THE CHALLENGES OF THE NEWBORN

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Outline

- Introduction
- Challenges of the Newborn
  - Pregnancy
  - Full-term Birth
  - Breathing
  - Newborn Stress
  - Feeding
  - Adaptation
  - Development

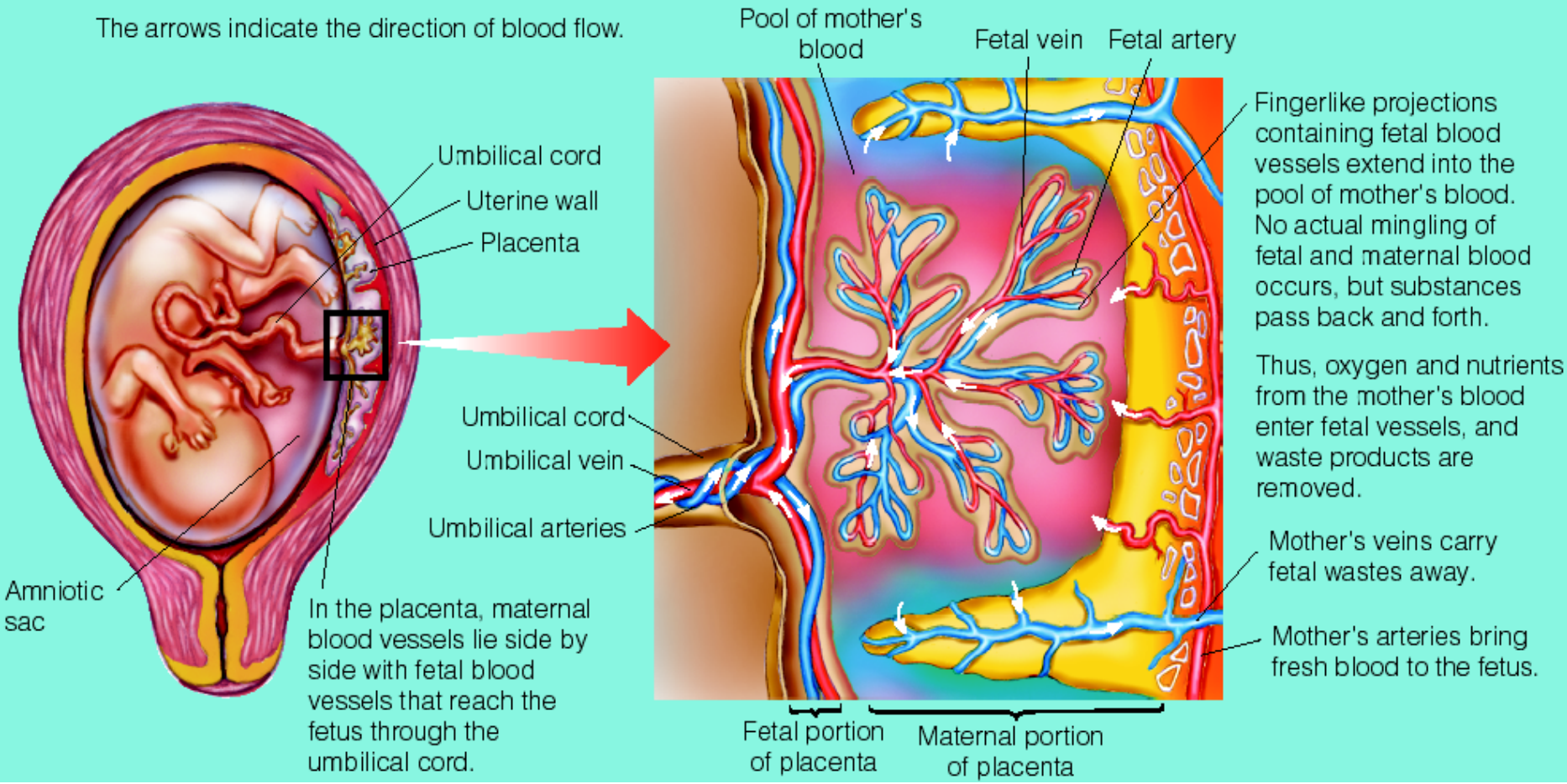
- The Premature Infant
  - Definition / Description
  - Growth
  - Oxygen
  - Antioxidant Enzymes
  - Diseases of Prematurity
  - Feeding
  - Human Milk
  - Developmental Outcome

PREGNANCY

- **F2-isoprostanes have been inversely correlated with birth-weight**
- **Term infants born SGA had elevated cord MDA and reduced Glutathione**
- **Markers of oxidative stress are consistently higher in pregnant vs non-pregnant women**
- **Oxidative stress may play a role in pathologies of pregnancy**

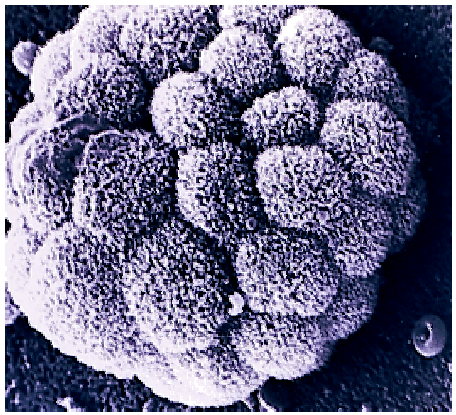
Placenta

- **Mitochondrion rich placenta favors the production of ROS**
- **Highly metabolic organ with 60 enzymes and hormones of its own**

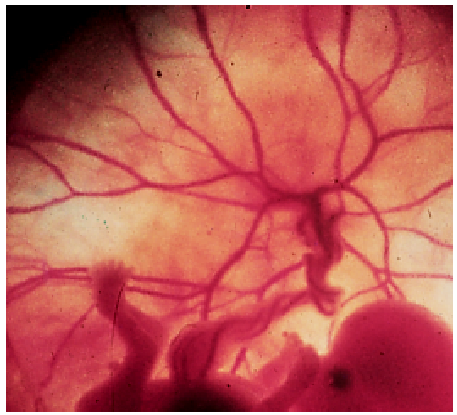


Full-term birth:

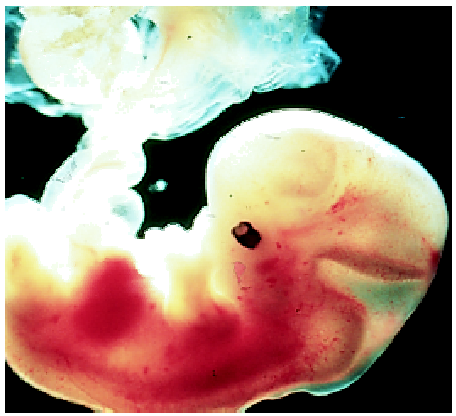
- 38-42 weeks gestation
- 2500-4000g
- 93% of all births



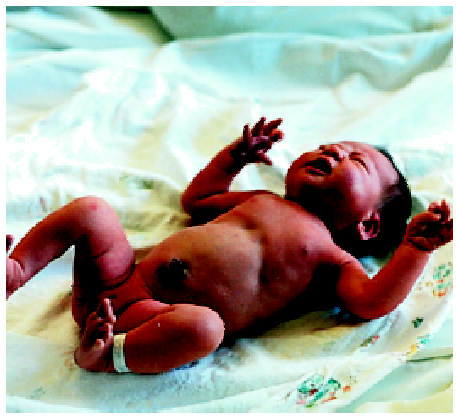
(1) *A newly fertilized ovum is about the size of the period at the end of this sentence. This zygote at less than one week after fertilization is not much bigger and is ready for implantation.*



(3) *A fetus after 11 weeks of development is just over an inch long. Notice the umbilical cord and blood vessels connecting the fetus with the placenta.*



(2) *After implantation, the placenta develops and begins to provide nourishment to the developing embryo. An embryo five weeks after fertilization is about ½ inch long.*



(4) *A newborn infant after nine months of development measures close to 20 inches in length. From eight weeks to term, this infant grew 20 times longer and 50 times heavier.*

BIRTH

- The fetus is in a warm protected environment, given O_2, nutrients that are pre-digested

- The newborn infant must carry out their own essential functions e.g. respiration, circulation all metabolic processes, temperature control, digestion absorption

- There is a relatively high mortality rate in the 1st 24 hours of life showing the trauma of transition

Birth: A Hyperoxic Challenge

- The evolutionary adaptation to extrauterine aerobic existence required the development of efficient cellular electron transport systems to produce energy

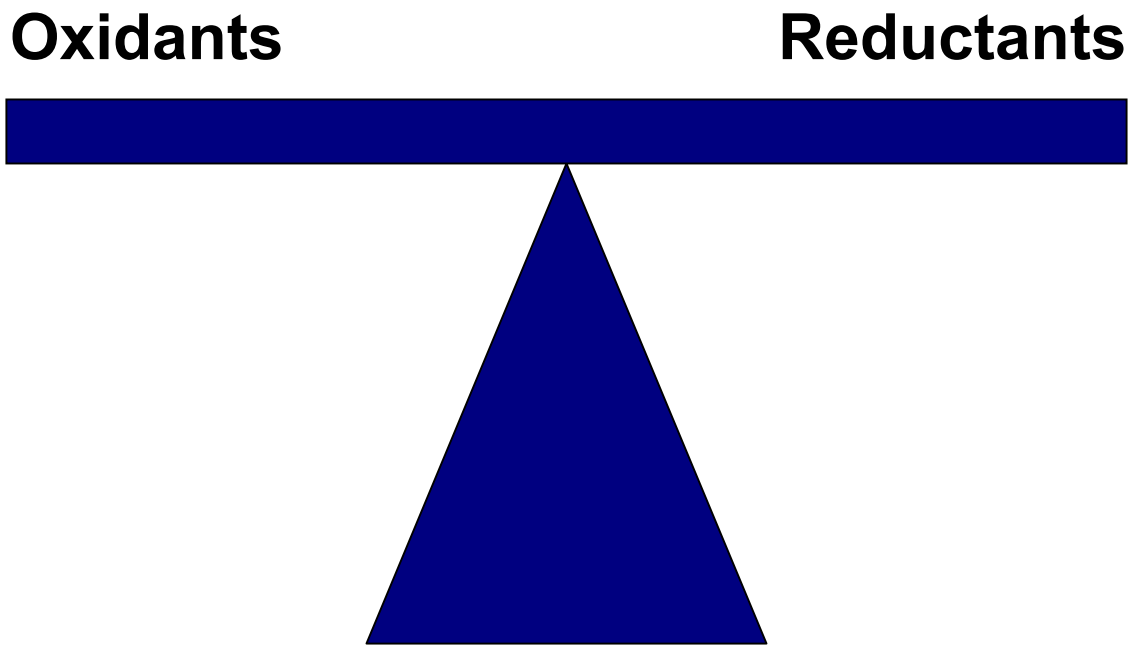
- Biochemical defenses including antioxidant enzymes, evolved to protect against oxidation of cellular constituents by ROS

- There is increased transfer of antioxidants including vitamins E, C, beta-carotenes and ubiquinone during the last days of gestation

BREATHING:

