Energy Metabolism and Thermoregulation in the Newborn Infant

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In this chapter the theoretical basis of energy metabolism and thermoregulation will be outlined. The experimental observations made by us and others in recent years on the relationship between thermogenesis and utilization of nutrients in the newborn infant will also be summarized. Selected aspects of neonatal energy metabolism and thermoregulation will be discussed in the following order: physiological and biochemical basis of thermogenesis; principles of measurements of heat production and heat loss; energy requirements in the thermoneutral environment; during metabolic response to cold; in a warm environment; and under pathological conditions such as malnutrition and hypoxia.

THE PHYSIOLOGICAL AND BIOCHEMICAL PRINCIPLES OF ENERGY METABOLISM AND THERMOREGULATION IN THE NEWLY BORN

A diagrammatic outline of the heat exchange routes in the body is depicted in Fig. 1. Body temperature is maintained within a normal range as the amount of stored heat is balanced by net heat gain and loss. Understanding of the various components of heat loss and heat gain is especially important for neonatologists, because until newborn infants and young children reach the advanced state of development when they can effectively use behavioral thermoregulation to maintain thermal comfort, nurture by parents and adults should protect them against the thermal hazards of the outside world. These vulnerable patients can easily lose heat by:

(a) Conduction ($H_d$) when they are placed on a nonheated table during diaper change, blood sampling, or tracheal suction, etc.
(b) Convection ($H_c$), for example in an incubator when the servo-control does not provide constant temperature of the circulating air.
(c) Radiant heat exchange ($H_r$), i.e., a transfer of electromagnetic energies between facing surfaces. Radiant heat loss is common in air-conditioned newborn nurseries, when the infants are kept in single-walled incubators.
(d) Evaporative heat transfer ($H_e$), which depends on thermal transfer during the conversion of a material from liquid to a gas phase. For example, heat disposition by evaporation from condensation on the skin and the surfaces of the respiratory tract. Through the transparent, watery skin of the premature infant the evaporative heat loss can comprise of up to 50% of total heat loss.

Many components of heat loss are dependent on the surface area of the subject. Newborn infants having a large surface area relative to body weight are disadvantaged from a thermoregulatory point of view and especially susceptible to radiation and evaporative heat losses in spite of all good intentions of the medical and nursing staff who take care of them. In order to keep the body temperature in the normal range, the heat loss should be compensated by the same amount of heat gained through metabolism or conduction ($H_d$), convection ($H_c$), and radiative ($H_r$) heat transfer. Metabolic heat production ($H_m$) relates to the transformation of chemical energy into heat and mechanical work by aerobic and anaerobic metabolic activities within the organism. In thermal physiology metabolism invariably relates to the transformation of chemical energy into free energy. Thus energy metabolism is the sum of the chemical changes in living matter in which energy is transformed.

From where is this chemical energy derived? Basically it is from two sources: from chemical energy of the food and from energy stores in the macronutrients of the body, namely carbohydrates, fat, and protein. Since the latter energy store is also built up from external sources, one can state that the only useful energy source for animals and man is the chemical energy supplied by food. Heat is a by-product of metabolism; in other words, heat is a fringe benefit of mitochondrial oxidation, and ATP is the net income that maintains life. Utilization of food energy in a living organism in steady state is demonstrated in Fig. 2. The transformation of chemical energy from food or from endogenous substrates such as glycogen, triglycerides, or protein to high energy phosphate bonds is never complete and insures the capture of about 55% to 60% of the initial energy in ATP.
FOOD ENERGY

Inefficiency of energy transfer

Heat 40-60%

ATP

55-60%

Cell maintenance

Internal work

Heat 20-40%

Muscle contraction

External work 0-20%

FIG. 2. Diagrammatic outline of the utilization of food energy in a living organism in steady state. (From Pike and Brown, ref. 3.)

rest is released as heat (40–60%). When ATP is utilized for cell maintenance, such as maintenance of membrane potential, the sodium pump, production of enzymes, or for internal work, such as to keep the heart muscle working, to maintain muscle tone, and to allow those body movements that are needed to obtain, consume, and digest food and drink, still more energy is wasted (20–40%). Muscle contraction is also a fairly expensive process from an energetic point of view. The overall ability of the human body to convert the potential energy of food to mechanical work amounts to only 20% to 25% of the total available energy. Thus the total energy expenditure is simply partitioned for heat loss plus external work. In the resting state when no external work is taking place, essentially all of the energy transferred within the body is dissipated as heat. The food energy is contained in the three macronutrients carbohydrates, fat, and protein. The two main energy sources for cellular metabolism are glucose and free fatty acids (FFA). Amino acids serve primarily for tissue synthesis and are used as a major source of energy only under pathologic conditions. The theoretical background of substrate utilization for energy metabolism at a cellular level is illustrated in Fig. 3. Glucose is derived either from glycogenolysis mostly through hepatic glucose production or from gluconeogenesis from glycogenic amino acids, lactate, pyruvate, and glycerol.

Fatty acids can be supplied to heat-producing cells through the following mechanisms: (a) from the metabolically very active fraction of plasma lipids, (i.e., the albumin-bound FFA pool, which is mostly derived from the endogenous lipid pool (i.e., adipose tissue); (b) from the plasma lipoproteins, mostly from the pre-β very low density lipoproteins (VLDL) synthesized in the liver; (c) from the chylomi-
BLOOD

PERIPHERAL CELL

dietary fat

Chylomicrons

LPL

FFA

cellular

Glucose

LPL

FFA

metabolism

FFA

Glucose

esterified fatty acids

enter metabolism

unesterified fatty acids

esterified and unesterified fatty acids in blood

FFAAlbumin

unesterified fatty acids enter metabolism

TG → FFA

adipose tissue lipolysis

Glycogen stores

Gluconeogenesis

Glycogenic amino acids

Lactate

Pyruvate

Glycerol

FIG. 3. Substrate utilization for energy metabolism at cellular level. FFA, free fatty acids; TG, triglycerides; VLD, very low density; LPL, lipoprotein lipase. (From Heim, ref. 4.)

crons, which are mostly derived from dietary fat absorbed from the gastrointestinal tract or administered intravenously as fat emulsion.

