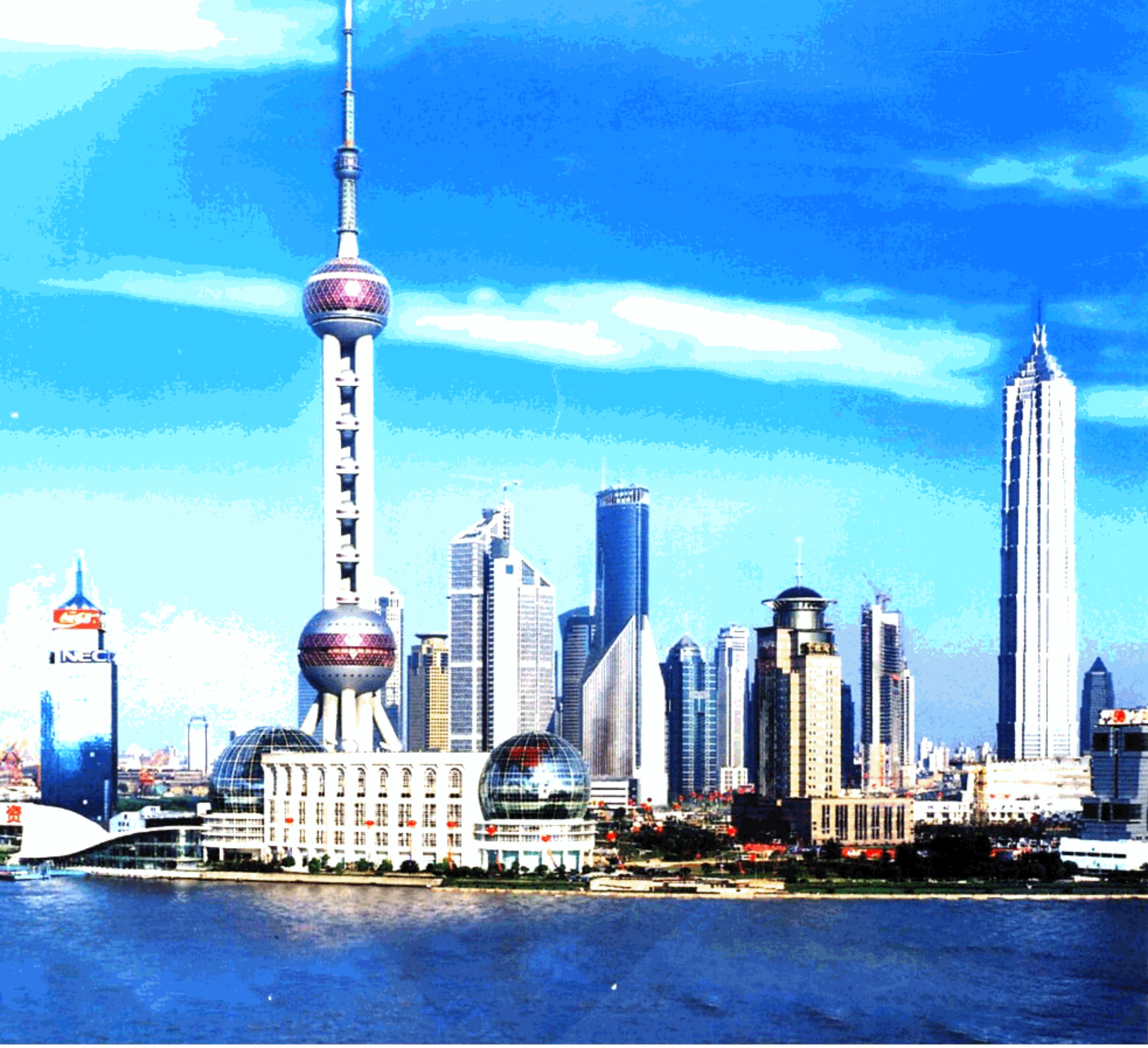
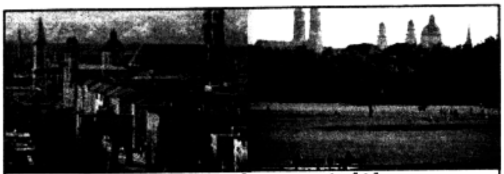
新生儿营养支持研讨会

（2005.6.上海）



目 录



Does early nutrition programme later health?

