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The partition of maintenance energy expenditure and the pattern of substrate utilization in intrauterine malnourished newborn infants before and during recovery

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Total heat production and its major components, as well as the pattern of substrate utilization were measured by indirect calorimetry during a period of several hours in 15 small-for-gestational-age infants between the 2nd and 15th postnatal day (non-growing period) and between 16th and 39th day (growing period).

1. Mean total heat production of the non-growing infants did not exceed 50 Cal/kg/24 hrs. Mean basal metabolism in this period was not higher than that reported for premature infants of similar body size and postnatal age. It is concluded that the caloric input necessary to meet the cost of maintenance was less than that calculated from the components of energy metabolism.

2. Total energy expenditure was significantly higher in the growing period, and its partitioning showed that all the three components (basal-, resting-, and activity metabolism) were contributing to the increment.

3. The increase in total heat production, as well as that of the components, was closely related to the difference in age and body weight at the first and second examination. The individual increment in heat production during growth was determined chiefly by postnatal age and weight gain.

4. Carbohydrate utilization was the dominant component of the total energy expended by the non-growing infants. During recovery, a further rise occurred in carbohydrate oxidation, while there was a moderate decrease in the participation of fat and protein.

Research on the relation of body size, postnatal age and basal metabolic rate [1, 6, 7, 8, 10, 11, 12, 13, 15, 17, 22, 25, 28, 31, 32] demonstrated that while in full term infants basal oxygen consumption per kg body weight increases rapidly during the first 24 hr after birth, in preterm infants it is not only significantly lower but its postnatal increase too occurs at a much lower rate than in full-size infants. A further important information provided by these studies concerns the great variation of minimal metabolism in low-birth-weight infants, which is mainly due to the heterogeneity of this group of newborns as far as birth weight, degree of immaturity and intrauterine growth rate are concerned. As regards body size and maturity, the lower the birth weight and gestational age the lower the basal energy expenditure per kg body weight. In contrast, intrauterine growth retarded infants tend to have a higher basal metabolic activity in terms of unit body weight than normally grown preterm infants of similar birth weight [12, 26, 27, 32]. This observation has led to the concept of "relative hypermetabolism" of the small-for-dates infant [26, 29, 30] pointing to the importance of body composition as an additional source of variation of the basal metabolic rate expressed per unit body weight.

While the changes of basal metabolism in relation to postnatal age and body size have extensively been studied, less attention has been paid to the maintenance energy metabbolism and its distribution between the various components. Studies carried out on preterm infants [18] demonstrated that the caloric requirement for maintenance at neutral temperature was considerably less than the figures generally used for approximation of the daily caloric need for infants weighing below 2000 g. These studies further showed that not only total heat production but also its partition between the different components needed a re-evaluation. In view of these experimental findings it seemed desirable to extend such investigations to intrauterine malnourished babies, another major group of low-birth-weight infants. This appeared all the more interesting, since the study of different aspects of energetics is a central issue in exploring the metabolic consequences of undernitrition [2, 3, 4, 5, 14, 19, 21].

In order to complete our knowledge concerning the physiological basis of caloric feeding of intrauterine malnourished newborn infants, the purpose of the present study was to collect information on the following aspects of the energy cost of maintenance:

1. In view of the difference in opinion [13, 25] concerning the level of basal metabolism in intrauterine growth retarded infants, it would be interesting to know what proportion of the calories produced in the neonatal and postneonatal period can be accounted for by basal energy expenditure.

2. What allowance should be made in caloric feeding for covering the extra energy expended above the basal in the non-growing and growing infant.

3. To what extent does recovery affect the partition of the components of energy expenditure.

4. As regards the sources of calories produced, it would be interesting to know in what proportions are the main nutrients oxidized providing energy for maintenance before and during recovery from undernutrition.

MATERIAL AND METHODS

Material

Data on total heat production and its components were obtained in 15 low-birth-weight infants. Their weight was between 1070 and 2400 g at birth, and their gestational age ranged from 34 to 40 weeks. Birth weight for gestational age was less than the 10th percentile on our local intrauterine growth chart.