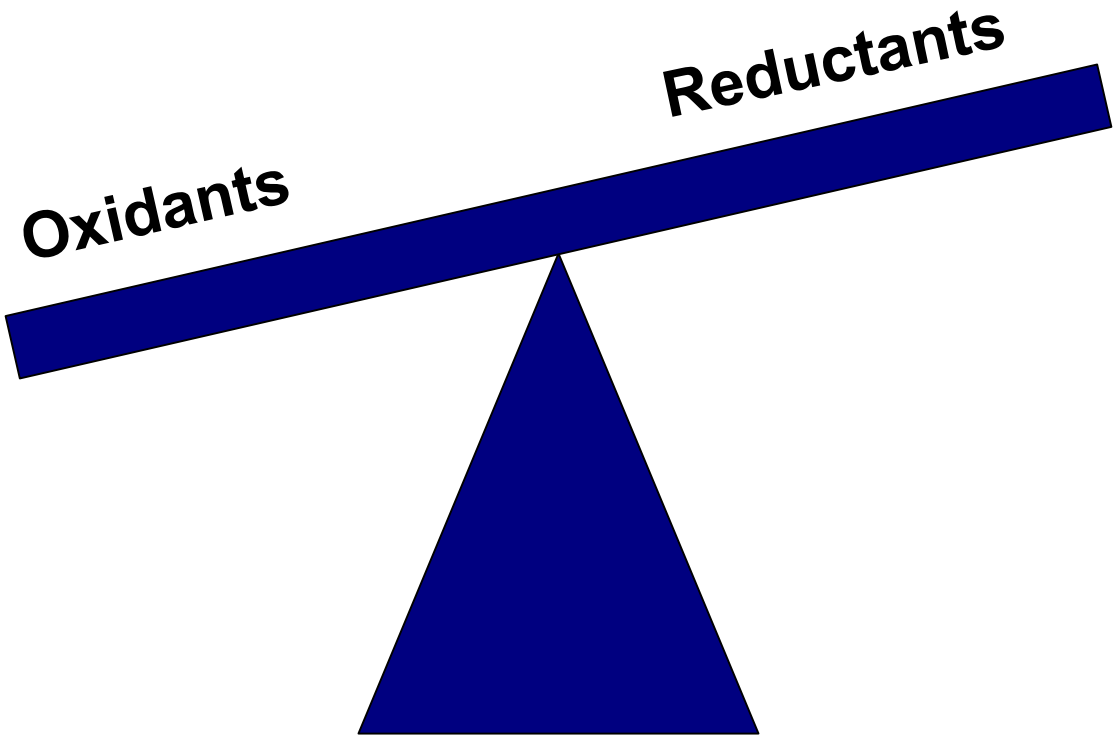
- Fetus transfers from an intrauterine “hypoxic” environment with a PaO_2 of 20-25 mm Hg to an extrauterine “normoxic” (yet relatively hyperoxic) environment with a PaO_2 of 100 mm Hg
- Most newborn lungs are relatively structurally immature
- Human lungs continue to develop until about 8 years of age.
- Immediately prior to birth there is an up ramping of antioxidant enzyme activity
- Upon exposure to oxygen newborn lungs of many species increase their normal complement of protective antioxidant enzymes

Oxidative Stress and Birth



INFANT HAS TO BALANCE…or

IMBALANCE



INJURY

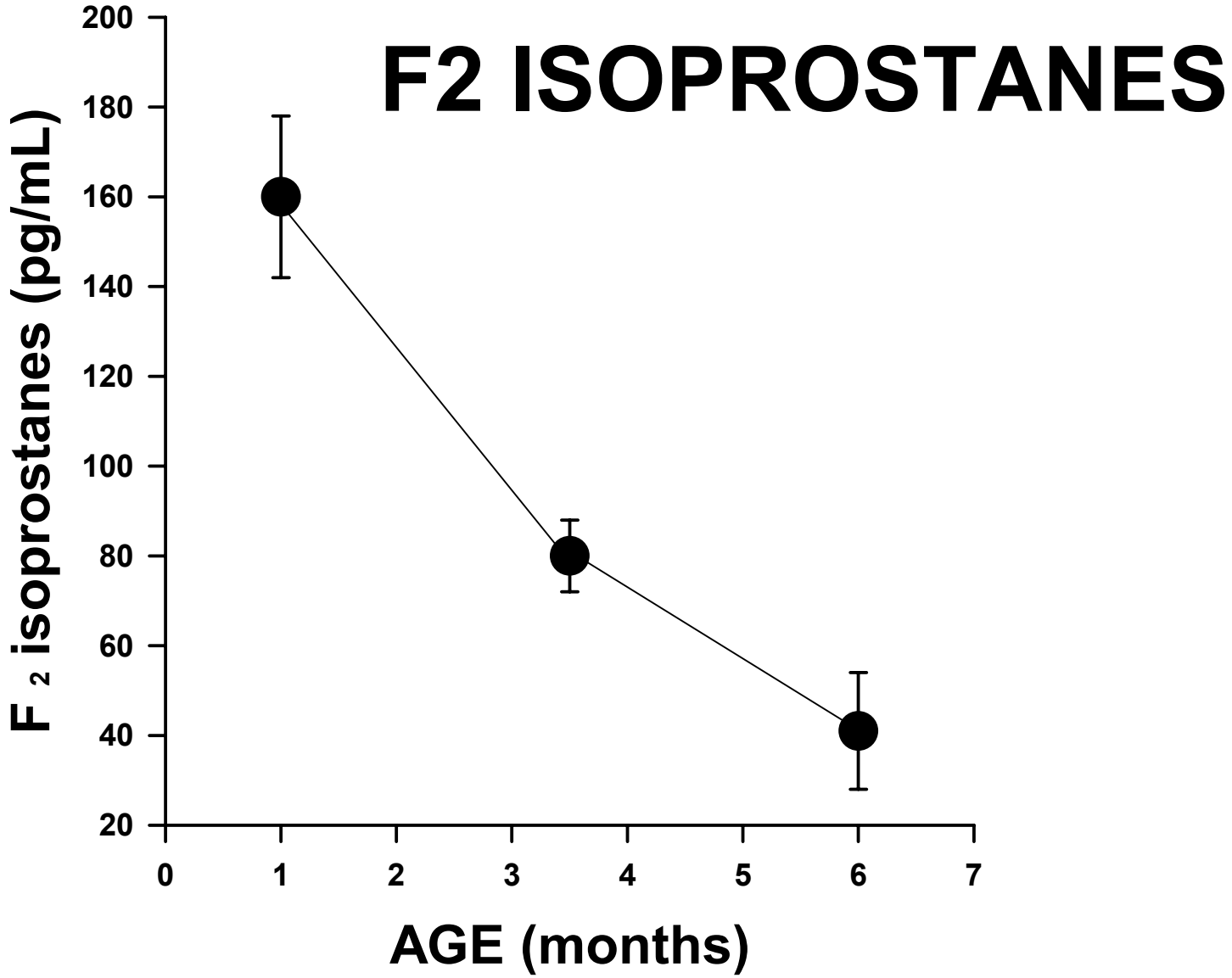
NEWBORN STRESS

- 67% of all infant deaths occur in the first month of life
- Coping with ambient (21%) oxygen is a challenge
- Newborns are more exposed to ROS than in utero because of high level of mitochondrial respiration and subsequent production of superoxide
- Fetal erythrocytes produce more superoxide and H_2O_2 than adult red cells
- MDA in cord blood > than in neonatal period > adults
- **Not all infants can cope**

Oxidative Status of Newborns

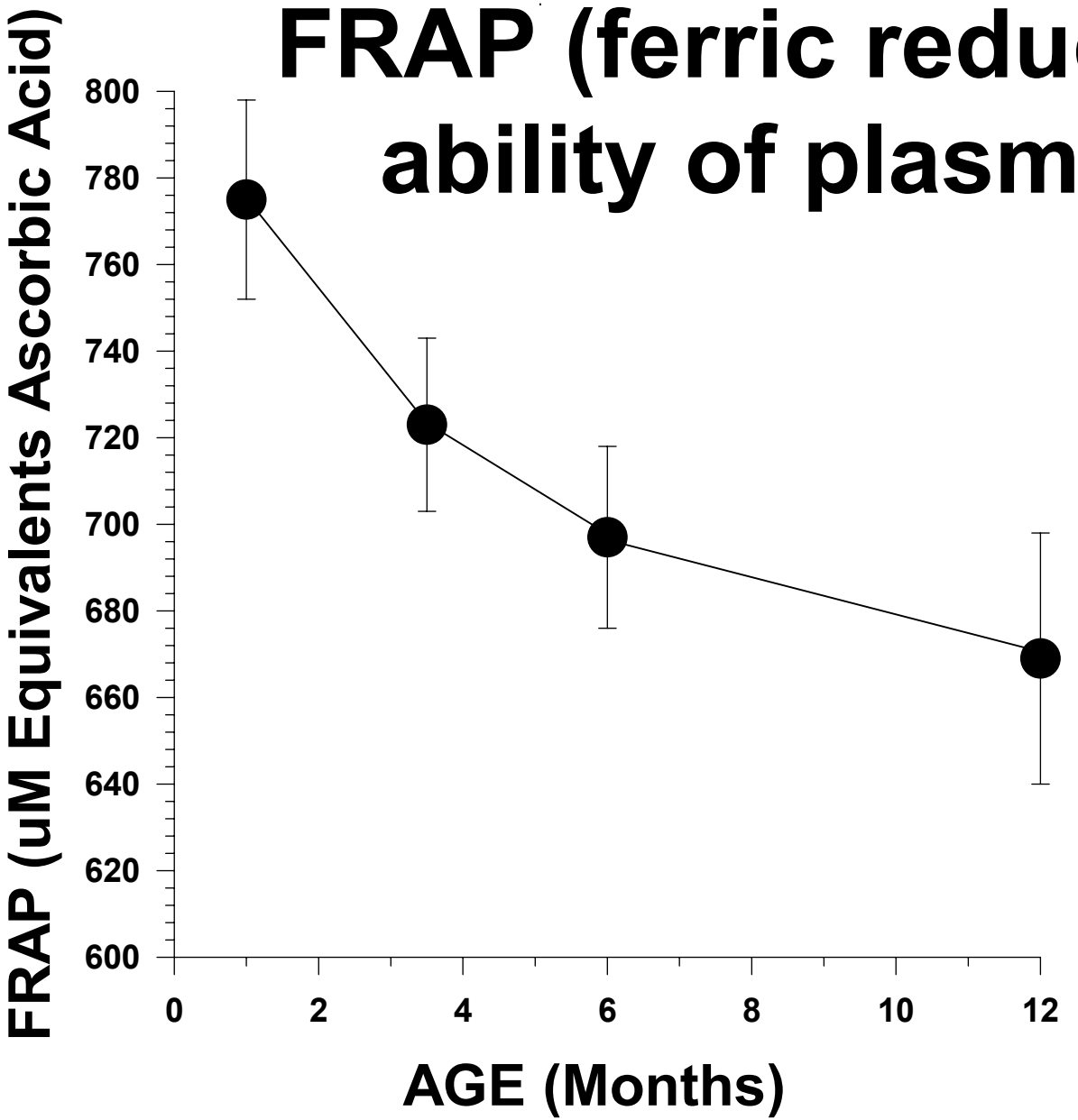
(as if birth wasn't hard enough!)

- What happens after birth?
- We studied seventy-seven healthy full-term infants uncomplicated pregnancies, all breast-fed...as normal as you can get!



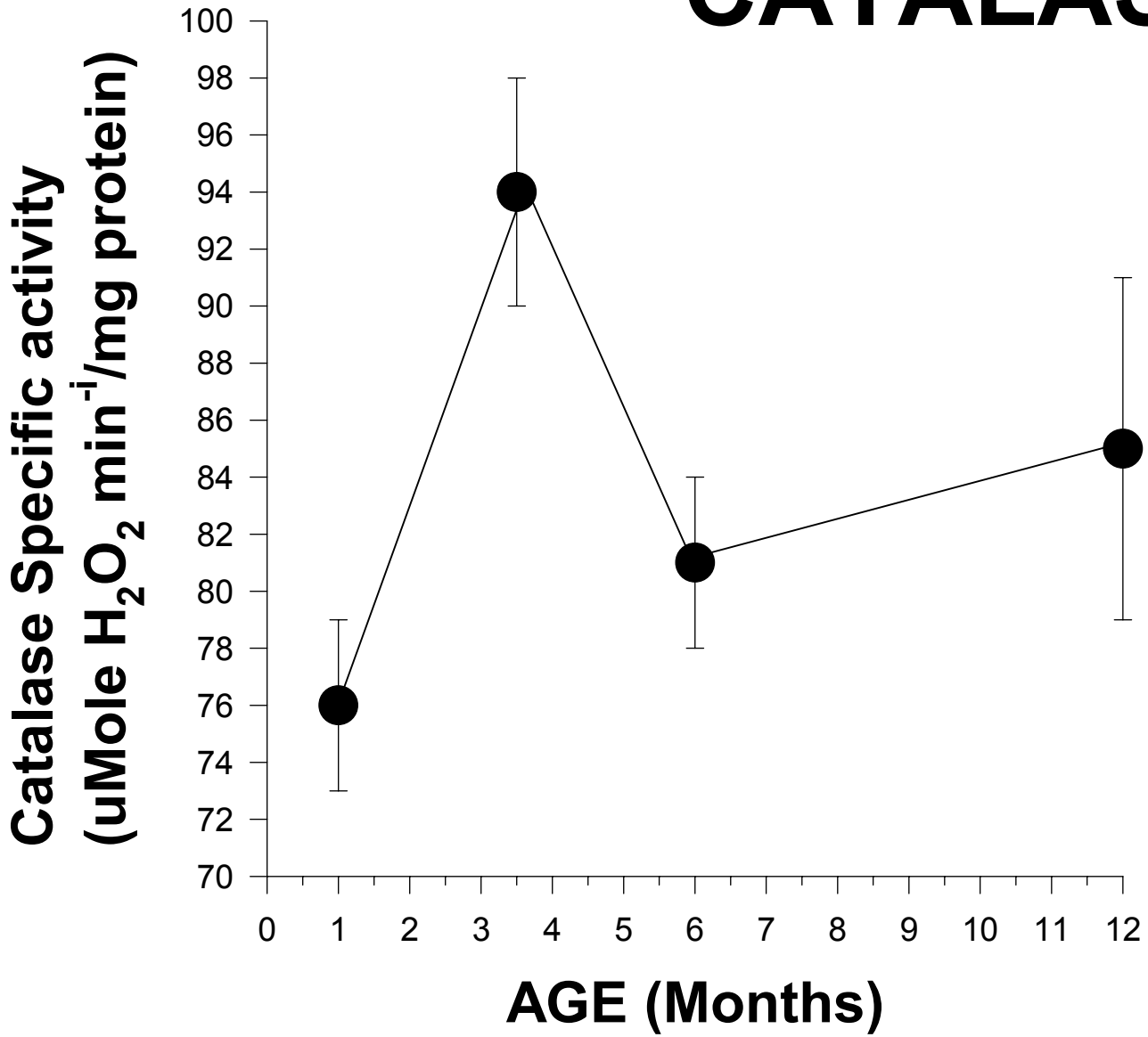
Lipid peroxidation was extremely high early in life declining to normal adult values at 6 months