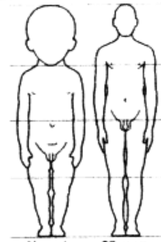
Berthold Koletzko, M.D.
Professor of Paediatrics
Dr von Hauner Children's Hospital,
University of Munich, Germany

Dr von Hauner Children's Hospital Univ. of Munich

Nutrition in the perinatal period is of greater importance than at any other age

- Very fast growth
- ↑↑ Nutrient needs / kg bw
- ↓↓ Body stores
- Immature gastrointestinal, metabolic & renal functions
- Rapid organ development

➔ Substrate supply has marked immediate and long-term effects

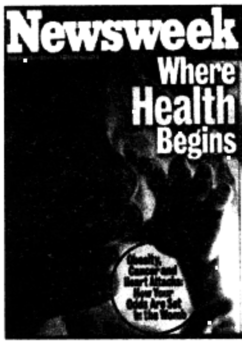


Breast is best

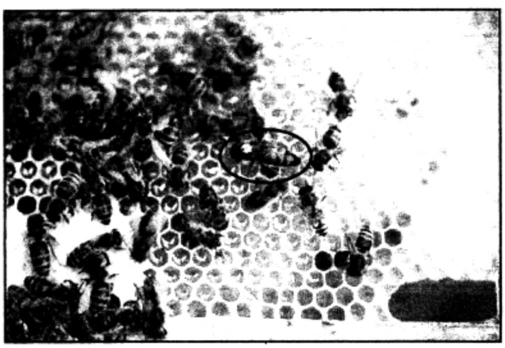
- Supports mother-infant bonding
- Matches infant nutrient needs
- Anti-infective, anti-inflammatory, ↑ bifidobacteriae, ↓ infectious risks
- ↓ Risk for some later diseases (Obesity, Diabetes type I, Crohn's disease, Celiac disease)
  Cognitive performance

Caveat:

- Some limitations: retrospective study designs, recall bias, potential confounding (education, socio-economic status, lifestyle, non-smoking)
- Further research into mechanisms necessary



- Programming of human adult functions and diseases by hormones, metabolites and neuro-transmitters during critical development periods
  Guenther Dörner, Berlin, Germany 1974
- Programming by early nutrition in man
  Alan Lucas, Cambridge, UK 1991
- Fetal Programming of adult disease by poor fetal nutrition and low birth weight *Nick Hales, David Barker, Oxford, Southampton, UK 1992*

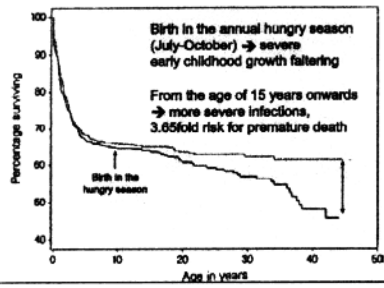


Early nutrition programmes health in human adults

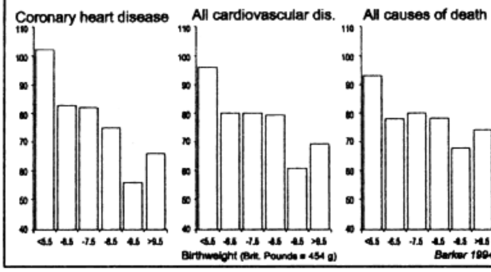
➔ Cardiovascular health
➔ Immune function, infection & allergy risk
➔ Autoimmune diseases, e.g. diabetes type I, inflammatory bowel disease, celiac disease
➔ Bone health
➔ Obesity
➔ Neural and brain function

Birth in the „hungry season“ → higher mortality in adults

3102 people born 1949-1994. Moore et al, Nature 1997



Birth weight and standardised mortality ratios at 20-74 y. in 10,141 men born in Hertfordshire 1911-1930



Low birth weight = ↑ later risk for coronary heart disease

Effect of Prenatal Nutrition?

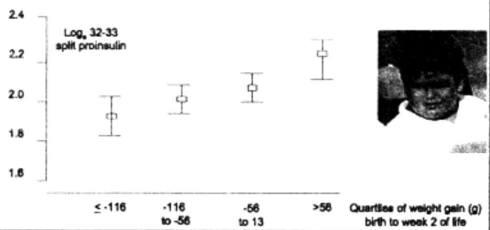
- Poor fetal growth
  → Fetal Origins of Adult Disease Hypothesis

Effect of Postnatal Nutrition?

- Compensatory excessive postnatal growth
  → Accelerated Postnatal Growth Hypothesis

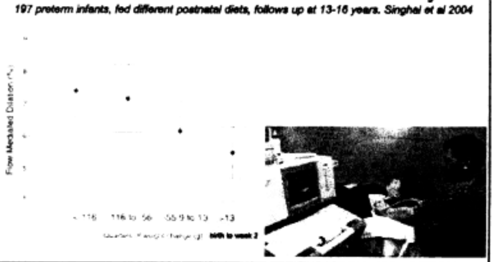
Higher postnatal weight gain => ↑ insulin resistance at 13-16 years

197 preterm infants, fed different postnatal diets, follows up at 13-16 years. Singhal et al 2003

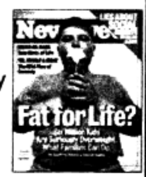


Higher postnatal weight gain => ↓ flow-mediated dilatation at 13-16 years

197 preterm infants, fed different postnatal diets, follows up at 13-16 years. Singhal et al 2004



