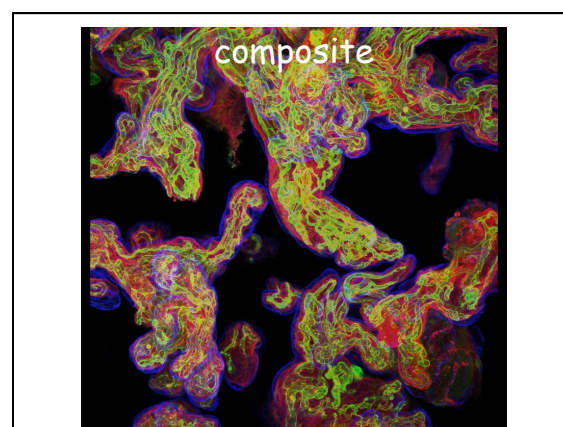
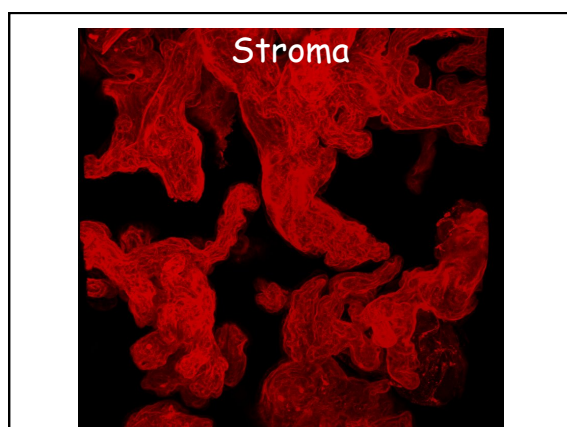


Syncytiotrophoblast



Fetal Capillaries





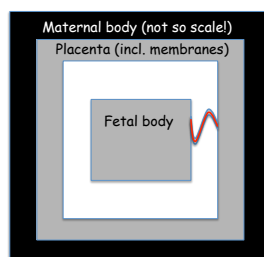
Maternal, placental, fetal connectedness

• Maternal to placental

- Cell-cell contact
- Maternal and fetal cells glued together
- No blood mixing
- Placental epithelial barrier (demarcates outside of body)

• Placental to fetal

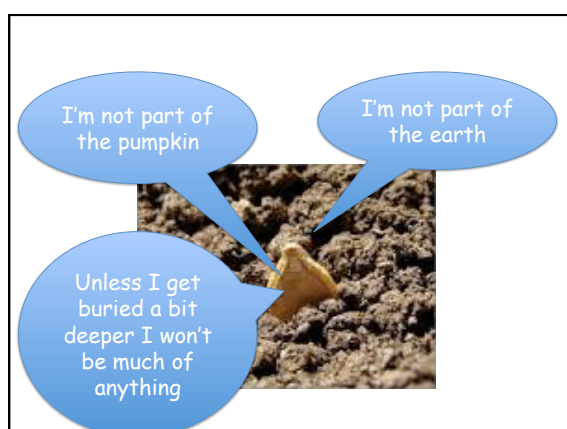
- Thin bridge of cell-cell connection
- Tight 'seamless' connection
- Blood flow



Like colours indicate genetic similarity
(other forms of information will reduce total similarity)

What does the placenta do?

- Barrier
 - protects fetus from maternal waste products, immune system, drugs and environmental toxins
- Transport
 - food to the fetus fetal wastes to the mother
- Endocrine signals (chemical communication)
 - suppresses mothers menstrual cycle
 - alters mothers metabolism to support the pregnancy
 - Stimulates changes in maternal anatomy
- Adapts to maternal signals (chemical signals)
 - changes activity in response to
 - indicators of maternal capacity to support the pregnancy
 - short and long term indicators of maternal nutrition
 - maternal hormones



Communication and fetal development

If the fetus can't talk to the mother it will be aborted

If the mother can't talk to the fetus it may be too big and poorly adapted to the external environment

Biological communication (transmission of information)

Types

- Within cells
- Between cells
- Within organism
- Between organisms
 - Within generations
 - Across generations
- (social communication)

Mediated by

- Ionised atoms
 - e.g. calcium ions Ca^{2+}
- Molecules
 - nutrients
 - hormones
 - Nucleic acids (ie DNA)
- Micro-particles
- Cells
 - microchimerism
- (language)

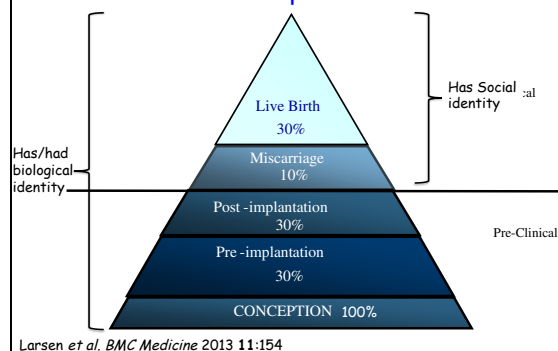
Timescales of communication

- **Short** (seconds - days)
 - molecular signals, nutrients hormones
 - but may cause changes which have longer term effects
- **Medium** (within the life of the organism)
 - epigenetic change (change in the way DNA is stacked)
- **Next generation**
 - DNA
 - some epigenetic changes
 - cells (microchimerism)
- **Across generations**
 - DNA
 - (social knowledge)

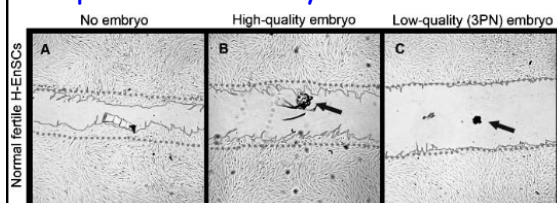
Why do the mother and fetus need to communicate?

