From biochemistry to clinical medicine glucose in neonatal medicine

- With oxygen, glucose is the most important metabolite during « intensive situations «
- There are specific aspects during fetal life
- There are specific aspects in the distressed newborn
- Metabolic regulation is concerning several hormones (insulin, glucagon, hGH, cortisol, NoA , A) and tissues (CNS, the liver, striated muscles, adipose tissue, intestines,…)
- That regulation needs to be integrated to growth and basal metabolic rate.

Croissance et nutrition périnatale

- Points intéressants concernant la croissance fœtale.
- Les paramètres de la croissance et les courbes de croissance
- Les paramètres de la nutrition
- Application et aide à la compréhension dans pratique à la clinique ou comment apprécier la croissance et la nutrition d'un nouveau-né

Les paramètres de la croissance et les courbes de croissance

Les paramètres anthropométriques de la croissance:

- *Valeurs absolues ponctuelles ou par semaine*:

  Poids, taille, PC, P et surface du thorax, P et surface de l' abdominal, P brachial, P cuisse, P jambe, H lobe frontal, D et surface du cervelet, Plis cutanés, masse musculaire, index hépatique, index splénique, index rénal, croissance du fémur, distance intervertébrale

- *Ratios calculés*:

  Index pondéral, indice de masse corporelle, P du bras Gauche / PC, dP / dT, dP / dPC, dPC / dT, Pcuisse / P jambe, rapports de surface: thoracique/abdominales, cardiaque/thoracique, thoracique/céphalique, hépatique/céphalique,

→ **Comme il y en a beaucoup, lesquels choisir et pourquoi ?**

Les courbes de croissance « in utero » et « postnatales:

→ Distinguer les formes « in utero » (de x semaines fetales: 24 ou plus à 42 semaines) et les formes postnatales (de x semaines fetales à 58 ou 60 semaines).

→ Tenir compte de la « complexité » des courbes et de leur « précision »;

→ Les situations des jumeux ou triplés demandent l'application de courbe de croissance PONDERALE spécifique.

→ Les situations des enfants < 1000 g ou < 30 semaines au cours des 4 premières semaines demandent une analyse particulière pour le poids.

→ Les situations des enfants nés avant 34 semaines et les enfants associant prématurité et retard de croissance fetal ou postnatale demandent une analyse particulière de la croissance jusqu'à 7 ans.

Les paramètres anthropométriques cliniques de croissance

- Le poids: incontournable, facile, « résume » tout, mais…
- La taille: incontournable, pas facile, indicateur de « choix » de la croissance;
- Le PC: incontournable, facile, résume la croissance cérébrale;
- La CBG: délaissé, intéressant, résume la croissance musculaire et adipeuse; il peut être décomposé en pli cutané tricipital et circonférence musculaire brachiale.
- Les différents ratios tentant d'apprécier l'harmonie de la croissance corporelle : index pondéral, Indice de masse corporelle, dP/dT, **dP/dPC**, **CBG/PC**, dT/dPC, CCG/CJG) ;

Les paramètres de croissance mesurés par des techniques spéciales

- Croissance du système nerveux par imagerie (écho, RMN): tissu cérébral (H lobe frontal), tissu cérébelleux (diamètre et surface); système ventriculaire (index d'hauteur, de largeur, de surface); indice d'Evans.
- Croissance musculaire: excrétion urinaire de créatinine;
- Croissance de viscères (écho): foie, pancréas, reins, rate,…
- Croissance des os: écho, RX ;

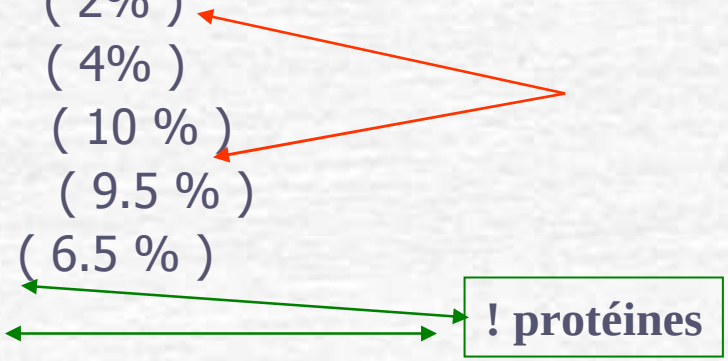
Les courbes de croissance

Auteurs	poids	taille	PC	« type »:in utero au terme ou en postnatal -> 60 semaines	Autres paramètres
Lubchenco 1966	22 %	11%	10 %	**Diagnostic**	**Index pondéral**
Usher-Mc Lean 1969	26 %	8 %	6 %	**Diagnostic**	
Babson 1970-1976	14 %	8 %	9 %	**Diagnostic**	
Gairdiner 1971	17 %	4 %	4 %	**Diagnostic Et postnatale**	
Battisti 1990	13 %	7 %	6 %	**Diagnostic Et postnatale**	**Index pondéral, CBG, CBG/PC, Pli tricipital, index SNC, viscères, muscles**
Dombrowski 1996	13 %	5 %	4 %	**diagnostic**	

Une population est « normale » si le CV < 19%, et si la moyenne = médiane = mode

Corrélations mathématiques de la croissance postnatale selon les indice cliniques

- P g sans RCIU = 174 APC s – 3665 (13 %)
- P g avec RCIU = 148 APC s – 3894 (18 %)
- T cm = 0.95 APC s + 11.53 (7 %)
- PC cm = 0.61 APC s + 9.72 (6 %)
- CBG cm = 0.26 APCs – 1.685 (2%)
- **CBGcm / PCcm** = 0.56 APCs + 6.5 (4%)
- dPg / dT cm = 18.5 APCs – 404 (10 %)
- **dP g / dPCcm** = 44 PCAs – 1138 (9.5 %)
- dT cm / dPCcm = 0.094 APCs – 1.543 (6.5 %)
- dPCcm = 0.1598 Pt in g/kg/j + 0.253
- dTcm = 0.336 Pt in g/kg/j + 0.253
- Index pondéral: uniquement à la naissance;
- Index de masse corporelle: pas avant 34 s APC



Corrélations des croissances tissulaires

- H Lobes frontaux mm = 0.864 APC s – 5.411
- H foie mm/s = 8.7 (1.25 si retard de croissance); in utero=1 (0.8);
- Volume splénique cm3/s = 1.8 ; in utero= 3.9 (0.6);
- Volume rénal cm3/s = 14.9 (2.9 si retard de croissance); in utero = 1.2 (0.7);
- Hauteur pancréatique mm/s = 0.26 (0.2 si retard de croissance); in utero = 0.13 (0.1);
- Largeur cervelet mm/s = 1.75 (1 si retard de croissance); in utero = idem (0.7);
- Surface cervelet mm2/s = 110 (85 si retard de croissance); in utero = 6.3 (5);
- Masse musculaire g = 51.58 APCs - 1299 (30.46 APCs – 70.8 si rc) ; in utero = 44.5 APCs – 1050 ;

Equivalences dans les indices des croissances tissulaires

1 cm PC	1200 (250) kcal	1 mm Lobe frontal
1 g cerveau	13.3 (9) kcal	18.6 (12) si retard croissance
1 g muscle	8.7 (1.6) kcal	19.5 (9) si rc
1 g poids	4.8 (0.6) kcal	8.9 (1) si rc
1 cm taille	800 (40) kcal	1280 (145) si rc
1 mm pli cutané tricipital	395 (108) g poids	25-30 graisses
1 cm CMBG	445 (94) g poids	98 (21) g muscles
1 g poids	0.086 g protéine	0.15 g graisse

Points intéressants concernant la croissance foetale

- La dépendance à la fonction placentaire (CDO2 et contenu protéique et synthèse protéique; les hormones placentaires et foeto-placentaires);
- La dépendance à la glycémie maternelle
- La nourriture fœtale: sa « voie » et sa composition
- Le parcours spontané de la croissance:

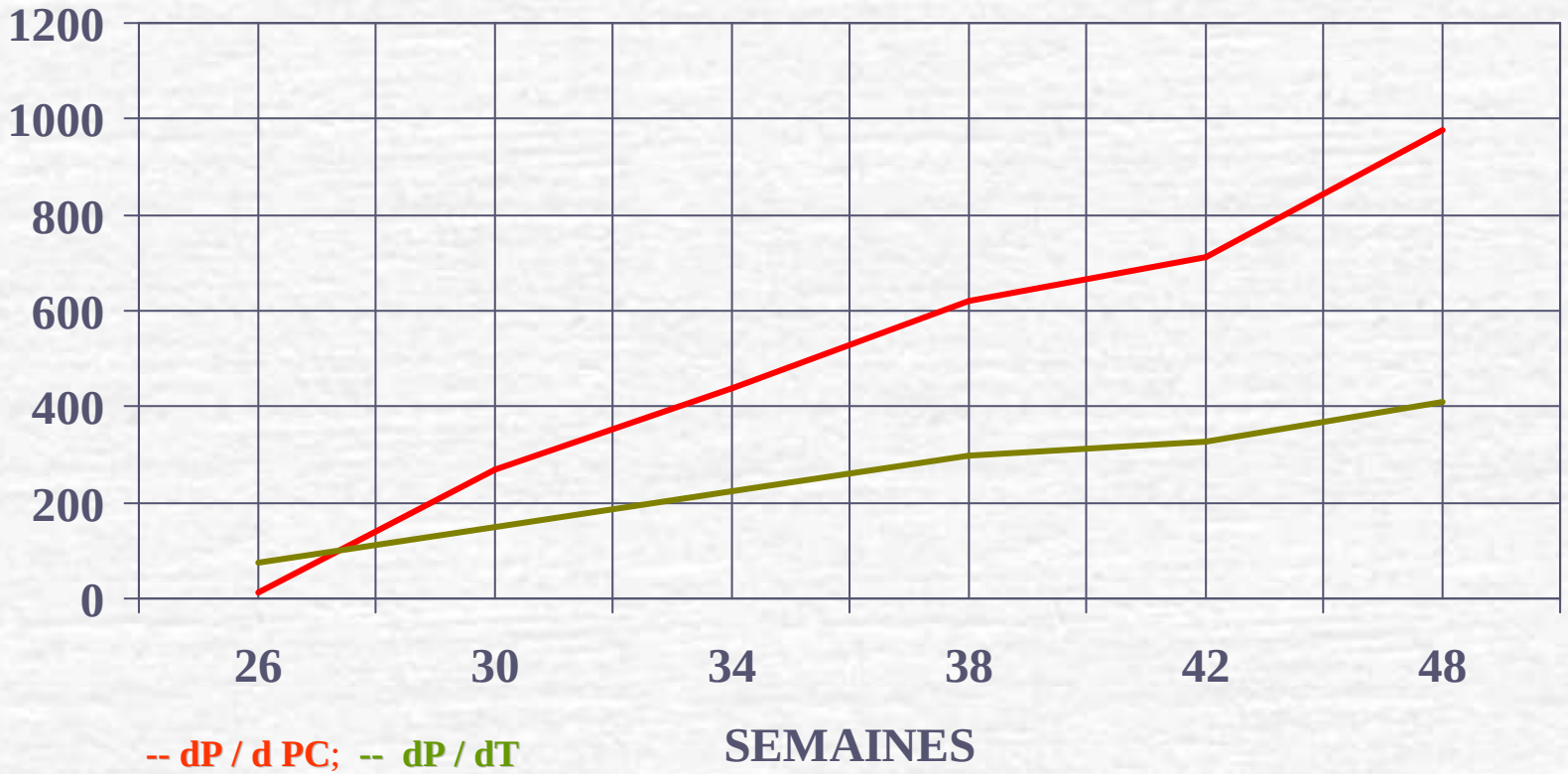
  →imposition du ralentissement pour les gains en PC et en taille;

