Energy partitioning, tissue growth and appetite control

BY A. J. F. WEBSTER

*Department of Animal Husbandry, University of Bristol, Langford House, Langford,
Bristol BS18 7DU*

Metabolizable energy (ME) and protein contained within the food consumed by an animal during growth are directed (almost) entirely towards heat production and the deposition of body protein and fat. The partition of nutrients between these three compartments or between the various organs and tissues in the growing animal is obviously determined by the amount of ME available for growth, the availability of other nutrients (protein, minerals, etc.) relative to ME and the animal's intrinsic 'growth plan' which is a function of its age, genotype and its physiological state.

I wish to propose that for most practical purposes the partition of ME and protein during growth into body protein, fat and heat can be described by a model of extreme simplicity (Fig. 1). When a growing animal is kept in a thermoneutral environment and given access to a diet or choice of diets that it can 'understand' in a metabolic sense (this definition excludes cafeteria diets) then regulation of nutrient supply is dominated by the impetus for lean tissue growth, or protein accretion. In Fig. 1 the rate of protein accretion is shown as a regulator for both ME and protein intake. This, in itself, is neither original nor controversial. The more interesting feature of Fig. 1 is what it leaves out. It contains (in the circumstances defined previously) no regulator for heat production or fat deposition or any mechanism whereby the rates of these processes may be transduced and fed back into the control of nutrient supply. These omissions are harder to defend.
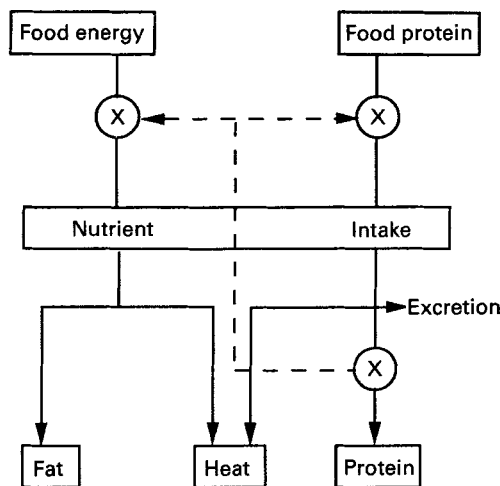

Fig. 1. A simple, hypothetical model to describe the regulation of dietary energy and protein during growth.

Table 1. *Gains (g) of protein and fat from 34 to 66 d of age in female lean and 'fatty' Zucker rats offered different diets* ad lib. *(from Radcliffe & Webster, 1978, 1979)*

Dietary variants (g/kg)	Lean		Fatty	
	Protein	Fat	Protein	Fat
300 Casein + 20 fat	25·1	29·4	23·9	135
700 Casein + 20 fat	24·3	20·1	24·3	78
300 Gluten + 20 fat	26·0	28·4	23·8	134
700 Gluten + 20 fat	26·0	18·9	23·5	85
300 Casein + 200 fat	26·8	34·2	24·9	178
700 Casein + 200 fat	25·4	26·8	25·1	135
300 Casein + 150 cellulose + 20 fat	26·2	23·1	26·2	153
300 Casein + 300 cellulose + 20 fat	25·6	22·0	25·3	128
Coefficient of variation	0·03	0·21	0·04	0·27

The evidence that first drew me to this dangerously simple concept came from the studies of Radcliffe & Webster (1978, 1979) who offered female, lean and congenitally obese, 'fatty', Zucker rats *ad lib.* access to a range of diets varying widely in protein concentration, protein quality, fat and fibre. The results are summarized in Table 1. During a period of rapid growth (34–66 d of age) both lean and fatty rats laid down protein in the whole body at exactly the same rate on all diets. The fatty rats deposited fat, on average, at five times the rate of the lean rats but the coefficient of variation in fat deposition was similar in both phenotypes (0·21 and 0·27 for lean and fatty) being least for the 700 g protein and 20 g fat/kg diets and greatest for the 300 g protein and 200 g fat/kg diets. In this special case of two sets of an inbred strain of rats differing, presumably, in a single gene, the following points can be made with confidence.

(1) The rate of protein accretion was regulated with high precision.

(2) Given *ad lib.* access to food but no choice of diet, the rats regulated the rate of protein accretion by adjusting total food intake.

(3) The rate of fat accretion appears to have been unregulated and determined simply by the quality of the diet.

