Ecological Clinical Embryology

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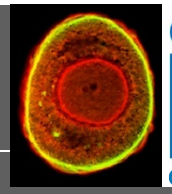

Presentation outline and learning objectives:

1. Discuss the environmental influence upon Developmental Biology and Human Disease

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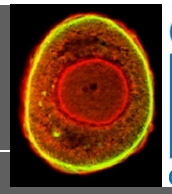
2. Re-evaluate the relevance of environmental influence in Gametogenesis and Preimplantation Development

3. Call for research in this area of Clinical Embryology



DISCLOSURE

CE Plancha does not have any commercial and/or financial relationship with manufacturers of pharmaceuticals, laboratory supplies and/or medical devices.

Organisms respond to challenges over a range of timescales

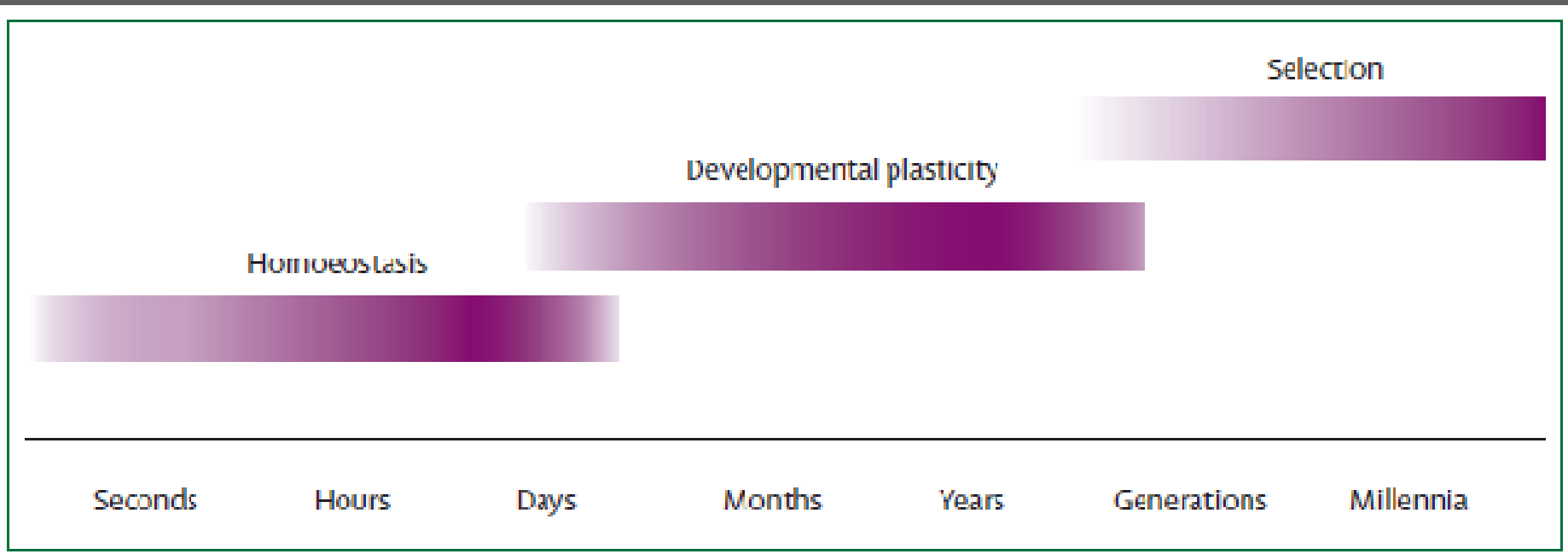
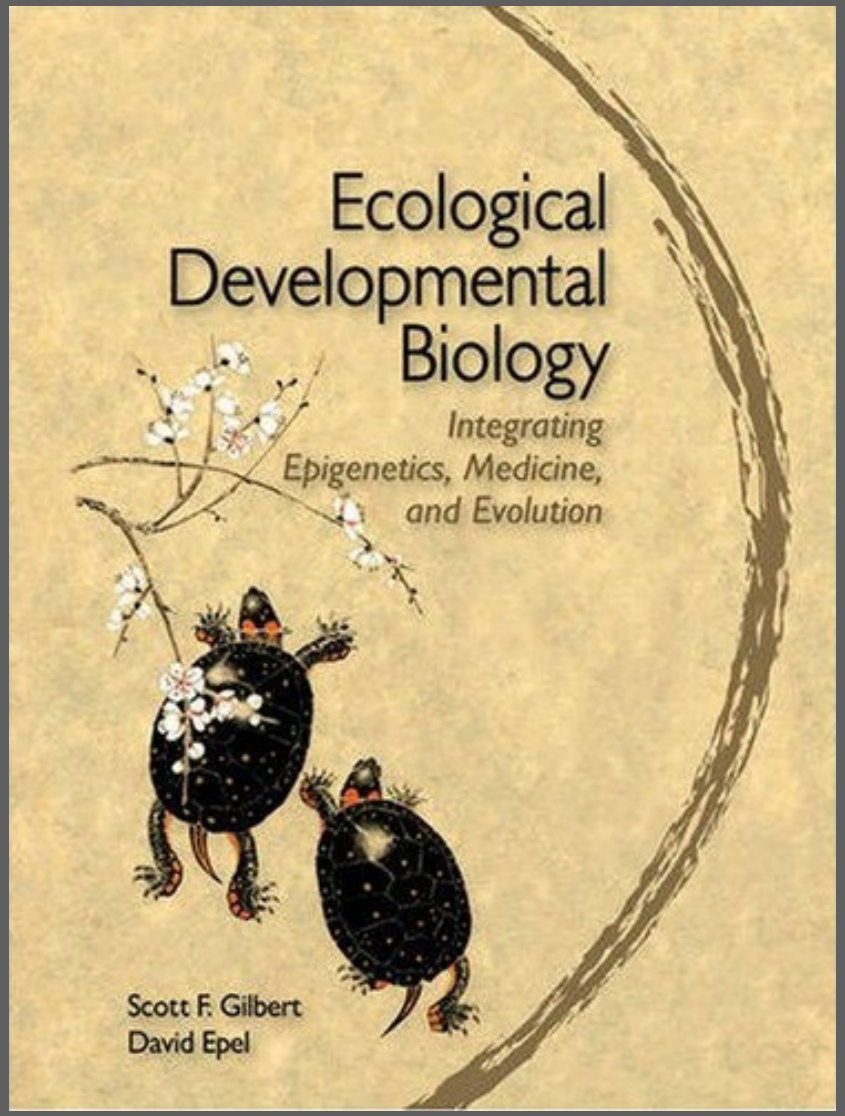


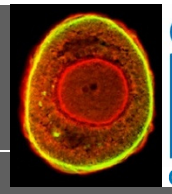
Figure: Modes of human adaptability

Gluckman PD *et al*. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. **Lancet 2009**; 373: 1654-57.



Scott F. Gilbert

David Epel

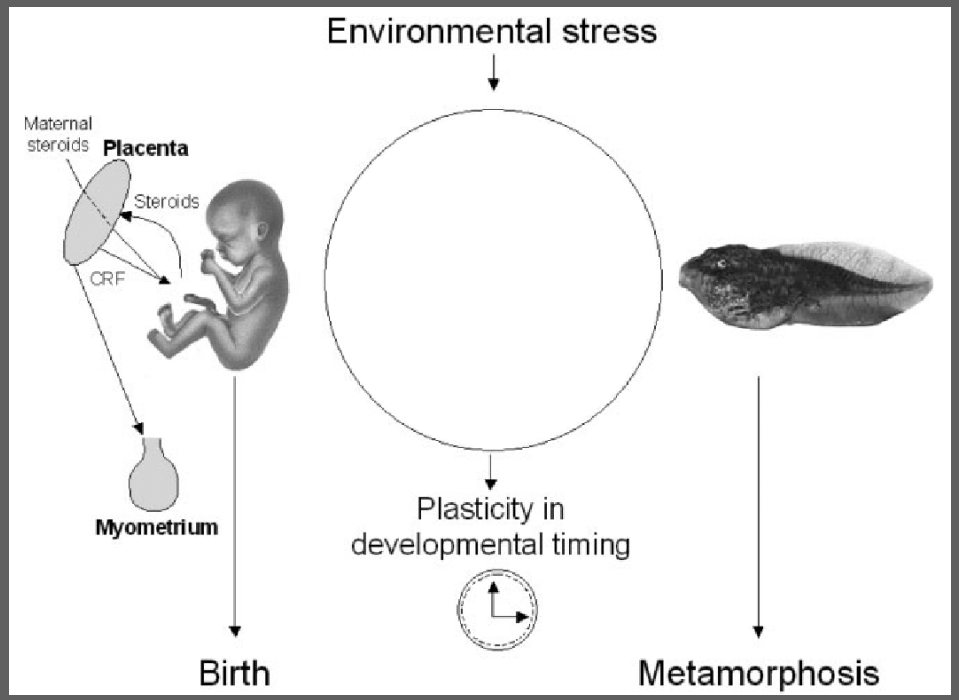


Ecological Developmental Biology

Concerns the interactions between developing organisms and their environmental contexts.

Environmental influences (predators, competitors, symbionts, toxic compounds, temperature changes, nutritional differences) can act upon the developing organism through epigenetic mechanisms leading to production of additionally different phenotypes (even from the same genotype).

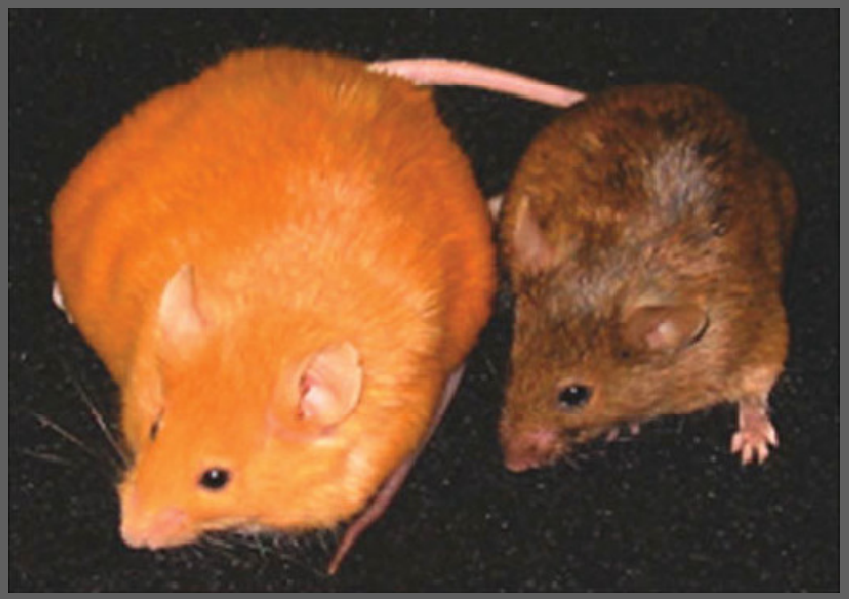
Mammals are parent-protected regarding external environment changes, but …



Crespi EJ, Denver RJ. Ancient Origins of Human Developmental Plasticity. **Amer J Hum Biol 2005**; 17:44–54.

Mammals are parent-protected regarding external environment changes, but …

…external factors can still have a major impact



Discordant appearance of two genetically identical mice

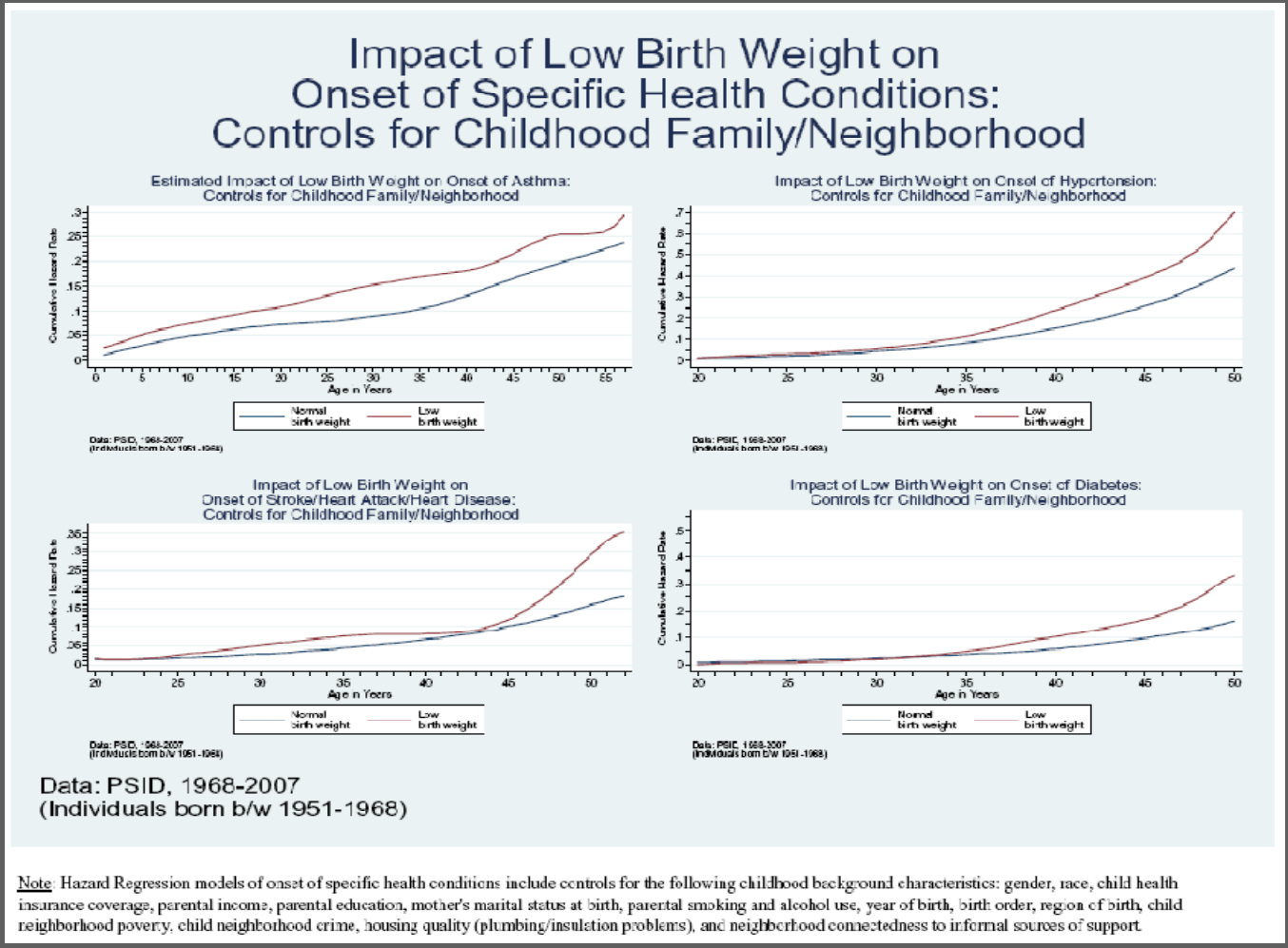
Their different appearance (phenotype) is because of the diet the mother ate while these embryos gestated *in utero*.

