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# Thermal Conditions and the Mobilization of Lipids from Brown and White Adipose Tissue in the Human Neonate

By

T. HEIM, M. KELLERMAYER and Maria DANI

Department of Paediatrics, and Institute of Pathology, University Medical School, Pécs

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Since SMITH had suggested that brown adipose tissue might play a role in non-shivering heat production [40], evidence has been obtained that this tissue is an important source of thermoregulatory heat production in hibernators as well as in cold-adapted and non-cold-adapted non-hibernators [10, 11, 41, 42] and even in the warm-adapted rat [12, 13, 43]. Large amounts of brown adipose tissue were detected in many new-born mammals and it has been shown to be the principal site of heat production in the new-born rabbit [7, 19, 20, 21, 25] and guinea pig [4]. The occurrence and anatomical distribution of brown adipose tissue in human embryos, foetuses and neonates has been known for decades [3, 5, 16, 17, 30, 44] and it has been recognized that brown and white adipose tissue represent distinct entities [3, 14, 17, 27, 37, 38]. Recent indirect evidence suggested that brown adipose tissue plays an important role in thermoregulatory heat production in the human neonate also [1, 2, 8, 39].

In the new-born rabbit white fat is used up during starvation independently of environmental temperature, while brown adipose tissue is depleted of fat only in cold surroundings [22, 23, 24]. In the present investigation an attempt has been made to furnish similar evidence for the effect of thermal conditions upon lipid mobilization from brown and white adipose tissue in the human neonate. Some of the results were already subject of a preliminary communication [24].

## MATERIAL AND METHOD

More than 350 sections of brown and white adipose tissue, taken at 80 consecutive necropsies from babies dying up to the age of 27 weeks from various causes, were analysed. The birth weight of 73 infants was under 2500 g. At each necropsy the amount and gross appearance of both brown and white adipose tissue were ascertained. Samples were taken from axillary and interscapular brown fat and from subcutaneous white adipose tissue of the lower abdominal and inguinal region. Frozen sections were stained with Sudan black and Scarlet Red, the paraffin sections with haematoxylin-eosin and toluidine blue. Brown adipose tissue was classified according to the fat content [2]. Similar criteria were set up for white adipose tissue.

Classification of brown adipose tissue (Fig. 1):

*Replete with fat:* a, b

(a) Mixture of two types of cells, partly with a single large fat droplet partly with multivacuolated cytoplasm. The univacuolar cells were always smaller and the rim of cytoplasm was thicker and more granular than that of the white fat cells. (These were mostly seen in stillborn infants.)

(b) Typical brown fat cells, multivacuolated with centrally located nucleus.

*Depleted of fat:* c, d

(c) Nearly all cells were practically depleted of fat and contained at most a few small fat droplets; others were totally depleted, with centrally placed nuclei.

(d) No fat in brown adipose tissue cells. The cells have large, round nuclei, a granular cytoplasm and are closely packed. A great number of dilated capillaries with numerous red blood cells can be seen.

"Replete with fat" corresponds approximately to groups 3 and 4, depleted of fat to groups 1 and 2 of the classification of AHERNE and HULL [2].

Classification of white adipose tissue (Fig. 2):

*Replete with fat:* a, b

(a) All cells contain a single large fat droplet. The nuclei are pressed to one side of the cell. Typical signet ring forms.

(b) All cells contain fat but the vacuoles were smaller than in group (a). More marked rim of cytoplasm and flattened nuclei were present.

*Depleted of fat:* c, d

(c) Elongated cells with ovoid nuclei. Most cells were depleted of fat.

(d) Fat-free white adipose tissue. The round nuclei are centrally located.

As quantitative methods proved to be in good agreement with this histological classification [2, KELLERMAYER and HEIM, unpublished] the latter was used as an index of fat content of adipose tissue cells. Classification of sections was carried out by one of us (M. K.) unaware of the clinical history.

The 80 babies were grouped according to one criterion, namely the thermal condition in which they had been nursed during extrauterine life.

"Warm group": nursed in incubators at 34—35°C since birth. In this group 3 stillborn infants were included.

