PROCEEDINGS OF THE NUTRITION SOCIETY

The Three Hundred and Thirty-second Scientific meeting of the Nutrition Society was held in the Wellcome Lecture Hall of The Royal Society, London on 18 *September* 1979

SYMPOSIUM ON 'NUTRITION OF THE MOTHER AND CHILD'

Maternal nutrition and the outcome of pregnancy—a critical appraisal

By D. J. NAISMITH, *Department of Nutrition, Queen Elizabeth College, Campden Hill, London W8 7AH*

Elevated perinatal and infant mortality rates are major health problems in the developing countries and in poor communities in most industrialized nations. Perinatal mortality is known to be particularly high in infants of low birth weight, and in those infants who survive a higher frequency of congenital defects, mental retardation and sub-normal growth is evident (Fitzhardinge & Steven, 1972). Of the many factors, hereditary and environmental, that are believed to influence birth weight, perhaps the most contentious is the diet of the mother. For the nutritionist concerned with child health it is important, therefore, to appreciate the extent to which growth and development of the foetus may be influenced by maternal undernutrition, to identify the nutrient deficiencies that are responsible and, conversely, to understand why the failure of the mother to satisfy what might be regarded as self-evident requirements, for example an increase in protein consumption, may have no appreciable effect on birth weight.

The only substantial results we have that may be used to evaluate the effects of acute severe malnutrition are the much quoted accounts of famine in Leningrad (Antanov, 1947) and Holland (Smith, 1947) during the Second World War. Estimates of maternal food consumption and values for weight gain during pregnancy were mere fractions of the normal. Nevertheless, birth weights were reduced, on average, by no more than one pound. Furthermore, the recent follow-up study of 20 000 of the infant survivors of the Dutch famine showed convincingly that, given adequate postnatal nutrition, there were no long-term adverse effects on mental performance or on adult stature (Stein *et al.* 1975). Such an acute form of deprivation is, however, rare. The more common situation is one of chronic undernutrition, varying seasonally from the mild to the moderately severe, and the interaction of other environmental and social factors such as bad sanitation, poor housing and long hours of work, make it impossible to quantify the contribution of undernutrition to the observed deficit in birth weight. Dietary intervention studies provide the only practical means of achieving this end, and two well-controlled experiments of this kind, recently completed in Guatemala

0029–6651/80/3913–3201 $01.00

Table 1. *Influence of supplementation of the maternal diet on birth weight*

(Values in parentheses are number of mothers in sample)

Group	Total dietary supplement: Energy MJ	Total dietary supplement: Energy kcal	Total dietary supplement: Protein* (g)	Birth weight: Mean (g)	Birth weight: <2500 g (%)
Guatemala:					
A (82)	6·6	1600	112	2960	21
B (89)	47·8	11 600	816	3020	18
C (71)	119·9	29 100	2046	3220	6
D (46)	232·0	56 300	3958	3230	4
Taiwan:					
E (111)	41·2	10 000	—	3067	7
F (114)	922·9	224 000	11 200	3111	3

*Value applies only to those mothers receiving the protein-containing supplement.

(Lechtig *et al.* 1975) and in Taiwan (Blackwell *et al.* 1973) are worth considering in some detail.

In the Guatemala project the mothers, who habitually existed on 6·4 MJ (1500 kcal)/d were offered a supplement providing either energy alone or energy with protein, and were later arbitrarily divided into four groups (Table 1; groups A–D) depending on the total additional energy consumed. In the Taiwan study, which was more robust in design, the subjects were better nourished, with an average intake of 8·4 MJ (2000 kcal)/d and 40 g protein/d derived solely from vegetable foods. Two supplements were used: one provided 40 g of milk protein and 3·4 MJ (800 kcal)/d along with vitamins and minerals, the other vitamins and minerals with a small amount of energy (0·17 MJ (40 kcal)/d). Supplementation was begun several months before conception and was continued throughout pregnancy. In the Guatemalan mothers a small but significant improvement in birth weight and a reduction in the proportion of low birth weight infants was apparent only when the supplement approached the energy cost of pregnancy (Group C), and occurred regardless of the presence or absence of protein in the supplement (Table 1). The superior nutritional status of the mothers in Taiwan is reflected in the higher mean birth weight and smaller proportion of low birth weight infants born to mothers of the control group (Group E), and in this instance, despite the prodigious scale of supplementation, no significant increase in birth weight was achieved.