In contrast to FFA the esterified fatty acids present in the VLDL or in chylomicrons do not generally have direct access to cellular metabolism. From these lipids, fatty acids have first to be liberated by the action of an enzyme, lipoprotein lipase (LPL), which specifically hydrolyzes the triglyceride component of chylomicrons as well as the VLDL. The LPL is present in endothelial cells of the blood vessels of heart, muscle, and adipose tissue, and its activity changes according to metabolic needs. For example, during fasting, LPL activity is reduced in adipose tissue, but increased in muscle and in the heart. Thus during starvation, when the glucose supply is short, the energy yielding fatty acids are less likely to be deposited in adipose tissue, but are utilized in muscular tissues. The uptake of fatty acids from all three lipid fractions will ultimately result in an increase of FFA levels inside the cell, thus providing a high potential for calorigenesis.

PRINCIPLES OF MEASUREMENTS OF THERMAL BALANCE, ENERGY EXPENDITURE, AND SUBSTRATE UTILIZATION IN THE NEWBORN INFANT

Total heat loss and/or metabolic heat production can be measured either by direct or indirect calorimetry. Direct calorimetry utilizes the direct physical measurement of heat. The subject is placed into an insulated chamber, and heat production
is measured directly by recording the total amount of heat transferred to the weighted quantity of water circulating in the walls of the calorimeter (5–8). Since the direct calorimeter is expensive and its operation involves considerable technical preparedness, indirect calorimetry has gained increased popularity.

The principle of the indirect calorimetry technique used by our research team for the determination of energy expenditure and substrate utilization in the newborn infant (4,9–24) is demonstrated diagrammatically in Fig. 4. This apparatus is an open-circuit system attached to the incubator by a long tube. The babies are wrapped in diapers but are otherwise naked under a plastic heat shield in the incubator. This double wall prevents radiational heat loss and ensures a truly thermo-neutral environment. The exhaust air, which is about 0.5% poorer in O₂ and 0.4% to 0.5% richer in CO₂ as a result of the infants’ respiration, is passed through the measuring cells of a paramagnetic Taylor-Servomex O₂ analyzer and a Beckman LB₂ infrared CO₂ analyzer. The second sample from the air in the incubator is similarly analyzed. The difference in O₂ and CO₂ concentration between air entering and leaving the hood is thus recorded together with the flow rate, from which the volumes of O₂ removed and CO₂ added by the infant can be calculated as a function of time. These gas volumes are reduced to standard temperature and pressure dry (STPD) and corrected for volume changes owing to variation in the respiratory quotient (RQ) from 1.0. During each test the urine is collected over a mea-

FIG. 4. Block diagram for continuous open-circuit computerized indirect calorimetry coupled with heart rate monitoring. P, pump; PT, pneumotachometer. (From Chessex et al., ref. 9.)
sured period so that the role of urinary nitrogen (N) production and therefore the amount of protein or amino acid oxidized (g of urinary N × 6.25) can be calculated and the nonprotein RQ derived. Finally when the laboratory results of the nutrient balance (intake-output) are completed and put into the computer program, oxidation and tissue disposition for all three principal nutrients are calculated. The indirect calorimeter determines the O₂ consumption and CO₂ production of the baby. Since the energy values obtained by combustion of the three basic nutrients are known (Table 1), the oxidation rate of the particular macronutrient may be calculated from the heat production and RQ. For instance, during oxidation of 1g of carbohydrate around 4.1 kcal heat is released. During the combustion of this 1g of carbohydrate, 0.75 liter of oxygen is consumed and an equivalent amount of CO₂ produced; thus the RQ is 1. The energy value of 1 liter of oxygen at this RQ is 5 kcal. The calculation of energy balance when lipids and proteins are oxidized is quite different because the caloric values of oxygen during combustion of lipids and protein are different.

EXPERIMENTAL DESIGN

In order to establish values for various components of energy metabolism in the newborn infant, the following experimental design was applied. (a) A 3-day nutritional balance was used from which the metabolizable intake of energy and macronutrients was determined by chemical analysis. (b) Energy expenditure and RQ were determined in a thermoneutral environment by open-circuit indirect calorimetry on the second day of the balance. (c) Urinary nitrogen excretion was measured concomitantly with the indirect calorimetry. (d) Daily measurements of weight were performed, as well as weekly determinations of length, head circumference, and skinfold thickness. From these data the energy and nutrient requirements for maintenance and growth could be calculated.

| TABLE 1. Metabolic values and O₂ and CO₂ equivalents of carbohydrates, lipid, and protein |
|---------------------------------|-----------------|-----------------|
| CH₂O kcal/g | Lipid kcal/g | Protein kcal/g |
| 4.1* | 9.3 | 4.3 |
| 0.75 | 1.43 | 0.78 |
| 0.75 | 2.03 | 0.97 |
| 1.00 | 0.7 | 0.80 |
| 5.0 | 4.7 | 4.5 |

*Mean for carbohydrate. Specific carbohydrates may differ, e.g., glucose (anhydrous) = 3.73 kcal/g, which is the value used for calculations in this chapter. (From Heim, ref. 4 and Kreutler, ref. 25.)
ENERGY METABOLISM IN A THERMONEUTRAL ENVIRONMENT

During our studies in a thermoneutral environment, the infants were maintained under optimal conditions, without blood sampling or diaper changing, and with minimal interference from their environment; they were asleep over 70% of the time. Under these optimal conditions in a well-equipped tertiary care unit, we have found that metabolic rate was influenced by three factors: postnatal age, energy intake, and weight gain. We have also observed that the postnatal increase in energy metabolism is primarily dependent on caloric intake and weight gain. Moreover, among the latter two, the weight gain, thus the rate of growth, appeared to be of primary importance.

We indeed found in our rapidly growing infants, a linear relationship between metabolic rate (MR) and weight gain (Fig. 5). From this relationship the energy cost of weight gain could be calculated using the regression equation MR = 51 + 0.67 weight gain. The slope of the regression line tells us that 1g increment in weight results in an increase in energy expenditure of 0.67 kcal; in other words, for each gram of weight gain, 0.67 kcal energy is utilized for tissue synthesis. Furthermore, the metabolic rate of a nongrowing infant is represented by the intercept of this slope (51 kcal/kg/day). This latter value was validated by five independent studies on infants who failed to thrive at the time of the investigation, having shown a mean metabolic rate of 50.3 kcal/kg/day. The linear increase in metabolic rate with weight gain (0.67 kcal/g) reflects the energy cost of tissue synthesis. If a premature infant grows at the same rate as the third trimester fetus, i.e., 15 to 16 g/kg/day, about 11 kcal/day are needed to synthesize new tissue, which represents around 7% of the energy content of the food consumed.