"Cold group": nursed conventionally, wrapped in swaddling clothes since birth. The temperature of the wards was recorded four times daily and proved to be between 22—27°C throughout the period of investigation (February to November, 1966).

Gestational age was calculated from the day of onset of the mother's last normal menstual period. In 15 out of the 80 infants the records regarding gestational age were incomplete, therefore in these cases the length of gestation and the deviation of birth weight from the median could not be established.

For assessing intrauterine growth LUBCHENCO's chart was used [32]. The use of this graph was justified since the percentile curves derived from 3119 liveborn infants between 30—44 weeks of gestation showed a similar pattern in our region (FEKETE, personal communication).

"Ideal" weight during the postnatal period indicates the body weight of healthy premature and full term thriving infants read off the DANCIS grid or LUKÁCS's table [6, 33].

For statistical evaluation Student's $t$-test and $\chi^2$ with Yates' correction was used.

## RESULTS

### *Analysis of the clinical history and pathological data*

In Fig. 3 the birth weights of 22 babies from the "warm" group (25 cases) are plotted on the intrauterine growth chart. Seventeen out of 22 weighed less at birth than the median weight and 6 less than the 10th per-

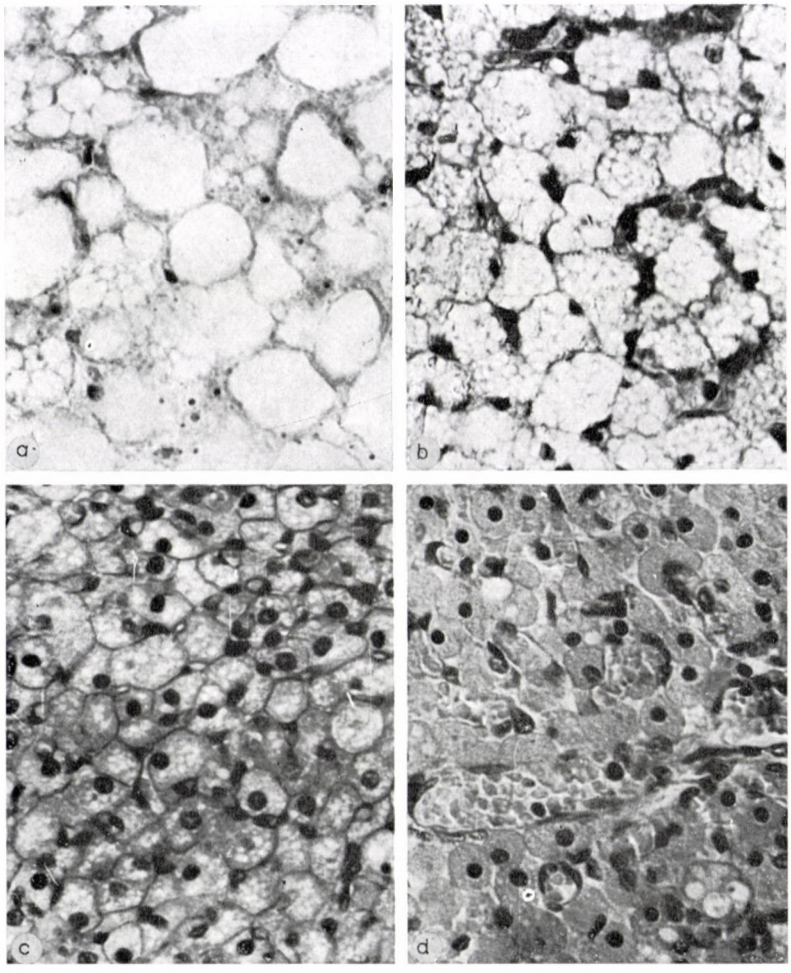


FIG. 1. Histological classification of brown adipose tissue sections according to the fat content of cells. *a*, *b*, replete with fat; *c*, *d*, depleted of fat. (Toluidine blue, magnification × 400)