  → les vitesses de croissance sont différentes suivant les tranches d'âge considérées;
- La répercussion bénéfique de la restriction placentaire après 35 semaines: **si CDO2 reste suffisant, c'est la préparation à la vie extrautérine !**

Points intéressants de la croissance foetale

apports	AA = 25-30 %	Glucose+lactate = 70 %	Lip = AG essentiels < 2 %
Gains moyens sur la grossess	**dP = 170 g/sem**	**dT = 1 cm/sem**	**dPC = 0.6 cm**
< 30 semaines	145g	1.13 cm	0.9 cm
30-32	170 g	1.2	0.7
32-34	208	1.23	0.8
34-36	242	1	0.7
36-38	213	0.8	0.5
38-40	143	0.7	0.33
40-42	70	0.25	0.17
Gains moyens sur ces périodes	dP: variable	Dt: variable	dT: variable

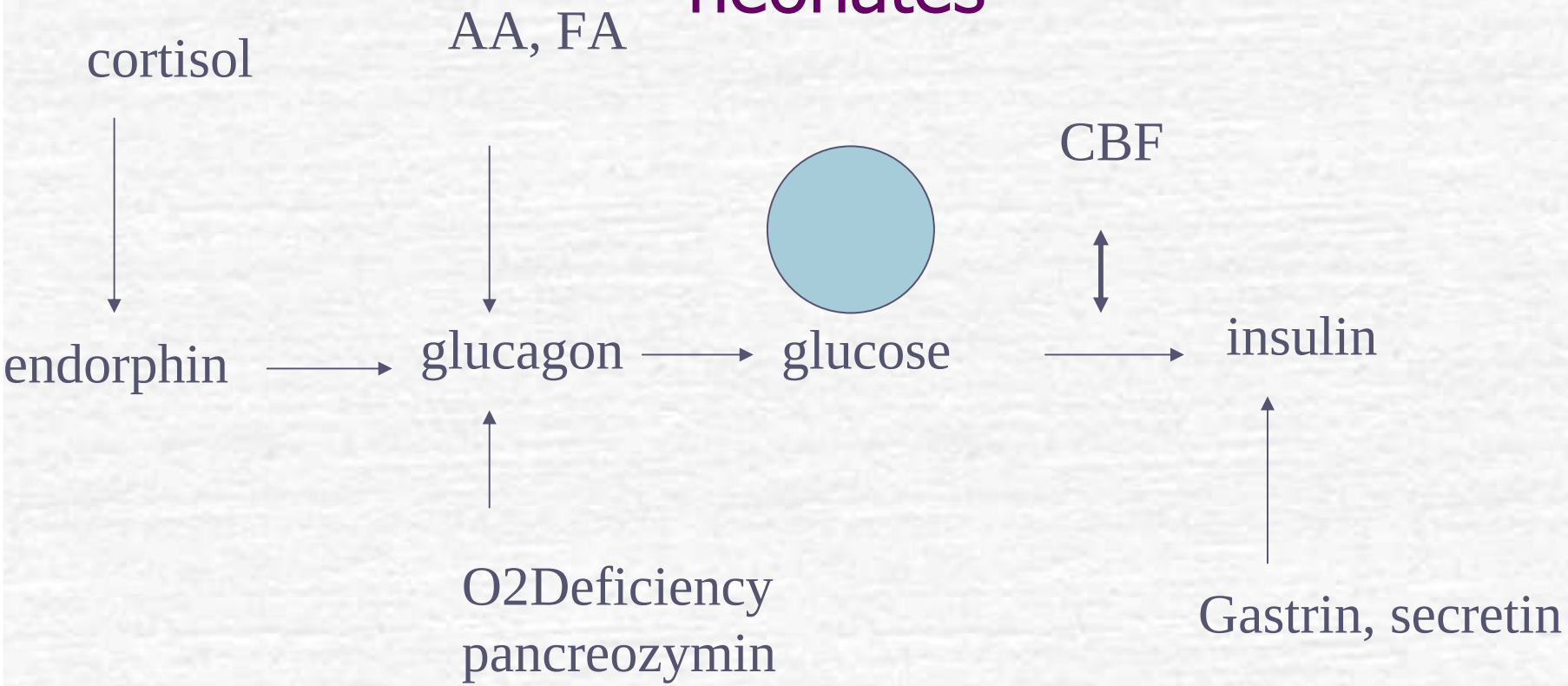
Appréciation de la croissance postnatale: dP/dPC et dP/dT



Les « nourritures » fœtales et postnatales

kcal/kg/J	120	120
QO2 ml/kg/m	6-8	6-8
% Pt	20-30	10-15
% Lp	< 5	25-30
% Gl	60-70	50-60

Insulin and glucagon relationships in neonates

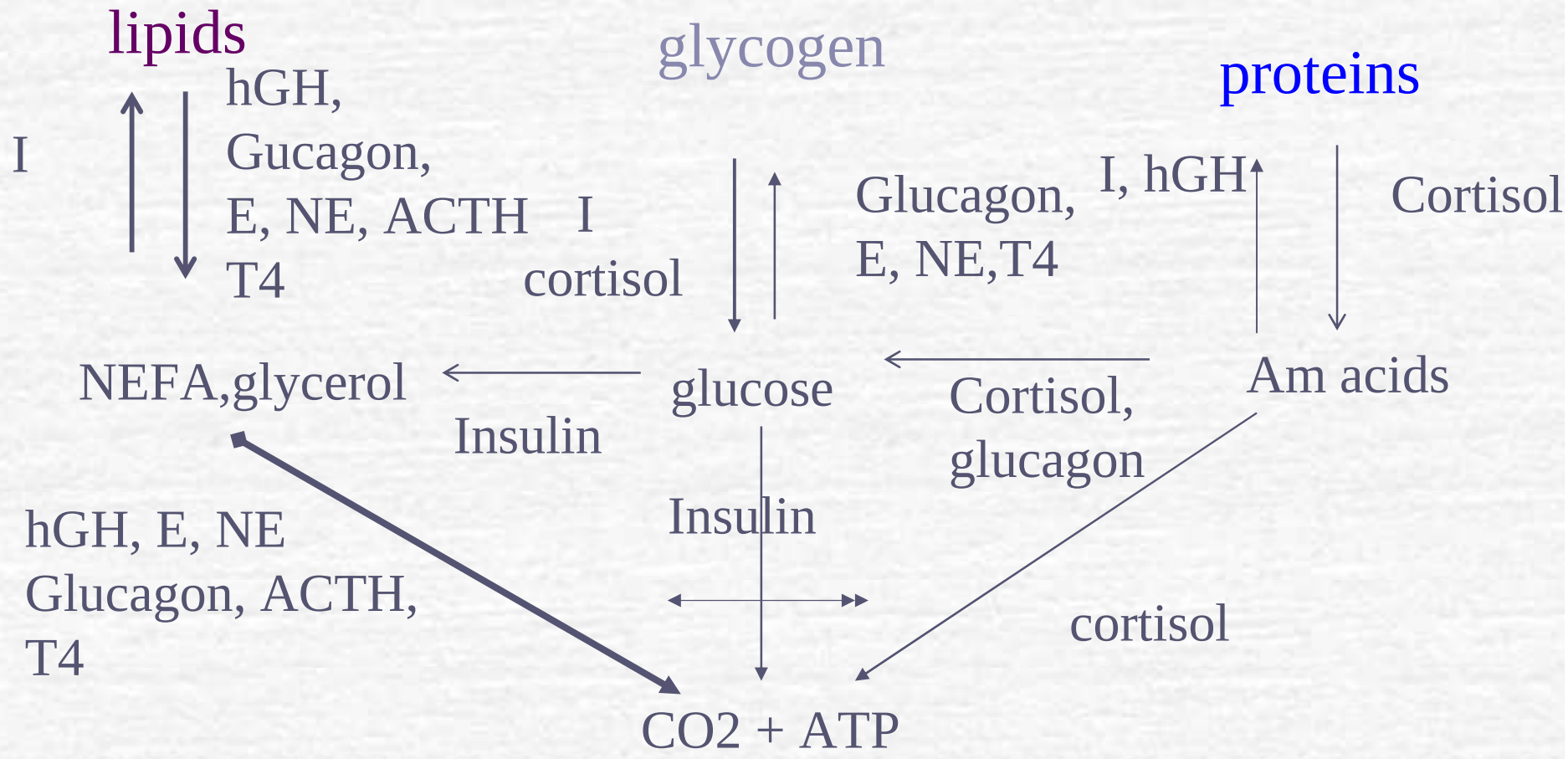


Glucose acute route in cells

In normal cell: G + O2 ⟶ ATP + CO2 + H2O

In cell with mitochondrial impairement: G + O2 ⟶ ATP + CO2 + lactic acid

Pathways relationships



Specific abnormalities

- ***In Growth retardation:***

- increase their hemoglobin;
- Relative high cerebral mass;
- Decrease of P-pyruvate kinase

- ***In very low birthweight:***

- lower effect of insulin on glycogenesis and on glycogenosis; these activities increase afer 34-40 w;
- Limited gluconeogenesis;
- Inappropriate (in excess) endogenous adrenergic activity;

From biochemistry to fetal medicine glucose

- Insulin secretion
- Insulin receptors
- Insulin function
- hGH secretion and function
- The role of placenta
- Glucose in the mother
- Drugs taken by the mother

