The energy cost of growth

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Energy requirements for growth can be separated into two components. One is the requirement for substrates from which to form the components of the new tissue, the other is the extra energy needed to meet the metabolic cost of growth. The first requirement is, of course, absolute in so far as 1 g of new tissue containing, say, 25% fat and 15% protein cannot be deposited without a dietary supply of about 13.4 kJ of appropriate energy. This is in fact the average energy content of tissue deposited in the rapidly growing malnourished child recovering on an energy-rich milk diet (Spady, Payne, Picou & Waterlow, 1976). The requirement will be variable as the composition of the new tissue varies. Thus, weight gain in older animals tends to involve the deposition of more energy because of the higher fat content. Similarly, in the malnourished child, measurements of muscle mass by Jackson, Picou & Reeds (1976) have clearly shown that new tissue can contain from as little as 5 to as much as 30 kJ/g according to the fat content.

However, this paper will be concerned with the second component of the energy cost of growth, the metabolic cost observed as heat production associated with growth.

The net efficiency of growth

The net efficiency of growth is of obvious practical importance since it represents an energy cost which is, both in theory and in practice, variable. Thus, any change in the energetic efficiency of growth will have to involve changes in this component. Energy balance trials have been performed on most animal species during growth. These have involved either direct measurement of intake and expenditure in respiration trials or measurement by means of calorimetry, or alternatively intake and deposition have been measured by means of carcass analysis (the comparative slaughter technique). The simplest question one can ask is whether heat production, i.e. the metabolic rate, during growth is higher than in the non-growing animal and, if so, in what way is it related to the growth rate. If the rate of heat production can be determined at different rates of growth, then it should be possible to answer this. This can be done most simply by means of a

linear regression of energy balance (Eb) on metabolizable energy intake (ME) which will yield an equation of the form:

$$Eb = f.ME - B = f\left(ME - \frac{B}{f}\right)$$

This equation incorporates three values, the intercept term B which is fasting heat production, the regression coefficient f which is the fraction of ME intake above maintenance intake (B/f) which is deposited, i.e. the net efficiency of growth. $1-f$ is the fraction of ME intake above maintenance appearing as heat production. While both fasting and maintenance heat production are values which can be determined (in these defined conditions), the concept of a maintenance component of heat production in the growing animal is physiologically artificial. It is needed however, if we want to express a net efficiency of growth; the only alternative being the use of gross efficiency. As we shall see, the estimation of maintenance costs in growing animals is a difficult problem.

Measurement of the net efficiency of growth

There appear to be two main experimental approaches which have been used, and we feel that they ought to be considered separately. In the first one, Method A, growth rates are varied by reducing intakes from the *ad lib.* level to maintenance level and in some cases to zero intake so that Eb is negative. This enables both maintenance and fasting heat production to be directly determined. A rather special case is the infant recovering from malnutrition who voluntarily increases his intake to achieve markedly increased growth rates, e.g. up to more than 20 times the normal rate (Ashworth, Bell, James & Waterlow, 1968). Table 1 includes results obtained by this method with milk-fed piglets, lambs and infants of similar weights. The net efficiency of deposition is shown in the first column and we might conclude that lambs are less efficient (at 0·66 and 0·69) than infants (0·82) or

Table 1. *Energy balances of milk-fed piglets, lambs and infants at different intakes*

| | Net efficiency (f) | Maintenance (B/f) | Energy balance at intakes of (kJ/kg per d) | | | |
| | | | 400 | | 850 | |
			Deposition	Heat	Deposition	Heat
Piglets[1]	0·78	380	16	384	367	483
Piglets[2]	0·88	391	8	392	404	446
Lambs[3]	0·69	300	69	331	380	470
Lambs[4]	0·66	251	98	302	395	455
Infants[5]	0·82	358	34	376	404	446

[1]Kielanowski & Kotarbinska (1970)
[2]Jordan & Brown (1970)
[3]Walker & Norton (1970)
[4]Walker & Jagusch (1969)
[5]Spady *et al.* (1976)

piglets (0·78–0·88). Thus a fixed increment of intake will result in a greater increment in deposition in the piglet than in the lamb. In order to evaluate the physiological implication of these differences, however, we must take into account the maintenance costs shown in Table 1, column 2. These are much lower in the lambs than in the infants or piglets. This means, as shown in the table, that at an intake of 400 kJ/g per d which is near to maintenance for the piglets, the lambs are producing less heat and depositing up to a quarter of the intake. At 850 kJ/g per d, which is within the *ad lib.* range of intakes for lambs and piglets and is often achieved by infants during catch-up growth, the total heat production and deposition (or the gross efficiency) is very similar in all cases.