The conspicuous lack of effect of protein supplements in both these investigations strongly suggests that energy rather than protein is the major determinant of foetal growth.

The few experiments on animals that have attempted to distinguish between the effects of protein deficiency and energy deficiency have been inconclusive for a number of reasons; total food restriction has been termed 'energy restriction', the influence of energy deprivation on protein utilization has been disregarded, and

food intakes have not been controlled nor, in some cases, even recorded. Furthermore, the restrictions of energy or protein intakes have been so severe as to cast doubt on the relevance of the experiments to human problems. (Zamenhof *et al.* 1973; Rider & Simonson, 1973; Young & Widdowson, 1975). These major pitfalls were avoided in an experiment on rats (D. J. Naismith and E. Todd, unpublished results) in which we first examined the effects on foetal growth and composition of a moderate reduction in food intake which was intended to simulate the deprivation experienced by the Guatemalan mothers. The composition of the diet used was also derived from the Guatemalan report. In two other groups of animals, also restricted, the intake of energy or of protein was restored to equal that of the group fed *ad lib.* Intakes of energy and protein for the four experimental groups are shown in Fig. 1, and the results of the analyses of the foetuses removed on the 21st day of pregnancy are recorded in Table 2. No differences were found in litter size among the four groups. Restriction of food (LE-LP) caused a reduction of 14% in foetal weight. With the supplement of energy (HE-LP) a considerable recovery was made, but the protein supplement

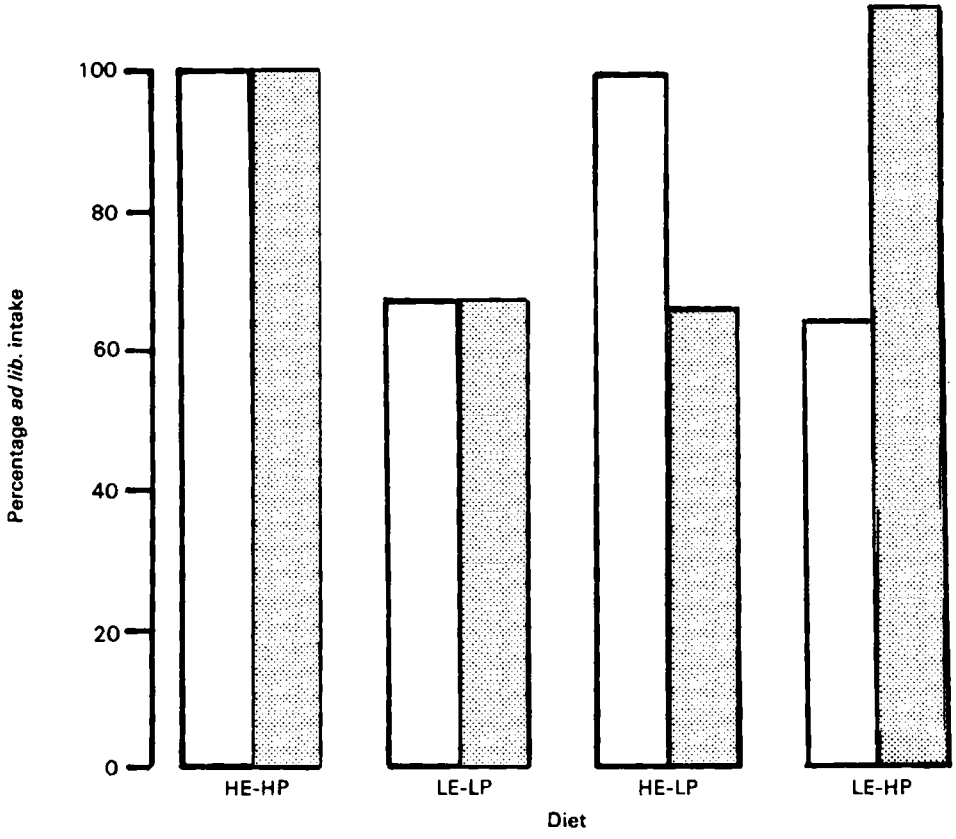


Fig. 1. Intakes of (□) energy and (▨) protein of pregnant rats fed on diets low in energy and protein (LE-LP), high in energy but low in protein (HE-LP) or low in energy but high in protein (LE-HP), shown as a percentage of the intakes of an *ad lib.* fed control group (HE-HP).