According to the history, in two instances the placentas were infarcted and one mother had pregnancy toxaemia. In eleven infants the immediate postnatal period was uneventful. In one infant, transient hypoglycaemia, in another apnoe spells were observed. Two infants were treated with antibiotics because of suspected infection.

The infants were divided into two age groups; the pertinent data are seen in Table I. The first series of examinations was carried out between the 2nd and 15th postnatal day (non-growing) and the second between the 16th and 39th day (growing period). These two age periods were chosen so as to show the difference between energy expenditure and metabolic pattern in non-growing and growing intrauterine malnourished infants. None of the babies examined between 2nd and 15th day showed a gain in weight, while all of the older ones were growing. All infants but one were involved in both series of examinations.

The infants were fed two or three hourly with a cow's milk formula (73.3 Cal/100 ml). The daily intake of fluid and calories in the non-growing and growing period are shown in Table I.

Technique

Oxygen consumption was measured by an open circuit method using the Kipp diaferometer, allowing a continuous measurement of respiratory gas exchange and respiratory quotient. The technique has been described in detail previously [18].

Measurements were started six hours after the last feed, and readings were made every minute except when reference was made to room air, and when a feed was offered.

Physical activity was recorded every minute by constant observation using the following arbitrary grading score:

0 = asleep, physically totally quiet;
1 = eyes closed with occasional jerks;
2 = eyes closed or open with slight movements of the head or extremities;
3 = awaken state with moderate activity moving arms and legs;
4 = intensive and more or less continuous activity;
5 = vigorous activity with crying and restlessness.

Total, resting, basal and activity metabolism were determined. Total metabolism equalled the average oxygen consumption (ml/kg/min) recorded over the total observational period. The mean activity scores obtained in the course of ten-minute periods of recording were used for differentiation between basal and resting oxygen consumption. The lowest mean O_2 consumption (ml/kg/min) obtained in the fasting and physically totally quiet and sleeping infants during a 10 minute period was regarded as basal heat production (mean activity score, 0.0). Average oxygen consumption (ml/kg/min) corresponding to a mean activity score from 0.0 to 0.1 represented resting metabolism which also included the specific dynamic action. Total minus resting metabolism gave the activity quota representing the increase due to a mean 10-minute activity score of 0.2 or higher. Fig. 1. illustrates how the different measures of oxygen consumption and activity levels were quantitated.

Total, resting, basal and activity metabolism were also expressed as Cal/kg/24 hrs. The caloric values for oxygen used to calculate heat production corresponded to the average RQ of 10-minute intervals on which the determination of the different measures of energy expenditure has been based.

Urine was collected during the observation period by an appropriate device for determination of urea excretion rate. The relative quantity of calories (fat and carbohydrate) produced was estimated from the non-protein RQ. This quantity was calculated from oxygen consumption

TABLE I

The relevant data of the underweight newborn infants studied prior and during weight gain

Number and sex of infant	Gestational age wks	Birth weight, percentile g	Postnatal age, days		Body weight, g		Fluid intake, ml/kg/day		Caloric intake, Cal/kg/day	
			A	B	A	B	A	B	A	B
1 ♀	36	$1850 < P_{10}$	4	17	1750	1950	171.4	164.1	115.1	105.2
2 ♂	36	$1740 < P_{10}$	5	22	1750	2070	171.4	193.2	115.1	123.9
3 ♀	35	$1710 < P_{10}$	5	30	1690	2320	156.2	137.9	104.9	88.4
4 ♂	38	$1950 < P_{10}$	4	23	1950	2370	135.3	168.7	90.9	108.2
5 ♀	35	$1450 < P_{10}$	7	32	1430	2000	167.8	160.0	112.7	102.6
6 ♂	40	$2400 < P_{10}$	4	36	2390	2740	100.4	204.3	64.4	131.0
7 ♂	36	$2050 < P_{10}$	4	20	2000	2210	132.0	144.7	88.6	92.8
8 ♀	35	$1070 < P_{10}$	10	39	1100	1730	240.0	184.9	161.2	118.6
9 ♂	37	$2380 < P_{10}$	4	22	2300	2470	104.3	161.9	66.9	103.8
10 ♂	40	$2160 < P_{10}$	7	16	2140	2250	149.5	213.3	95.9	136.8
11 ♀	38	$2080 < P_{10}$	7	19	1930	2210	161.6	144.7	108.6	92.8
12 ♀	39	$1850 < P_{10}$	4	24	1800	2240	134.4	142.8	98.5	91.6
13 ♀	36	$1350 < P_{10}$	2	23	1320	1700	109.0	141.1	73.3	94.8
14 ♂	34	$1550 < P_{10}$	15	31	1550	2110	203.6	151.6	136.8	97.2
15 ♂	36	$2100 < P_{10}$	2	—	2100	—	114.2	—	73.3	—
Average	36.7	1846.0	5.6	25.2	1826.3	2169.2	150.1	165.2	100.4	106.3
± SE	0.46	108.76	0.92	1.98	100.69	87.54	10.67	7.49	7.33	4.74
Range	34–40	1070–2400	2–15	16–39	1200—2390	1700–2740	100.4–203.6	141.1—213.3	64.4–161.2	88.4—136.8