FRAP (ferric reducing ability of plasma)

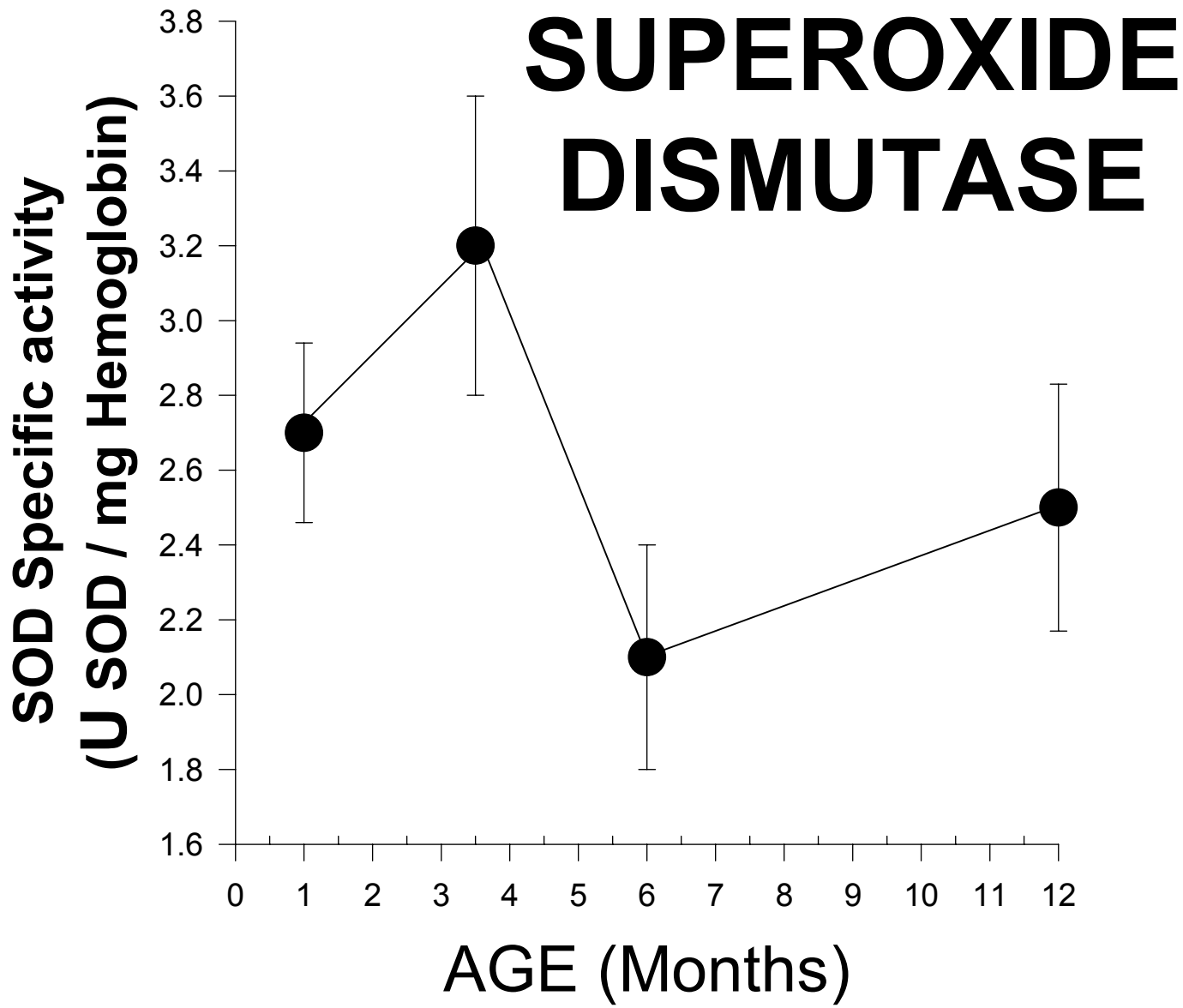


Ability to resist oxidative stress declines with age.

CATALASE



Rise and fall may have to do with changeover of fetal to adult RBCs



Early adaptation to life is reflected by adjusting oxidative status

FEEDING

- TAKEN FOR GRANTED
  - MULTITUDE OF FOODS TO MEET NEEDS
- CRUCIAL FOR THE NEWBORN
  - OFTEN A SINGLE SOURCE FOR THE FIRST 6 MONTHS OF LIFE
  - As much medicine as food i.e. Premature

FEEDING AS A WAY OF COPING WITH ROS

- Beginning of food intake stimulates higher hepatic metabolism rate as well as oxygen consumption and may affect antioxidant defenses
- Human milk provides antioxidant protection in early life with the direct ability to scavenge free radicals, not seen in artificial infant feeds
- Antioxidant enzymes glutathione peroxidase (GPx), catalase (Cat) and superoxide dismutase (SOD) are present in human milk, but not in formula

SUMMARY

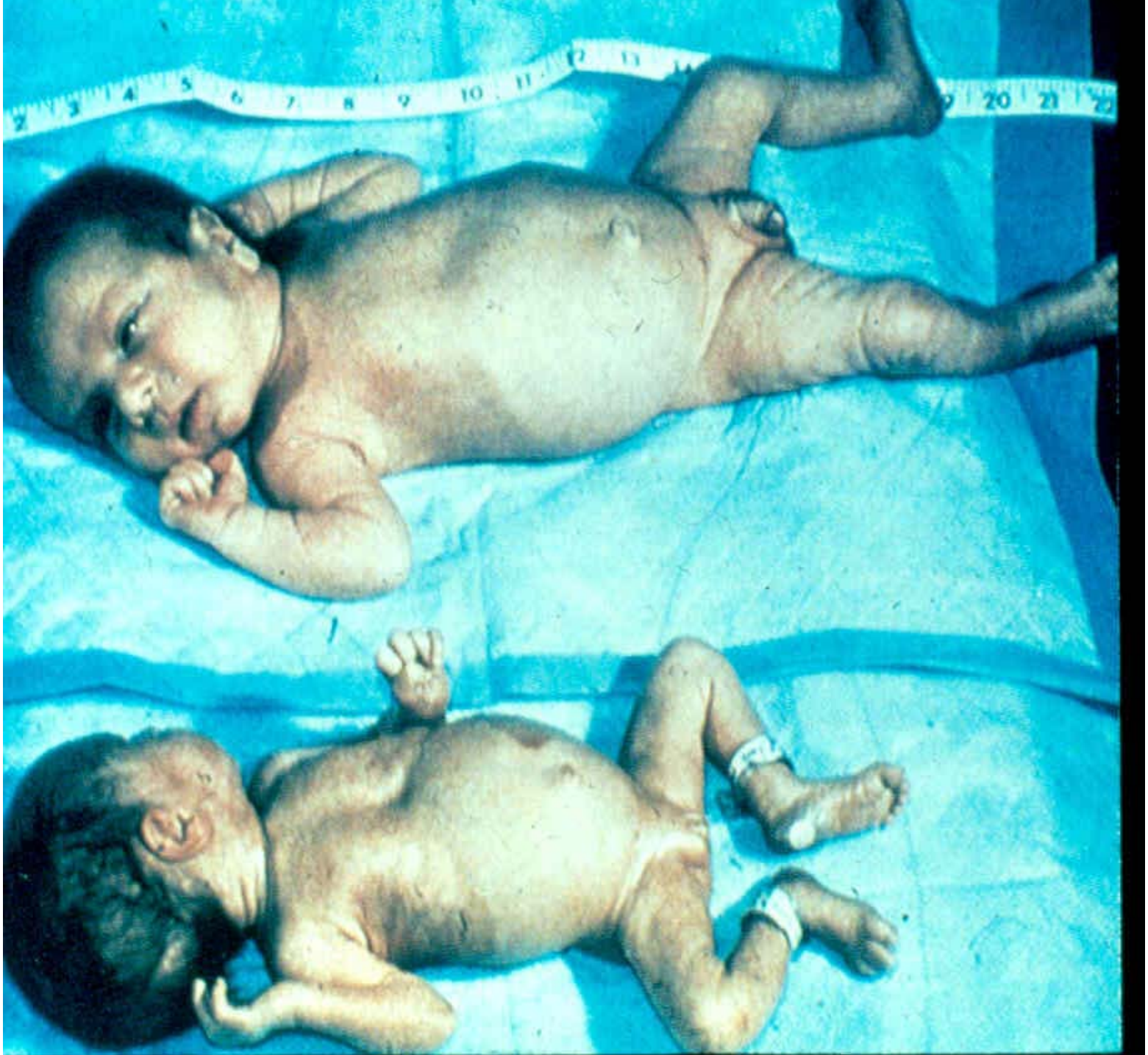
- Full-term births are about 93% of all births
- Transition from hypoxia to relative hyperoxia poses problems for some
- Endogenous defenses can be complimented with human milk feeding

THE PREMATURE INFANT

DEFINITION

- < 37 weeks gestation
- LBW less than 2500 g birthweight
- VLBW less than 1500 g birthweight
- ELBW less than 1000 g birthweight

- Leaving the uterus early is not in itself harmful whereas growing less than normally during a full uterine stay may imply pathology of fetus, placenta or mother.



THE PREMATURE INFANT

- Preterm births account for 7.1% of birth
- The incidence of preterm birth has increased 3.2% between 1978 and 1996 and continues to increase
- Preterm births are responsible for 75-85% of all neonatal (first month) deaths