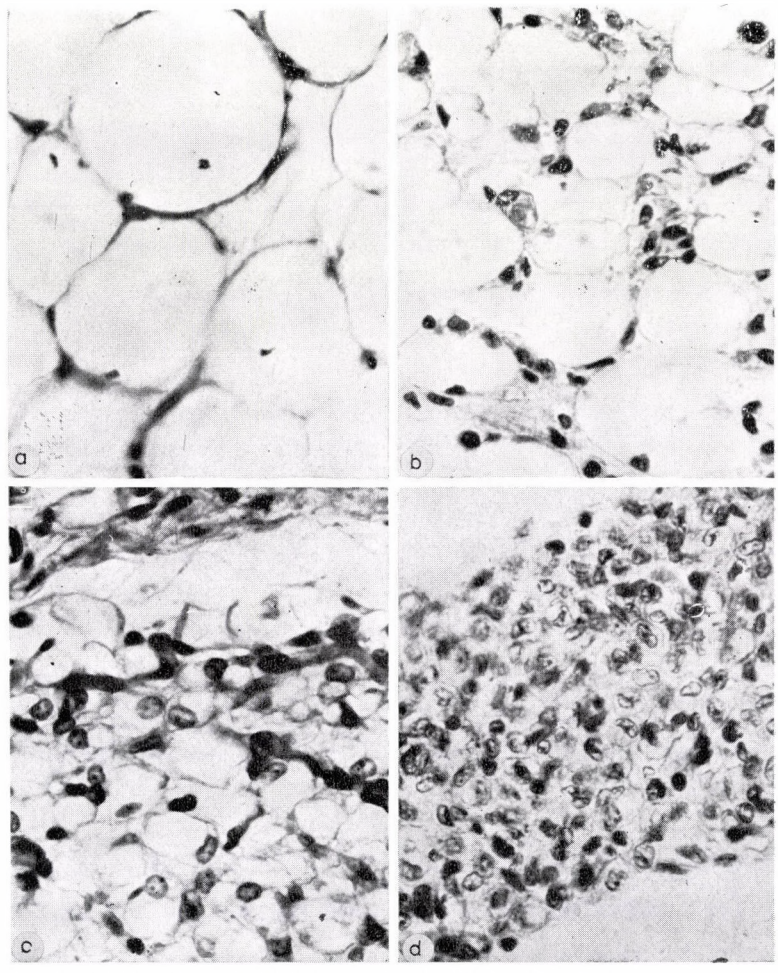


FIG. 2. Histological classification of white adipose tissue sections according to the fat content of cells. *a*, *b*, replete with fat; *c*, *d*, depleted of fat. (Toluidine blue, magnifcation × 400)

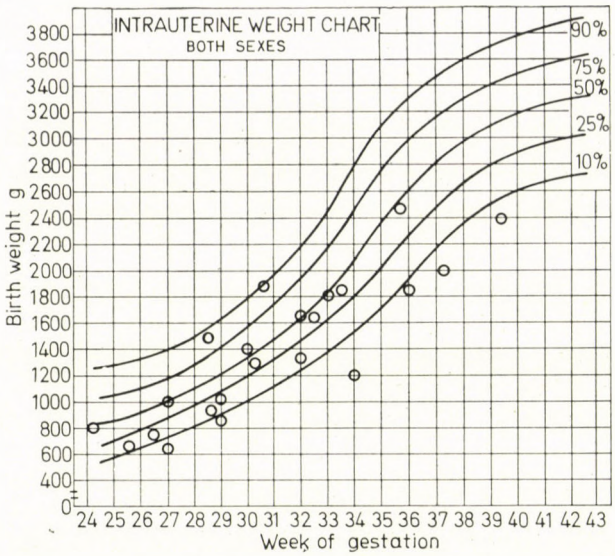


FIG. 3. Birth weight of 22 infants nursed in incubators (34—35°C), in relation to the duration of gestation

centile and were therefore regarded as intrauterine malnourished "small for date" babies.