Whilst we can subtract maintenance heat from the total heat output at the high intake and thereby show that lambs produce, on average, twice the growth-related heat of the piglets, it is doubtful if this partition has any physiological or biochemical meaning. We could perhaps better describe the physiological difference between lambs and piglets by saying that at *ad lib.* intakes heat production and growth rates are similar, but when intakes are reduced the lamb reduces its metabolic rate to a greater extent than the piglet.

In the second main experimental design, Method B, growth rates are varied by choosing normally growing animals of different body-weights for the trials, taking advantage of the developmental fall in intake and, in most cases, growth rate. The analysis of these experiments is, however, both practically and conceptually much more difficult. To determine the net efficiency of growth, heat output must be partitioned between maintenance and growth costs as before, but now maintenance costs are not directly determined. Furthermore, maintenance costs are assumed to vary as the animals increase their body-weight, and so before the energy balance data can be analysed an assumption must be made about how these costs vary with body-weight.

In practice most workers assume that maintenance costs will vary according to the body-weight raised to some power less than 1, so that a linear regression performed on intakes and deposition (or heat production) raised to this power will account for this changing maintenance cost. Total heat production in growing pigs appears to vary as body-weight $W^{0.56}$ (Kielanowski, 1969; Thorbeck, 1969; Bowland, Bickel, Wenk, Pfirter & Schurch, 1970) as it does in the rat, at least according to the findings of Walker & Garrett (1970) and McCracken (1975). Fasting heat production in the pig also varies as $W^{0.56}$ (Breirem, 1939), so it is possible that this is a general physiological relationship. What this means of course is that if energy balance values were analysed by a regression of data expressed as $W^{0.56}$, there would be constant amounts of heat partitioned towards maintenance and growth so that no clear correlation between growth and heat production would be obtained. In mature animals fasting heat production varies as $W^{0.75}$ between species (Klieber, 1961), and this power is often used since it appears to give the best linear fit in most cases. Regardless of the physiological significance of this, such a regression will partition heat into a maintenance component which is a fixed function of $W^{0.75}$ and growth costs. It is obvious then that the choice of the power

to which the results are expressed and the resulting value for maintenance costs are obviously crucial for the analysis. This is best illustrated by considering the similar balance trials on pigs growing from 30 to 85 kg reported by Kielanowski & Kotarbinska (1970) and Thorbeck (1969, 1970). In the former study, energy balance data was calculated as $W^{0.75}$. Actual heat production varied as $W^{0.56}$, so that in the smaller animals a larger proportion of energy was partitioned towards growth and less towards maintenance. The smallest of Kielanowski's pigs were growing more rapidly (per kg) so the regression indicates an apparently sensible result, i.e. Eb=0·59ME−251 kJ/kg$^{0.75}$. The smallest of Thorbeck's pigs were not growing as rapidly (per kg) as the larger ones so the same analysis would produce a quite different equation, i.e. Eb=1·66ME−1·56 MJ/kg$^{0.75}$ (indicating that growth is 166% efficient because high maintenance costs fall with increasing growth rates). Thorbeck therefore used an analysis which partitioned much more of total ME intake towards maintenance in smaller animals. Maintenance costs were assumed to be 7·04+0·03 W MJ and these were subtracted from the intake at each body-weight. As a result an answer was obtained which was similar to that of Kielanowski. It appears to us then that the value of the energy cost of growth determined in this type of study results just as much from the analytical approach as from the experimental data. Other values of maintenance costs have been reviewed by Kielanowski (1972).