A = first examination
B = second examination

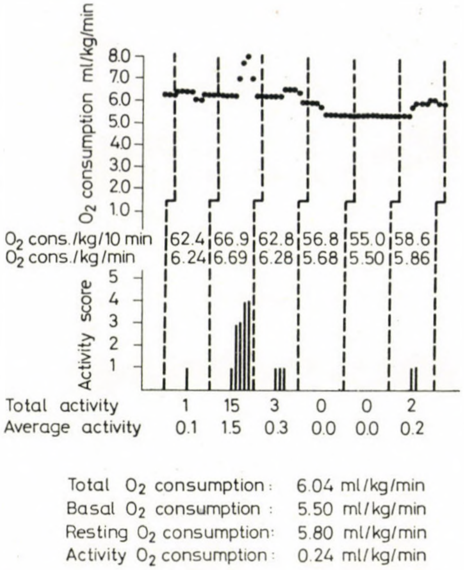

FIG. 1. One hour record of oxygen consumption (• • • •) and activity showing how the records were evaluated, and the different components of energy metabolism quantitated. For this purpose consecutive ten-minute periods were chosen. Owing to the two-minute time lag of the diaferometer, the record of oxygen consumption was shifted to the right in relation to the activity-record. The mean total, basal, resting and activity oxygen consumptions expressed as ml/kg/min calculated from the one-hour record are indicated. The average activity level of a ten-minute period was obtained by dividing by ten the sum of the scores. A mean score between 0.0 and 0.1 was regarded as a resting period, and the corresponding oxygen consumption as resting oxygen consumption

and carbon dioxide production after subtraction of the oxygen and carbon dioxide related to protein metabolism derived from urinary urea excretion rate.

Experimental procedure and conditions

The infants were placed in an incubator under a perspex hood through which room air was drawn at a rate of 1.6—4.0 l/min. The temperature within the incubator was maintained between 32 °C and 36 °C depending on size and postnatal age. The lower parts of the trunk and legs outside the hood were loosely covered by a nylon-sheet attached around the air inlet of the hood, ensuring that the infants expired only into the air flowing over the face. Relative humidity ranged between 45—60%.

In the second series of examinations the infants swaddled in soft down feather quilts were kept at a room temperature of 26—27 °C. The head and upper limbs were under a perspex hood with an air temperature 2—3 °C higher than that of the room. Periods during which oxygen consumption was followed varied between 6 and 13 hours.