https://doi.org/10.1079/PNS19800002 Published online by Cambridge University Press

Table 2. *Mean values for weight, protein and DNA content of foetuses from rat dams fed on an adequate diet (HE-HP), a diet low in energy and protein (LE-LP), high in energy but low in protein (HE-LP) or low in energy but high in protein (LE-HP)*

(Values are means with their standard errors for eight litter-matched dams /group)

	HE-HP		LE-LP		HE-LP		LE-HP	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Foetal weight (g)	3·55	0·13	3·00	0·09	3·33*	0·09	3·09	0·07
Foetal protein (mg)	327	10	238	19	296**	8	277	8
Foetal DNA (mg)	16·2	0·43	13·0	0·49	15·3***	0·45	14·1*	0·34

Value differs from that for LE-LP; *$P<0.05$, **$P<0.02$, ***$P<0.01$.

(LE-HP) had no effect. Likewise the deficit in total body protein (27%) and in DNA (19%) in the pups of the undernourished dams was greatly reduced when additional energy was supplied, but only moderately so with extra protein.

The value of extrapolating from one species to another is frequently questioned, but when one considers that during pregnancy the rat dam must synthesize about ten times as much protein, per unit time per unit body-weight, as does a woman (Blaxter, 1963) then the paramount role of dietary energy in the reproductive process is very clearly affirmed.

Why then under the conditions that prevail in most developing countries is the effect of a lack of energy on birth weight so slight? Under optimal conditions a woman is in positive energy balance throughout gestation, and ends her pregnancy with a substantial increment in her fat reserve (Hytten & Leitch, 1971). The deposition of fat, in response to the action of progesterone (Galletti & Klopper, 1964; Hervey & Hervey, 1967) secreted by the foeto–placental unit, begins during the first trimester of pregnancy, but ceases shortly after the end of the second trimester, when mobilization of fat occurs (Burt, 1960). The hormone oestriol, also produced by the foeto–placental unit, is believed to curtail fat deposition by antagonizing the action of progesterone (Klopper & Billewicz, 1963), and placental lactogen, secreted in increasing amounts during the third trimester, has been shown to stimulate the release of fatty acids from adipose tissue (Strange & Swyer, 1974; Williams & Coltart, 1978). The mobilization of fat in late pregnancy provides an alternative fuel for oxidation by the maternal tissues, and so spares glucose for use by the foetus. Thus the endocrine function of the foeto–placental unit is responsible, initially, for conserving energy, then later for the redirection of available energy from furthering maternal storage to satisfying its own increasing demands. As a result of these profound changes in energy economy, superimposed on a modified homoeostatic regulation of the mother's blood glucose, an uninterrupted supply of energy to the foetus is assured.

The cycle of fat retention in early pregnancy followed by fat mobilization in late pregnancy has obvious advantages when food supplies are variable, inasmuch as the energy cost of pregnancy may be distributed over the entire gestational period.

In the well-nourished woman, however, fat deposition invariably exceeds withdrawal. Whether a net gain of fat should be regarded as physiological or merely an indication of failure to adjust energy intake to correspond with reduced physical activity in late pregnancy is a question that has long been disputed. Current thinking now favours the former opinion. In the laboratory rat the accumulation of fat during pregnancy and its use to subsidize the high energy cost of milk production has clearly been demonstrated (Naismith, 1966; 1971). In man, however, the argument has, until recently, rested on hearsay evidence only, and the teleological conviction that it made good physiological sense.

In 1975, Naismith & Ritchie measured the changes in weight and in body fat in twenty primiparous women during pregnancy and lactation. Food intakes were also measured during lactation. The infants were healthy and of normal birth weight, and were wholly breast-fed for 14 weeks. The main findings of the study are summarized in Table 3. Weight gain during pregnancy was very variable, ranging from 8·0 kg to 21·0 kg. If 8 kg is allowed for the identifiable components of weight gain (Hytten & Leitch, 1971) then from 0–13 kg fat was added to the reserve as a result of pregnancy. The changes in body-weight experienced by the mothers during their 3 month period of breast-feeding and their average daily food intakes appeared to be related to their weight gain in pregnancy. The mothers with the highest gains showed a greater than average loss of weight during lactation and had a smaller than average food intake, whereas the mothers with the lowest gains in weight lost least weight during lactation and ate considerably more food. While restricting weight gain, and hence fat deposition, in mothers living in more affluent societies can thus be compensated by unlimited food consumption should the mother choose to breast-feed her infant, the same cannot be said for mothers living in impoverished circumstances. For these women fat storage during pregnancy assumes much greater significance.