Childhood Obesity

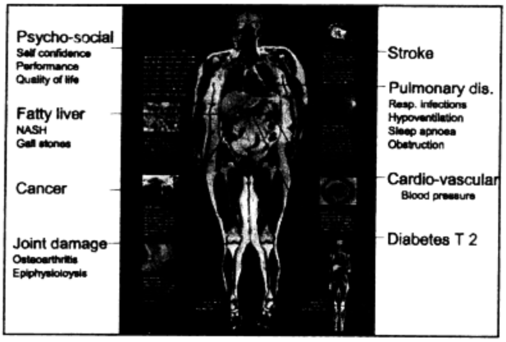


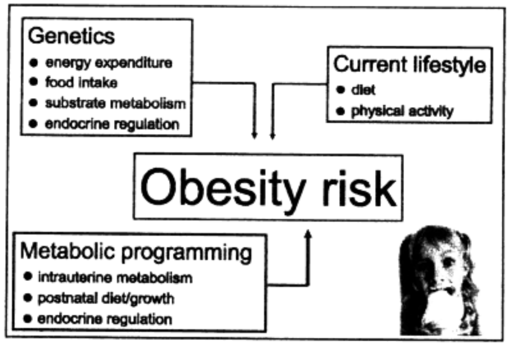
- Global epidemic, alarming increase of prevalence & severity
- Severe psychosocial & health burdens, huge costs
- Difficult to treat

Primary prevention greatly needed

Koletzko B, Girardet J P, Klish W, Tabacco O. Obesity in children and adolescents worldwide: current views and future directions. JPGN 2002; 5:S205-S212

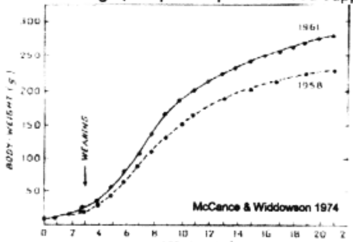
Fisberg M, Baur L, Chen W, Hoppin A, Koletzko B, Lau D, Moreno L, Nelson T, Strauss R, Uauy R. Obesity in children and adolescents. JPGN 2004;39:S678-87





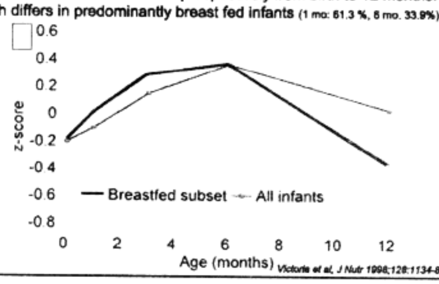
The determinants of growth and form

Manipulation of postnatal diet with lower early growth in rats
➔ low adult weight, despite ample later food supply



Growth of breast and bottle fed infants

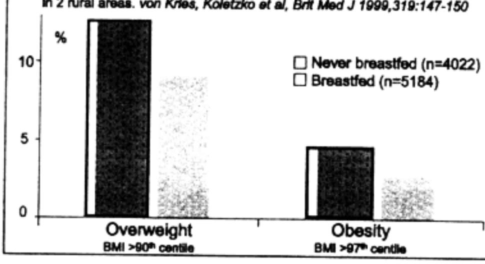
5,304 Brazilian infants followed prospectively from birth to 12 months.
Growth differs in predominantly breast fed infants (1 mo: 61.3 %, 6 mo. 33.9%).



Victora et al, J Nutr 1998;128:1134-8

Breastfeeding: ↓ obesity at school age

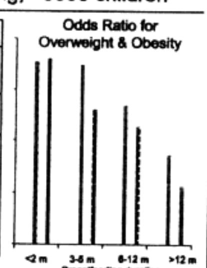
Data from obligatory school health examination, Bavaria, BMI centiles calculated for total cohort of 134,577 children, data on infant feeding in 9,206 children in 2 rural areas. *von Kries, Koletzko et al, Brit Med J 1999,319:147-150*



Adjusted OR (95 %CI) for overweight and obesity by duration of breastfeeding, >9000 children

Breast	Overwt	Obese
Ever	*0.79* (0.68-0.93)	*0.75* (0.57-0.98)
<2 mon. (n=2084)	0.89 (0.73-1.07)	0.90 (0.74-1.02)
3-5 mon. (n=2052)	0.87 (0.72-1.05)	0.65 (0.44-0.95)
6-12 mon. (n=863)	0.67 (0.49-0.91)	0.57 (0.33-0.99)
>12 mon. (n=121)	0.43 (0.17-1.07)	0.28 (0.04-2.04)

von Kries, Koletzko et al, Brit Med J 1999,319:147-150



Breastfeeding and childhood obesity: Systematic review

Arenz, R¸ckerl, Koletzko, von Kries. Int J Obesity 2004;28:1247-1256

- First systematic review, prospective study protocol

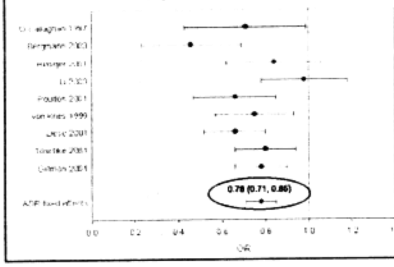
Inclusion criteria:

- Cohort-, cross-sectional- or case-control studies
- Published 1966–Jan 2004 (in English, French, German, Italian, or Spanish)
- Adjustment for ≥3 relevant confounders (birth weight, parental overweight, parental smoking, dietary factors, physical activity, socio-economic status)
- Risk estimates as odds ratio or relative risk
- Age at follow-up 5-18 years
- Infant feeding mode assessed and reported
- Obesity defined by BMI percentiles

Breastfeeding and childhood obesity: A meta-analysis

Covariate adjusted odds ratios, pooled odds ratio

Arenz, R¸ckerl, Koletzko, von Kries. Int J Obesity 2004



Breastfeeding: moderate but consistent protection against later obesity

↓ *22 % risk*

Dose response effect of breast feeding duration in 4/9 studies

→ Promotion and support of breast feeding

Why does breastfeeding protect?