- **<u>Global growth of the fetus:</u>**

< BW g = 17 GA – 3665

< BL cm = 0.95 GA + 11.3

< HC cm = 0.61 + 9.72

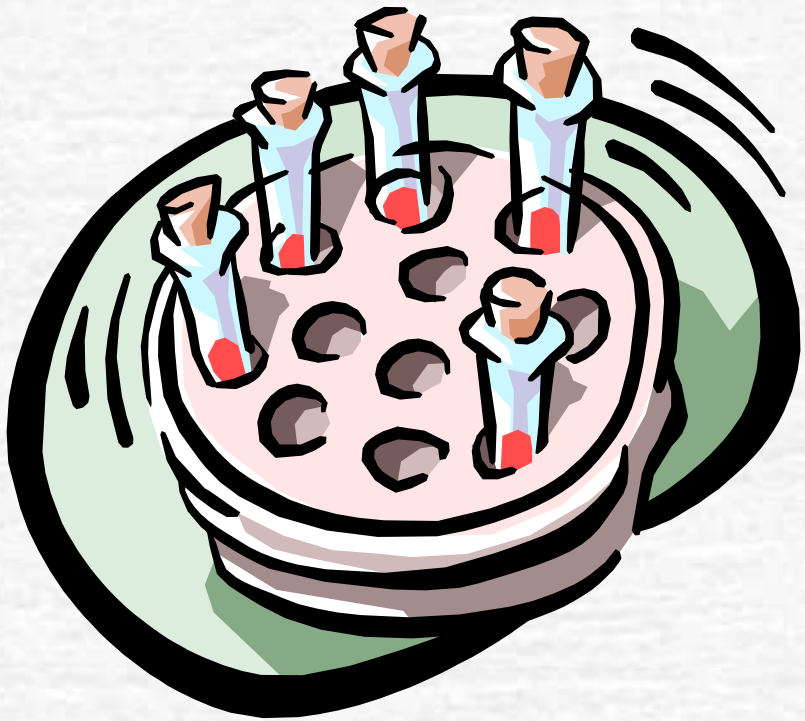
- **<u>Nutrition of the fetus: through the liver</u>**

- AA = 25 – 30 %

- CH = 60 – 70 %

- LP < 3 %

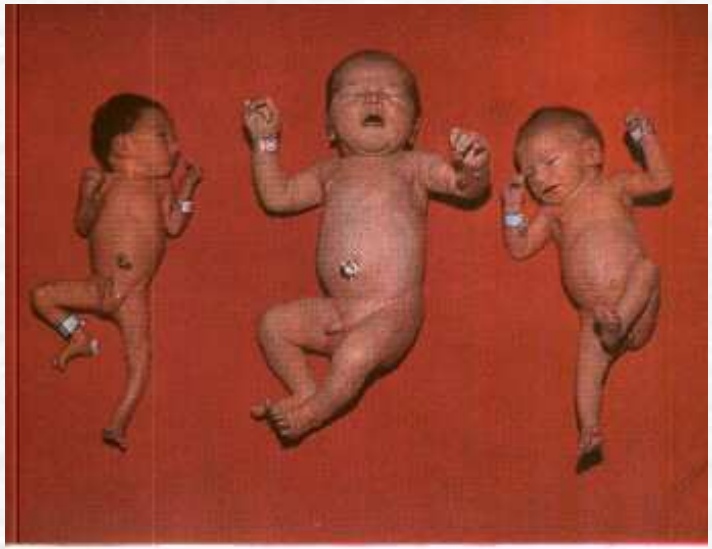
The fetal growth



- **MRO2**: 6 – 8 ml/kg/m
- **BMR and MRO2** increase with GA
- **CH:**

  glucose (proportional to mother) and lactate (from the placenta)
- **High de novo synthesis of lipids**

Transition from fetal to postnatal life



Time present and time past
Are both perhaps present in time future,
And time future contained in time past.

Burnt Norton
Thomas Stearns Eliot.

- **<u>Composition of body:</u>**

- brain : 14- 15 %
- Bones: 25 – 30 %
- Muscles: 20- 25 %
- Skin: 10-20 %
- Intestines: 15 – 20 %
- < 2 % : heart, lungs, kidneys
- Pt: 7 – 10 %;
- Lp: 2 – 15 %;
- CH: 0.7 – 1 %

Extra-uterine life: energetic balances

%	**retained**	**Expended**	**lost**
Kcal	46	42	12
CH	11	88	1
Pt	60	23	17
Lp	70	10	20

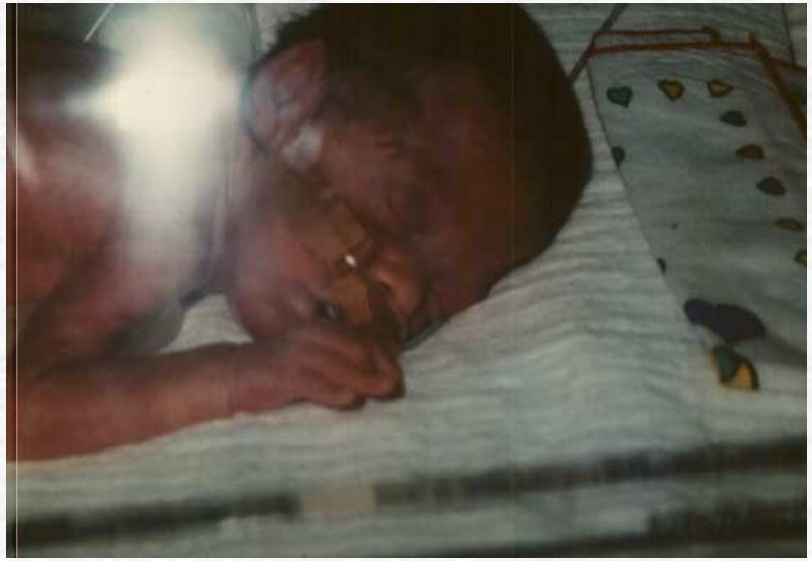
Extra-uterine life after IUGR: basal metabolic rate (Sinclair JC)

	Non growing	**growing**
BMR kcal/kg/d	51.6 (2.3)	64.5 (4.9)
CH %	66.6 (2.5)	80.2 (4.6)
Lp %	24.1 (3.9)	13 (5)
Pt %	9.1 (2)	6.6 (0.8)

Extra-uterine life: Costs for growth

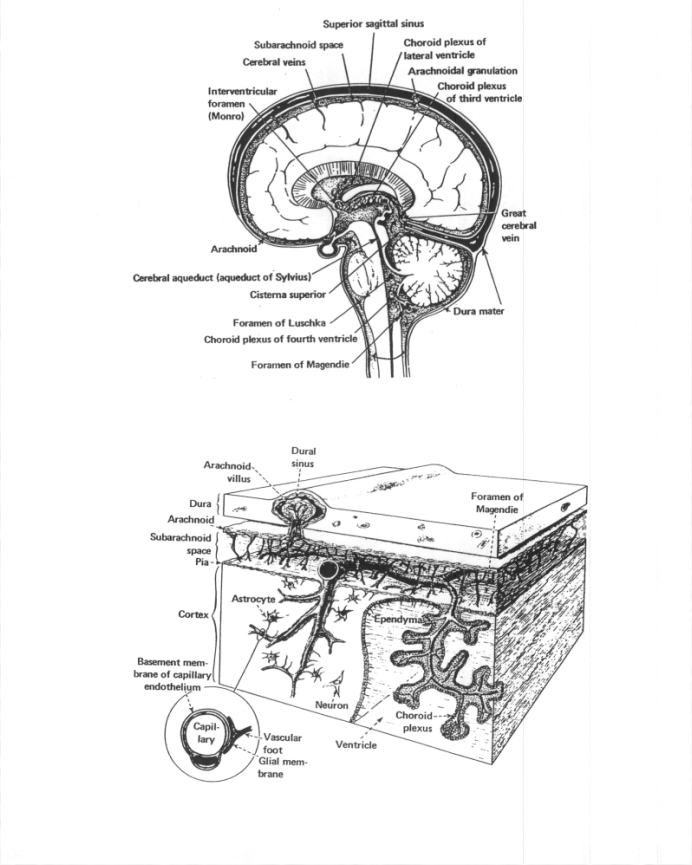
	Normal growth	Retarded growth
g BW	5 (2.7)	9 (4.2)
G Pt	7.5	7.5
G Lp	11.6	11.6
Cm BL	800 (335)	1280 (600)
Cm HC	1150 (541)	1170 (215)
G brain	34 (18)	39 (23)
G muscles	18 (210)	20 (9)

The basal metabolic rate



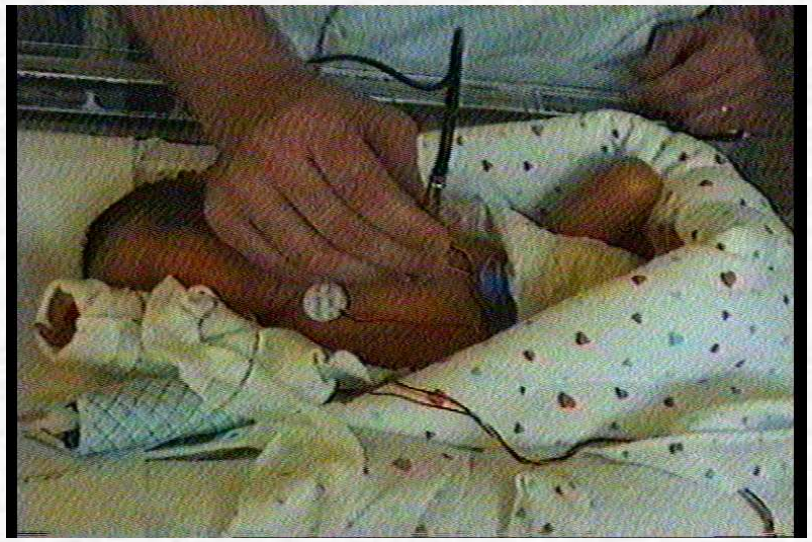
- Correlated to HR and CRO2, wich are correlated to cellular levels of activites
- Correlated to proteins turnover, which is correlated to enzymes turnover (high in brain and liver, low in muscles)

Specific aspects in brain



- Total body's requests are due to brain for 40 % from caloric and O2 needs, and 56 % from proteic needs.
- Role of insulin and hGH
- Particular relationship between flow and cells