Table 3. *Energy intakes and changes in body-weight measured in twenty-two primiparous women during* 14 *weeks of lactation*

Group	Initial body-weight (kg)	Weight gain during pregnancy (kg)	Weight change during lactation (kg)	Energy intake during lactation	
				MJ/d	kcal/d
High gain	54·0	21·0	−4·5	11·49	2790
	56·5	20·5	−3·0	10·42	2530
	60·5	16·0	−4·0	11·78	2860
Mean	55·8	13·2	−2·6	12·07	2930
Low gain	65·5	10·0	+0·5	13·88	3370
	49·0	9·5	−3·0	18·38	4460
	56·0	8·0	−1·0	14·26	3460
Lactational failure	60·5	4·5	−1·5	12·00	2910
	60·5	5·0	−4·0	9·97	2420

https://doi.org/10.1079/PNS19800002 Published online by Cambridge University Press

There is a widely held view that modern woman has lost the art of breast-feeding, but in our own investigation only two women out of more than forty who began breast-feeding experienced lactational failure. Both persisted with breast-feeding, but had to supplement their own milk supply with regular artificial feeds. Both enjoyed good health, and had food intakes that fell within the range of our twenty successful subjects. They did differ strikingly, however, in one respect. Their total weight gains during pregnancy were extremely low (Table 3), and a sizeable loss from their own tissues, approximately 4 kg, must have occurred during pregnancy. Neither of the mothers was lacking in body fat, and both demonstrated an ability to mobilize fat. Hytten & Leitch (1971) have reported a correlation between performance in lactation and growth in size of the breast during pregnancy. We suggest therefore that under conditions of negative energy and probably negative nitrogen balance, normal development of the mammary gland may have been affected.

Although the role of dietary protein may now be relegated to one of minor importance in determining the successful outcome of pregnancy, it cannot be dismissed without further consideration. It has been estimated that during a

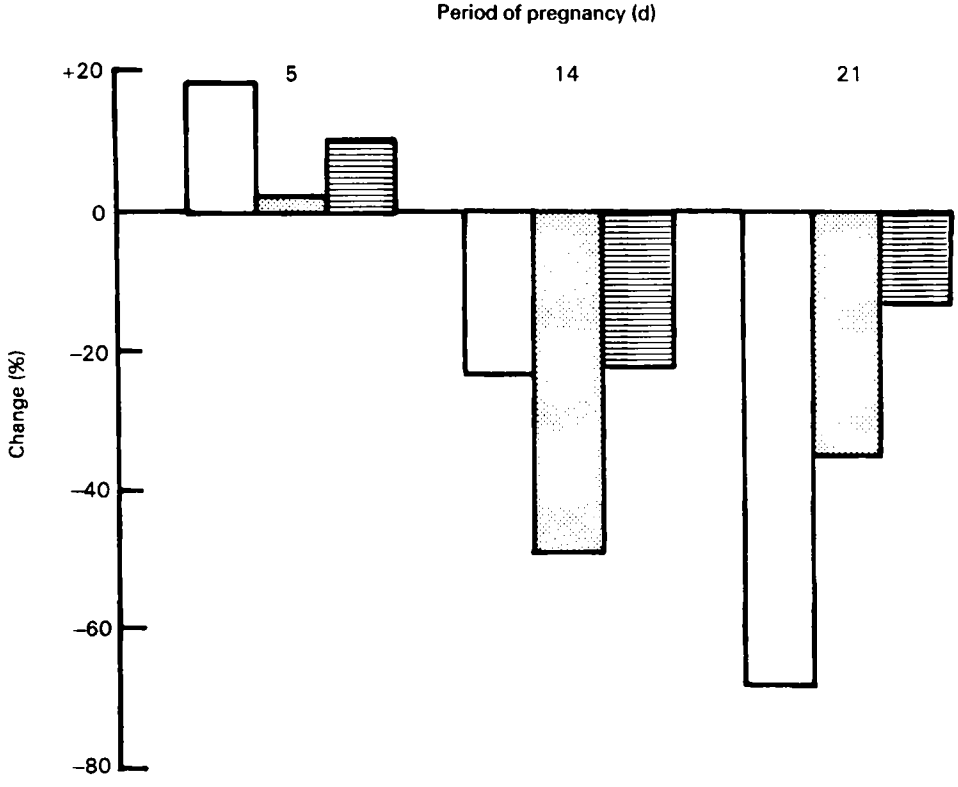


Fig. 2. Changes in activity of (□) hepatic alanine aminotransferase and (▣) argininosuccinate synthetase, and in the concentration of (▤) urea in the plasma of rats at different stages of pregnancy.