Residual confounding

Behaviour

- Suckling behaviour
- Differences in meal sizes & intervals
- Different taste experience → later food choice

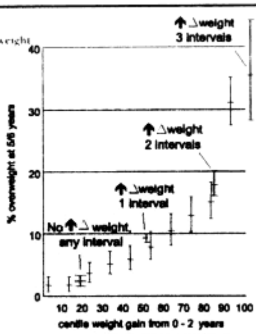
Growth / substrate supply / endocrine regulation

- Early weight / length gain
- Energy supply
- Protein supply
- Insulin / IGF 1
- Leptin resistance

Identifying Children at High Risk for Overweight at School Entry by Weight Gain During the First 2 Years

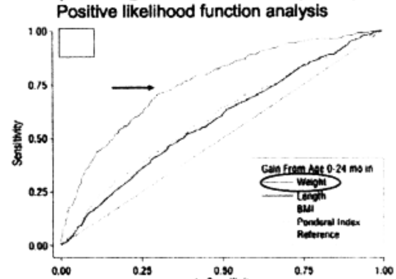
Toschke, Grote, Koletzko, von Kries
Arch Pediatr Adolesc Med 2004;158:449-452

Height and weight in 4,235 children at birth, 6, 12 & 24 months (preventive health checks by paediatricians/GPs) & at 5-6 years (school entry examination), 6 communities in Bavaria, Southern Germany



Receiver operating characteristics (ROC) curves

Positive likelihood function analysis



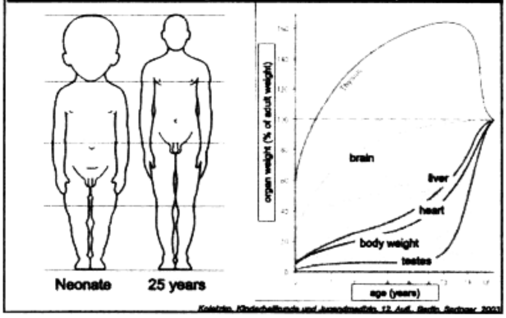
Arch Pediatr Adolesc Med 2004;158:449-52

Avoid very high weight gain in infancy

Factors related to ↑ infant weight gain:

- Genetics
- Mode of feeding
- Nutrient density/supply
- Very sweet taste of formula/compl. food
- Others

The dynamics of growth and tissue development



Koletzko, Kinderheilkunde und Jugendmedizin, 12. Aufl., Berlin, Springer, 2003

Infant feeding and infections during the first 3 months

	Full Breast n=95	Partial Breast n=126	Formula n=257	p
Gastrointestinal Infections	2.9 %	5.1 %	15.7 %	<0.001
Respiratory Infections	25.6 %	24.2 %	37.0 %	<0.05

Prospective study, corrected for social class, maternal age and parfental smoking.
Howie et al 1990

Breastfeeding may reduce risk for later autoimmune disorders

Disease	Rel. Risk if not breast fe.d	p	Subjects	Author/yr.
Malignant lymphomas	150 %	<0.002	201 patients 181 controls	Davies et al 1988
Diabetes type I	230 %	<0.02	188 diabetes pats., 165 siblings	Borch-Johnson et al 1984
Crohnêsdisease	380 %	<0.005	114 Crohnêsdis., 180 siblings	Koletzko et al 1988

Some anti-infectious factors in breast milk

Humoral components

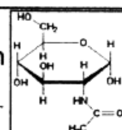
- sIgA, IgG, IgM, IgD
- Lactoferrin
- Lysozyme
- k-Casein
- Lactoperoxidase
- Haptocorrin
- Fibronectin
- a-Lactalbumin
- Nucleotides
- Oligo- and polysaccharides, glycoconjugates
- Monoglycerides, non esterified fatty acids
- Mucines

Cellular components

- Neutrophil ganulocytes, macrophages
- Lymphocytes
- Membranes of epithelial cells
- Membranes of milk fat globuli

modified after Koletzko & Schroten 1999

Human milk contains prebiotic substances that stimulate growth of Lactobacilli & Bifidobacteria



