

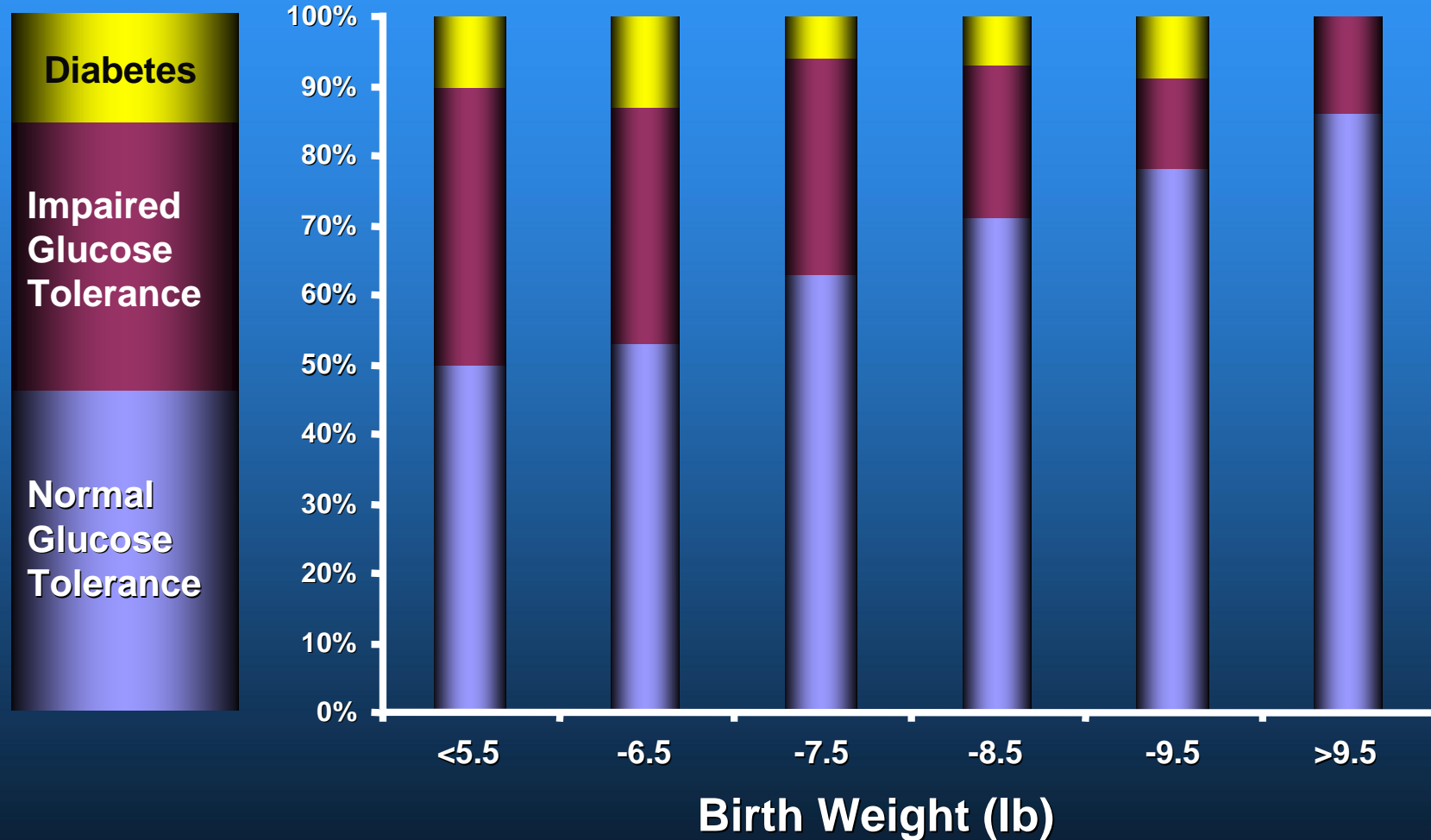
Programming of the Appetite regulatory System