Apart from the problem of the partition between growth and maintenance, the two main methods described above could well be examining variations in heat production which result from fundamentally different metabolic responses. The changing energy balance observed in an animal at a particular age and weight as its intake is reduced may well involve adaptive metabolic changes. On the other hand, the changing heat production which is observed as animals grow must include those developmental changes which result in alterations of the metabolic activity in different organs, as well as changes in body composition. The ideal experimental

Table 2. *Net efficiency of growth: fractional deposition of* ME *intake above maintenance requirement*

		Method[8]
Mature idle horses[1]	0·92	A
Growing chickens[2]	0·78	BA
Young rats[3]	0·74	A
Veal calves[4]	0·68	BA
Pigs (25–40 kg)[5]	0·67	BA
Pigs (30–90 kg)[6]	0·59	B
Sheep[7]	0·59	AB

[1]Knox, Crownover & Wooden (1970)
[2]Burlacu, Baltec & Paraschiv (1970)
[3]McCracken (1973)
[4]Van Es (1970)
[5]Close, Verstegen & Mount (1973)
[6]Kielanowski & Kotarbinska (1970)
[7]Graham (1970)
[8]Methods are described in the text, pp. 340–341.

design to determine the maximum efficiency of growth would be one in which a change in growth was induced at a particular body-weight with minimum metabolic alteration, say by increasing intakes. The experiment with milk-fed piglets may come close to this, since these animals do appear to be able to increase their intakes voluntarily over a wide range (Holub, 1969).

Some investigators have in effect combined the two methods by including a combination of different body-weights and limited reductions in intakes to achieve the variation in growth rates. The results from these studies are therefore more difficult to interpret physiologically since they involve changes in heat production resulting from the two factors of reduced intake and the developmental change.

Table 2 shows a selected range of values obtained by Methods A and B as well as by the combined method (BA). The values vary from 0·59 to 0·92 indicating that between 8 and 40% of ME intake above maintenance may be lost as heat.

The energy costs of protein and fat deposition

It appears then that the metabolic rate of growing animals does vary with the growth rate, whether the change results from a direct manipulation of intake or simply as a result of an increase in body-weight. Because much of this extra heat production can be partitioned towards growth, and since growth can be considered as the deposition of fat and protein, then the cost of growth can be expressed as the cost of protein and fat deposition. This is usually done by regression analysis in the same way as described above for the determination of over-all net efficiency except that instead of energy gain, protein and fat deposition are included in a multiple regression. Kielanowski initiated this approach and has recently summarized the results of his and other studies (Kielanowski, 1976). The most recent studies have been listed by Pullar & Webster(1977). The latter workers report a novel approach. The marked differences in the relative retentions of energy as fat and protein in obese and lean Zucker rats enabled simultaneous equations relating ME intake to maintenance expenditure and deposition of protein and fat to be set up and solved for all three parameters. No assumptions were made about maintenance costs but it was assumed that the cost of fat and protein deposition was the same in each animal.

All of the results indicate that heat production during growth occurs primarily in relation to protein deposition rather than fat. Most of the reported values are between 0·7 and 1·85 kJ heat/kJ protein deposition, and this wide range reflects the variation in net efficiencies shown in Table 2. However, in those studies in which over-all net efficiency is high the apparent cost of protein deposition has to be lower than these values. McCracken (1973) reports a value of 0·32 kJ/kJ for his young force-fed rats, while the value for over-all net efficiency of 0·88 reported by Jordan & Brown (1970) and 0·92 by Knox, Crownover & Wooden (1970), must indicate negligible heat associated with fat deposition and near theoretical heat production (0·15 kJ/kJ) with protein deposition.

While the statistical identification of part of the heat production observed in growth with protein and fat deposition is reasonable and necessary in order to

predict growth performance in animals, it is arguably misleading in mechanistic terms. The fact is that protein deposition should be seen as lean tissue growth, and it is alterations in lean tissue growth that are liable to alter the pattern of heat production. Conservation of lean tissue becomes the priority when intakes are reduced and it is the deposition of lean tissue during growth which causes the developmental changes in metabolism. Thus, it is not surprising that when heat production during growth is partitioned statistically between fat and protein, the deposition of protein should appear responsible for most of it.