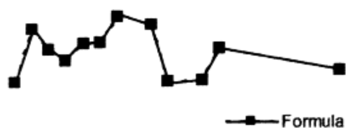
N-acetylglucosamine

- Lactose *(only partly digested → fermented in the colon)*
- N-acetyl glucosamine *Gy'rgy 1971*
- Human milk oligosaccharides *(several hundred HMOs)* *Kunz et al 1999*
- Bifidogenic peptides derived from lactoferrin, the secretory component of sIgA *Liepke et al 2002, L'n nerdal 2003*

ESPGHAN Committee on Nutrition. Non-digestible carbohydrates in the diets of infants and young children. JPGN 2003;36:329-337

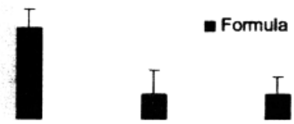
Bifidobacterium flora in breast- and formula-fed babies

Fluorescence in situ hybridisation, Harmsen et al, JPGN 2000



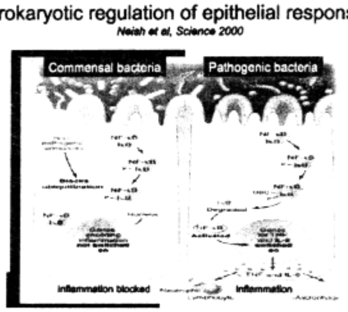
Microflora in breast- and formula fed babies (d 7)

Fluorescence in situ hybridisation, Harmsen et al, JPGN 2000



Prokaryotic regulation of epithelial responses

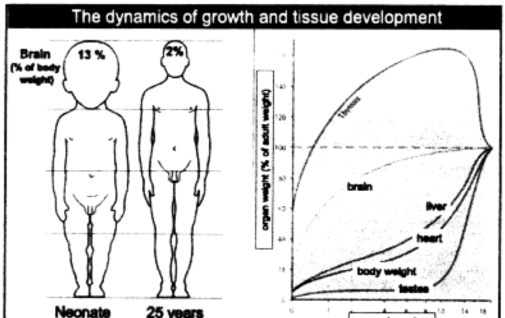
Neish et al, Science 2000



Modulation of T-cell subpopulations by commensal bacteriae

Th1	Th2	Tr1/Th3
IL-2, -INF, IL-12	IL-4, IL-5, IL-6	TF-ß, IL-10
↓	↓	↓
DTH, Cellular immunity	Humoral immunity, Antibody secretion, IgE-response	Inhibition of inflammation, Oral tolerance

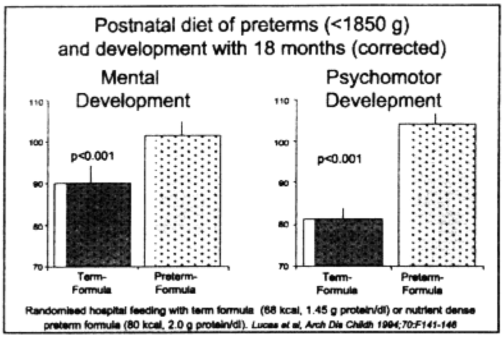
The dynamics of growth and tissue development

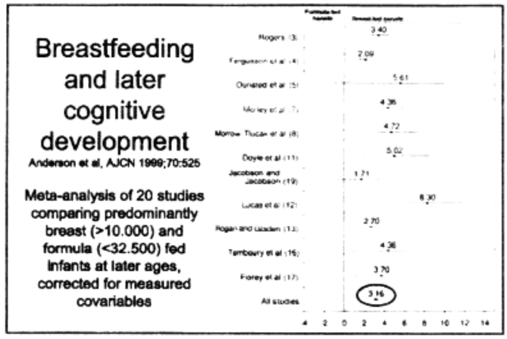


Koletzko Kinderheilkunde und Jugendmedizin 12. Aufl. Berlin Springer 2003

The brain

Fast growth, rapid maturation & differentiation depend on sufficient, balanced supply of nutrients



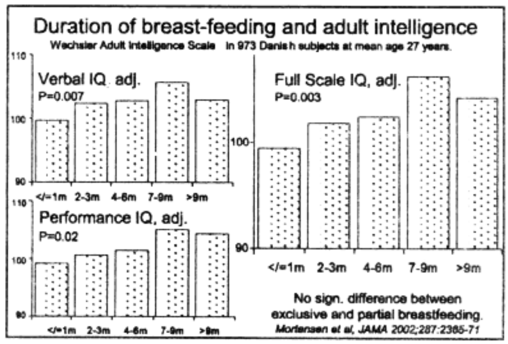


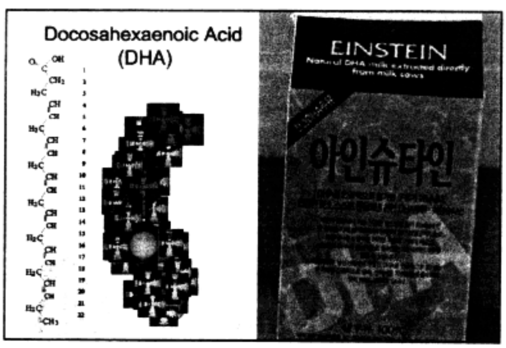
Breastfeeding and cognitive development: a meta-analysis