The sleek brown mouse was born from a mother that had ample supplementation of methyl groups in her diet (i.e., Vitamin B12), whereas the obese yellow mouse was born to a mother who did not have that supplementation. The methyl groups bound to DNA and prevented the Agouti gene from being expressed.

The endocrine disruptor bisphenol-A also acts through DNA methylation and can undo the gene repression by the methyl donors, causing those mice to also be yellow and obese.

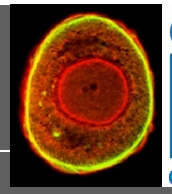
Gilbert SF. When ‘‘Personhood’’ Begins in the Embryo: Avoiding a Syllabus of Errors. **Birth Defects Research (Part C) 2008**; 84:164–173.

Epidemiological evidence to link low (<2,5Kg) and high (>4kg) birth weight and adult diseases



Note: Hazard Regression models of onset of specific health conditions include controls for the following childhood background characteristics: gender, race, child health insurance coverage, parental income, parental education, mother's marital status at birth, parental smoking and alcohol use, year of birth, birth order, region of birth, child neighborhood poverty, child neighborhood crime, housing quality (plumbing/insulation problems), and neighborhood connectedness to informal sources of support.

Rucker C. Johnson and Robert F. Schoeni (2010) Early-life origins of adult disease: National longitudinal population-based study of the U.S.

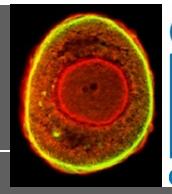


Both experimental model and clinical studies

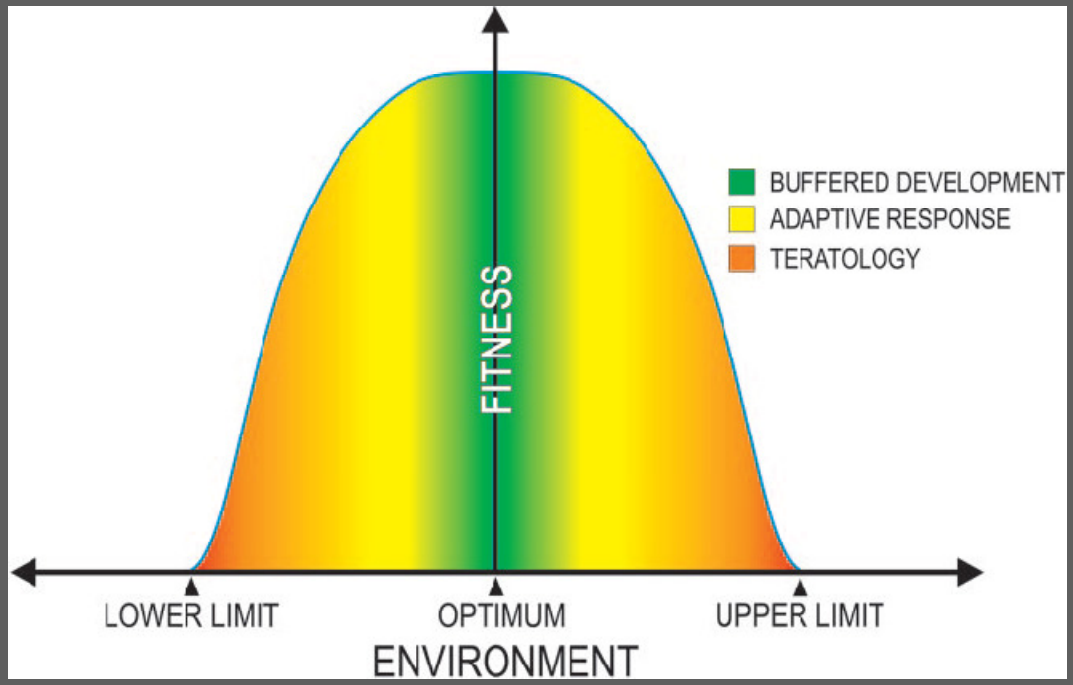
Table 1 Adult phenotypes of intrauterine growth restriction

Metabolic	Nonmetabolic
Dyslipidemia	Attention deficit disorder
Hypertension	Chronic lung disease
Insulin resistance	Immunodeficiency
Poor postnatal growth	Neurodevelopmental delay
Renal insufficiency	Schizophrenia

LA Joss-Moore and RH Lane (2009) The developmental origins of adult disease. Current Opinion in Pediatrics 21:230–234.

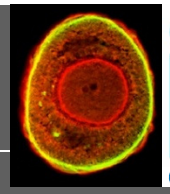


Ecological Developmental Biology (developmental plasticity)

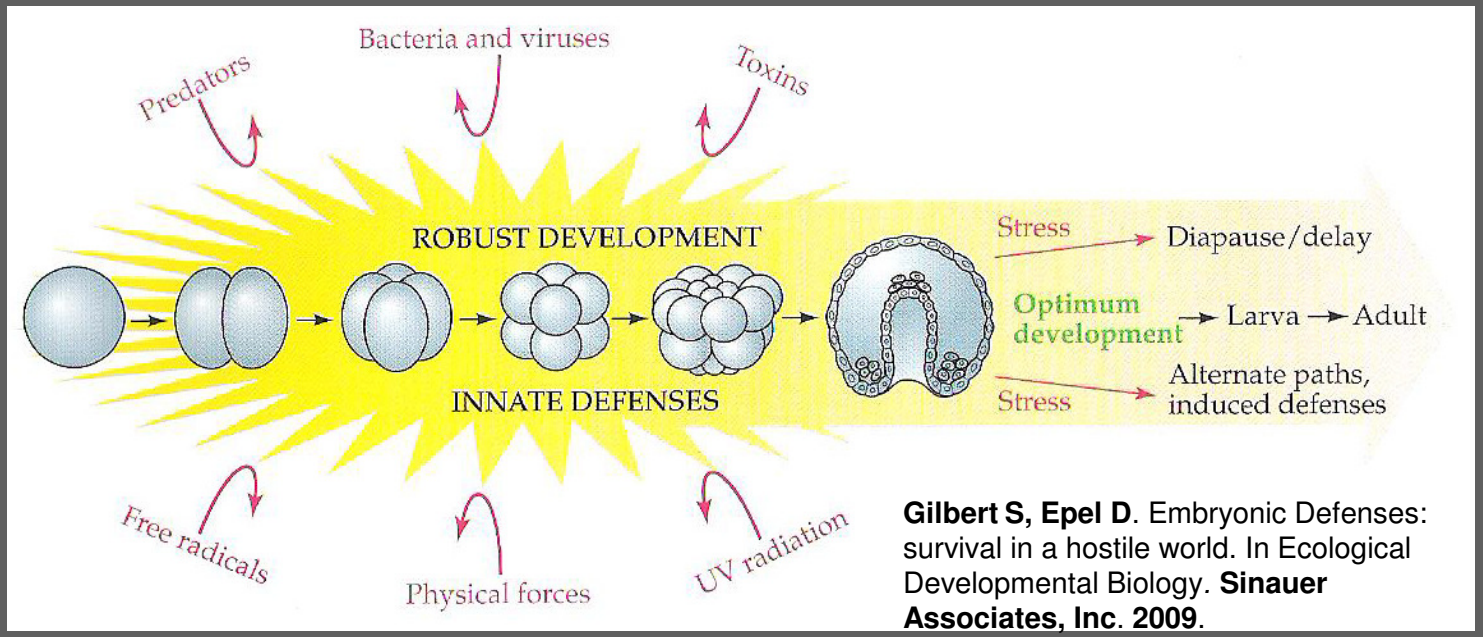


Some effects will be well adapted and advantageous to the developed organism.
Other effects will be maladapted or even pathological to the developed organism.
In either situation natural selection will take place and evolution will occur over generations.

Hamdoun A, Epel D. Embryo stability and vulnerability in an always changing world. **PNAS USA 2007**; 104:1745-1750.



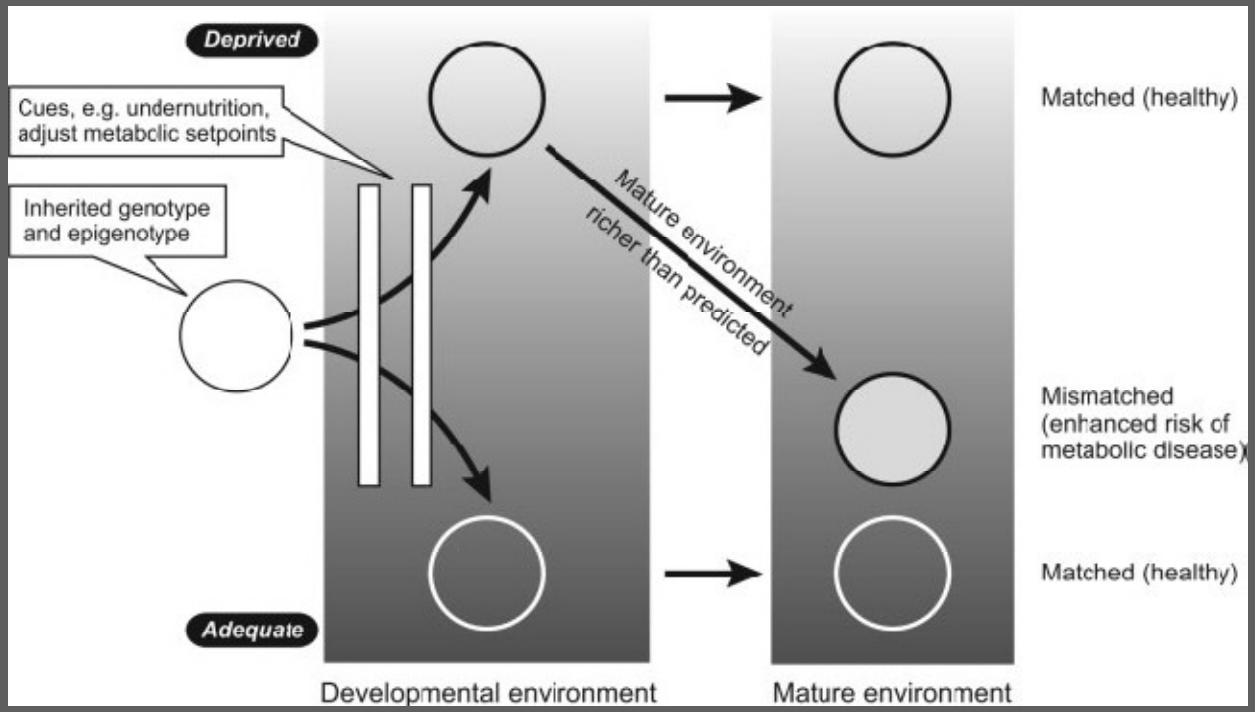
The embryo has not only a plan for development, but also a battery of defenses in order to survive in its antecipated environment



Gilbert S, Epel D. Embryonic Defenses: survival in a hostile world. In Ecological Developmental Biology. **Sinauer Associates, Inc. 2009**.

Hamdoun A, Epel D. Embryo stability and vulnerability in an always changing world. **PNAS USA 2007**; 104:1745-1750.

The match–mismatch model in mammals:
Prenatal and postnatal factors interaction leading to disease risk in adulthood



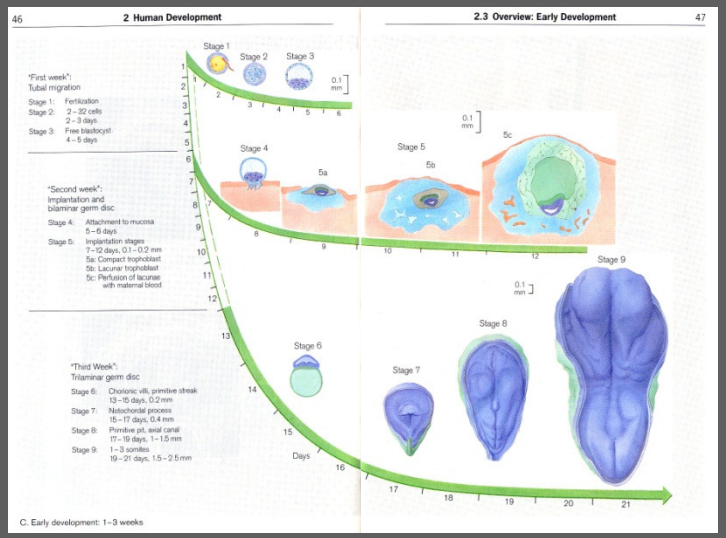
The developing organism senses maternally transmitted environmental cues, such as undernutrition, during prenatal and early postnatal life.