DESCRIPTION

- Cannot maintain body temperature

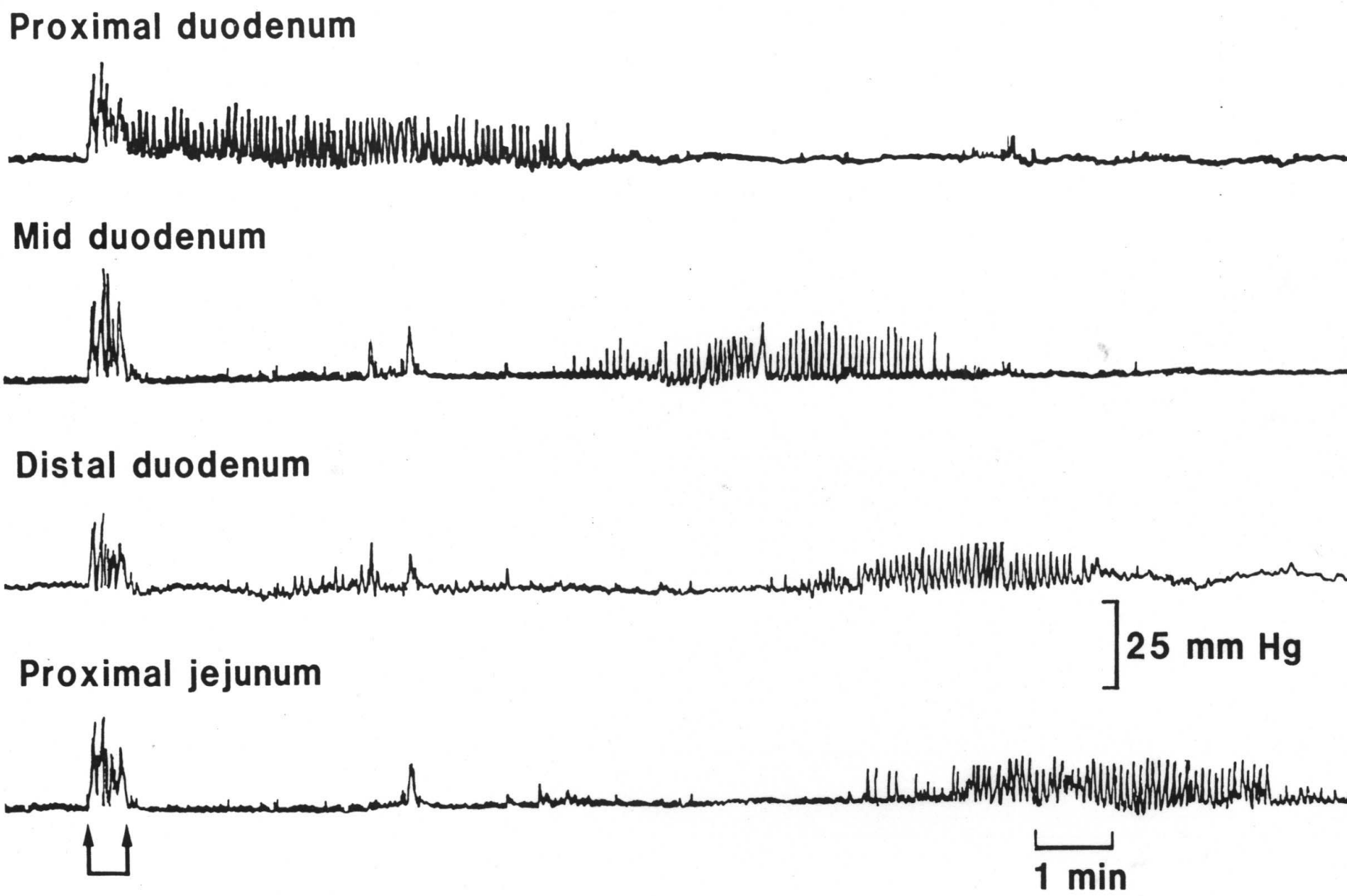
  Therefore O_2 consumption ↕ → ↑ hypoglycemia → ↑ acidosis → ↑ chilling
- Low fat + thin transparent skin

  Blood supply → ↑ permeability → ↑ H_2O & electrolyte loss
- Immature lung-respiratory control

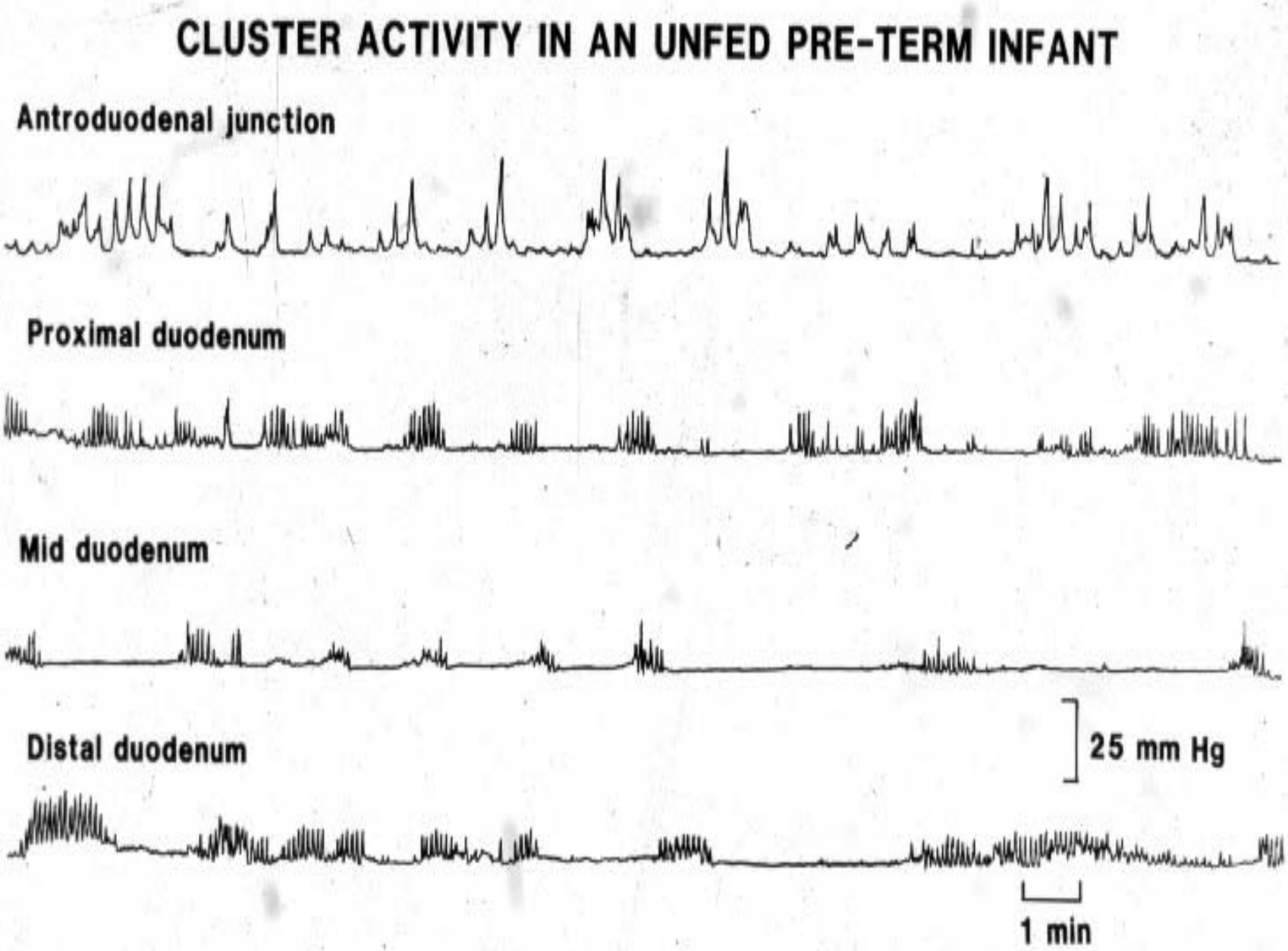
  respiratory distress syndrome
- Immature liver

  jaundice, bilirubin ↑(kernicterus)
- Many premature infants cannot suckle and swallow

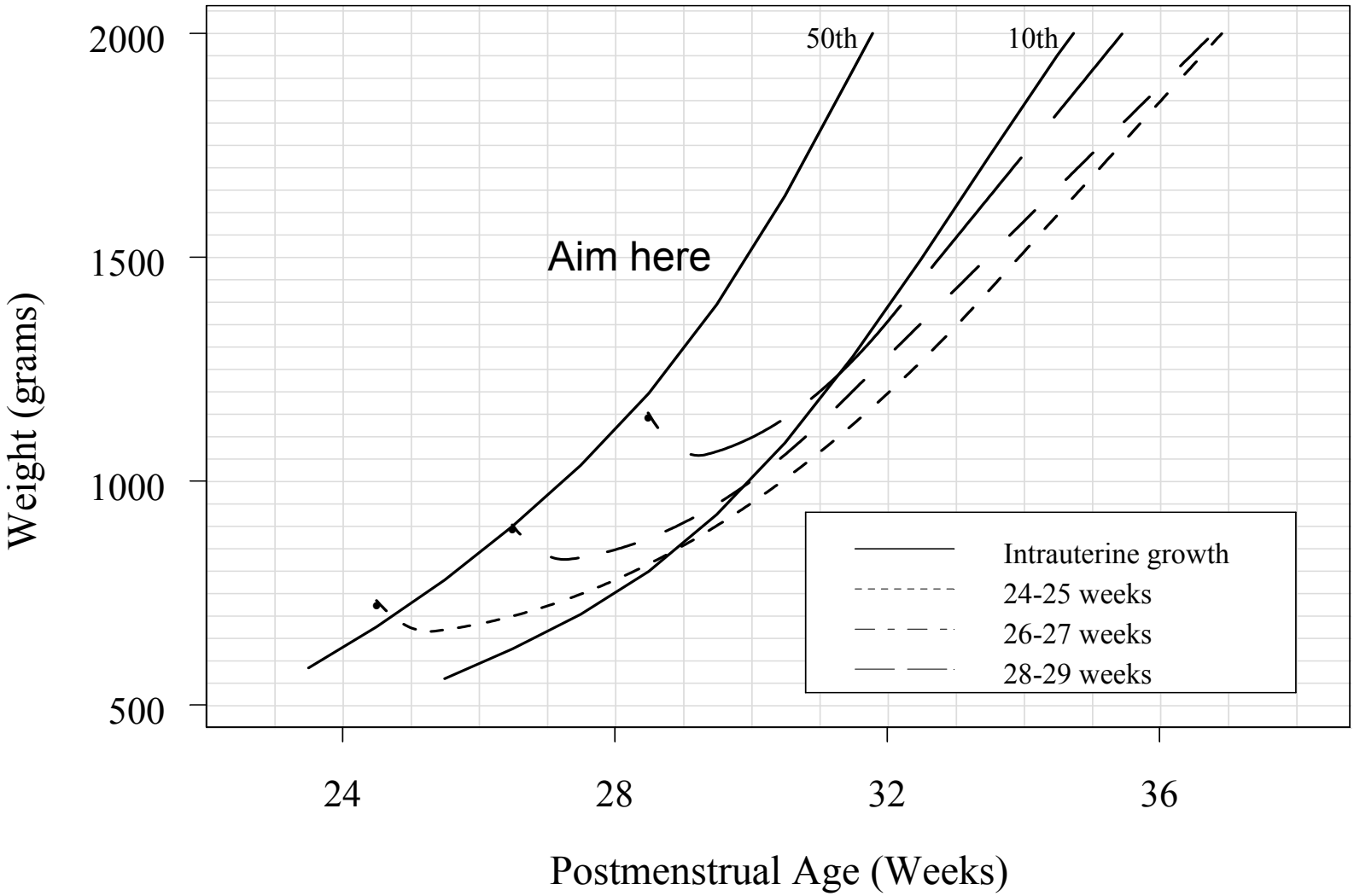
MIGRATING MOTOR COMPLEX (MMC) IN A TERM INFANT



Small intestinal motor patterns are more immature in neonates than children and adults