In addition to the energy cost of tissue synthesis, we determined the other com-

![METABOLIC RATE](kcal/kg\_day)

![WEIGHT GAIN](g/\_kg\_day)

**FIG. 5.** Relationship between metabolic rate (MR, kcal/kg/day) and weight gain (g/kg/day) in 26 studies in 13 appropriate for gestational age, formula-fed, very low birth weight infants. MR = 51 + 0.67 weight gain \((r = 0.86; p < 0.001)\); cost of tissue synthesis: 0.67 kcal/g of weight gain. (From Chessex et al., ref. 16.)
ponents of energy utilization in the formula-fed premature infant (Fig. 6). Around 12% of the total energy intake is lost in the excreta, mostly as stool fat; the resting metabolic rate utilizes 31.6% of the total energy intake. Activity takes only 2.9% and tissue synthesis 7.6%, leaving 45.6% for storage.

During these measurements the infants were maintained under optimal conditions with minimal interference with their environment. Deviations from these experimental conditions would probably increase the energy requirement for activity. Furthermore, under the thermoneutral conditions of our study, the energy requirement for thermoregulation was negligible and was thus omitted from the evaluation of energy balance. If energy intake remained constant, a thermal environment outside the neutral range would increase maintenance energy requirements, thus decreasing the amount of energy available for growth.

ENERGY REQUIREMENTS DURING THE METABOLIC RESPONSE TO COLD

Energy metabolism and thermal homeostasis was tested in 20 newborn infants having different body weights at birth (Fig. 7). One can observe that the oxygen consumption in the cool environment increased significantly over the basal metabolic rate. The RQ was around 0.7, indicating a predominant fat oxidation. Since the cold exposure was not severe and did not last longer than 30 to 40 min, there was no change in the colonic temperature of the larger infants, but it decreased significantly in the low birth weight infants, indicating the vulnerability of this patient population to even minor changes in ambient temperature.

<table>
<thead>
<tr>
<th>Energy Intake</th>
<th>% of Energy Intake</th>
<th>kcal/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global energy intake (148.6)</td>
<td>Growth (79.1)</td>
<td>Energy stored 67.8</td>
</tr>
<tr>
<td>Metabolizable energy intake (130.4)</td>
<td>Tissue synthesis 11.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Maintenance metabolism (51.3)</td>
<td>Activity 4.3</td>
<td>2.9</td>
</tr>
<tr>
<td>&quot;Basal&quot; metabolic rate</td>
<td>Energy losses (18.2)</td>
<td>Energy losses 18.2</td>
</tr>
</tbody>
</table>

FIG. 6. Partition of energy utilization in very low birth weight, formula-fed infants (n = 22), under thermoneutral conditions. Results are expressed as mean kcal/kg/day and percent of gross energy intake. Numbers in parentheses are in kilocalories. (From Reichman et al., ref. 17.)
To translate this physiological observation into practical terms, one has to convert the values of oxygen consumption into kilocalories. Using the energy equivalent to oxygen at this measured RQ of 0.7, one can calculate that even this mild cold exposure associated with the elevation of the incubator hood at a room temperature of 25 to 26°C may result in 26 kcal/kg/day extra heat production.

The increased heat production associated with cold exposure elicited a vigorous metabolic response characterized by increased glycogenolysis as indicated by the elevated blood lactate levels and lipolysis as demonstrated by the large rise in plasma FFA and plasma free glycerol (Fig. 8). If the exposure to cold is pro-
FIG. 8. Metabolic response of 20 newborn infants with different body weights at birth, under thermoneutral conditions and in a cool environment. All infants were tested within the first 30 hr of life. White columns, measurements in thermoneutral environment (34–35°C); black columns, measurements at ambient temperature (25–26°C). (From Heim, ref. 22 and from Heim et al., ref. 11.)

longed, the above changes in carbohydrate metabolism may lead to hypoglycemia, with a potential for neurologic damage that cannot be overstressed.

A large increase in FFA levels is most commonly associated with cold-induced thermogenesis. Since FFA have a strong affinity for albumin they may compete with bilirubin for albumin binding. This may contribute to the binding of bilirubin to other ligands and facilitate the diffusion of bilirubin into the brain thus causing kernicterus. A cold-induced increase in metabolic rate also necessitates an enhanced oxygen uptake and an increase of the cardiac output. This imposes a bur-
den on the cardiorespiratory system of the newborn, especially on that of the low birth weight infant. As a consequence, blood flow increases to the thermogenic organs, and tissue hypoxia occurs in the rest of the body. The latter induces conversion to anaerobic metabolism and an increase in lactic acid production. Acidosis may lead to pulmonary vasoconstriction, further aggravating the vicious circle. With increased pulmonary resistance, right-to-left shunting through the foramen ovale and ductus arteriosus occurs, thus leading to a decline in arterial oxygenation. A decrease in pulmonary perfusion impairs surfactant production as well, which might then contribute to the development and severity of the respiratory distress syndrome (RDS). If one puts together the above listed elements, a picture of the vicious circle emerges, and it becomes easily understandable why and how cold stress and hypothermia contribute to the increased mortality of the immature newborn infant. From critical evaluation of a few nursing situations in the delivery room, during transport to a referral hospital and under normal conditions in intensive care units well equipped with incubators, one realizes that cold exposure may still occur. Fig. 9 demonstrates that in spite of all our efforts, the thermal hazard in the very low birth weight infant could not be fully eliminated. When the servo-controlled incubator was regulated by the abdominal skin temperature at a set point of 36.5°C in a very low birth weight infant (<1000 g), the air temperature surrounding the baby alternated between 33 and 37°C. Oxygen consumption and ab-

![Fig. 9](image_url)

**FIG. 9.** Air temperature surrounding the body, oxygen consumption, abdominal skin temperature, and deep colonic temperature of a 7-day-old premature infant with a body weight of 780 g (gestational age, 27 weeks) in a servo-controlled incubator regulated by the abdominal temperature of the infant. At the arrow (↓) the incubator was switched over to a manual temperature control at a set-point of 34°C operative ambient temperature. (From Heim et al., ref. 11.)
dominal and deep colonic temperatures undulated along a regular sinusoidal pattern over several hours of observation in a manner analogous to the incubator temperature.