If the prenatal and postnatal environments match, the physiological settings achieved through the processes of developmental plasticity will leave the organism well prepared for the postnatal environment.

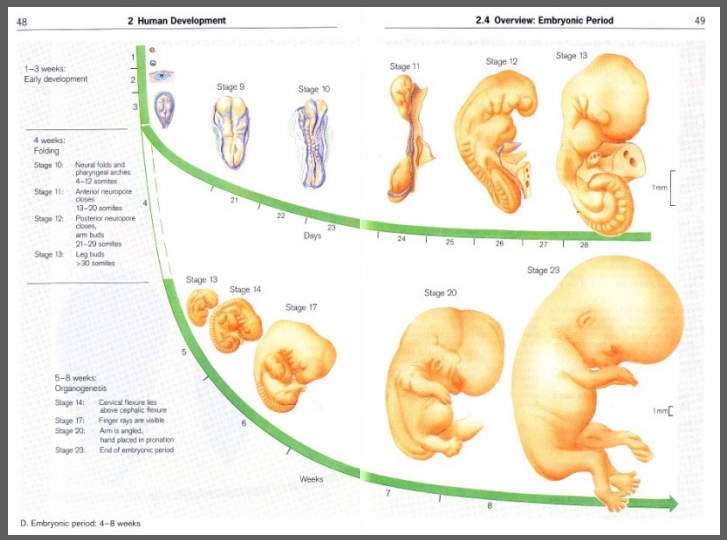
If there is a mismatch between the predicted and actual mature environments, particularly if the mature environment is richer than anticipated, then the risk of metabolic disease is enhanced.

Gluckman PD *et al*. Early Life Events and Their Consequences for Later Disease: A Life History and Evolutionary Perspective. **Amer J Hum Biol 2007**; 19:1–19.

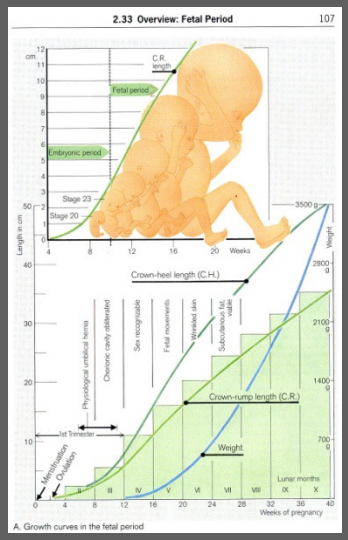
Human Development can be divided in three periods: **Early, Embryonic and Fetal**



Early period



Embryonic period



Fetal period

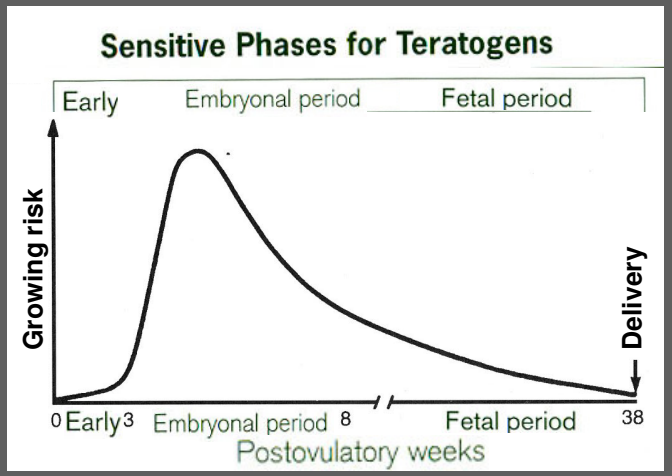
Drews U. Color Atlas of Embryology. **Thieme. 1995**.

Are these periods equaly sensitive to environmental cues?

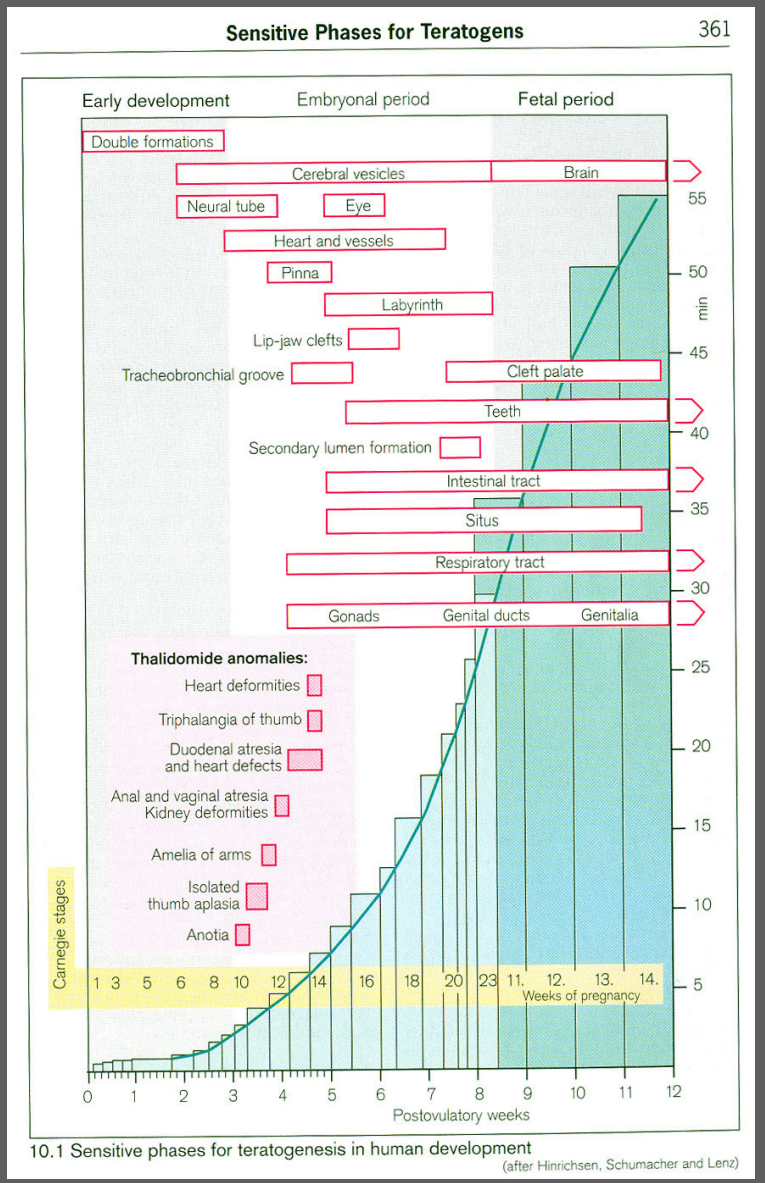
The periods of human development

(early, embryonic and fetal)

relate with higher or lower risk of congenital malformation

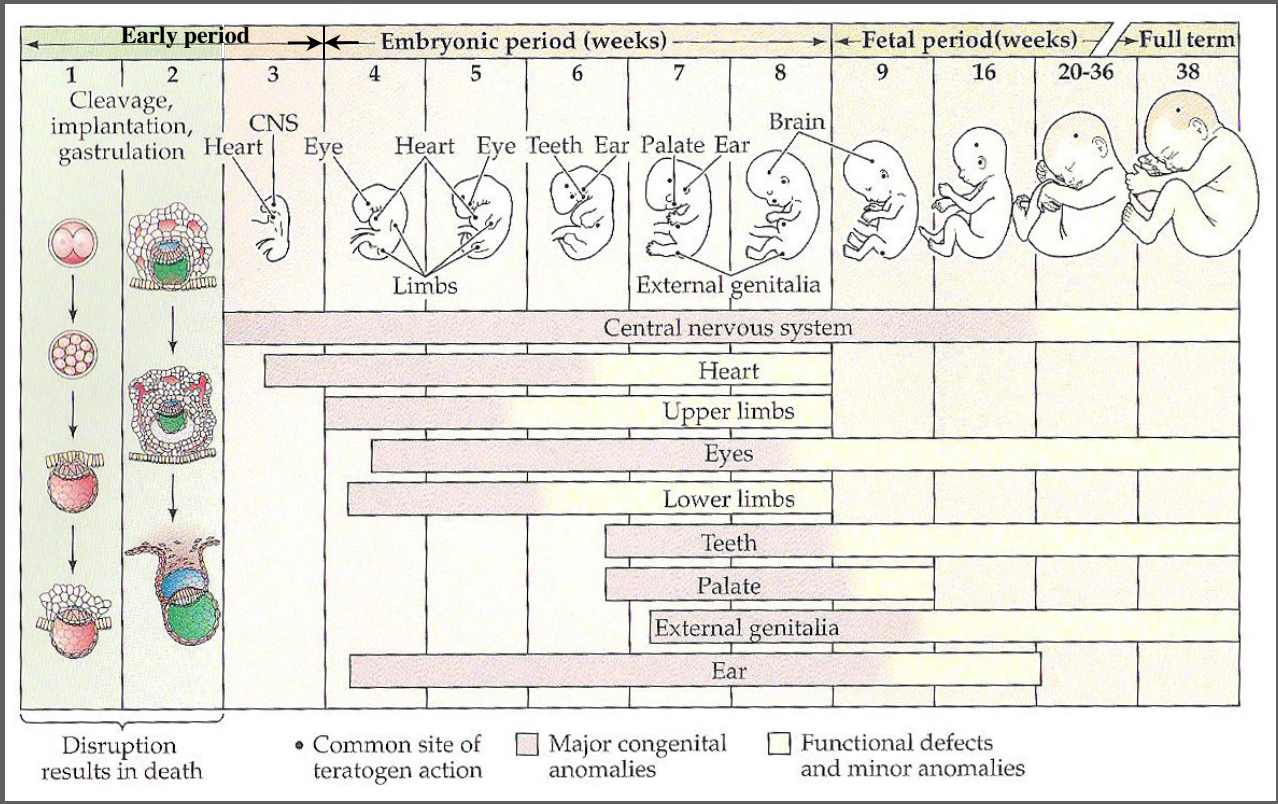


Drews U. Color Atlas of Embryology. **Thieme. 1995**.



10.1 Sensitive phases for teratogenesis in human development (after Hinrichsen, Schumacher and Lenz)

Periods of Human Development and degrees of sensitivity to teratogens

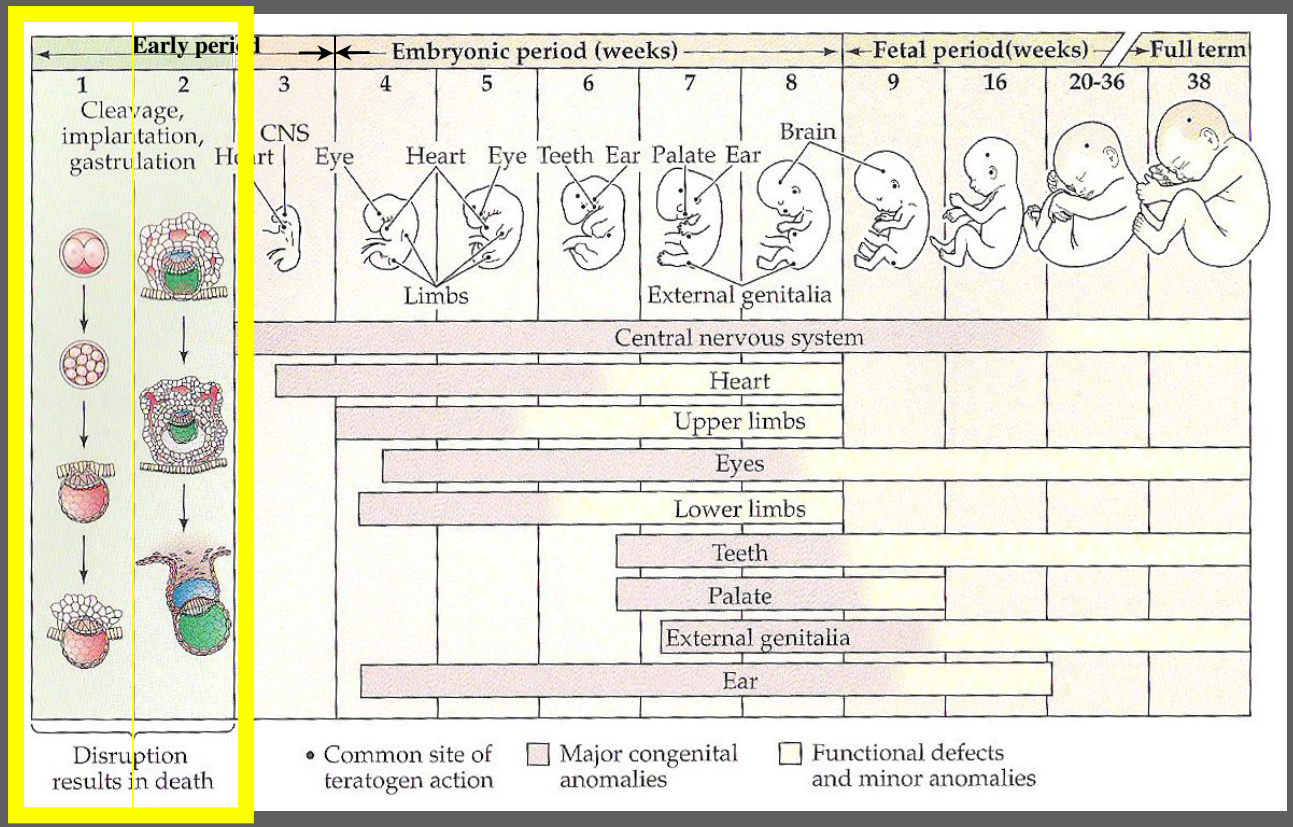


The sensitive phases to teratogens may reflect sensitivity to environmental cues

Gilbert S, Epel D. Teratogenesis: environmental assaults on Development. In Ecological Developmental Biology. **Sinauer Associates, Inc. 2009**.