(4) The heat production of all the rats was consistent with the efficiency terms of Pullar & Webster (1977) for the efficiencies of protein and fat deposition (0·45 and 0·75 respectively) and a maintenance requirement of 1530 kJ/kg body protein$^{0·75}$ per d for all rats. There was no 'regulatory' element of thermogenesis (Webster, 1983).

In a sentence then, protein growth was regulated through control of food intake, fat deposition was not, and heat production simply reflected the normal energy costs of maintenance and growth.

FACTORS INFLUENCING PROTEIN REQUIREMENT

How far can we extrapolate this special case towards a general principle that the impetus for lean tissue growth is the predominant regulator of nutrient supply? The expression 'impetus for lean tissue growth' may be equated to maximum possible rate of protein accretion per d (dP_{max}/dt), related for purposes of interspecies comparisons to mature, lean (i.e. fat-free) mass $(A_l^{0·75})$; thus $(dP_{max}/dt).A_l^{-0·75}$. The problem with this expression, the first differential of the growth curve, is that it is a continuously changing

variable defined by stage of maturity. Moreover, it says nothing about differing rates of growth in different tissues nor does it recognize the fact that protein accretion is simply the net balance between synthesis and degradation. It is, therefore, very difficult to measure impetus for lean tissue growth in absolute terms, but it is possible to examine the consequences of factors known to vary dP_{max}/dt in a consistent fashion.

The main sources of variation in impetus for growth and, thus, protein requirement, are stage of maturity, genotype and the effects of growth promoters. Maturity is conventionally defined by size of the body and specific organs relative to mature weights and described by allometric equations (Huxley, 1932). It is also useful to include an element of real time to allow for the phenomenon of compensatory growth. An immature animal that is underweight for age through underfeeding, eats more and grows faster when food supply is restored than one that has reached the same proportion of mature weight in quicker time (O'Donovan, 1984). It is, of course, equally possible and equally valid to attribute increased appetite during compensatory growth simply to differences in body composition. Animals may sense that they are insufficiently fat or that muscle development does not yet conform to their genotype. Only the latter explanation is consistent with my general hypothesis.

Within any species, genotype, which includes sex, determines both rate of growth and body composition during growth. Most of the apparent differences in growth rate within and between species disappear when scaled according to metabolic body weight at maturity ($A^{0.75}$; Taylor, 1980; Kirkwood & Webster, 1984). However, both body composition and relative rates of accretion in different body tissues do differ, for example between males, females and castrates, and can be manipulated by genetic selection.

Growth rate and body composition can also be manipulated (if not legally) by direct administration of hormones or hormone analogues such as anabolic steroids, growth hormone and β-adrenergic agonists (van der Wal *et al.* 1990) by immunological manipulation of the endocrine system (Flint, 1990) or by insertion of 'foreign' genes, e.g. insertion of metallothionine–growth hormone fusion genes into mice (Palmiter & Brinster, 1985). All these approaches to the manipulation of growth can be used to explore how a growing animal transduces its own development and regulates nutrient intake accordingly.

VARYING PHYSIOLOGICAL STATE

The hypothesis generated by the Zucker rat findings (Table 1) may be restated, in its general form, as 'The nutrient requirements of a growing animal are determined principally by its impetus for lean tissue growth and the partition of nutrients between protein, fat and heat become thereafter inevitable consequences of its physiological state and the availability of different nutrients.'

Fisher *et al.* (1986) have measured effects of castration and implantation with anabolic steroids on appetite and growth in twin cattle. Implanted castrate males achieved a lean tissue growth rate approximately halfway between that of castrate and entire males but deposited fat at the same rate as castrates. Entire bulls deposited lean faster but fat slower than any other group.

Campbell *et al.* (1988) examined the effects of exogenous porcine growth hormone (pGH) on food intake and rates of protein and fat gain in North American pigs which

Table 2. *Effects of growth hormone (pGH) on growth and food intake in pigs (from Campbell et al. 1988)*

	Male		Female	
	Control	pGH	Control	pGH
Food intake (kg/d)	3·21	2·96	3·37	2·73
Daily gain (kg/d)	1·18	1·34	1·01	1·24
Accretion rates (g/d):				
Protein	197	238	148	234
Fat	317	202	410	185
ME_m (kJ/kg live wt$^{0.75}$ per d)	576	582	580	519

had a far greater propensity to fatness than most UK strains (Table 2). In both sexes administration of pGH simultaneously increased the rate of protein deposition and decreased fat deposition when pigs were given a balanced diet *ad lib*. When the propensity to deposit fat during growth was reduced the pigs were able to achieve their target for protein deposition at a lower food intake. These findings and those of Fisher *et al.* (1986) are entirely consistent with my general hypothesis, although they do not exclude alternative explanations.