Susan Ozanne



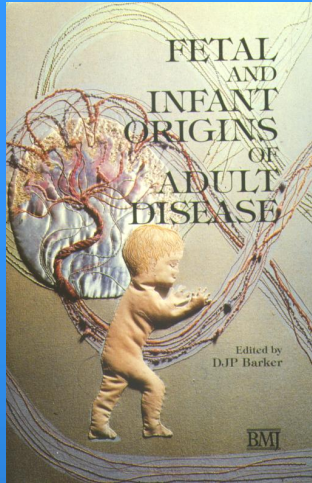
UNIVERSITY OF
CAMBRIDGE

Hertfordshire Data



Associations with Low Birth Weight

- **Type 2 Diabetes**
- **Cardiovascular Disease**
- **Insulin Resistance**
- **Obesity**
- **Hypertension**
- **Cancer**



Thrifty Phenotype Hypothesis

(Hales & Barker, 1992)

Poor Maternal Nutrition

Placental Dysfunction

Fetal Malnutrition

Altered organ structure/function
(β -cells, muscle, adipocytes, kidney, liver)

Obesity
Ageing

Organ Malfunction, Type 2 Diabetes, Hypertension

METABOLIC SYNDROME

Results from Danish Twin Registry

Birth weights (g) of MZ (67 years) and DZ (64 years) twins discordant for NIDDM (same sex)

	Diabetic (g)	Non-diabetic (g)	
MZ	2644	2815	P<0.05
DZ	2490	2842	P<0.02

'Our study supports an important role of intrauterine malnutrition for the development of NIDDM later in life. The intrauterine component is independent of genotype and may not be explained by gestational age, maternal height, birth order or sex.'

Detrimental Effects of Rapid Postnatal Growth Following IUGR

- ✓ Hypertension (Leon *et al.*, 1996)
- ✓ Cardiovascular disease (Eriksson *et al.*, 1999)
- ✓ Type 2 diabetes (Forsen *et al.*, 2000)
- ✓ Obesity (Ong *et al.*, 2000)

Rapid Postnatal Growth Is Associated With Later Obesity

Systematic Reviews:

- ✓ Ong et al., 2008
- ✓ Monteiro & Victoria 2005
- ✓ Baird et al., 2005

Neonatal Nutrition

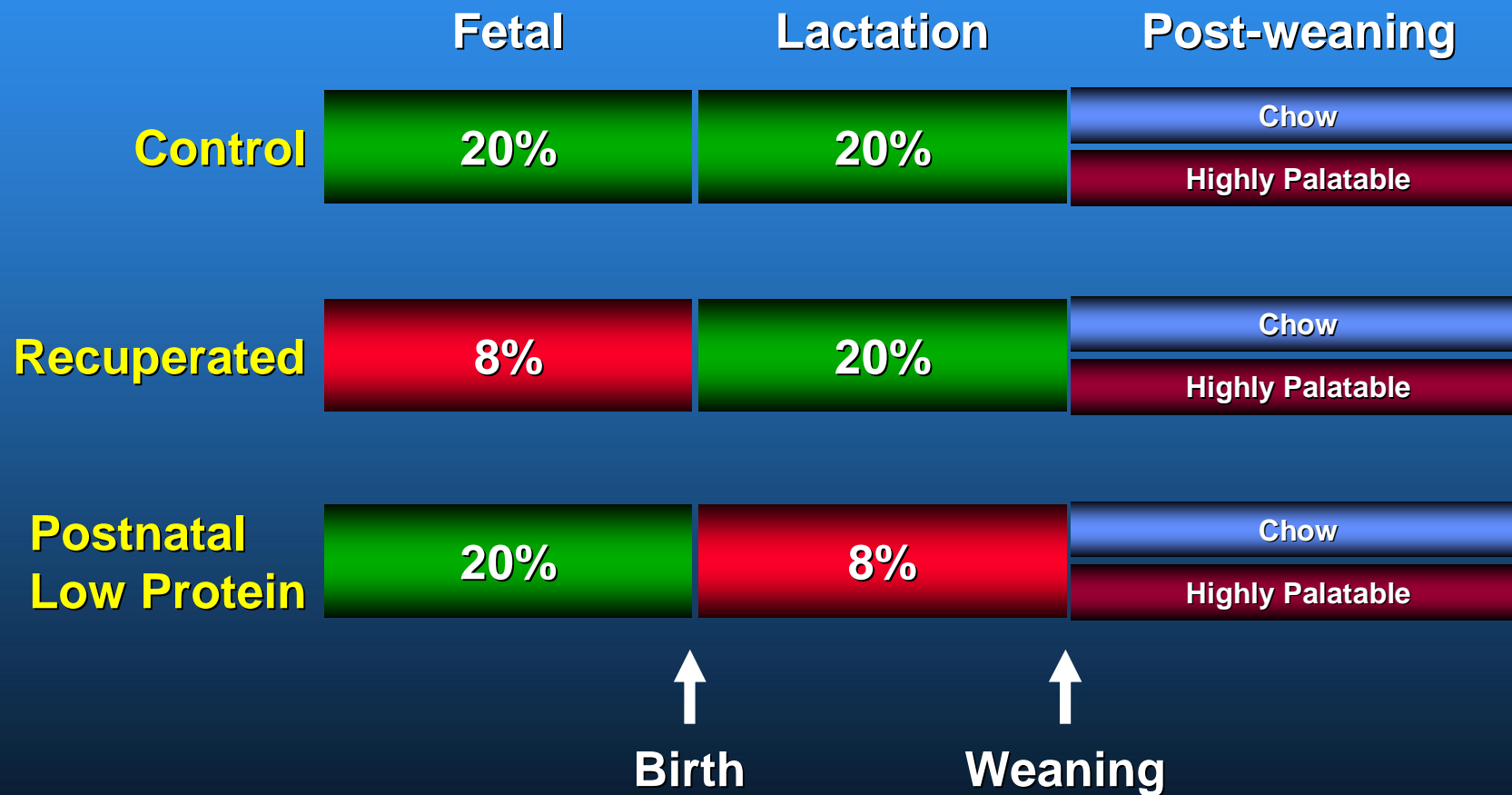
Breast fed infants at reduced risk of:

- ✓ Obesity
- ✓ Cardiovascular risk factors
- ✓ Type 2 diabetes
- ✓ Raised blood pressure

Rodent Models

- Low protein
- Calorie restriction
- Iron restriction
- Intrauterine artery ligation
- Dexamethasone treatment
- High fat
- Obesity
- Gestational diabetes

Experimental Design



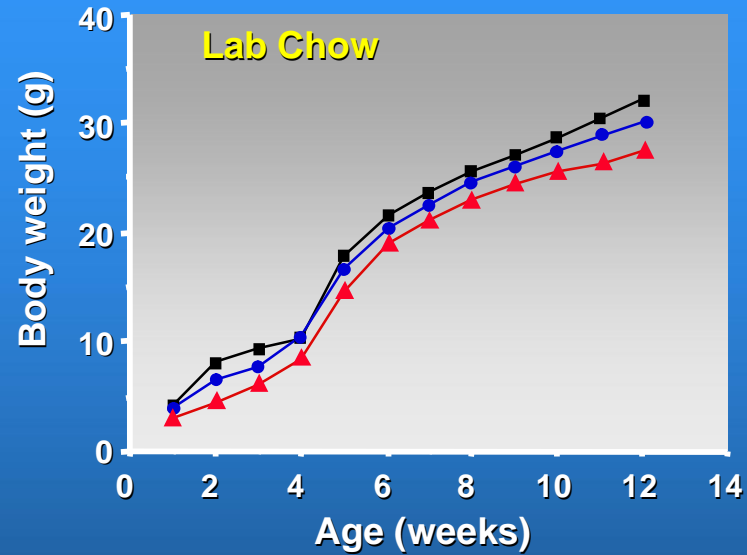
Early Growth Data

GROUP	Day 0 (g)	Day 3 (g)	Day 7 (g)	Day 14 (g)	Day 21 (g)
Control	1.57 ± 0.06	1.77 ± 0.03	3.82 ± 0.04	6.53 ± 0.05	7.75 ± 0.14
PNLP	1.57 ± 0.06	1.76 ± 0.03	3.10 ± 0.09***	4.47 ± 0.07***	5.96 ± 0.20***
Recuperated	1.13 ± 0.03**	1.70 ± 0.04	4.23 ± 0.06***	8.13 ± 0.10***	9.33 ± 0.15***