https://doi.org/10.1079/PNS19800002 Published online by Cambridge University Press

normal pregnancy some 900 g of new protein is synthesized in the products of conception and in the maternal reproductive tissues (Hytten & Leitch, 1971). How can this be achieved without, apparently, raising protein intake above the minimum level of requirement of the non-gravid woman?

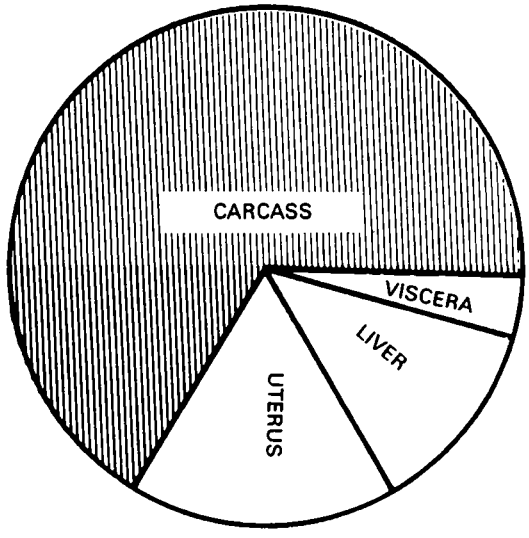
The answer to this paradox is found in the results of experiments on the rat. The use of protein, like the use of energy, is modified during pregnancy by the endocrine function of the foeto-placental unit.

The major factor contributing to the more economical use of protein is the adjustment that occurs in the intermediary metabolism of amino acids (Naismith & Fears, 1971). The activity of enzymes that regulate the rate of amino acid deamination and of urea synthesis in the liver has been shown to decline markedly throughout pregnancy (Fig. 2). This suppression of amino acid catabolism, which is reflected in lower plasma urea concentrations and confirmed by a fall in urea excretion, has been reproduced in the non-pregnant rat by the administration of progesterone. (Naismith & Fears, 1972). In this way a limited amino acid supply for foetal growth may be augmented without increasing the dietary intake.

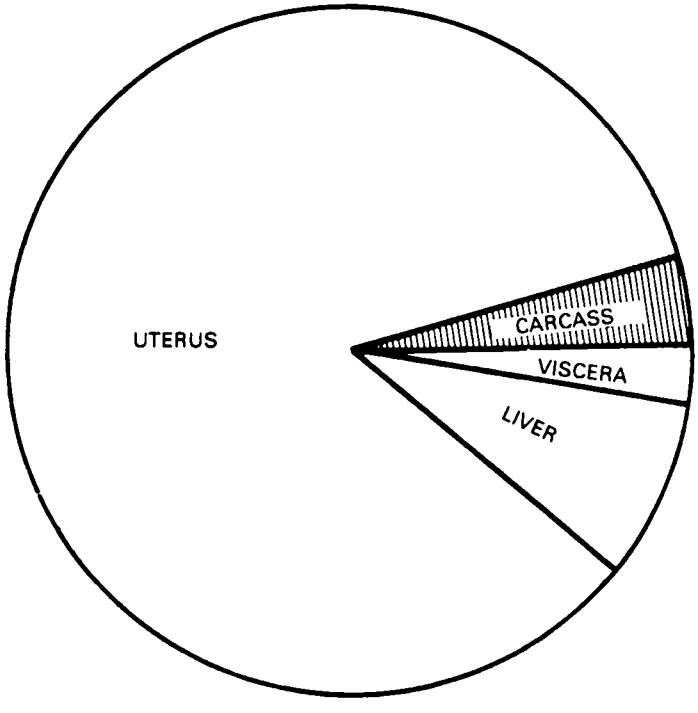
Although, for obvious ethical and practical reasons, metabolic studies of this kind cannot be contemplated in human subjects, there is indirect evidence for similar alterations in protein metabolism in pregnant women. For example, it has long been known that the plasma urea concentration in women is reduced from early pregnancy (Sims & Krantz, 1958), the pattern of change in the secretion of hormones that are known to influence amino acid metabolism are similar in the rat and in man (Naismith, 1979), and Calloway (1979) has recently concluded, from measurements of N-balance during the menstrual cycle, that progesterone also exerts an anabolic effect on protein metabolism in women.