RESULTS

Total energy expenditure of maintenance

The mean and individual levels of total energy metabolism obtained within the two time periods are shown in Fig. 2 and 3. It is apparent that total energy expenditure mark-

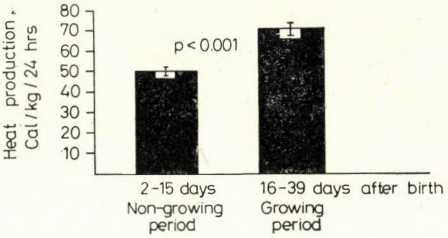

FIG. 2. Mean (± SE) total heat production of underweight infants obtained in the two time periods after birth. Gain in weight is associated with a significantly higher total energy expenditure ($p < 0.001$)

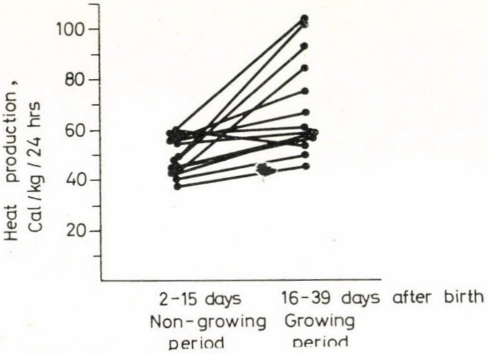

FIG. 3. Individual values of the daily caloric output in non-growing and growing intrauterine malnourished infants

edly increased during recovery. The difference between the means of the two examination periods was highly significant ($p < 0.001$). The changes in total heat production of the individual infants are shown in Fig. 3. It is seen that the rate of increase was variable resulting in a wide scatter of values from 16 to 39 days of age. While in some growing babies total energy expenditure markedly exceeded that obtained earlier in extrauterine life, in others the rise was moderate. In one infant it was less than prior to weight gain.

Total heat production as a function of postnatal age is shown in Fig. 4. From the close direct relationship it undoubtedly follows that postnatal age is an important determinant in energy metabolism. This can also be concluded from Fig. 5, where the increment in total heat production (ΔCal/kg/day) is plotted against the difference in postnatal age between the two examinations (Δ postnatal age in days). Thus, the variable increase in total heat production was mainly due to the different time intervals between the first and second examination.

It seemed interesting to relate the increment in total metabolism to the increment in body weight observed at the second test (Fig. 6). A close relationship could be demonstrated between the two measures. Thus, the widely differing increase in energy

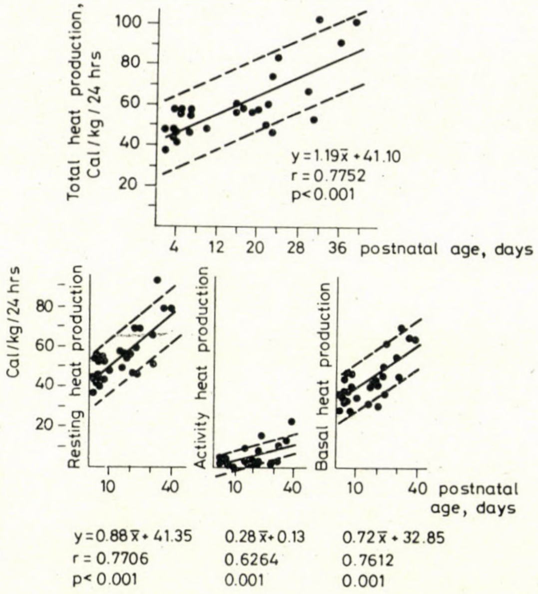

FIG. 4. Relationship between postnatal age and total, resting, activity, and basal heat production

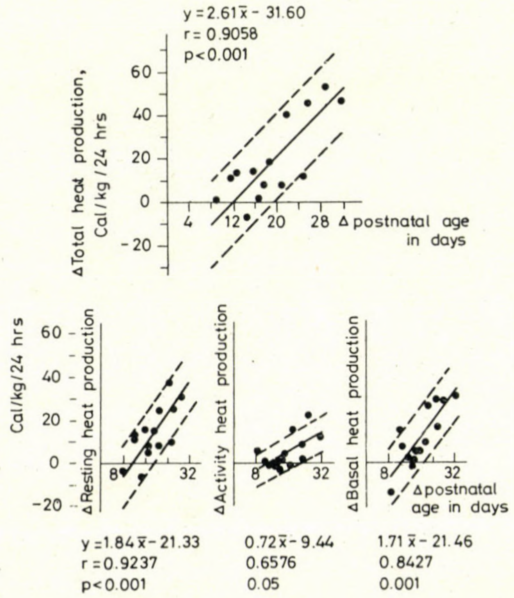

FIG. 5. Relationship of the increment in total, resting, activity and basal heat production (Cal/kg/24 hr) with the difference in postnatal age between the two examinations (postnatal age in days)