Fig. 4 contains the same data of 43 out of the 55 cases of the "cold" group. Birth weights of 20 out of the

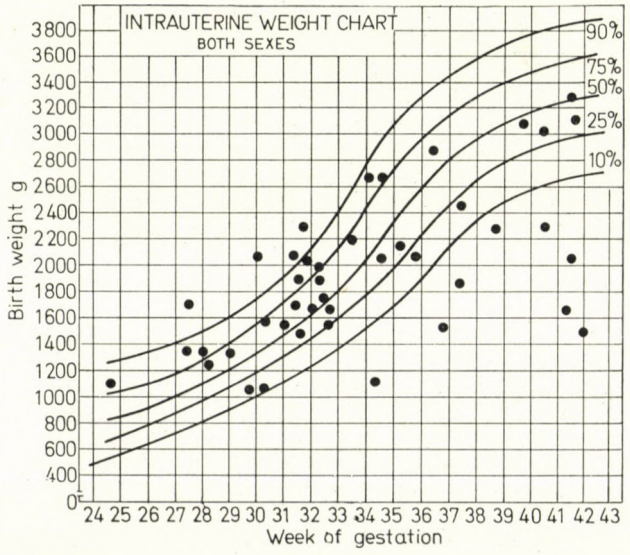


FIG. 4. Birth weight of 43 infants nursed conventionally swaddled at room temperature (22—27°C), in relation to the duration of gestation

43 babies fell below the 50th percentile and 8 under the 10th percentile; the latter were regarded as dysmature babies.

Gestation, postnatal age, birth weight, body weight at death, deviation from ideal body weight, daily calorie intake and cause of death in both the "warm" and the "cold" groups are presented in Table I. Mean gestational age was significantly less ($p < 0.001$) in the "warm" group than in the "cold" one. This was due to the fact that the two groups were non-random samples, because the limited number of incubators prevented nursing all small and dysmature babies of older gestational age under such conditions. Postnatal age varied between 0—25 days in the "warm" group and 0 —190 days in the "cold" group, thus mean age was nearly five times higher in the latter; birth weight was lower in the former. The most important

TABLE I

Analysis of 80 infants dying before 27 weeks of age
Mean ± S. E.

| | Nursed at ambient temperature | |
|---|---|---|
| | 34—35°C (in incubator) | 22—27°C (in room) |
| Number of babies | 25 | 55 |
| Gestational age, weeks* | 30.9±0.8 | 34±0.3 |
| Postnatal age, days | 3.7±1.4 | 18.4±2.9 |
| Birth weight, g | 1435±102 | 2005±83 |
| Body weight at death, g | 1380±99 | 1999±103 |
| Difference between "ideal" body weight and real body weight, at death, g** | —70±25 | —523±104 |
| Daily calorie intake/kg body weight | 18±8 | 60±6 |
| Cause of death: | | |
| Stillbirth | 3 | — |
| Intracranial haemorrhage | 18 | 17 |
| Pulmonary atelectasis | 1 | — |
| Congenital malformation | — | 10 |
| Enterocolitis, *E. coli* infection | 2 | 16 |
| Other infections | 1 | 7 |
| Aspiration of food | — | 3 |
| Neoplasms | — | 1 |
| Haematoma of liver | — | 1 |

* Reliable data for calculation of gestational age were obtained in 22 out of 25 and 43 out of 55 cases of the "warm" and "cold" group, respectively.

** "Ideal" body weight was read from either the Dancis grid [6] or Lukács' table [33].

common feature of both groups was that body weights at death were invariably less than the ideal body weight ($p < 0.001$ for the "warm" group; $p < 0.02$ for the "cold" group). Thus the great majority were malnourished in some way or another. Mean calorie intake up to 3 days before death proved to be much less in both groups than that of healthy babies of the same age, since an adequate level of food intake could not be maintained in consequence of severe disease. Particular attention was paid to adequate fluid intake and replacement of fluid losses.

In the "warm" group, intracranial haemorrhage was the preponderant cause of death; in the "cold" group, intracranial haemorrhage and enterocolitis were the two main diseases leading to death.

*Histological appearance of brown and white adipose tissue*

Table II summarizes the data on the fat content of brown and white adipose tissue. Brown adipose tissue was full of fat in all babies nursed in incubators from birth until death while in 82% of the babies nursed conventionally at room temperature brown adipose tissue was found partially or completely depleted of fat.