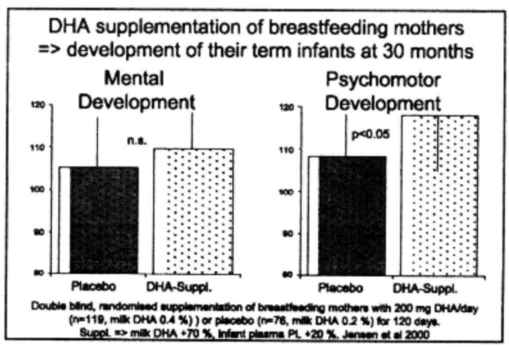
Anderson et al, AJCN 1999;70:525

Effect of birth-weight on weighted mean difference in cognitive development score between breast and formula fed infants

	Mean Δ	SE	95 % CI
Normal / mixed birth-weight	2.66	0.26	(2.15-3.17)
Low birth-weight	5.18	0.81	(3.59-6.77)







LCPUFA improve stereoacuity at 3.5 years: 435 children born full-term

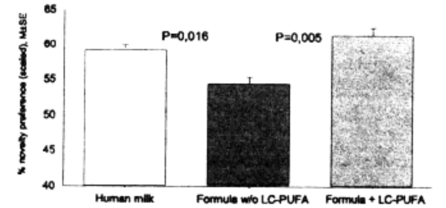
ALSPAC study: Williams et al, Am J Clin Nutr 2001;73:316-22

Stereoacuity is independently associated with
(adjusted logistic regression)

Breast feeding	
Never	1.00
≥4 months	2.77 (1.54-4.97)
Maternal oily fish consumption	
No	1.00
Yes	1.57 (1.00-2.45)

LCPUFA and cognitive development of healthy term infants

Novelty preference (%) in the Fagan-Infantest at 9 months in 61 term infants, postnatally fed human milk or randomised to formula ± LC-PUFA

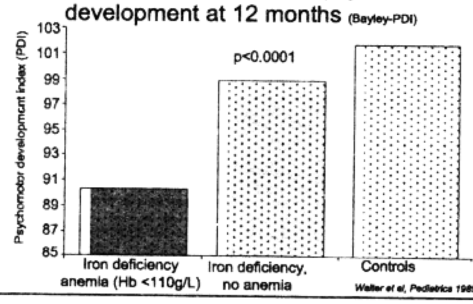


Nutrients & brain growth

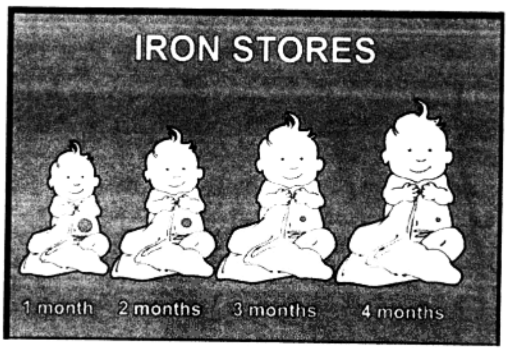
➔ Early nutrient & micronutrient supply modulate brain growth, development and later function

➔ Optimize nutrient supply during early growth

Infant iron deficiency affects psychomotor development at 12 months (Bayley-PDI)



Walter et al, Pediatrics 1989



After the first ½ year, breastfeeding alone does not secure sufficient iron supply

Absorbed Iron

Estimated requirement	≈ 0.55-0.75 mg/d
Suppy with breast milk	≈ 0.13 mg/d

Fomon SJ, Nutrition of normal infants. Mosby 1993

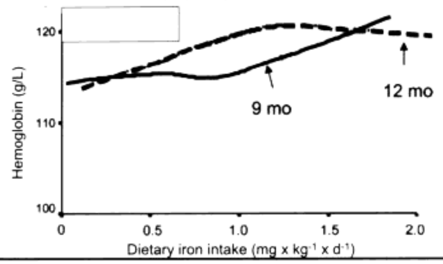
Iron status at 9 months is related to feeding

Hertrampf et al, Pediatrics 78;60-5

	Breastfed	+Iron enriched infant formula
Anemia (Hb<11g/dl)	27.3 %	4.3 %
Microcytosis (MCV<70)	50 %	16 %
Iron deficiency (Ferr<10)	44 %	25 %

Dietary iron intake after 6 months *(complementary feeding w. iron, iron-fortified formula)* affects hemoglobin in infancy

245 Swedish infants followed prospectively from 6-18 months. Lind et al, J Nutr 2004



From 6 months onwards infants need additional micronutrients from complementary foods and/or iron fortified formula

Infant feeding concepts today

- Protection, promotion and support of breast feeding
- Adequate and safe complementary feeding
- Safe infant formulae & follow-on formulae of highest quality

WORLD HEALTH ORGANIZATION

Infants who cannot be fed at the breast, or should not receive breast milk, or for whom breast milk is not available, require breast milk substitutes of high quality