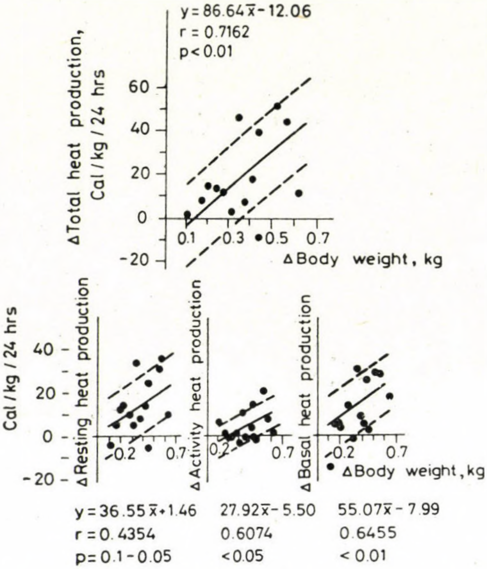

FIG. 6. **Relationship** of the increment in total, resting, **activity** and **basal** heat production (Cal/kg/24 hr) **with** the increment in body **weight** (body weight in kg)

expenditure during recovery was chiefly determined by the two closely interrelated variables, postnatal age and weight gain.

The components of total energy expenditure of maintenance

Under thermoneutral conditions, basal metabolism, physical activity and the specific dynamic action of food are the main components of the energy cost of maintenance. It seemed of interest to study the partitioning of total heat production between these components in the non-growing and growing period within 40 days of extrauterine life. In this analysis two "basal rates" of metabolism were distinguished and quantitated: basal and resting metabolism. The former represented the minimum oxygen consumption in the sleeping and fasting infant without visible activity (mean activity score, 0.0); the latter indicated oxygen uptake of the fed infants in whom occasional jerks, slight movements of the head and extremities were observed (mean activity score, between 0.0 and 0.1). Thus, in addition to the basal metabolic rate, resting metabolism included the oxygen consumption due to slight activity and the specific dynamic action of food.

The mean amounts of heat corresponding to the different factors of maintenance energy metabolism in the non-growing and growing period are shown in Fig. 7. It is seen that basal and resting energy expenditure was significantly higher in the recovery phase than that observed when the infants failed to gain in weight.

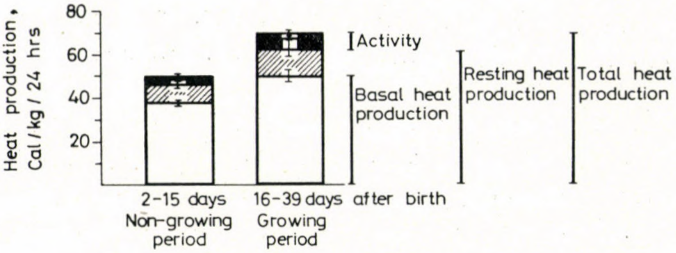

FIG. 7. Mean amounts of heat corresponding to the different components of maintenance energy metabolism before and during gaining in weight

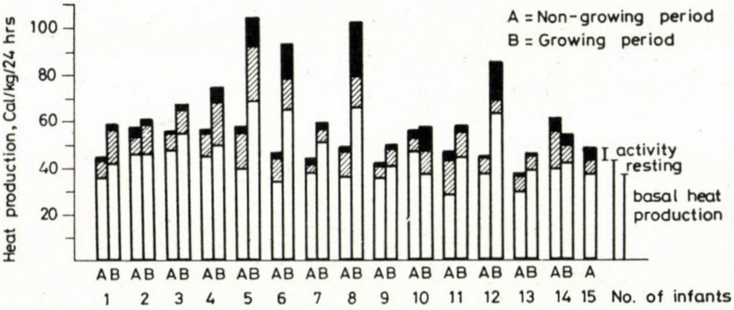

FIG. 8. Distribution of calories between the three components of heat production in individual infants

It is also seen that the increment due to the resting state was the largest component contributing to the extra heat produced above the basal value. The mean quota of more intensive activity was less pronounced.