The decrease in environmental temperature immediately evoked a typical on-off control of thermoregulation, and the oxygen consumption ranged between 6 and 8.5 ml/kg/min. This accentuated on-off regulation imposed a considerable load on energy metabolism, increasing it by 42% over the resting level.

When the incubator was switched over to a manual control at a set point of 34°C operative ambient temperature, the undulation of the isolette temperature became minimal and the on-off variation in energy metabolism as judged by the oxygen consumption (VO₂) was also substantially reduced to a variation of about 18% above the resting level.

This observation clearly indicates that, even with sophisticated neonatal care, the maintenance of the thermal microclimate in the neonatal period is not as simple as it may appear.

WARM ENVIRONMENT

Energy requirements may also be thoroughly influenced by placing an infant in a warm environment, i.e., higher than the thermoneutral zone. Since a heat wave can strike the pregnant women in countries of hot climate, it seems to be relevant to discuss first the effect of heat exposure on the fetus. The effects of heating and cooling are demonstrated by one of the experiments performed by Moroshima and colleagues (26) on the pregnant baboon (Fig. 10). The figure depicts an individual experiment performed at 147 days of gestation (term 185 days) and a fetal weight of approximately 900 g. Maternal temperature, fetal temperature, and feto-maternal temperature difference were continuously recorded and the fetal pH and arterial oxygen tension (PaO₂) were determined each hr throughout the study.

These experiments on the pregnant baboon have demonstrated that maternal hyperthermia (42°C rectal temperature for 1 hr, elicited by external heating) caused a marked increase in uterine activity. Concomitantly hypotension, tachycardia, hypoxia, hypercapnia, and metabolic acidosis developed in the fetus. The feto-maternal temperature difference (0.5°C in normothermic conditions) increased during maternal hyperthermia to 0.7 to 0.8°C, indicating that the fetal temperature does not merely follow the maternal one, but that an active metabolic response to heat stress was elicited in the fetus itself. During prolonged maternal hyperthermia, the fetus became gradually asphyxiated and the feto-maternal temperature difference diminished, indicating a decrease in heat production by the fetus. In the seriously compromised fetus, the feto-maternal temperature gradient may disappear.

Another observation relevant to the hazards of hot climates on a pregnant woman and her offspring is related to repeated heat exposure. Human adults from or living in hot climates long enough become acclimatized and suffer from heat
illness only if overexposure or excessive exercise is undertaken. Repeated exposure of a pregnant woman to an environmental temperature of 42.5°C for 1 hr daily does not necessarily cause acute fetal distress or death, but might seriously compromise fetal development. This statement is based on the results of animal experiments. A daily exposure for 1 hr, of the pregnant guinea pig to 42.5°C between the 18th and 25th days of gestation (total length of gestation 66 days) results in a 26% to 28% deficit in the wet brain weight of the newborn. The smaller brains of the newborn guinea pigs from heat-stressed mothers contained less DNA than those from control animals, indicating a reduction in cell numbers. The learning ability of the offspring of the heat-stressed mothers was also impaired. Thus prenatal hyperthermia results in brain retardation in the newborn guinea pig. In severe cases the newborn and young animals were clumsy, slow and uncoordinated in their movements, or unresponsive to external stimuli. The less severely affected individuals also were inactive, and their learning ability was affected too.

In the human neonate only acute exposure to moderate environmental heat of up to 37°C at a relative humidity of 50% could be studied (Fig. 11). Under these conditions Sulyok et al. (27) found that the first defense mechanism against acute heat exposure is a sharp increase in evaporative heat loss and cutaneous thermal conductance, i.e., skin blood flow. Metabolic rate measured by either direct or indirect calorimetry increases above an esophageal temperature of 37.2°C. It is in-
EVAPORATIVE HEAT LOSS
watt/kg Kcal/kg/d

2.0- 41
1.6- 33
1.2- 25
0.8- 17
0.4-

37.0 37.2 37.4 37.6 37.8 38.0

ESOPHAGEAL TEMPERATURE

0.4 8
2.0- 41
1.6- 33
1.2- 25
0.8- 17
0.4-

CUTANEOUS THERMAL CONDUCTANCE
cal sec⁻¹ m²°C⁻¹

FIG. 11. A: Relation between the esophageal temperature and evaporative heat loss for 22 full-term (\(y = 4.704x - 175.714, r = 0.825, P < 0.005\)), 9 SGA (\(y = 7.055x - 266.205, r = 0.775, P < 0.025\)), and 8 premature infants (\(y = 3.607x - 135.66, r = 0.94, P < 0.005\)). B: Evaporative heat loss as a function of cutaneous thermal conductance. Number of infants and symbols are the same as in A. Regression equation: \(y = 0.293x - 0.214, r = 0.926, P < 0.001\). (From Sulyok et al., ref. 27.)

It is interesting to note that the sweat threshold is lower in full-term infants than in premature and small-for-date infants. A relatively small increase in core temperature (i.e., 0.2°C from 37.5 to 37.7°C esophageal temperature) may elicit a large rise in evaporative heat loss (from 8 to 41 kcal/kg/day) indicating that thermal control above the thermoneutral zone is also an important aspect of neonatal care. Nursing of newborn infants above thermoneutrality may result in enhanced energy expenditure; thus at a fixed caloric intake less energy is available for growth.
ENERGY METABOLISM UNDER PATHOLOGICAL CONDITIONS

Energy requirements may vary to a wide range under pathologic conditions such as intrauterine malnutrition, sepsis, fever, etc. Thermoregulation can also be thoroughly affected by hypoxia, hypercapnia, intracranial edema, brain injury, and so forth.

Among the many possibilities only two will be briefly discussed here: intrauterine malnutrition and hypoxia.