Specific aspects for liver , pancreas and intestines

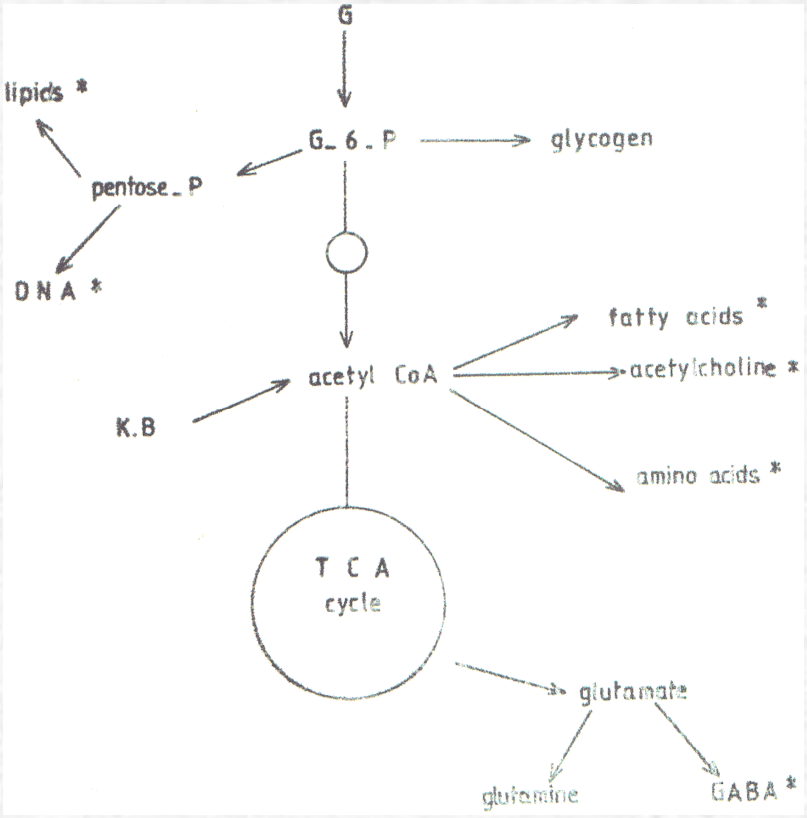


- Blood flow autoregulation
- Biochemical activities in liver
- Biochemical activities in intestines
- Biochemical activities in pancreas

Control of insulin secretion

-	+	+
secretion catecholamines, somatostatin	**secretion** glucose, fructose	**resistance** GH, cortisol, T4, HPL, glucagon, endorphins
Hypo-K+	AA, Leu, ILeu	KB, acidosis, hypoxia, FFA
Beta-blockers, chlorpromazine, DPH, diazoxide	Kupfer cells, Xth nerve, beta-stimulators	Prematurity,
	Glucagon, pancreozymin	
rest	exercise	

Central role of glucose for energy an synthesis

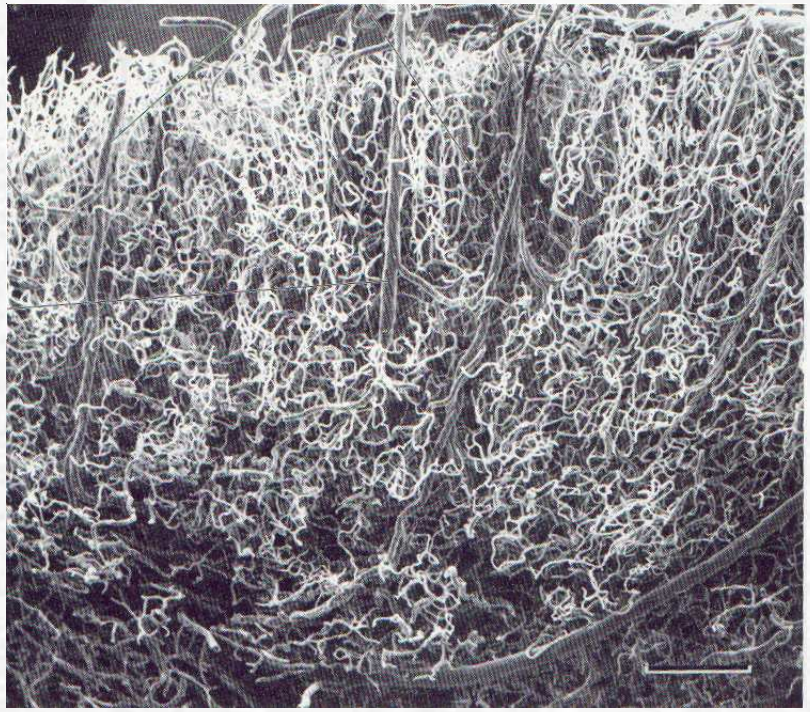


- ATP and 5-Pentose;
- In- and out-cells composition
- Defenses against FR and EAA
- BMR
- Muscles (FFA) and intestines (glutamine and KB) have alternatives

Influence of gestational age on CRO2 and CRG

- Fetal glucose uptake
- Insulin receptors: number and affinity
- CMR O2, glucose; CBF; SBP
- Hb level
- Enzymes level and turnover
- Adipose tissue
- Placenta competence

glycaemia
importance of quantitative and velocity of variations



- **Hypoglycaemia:** loss of CBF autoregulation, isoelectric EEG from energy failure and enhanced vulnerability, concerned structures are layers 3,5,6 and thalamus,…
- **Hyperglycaemia:** CBF, pH, diuresis
- **Attention to high Hb levels !**
- **Attention to «large heads«**

Treatments of glucose unstability: hypoglycaemia

- **Searching the specific explanation**
- **Glucose administration iv:** 1 cc /kg G5% will increase glycaemia of 10 mg/dL
- **Stimulating neoglucogenesis:** glucagon IV or IM (bolus 200 microg/kg, continuous infusion of 8 microg/kg/hr)
- **Antagonizing insulin**: hydrocortisone 5 mg/kg/12h
- **Correct parameters**: pH, respiratory and circulatory functions, liver function, mode of feeding, brain requirements

Glucose and O2 needs in the distressed brain

Cbf ml/100g/m	[aG] ->I	[aG]-> W	[aO2]->I	[aO2]-> W
20	21	36	10	22
15	30	50	13	29#
10	40	72	19	44#
2	82	143	28#	62#

Treatments of glucose unstability: hyperglycaemia

- **Searching for a specific explanation**
- **Insulin continuous infusion:** 0.5-0.8 iu/kg/h
- **Decrease glucose input down to calculated required amounts for brain:**

  first calculate brain mass according to head circumference, then plot glucose input to brain demands (3-5mg/100g/m)

Elements of perinatal nutrition

- The proteins
- The carbohydrates and lipids
- Cotside metabolic balance
- Placing these aspects in clinics

Taking into account the body weight progress in the neonatal period and infancy for later mental development

- **IQ global at 7.5 – 8 years**= dBWg/kg/day + 84.5 ; this should be comprised between 14.5 and 17 g / kg / day.
- **IQ verbal at 7.5 – 8 years** = 1.29 dBW/kg/day + 79.
- But also other parameters … (i.e. head circumference at 9 months, mother status, …)

The place of proteins in perinatal and neonatal growth

- Proteins have a central role in nutrition and in growth. There is none storage, even if their turnover is high.
- d **BW** g/kg/d = 3.44 Pt **intake** g/kg/d + 7.34 (Rahia, 1994)
- Pt **needs** g/kg/d = 3.5 – 0.00354 **GA** (Rahia, 1994)
- Pt **synthesis** = 0.0269 GA + O.785 (Widdowson, 1977)
- Pt synthesis = 0.173 **BMR** – 2.56 (Beaufrère, 1990)
- d BW g = 3.6 Pt intake + 0.095 Energy intake – 0.0047 BW + 1.7 (Heird, 1989)
- d **PC** = 0.1598 Pt intake + 0.253 (Battisti, 1990)
- d **BL** = 0.336 Pt intake + 0.253 (Battisti, 1990)
- Pt **content % BW** = 0.7 GA + 1.86 (Widdowson, 1977):
- VO2 directly correlated to body content in proteins (Battaglia, 1997)

Proteins in the fetus and in the newborn

- Proteins are the main component in nutrition;
- Even if proteins are done of aminoacids, proteins and aminoacids need to be considered in different ways;
- Proteins turnover is linked to metabolic rate and to oxygen consumption

Aminoacids in fetal life

- Aminoacids coming from mother: the sources are her intakes and her muscles;
- From these sources, 70 % go to the fetus and 20 % to the placenta;
- [Fetus / Mother] AA ratio is 1.5 - 2
- Three types of transporters for AA in the placenta = A, L, ASC;
- This transport is depending on delivery of O2 to the fetus;

when O2 delivery the fetus decreases, AA delivery of AA also decreases.

Aminoacids and tissues preferences

Liver:	Muscles:	shared:
Phe,Try, Thre, Lys, Met, His, Arg	Leu, Ileu, Val	Glu+ gutamic acid, Gly, Pro, Aspartic acid, Tyr, Ala

Alanine:from muscles and intestines to liver;

Glutamine: important for intestines and kidneys;

Some AA are toxic, other protect the brain

Difficulties in neonatal nutrition

- «**fetal milk**» contains 25-30 % of AA, 60-70 % of carbohydrates (glucose and lactate) and less than 3 % of EFA; and that fetal milk is passing essentialy through the liver.
- After birth, the offered nutrition is very different from fetal period;
- Enteral feeding should always be encouraged: from minimal or trophic feeding to total feeding;
- A transitional phase of IV feeding is frequently needed;
- Babies below 30 weeks, IUGR and some other conditions may present difficulties during the first week of life;
- About 30 % of babies below 30 weeks have IUGR; and many of these experience growth retardation during the neonatal period;

Requirements according to gestational age:

values / KG / day

GA	TMR kcal	BMR kcal	needs g	Pt syn g
24	82	35	3.42	1.43
28	84	38	3.40	1.54
32	86	41	3.38	1.65
36	88	44	3.36	1.76
40	90	47	3.34	1.87
44	92	50	3.32	1.98

Cerebral requirements (values / 100g CM)

	Pt g	Lp g	Kcal
IUGR	2.8-4	4.2-6	82
AGA	2.1-3	3.2-4.5	67

Proteins synthesis in the body

	25	30	35	40	% VO2
Brain (14)	1.6	1.5	1.4	1.3	9
Heart (0.4)	0.6	0.6	0.6	0.6	6
Lungs (0.8)	O.6	0.7	0.7	0.8	?
Muscles (24)	35	34	33	33	14
Liver (4)	14	14	14	15	16
Intestines (20)	30	29	28	28	11

% body weight

The proteins turnover

- **3 Purposes of that turnover**:

  - primary protection,
  - losses replacements,
  - degradations of peptides;

- **Within tissues**:

  in fetus and neonate, the proteins turnover is very high in the liver (50 %) and in the brain (44 %);Proteins turnover is low in the other tissues (in muscles= 3.2 %).

  These values are different in the adult: 57 % in liver, 50 % in kidney, 17 % in brain, 18 % in heart, 15 % in skeletal muscles.

- **Within body**:

  proteins turnover is mainly represented by the muscles and intestines;

Qualitative perinatal growth

- **Overall:**

1 g tissue growth = 3 – 3.5 kcal;
0.086 g PT;
0.105 G Lp;

1 g brain <- 0.67 kcal (0.89 if IUGR);
1 g muscles <- 0.69 kcal

- **Protein synthesis:**

  is correlated to activities of hormones (hGH, somatomedins, insulin , T4), to a caloric intake well proportionated and higher than 70 kcal/kg/d, and activities of skeletal muscles.

- **The quantitative needs of proteins**

  can be estimated to values comprised between 2.5 (TPN) to 3.5 (EN) g/kg/d and these should be accompanied by 35 kcal/g of proteins;

- **The qualitative needs of proteins**

  should contain 48 % essential AA (mixture of casein and albumin).