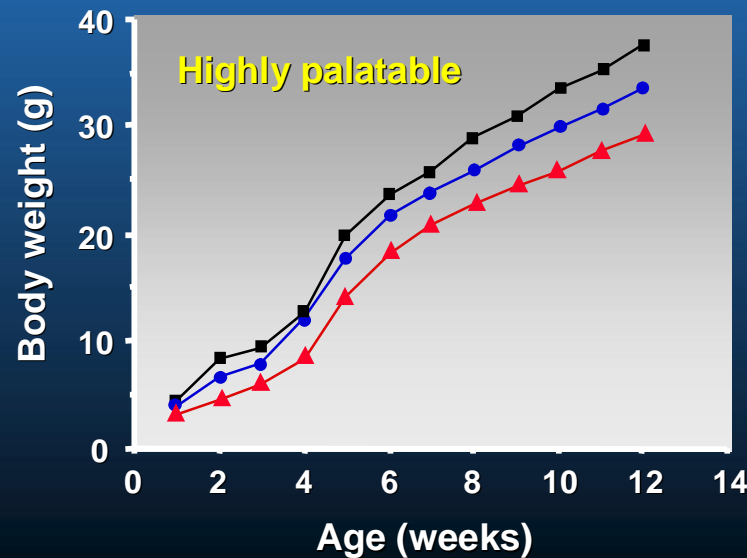
** p < 0.01 compared to controls

*** p < 0.001 compared to controls

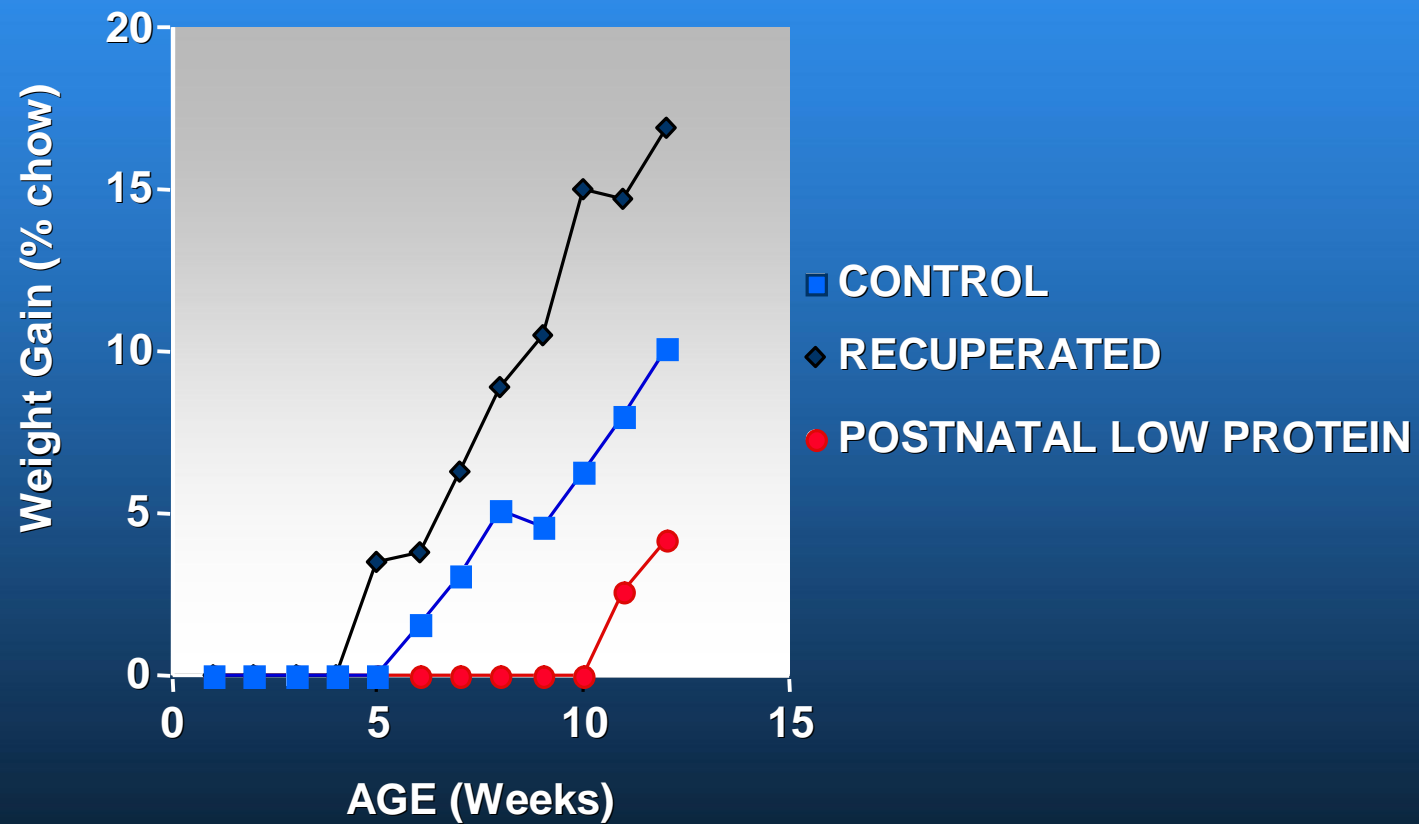
Mice Early Postnatal Weight Gain



- Recuperated
- Control
- ▲ Postnatal low-protein



Mice Weight Gain Increment on Highly Palatable Diet



Mechanisms of Obesity

- ✓ Changes in energy intake