Energy Metabolism in the Small for Gestational Age Infant

The very low birth weight premature infant who has suffered from intrauterine growth retardation is potentially at risk for continued growth retardation as well as for neurological sequelae. We have evaluated the utilization and storage of energy and macronutrients and the quality of growth in preterm and small for gestational age (SGA) infants during the first 6 weeks of life. All infants were fed formula and the intakes of energy, protein, fat, and carbohydrate were similar in the two groups. The intrauterine malnutrition greatly influenced the digestive process and the absorption of the three principal nutrients (Fig. 12). In the SGA group only 81% of the energy intake was absorbed whereas in the appropriate for gestational age (AGA) group 88% was. Profound differences were found in the absorption of

![Diagram showing energy and macronutrient absorption (% of gross intake) in AGA and SGA infants.]
protein (67% in SGA vs 80% in AGA) and fat (69% in SGA vs 80% in AGA infants). These significant differences in protein and fat absorption imply that the development and function of the exocrine pancreas and the intestinal tract are compromised during intrauterine growth retardation of the human infant. Intrauterine malnutrition affects not only the absorption of energy and macronutrients but also energy metabolism and substrate utilization (Fig. 13). SGA infants had a significantly higher energy expenditure (67.4 kcal/kg/day). The oxidation of protein (SGA, 0.73 g/kg/day; AGA, 0.73 g/kg/day) and carbohydrate (SGA, 13.2 g/kg/day; AGA, 13.3 g/kg/day) were similar in both groups, and it appears that the excess energy expenditure was derived from an increase in fat oxidation in the SGA infants (SGA, 1.2 g/kg/day; AGA, 0.6 g/kg/day). The impaired absorption and the altered oxidation of nutrients thoroughly influenced the composition of weight gain in the SGA infant. These differences in energy and macronutrient metabolism in the preterm SGA infant may be of particular significance when defining the optimal feeding regimen for this group of high-risk infants.

THERMOREGULATION IN HYPOXIA AND HYPERCAPNIA

From the classical experiments of Karlberg and Oliver (28) in Sweden we have learned (Fig. 14) that the healthy newborn infant breathing air increases its metabolic rate vigorously as the environmental temperature decreases below the lower limit of the thermal neutral zone. When the same infants were made hypoxic by allowing them to breathe a mixture of 12% oxygen and 88% nitrogen, the meta-

![FIG. 13. Energy and macronutrient oxidation (mean ± standard error) in AGA and SGA infants.](image-url)
bolic response to cold ceased and the body temperature rapidly decreased. Hypoxia affects not only metabolic heat production but also substrate utilization for thermogenesis. Results of measurement of energy expenditure and substrate mobilization in hypoxic babies suffering from RDS or after aspiration of amniotic fluid are shown in Fig. 15. No metabolic response to cold was found.

Body temperatures declined during cold exposure. There was no appreciable increase in substrates for thermogenesis except that of the blood lactate indicating that anaerobic glycolysis was called upon to support calorigenesis. Utilizing energy for heat production from anaerobic glycolysis is most uneconomical. Maintaining the same metabolic rate by anaerobic metabolism requires 12 times the amount of glucose that is required during aerobic metabolism. The production of lactic acid indicates the degree of hypoxia, i.e., the extent of anaerobic glycolysis. Since the carbohydrate reserves are meager in the immediate postnatal period, the increased heat production in the cold cannot be maintained at the expense of anaerobic metabolism of glucose or glycogen as a primary substrate.

Severe anemia, induced in the immediate neonatal period by Rh isoimmunization produces a test situation for elucidating the effect of anemic hypoxia on thermogenesis (Fig. 16). No metabolic response to cold is observed before the ex-
FIG. 15. Metabolic response to cold (energy expenditure and substrate utilization for thermogenesis) in a hypoxic infant. FFA, free fatty acids; glyc, glycerol. Body temperature, colonic (-----) and axillary (---).

FIG. 16. Metabolic response to cold (energy expenditure and substrate utilization for thermogenesis) in a severely anemic full-term infant (Rh isoimmunization) before and after correction of hypoglycemia. FFA, free fatty acids; glyc, glycerol. Body temperature, colonic (-----) and axillary (---).
change transfusion in this full-term infant with a hemoglobin level of 5.0 g/100 ml blood. The severity of hypoxia is indicated by the extremely high blood lactate level (65 mg/100 ml blood). Cold exposure was not accompanied by the usual increase in FFA and glycerol. Since this particular baby was also profoundly hypoglycemic, the possible effect of hypoglycemia on thermoregulatory heat production also had to be excluded. Providing glucose intravenously as a substrate for heat production did not restore thermogenesis. Following exchange transfusion, the baby responded normally to cold, indicating that anemic hypoxia might have been the decisive factor in impaired thermoregulatory heat production.

Although our task was to focus attention on the physiologic aspects of neonatal energy metabolism and thermoregulation, we have stressed also that the weak or insufficient response of the sick newborn infant to nutrients and environmental conditions may aggravate already existing disease, thereby confirming that the maintenance of thermal homeostasis continues to occupy a prominent place in perinatal care.

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DISCUSSION

Dr. Vileisis: You described how in intrauterine malnutrition there are changes in protein and fat absorption and increases in fat oxidation. How does that compare with postnatal malnutrition and what kind of changes do you see there?

Dr. Heim: I have not studied postnatal malnutrition in particular, but I can certainly tell you that these infants, who were born in our nursery or transferred from other hospitals, whether they are born AGA or SGA, lose weight during their first 2 to 3 weeks of life. Therefore they should be regarded as being extraterine malnourished as well.

Dr. Schwartz: There are some excellent studies that I think the group ought to see that were completed by Douglas Keer (1,2) at the Tropical Metabolism Research Unit in Jamaica 10 years ago and for which Dr. Heim is providing us an excellent background. Since we are discussing sick infants, it seemed to me appropriate to show you some of these data to put this topic in a slightly different perspective.