A second factor affecting protein utilization is the operation of a cycle of protein storage in early pregnancy followed by protein breakdown in late pregnancy analagous to the deposition and mobilization of fat described earlier (Naismith, 1966; 1969). After two weeks of gestation, a pregnant rat, compared with a virgin litter-mate control, has increased the protein content of her muscles by an amount roughly equivalent to half the protein content of the conceptus at term (Fig. 3). During the final week, when rapid growth of the foetus occurs, the protein reserve is withdrawn. This 'catabolic phase' occurs irrespective of the protein intake of the mother, indicating that it is under hormonal rather than dietary control. Experiments in which a protein supplement was given to malnourished rat dams, for 5 d only, in early pregnancy showed convincingly that the protein store is transferred to the uterus, promoting an increase in cellularity and protein content of the foetuses (Naismith & Morgan, 1976). (Table 4.)

In human subjects the measurement of N-balance is one of the few procedures available for the study of protein metabolism, but the problems involved are notorious. The balance studies of Macy *et al.* in the 1930s (Macy & Hunscher, 1934) produced gross overestimates of N-retention in pregnancy which fostered the notion of a protein store to support the ensuing lactation. Since protein contributes 6% only of the energy content of breast milk, it is extremely unlikely



After 14 d



After 21 d

Fig. 3. Distribution of additional N retained by pregnant rats after 14 d and 21 d of gestation. The areas of the circles are proportional to N retention.

https://doi.org/10.1079/PNS19800002 Published online by Cambridge University Press

Table 4. *Analyses for protein and DNA in foetuses from rats fed on a low-protein diet throughout pregnancy or given a protein supplement in early pregnancy (days 6–10 inclusive)*

(Mean values with their standard errors for eleven litter-matched pairs of dams)

	Foetal carcass					
	Weight (g)		Protein (mg)		DNA (mg)	
	Mean	SE	Mean	SE	Mean	SE
Unsupplemented	3·29	0·18	203	10	13·0	0·17
Supplemented	4·74**	0·28	296**	16	16·9**	0·64
	Foetal brain					
	Weight (mg)		Protein (mg)		DNA (mg)	
	Mean	SE	Mean	SE	Mean	SE
Unsupplemented	183	9·1	9·37	0·42	0·42	0·01
Supplemented	216**	5·3	10·57*	0·36	0·62**	0·04

*$P<0.05$, **$P<0.01$.

that dietary protein would ever be a factor limiting milk volume. In an adult subject N-balance is not affected by N-intake as long as the minimum requirement for protein is met. In the pregnant woman, in contrast, one would expect that, as the rate of uptake of N by the foetus increased, N-balance would become progressively more positive. In the meticulous balance studies of King *et al.* (1973), however, in which more modest estimates of N-retention were reported, no significant differences in balance were observed at different stages of pregnancy, although the rate of N accretion by the foetus shows an eight-fold rise between the second and last quarters of pregnancy (Hytten & Leitch, 1971). A system of protein metabolism involving an internal redistribution of amino acids would not, of course, affect the N-balance. Until a few years ago, no method for measuring body composition was sufficiently sensitive to detect changes in protein of the magnitude encountered in pregnant women. This situation has changed with the discovery of the amino acid 3-methylhistidine in muscle proteins. The dietary amino acid plays no part in muscle metabolism, since histidine undergoes methylation after it is incorporated into the peptide chains of actin and myosin (Asatoor & Armstrong, 1967), and the 3-methylhistidine released when muscle protein is degraded is quantitatively excreted in the urine (Young *et al.* 1972; Long *et al.* 1975). We thought that the excretion of 3-methylhistidine by pregnant women might show whether they, like their rodent counterparts, experienced a phase of muscle protein catabolism in late pregnancy (D. J. Naismith & P. Emery, unpublished results). N-balance and the excretion of 3-methylhistidine were measured for 3 consecutive days at monthly intervals in 4 women. All subjects were found to be in positive N-balance, but like Calloway and her colleagues, we

did not detect an upward trend with time. The excretion of 3-methylhistidine was stable until the end of the second trimester when a pronounced rise in excretion was observed (Fig. 4), indicating increased muscle protein catabolism. The biphasic character of protein metabolism in pregnancy may thus play a major role in modulating the effects of chronic malnutrition on foetal growth and development.