Postnatal Growth of VLBW Infants vs Expected Intrauterine Growth

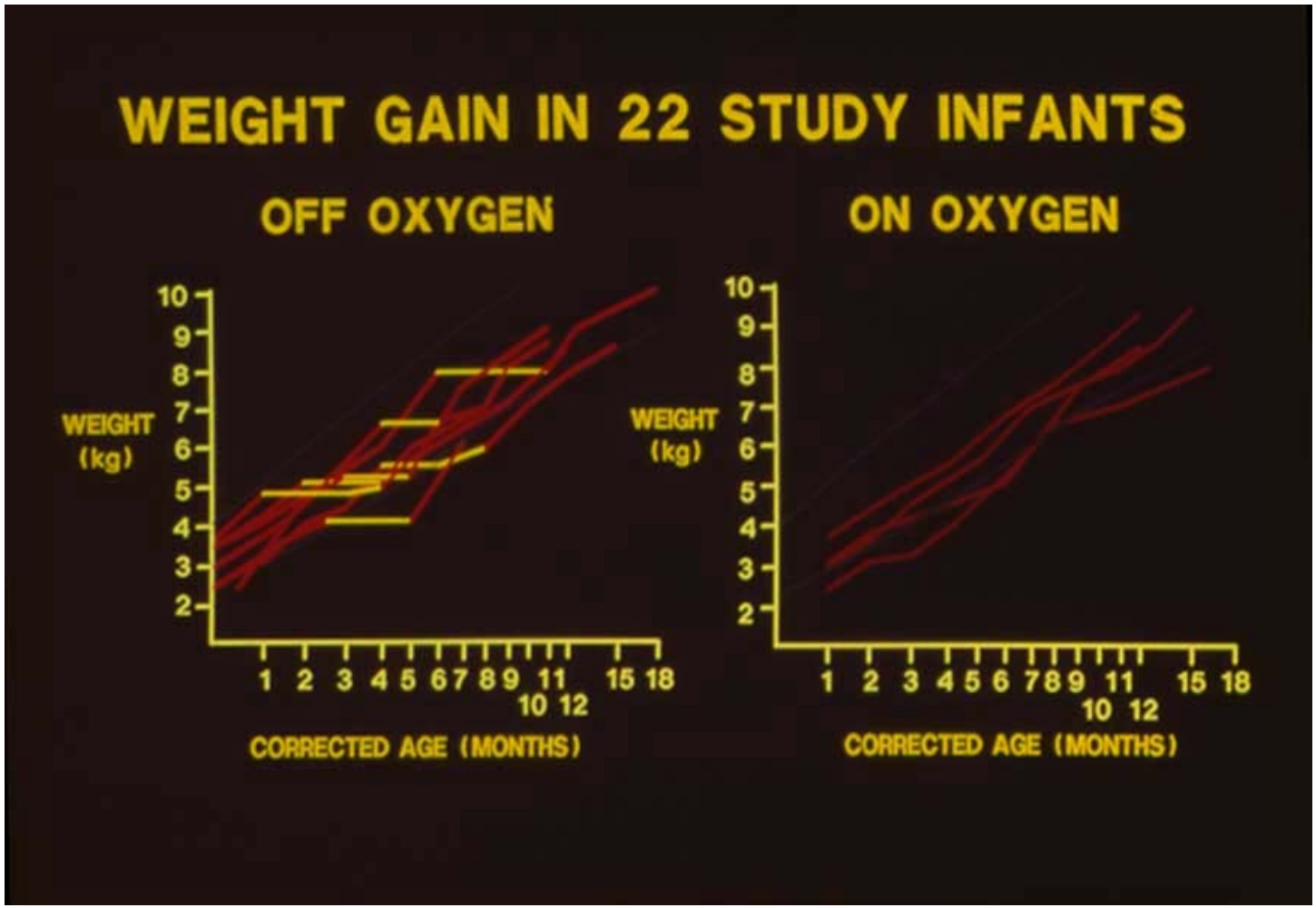


Infants born prematurely do not grow as well as if they had stayed in the womb

OXYGEN

- Too little at birth - lungs don't work (Hypoxia)
- Too much during treatment after birth (Hyperoxia)
  - ***Oxygen is a nutrient? Drug?***

Infants with Bronchopulmonary Dysplasia (BPD) did not grow when their parents took them off oxygen. (Groothuis and Rosenberg)



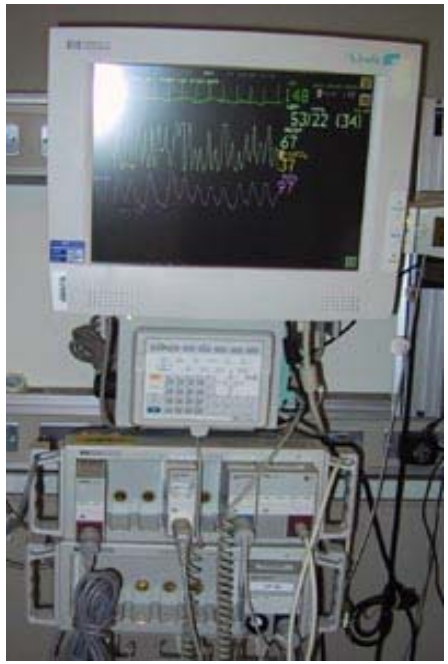
Supplemental Oxygen

- COMMON for treatment in premature neonates with immature lungs
- Source for oxidant stress (ROS)
- Oxygen can also be delivered with a mechanical ventilator

INCUBATOR

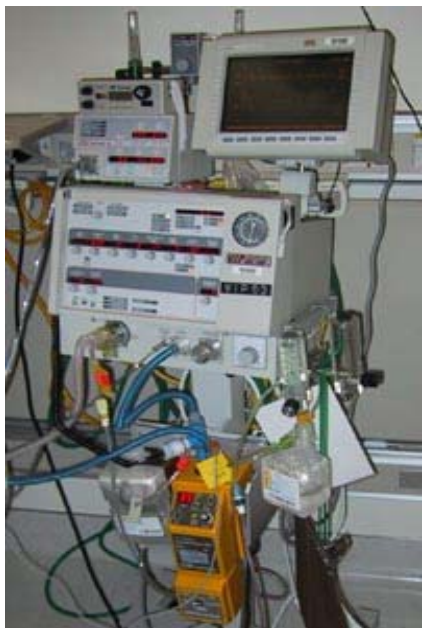
PHOTOTHERAPY

PHYSIOLOGIC MONITOR



Some of the equipment needed to keep infants alive

VENTILATOR



PULSE OXIMETER

INFUSION PUMP

PERINATAL OXYGEN CONSUMPTION

	mL/kg/min
Fetus (estimate)	5.0
Newborn, at birth (n=32)	5.4 ± 2.3
RDS, ventilated (n=14)	6.8 ± 2.3
RDS, not ventilated (n=14)	8.3 ± 3.5
BPD, ventilated (n=10)	9.2 ± 2.4
BPD, not ventilated (n=7)	10.4 ± 1.8

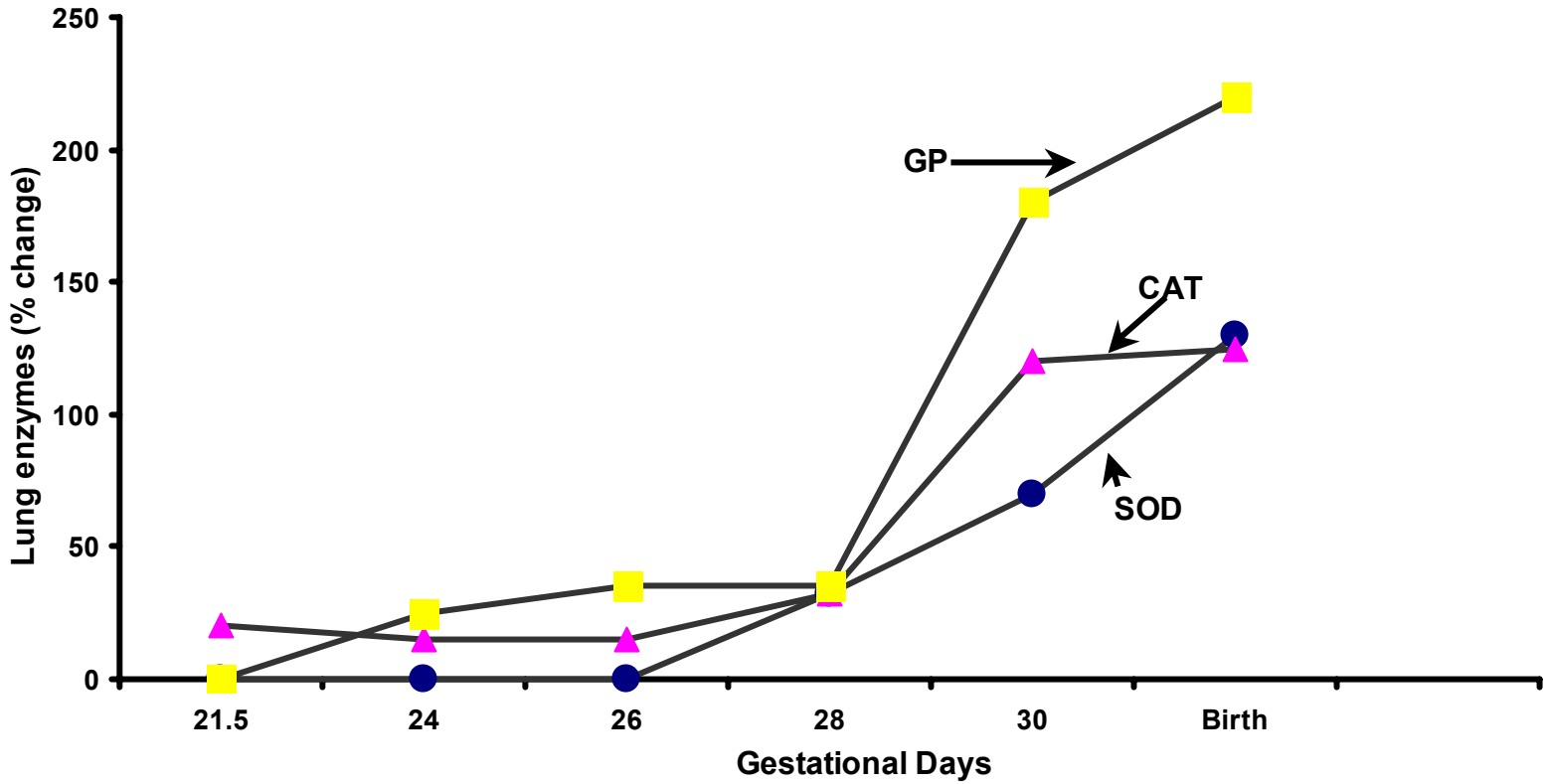
$\bar{X} \pm SD$

Oxygen consumption goes up with disease

Anti-oxidant enzymes & Hypoxia

- The maturity of the antioxidant enzymes CAT, SOD, GPx, peak in late gestation in different species
- Severe hypoxia possibly enhances inactivation of SODs and other AOE
- Prenatal hypoxia disrupts normal developmental expression of EC-SOD
- Postnatal hypoxia $\rightarrow$ $\downarrow$ MnSOD activity (most studies) but $\uparrow$ MnSOD activity w/ tolerance to hyperoxia (rats)

AOE maturation



Adapted from Frank et al, 1987

Hyperoxia

- Postnatal hyperoxia → induction of MnSOD; little/no change in CuZnSOD/ CAT; GPx ↓; ECSOD →age dependant & susceptible to oxidative/nitrosative damage

- After birth, CAT and GPx increase continuously to 9 days with oxygen exposure in a rat model (but not SOD)

Postnatal oxygen exposure will tax the ability to maintain homeostasis

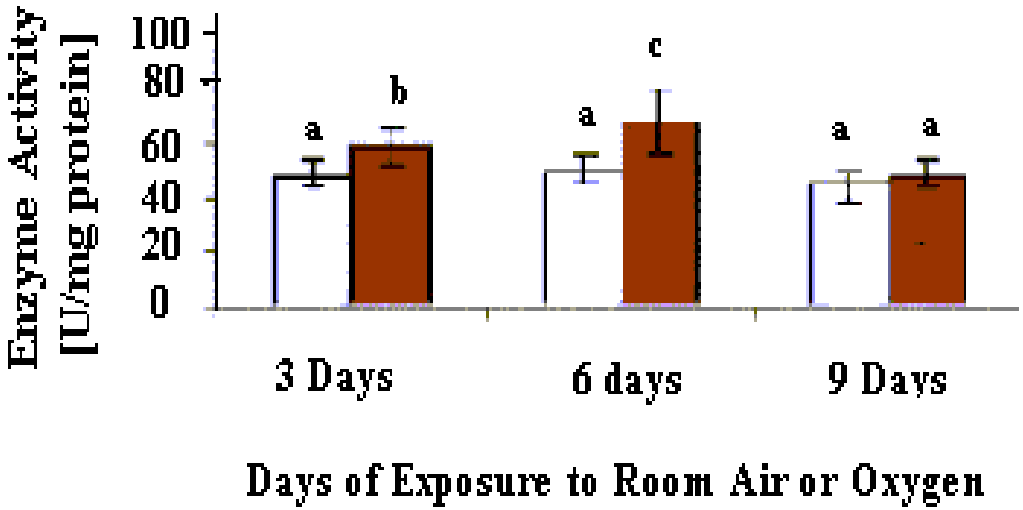


Fig. 1 The effects of high O_2 on Cu/Zn-SOD activity in newborn rat liver. The light bars represent room air, the dark bars oxygen exposure. Groups with different letters are different from each other. Data are mean ±SEM.

ROS: their effects

- Plasma and urinary MDA is increased in premature infants exposed to supplemental oxygen
- Berger found increased oxidative stress in premature infants due to unbound iron in the blood
- Ethane and pentane, both volatile products of peroxidation were correlated with poor respiratory outcome and death
- Protein carbonyls in lung tissue were increased in subjects with BPD
- Schmidt found both increased MDA and 4-hydroxy non-2-enol in cord blood of hypoxic infants as well as reduced GSH
- Increased urinary o-tyrosine was associated with increased inspired oxygen
- Buonocore found increased oxidation in the cord blood of hypoxic newborn infants
- Kelly suggests that ***Free radical production exceeds the normal antioxidant capacity of the infant.***

How do ROS affect the Diseases of Prematurity?