Dr. Kerr studied 5 very malnourished infants, who were 1 year old when they were malnourished, and then a year later when they had completely recovered. He did exactly what Dr. Heim has done with these very small intrauterine growth retarded (IUGR) infants but, in addition, he carried out U-13C-glucose turnover studies in order to look at metabolic fluxes. He also measured a variety of substrates and hormones in the circulation. He did all the calculations that you have seen, and he also subjected the infants to 24 hr of complete starvation, when they were malnourished and subsequently when they had recovered. With 24 hr of starvation, in both circumstances, plasma glucose fell from about 70 mg/dl to about 40 mg/dl without change in mental status. Plasma urea did not increase in the malnourished group, but did so after recovery. In both groups plasma insulin fell to very low levels with starvation. No significant differences were found for plasma growth hor-
mone, or urinary epinephrine or norepinephrine excretion. When you are dealing with starvation in a malnourished or a normally nourished individual, the metabolic changes, as far as hormonal controls are concerned, depend on having virtually no insulin. The total stable glucose turnover studies showed similar glucose production rates, using the metabolic balance technique that Dr. Heim has just shown. Kerr could account for the amount of total glucose being consumed, which is of the order of 3 mg/kg/min. He could only account for about a third of it from amino acids, glycogen stores, and glycerol. He speculated that the difference was likely owing to lactate-pyruvate recycling. The recovered infants had less of a discrepancy, but it certainly was not striking; so there was an unexplained flux of substrate that was not evident. The sequential changes in the malnourished and recovered infants, who were 1 year old, indicated that the sources of glucose were glycerol and glycogen, plus initial diet. Protein or amino acids contributed very little. After 24 hr of fasting, exogenous diet and glycogen stores have disappeared as expected, but the contribution of protein remains relatively small. Proportionally it is large, but in terms of the absolute change, after 24 hr, there is very little increase. Finally, the total energy balance, i.e., the proportion of fat, carbohydrates, and protein for a malnourished baby, has been compared with a recovered baby. Exactly what is expected happened, that is, the carbohydrate disappeared, so that the source of energy for a malnourished baby, just as in the IUGR babies, is fat, and again protein contributes very little. I think these are excellent studies and, Dr. Heim, they complement beautifully what you have been doing with the IUGR baby.

Dr. Heim: Thank you very much for this very valuable comment. One phenomenon that I would like to emphasize is the high catecholamine and nonadrenaline secretion in the malnourished infants during recovery. This is typical of the so-called diet-induced thermogenesis. If you try to help a malnourished individual to recover, you are caught between two extremes. You want to achieve higher storage levels but in certain situations you cannot because this would cause diet-induced thermogenesis and epinephrine and norepinephrine secretion, and the heat production increases.

Dr. Raihâ: One of your figures on macronutrient oxidation rates shows that 0.73 g/kg/day of protein was oxidized in both the SGA and AGA infants. What was the protein intake in these babies? We have some data that are not yet published showing that infants with a high protein intake are probably oxidizing more protein than when they have a low protein intake. Were these infants on a high or relatively low protein intake?

Dr. Heim: The protein intake from the formula in both groups of infants was around 3 g/kg/day. This is an intermediate level of protein intake. But, you are right; when the protein intake increases, more protein is oxidized and more nitrogen is found in the urine. But at the same time, with the higher protein intake, energy expenditure is increasing and therefore the contribution of protein to the total energy expenditure remains more or less the same, around 7% to 8%. The overall contribution of protein oxidation to the total energy metabolism is quite constant.

Dr. Priolisi: Could you please comment on the differences in energy cost of weight increments, according to the composition of the tissue that is laid down?

Dr. Heim: The composition of weight gain is certainly quite different according to the diet and the energy expenditure. We can compare the composition of weight gain in formula-fed infants and in fetuses between 28 and 40 weeks of gestation. In all infants, the amount of protein that is absorbed is about the same as the fetus, around 12%, but the proportion of fat accumulation is much higher in infants than in fetuses of comparable gestational age. This large fat accumulation occurs at the expense of water, carbohydrate, and minerals. The composition of weight gain is also very different in SGA and AGA infants. SGA in-
fants deposit less protein (around 8% of the intake) than AGA infants; fat deposition is higher in AGA than in SGA infants, again at the expense of water space. Thus, the premature newborn is actually in the hands of the neonatologist-nutritionist who can manipulate the diet and can therefore modify the body composition. This may have far-reaching consequences because laying down 32% of the weight gain as fat might induce proliferation of fat cells. These cells can be dormant, but they are there for life and might induce obesity 20 years later if this particular individual starts to increase his energy intake for some psychological or other reasons. It may be that these patients will be potentially very vulnerable for later obesity.

Dr. Rubaltelli: As you know, in recent years we have studied the adipose tissue, mostly on newborns born to mothers with diabetes, either gestational or true diabetes. We have found that the number of adipocytes at birth is normal, in comparison with normal newborns and, when these infants are kept on a strictly controlled diet, they have a normal weight by the time they are 1 year old and again a normal number of adipocytes. These data seem to contradict your hypothesis that diet can increase the number of adipocytes.

Dr. Heim: The number of adipocytes is really a very controversial issue, but there is very strong experimental evidence that when the fat content of the adipocytes reaches 55 microgram lipid per adipocyte, they then start to proliferate. This was shown in vivo by Swedish group, while Carey in Toronto studied adipocytes taken from white adipose tissue samples of adults with morbid obesity in vitro. He was also able to show that these adipocytes started to proliferate when the cell size exceeded the magic number of 55 micrograms per fat cell. Thus, there is apparently a critical size of the fat cells above which the cells start to proliferate independently, whether taken from a newborn or an adult or any man. We have a biological phenomenon during which the physical chemical properties of the membrane of the cell are modified and induce proliferation when the cell size increases.