- To negotiate the implantation process
- To negotiate the allocation of maternal resources
- To give the fetus information about the current external environment
 - Modify developmental pattern to optimise postnatal survival and reproductive fitness
 - This is in addition to genetic information

The outcome of spontaneous human conceptions



The endometrium and pre-implantation embryo communicate



- The embryo needs to say I'm healthy, its worth your while investing your resources in me
 - It's likely that the embryo 'talks' by not secreting chemicals only made by metabolically unhealthy embryos
- Otherwise the womb will not allow implantation

Macklon NS, Brosens JJ (2014) The human endometrium as a sensor of embryo quality. Biol Reprod 91:98

Maternal placental fetal communication

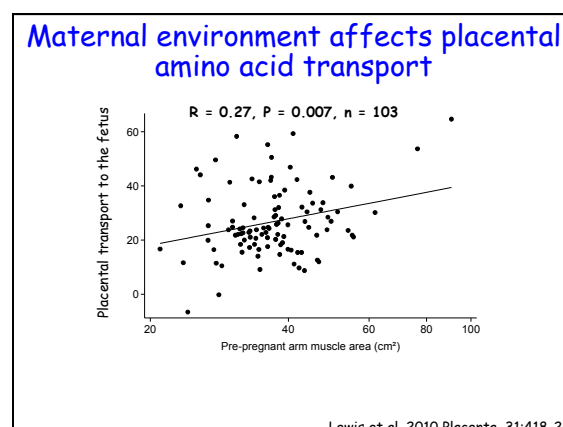
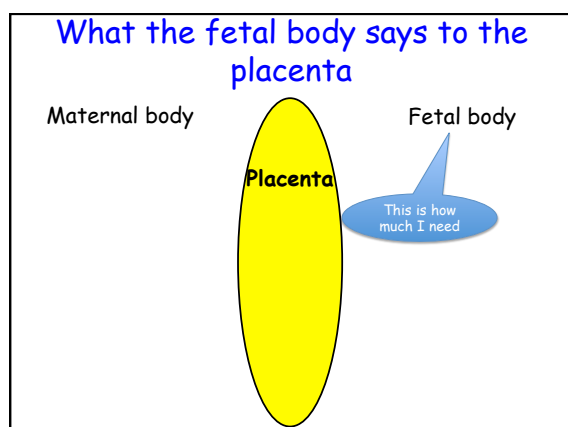
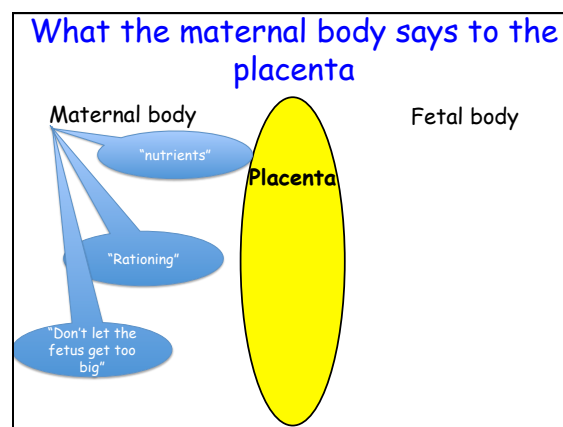
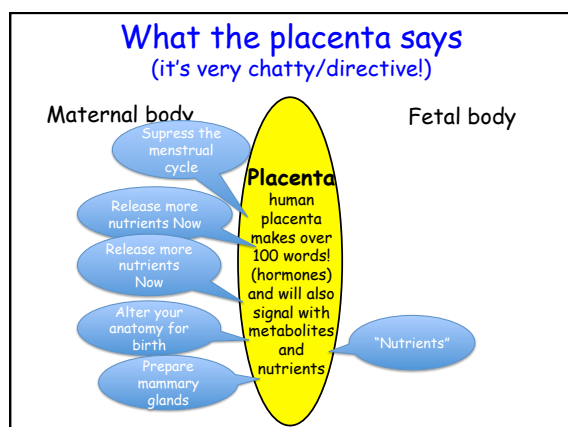
Maternal body

Fetal body

The maternal body speaks to the placenta and the placenta speaks back

Placenta

The fetal body speaks to the placenta and the placenta speaks back



Is the fetus biologically autonomous?