Moore KL, Persaud, TNV. The Developing Human: Clinically Oriented Embryology. **Elsevier. 2007**.

Periods of Human Development and degrees of sensitivity to teratogens

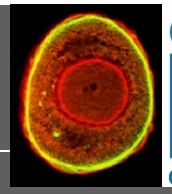


(implantation failures)

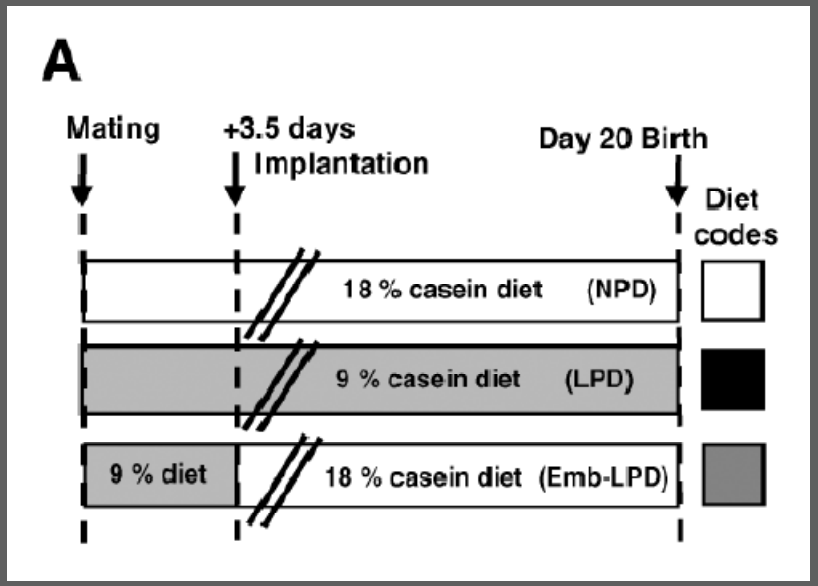
Clinical Embryology

Gilbert S, Epel D. Teratogenesis: environmental assaults on Development. In Ecological Developmental Biology. **Sinauer Associates, Inc. 2009**.

Moore KL, Persaud, TNV. The Developing Human: Clinically Oriented Embryology. **Elsevier. 2007**.



In mammalian experimental models:



Maternal protein diet plan codes:

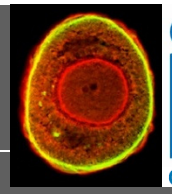
- NPD
- LPD
- Emb-LPD

TABLE 1. Litter size and birth criteria (± SEM) of offspring for different treatment groups.[a]

Treatment group	Litter no.	Gestation length (days)	Mean litter at birth	Offspring no. at birth	Male:female ratio
NPD	19	20	11.11 ± 0.571	211	0.97 ± 0.102
LPD	19	20	9.89 ± 0.55	188	0.893 ± 0.110
Emb-LPD	19	20	10.32 ± 0.622	196	1.031 ± 0.103

[a] No differences were observed between treatment groups for gestation length, litter size, or gender ratio ($P > 0.05$).

Watkins AJ *et al*. Adaptive Responses by Mouse Early Embryos to Maternal Diet Protect Fetal Growth but Predispose to Adult Onset Disease. **Biol Reprod 2008**; 78:299-306.



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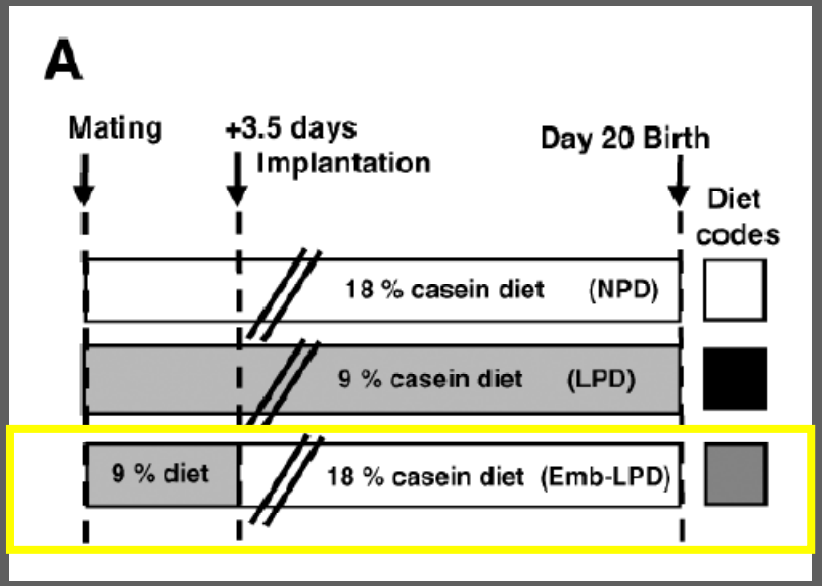

Maternal protein diet plan codes:

- **NPD**
- **LPD**
- **Emb-LPD**
  (just during preimplantation development)

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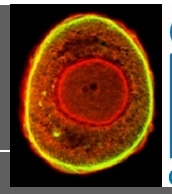
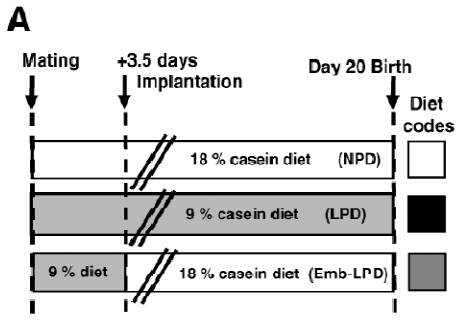
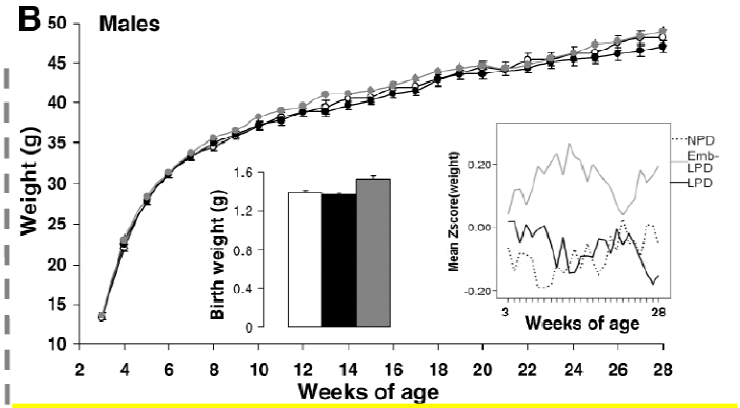
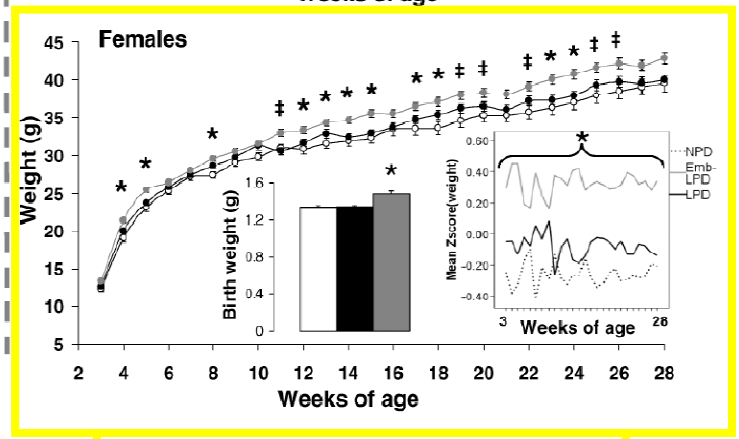
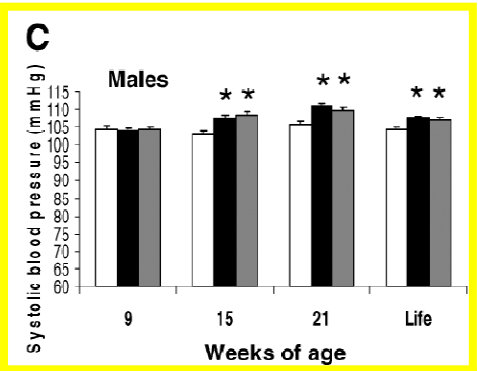


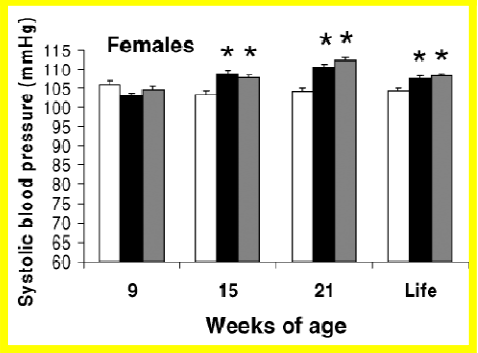
Maternal protein diet during mouse preimplantation development affects postnatal parameters

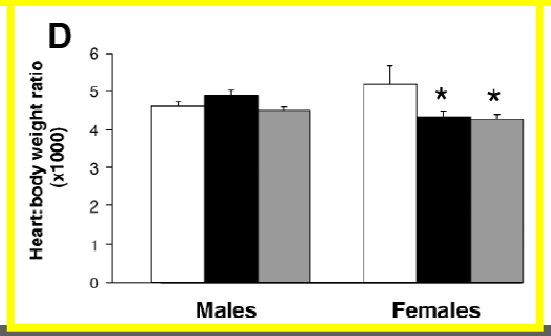












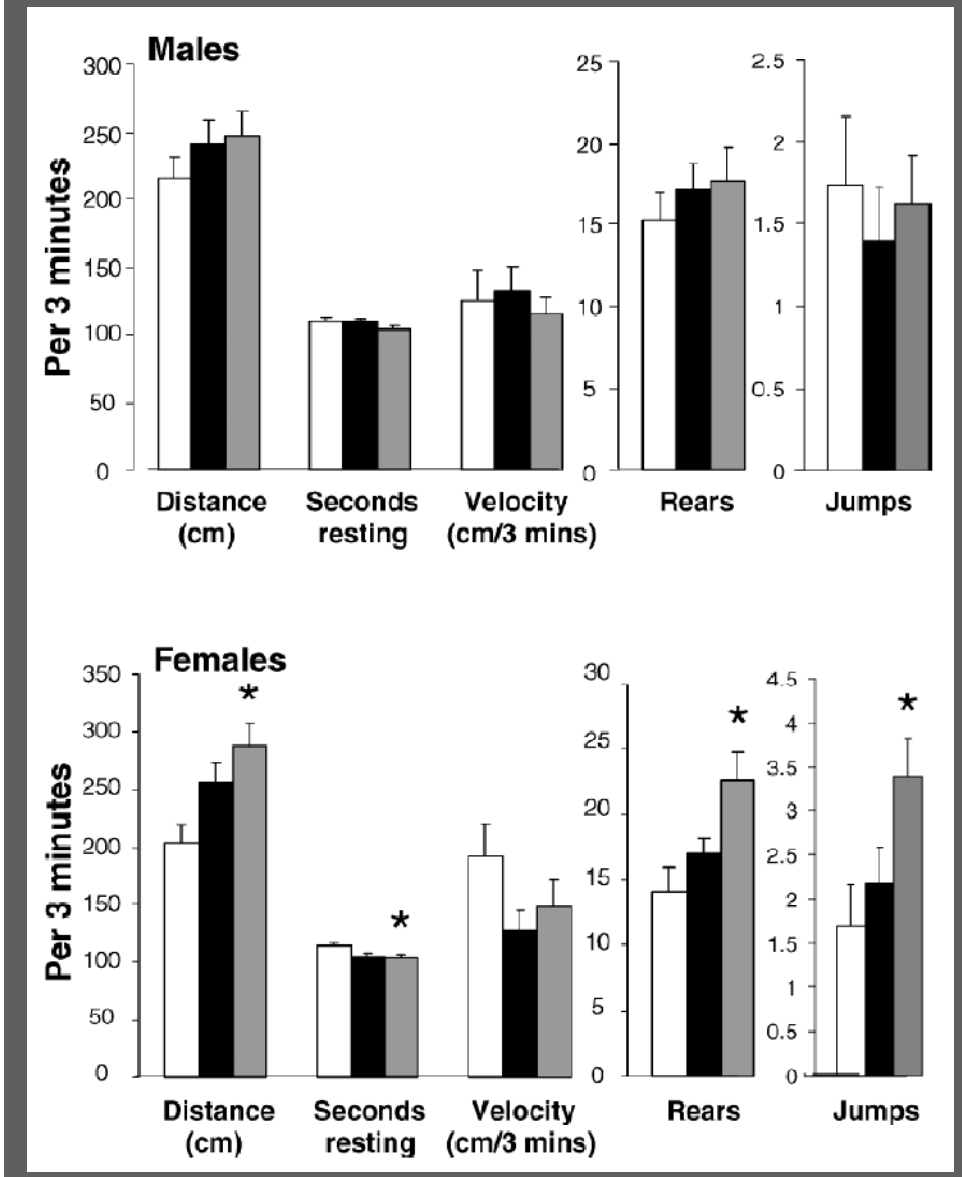
B) Birth weight and growth profiles of offsprings are increased in females

C) Sistolic Blood Pressure at 9, 15, and 21 wk; are increased in both sexes

D) Heart:body weight ratio at 28 wk is increased in females

Data sets derive from 19 litters per treatment with litter size controlled to six after birth weight determination;
* P , 0.05

Watkins AJ *et al*. Adaptive Responses by Mouse Early Embryos to Maternal Diet Protect Fetal Growth but Predispose to Adult Onset Disease. **Biol Reprod 2008**; 78:299-306.