Sources of heat during growth

The most obvious source of heat in a growing animal is that associated with the biochemical transformations involved in energy deposition. Estimations of these costs are shown in Table 3. The most efficient process is the deposition of dietary fat as fat which can occur with the loss of only 0·01 kJ/kJ deposited. This probably occurs particularly in young animals. Kielanowski & Kotarbinska (1970) report that there is negligible heat production associated with fat deposition in milk-fed piglets. The deposition of 1 kJ of fat from dietary carbohydrate produces 0·15 kJ heat, the same amount as produced in the course of protein synthesis. The most inefficient process is probably the deposition of excess dietary protein as fat. If this occurs via the intermediate formation of glucose and ketones in the liver then 0·31 kJ heat would be produced. We do not know, however, the extent to which this occurs. Lindsay (1976) has discussed the metabolism of excess amino acids and concluded that most of them are directly oxidized. Then, if this occurs because several of the oxidative steps in amino acid catabolism are not linked to ATP production, the heat production associated with a given amount of ATP production would be about 10% higher than from other sources, (i.e. 86·6 kJ/mole ATP compared with 78·7 kJ/mole ATP from dietary glucose). Thus heat production associated with the disposal of excess dietary protein could vary between 10 and 30% of its energy content.

Table 3. Heat production from energy deposition[1]

	Heat kJ/kJ deposited
Fat into fat[2]	
Triglyceride → free fatty acids → Triglyceride	0·01
Carbohydrate into fat[3]	
14 glucose + 12 O_2 → Tripalmitylglycerate + 33 CO_2 + 21 ATP	0·15
Protein into fat[4]	
21 Amino acids + 48·3 O_2 → Tripalmitylglycerate + 36 CO_2 + 14·4 Urea	0·31
Protein into protein	
1 Amino acid + 5 ATP → 1 peptide	0·15

[1]Calculations based on molecular wts of 806, 162 and 110 and heat contents of 39·6, 17·5 and 18·1 kJ/g for triglyceride, carbohydrate and protein. ATP is assumed to be formed from dietary carbohydrate at a rate of 36 mol/mol glucose.
[2]Assuming a requirement of 6 ATP per mole triglyceride.
[3]Assuming conversion as described in McGilvery (1970).
[4]Assuming conversion via glucose and ketones as described in McGilvery (1970).

As far as fat deposition goes, these theoretical values are very similar to those observed in practice during the fattening of mature animals. Blaxter (1969) reports a value of 0·18 kJ/kJ fat deposited from mixed feeds, although Kielanowski (1972) reports a somewhat higher value of 0·35 kJ/kJ. In theory, a ration comprising 20% protein and 80% carbohydrate converted to new tissue, with the retention of 40% of the dietary nitrogen, should involve 14·5% of the intake appearing as heat and 77% being deposited as fat (this would be 60% lean and 40% fat tissue). This net efficiency of 0·855 would be higher if the diet contained fat and lower if the protein content was higher or if less protein was retained. Thus net efficiencies of over 0·8 may be in line with known costs of energy deposition. In fact, the highest figure in Table 2 (0·92) is (according to these figures) theoretically impossible since the horses were not fed a high fat diet. On the other hand net efficiencies much below 0·8 cannot be explained by these costs.

Protein turnover as a source of heat production

There has been increasing interest in the idea that increased protein turnover could be responsible for the extra heat production observed in growing animals. Extensive degradation and replacement of tissue proteins certainly appears to be a common metabolic finding in the animals in which it has been measured. Furthermore, in skeletal muscle in the rat, rates of protein turnover are increased during rapid growth (Millward, Garlick, Nnanyelugo, Stewart & Waterlow, 1975). The questions we have to ask are: how much heat does whole body protein turnover produce and do changes in whole body protein turnover occur in concert with changes in heat production?