The fat content of white adipose tissue failed to show similar differences. In 44% of the babies nursed and dying in incubators white adipose tissue was full of fat, while that of the others was totally or partially depleted. In babies nursed at room temperature until death, white adipose tissue was replete with fat in 40% of the cases and partially or

TABLE II

Histological appearance of brown and white adipose tissue of 80 babies dying between 0—27 weeks of life. 25 were kept in incubators (34—35°C) and 55 conventionally swaddled at room temperature (22—27°C)

| Nursed at ambient temperature of | Brown adipose tissue | | White adipose tissue | |
|---|---|---|---|---|
| | replete with fat | depleted of fat | replete with fat | depleted of fat |
| 34—35°C | 25 | — | 11 | 14 |
| 22—27°C | 10 | 45 | 22 | 33 |

Brown adipose tissue $\chi^3 = 43.5 \quad p < 0.001$
White adipose tissue $\chi^3 = 0.11 \quad p \simeq 0.8$

completely depleted in the rest. The difference in the fat content of brown adipose tissue was highly significant between the two groups, whereas no significant difference was found in the fat content of white adipose tissue.

comparable in these "warm" and "cold" groups. Birth weight of 14 out of 20 babies in the "warm" group fell under the 50th percentile and 5 below the 10th percentile. Birth weights of the "cold" groups scattered

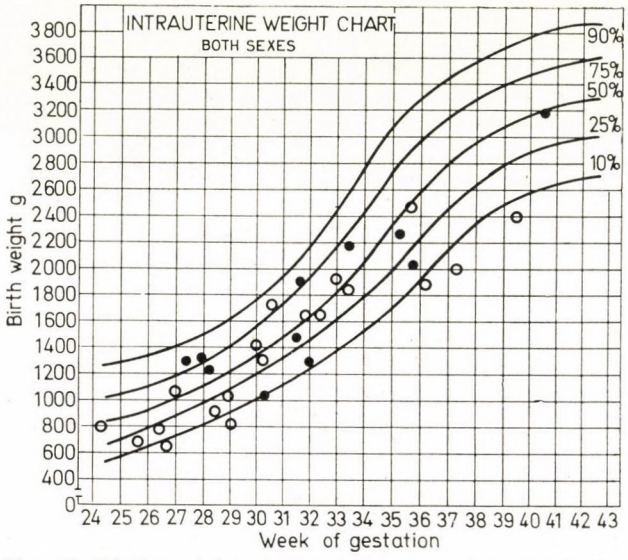


FIG. 5. Birth weight of 20 infants nursed in incubators (34—35°C, open circles) and 10 babies conventionally swaddled at room temperature (22—27°C solid circles) in relation to the duration of gestation

*Clinical history and pathological data of 38 infants dying within the first 4 days of life*

Since postnatal age was not strictly comparable in the two groups because the members of the "warm" group were significantly younger at death than those of the "cold" group, the fat content of brown and white adipose tissue of infants dying within the first 4 days of life has been analysed separately. Fig. 5 and Table III show that the parameters of gestational and postnatal ages were around the median. This difference is underlined by the fact that intrauterine growth deficit (median body weight minus birth weight at a certain gestational age) was $-163 \pm 66$ g in the "warm" group and $-10 \pm 91$ g in the "cold" group (mean $\pm$ S. E.). These data show that more intrauterine malnourished infants were included into the "warm" group than into the "cold" one.

Body weights at birth and death were still higher in the "cold" group than in the "warm" one, for reasons already mentioned.

TABLE III

Analysis of 38 infants, dying 0—4 days of age
Mean ± S. E.

| | Nursed at ambient temperature | |
|---|---|---|
| | 34—35°C (in incubator) | 22—27°C (in room) |
| Number of babies | 22 | 16 |
| Gestational age, weeks* | 30.9±0.9 | 32.2±1.3 |
| Postnatal age, hours | 30±6 | 41±8 |
| Birth weight, g | 1444±115 | 1863±146 |
| Body weight at death, g | 1392±111 | 1793±132 |
| Difference between birth weight and body weight at death, g | −52±25 | −70±36 |
| Daily calorie intake/kg body weight | 6.3±5 | 13.4±4 |
| Cause of death: | | |
| Stillbirth | 3 | — |
| Intracranial haemorrhage | 18 | 11 |
| Pulmonary atelectasis | 1 | — |
| Congenital malformation | — | 3 |
| Aspiration of food | — | 1 |
| Infection | — | 1 |

* Reliable data for calculation of gestational age were obtained in 20 out of 22 and 10 out of 16 cases of the "warm" and "cold" group, respectively.