Dr. Stern: Dr. Heim, you suggested that the FFA are capable of displacing bilirubin from albumin. That is true, but the displacement is not a simple linear phenomenon. The reason it is complex is that unlike other anions like the sulfonamides, for example, which are totally competitive at the same binding site, the FFA have at least two and probably three preferential binding sites, before they displace bilirubin, which means that you need a specific quantitative level. In studies we carried out some 10 to 12 years ago, the level required was about 1.5 mEq/liter while the normal range is about 0.5 to 1.0. It is difficult to reach that range clinically. There are a couple of things that will however increase FFA to such high levels, heparinization, for example. Heparin is frequently used to clear umbilical artery catheters. If there is accompanying hypoglycemia, there is an inverse relationship between FFA and glucose that will push up the level even higher. Interestingly enough, the highest increases occurred when it was decided to abandon hexachlorophene bathing of infants and to replace that with regular soap flakes. Soap flakes are almost pure FFA, and the skin that absorbs hexachlorophene also absorbs soap. Dr. Odell measured some plasma concentration in Baltimore and recorded levels of 6.0 mEq/liter, which were clearly dangerous. There is no question that hypothermia or previous cold exposure is a powerful stimulus towards kernicterus at low levels. Is this owing to the FFA alone? I do not think so. I think that what happens, particularly in a small premature infant, is that there is, as you mentioned, powerful peripheral vasoconstriction because of the cold. The small premature infant has very little muscle or fat insulation so that virtually everything vasoconstricts to conserve heat. When that happens, the pH falls rapidly, and a low pH is a powerful dissociator of bilirubin from its albumin bond. The dangerous thing about dissociation in the cold is that once it dissociates below pH 7.3, it does not reassociate until about 7.5 or 7.6.
The reason for this is that the molecule apparently undergoes a conformational change at low pH and just does not rebind the anion. From a clinical point of view, even though you have now corrected the temperature and the thermal balance is all right, this does not protect you against the negative influences of the past.

**Dr. Heim:** This is a very important comment because in many cases in the delivery room we do not have very much temperature control thereby easily causing cold exposure for half an hour.

**Dr. Frenk:** Dr. Heim, could you please comment on the cooling effect of intravenous infusions?

**Dr. Heim:** I have not seen any studies on the effects of cold infusions, but the cooling effect of cool infused blood, during exchange transfusions, has been thoroughly investigated by Edmund Hay in England who infused blood, preheated up to body temperature, versus cool blood, at a temperature of 20°C, and which evoked a tremendous metabolic response to cold blood during exchange transfusion. Fakata who used to work with David Milner in England at that time repeated these studies and measured the hormonal profile during this exchange transfusion with warm and cold blood. He found a large increase in many hormones, growth hormone, glucagon, and so forth. This illustrates the metabolic response to cold blood infusion.

**Dr. Frenk:** There is obviously a huge difference between the energy metabolism and the hormonal profiles of small, emaciated, atrophic infants and rather fatty preschool children with kwashiorkor. Could you comment on that?

**Dr. Heim:** The thermal regulation of postnatally malnourished infants was thoroughly investigated by the late Professor Varga in Pecz, in Hungary, who found that these postnatally malnourished 1-to-3-year old babies were very sensitive to cold exposure. Their basal metabolic rate was already 60% to 75% of the normal in a thermoneutral environment. Their energy expenditure did not increase, and they became hypothermic in many situations. So, postnatal malnutrition makes these infants as vulnerable to cold exposure as I demonstrated in newborns.

**Dr. Priolisi:** Dr. Heim, you showed that IUGR babies oxidize fat twice as fast as normally grown infants. We know from the literature that the clearance of intravenous fat emulsions is slower in IUGR babies. Could you comment on this?

**Dr. Heim:** The reduced LPL activity in the adipocytes may explain this phenomenon. Experiments are actually conducted in Toronto on the LPL activity of adipocytes and on lipid uptake by adipocytes in newborns. Maybe in the coming years we shall have a lot more information on this phenomenon.

**Dr. Rubaltelli:** Preliminary data obtained in our laboratory seems to show that there is a close relationship between the clearance of intravenous fat emulsions and the adipose tissue mass in the SGA preterm and term infant. Thus the clearance of these emulsions in SGA infants depends probably on the low level of LPL and on the mass of adipose tissue.

**Dr. Tsang:** Dr. Heim, could you comment on the potential and the implications of rigid temperature control in the environment for the infant? You are familiar of course with the studies conducted at our center, looking at computerized incubator control with very low birth weight infants, during which, in a randomized prospective trial, the mortality dropped by 40% in the very small sick babies. I wonder what the implications are of this technique and also of the widespread use now of overhead warmers. What do you think about their potential impact?

**Dr. Heim:** I studied these publications on the computerized control of environmental temperature very carefully. They are based on solid experimental measurements, and their
practical implications are tremendous because this computerized control really could pro-
vide a true thermoneutral environment. On the other hand, as I emphasized, the major fac-
tor of heat loss in the incubator is the radiation because these nurseries are air-conditioned
for the sake of the nursing staff, which is fine, but the temperature difference between the
incubator and the nursery is 10 to 15° C. Therefore, the radiation heat loss is tremendous.
These studies clearly suggested that we should use double-walled incubators plus a heat
shield. It took 15 to 20 years before the industry realized that it really should be done. Now
they are trying to produce these double-walled incubators, which can prevent the radiation
heat loss and provide true thermoneutral environment.

Dr. Stern: I think the other feature in that is that the partition of heat loss in newborn
infants has a much higher proportion of radiant heat loss than in the adult, close to about
50%, so that becomes a major avenue of losing heat.

Dr. Schwartz: Dr. Heim, I was impressed by the fact that infants in the neutral thermal
environment have only 2.9% of their energy expended as activity, which to me seems an
extraordinarily low figure. I would like to have your comments about that.

Dr. Heim: We use the so called Brux scale, which is an artificial scale, ranging from
+4 to −4. We observed our infants very carefully, and it turned out that for 70% of the
time they score −2 to −4 on the Brux scale, because they are sleeping. Some present with
rapid eye movement (REM) sleep, and I must emphasize that the energy expenditure is
significantly higher during REM sleep than during deep sleep. But in spite of that, these
tiny, very low birth weight infants in a thermoneutral environment are quiet, and they do
not move much. The full-term infant obviously moves a bit more and then the energy ex-
penditure is much higher. But I agree that we should work out the energy expenditure along
with the scoring system of the Brux scale. Nobody has done this so far.

Dr. Schwartz: For those of us who are not experts in the area, I would like to make
another comment: the figure of 4.1 kcal/g carbohydrate is really for polysaccharide. If you
use the figure of 4.1 for glucose, you overestimate the energy level because it is 3.67 or
3.82. It is a much lower figure for pure monosaccharide.

Dr. Heim: For intravenously fed infants we use a caloric value for glucose of 3.75 kcal/g
and for a formula-fed infant we use 3.95.