Table 4. *Whole body protein turnover as a source of heat production*

Animals	Wt (kg)	Protein synthesis		Heat production[1] (% total)
		(g/kg per d)	(g/kg live wt$^{0.75}$/d)	
Pig[2]	76	9	26·6	12·7
Sheep[3] (a)	40	6·3	15·9	8·4
(b)	40	3·4	8·6	4·5
Infants[4]				
(Catch-up growth)	5	8·2	12·3	6·6
Lambs[5]	5	33	49	25
Rats[6]	0·037	78	34·5	18
	0·116	45	25·4	15
	0·511	20·5	17·4	15

[1] Assuming heat production from protein synthesis = 3·57 kJ/g protein.
[2] Garlick, Burk & Swick (1976). Total heat production taken as 1·64 MJ/kg$^{0.56}$ (mean of values from Kielanowski & Kortarbinska, 1970, and Thorbek, 1969).
[3] (a) Reilly & Ford (1971). Total heat production taken as 1·35 MJ/kg$^{0.56}$/d (Webster, 1976).
[3] (b) Buttery, Beckerton, Mitchell, Davies & Annison (1975). Assuming lysine = 7% protein. Total heat production as 3a.
[4] Golden, Picou & Waterlow (unpublished). Value for 5 kg child on intake of 850 kJ/kg per d. Total heat production from Table 1.
[5] Soltesz, Joyce & Young (1973). Total heat production from Table 1.
[6] Millward (unpublished). Calculated from tyrosine flux assuming tyrosine = 3% protein. Total heat production from Walker and Garrett (1970), 356 kJ/kg$^{0.56}$.

So far, estimates of whole body turnover rates have been reported for the pig, sheep, lamb, infant and rat, and these findings are shown in Table 4. In all cases, excepting that of the infant (see later), the rate has been calculated from the plasma amino acid flux measured by means of the continuous infusion of a labelled amino acid (Waterlow & Stephen, 1967). Some uncertainty must be attached to these values because of the possible sources of error in this method. Firstly, the flux is calculated from the specific activity of the plasma amino acid after it has achieved a constant value. This is higher than the tissue intracellular specific activities and may, therefore, underestimate the real flux. Because of the uncertainties about the site and specific activity of the actual amino acid precursor of protein synthesis, the magnitude of the possible error is not accurately known. Secondly, the amino acid flux includes oxidation (as well as protein synthesis) and the extent of this is not always measured. However, this source of error (i.e. an overestimation) will tend to cancel out the previous error. Finally, different amino acids were used (tyrosine for the pig and rats, leucine for the lamb and lysine or an amino acid mixture for the sheep). Differences in the distribution of these amino acids among individual proteins with different turnover rates could result in variable answers. The value for the infant was calculated from the 24 h excretion of [^{15}N]urea after a single oral dose of [^{15}N]glycine (Golden, Picou & Waterlow, unpublished results). One guide to the accuracy of these values is that the measurements in the pig, lambs, sheep (b) and rats, included values for turnover rates in skeletal muscle and in some cases other tissues. In each case the whole body values agree with values predicted from these tissue turnover rates.

The values were obtained in animals at different stages of development and so interspecies comparisons are difficult. Rates per kg body-weight$^{0.75}$ are highest in the new-born lamb and weanling rat, with rather similar values for growing pigs and older rats. Rates in mature sheep and in the infant are much lower. The heat produced by this protein turnover is expressed as a percentage of total heat production estimated from the literature. Protein turnover may account for 25% of total heat in the neonatal lamb, some 10–20% in the pig and rat, but does not appear to account for much heat production in infants or in mature sheep.

If changes in protein turnover are responsible for the developmental fall in heat production and are involved, therefore, in the energy cost of growth determined by Method B, we should observe with development a marked fall in heat production from protein turnover as a proportion of the total. This does not appear to occur in the rat, at least from weaning onwards. Since the total heat production is calculated as a function of $W^{0.56}$ it appears that protein turnover also follows $W^{0.56}$. On the other hand there is a marked fall in the proportion of heat production in the sheep compared with the neonatal lambs. The single value for the growing pig does not enable us to determine the role of protein turnover in the developmental changes in this animal. We obviously need more information on these developmental changes in protein turnover.