- ✓ Changes in energy expenditure

Food Intake

GROUP	FOOD INTAKE (3-8 weeks) (g)
CONTROL	88.3 ± 1.4
RECUPERATED	96.7 ± 2.0**
PNLP	78.6 ± 3.5**

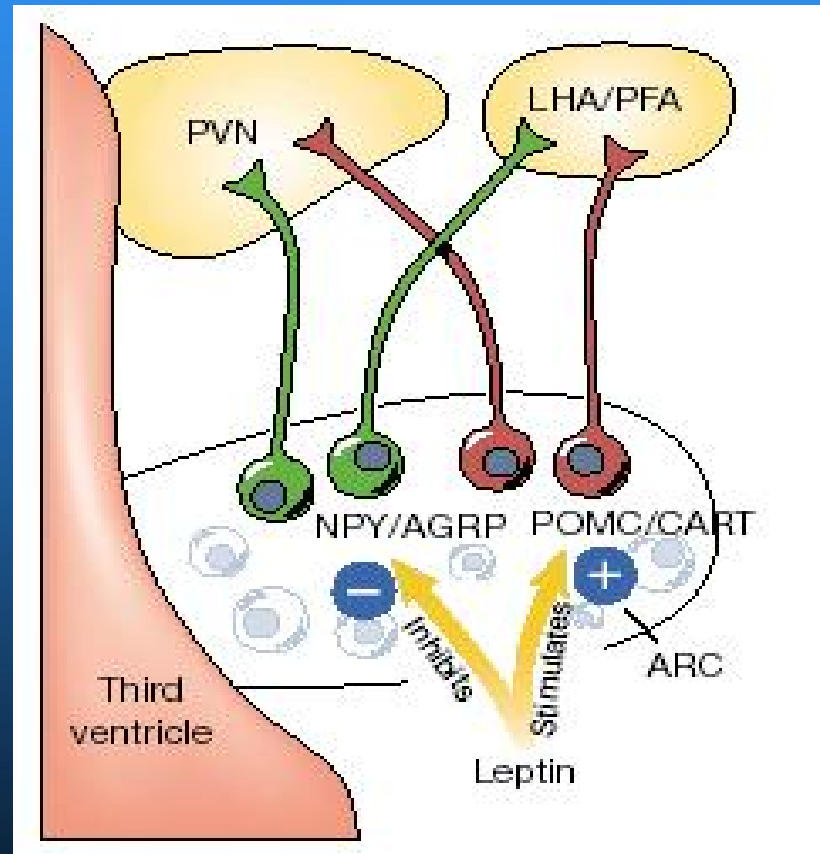
P < 0.01 compared to controls

Body Fat

GROUP	FAT PADS (g)	% FAT
CONTROL	1.00 ± 0.05	3.11 ± 0.15
RECUPERATED	1.50 ± 0.13***	4.54 ± 0.29***
PLP	0.77 ± 0.03**	2.44 ± 0.33*