Dr. Chouraqui: In one of your last slides you showed increased carbohydrate deposition.
This carbohydrate is not transformed into fat. Where does this carbohydrate go, into the
liver or the muscle?

Dr. Heim: We discussed this several times in our unit: where does this so-called carbohy-
drate deposition go? First of all, if you study published results of those who combined en-
ergy, carbohydrate, fat, and protein balance with indirect calorimetry, you will see that
they all found carbohydrate retention. Jécquier and Felber in Lausanne are really the experts
on this subject, but they never tried to establish where the carbohydrate went. I think they
intentionally avoid this subject because it is so controversial. During intrauterine and extra-
uterine development, we repeatedly found that something like 1.95 g protein is deposited
per kg each day; half of this protein deposition consists of nonessential amino acids, half
of essential amino acids. Therefore theoretically 1 g of protein per kg and per day can be
deposited from the carbohydrate pool. Let us examine the glycerol pool, a large pool which
is carbohydrate, not FFA. The fat deposition normally is 2 to 3 g/kg/day, but it can go up
to 5; a part of it is glycerol, which can be something like 0.75 g/kg/day and can disappear
in this pool. These are two forms of carbohydrate deposition, and together are something
like 1.8 g/kg/day. I asked Dr. Schwartz what he thinks about the glycogen deposition in
premature infants because we know that the glycogen store in the liver of these infants is
about 11 g/kg; we do not know the exact figure for the muscle. But, Peter Hahn and Milan Novak published a paper many years ago, in which they described a very large glycogen deposition in the white adipose tissue of the newborn infant; so part of the glucose can be deposited as glycogen, not only into the liver and the muscle, but in adipose tissue, too. If you add another gram per kg per day, carbohydrate deposition into this glycogen store, you end up with a figure of 2.8 g/kg/day carbohydrate disappearing into these pools and that is exactly the figure Jéquier, Felber and we found all the time: 2.8 to 2.9 g/kg/day. If you give a high calorie and high glucose diet, this natural deposition can increase, but all carbohydrate goes to fatty acid synthesis and if you give a large carbohydrate load to the newborn infant, up to 17 to 18 g/kg/day, then fatty acid synthesis exceeds utilization.

Dr. Schwartz: I agree; I think the emphasis on fat is very important. I believe that Dr. Saphir in Israel made the observation 20 or 30 years ago that there is sequence of glycogen deposition in fat cells in the fetus before triglyceride formation.

Dr. Phienvit: You mentioned that there was no appreciable increase in substrates for thermogenesis during cold stress, except that of blood lactate, indicating that in a way carbohydrates were called upon to support calorigenesis. The FFA did not change. Does this imply that there is no increase in lipolysis and protein breakdown during cold stress?

Dr. Heim: The lactate did not increase in the large full-term infants, but in premature low birth weight infants, there was an increase of blood lactate levels during any exposure to cold. At the same time, there was no increase of the α-amino nitrogen level in the blood, indicating that there was no increase in protein catabolism during exposure to the cold.

Dr. Phienvit: Do you mean that glucose is the main source of energy?

Dr. Heim: Yes, glucose is also a source of energy during cold exposure, but it cannot be compared with the large increase in the use of FFA utilization. So they all, except protein, contribute to this energy metabolism: fatty acids, glycerol, lactate, and perhaps glucose.

Dr. Phienvit: I find it hard to understand why there is no increase in protein breakdown because during those tests, owing to the stress, there is an increased secretion of catecholamines or corticosteroids, which are insulin antagonists. Insulin antagonists always induce an increase in glycogen and protein breakdown, and increased lipolysis. Why do these organisms respond in a different way to insulin antagonists?

Dr. Heim: These were acute experiments going on for 30 to 40 min; this is quite different from a chronic situation. In these experiments, the protein pool is rather protected, and it really does not respond as quickly to this stimulus. But this does not contradict what you are saying because in a situation of chronic malnutrition obviously the protein reserves are also mobilized or called upon. However, we have found a lot of situations in the newborn infant, during total parenteral nutrition and so forth, where the protein pool was very much protected against these environmental influences. Newborn infants preferentially use amino acids for protein synthesis and once the protein is synthesized, they protect it against all environmental influences, until the very end.

Dr. Stern: Dr. Heim, you have given us an excellent presentation in which I think you have suggested, and made a good case for, the fact that if one maintains thermal neutrality, you will have some caloric sparing that would provide for better growth. The evidence for that is very good. Another very important feature of thermal neutrality is that the mandatory increase in oxygen consumption that occurs in the cold may not be possible for a newborn infant, particularly a compromised infant. The critical feature depends on how newborns respond to a demand for increased oxygen consumption. If one needs to increase oxygen consumption, one must take in more oxygen per minute and needs therefore to increase
minute ventilation. Minute ventilation is a multiple of respiratory rate and tidal volume. An adult can take a deeper breath and increase the tidal volume, but a newborn infant cannot. All that newborn infants can do is breathe faster and increase the respiratory rate. If they already have hyaline membrane disease and are breathing at 60 minutes, all they do when they raise the rate is rebreathe CO\(_2\) in the dead space because they do not have enough space from a low tidal volume to exchange oxygen. The point that I wanted to make is that many people have not basically understood that the neutral zone is not simply a thermal zone, but a thermal zone in which it is assumed that the four mechanisms of heat loss, i.e., evaporation, radiation, conduction, and convection, are minimized at the same time. A most harmful arrangement is the use of cold oxygen in a face mask because the thermal receptors for oxygen consumption are over the trigeminal distribution of the face. Oxygen coming out of a wall is ice cold, and whatever the temperature of the rest of the body, using a face mask with cold oxygen will double the oxygen consumption. Much of the theory that you have been talking about is reflected in better environmental practices, not only for ultimate growth, but also for immediate survival and energy metabolism.

Dr. Heim: This is a very important comment. As you emphasize for the thermoneutral environment, we suppose that there is a minimum rate of respiration. Another situation that increases energy expenditure and also the rate of respiration tremendously is when increasing amounts of glucose are given by infusion to the newborn infant. There is a highly significant correlation between the CO\(_2\) production and the glucose infusion, which therefore puts a tremendous pressure load on the respiratory system of the newborn infant who must eliminate a larger amount of CO\(_2\). We are now trying to calculate the energy cost of breathing.

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