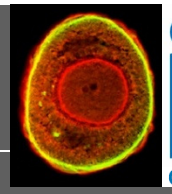


Maternal protein-deficient diet during mouse preimplantation development leads to altered anxiety-related behavior in female offspring

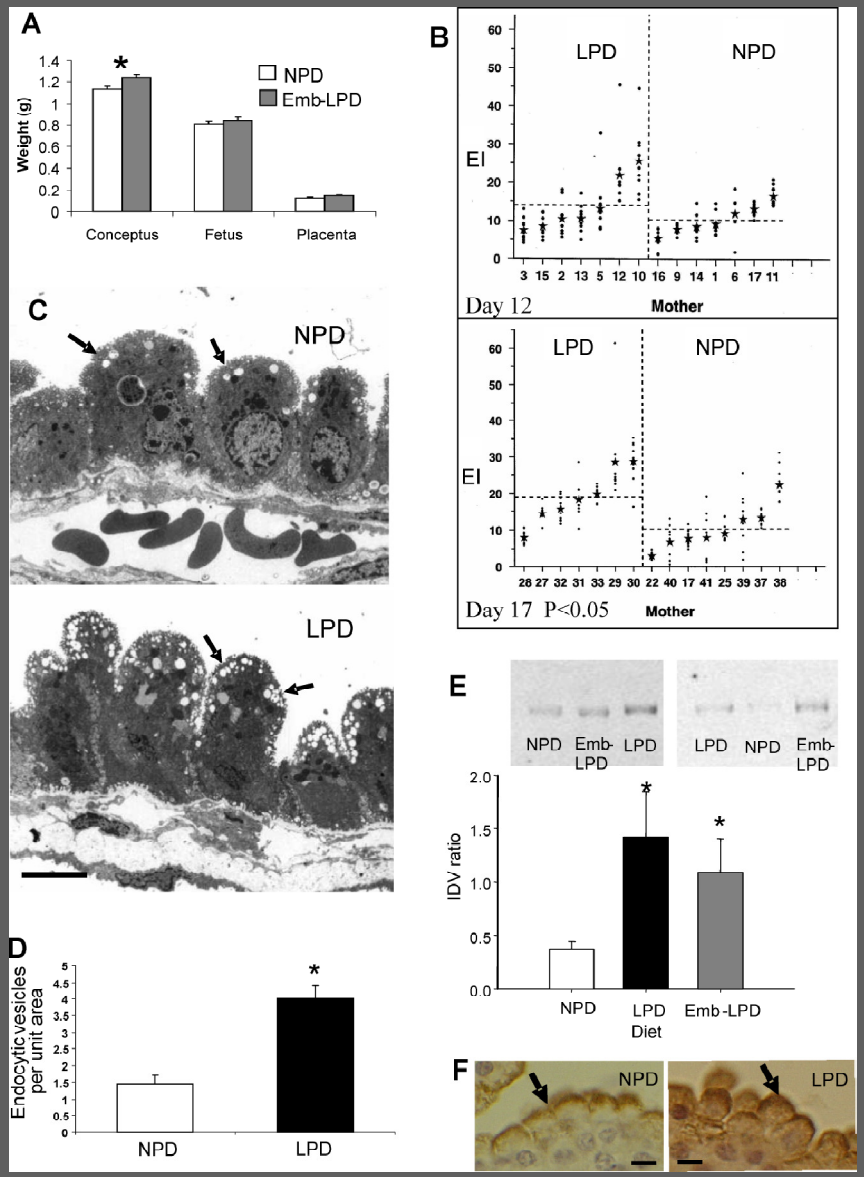
Mean responses to open-field behavioral tests; white, black, and gray bars correspond to NPD, LPD, and Emb-LPD treatments, respectively.

Data sets derive from 19 litters per treatment with litter size controlled to six after birth weight determination;
* P , 0.05.

Watkins AJ *et al*. Adaptive Responses by Mouse Early Embryos to Maternal Diet Protect Fetal Growth but Predispose to Adult Onset Disease. **Biol Reprod 2008**; 78:299-306.



Preimplantation responses to maternal diet are inherent to the embryo and lead to changes in Visceral Yolk Sac Endoderm nutrient uptake capacity



A) Weight of conceptuses and their component parts at Day 17 postcoitus derived from NPD and Emb-LPD blastocysts after transfer to NPD recipients.

B) Endocytic index (EI ¼ Il fluid captured hr/mg protein) of isolated yolk sacs at Day 12 and 17 postcoitus following culture in medium containing the fluid-phase endocytic marker, [14C]-sucrose.

C) Representative ultrastructure of **Visceral Yolk Sac Endoderm** derived from LPD and NPD mothers; note the enrichment of apical translucent endocytic vesicles (arrows) within LPD sample.

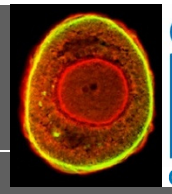
D) Number of endocytic vesicles/unit area is increased in LPD-derived **Visceral Yolk Sac Endoderm** cells; six yolk sacs, from separate mothers, per treatment.

E) Expression of megalin protein is increased in yolk sacs following maternal LPD and Emb-LPD treatments; eight yolk sacs, from separate mothers, per treatment.

F) Immunoperoxidase labeling of megalin (arrows) at apical membrane and cytoplasm within NPD-derived and LPD-derived **Visceral Yolk Sac Endoderm**;

* P , 0.05 compared with NPD.

Watkins AJ *et al*. Adaptive Responses by Mouse Early Embryos to Maternal Diet Protect Fetal Growth but Predispose to Adult Onset Disease. **Biol Reprod 2008**; 78:299-306.



Main conclusions:

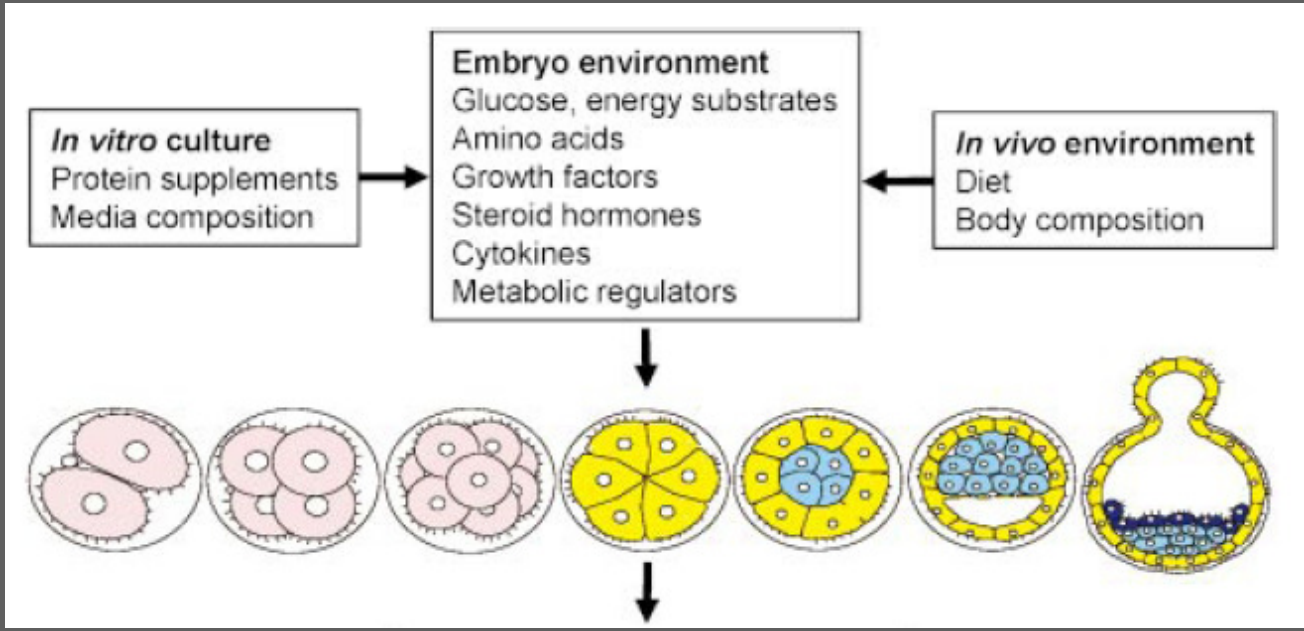
Maternal protein-deficient diet during mouse preimplantation period:

1. Affects postnatal health parameters particularly in female offspring
2. Induces adaptive response within the blastocyst
3. Alters nutrient retrieval capacity of the visceral yolk sac endoderm

Preimplantation responses to maternal diet are inherent to the embryo and lead to changes in Visceral Yolk Sac Endoderm nutrient uptake capacity

Watkins AJ *et al*. Adaptive Responses by Mouse Early Embryos to Maternal Diet Protect Fetal Growth but Predispose to Adult Onset Disease. **Biol Reprod 2008**; 78:299-306.

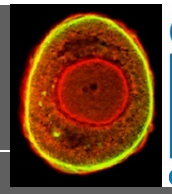
Challenge to research: to extend findings from maternal diet to culture conditions



TP Fleming *et al*. The Embryo and Its Future. **Biol Reprod 2004**;71:1046-1054.

New outcome markers

Detect and Register more parameters



Human Reproduction, Vol.24, No.4 pp. 922–928, 2009
Advanced Access publication on January 16, 2009 doi:10.1093/humrep/den466

human reproduction

ORIGINAL ARTICLE *Reproductive biology*

Effect of *in vitro* maturation of mouse oocytes on the health and lifespan of adult offspring

J.J. Eppig[1], M.J. O'Brien, K. Wigglesworth, A. Nicholson, W. Zhang, and B.A. King

The Jackson Laboratory, Bar Harbor, ME 04609, USA

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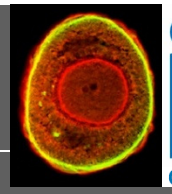
Mouse oocytes were matured ***in vitro*** using both an established optimized system and in the absence of amino acids to produce a suboptimal condition for maturation.

Oocytes induced to mature ***in vivo*** with gonadotrophins were the control group.

All M-II oocytes were fertilized ***in vitro*** and transferred at the 2-cell stage to the oviducts of pseudo-pregnant foster mothers for development to term.



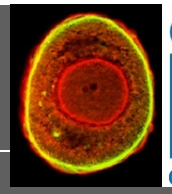
Effect of amino acid deprivation during *in vitro* oocyte maturation on developmental competence

Table I Developmental competence of mouse oocytes matured *in vitro* (IVM) in the presence (+) or absence (−) of amino acids (AA)

	% 2-Cell[1]	% 2-Cell to blastocyst[2]	% Total blastocyst[3]
IVM + AA	75.5 ± 3.07	79 ± 1.35	59.7 ± 2.17
IVM − AA	57.7 ± 5.44	82.7 ± 3.71	47.5 ± 4.73
P-value	0.0312	0.3661	0.0575

[1]Mean percentage ± SEM of MII oocytes developing to the 2-cell stage after IVF.
[2]Mean percentage ± SEM of 2-cell stage embryos developing to the blastocyst stage.
[3]Mean percentage ± SEM of MII oocytes developing to the blastocyst stage.

JJ Eppig (**2009**) Effect of *in vitro* maturation of mouse oocytes on the health and lifespan of adult offspring. **Hum Reprod** 24 (4):922–928.



Offspring physiological and behavioral testing:
No differences were detected, except for a reduction in pulse rate and cardiac output

Table II Results of physiological and behavioral testing

Category	Test	Measurements	*In vivo* versus IVM + AA
Physical		Weight	ND (dns)
Metabolic	Comprehensive cage monitoring system	Volume of O_2 consumed	ND (dns)
		Volume of CO_2 produced	ND (dns)
		Respiratory exchange ratio	ND (dns)
		Heat	ND (dns)
		Accumulated feed	ND (dns)
		Accumulated drink	ND (dns)
		Ambulation	ND (dns)
Cardiopulmonary	Electrocardiography	Heart rate	ND (dns)
	Echocardiography	Heart rate	ND (dns)
		Left ventricle % ejection fraction	ND (dns)
		Left ventricle % fractional shortening	ND (dns)
		Cardiac output	$P = 0.0197$ (Fig. 1B)
	Blood pressure	Systolic pressure	ND (dns)
		Pulse rate	$P = 0.0119$ (Fig. 1A)
Neuromuscular	Grip-strength	Force	ND (dns)
	Rotarod	Duration	ND (dns)
Behavioral	SHIRPA	Aggression	ND (dns)
		Startle response	ND (dns)
		Transfer arousal	ND (dns)
	Exploratory Board	Stretched attends	ND (dns)
		Hole visit	ND (dns)
		Defecation	ND (dns)
Lifespan		Age at death	ND (Fig. 2)

ND, not significantly different; dns, data not shown.