***p < 0.001, **p < 0.01, *p < 0.05

Hypothalamic Regulation of Energy Balance



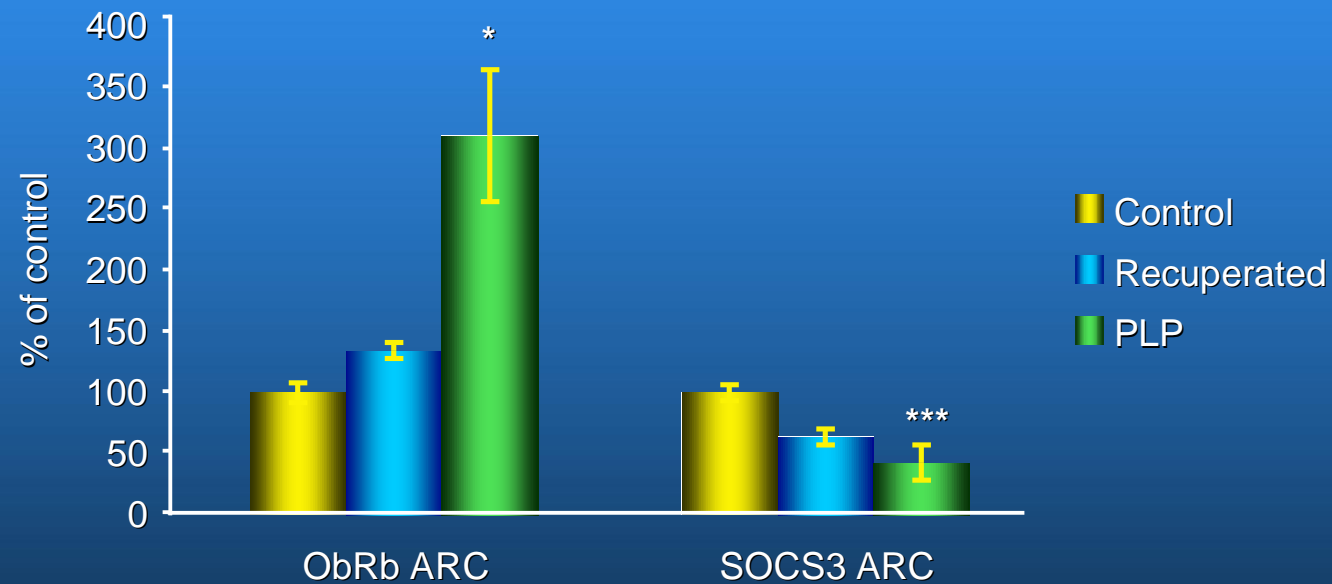
Fed/fasted Leptin at Weaning

	Control	Recuperated	Postnatal low protein
Fasted leptin (nM)	0.06 ± 0.004	0.09 ± 0.009 *	0.03 ± 0.007 *
Fed leptin (nM)	0.23 ± 0.021	0.11 ± 0.014 ***	0.09 ± 0.013 ***