Thirty-Ninth World Health Assembly, 1986

Breast Feeding: Some potential limitations

- ☹ ↓ Milk production, major breast anomalies
- ☹ Painful mastitis / abscess
- ☹ Maternal malnutrition, poor nutrient supply *(e.g. vit. K, B_{12}, iodine)*
- ☹ Some maternal infections & diseases *(e.g. HIV, CMV in preterms, tuberculosis, syphilis, malignancy, malnutrition, psychosis)*
- ☹ Some drugs, contaminants *(e.g. cytostatic drugs, some antibiotics, smoking, alcohol)*
- ☹ Severe postnatal weight loss *(e.g. SGA, preterms)*
- ☹ Some infant diseases (e.g. galactosaemia, PKU, severe icterus)
- ☹ Nutrient needs after 6 months not always met (e.g Fe)

European Union Concepts

Scientific Committee on Food 2003

Infant formulae

May satisfy as the sole source of feeding the nutritional requirements of by infants during the first four to six months of life

Follow-on formulae

Intended for use by infants aged over four months and young children and constituting the principal liquid element in a progressively diversified diet

EU Standards Infant Formulae

Current EU Directive (1991-1999), SCF 2003

Nutrient	Current Directive	SCF Proposal
Energy (kcal)	60-80 kal/100ml	60-70 kal/100ml
Cowsi milk protein (meeting quality criteria)	1.8-3.0 g/100 kcal	1.8-3.0 g/100 kcal
Fat	4.4-6.5 g/100 kcal	4.4-6.5 g/100 kcal
Linoleic acid	300-1200 mg/100 kcal	500-1200 mg/100 kcal
Linoleic/ -Linolenic	5-15	5-15 (5-20 if + LCPUFA)
Carbohydrates	7-14 g/100 kcal	9-14 g/100 kcal
Lactose	50 % of min. CHO	50 % of min. CHO

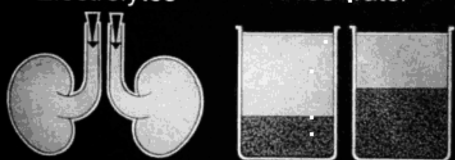
Which milk for weaned babies >6 months?

Healthy infants randomized from 6-12 months to cows' milk or infant formula (with iron), similar compl. feeds. *Tunessen & Oski 1987*

	Cowsi milk (n=69)	Infant formula (n=98)
Anemia (Hb <11 g/dl)	25 %	11 %
Microcytosis (MCV <72)	35 %	13 %
Iron deficiency (Ferr. <12)	17 %	1 %

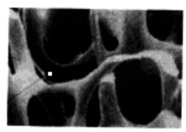
Unmodified cows' milk:
↑ Iron deficiency, ↑ Anemia

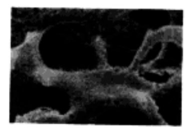
Cows' milk: renal molar load



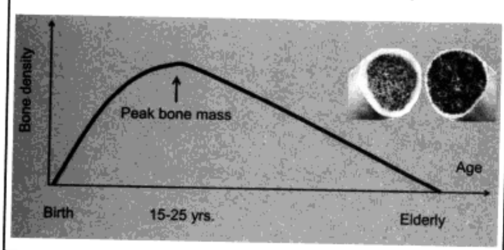
Supply of bioavailable calcium and bone mineralisation

- Total body calcium (adult) ≈1,5 kg
- 99 % in bone/teeth
- Accretion in childhood/adolescence





Early calcium uptake and bone mineralisation modulates fracture risk at later age



BF & Formula for 12 months Cows' milk => from 2nd year

Unmodified cows' milk:

- ↑Protein & salt intake, ↑ renal molar load
- ↑Risk of dehydration under stress (diarrhea, fever)
- ↓Iron content, ↓ iron absorption from milk and complem. feeds, ↑ risk of iron deficiency & anemia
- ↑Allergenicity *(heat treated formula protein ↓ allergenic)*
- ↑Mucosal damage, microbleeding
- ↓Bioavailable calcium

→ Limit cows' milk intake during first year of life

Micronutrients

Vitamins

Minerals

Trace elements

Other compounds

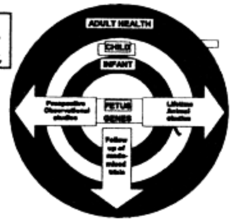
Vitamin A	60-180 ug RE
Vitamin D	1-2.5 ug
Vitamin E	0.5 mg aTE/g PUFA (corrected f. double bonds)
Vitamin K	4-20 ug
Vitamin B_1 (thiamine)	60-300 ug
Vitamin B_2 (riboflavin)	80-400 ug
Vitamin B_3 (niacin)	300-1200 ug NE
Vitamin B_6 (pyridoxine)	35-165 ug
Vitamin B_{12} (cobalamin)	0.1-0.5 ug
Pantothenic acid	400-2000 ug
Folic acid	10-30 ug
Vitamin C (ascorbic acid)	10-30 mg
Biotin	1.5-7.5 ug

FOOD QUALITY AND SAFETY — EARNEST — DG Research — European Commission

EARNEST: Early Nutrition Programming of Adult Health (IP)