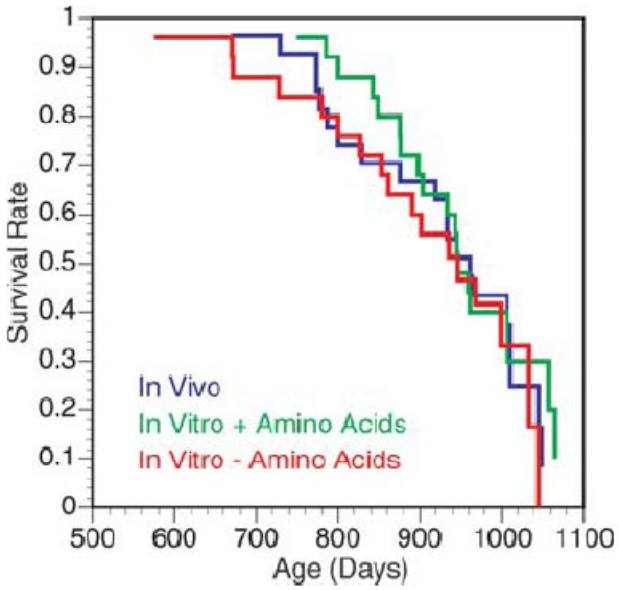


Figure 2 Effect of *in vitro* maturation on lifespan of the offspring. No differences were observed.

JJ Eppig (**2009**) Effect of *in vitro* maturation of mouse oocytes on the health and lifespan of adult offspring. **Hum Reprod** 24 (4):922–928.

Surprisingly, these differences were abrogated by *in vitro* maturation in the absence of amino acids.

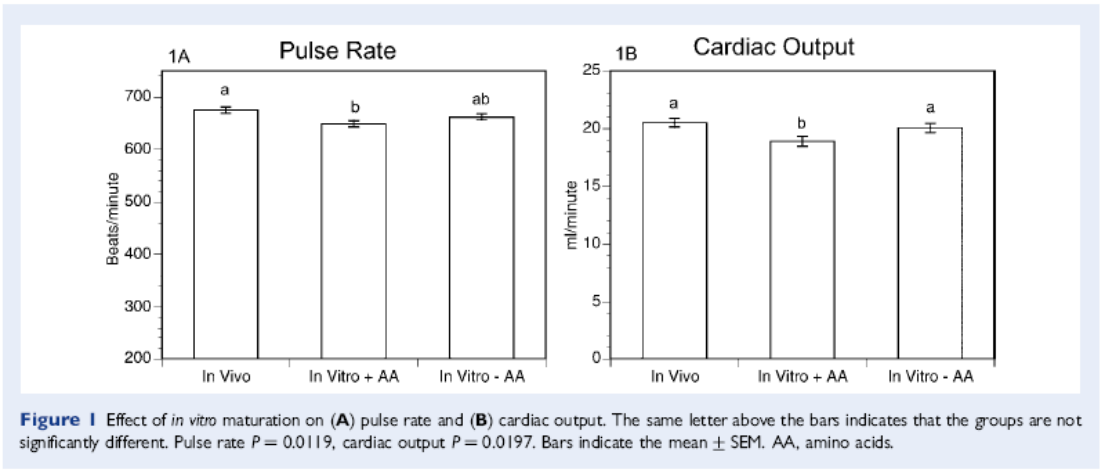


Figure 1 Effect of *in vitro* maturation on (**A**) pulse rate and (**B**) cardiac output. The same letter above the bars indicates that the groups are not significantly different. Pulse rate $P = 0.0119$, cardiac output $P = 0.0197$. Bars indicate the mean ± SEM. AA, amino acids.

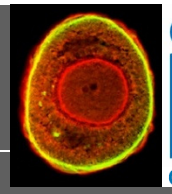
Main conclusions:

1. The use of the mouse model suggests that the *in vitro* maturation of oocytes has minimal effects on the long-term health of offspring.

2. A finding of slight reductions in pulse rate and cardiac output may focus future clinical attention.

3. Culture media composition during the last stages of gamete differentiation can have long-term effects.

JJ Eppig (**2009**) Effect of *in vitro* maturation of mouse oocytes on the health and lifespan of adult offspring. **Hum Reprod** 24 (4):922–928.



Commercial companies that sell embryo culture media:
Must disclose precise and full media composition

Table 41.1 Media Formulations. Products included in this table are representative of media products sold in the United States. Actual concentrations are included (mM, g/L or as indicated) if published. Symbols are as follows: "X" indicates the product is present, but concentration is not published "ne" designates non essential amino acids, "e" designates essential amino acids

Media for fertilization & cleavage culture

	Sage Quinn's Advantage fertilization	Vitro Life GIVF	Irvine P1	Irvine HTF	Many HF10	Medicult Universal IVF	Cook Sydney fertilization	Sage Quinn's advantage cleavage
Inorganic salt								
Calcium chloride		X	2.01	1.84	0.285	X		
Cupric sulfate					9.5 nM			
Ferrous sulfate					0.003			
Magnesium chloride						X	X	
Magnesium sulfate (anhyd)	X	X	0.20	0.18	0.591	X	X	X
Other						EBSS		
Orthophosphate 1 hydrate		X					X	
Potassium chloride	X	X	4.69	4.22	3.630	X	X	X
Potassium phospate	X			0.33	0.580	X		
Sodium choride	X	X	101.6	91.44	121.0	X	X	X
Sodium dihydrogen		X						
Sodium phosphate					1.030	X		
Zinc sulfate					0.000			
Energy source								
Calcium lactate	X				1.170		X	X
Fructose		X						
Glucose	X	X		2.50	5.810	X	X	X
Pyruvate (sodium)	X	X	0.33	0.30		X	X	X
Pyruvic acid					1.190			
Sodium lactate		X	21.40	19.30				
Antibiotics								
Gentamycin	X	X	10 µg/ml	9 µg/ml	X		X	X
Penicillin					X	X		
Streptomycin						50 mg/L		
Other								
Choline chloride					0.005			
EDTA	X	X					X	X
HEPES								

	Sage Quinn's Advantage fertilization	Vitro Life GIVF	Irvine P1	Irvine HTF	Many HF10	Medicult Universal IVF	Cook Sydney fertilization	Sage Quinn's advantage cleavage
Heptahydrate		X						
Hyaluronan								
Lipoic acid								
Pantothenate	X						X	
Phenol red (sodium)	X		0.005 g/L	4.50	0.003	X		X
Sodium bicarbonate	X		25.00	22.50	23.800	X	X	X
Sodium hydrogen carbonate		X						
Sodium citrate	X	X	0.15 mg/L					X
Taurine	X	X	0.05				X	X
Vitamins								
Biotin					X			
Folic acid					0.003			
Inositol								
Niacinamide					0.005			
Thiamine					0.003			
Vitamin B12					0.001			
Amino acids (L)	6 ne	8 ne	0	0	18 ne 9 e	0	8 ne	6 ne
Alanine		X			0.096		X	
Alanyl glutamine	X	X			0.950		X	X
Arginine	X	X			1.150		X	X
Asparagine	X	X			0.108		X	X
Aspartic acid	X	X			0.095		X	X
Calcium pantothenate								
Cysteine					0.190			
Cystine					0.190			
Gluathione		X						
Glutamate		X					X	
Glutamine		X			0.095			
Glycine	X	X			0.095		X	X
Histidine (e)					0.141			
Isoleucine (e)					0.019			
Leucine (e)					0.095			
Lysine (e)					0.191			
Methionine (e)					0.029			
Proline	X	X			0.095		X	X
Pyridoxine					0.001			
Riboflavin					0.001			
Serine	X	X			0.095		X	X

Jackson KV, Racowsky C. Embryo culture techniques. In: Carrell DT, Peterson CM, eds. Reproductive Endocrinology and Infertility: Integrating Modern Clinical and Laboratory Practice. Springer, **2010**: 613-632.

Birthweight of singletons from Vitrolife were compared with singletons from Cook.

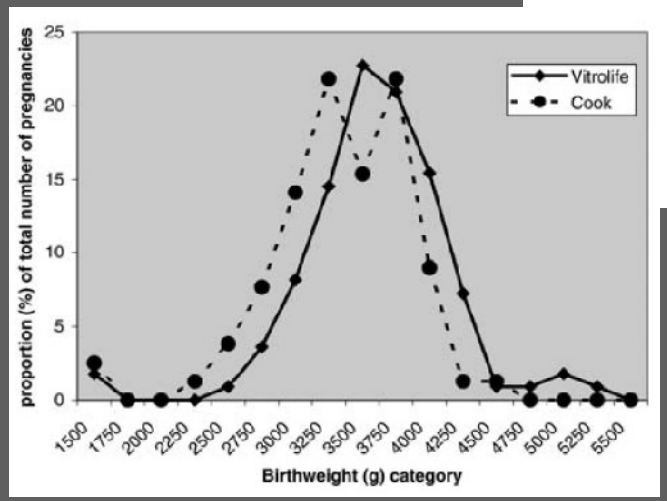
Human Reproduction, Vol.25, No.3 pp. 605–612, 2010
Advanced Access publication on January 18, 2010 doi:10.1093/humrep/dep456

human reproduction

ORIGINAL ARTICLE *Embryology*

Effect of *in vitro* culture of human embryos on birthweight of newborns

John C. Dumoulin[1,2,6], Jolande A. Land[3], Aafke P. Van Montfoort[1,2], Ewka C. Nelissen[1,2], Edith Coonen[1,2], Josien G. Derhaag[1,2], Inge L. Schreurs[1], Gerard A. Dunselman[1,2], Arnold D. Kester[4], Joep P. Geraedts[2,5], and Johannes L. Evers[1,2]



Comparisons were done after adjustment for gestational age and gender, together with other variables that could affect birthweight as covariates, by **multiple linear regression analysis**.

Singleton birthweights were found to be significantly higher in the Vitrolife group.

Birthweight of singletons from Vitrolife were compared with singletons from Cook.

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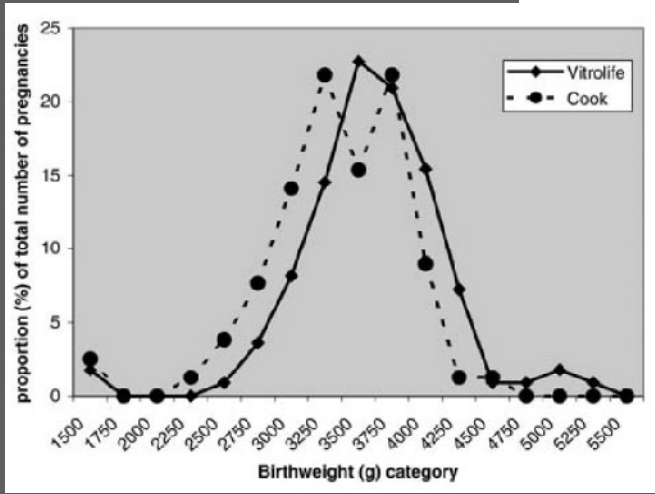
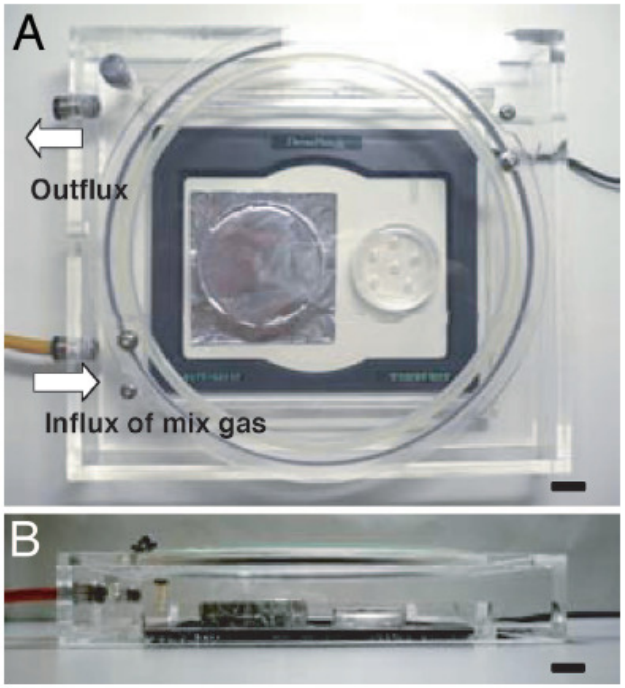


"The use of optimal culture media during IVF treatment may help to avoid low birthweight (… and …) place a huge responsibility on the shoulders of manufacturers of culture media for human IVF and on those of the IVF practitioners that use them."