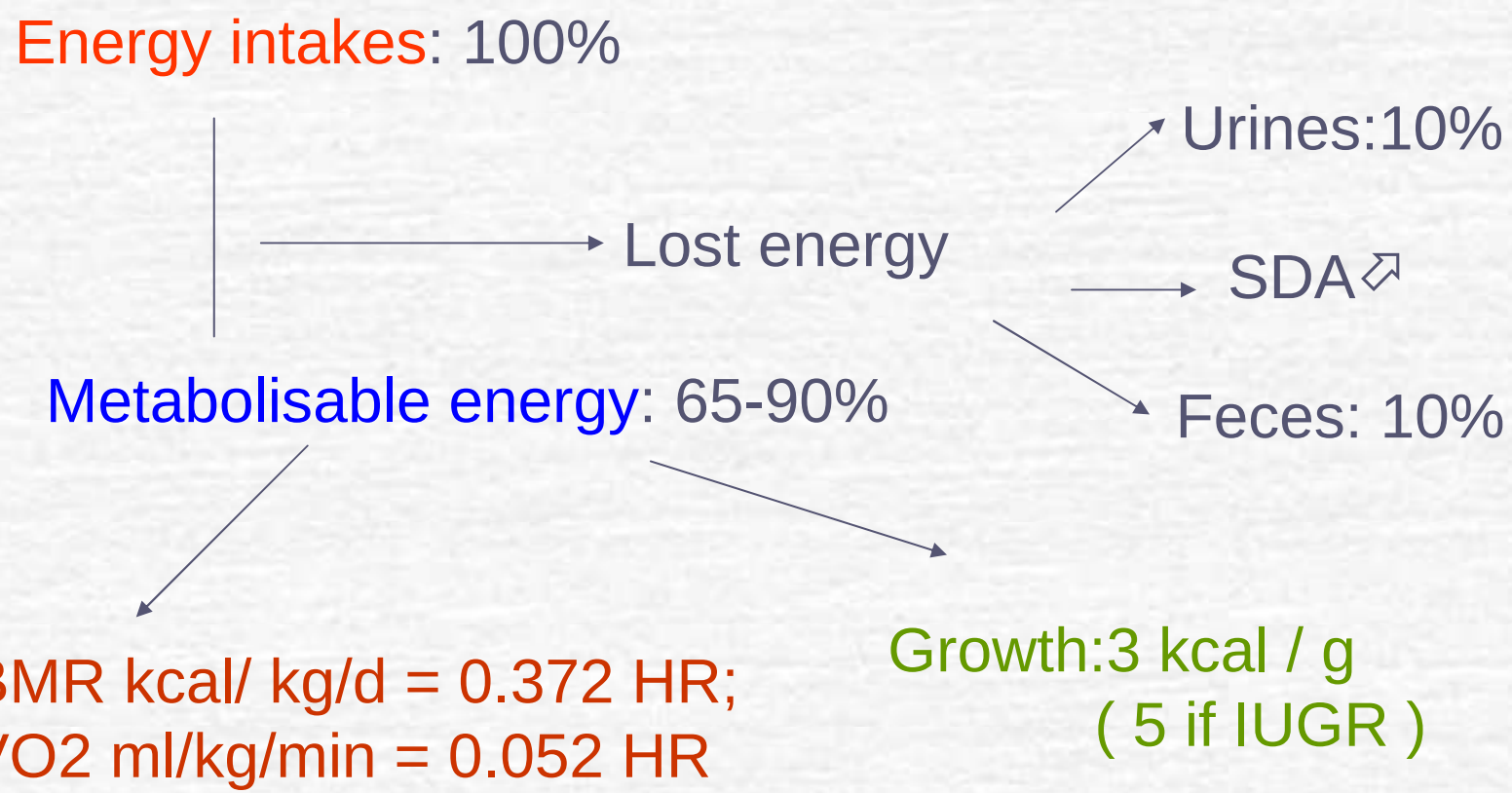
Ongoing difficulties

- Questions and choices:
  - immediate or early minimal or trophic feeding;
  - prokinesis (erythromycin, cisapride);
  - glutamine, IV lipids, multivitamins;
  - oral stimulation;
- Ongoing difficulties:
  - growth retardation;
  - osteopenia;
  - oxydative stress;
  - infection;
  - hormones;

Not all proteins have the same values

Types of milk: Efficiency →	d BW g / g Pt	d Length Cm / 100g Pt	d HC Cm / 100g Pt
Breast Milk	10.5	4	3.9 *
PreTerm Formulas	10.9 *	4.8 *	3.3
Hydroysates formulas	7	4	3.4
Term formulas	8	5 *	3.4

The cotside metabolic balance



Simple rules to assess body growth

- **Ratio δ BWg / δ HC cm**

  = 44 PCA w – 1138

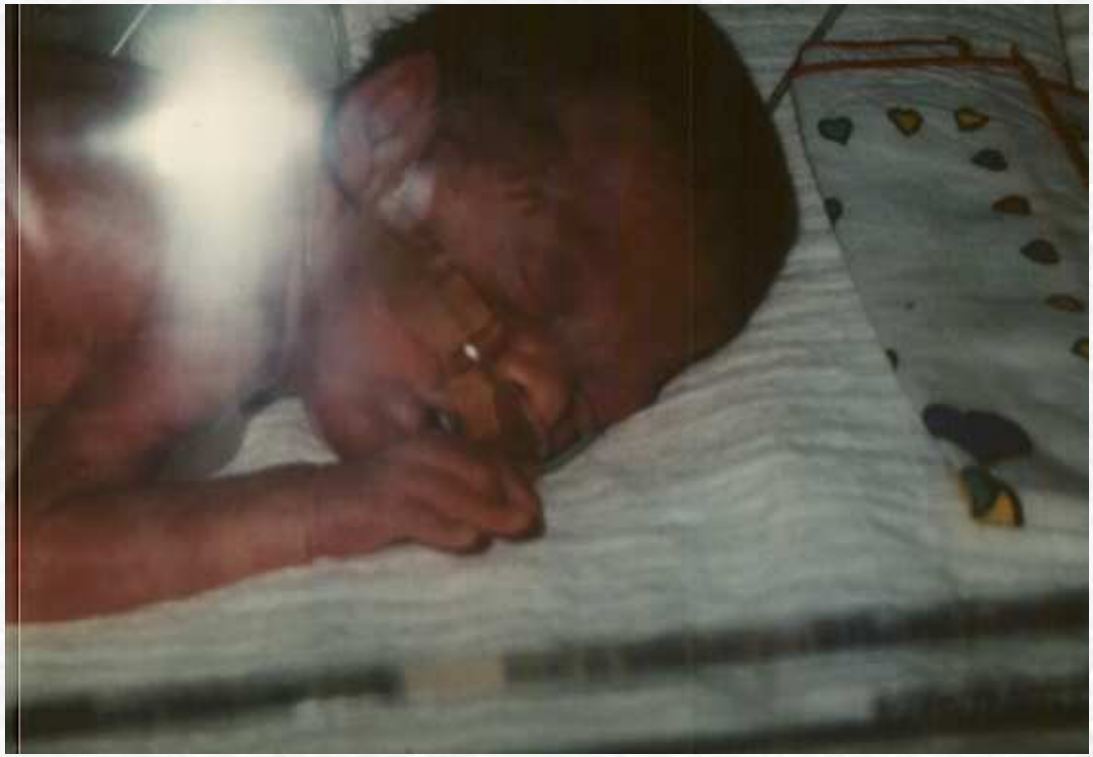
  i.e: at 28 PCA, this ratio = 94 or 94 g of BW gain = 1 cm HC gain;

- **Ratio LAC/ HC**

  = [0.56 PCA w + 6.5] / 100

  i.e: at 28 PCA, this ratio = 22.2 or a HC of 25 cm should correspond to a LAC of 5.6 cm

Please, keep my nutrition as good as possible, thank you…



Glimses to perinatal nutrition

- The proteins
- The aminoacids
- Metabolic balance
- Placing these aspects in clinics

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- d BW g/kg/d = 3.44 Pt intake g/kg/d + 7.34 (Rahia, 1994)
- Pt needs g/kg/d = 3.5 – 0.00354 GA (Rahia, 1994)
- Pt synthesis = 0.0269 GA + O.785 (Widdowson, 1977)
- Pt synthesis = 0.173 BMR – 2.56 (Beaufrère, 1990)
- d BW g = 3.6 Pt intake + 0.095 Energy intake – 0.0047 + 1.7 (Heird, 1989)
- d PC = 0.1598 Pt intake + 0.253 (Battisti, 1990)
- d BL = 0.336 Pt intake + 0.253 (Battisti, 1990)
- Pt content % BW = 0.7 GA + 1.86 (Widdowson, 1977)
- VO2 = 62 + 2 ml/kgProtein/min (Battaglia, 1997)

Aminoacids in fetal life

- Aminoacids coming from mother: the sources are her intakes and her muscles;
- From these sources, 70 % go to the fetus and 20 % to the placenta;
- [Fetus / Mother] AA ratio is 1.5 - 2
- Three types of transporters for AA in the placenta = A, L, ASC;
- This transport is depending on delivery of O2 to the fetus; when O2 delivery t the fetus decreases, AA delivery decreases also.

Aminoacids in fetal life: the placenta transport systems

- A : GABA, glycine (return from serine*, leucine, isoleucine and valine), serine*, threonine*, gutamine* and alanine*;
- L: proline, serine*, threonine*, glutamine*, alanine*, leucine, isoleucine,valine, phenylalanine;
- ASC: serine*, threonine*, glutamine*, alanine*
- * use the three types of transporters;
- Remember that « **fetal milk** « contains 25-30 % of AA, 60-70 % of carbohydrates (glucose and lactate) and less than 3 % of EFA; and that fetal milk is passing essentialy through the liver.