Preterm infants:

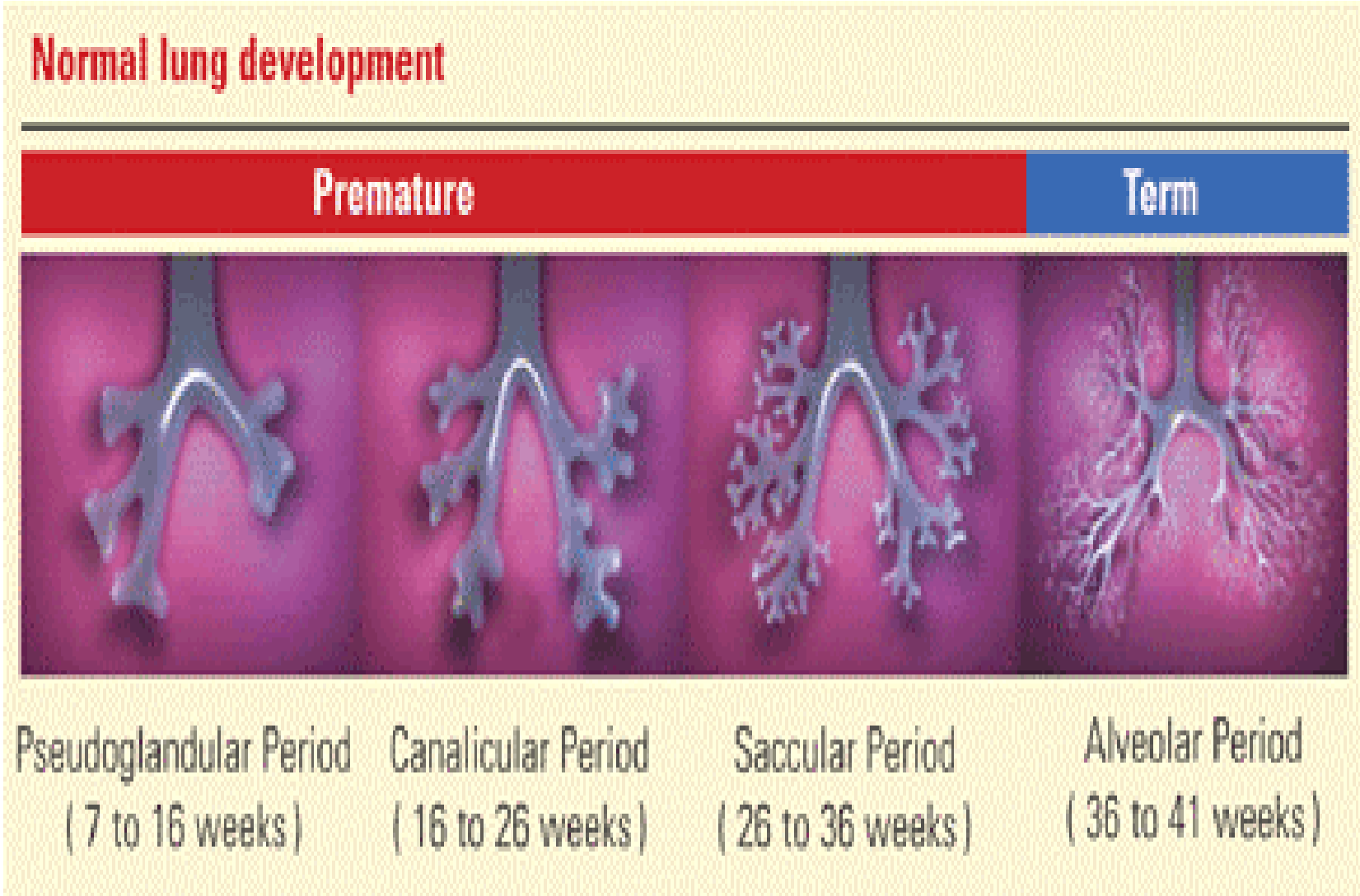
1. Low endogenous antioxidant enzymes
2. Low levels of free radical scavengers
3. Higher production and lower protection against ROS

- Respiratory distress syndrome (RDS)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Retinopathy of prematurity (ROP)
- Bronchopulmonary dysplasia (BPD)
- Necrotizing enterocolitis (NEC)

Bronchopulmonary Dysplasia (BPD)

- Chronic lung disease when treated with oxygen and mechanical ventilation (barotrauma)
- Results in disordered lung growth (dysynaptic) and ↓ in # alveoli
- May interfere with nutrition and growth
- Life long decrease in lung function

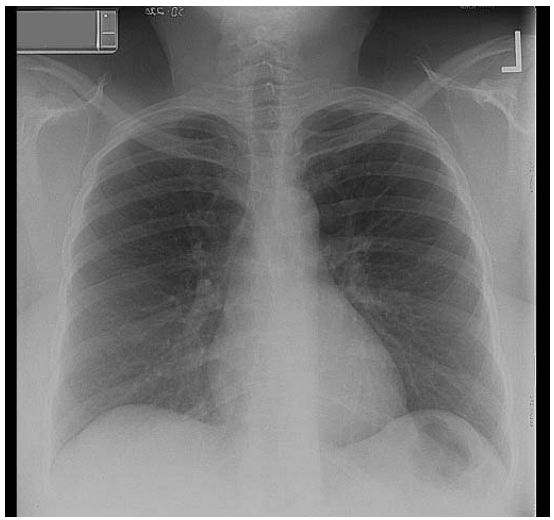
- **WHY??**



Retrieved from:http://www.synagis.com/images/hcp_sub/content_pics/chart28.gif

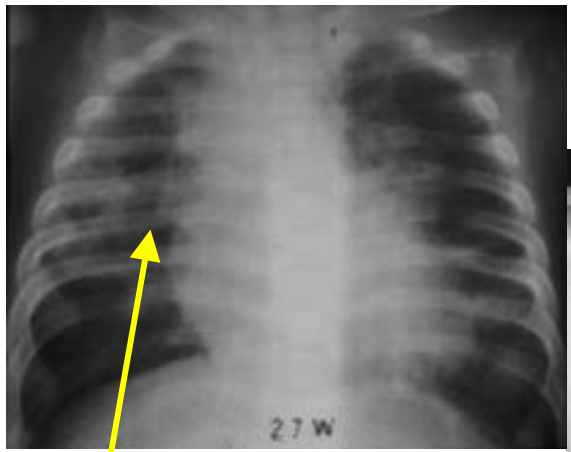
BPD

- Normal CXR



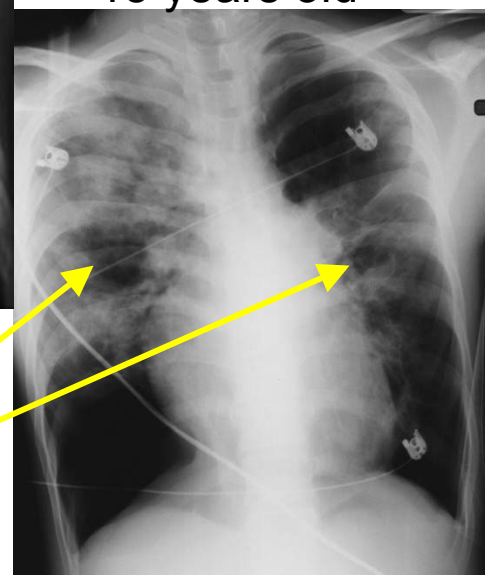
- BPD

6 months old



Early changes

15 years old



Chronic changes

BPD

- Postnatal therapies exist to reduce severity of BPD include surfactant/ Vitamin A/ Postnatal steroids/nutrition
- Costs > $60 000 USD/infant (NICU costs alone, doesn't include significant post infancy health care/societal costs)
- Could be practically eliminated if NO premature births (but premature birth rates are increasing)
- Baby boys have a 40% greater incidence of BPD

FEEDING

is more difficult in the premature

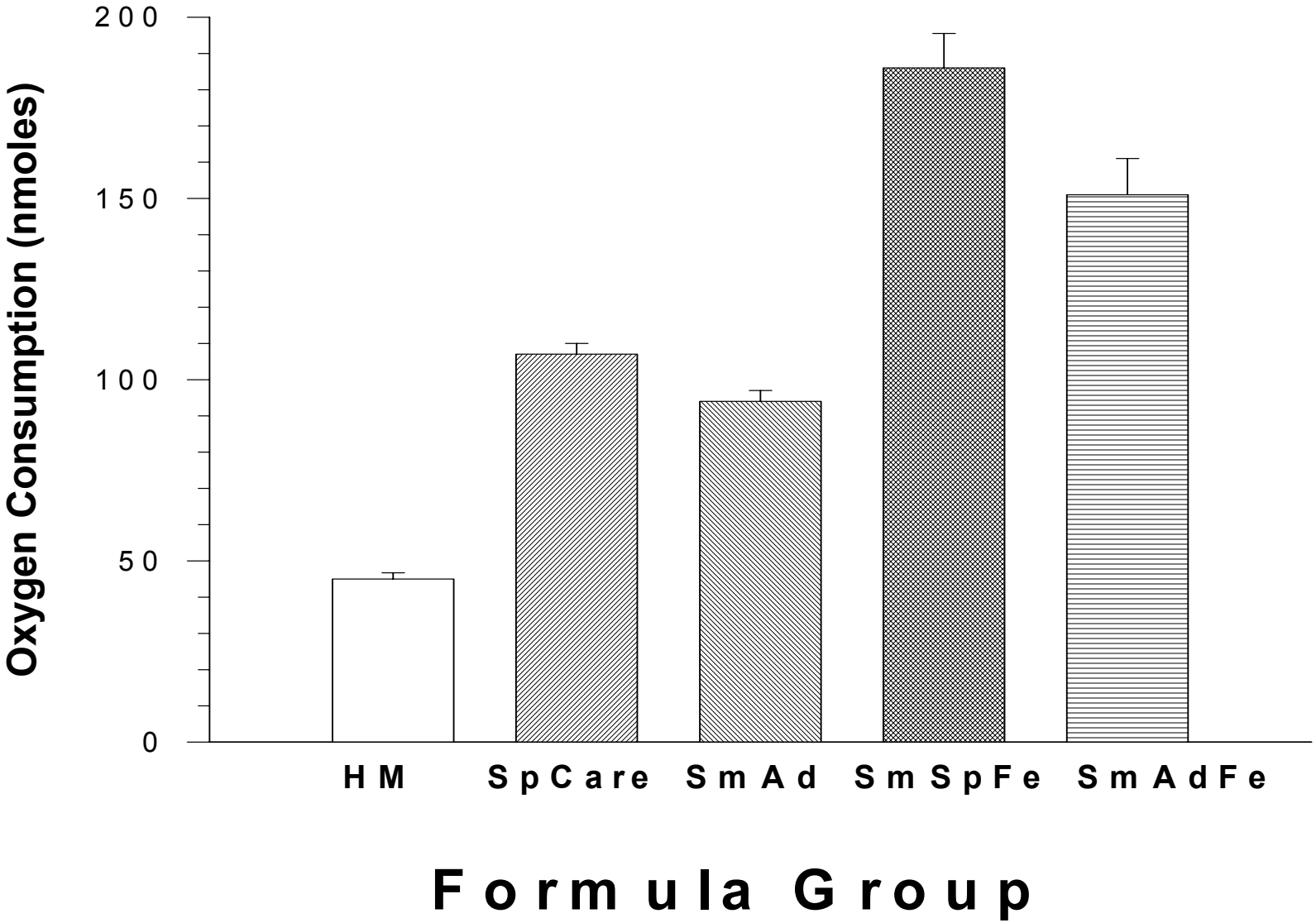
- Enteral Feeding: usually by tube
  - First feeds are to “prime” the gut
  - Optimal feeding: human milk + supplements
  - *Oxidative products*?

- Parenteral Nutrition
  - Central vs peripheral access to bloodstream
  - Complete nutrition in “elemental” form
  - *Are oxidative products formed*?