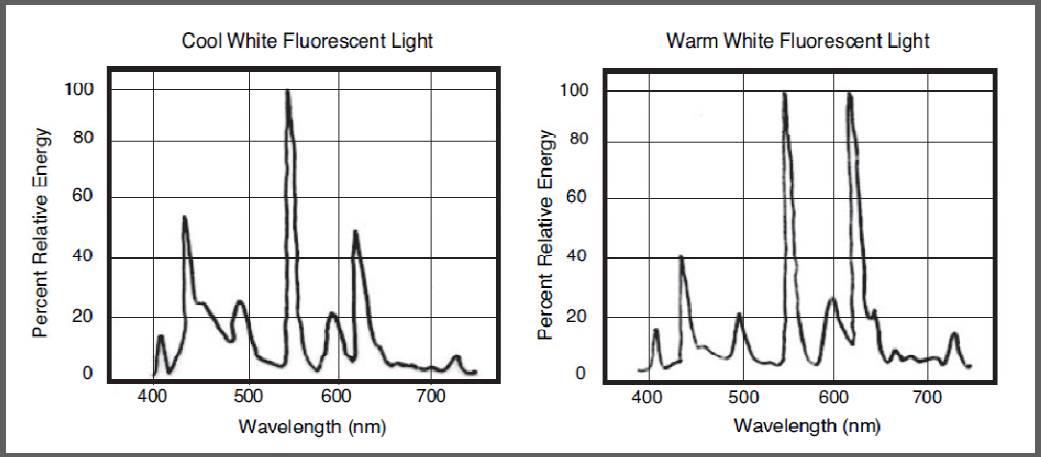
Comparisons were done after adjustment for gestational age and gender, together with other variables that could affect birthweight as covariates, by **multiple linear regression analysis**.

Singleton birthweights were found to be significantly higher in the Vitrolife group.

Challenge to find other factors involved: Effects of exposure to light on development of hamster and mouse zygotes

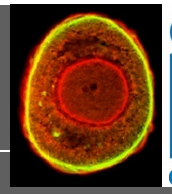


Incubator for light exposure of zygotes



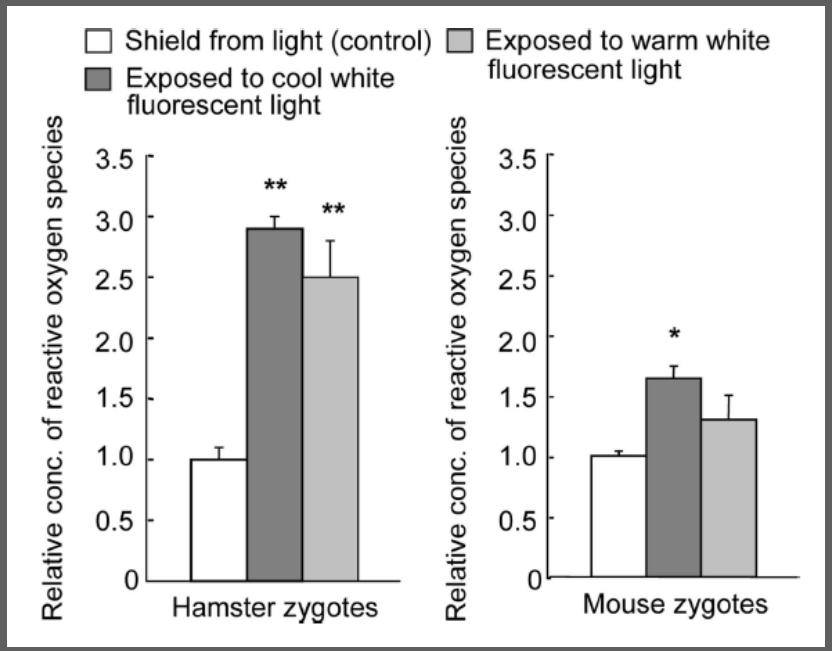
Spectral of cool and warm white fluorescent light

Takenaka M et *al*. Effects of light on development of mammalian zygotes. **PNAS USA 2007**; 104:14289-14293.



Preimplantation development of hamster and mouse zygotes after 15 min exposure to fluorescent (cool + or warm –) light

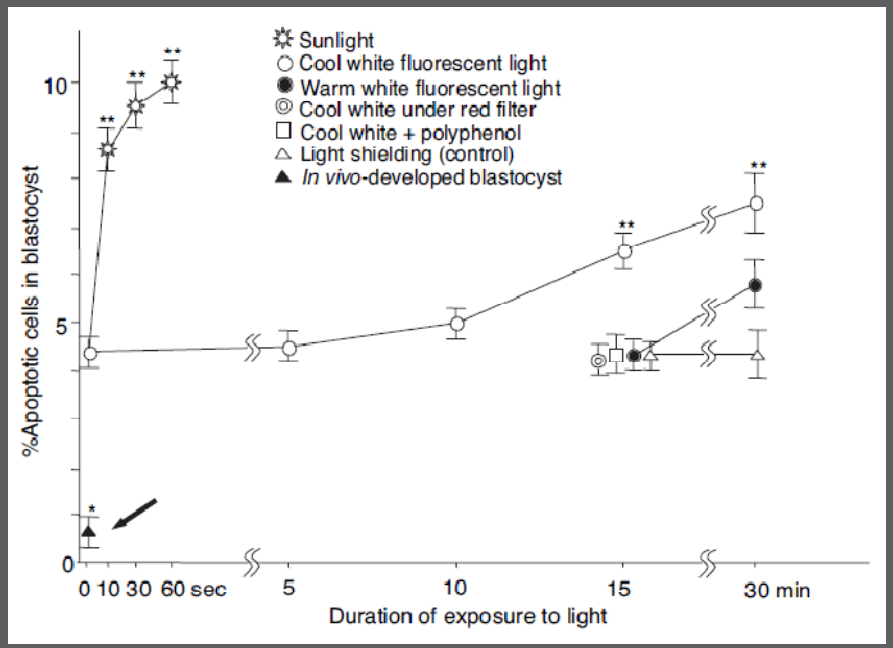
Species	Exposure of zygote to light*	No. of zygotes cultured	No. (%) of zygotes developed to		
			Two-cell	Morulae	Blastocysts
Hamster	–	37	36 (97)	34 (92)	25 (68)
	+	37	36 (97)	0 (0)†	0 (0)†
Mouse	–	41	41 (100)	41 (100)	40 (98)
	+	40	40 (100)	40 (100)	40 (100)

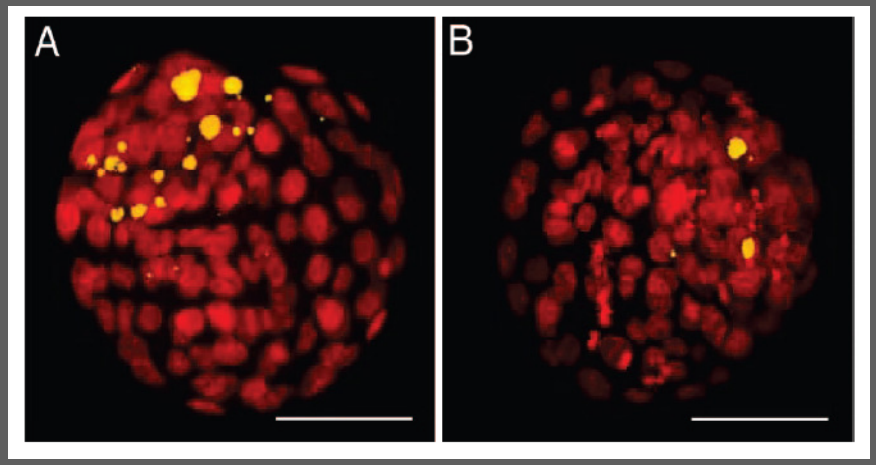


Production of ROS in hamster and mouse zygotes after 15 min exposure to fluorescent light

Takenaka M et *al*. Effects of light on development of mammalian zygotes. **PNAS USA 2007**; 104:14289-14293.

Apoptotic cells in mouse blastocysts after exposure to light as zygotes

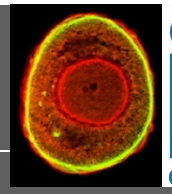




Exposed to cool fluorescent light (15min)

Control (no exposure)

Takenaka M et *al*. Effects of light on development of mammalian zygotes. **PNAS USA 2007**; 104:14289-14293.



Postimplantation development of mouse zygotes after 15 min exposure to fluorescent light (or after 1 min in sunlight)

Zygotes exposed to*	Total no. blastocysts transferred (no. of replications)	No. of recipients†	Total no. (%, mean ± SEM)	
			Live term fetuses‡	Resorbed fetuses‡
No light (control)	107 (4)	10	73 (66 ± 13)	18 (20 ± 7)
Warm white fluorescent light	100 (4)	10	58 (58 ± 17)	19 (25 ± 16)
Cool white fluorescent light	108 (3)	10	44 (42 ± 14)§	20 (24 ± 23)
Sunlight	100 (4)	10	25 (25 ± 14)§	35 (57 ± 24)§

Main conclusion:

Light is one of the physical factors affecting embryonic environment and its effects on cultured mammalian zygotes and embryos should not be overlooked.

Takenaka M et *al*. Effects of light on development of mammalian zygotes. **PNAS USA 2007**; 104:14289-14293.

Cardiometabolic Differences in Children Born After in Vitro Fertilization: Follow-Up Study.

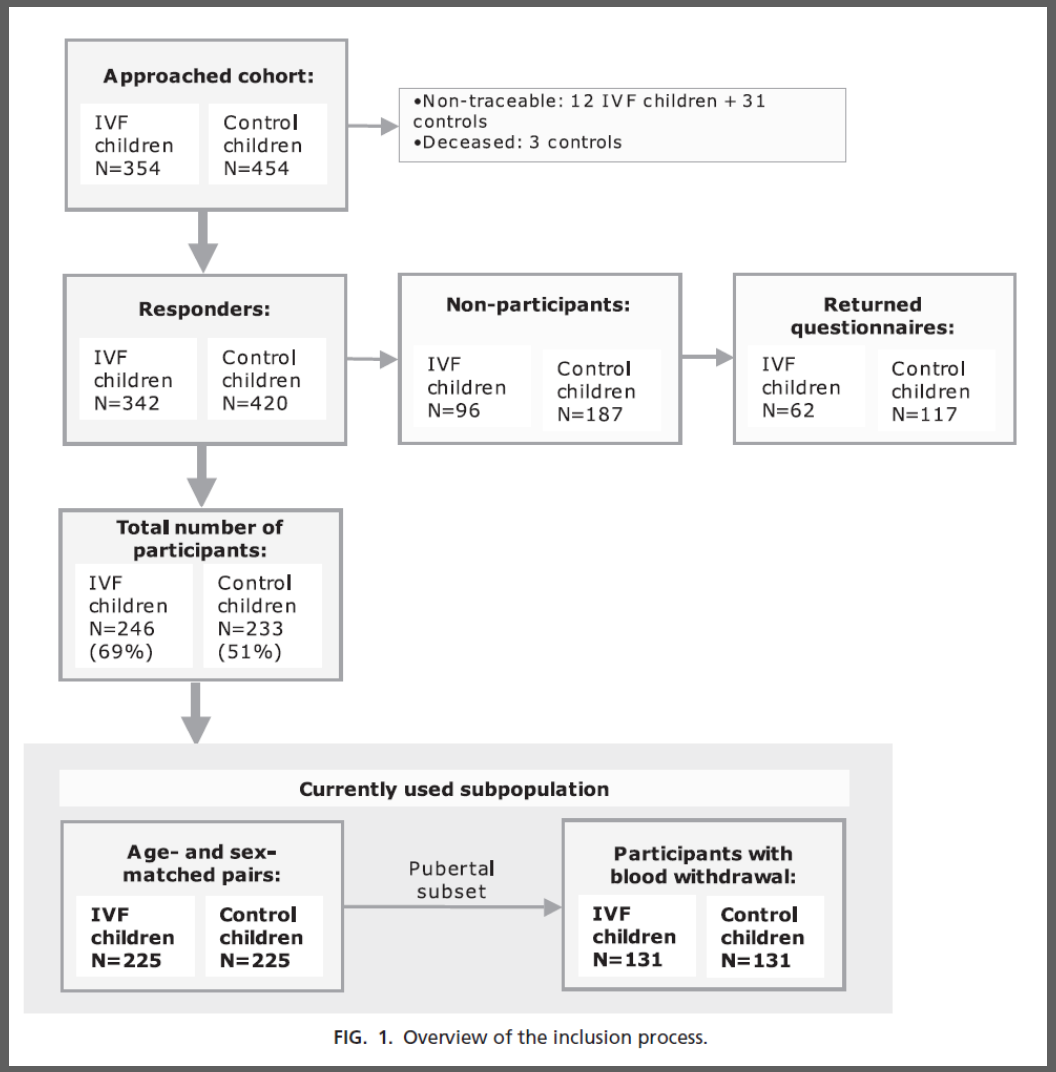
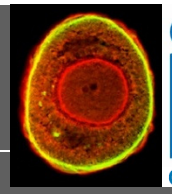


FIG. 1. Overview of the inclusion process.

Ceelen M *et al*. Cardiometabolic Differences in Children Born After *in Vitro* Fertilization: Follow-Up Study. **J Clin Endocrinol Metab 2008**; 93:1682-1688.



Differences in blood pressure and fasting glucose between IVF children and control children after adjustment for confounders: multivariate analysis.