Long term follow up of efficacy and safety trials and integrated epidemiological, genetic, animal, consumer and economic research

12 countries: DE, BE, CZ, DK, ES, FI, FR, HU, NL, NO, PL, UK,



Deliverables:
Health promotion
Improved policy
Improved dietary products

EU budget/duration:
EU 13.4 Mio €/Total 18.5 Mio €
[≈17.3 Mio US$/ 23.9 Mio US$]
2005-2010

Coordination:
Hauner Children's Hospital,
Univ of Munich, Germany

www.metabolic-programming.org

- Early nutrition of huge importance for long-term child health
- Support optimal feeding of mothers and infants: Protection and support of breast feeding, high quality infant formulae follow-on formulae & complementary feeds
- Importance of early nutrition for long term health justifies major investments in practice & research

Thanks to my co-workers

Thank you for your kind attention

新生儿创伤应激反应和营养支持

苏州大学附属儿童医院
汪 健

1949年，新生儿外科的总死亡率高达72%，导致PeterRicham坦言："除非在少数非常有经验的外科医师手中对少数有选择的病例进行手术，大手术的死亡率出奇的高。"在过去的60年，死亡率已有了明显的下降

Rowe MI, et al. Am J Surg 2000:345-352

一个对50年胸腔和腹腔畸形的治疗回顾提示：几乎全球范围生存率的改善并不是新的或改良的外科技术的缘故，许多基本的外科技术在1950年已运用

Rowe MI, et al. Am J Surg 2000:345-352

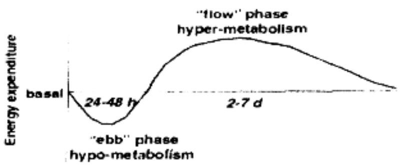
8个医学和工业化的进展可能是提高生存率的主要原因，这些进展中，一个重要的代表就是引入了人工营养支持(artificial nutritional support)，特别是静脉营养。

这些都取决于我们对以下两个方面的深入了解：

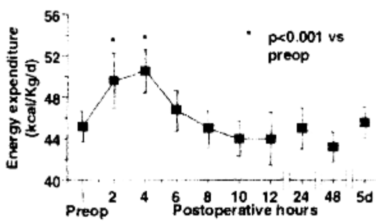
- 外科患儿的热卡需要
- 代谢反应一对饥饿、麻醉、手术应激和全身炎症反应

一、手术创伤后的代谢反应

在成人，创伤和手术引起一个短暂的低潮阶段(ebb phase)，特点为血压、心排血量、体温和氧耗均下降；然后是高潮阶段(flow phase)，特点为高心排血量及高代谢，即组织分解代谢增强，糖代谢改变和尿氮丢失增加



在新生儿，腹部大手术引起氧耗和静息能量消耗中等(15%)和即刻(高峰在4小时)的升高，手术后12－24小时恢复至基础水平



这些改变的时间与Anand等报告的手术后儿茶酚胺水平的升高相仿

内分泌和生化改变的最大值出现在手术后早期，在接下来的24小时逐渐恢复正常

Chawals,et al:

- 手术后能量消耗(energy expenditure)升高可能是其本身的严重疾病(通常需要手术，特别是感染)所引起
- 静息能量消耗与健康婴幼儿的生长率有直接的比例关系，在急性代谢应激时，生长出现延迟
- 系列测定手术后静息能量消耗可用来区分损伤的严重程度，可能是监测手术患儿恢复正常生长代谢的一个有效的指标

最近，相当大的兴趣集中在细胞因子TNF和IL作为应激反应的介质和指标

细胞因子与靶器官的特异膜受体结合，在急性应激反应中的作用包括：

- 基因表达和增殖出现改变，影响伤口的愈合和免疫活性
- 释放抗调节激素
- 便于细胞与细胞的联络

新生儿IL-6水平的升高在大手术后12小时达最高，而这种升高与手术创伤的程度成比例，提示IL-6是新生儿应激反应的一个指标

PierroA, et al. Br JSurg 1994

江健、朱锦祥等：

表1 手术前后细胞因子及皮质醇的变化(x̄±s)

项目	例数	术前	术后	术后6小时	术后12小时	术后24小时
IL-6(pg/ml)	22	6.23±5.10	36.75±10.56*	96.56±23.60*	73.60±30.60*	65.30±19.65*
IL-8(pg/ml)	18	10.65±6.10	12.36±4.56	15.63±7.63	80.73±20.48*	13.60±7.28
TNF-α(pg/ml)	18	13.54±10.61	20.34±12.64	15.37±15.44	13.42±14.86	19.54±5.64
皮质醇(nmol/l)	22	0.88±0.32	1.36±0.38*	1.48±0.33*	1.34±0.37*	0.9±0.28

注：*P<0.05

二、重症和感染时的代谢反应

不管疾病有多么严重或出现器官衰竭仍应保持营养的完整性，特别是在新生儿期，其能量和蛋白储存都是有限的

婴幼儿和儿童需要营养：

- 保持蛋白质状态
- 生长
- 伤口愈合