HUMAN MILK IS BETTER THAN ANY FORMULA

- Bioactive molecules including enzymes
- Better scavenger of ROS
- Less disease
- Human milk was superior in resisting oxidative stress in all studies where compared to formula

Human milk (HM) consumed less oxygen when exposed to ROS than did premature formulas

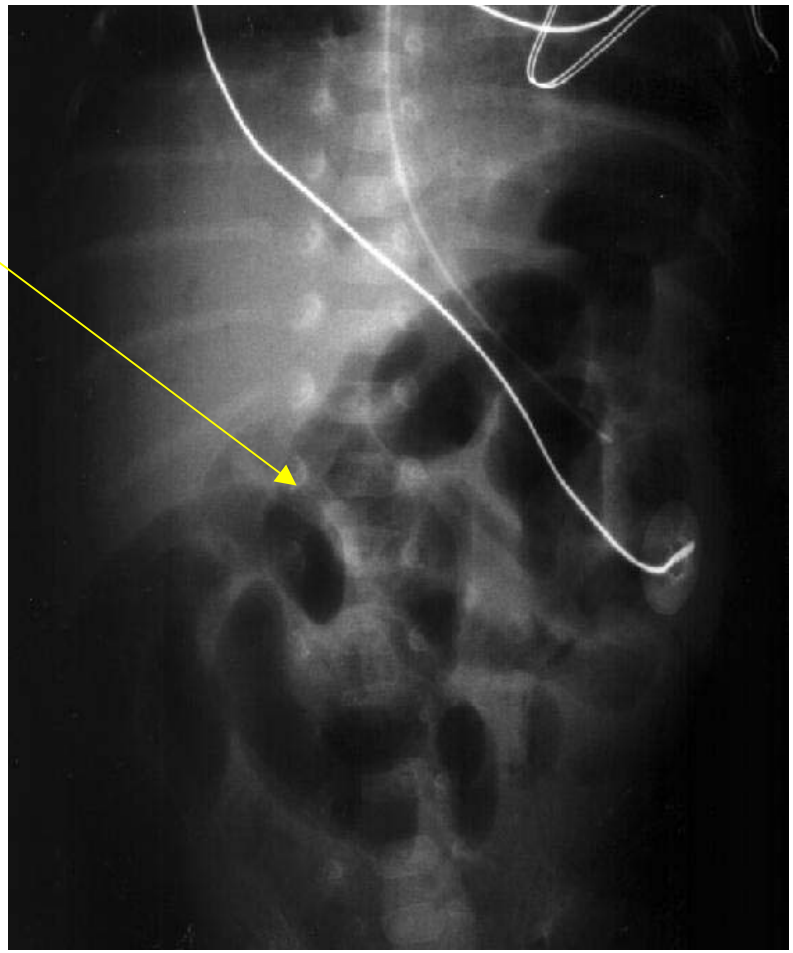


DO WE UNWITTINGLY CONTRIBUTE TO OXIDATIVE STRESS?

- When feeding the premature infant, nutrient supplements are routinely added to HM
- Routine supplements provide energy, iron, vitamins and minerals
- There is no established protocol for preparation of these supplements
- What is the food chemistry involved? What risk for lipid peroxidation? Could we contribute to gut disease (NEC)?

Necrotizing Enterocolitis

- Inflammation and necrosis of intestinal tissue
- Incidence- 2.4 in 1000 live births in U.S.
- Occurs a week to ten days after the initiation of feedings
- Death rate- 25%



Fenton Chemistry

- Ferric iron generates reactive oxygen species as follows

$Vit\ C/\ E + Fe^{3+} \rightarrow Fe^{2+}$

$Fe^{2+} + O_2 \rightarrow Fe^{3+} + \cdot O_2$

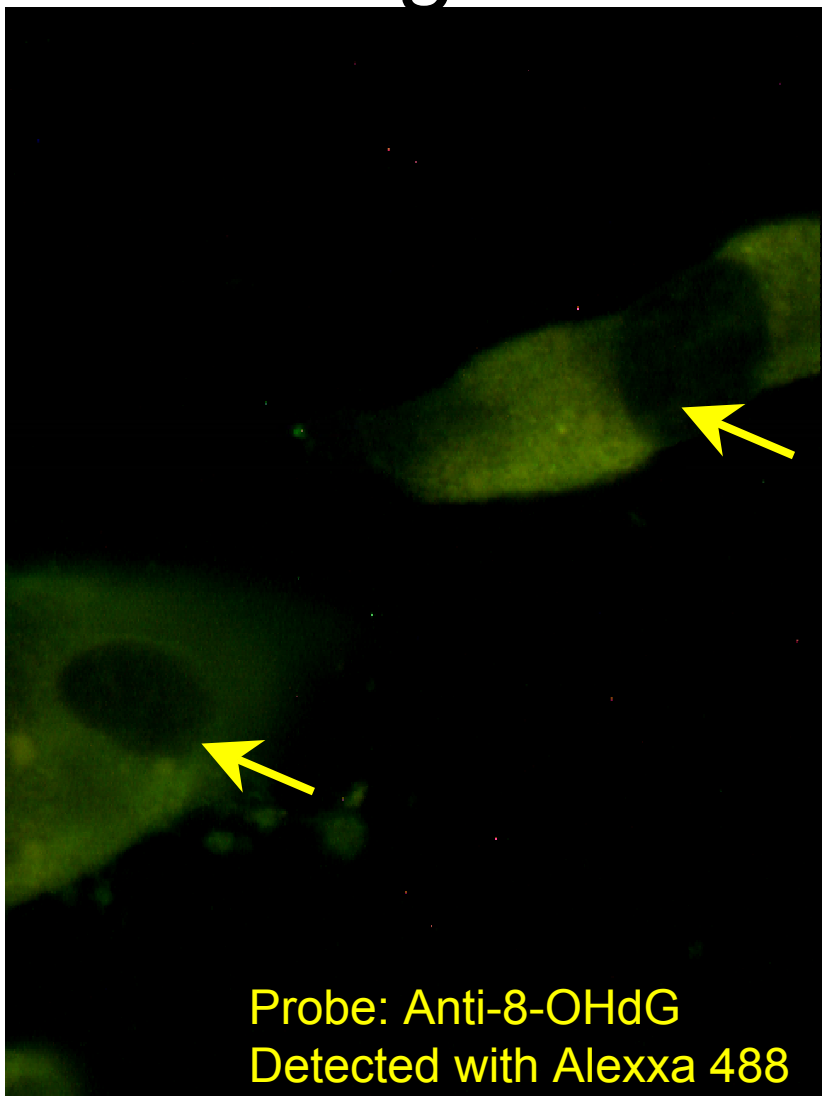
$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$

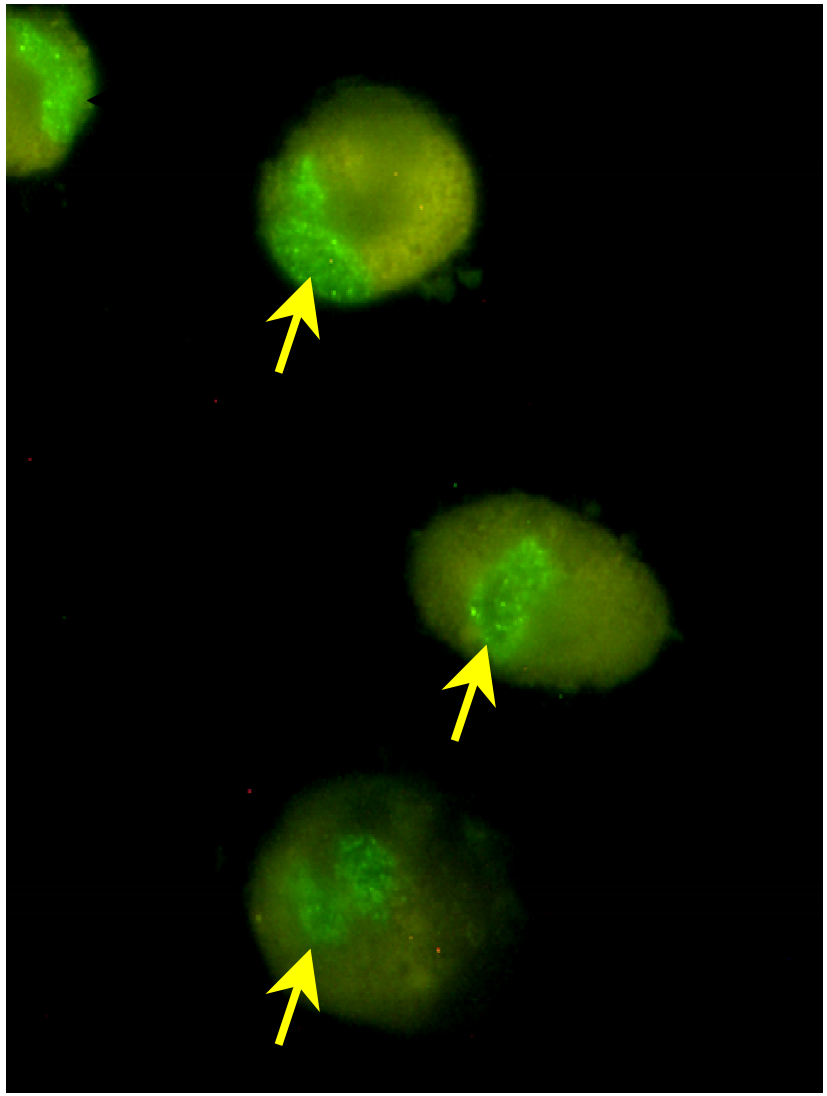
Human milk with or without iron was added to cell culture (next slide)

Left-no iron; Right-iron, damages nucleus

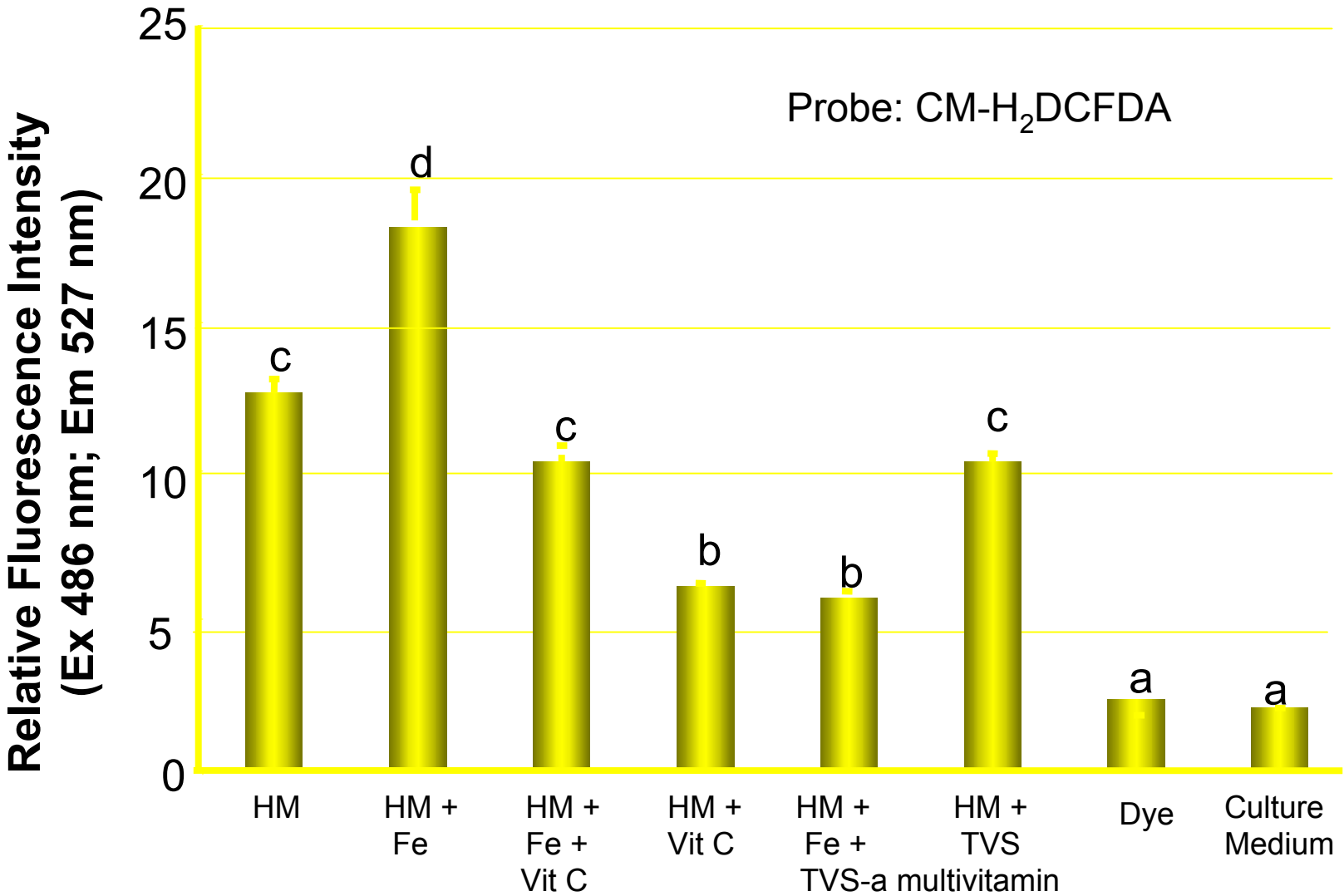
http://www.meadjohnson.com/products/hcp-infant/....html