Aminoacids and tissues preferences

Liver:	Muscles:	shared:
Phe,Try, Thre, Lys, Met, His, Arg	Leu, Ileu, Val	Glu+ gutamic acid, Gly, Pro, Aspartic acid, Tyr, Ala

Alanine:from muscles and intestines to liver;

Glutamine: important for intestines and kidneys;

Some AA are toxic, other protect the brain

Aminoacids in the cells

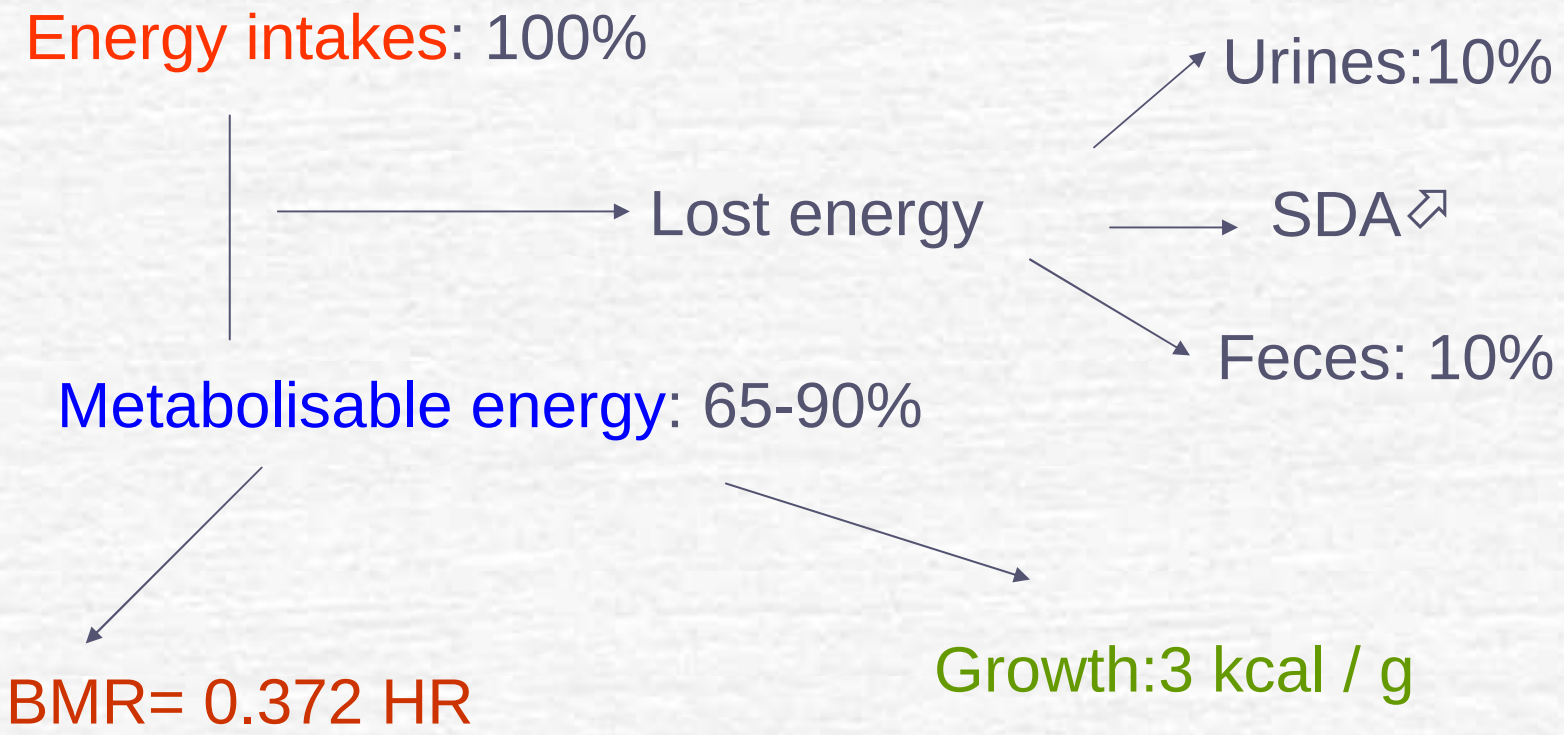
- The monitors are the liver and the muscles;
- The possible biochemical routes in a cell are:

- NH3, urea;
- Lactate, pyruvate;
- Proteins;
- ATP, glucose;
- Hormones;
- Neurotransmitters;
- 3-methyl-histidine

Not all proteins in the intakes are the same

Source	EF BW g/g Pt	EP BL Cm / 100g Pt	EP HC Cm / 100g Pt
Breast Milk	10.5	4	3.9 *
PreTerm Form	10.9 *	4.8 *	3.3
Hydrolysates Form	7	4	3.4
Term Form	8	5 *	3.4

The «at bed » metabolic balance



Taking into account the body weight progress in the neonatal period and infancy for later mental development

- IQ global at 7.5 – 8 years= dBWg/kg/day + 84.5 ; this should be comprised between 14.5 and 17 g / kg / day.
- IQ verbal at 7.5 – 8 years = 1.29 dBW/kg/day + 79.
- But also other parameters … (i.e. head circumference at 9 months, mother status, …)

The proteins turnover

- **3 Purposes of that turnover**:

  - primary protection,
  - losses replacements,
  - degradations of peptides;

- **Within tissues**:

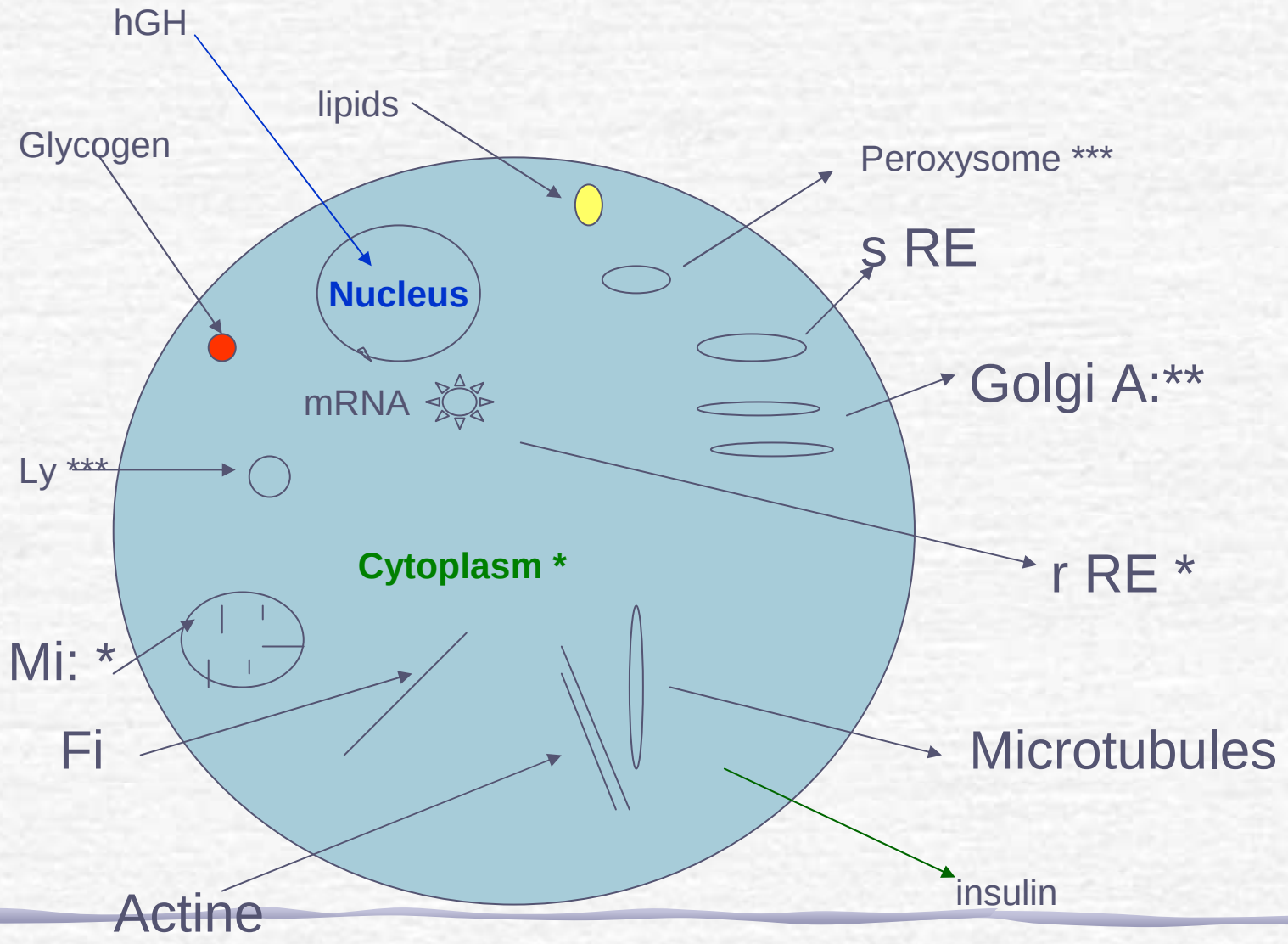
  in fetus and neonate, the proteins turnover is very high in the liver (50 %) and in the brain (44 %);Proteins turnover is low in the other tissues (in muscles= 3.2 %).

  These values are different in the adult: 57 % in liver, 50 % in kidney, 17 % in brain, 18 % in heart, 15 % in skeletal muscles.

- **Within body**:

  proteins turnover is mainly represented by the muscles and intestines;

Structure of any cell



Qualitative perinatal growth

- **Overall:**

  1 g tissue growth = 3 – 3.5 kcal;
  0.086 g PT
  0.105 G Lp;

- **Protein synthesis:**

  is correlated to activities of hormones (hGH, somatomedins, insulin , T4), to a caloric intake well proportionated and higher than 70 kcal/kg/d, and activities of skeletal muscles.

- **The quantitative needs of proteins**

  can be estimated to values comprised between 2.5 (TPN) to 3.5 (EN) g/kg/d and these should be accompanied by 35 kcal/g of proteins;

- **The qualitative needs of proteins**

  should contain 48 % essential AA (mixture of casein and albumin).

Cerebral requirements (values / 100g CM)

	Pt g	Lp g	Kcal
SGA	2.8-4	4.2-6	82
AGA	2.1-3	3.2-4.5	67

Requirements according to gestational age:

values / KG / day

GA	TMR kcal	BMR kcal	needs g	Pt syn g
24	82	35	3.42	1.43
28	84	38	3.40	1.54
32	86	41	3.38	1.65
36	88	44	3.36	1.76
40	90	47	3.34	1.87
44	92	50	3.32	1.98

Simple rules to assess body growth

- **Ratio δ BWg / δ HC cm** = 44 PCA w – 1138 (i.e: at 28 PCA, this ratio = 94 or 94 g of BW gain = 1 cm HC gain);
- **Ratio LAC/ HC** = [0.56 PCA w + 6.5] / 100 (i.e: at 28 PCA, this ratio = 22.2 or a HC of 25 cm should correspond to a LAC of 5.6 cm)