In Fig. 8 the individual partitioning of the total heat production. is demonstrated It is apparent that growth was associated with a large individual variation in the distribution of calories between the three components. Like total energy expenditure, basal, resting, and activity heat production were also significantly related to postnatal age (Fig. 4).

The individual variation in the three components, similarly to total heat production, can also be explained by the different age intervals and weight gains between the first and second tests. Fig. 5 and 6 show a convincing relationship between the increment in basal, resting, activity heat production and Δ postnatal age, as well as weight gain. This shows that in newborn infants postnatal age and weight gain increase the energy cost of maintenance, and in this increase all the measurable components are involved.

Participation of the three main nutrients in energy expenditure of maintenance

The metabolic pattern, as described under Methods, was also investigated. The mean contribution of fat, carbohydrate and protein oxidation to total heat production in the non-growing and growing periods is demonstrated in Fig. 9. Carbohydrate utilization was already the dominant component of the total energy expended by the 2—15 day old non-growing infants. In the growing period a further and significant rise occurred in carbohydrate oxidation, while there was a moderate decrease in the participation of fat and protein metabolism. From Fig. 9 it can also be stated that the increase of maintenance energy expenditure during recovery was entirely due to carbohydrate oxidation.

The mean proportions of the three main nutrients in the daily caloric output are seen in Fig. 10. Although there was a considerable individual variation in the contribution of the substrates to the energy cost of maintenance, the metabolic pattern showed similar changes in each infant as they were gaining in weight.

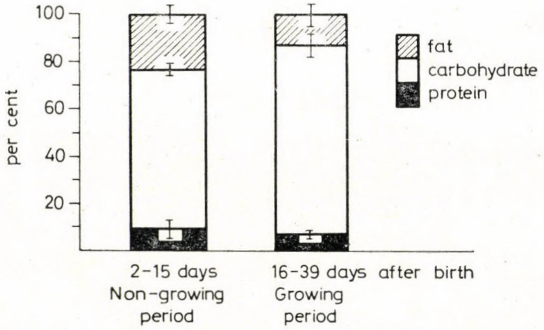

FIG. 9. Mean contribution of fat, carbohydrate and protein oxidation to total heat production in the non-growing and growing periods

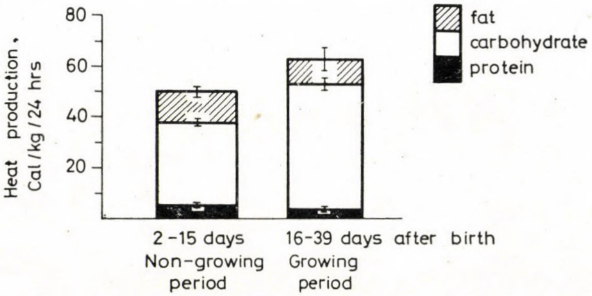

FIG. 10. Mean proportions of the utilization of the three main nutrients in daily energy expenditure before and during recovery

DISCUSSION

The basal metabolic value as the largest component of energy metabolism is generally used for estimating the daily caloric requirement of maintenance in the newborn infant. As pointed out previously [18], the widely employed classical figures proposed by Gordon and Levine [9] are overestimates for low-birth-weight infants, and do not reflect the great variation of the basal metabolic expenditure. But even the results of studies performed on low-birth-weight infants during the last 15 years are only rough approximations of the basal caloric needs [1, 6, 17, 23, 27, 32]. Thus, in every-day practice the estimate of the daily caloric intake is still mostly based on a basal metabolic rate of 50 Cal/kg/24 hr leaving out of consideration the large variation due to body size, maturity, postnatal age and nutritional status. More attention should be paid to these important determinants of basal heat production, which allow a more physiological and individual approximation of the caloric requirement, and should be used as guidelines in nutrition and infant practice in the early and late neonatal period.