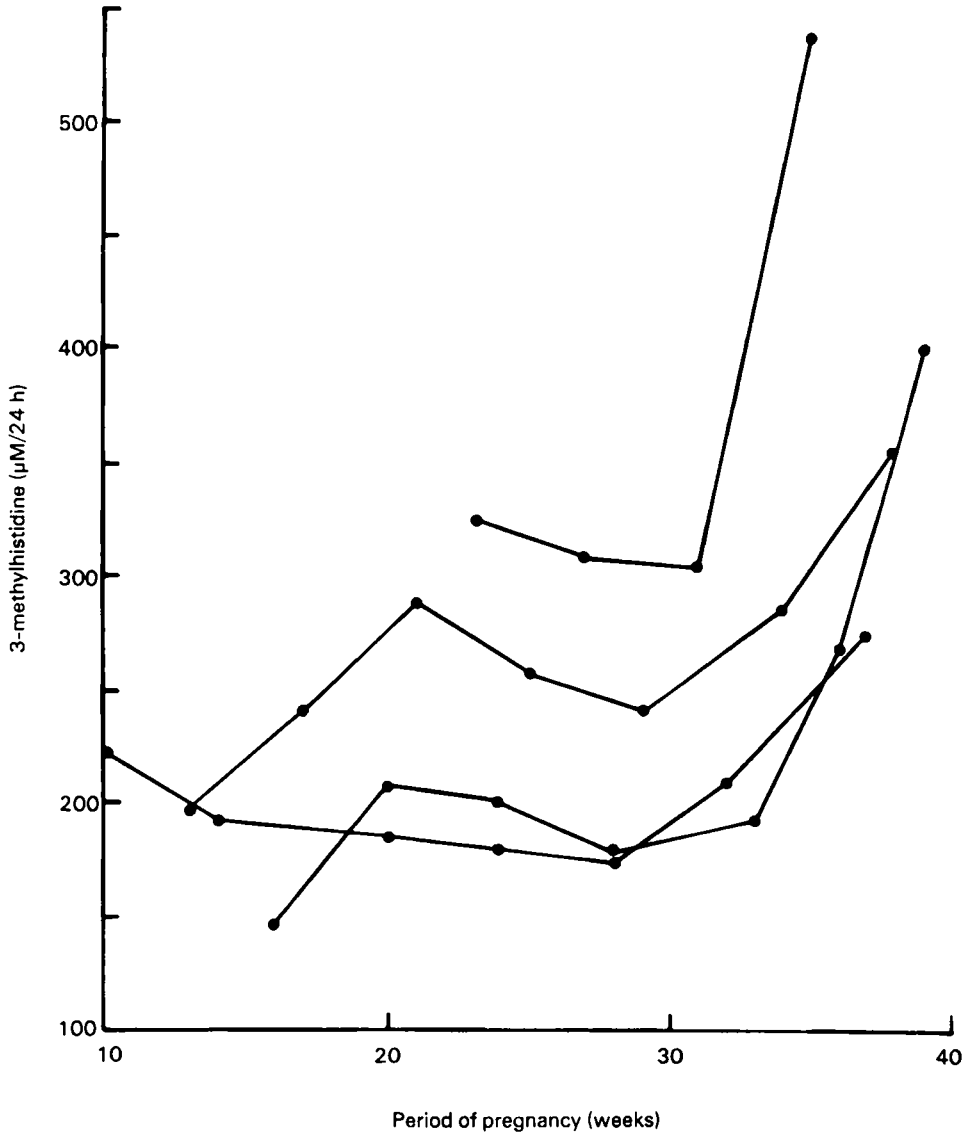


Fig. 4. Urinary excretion of 3-methylhistidine by four primiparous young women at different stages of pregnancy.

https://doi.org/10.1079/PNS19800002 Published online by Cambridge University Press

In this introductory paper I have confined myself to the major dietary factors, energy and protein, and to birth weight as an index of the adequacy of the maternal diet. Deficiencies of other nutrients are no doubt implicated in the impairment of foetal growth as the elegant experiments of Morgan & Winick (1978) with folic acid have shown, and I have ignored the question of foetal stores as a factor contributing to infant morbidity, and the more recherché aspects of foetal nutrition, such as the metabolism of the polyunsaturated fatty acids. I hope, nevertheless, that I have succeeded in putting in clearer perspective the role of maternal nutrition in determining the survival of the newborn infant and its future development.