Postnatal weight loss was slightly higher in the "cold" group than in the "warm" group in spite of a slightly higher calorie intake in the former. Neither of the differences were, however, significant statistically.

### *Histological appearance of brown and white adipose tissue of 38 babies dying within the first 4 days of life*

Table IV shows that brown adipose tissue was full of fat in all babies

TABLE IV

Histological appearance of brown and white adipose tissue of 38 babies dying within the first 4 days of life. 22 were kept in incubator (34—35°C) and 16 conventionally swaddled at room temperature (22—27°C)

| Nursed at ambient temperature of | Brown adipose tissue | | White adipose tissue | |
|---|---|---|---|---|
| | replete with fat | depleted of fat | replete with fat | depleted of fat |
| 34—35°C | 22 | — | 11 | 11 |
| 22—27°C | 6 | 10 | 10 | 6 |

Brown adipose tissue $\chi^2 = 17.2$ $p < 0.001$

White adipose tissue $\chi^2 = 1.28$ $p \cong 0.3$

nursed in incubators, whereas it was completely or almost completely depleted of fat in 63% of the infants nursed at room temperature. Fat content of white adipose tissue showed no such difference. It was replete with fat in 50% of babies in the "warm" group, in 63% in the "cold" group, and depleted in the rest. Comparing all cases with those dying in the first four days of life it is evident that age at death did not materially affect the results.

### *Mobilization of fat from brown adipose tissue in babies suffering from intracranial haemorrhage*

Since intracranial haemorrhage occurred frequently in both the "warm" and "cold" groups it seemed to be of interest to examine whether damage of the central nervous system might have led to the failure of fat mobilization from brown adipose tissue. Table V shows that brown adipose tissue was full of fat in all babies nursed in incubators (34—35°C) also when dying from various diseases other than intracranial haemorrhage.

In the "cold" group, however, brown adipose tissue was depleted of fat in 65% of babies with intracranial haemorrhage, and was replete with fat only in 35% of the cases. This finding also shows that intracranial haemorrhage was not a major factor in preventing lipid mobilization from brown fat cells.

Among babies of the "cold" group dying from various diseases other than intracranial haemorrhage, brown adipose tissue was depleted of fat in 89% of the cases and replete with fat in 11 per cent. This also shows that intracranial haemorrhage did not basically affect the results.

TABLE V

Histological appearance of brown adipose tissue of 80 babies dying before 27 weeks of age.
In the "warm" group ($n = 25$) 18 babies died from intracranial haemorrhage and 7 from other diseases.
In the "cold" group ($n = 55$) 17 babies died from intracranial haemorrhage and 38 from other diseases

| Cause of death | Nursed at 34—35°C | | Nursed at 22—27°C | |
|---|---|---|---|---|
| | B.A.T. replete with fat | B.A.T. depleted of fat | B.A.T. replete with fat | B.A.T. depleted of fat |
| Intracranial haemorrhage | 18 | — | 6 | 11 |
| Other diseases | 7 | — | 4 | 34 |

At 22—27°C $\chi^2 = 3.32$ $p \cong 0.1$

## DISCUSSION

Starvation experiments on newborn rabbits [22, 23, 24] provided the starting point for the present investigation. In clinical material, however, changes in brown and white adipose tissues are more difficult to evaluate than in well-controlled animal experiments. In the latter, at the beginning of starvation both brown and white adipose tissues were replete with fat and the diminution of fat content could be accounted for by either thermoregulatory heat production or by starvation. In clinical

material the prenatal and postnatal accumulation of fat as well as the fat loss have to be considered. Fat begins to accumulate and brown fat lobules can be clearly distinguished from white fat lobules in the 235 mm human foetus (vertex to anus) [17, 44]. Since in our material the youngest premature baby was 248 mm long and the mean crown-rump length was over the 280 mm in both the "warm" and "cold" groups, the absence of fat cannot be regarded as a physiological characteristic of a certain intrauterine age but is evidently due to physiological or pathological processes.