A further difficulty in estimating energy requirements for maintenance in newborn infants concerns the summing of additional calories imposed by muscular activity, specific dynamic action, faecal loss, and, if the infants are kept below the neutral temperature, thermoregulatory heat production. Partitioning of energy expenditure by rough predicted values can also be a source of overestimation of the cost of maintenance and hence of an unnecessary high intake of calories in the early and late neonatal period. Here again, the wide range of extra calories above the basal, which in a thermal neutral environment is accounted for mainly by differences in duration and intensity of physical activity, should carefully be considered in approximation of the energy cost of maintenance.

Although basal metabolic values provide a basis for estimating caloric requirements, measurements for several hours of the total energy expenditure are needed for establishing a more physiological and individual approach of caloric feeding of the newborn infant. Such measurements and experimental observations, as it has been shown in premature infants aged 2 to 31 days [18], provided not only data on the total energy cost of maintenance, but have made it possible to quantitate the factors known to affect metabolic expenditure. This experimental approach has led to the conclusion that in premature infants the maintenance caloric requirement varies greatly, and is considerably lower than the widely employed figures used for approximation. These observations already pointed towards the importance of a re-evaluation of the caloric feeding of premature infants, and of the desirability of extending such studies to small-for-gestational-age newborns.

Total energy expenditure of small-for-gestational-age infants

In comprehensive studies concerning the relationship between body size and metabolic rate, Sinclair and Silverman [26, 27] observed that oxygen consumption per kg body weight was higher in infants whose birth weight was low for their calculated gestational age than in preterm babies of equal size. In explaining this phenomenon, these authors concluded that this "relative hypermetabolism" might probably be due to the higher proportion of metabolically active tissue mass resulting from the relative loss of extracellular fluid. This would suggest that in approximating the daily caloric requirement of maintenance in small-for-gestational-age infants, higher values of basal expenditure (50—60 Cal/kg/24 hr) should be used than in preterm infants of similar body weight (40—50 Cal/kg/24 hr).

The present observations showed that basal heat production of the non-growing small-for-gestational-age infants (within the first two weeks) related to body weight was not higher than that reported by different authors for premature infants of similar body size and postnatal age. The values obtained varied between 35—42 Cal/kg/24 hr and did not suggest any relative hypermetabolism; so they appeared to be in line with the observations of Jonxis et al. [13] and Senterre and Karlberg [25] in that the basal O_2 consumption of newborns weighing less than the 10th percentile for gestational age was lower than of normally grown infants and did not differ from that reported for preterm infants.

The extra calories above basal were partly due to the resting state when the infants with closed or open eyes showed slight intermittent movements (activity score < 0.2), and partly due to a more intensive physical activity (activity score ≥ 0.2). The former and larger component (about 10 Cal/kg/24 hr) included the metabolic increase caused by feeding, i. e. the specific dynamic action. This increment combined with the basal metabolism constituted the so-called "resting energy expenditure" which, on the average, amounted to 48—50 Cal/kg/24 hr. The contribution of activity levels higher than 0.2 to the total energy expenditure in the non-growing period was 3 Cal/kg/24 hr on the average, and essentially identical with the activity quota previously observed in preterm infants [18]. This small contribution was consistent with the reduced activity of low-birth-weight infants maintained in a thermoneutral environment.

From these data it seems justified to conclude that the mean total heat production of non-growing malnourished infants does not exceed 50 Cal/kg/24 hr, and hence the food energy intake necessary to meet the cost of maintenance is much less than that calculated from roughly approximated components of caloric expenditure.

It is mainly the basal and activity quota which is overestimated, and which can cause a significant and unnecessary load on the metabolic adjustment in the non-growing intrauterine malnourished infant. In partitioning total energy expended at neutral temperature in the early neonatal period, it appears useful to combine the basal and resting component as "resting metabolism" which includes an allowance for the calorigenic effect of food ingested and for slight activity. To this only a few calories should be added to meet the requirement of more intensive activity.