Multivariate models	Unstandardized regression coefficient	95% CI	*P* value
SBP difference (mm Hg) after adjustment for birth weight, gestational age, and sum of skinfolds	3.0	1.1–5.0	0.003
DBP difference (mm Hg) after adjustment for birth weight, gestational age, parity, and sum of skinfolds	1.4	0.03–2.8	0.046
Glucose difference (mmol/liter) after adjustment for subfertility cause	0.11	0.02–0.21	0.02

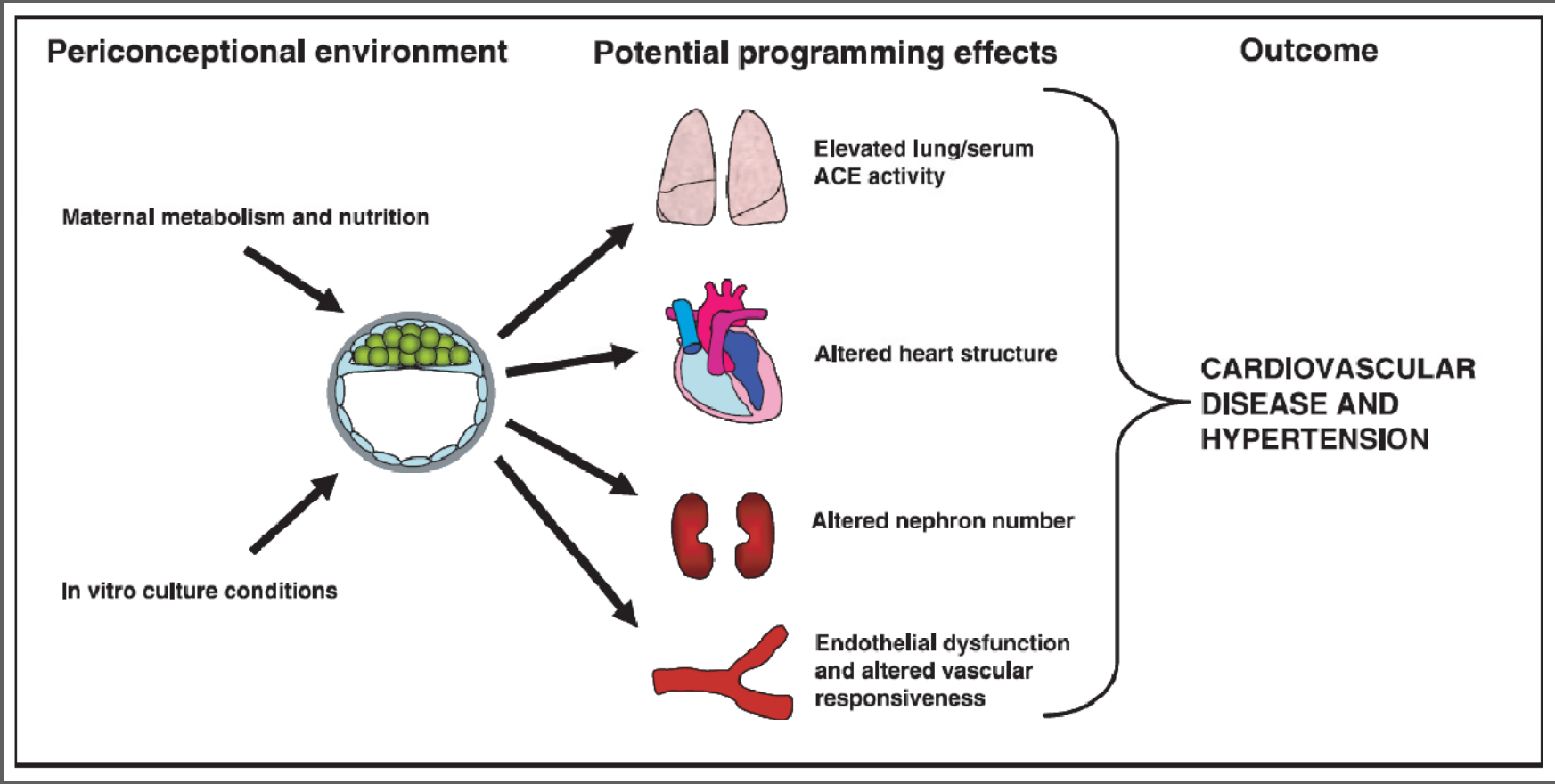
DBP, Diastolic blood pressure; SBP, systolic blood pressure.

Main conclusion:

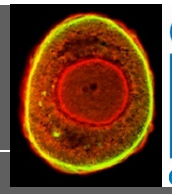
These findings highlight the importance of continued cardiometabolic monitoring of IVF-conceived children and might contribute to current knowledge about periconceptional influences and their consequences in later life.

Ceelen M *et al*. Cardiometabolic Differences in Children Born After *in Vitro* Fertilization: Follow-Up Study. **J Clin Endocrinol Metab 2008**; 93:1682-1688.

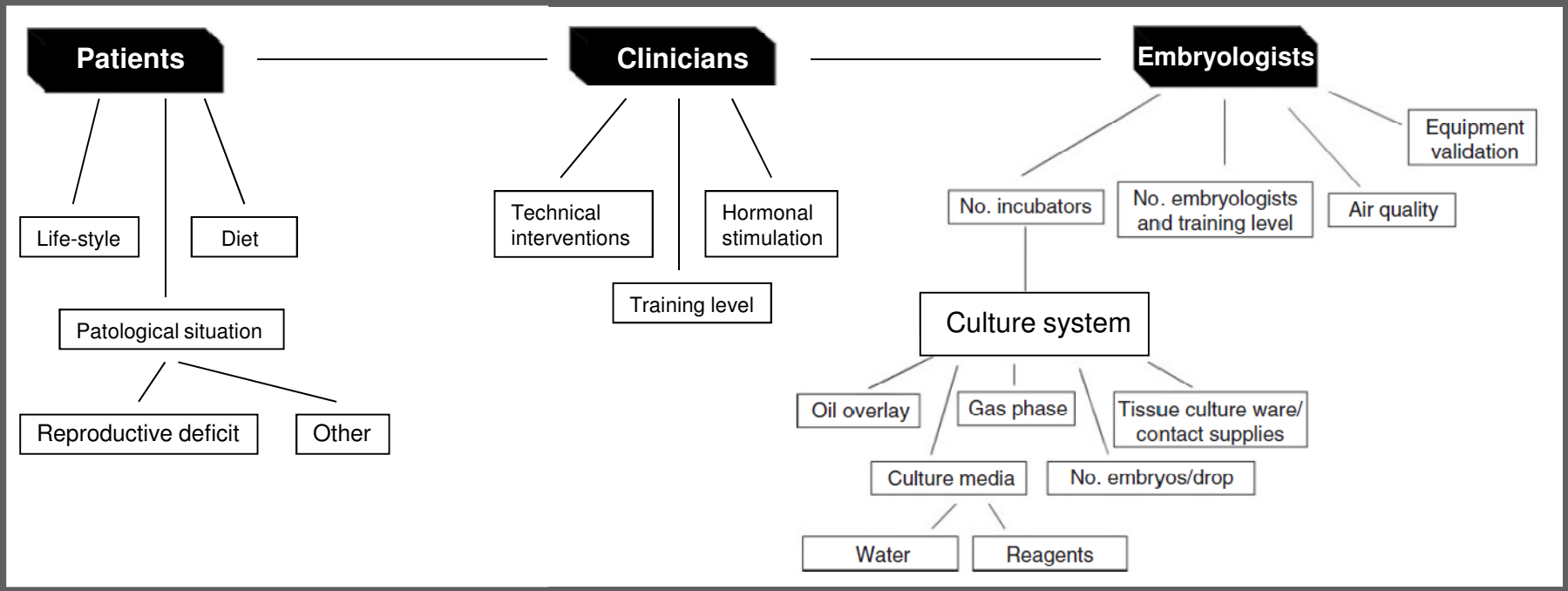
Periconceptional environmental factors (*in vivo / in vitro*) on embryo development and adult cardiovascular phenotype



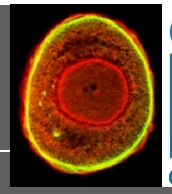
Watkins AJ, Fleming TP. Blastocyst environment and its influence on offspring cardiovascular health: the heart of the matter. **J Anat 2009**; 215:52-59.



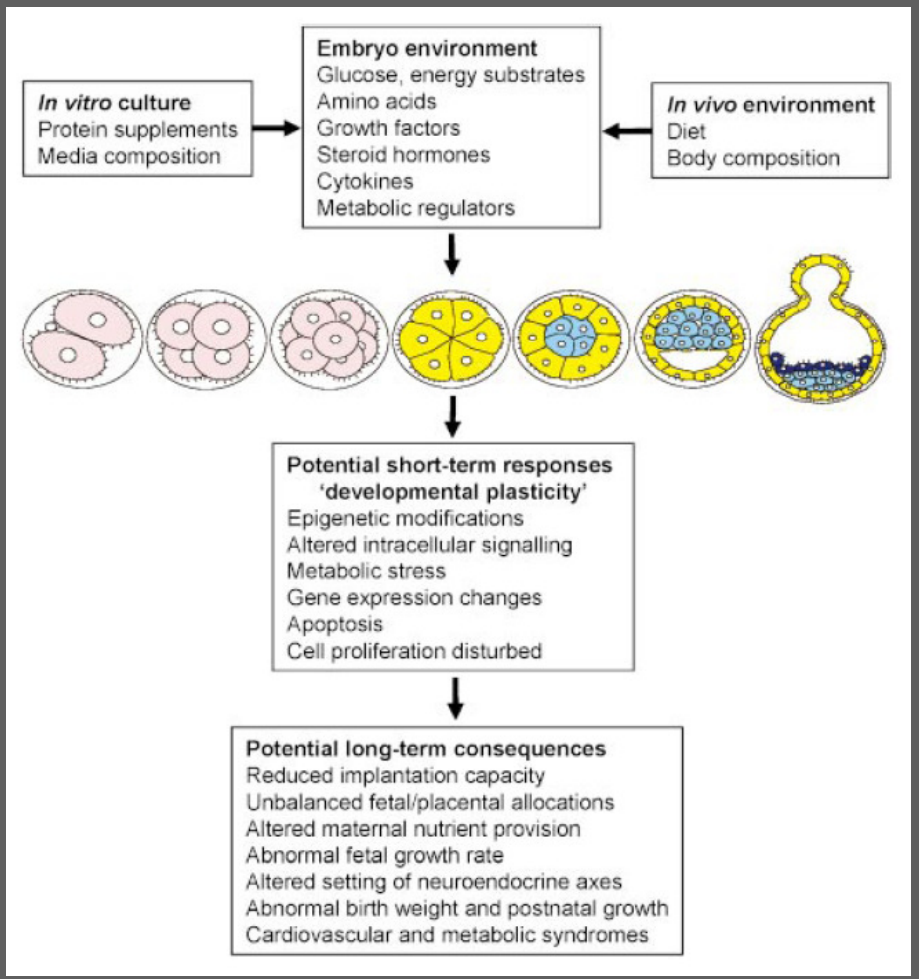
The challenge for all of us (clinical team and embryologists) **will be how to integrate the different aspects of short-term monitoring presently used …**



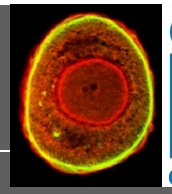
Modified from: Lane M *et al*. To QC or not to QC: the key to a consistent laboratory? **Repr Fert Dev 2008**; 20:23-32.



… with the knowledge that environment-embryo interactions, besides short-term responses, may also have long-term consequences.



TP Fleming *et al*. The Embryo and Its Future. **Biol Reprod 2004**;71:1046-1054.



Research agenda in the area of Ecological Assisted Reproduction

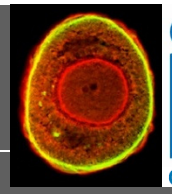
Basic research

- Which mechanisms link early-gamete and early-life events with long-term effects?
- Can the developmental pathways be altered or reversed?
- What are best gamete, embryo and fetal development?
- Identify the indicators of best pregnancy outcome. - eg, birth size?
- Could markers of specific nutrient status before and during pregnancy inform us about long-term outcomes?

Applied research

- What is the weight of early-gamete and early-life events in adult-onset diseases?
- Define approaches to intervene during different stages of the life-course.
  - eg. preconception, pregnancy, lactation, childhood, adult, parent?
- How can developmental interventions be made context-specific, balancing prevention of undernutrition against the later-life consequences of rapid postnatal weight gain?

Modified from: **Gluckman PD** *et al*. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. **Lancet 2009**; 373: 1654-57.



0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(9):3441–3445

doi: 10.1210/jc.2006-2465

In Vitro Fertilization Improves Childhood Growth and Metabolism

Harriet L. Miles, Paul L. Hofman, John Peek, Mark Harris, Dyanne Wilson, Elizabeth M. Robinson, Peter D. Gluckman, and Wayne S. Cutfield

The National Research Centre for Growth and Development and Liggins Institute (H.L.M., P.L.H., M.H., D.W., P.D.G., W.S.C.) and Department of Community Health (E.M.R.), University of Auckland, Auckland 1010, New Zealand; and Fertility Associates (J.P.), Auckland 1051, New Zealand

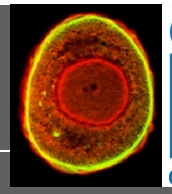
Main conclusions:

IVF children are taller with higher IGF-I and IGF-II levels and have a slightly more favorable lipid profile.

The authors speculate that IVF results in epigenetic change through altered methylation of genes involved in growth and metabolism.

IVF programs should consider long-term longitudinal follow-up of IVF offspring.

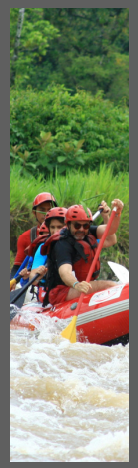
HL Miles et al. (**2007**) *In Vitro* Fertilization Improves Childhood Growth and Metabolism. **J Clin Endocrinol Metab** 92:3441-3445.



Take-home messages:

1. Environmental cues modify developmental patterns in several organs, influencing susceptibility to adult onset diseases.

2. These cues are relevant even during Gametogenesis and Preimplantation Development.



3. The **challenge** for all of us (clinical team and embryologists) will be how to integrate our current knowledge regarding environment-embryo interactions, to understand and compensate their long-term consequences.

Ecological Clinical Embryology

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