REFERENCES

Antanov, A. N. (1947). *J. Pediat.* **30**, 250.
Asatoor, A. M. & Armstrong, M. D. (1967). *Biochem. biophys. Res. Commun.* **26**, 168.
Blackwell, R. Q., Chow, B. F., Chinn, K. S. K., Blackwell, B. & Hsu, S. C. (1973). *Nutr. Rep. Int.* **7**, 517.
Blaxter, K. L. (1963). In *Mammalian Protein Metabolism*, Vol. 2, p. 173 [H. N. Munro and J. B. Allison, editors]. Academic Press: New York.
Burt, R. L. (1960). *Obst. Gynec., N.Y.* **15**, 460.
Calloway, D. H. (1980). In *Maternal Nutrition During Pregnancy and Lactation.* Basel: Karger.
Fitzhardinge, P. M. & Steven, E. M. (1972). *Pediatrics, Springfield* **49**, 671.
Galletti, F. & Klopper, A. (1964). *Acta Endocr. (Kbh.)* **46**, 379.
Hervey, E. & Hervey, G. R. (1967). *J. Endocr.* **37**, 361.
Hytten, F. E. & Leitch, I. (1971). *The Physiology of Human Pregnancy*, 2nd ed. Oxford: Blackwell.
King, J. C., Calloway, D. H. & Morgan, S. (1973). *J. Nutr.* **103**, 772.
Klopper, A. & Billewicz, W. (1963). *J. Obstet. Gynaec. Br. Commonw.* **70**, 1024.
Lechtig, A., Habicht, J. P., Yarbrough, C., Delgado, H., Guzman, G. & Klein, R. E. (1975). *Proc. IXth Int. Congr. Nutr. Mexico*, vol. 2, p. 44. [A. Chavez, editor]. Basel: Karger.
Long, C. L., Haverberg, L. N., Young, V. R., Kinney, J. M., Munro, H. N. & Geiger, J. W. (1975). *Metabolism* **24**, 929.
Macy, I. G. & Hunscher, H. A. (1934). *Am. J. Obstet. Gynec.* **27**, 878.
Morgan, B. L. G. & Winick, M. (1978). *Br. J. Nutr.* **40**, 529.
Naismith, D. J. (1966). *Metabolism* **15**, 582.
Naismith, D. J. (1969). *Proc. Nutr. Soc.* **28**, 25.
Naismith, D. J. (1971). *Proc. Nutr. Soc.* **31**, 92A.
Naismith, D. J. (1980). In *Maternal Nutrition During Pregnancy and Lactation.* Basel: Karger.
Naismith, D. J. & Fears, R. B. (1971). *Proc. Nutr. Soc.* **31**, 8A.
Naismith, D. J. & Fears, R. B. (1972). *Proc. Nutr. Soc.* **31**, 79A.
Naismith, D. J. & Morgan, B. L. G. (1976). *Br. J. Nutr.* **36**, 563.
Naismith, D. J. & Ritchie, C. D. (1975). *Proc. Nutr. Soc.* **34**, 116A.
Rider, A. A. & Simonson, M. (1973). *Nutr. Rep. Int.* **7**, 361.
Sims, E. A. H. & Krantz, K. E. (1958). *J. clin. Invest.* **37**, 1764.
Smith, C. A. (1947). *J. Pediat.* **30**, 229.
Stein, Z., Susser, M., Saenger, G. & Marolla, F. (1975). *Science, N.Y.* **178**, 708.
Strange, R. C. & Swyer, G. M. (1974). *J. Endocr.* **61**, 147.
Williams, C. & Coltart, T. M. (1978). *Br. J. Obstet. Gynaec.* **85**, 43.
Young, M. & Widdowson, E. M. (1975). *Biol. Neonate* **27**, 184.
Young, V. R., Alexis, S. D., Baliga, B. S., Munro, H. N. & Muecke, W. (1972). *J. biol. Chem.* **347**, 3592.
Zamenhof, S., van Marthens, E. & Grauel, L. (1973). *Nutr. Rep. Int.* **7**, 371.

Printed in Great Britain