Our results suggest that brown and white adipose tissues are not equally affected by intrauterine malnutrition (Fig. 5, Table IV). Brown adipose cells were full of fat in the 5 "dysmature" babies of the "warm" group dying in the first 4 days of life, whereas white adipose tissue cells were totally depleted of fat in all of them. Intrauterine environment being thermoneutral, these findings are in complete agreement with the observations made during extrauterine life.

Starvation is one of the most powerful stimuli of fat mobilization. Postnatal starvation, however, was not necessarily always the consequence of reduced food intake, since vomiting and diarrhoea frequently occurred in the babies nursed at either environmental temperature. Nevertheless the fact that mean body weight at death was significantly less ($p < 0.01$) than the "ideal" body weight in both the "warm" and "cold" groups (Table I) suggests that the great majority of our babies were malnourished for one reason or another in their extrauterine life and were, therefore, under the constant influence of starvation.

Thermoregulatory heat production being regulated by a nervous mechanism, and since various lesions of the central nervous system may abolish or impair thermoregulation [9, 15, 28, 29, 34, 45], the possibility had to be considered that intracranial haemorrhage might have played a role in preventing the loss of fat from brown adipose tissue in the course of undernutrition. The fact that fat mobilization from interscapular brown adipose tissue is inhibited by denervation might point in the same direction [18, 26]. Analysis of the effect of intracranial haemorrhage upon fat mobilization from brown adipose tissue (Table V) showed that in a thermoneutral environment brown adipose tissue was full of fat in all cases irrespective of the presence or absence of intracranial haemorrhage, and that in the "cold" group brown adipose tissue was depleted of fat in the majority of babies with and without intracranial haemorrhage.

Independently of the underlying disease, brown adipose tissue was replete with fat in all babies nursed from birth in a thermoneutral environment (34—35°C), although in about half of the cases white adipose tissue was completely or almost completely depleted of fat. In contrast, in conventionally wrapped and swaddled infants nursed at room temperature

(22—27°C), brown adipose tissue was depleted of fat in 83% of the cases, whereas the fat content of white adipose tissue was similar as in those nursed in a thermoneutral environment.

Heat production was not measured in this investigation, but it has been demonstrated earlier that thermoregulatory heat production is activated in premature babies and even in some healthy full term infants conventionally swaddled at room temperature [31, 35, 36].

In 26 babies with a birth weight of less than 2000 g, heat production was found to be 25—30% higher wrapped in swaddling clothes at room temperature (22—23°C) than in incubators (35—36°C). Increased oxygen consumption in the swaddled infants exposed to room temperature was not accompanied by gross movements or visible shivering [36]. The fact that considerably more heat is produced by premature infants swaddled at room temperature than in incubators at 34—35°C offers a plausible explanation for the observation that brown adipose tissue was depleted of fat in almost all of the babies in the "cold" group.

In the human neonate, like in the new-born rabbit [22, 23, 24], brown fat is mobilized in response to cold but not during undernutrition in a thermoneutral environment, whereas white fat apparently serves as a general metabolic reserve and is used during undernutrition both in the absence and the presence of cold-induced increase in heat production.

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## Summary

The fat content of brown and white adipose tissue of 80 infants dying before the age of 27 weeks was estimated histologically. The birth weight of 73 babies was under 2500 g, and all were underweight at death. Independently of the underlying disease, brown adipose tissue was replete with fat in infants nursed from birth in a thermoneutral environment (34—35°C), although in about half of the cases white adipose tissue was completely or almost completely depleted of fat. In contrast, in conventionally wrapped and swaddled infants nursed at room temperature (22—27°C) brown adipose tissue was depleted of fat in 83% of the cases. The fat content of white adipose tissue was similar as in those nursed in a thermoneutral environment.

Brown fat is an important source of thermoregulatory heat production in the human neonate, and is mobilized in response to cold but not during undernutrition in a thermoneutral environment, whereas white fat apparently serves as a general metabolic reserve and is used during undernutrition both in the absence and the presence of cold-induced increase in heat production.

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Dr. T. Heim
József A. u. 11.
Pécs, Hungary