In the growing small-for-gestational-age infant, total energy expenditure per kg body weight was found to be substantially higher than that observed before. The infant had started to gain weight. Partitioning of the energy cost of maintenance revealed that all the three components measured had contributed to the mean increase of nearly 20 Cal/kg/24 hr. The rise in basal heat production amounted to about 10 Cal/kg/24 hr, reaching the level of total maintenance metabolism obtained before growth had started. Resting heat production comprising the cost of basal metabolism, slight activity and specific dynamic action of food showed a similar increment in relation to the non-growing period. The participation of activity increased considerably, its quota was found to be three times higher than previously.

From these changes in the structure of total energy cost of maintenance it can be inferred that growth is associated with an increased basal, resting and activity heat production expressed in unit body weight. The increase in these components, and hence the increment in the total, shows great individual variations that should be taken into consideration whenever the caloric need for maintenance during recovery from growth failure is to be estimated. The question might be raised whether this energy expenditure is the metabolic reflection of recovery from undernutrition, or merely the function of postnatal age, independent of gaining in weight. Considering the metabolic changes and adjustments taking place in newborn infants and closely related to postnatal age, the question appears unreasonable. In principle, preterm, term and small-for-gestational-age infants do not differ as far as the neonatal catabolic state, the more or less insufficient caloric input, and the pattern of changes of body weight are concerned. Every newborn infant, in fact, fails to grow for a period after birth which is then followed by forming new tissues resulting in a steadily increasing body size.

In view of the closely interrelated variables such as postnatal age, body size, weight gain, body composition, energy input and output, it is difficult if not impossible to determine which is the determinant variable as far as the changes in energetics and its structure are concerned. The dynamics of postnatal changes in basal metabolic rate is well-known, and it can be stated that it increases at different rates with postnatal age in different newborn categories, on the one hand, and that it starts before gaining body weight, on the other hand. From this it would, however, be erroneous to infer that postnatal age in itself is the most important determinant in energy expenditure. It is not unreasonable to suggest that the increase in metabolism preceeding the increase in body size by forming new tissues can be regarded as the first indication of recovery from intrauterine and/or neonatal caloric deficiency. In general, postnatal energetics seems to be similar to that of extrauterine malnutrition, where the depressed basal metabolic rate increases within a short time after abolishing the cause of growth failure [20, 33].

If compartmentalization is still an acceptable approach to exploring whole-body energy metabolism, the rise in heat production associated with recovery could be classified as the measurable component of caloric demand for growth. This increment might in fact represent the energy cost of storage, forming new tissues, different functions and processes involved in growth, and as such contributes to the energy expended on maintenance. Recovery rate from undernutrition (or the rate of growth in general) could set the pace of the caloric requirement of this component, and this could partly be responsible for the individual variations in its magnitude.

The second component of the caloric requirement of growth concerns the storage of energy and of new tissue formation by storing nutrients in the form of protein, fat and carbohydrate. This retained amount of energy represents the caloric demand above maintenance which is difficult to quantitate, and whose magnitude is far less than the maintenance energy expenditure of the growing infant.

The metabolic pattern

The pattern of substrate utilization calculated for the non-growing period already showed that most of the calories expended originated from carbohydrate oxidation. The caloric input within this period mostly reached or exceeded the caloric expenditure of maintenance. Thus, the metabolic pattern obtained was quite different from that characteristic of the immediate postnatal period, when the fasting metabolic state is dominated by fat utilization. The mean participation of protein metabolism in total heat production amounted only to 5% which corresponded to the proportion reported for full size [16] and for preterm infants [24]. It is interesting that the contribution of protein catabolism to energy expenditure was considerable less than in adults in whom it was found to provide up to 17% of the calories produced [16].

The metabolic pattern observed in the period of growth indicates that the rise in total energy expenditure on maintenance can fully be accounted for by the increasing utilization of carbohydrate as oxidable fuel. The dominance of carbohydrate utilzation does not yet mean that protein and lipid metabolism has a negligible role in energetics of the various biochemical physiological functions and processes involved in growth. With respect to quantification and partition of whole body energy metabolism it should be kept in mind that the classical method of adding the various components does not reflect the complicated metabolic interrelationships of the nutrients. Instead, an integrated summation and analysis of the energetics of basic biochemical reactions would be necessary for a better understanding of the structure of energy metabolism and the relationship between energy input and output in the early and late neonatal period.

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