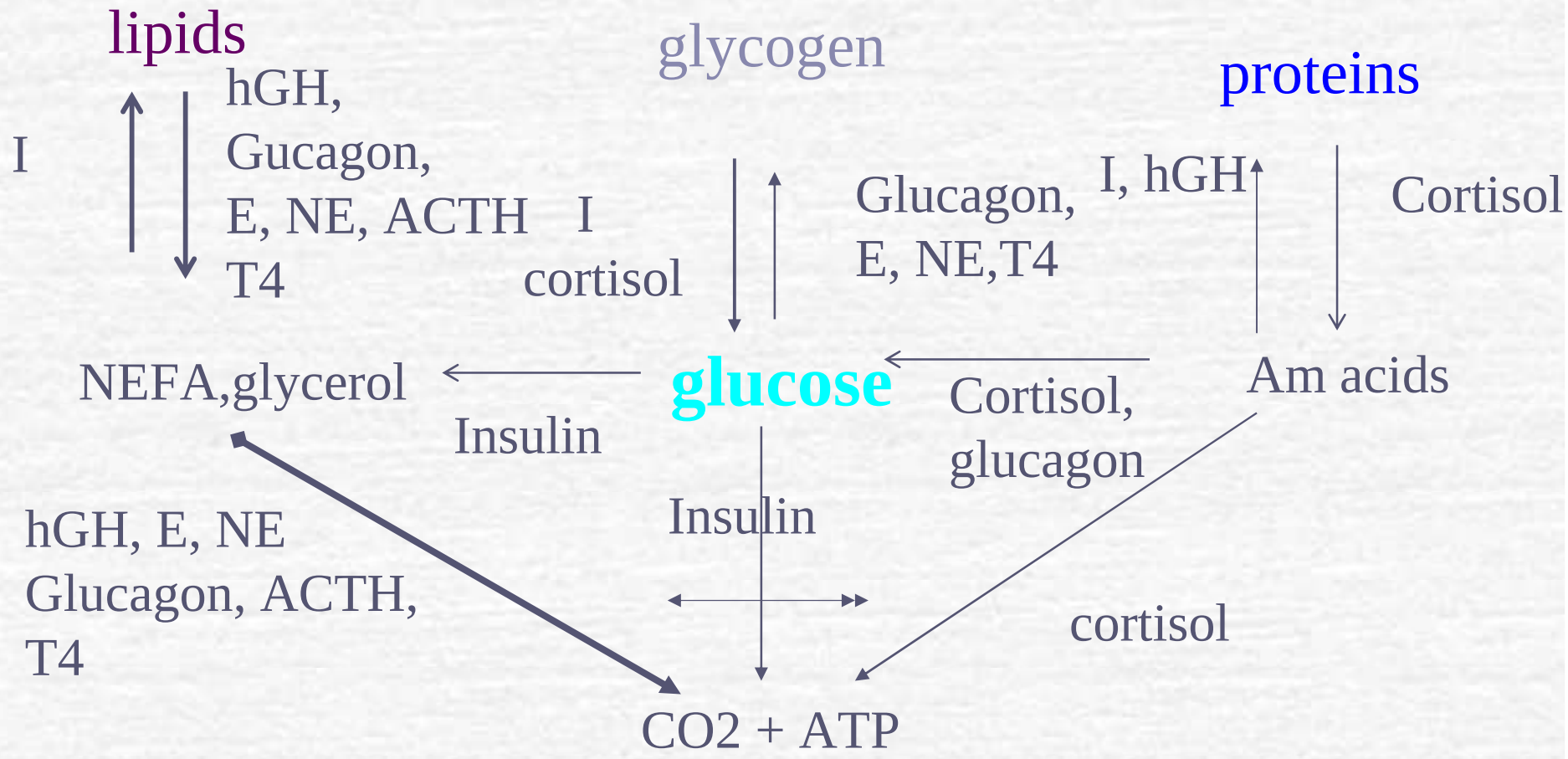
Making a biochemical protocol from aminoacids measurements

- **In blood:** first have a look at the global profile and then think on tissues preferences, mainly the brain, the skeletal muscles, the intestines. This step is important to assess the global health of patient and the adequacy of nutrition. In metabolic diseases, values are 5-10 higher than normal.
- **In CSF:** this is interesting to assess the brain hypoxia, and in some metabolic diseases (see glycine);
- **In urines** this is interesting in presence of high blood NH3, in some cases of muscles diseases and of renal syndromes.

From biochemistry to clinical medicine glucose in neonatal medicine

- With oxygen, glucose is the most important metabolite during « intensive situations «
- There are specific aspects during fetal life
- There are specific aspects in the distressed newborn
- Metabolic regulation is concerning several hormones (insulin, glucagon, hGH, cortisol, NoA , A) and tissues (CNS, the liver, striated muscles, adipose tissue, intestines,…)
- That regulation needs to be integrated to growth and basal metabolic rate.

Pathways relationships



From biochemistry to fetal medicine glucose

- Insulin secretion
- Insulin receptors
- Insulin function
- hGH secretion and function
- The role of placenta
- Glucose in the mother
- Drugs taken by the mother

- **<u>Global growth of the fetus:</u>**

< BW g = 17 GA – 3665

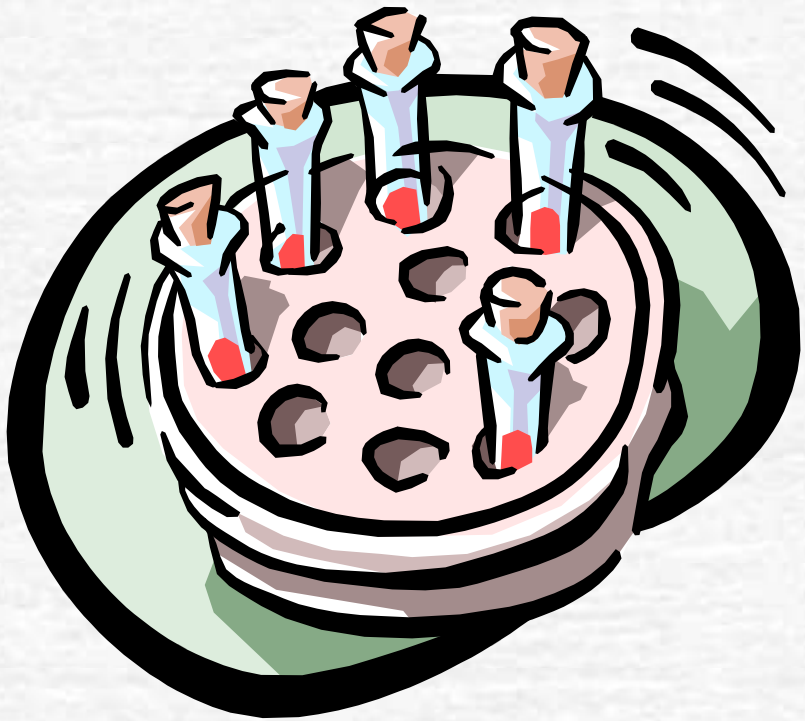
< BL cm = 0.95 GA + 11.3

< HC cm = 0.61 GA + 9.72

- **<u>Nutrition of the fetus: through the liver</u>**

- AA = 25 – 30 %
- CH = 60 – 70 %
- LP < 3 %

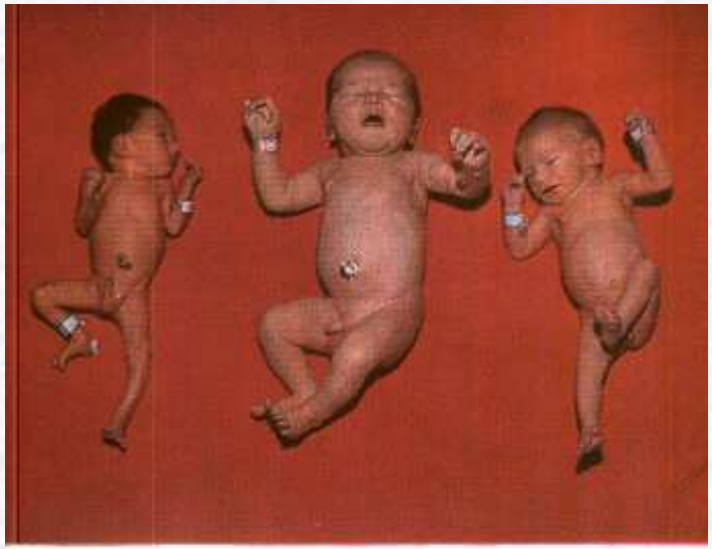
The fetal growth



- **MRO2**: 6 – 8 ml/kg/m
- **BMR and MRO2** increase with GA
- **CH:**

  glucose (proportional to mother) and lactate (from the placenta)
- **High de novo synthesis of lipids**

Transition from fetal to postnatal life



Time present and time past
Are both perhaps present in time future,
And time future contained in time past.

Burnt Norton
Thomas Stearns Eliot.

- **<u>Composition of body:</u>**

- brain : 14- 15 %
- Bones: 25 – 30 %
- Muscles: 20- 25 %
- Skin: 10-20 %
- Intestines: 15 – 20 %
- < 2 % : heart, lungs, kidneys
- Pt: 7 – 10 %;
- Lp: 2 – 15 %;
- CH: 0.7 – 1 %

Extra-uterine life: energetic balances

%	retained	Expended	lost
Kcal	46	42	12
CH	11	88	1
Pt	60	23	17
Lp	70	10	20

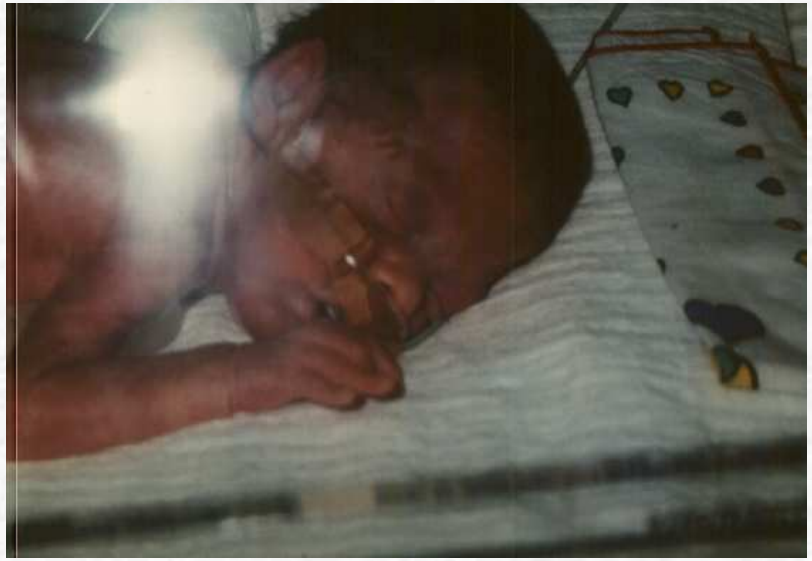
Extra-uterine life after IUGR: basal metabolic rate (Sinclair JC)

	Non growing	**growing**
BMR kcal/kg/d	51.6 (2.3)	64.5 (4.9)
CH %	66.6 (2.5)	80.2 (4.6)
Lp %	24.1 (3.9)	13 (5)
Pt %	9.1 (2)	6.6 (0.8)