* p < 0.05 compared to control

*** p < 0.001 compared to control

Leptin Signalling



* p < 0.05 compared to control

*** p < 0.001 compared to control

Conclusions

Early nutrition and growth

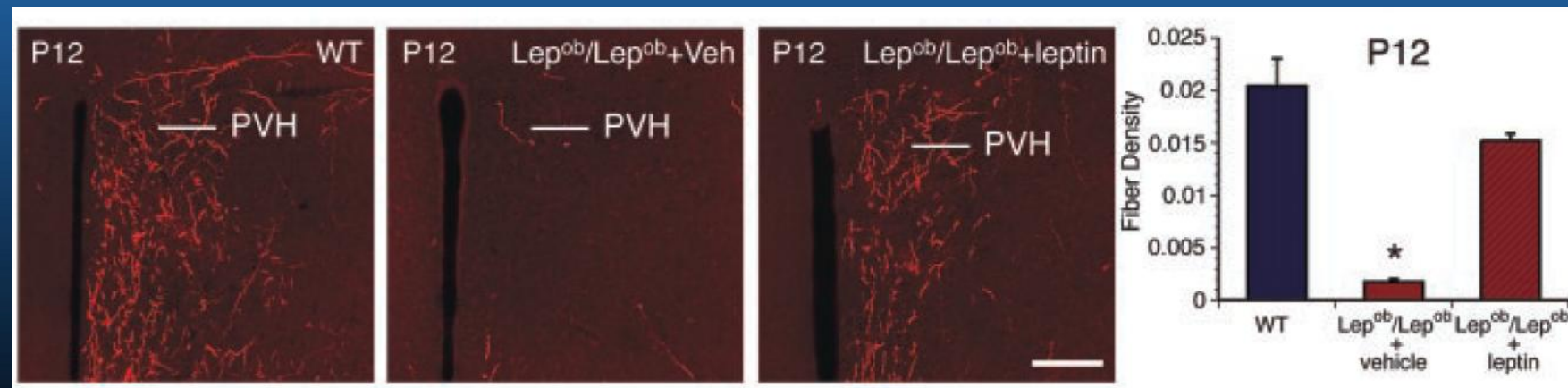
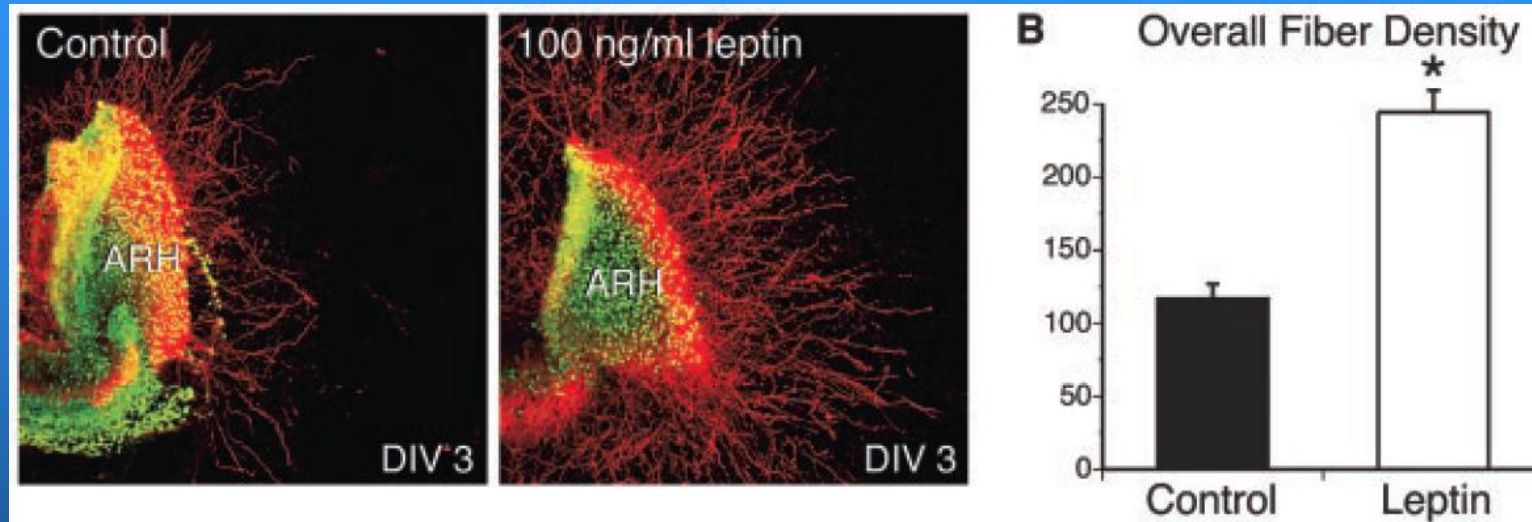
- ✓ Influences risk of obesity
- ✓ Alters hypothalamic gene expression
- ✓ Alters leptin production