- It feeds off its environment
 - as do we
- It manipulates its environment
 - Placental hormones alter maternal physiology and anatomy
- It has co-evolved with its environment
 - evolution driven by both fetal and maternal needs
- It can't go where it wants (assuming it wanted to!)
 - but neither can trees* and we are dependent on them for oxygen so we can't go wherever we want either

* by which I mean all plants big and small

Genomic conflict hypothesis

portrayed as a battle of the sexes

Genomic conflict hypothesis

- One copy of each gene from each parent
 - (except sex chromosomes & mitochondrial genes)
- But some genes exhibit parent of origin specific expression (imprinted genes)
 - approx 300/30000 are imprinted
- Imprinted genes often affect fetal growth
 - growth promoters turned off by maternal germ line
 - growth inhibitors turned on by paternal germ line

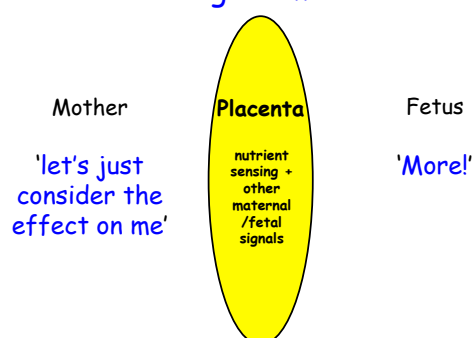
Battle of the sexes!

- Do fathers want big babies at no cost to themselves?
- Do mothers want to limit fetal size as this costs?

Is this the right interpretation?

- It makes a good story and people relate to good stories
- Biologically the aim is to increase reproductive fitness
 - bigger is not always fitter!
- Is it rather the case that the placenta mediates cooperation between mother and fetus?

Maternal fetal dialog at organism level



Maternal and fetal priorities (Biologically speaking!)

Maternal Priorities

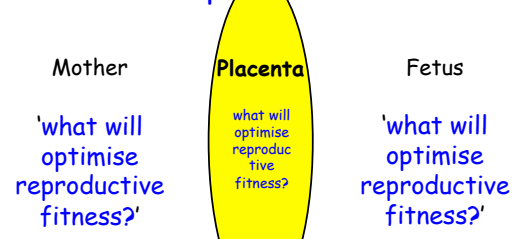
- Increase reproductive fitness
 - more babies that survive to reproduce
- If you invest in a pregnancy you want to invest enough so that it is likely to succeed
 - pregnancy costs!
 - note the early culling process!
- But not to invest too many resources in any one offspring
 - limits mothers ability to care for baby
 - limits availability of resources for future pregnancies

Fetal Priorities

- Nutrient supply to match growth potential
- But not always
 - If the mother does not have a lot of food growing fast is not the best option
 - And if the fetus grows too big it cannot be delivered easily

Ideally the placenta would match transport with fetal demand but also take into account mothers ability to provide

Maternal fetal dialog at species level



Getting the answer to this question right determines the information passed to the next generation, and thus human identity

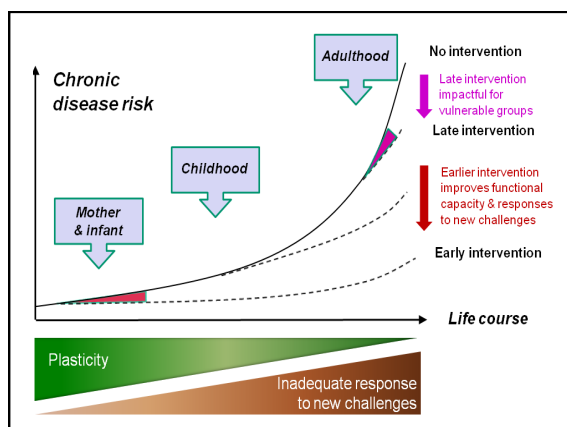
Parasitism vs mutualism

- Hosts don't evolve to support the parasite
 - The maternal body is evolved to support the fetus and vice versa
- The mother and fetus have co-evolved across generations
 - Grandparental environment can affect the information inherited by the fetus
- At the species level species its not even mutualism



Maternal-placental-fetal communication and disease

- I argue there is a fine tuned maternal/placental/fetal relationship
 - optimises reproductive fitness
- This may not be great for the individual
 - babies born small may survive better in famines but have more disease throughout the life course
- This fine tuning was done in the past
 - the (current) present is fatter than the past!
 - this may lead to mismatches & health consequences



Conclusions



No going back

- New biological units form is when there is no going back (to my mind anyway!)
- The mature gametes are separate units from the parent
 - 1st generation of distinction from the parents
- The embryo as a biologically distinct from the gametes
 - 2nd generation of distinction from the parents
- Pregnancy is a time in which two units cooperate to meet biological objectives
 - The species level aim of optimising reproductive fitness

Back to Rohan's classifications

- Unitary identity
 - need to pick a level!
- Descriptive identity
 - Determined by information
 - provided by genes/environment interaction
 - transmitted across generations of organism
- Social identity
 - another form of information, so part of descriptive

Final thoughts

- If you're talking to a scientist they will give you the tabloid version
 - a little knowledge ...
- Always ask your scientist about the weaknesses in their theories
 - the good ones will be happy to tell you for hours

• Acknowledgements

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