Extra-uterine life:Costs for growth

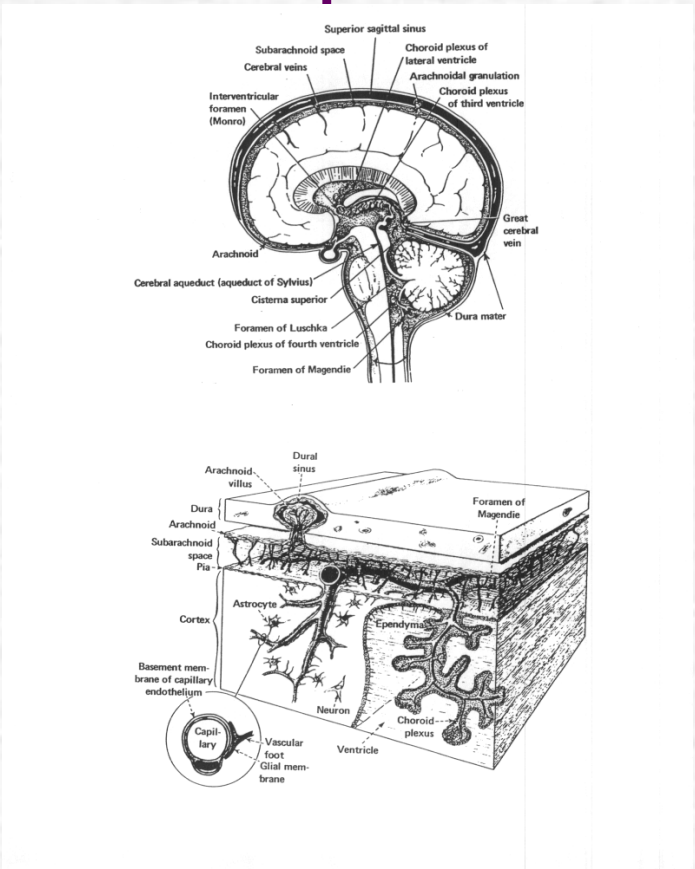
	Normal growth	Retarded growth
g BW	5 (2.7)	9 (4.2)
G Pt	7.5	7.5
G Lp	11.6	11.6
Cm BL	800 (335)	1280 (600)
Cm HC	1150 (541)	1170 (215)
G brain	34 (18)	39 (23)
G muscles	18 (210)	20 (9)

The basal metabolic rate



- Correlated to HR and CRO2, wich are correlated to cellular levels of activites
- Correlated to proteins turnover, which is correlated to enzymes turnover (high in brain and liver, low in muscles)

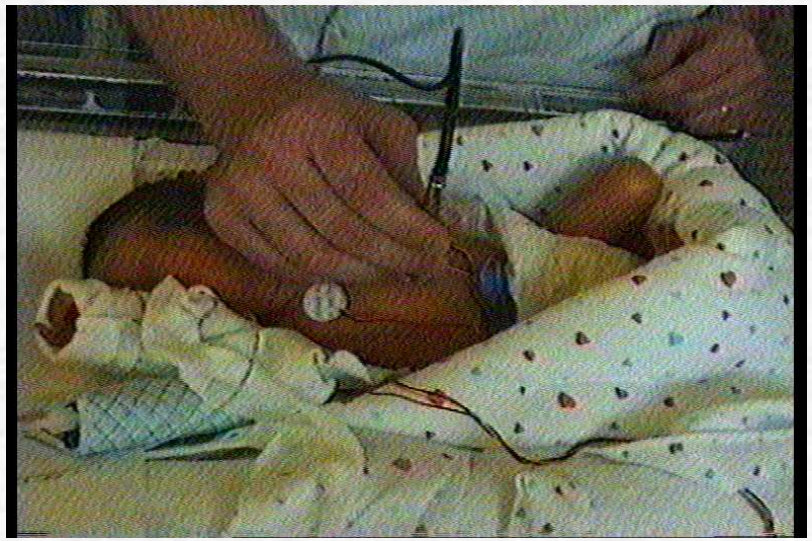
Specific aspects in brain



- Total body's requests are due to brain for 40 % from caloric and O2 needs, and 56 % from proteic needs.
- Cellular development
- Role of insulin and hGH
- Particular relationship between flow and cells

CMg= (HCcm3/100 – (1500/HCcm)

Specific aspects for liver , pancreas and intestines

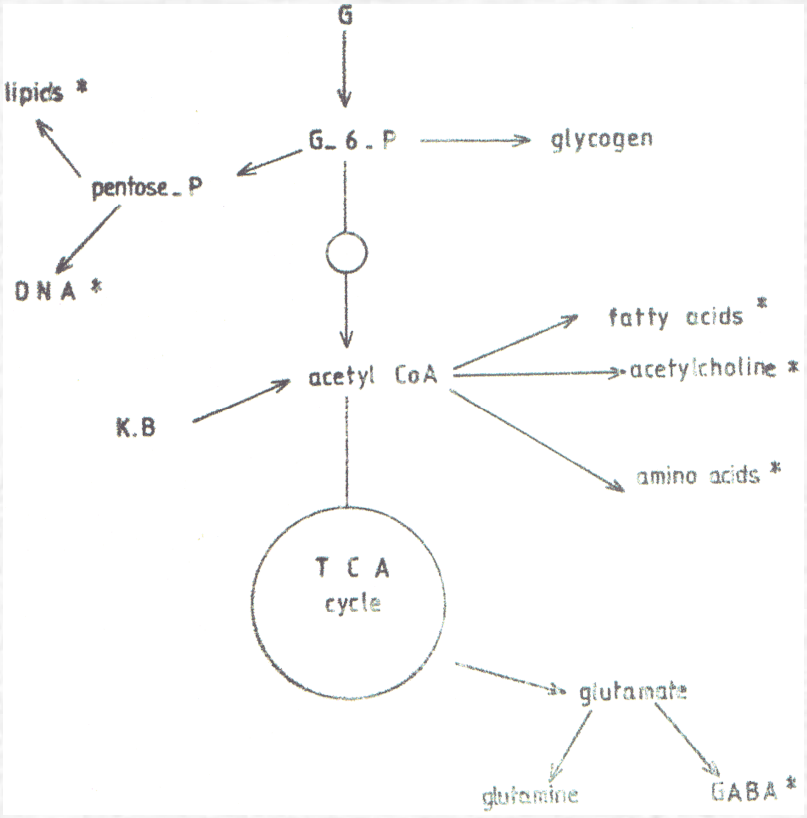


- Blood flow autoregulation
- Biochemical activities in liver
- Biochemical activities in intestines
- Biochemical activities in pancreas

Control of insulin secretion

-	+	+
secretion catecholamines, somatostatin	**secretion** fructose	**resistance** cortisol, T4, HPL, glucagon, endorphins
Hypo-K+	AA, Leu, ILeu	KB, acidosis, hypoxia, FFA
Beta-blockers, chlorpromazine, DPH, diazoxide	Kupfer cells, Xth nerve, beta-stimulators	Prematurity,
	Glucagon, pancreozymin	
rest	exercise	

Central role of glucose for energy an synthesis



- ATP and 5-Pentose;
- In- and out-cells composition
- Defenses against FR and EAA
- BMR
- Muscles (FFA) and intestines (glutamine and KB) have alternatives

Influence of gestational age on CRO2 and CRG

- Fetal glucose uptake
- Insulin receptors: number and affinity
- CMR O2, glucose; CBF; SBP
- Hb level
- Enzymes level and turnover
- Adipose tissue
- Placenta competence

Specific abnormalities

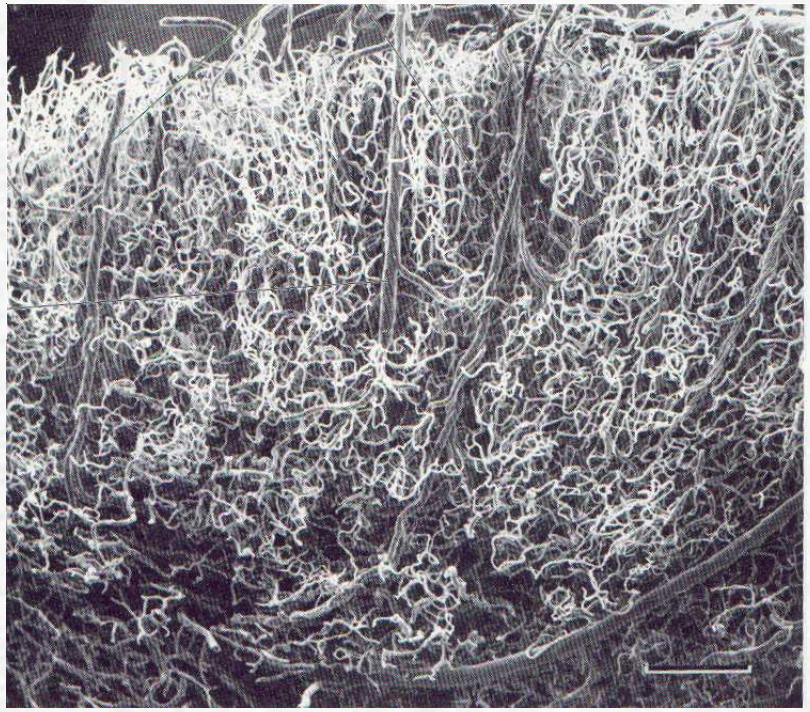
- ***In Growth retardation:***

- increase their hemoglobin;
- Relative high cerebral mass;
- Decrease of P-pyruvate kinase

- ***In very low birthweight:***

- lower effect of insulin on glycogenolysis and on glycogenosis; these activities increase afer 34-40 w;
- Limited of gluconeogenesis;
- Inappropriate (in excess) endogenous adrenergic activity;

glycaemia
importance of quantitative and velocity of variations



- **Hypoglycaemia:** loss of CBF autoregulation, isoelectric EEG from energy failure and enhanced vulnerability, concerned structures are layers 3,5,6 and thalamus,…
- **Hyperglycaemia:** CBF, pH, diuresis
- **Attention to high Hb levels !**
- **Attention to «large heads«**

Glucose and O2 needs in the distressed brain

Cbf ml/100g/m	[aG] ->I	[aG]-> W	[aO2]->I	[aO2]-> W
20	21	36	10	22
15	30	50	13	29#
10	40	72	19	44#
2	82	143	28#	62#

Treatments of glucose unstability: hypoglycaemia

- **Searching the specific explanation**
- **Glucose administration iv:** 1 cc /kg G5% will increase glycaemia of 10 mg/dL
- **Stimulating neoglucogenesis and increasing resistance to insulin:** glucagon IV or IM (bolus 200 microg/kg, continuous infusion of 8 microg/kg/hr)
- **Antagonizing insulin**: hydrocortisone 5 mg/kg/12h
- **Correct parameters**: pH, respiratory and circulatory functions, liver function, mode of feeding, brain requirements

Treatments of glucose unstability: hyperglycaemia

- **Searching for a specific explanation**
- **Insulin continuous infusion:** 0.5-0.8 iu/kg/h
- **Decrease glucose input down to calculated required amounts for brain:**

  first calculate brain mass according to head circumference, then plot glucose input to brain demands (3-5mg/100g/m)