A second question we can ask concerns the rate and extent of possible falls in protein turnover when food intake is reduced. This would involve changes in

protein turnover in the cost of growth measured by Method A. Once again, if the fall in heat production results from a fall in protein synthesis specifically, we should observe marked changes in the proportion of total heat production when food intake is reduced. Here we are limited to data on rats, and the obese human adult. The first measurement of flux changes in malnourished rats (Waterlow & Stephen, 1967) revealed a remarkably constant value for animals in a range of nutritional states, and we have observed this repeatedly since (e.g. Garlick, Millward, James & Waterlow, 1975). Table 5 gives the effect of starvation for 1 and 4 d, prolonged protein deficiency, and refeeding on protein turnover together with findings on obese man. There seems to be rather small short term changes in protein turnover in the rat. In contrast, 28 d of protein deficiency induces a marked fall in turnover rates although there is a rapid return to normal values with refeeding. The proportion of metabolic rate (estimated from the findings of Walker & Garrett, 1970) due to protein turnover remains constant except in the case of prolonged protein deficiency. A similar effect of prolonged dietary restriction is seen in obese man when a 1250 kJ/d regime induces a halving of the turnover rate (Sender, James, Garlick, Heard & Waterlow, 1975). Once again the limitations of these values must be accepted. Certainly this whole body response is different to that of muscle since, as we have shown, synthesis rates in this tissue fall quickly and extensively in starvation and on a protein-free diet (Millward, Garlick, Nnanyelugo & Waterlow, 1976). This seems to be a response of muscle to any regime which interrupts growth. However, in the rat, muscle only accounts for a small fraction of whole body turnover and other tissues do not appear to be as sensitive as muscle (Garlick *et al.* 1975; Millward, Garlick, Sender, James & Waterlow, 1976).

We must conclude therefore that at least in the rat there is no evidence to connect the acute changes in heat production which accompany fasting with specific changes in protein turnover, since the rate of this process seems to fall in parallel with that of other heat producing pathways. Once again we obviously need more information.

Table 5. *Effect of diet on whole body protein synthesis as a source of heat production in rat and man*

Rat[1]	Wt. (kg)	Whole body synthesis (g/kg)	Heat production (% total)
Fed	0·124	49	19·6
Starved 1 d	0·108	42	24
Starved 4 d	0·082	38	22
Protein free diet 28 d	0·056	16	12
Refeeding 3 d	0·078	45	20
Man (Obese)[2]			
8370 kJ/d	90	4·44	12·5
1255 kJ/d	85	2·28	9·2

[1]Millward (unpublished). Heat production calculated from Walker & Garrett (1970).
[2]Sender, James, Garlick, Heard & Waterlow, (1976).

Conclusions

We have discussed in this paper the magnitude of the increased heat production in growing animals and the consequent net efficiency of growth. Food conversion costs as shown in Table 3 may be responsible in some cases but not all, and we have not been able conclusively to identify protein turnover as the source of all the extra heat. We have not discussed changes in ion transport which may account for some 40% of basal heat production (Keynes, 1975) since we know of little evidence one way or the other to suggest that the ionic flux is altered during growth. It may be that there is an increase across the board in all heat producing processes in the rapidly growing animal. Indeed, this is supported by those studies which show that elevated rates of heat production are apparent more or less continuously throughout the day in the young pig (Neergaard & Thorbeck, 1969) compared to the marked post-prandial increase in heat production observed in older animals. Finally, we ought to bear in mind the energy cost of physical activity. While changes in the pattern of activity which are linked to growth rates are not generally thought to account for the extra heat production, it should be remembered that work is a potent stimulator of muscle growth, so that a correlation between lean tissue growth and physical activity would not be surprising. This is especially true in the rapidly growing infant recovering from malnutrition, since resting metabolism and post-prandial heat production (Brooke & Ashworth, 1972) account for only 75% of the heat production measured by Spady et al. (1976). Since the pattern of physical activity may change anyway during recovery, a mechanistic evaluation of heat production in these children is very difficult.

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