Future Perspectives

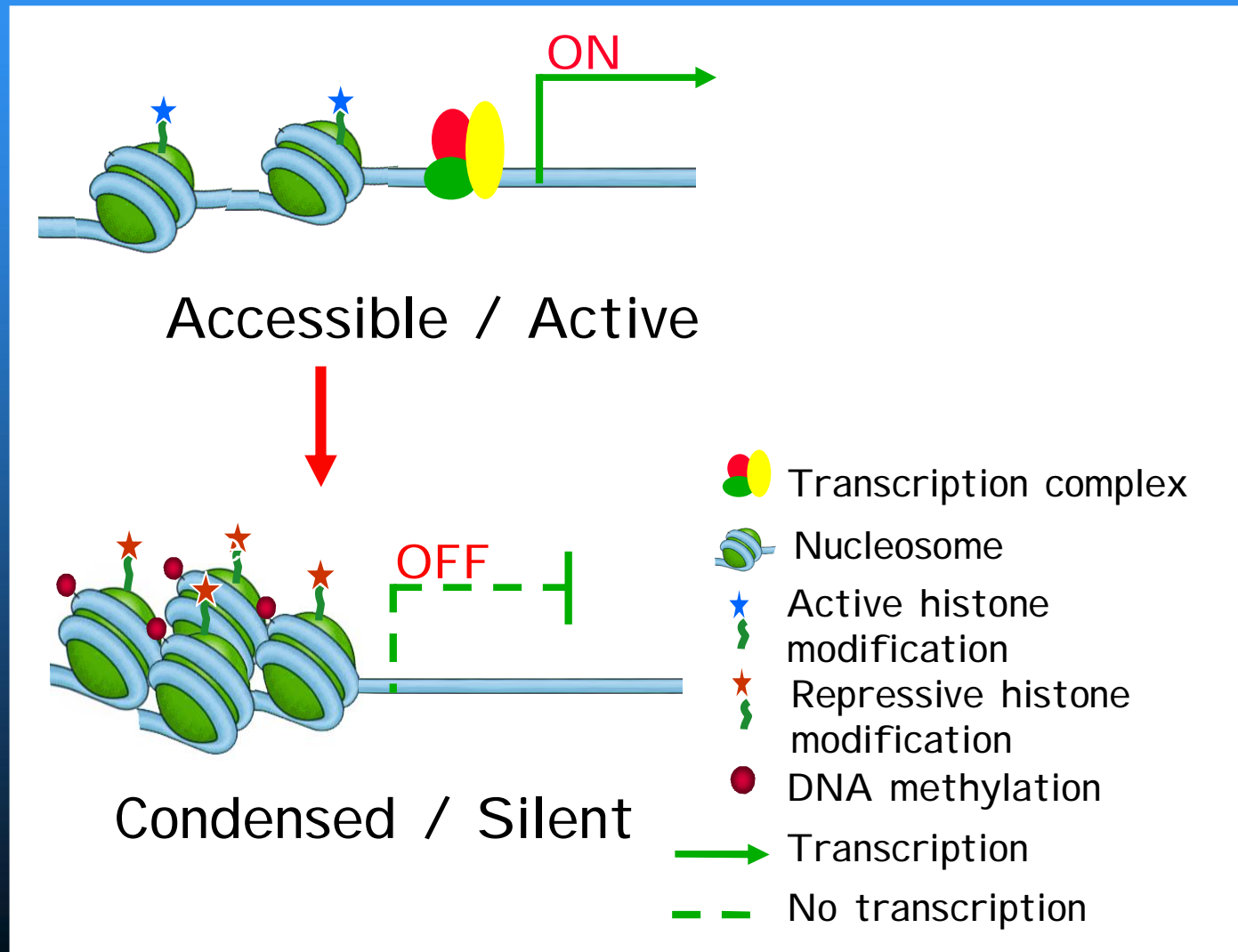
Defining Mechanisms

- Establishing Intervention Strategies

Permanent Structural Changes



Epigenetic Mechanisms



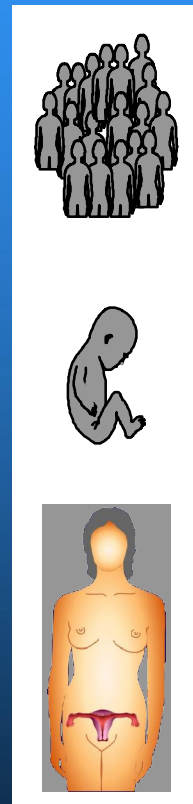
Integrative Strategy

Epidemiology

- Disease associations
- Growth and Diet
- Other factors
- Interaction with genes

Human Studies

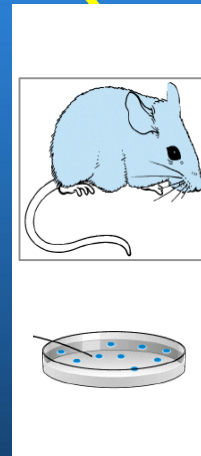
- Biomarkers
- Identification of at risk individuals
- Intervention



Hypotheses
to be tested

Animal Models

- Maternal diet
- Disease outcomes
- Other factors
- Interaction with genes
- Intervention



In Vitro Studies

- Molecular Mechanisms
- Biomarkers of risk

Novel mechanisms &
hypotheses to be tested