Effect of Supplements on DNA Damage in FHS 74 Int Cells …





Effect of Other Supplements on ROS in FHS 74 Int Cells

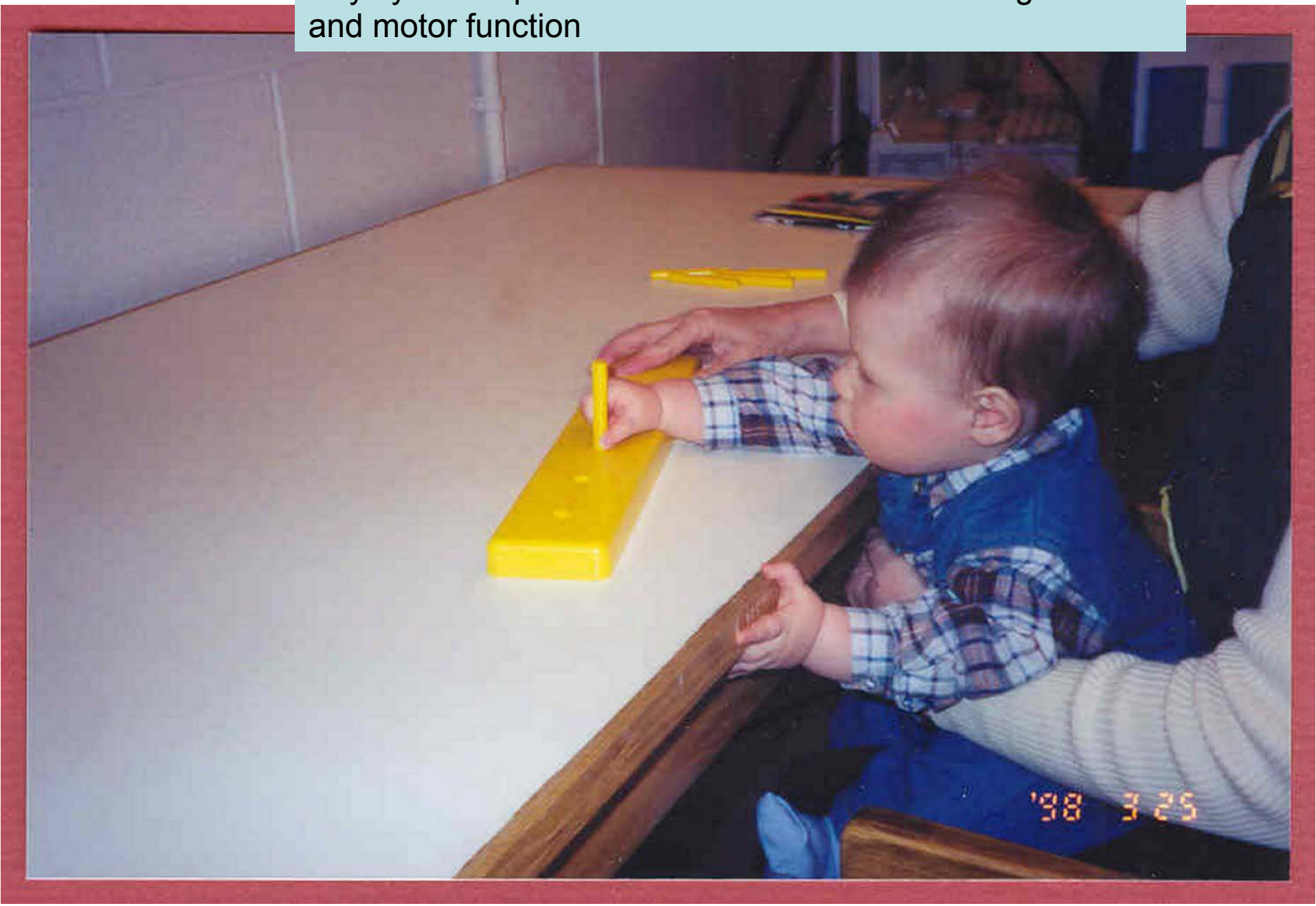


BRAIN/COGNITIVE DEVELOPMENT IN THE PREMATURE INFANT

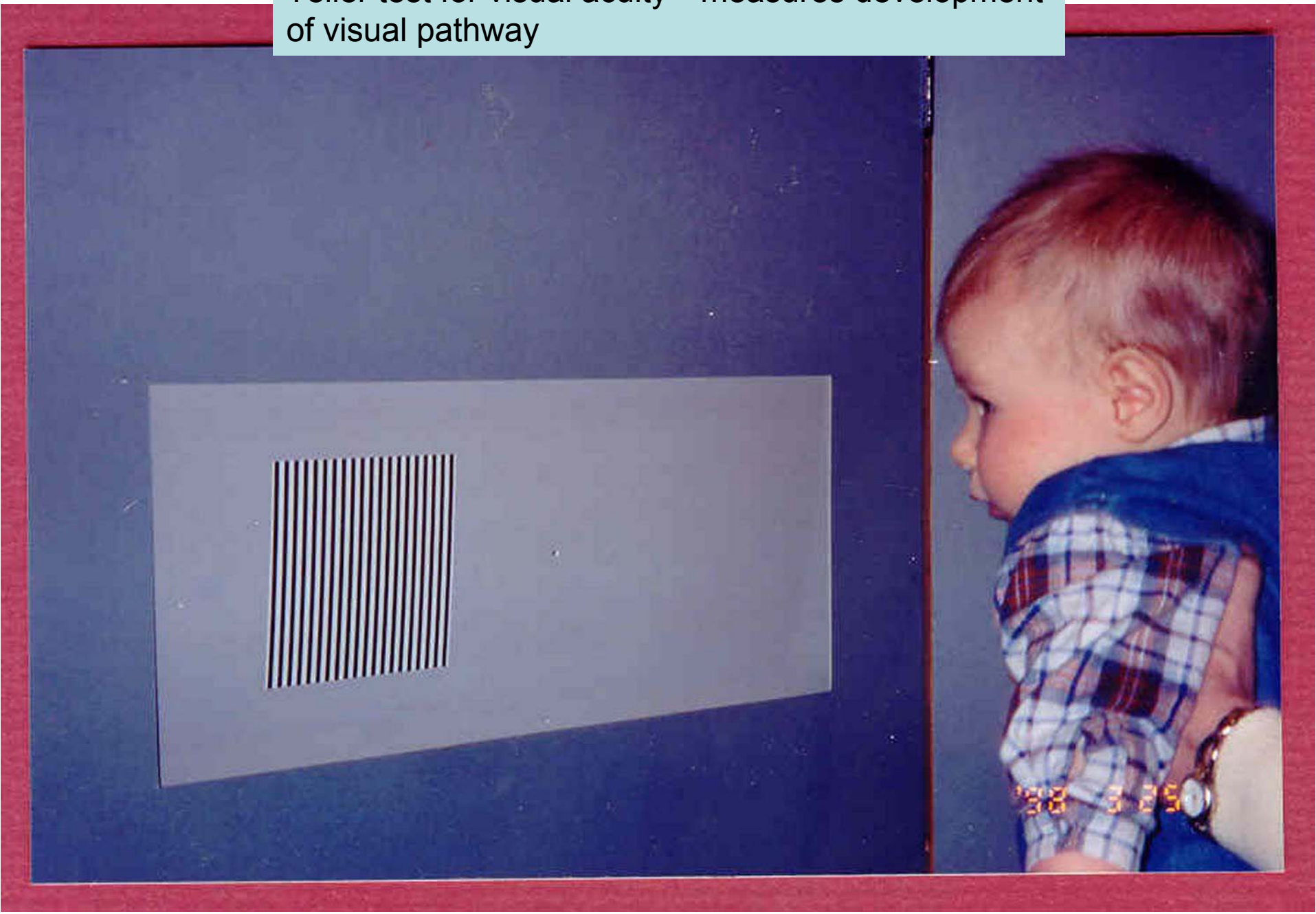
- THE STORY DOES NOT END THERE

- ROS affect the infant before during and after birth
- ROS affect the infant LATER

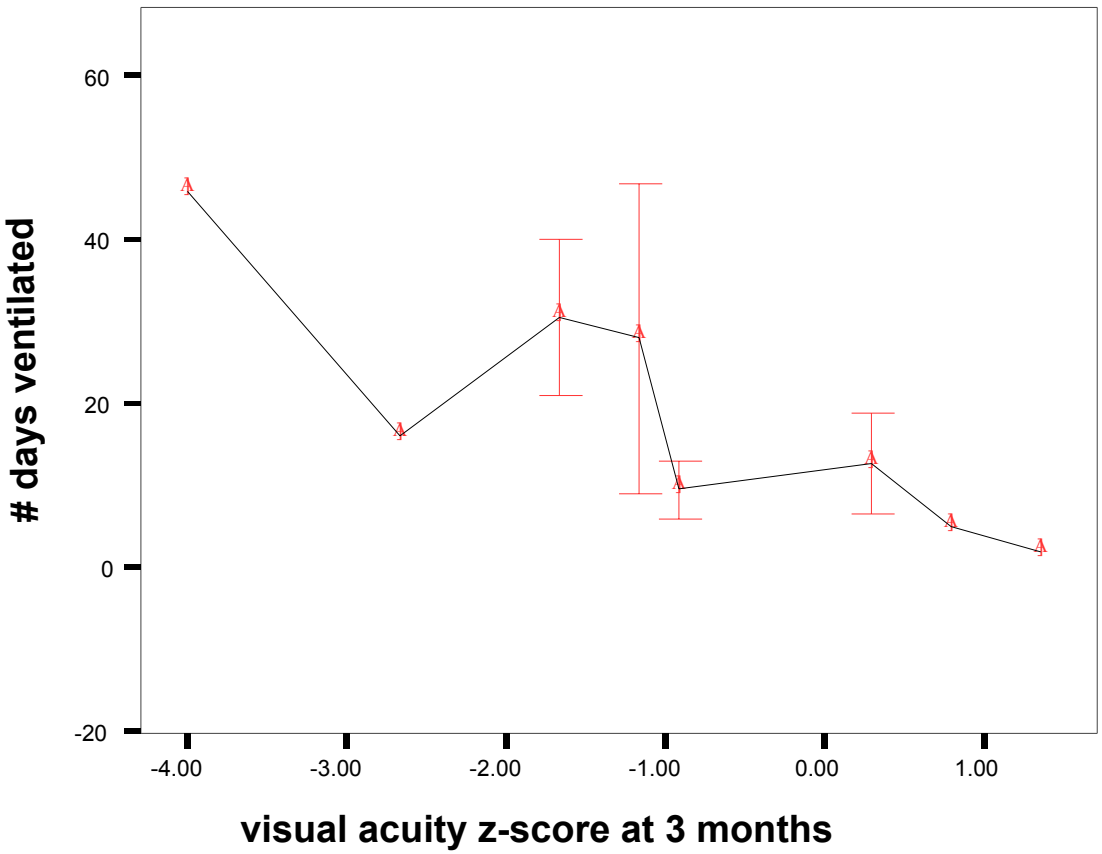
Bayley developmental assessment-measures cognitive and motor function



Teller test for visual acuity—measures development of visual pathway



Pilot study: Duration of exposure to supplemental oxygen in the neonatal period was negatively related to visual outcome at 3 months (n=27).



RESULTS (P < 0.05)

- ***# Days on Assisted Ventilation (oxygen administered by mechanical pump from birth), related to…….***
  - CAT-Day14 r = 0.97 (n=7)
  - F2 Isoprostane-Week 3 r = 0.89 (n=5)
  - F2 Isoprostane-Week 8 r = 0.75 (n=7)

- ***Visual acuity Scores at 3 months Related to***
  - MDI (3-12) r = 0.70 (n=17)
  - # days Ventilated r = -0.61 (n=15)
  - GHSPx-Day28 r = -0.79 (n=8)
  - SOD-Day14 r = -0.77 (n=7)
- ***Visual acuity Scores at 6 months Related to***
  - CAT 3 Month r = -0.63 (n=14)
  - CAT 6 Month r = -0.61 (n=14)

SUMMARY

- Birth is a hyperoxic challenge
- Month 1 is an adaptive challenge
- Year 1 of life is a vulnerable time

- Oxidative stress can exact a toll in mortality and morbidity at each stage

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