NUTRIENT INTAKE, TISSUE GROWTH AND METABOLIC RATE

The argument so far has dealt only with energy and protein intake and its partition between protein, fat and metabolic heat. Since the mass of the most metabolically active tissues, liver, gut epithelium and kidney, expressed as a proportion of lean body weight, correlates closely with food intake (Koong *et al.* 1985; Webster, 1989) one would expect the proportional weight of, for example, liver during unrestricted growth to be related to the impetus for growth. The most dramatic confirmation of this comes from studies with transgenic giant mice containing the metallothionine–human growth hormone fusion gene (Shea *et al.* 1987). Table 3 compares body weight, proportional weights of selected organs and allometric growth coefficients (*k*) in normal and giant mice at 300 d of age. Proportions of heart and lung were normal in giant mice, the brain was the same size, i.e. relatively smaller. However, the liver was proportionally 53% greater in the giant mice. All the allometric coefficients in the giant mice were similar to those in the controls, indicating that organ size was responding normally to the work it had to do; heart and lung sizes reflect differences in body mass, liver size implies a sustained increase in food intake per unit body mass. I have been unable to confirm whether this is so.

Taylor *et al.* (1986) and Taylor & Murray (1991) have measured equilibrium body and organ weights and estimated maintenance requirement in different breeds of mature cows, when equilibrium weight was achieved by fixing food intake at levels ranging from 0·7 to 1·3 times maintenance. In this case the comparison between extreme beef and dairy types reveals a substantial difference in estimated ME requirement for maintenance, 600 *v.* 715 kJ/kg body weight$^{0.75}$ per d for Hereford (H) and British Friesian (BF) respectively. These results are difficult to reconcile with the generalizations that I have made so far. The BF has a greater peak capacity for protein synthesis (during lactation) than the H and a greater ME requirement for maintenance. At peak

Table 3. *Growth allometry in transgenic giant mice (from Shea et al. 1987)*

Body wt (W) at 300 d (g) . . .	Control 28·8			Transgenic 52·7		
	mg	mg/g W	k	mg	mg/g W	k
Heart	202	7·0	0·77	380	7·0	0·88
Lung	415	14·4	0·81	647	12·2	0·81
Liver	1615	56·0	0·95	4534	86·0	1·17
Kidney	397	13·7	1·17	856	16·2	1·14
Brain	371	12·8	0·35	395	7·5	0·32

k, Allometric growth coefficient.

Table 4. *Equilibrium values for energy exchanges and tissue distribution in cattle (from Taylor et al. 1986, 1991)*

	Hereford	British Friesian
Mature wt (W; kg)	560	595
Proportion of W (g/kg):		
Muscle	377	386
Heart + lungs	17	20
Liver + kidney	10·5	12·8
Empty gut	44	47
Intra-abdominal fat	38	57
Estimated maintenance (kJ/kg $W^{0.75}$ per d)	600	715

production one would expect proportional weights of liver, gut wall, kidney, etc. to be greater in BF than H cattle. At equilibrium weights constrained by restricted feeding, however, the proportional weights of liver, kidney and gut wall were similar in BF and H (10·0 and 9·7% mature weight respectively) yet the difference in maintenance requirement persists. This implies breed differences in metabolic rate per unit specific tissue mass.

One of the most convincing demonstrations of the effect of varying energy supply on tissue growth and, thereby, on energy expenditure has been that of Koong *et al.* (1985). They brought congenitally lean and obese pigs to the same body weight (40 kg) on high:low (HL) low:high (LH) planes of nutrition, measured fasting heat production (F) then killed the pigs and measured organ weights. Plane of nutrition had major effects on the weights of gut and liver (LH:HL for gut 1·32, LH:HL for liver 1·44). However, the increase in weight of gut plus liver was still very small as a proportion of body weight being 0·04 and 0·06 in HL and LH pigs respectively. In the lean pigs a proportional increase in visceral mass by 30% increased F by 50%; in obese pigs the equivalent increases in visceral mass and F were 42 and 32% respectively. These results of Koong *et al.* (1985) have been summarized in tabular form by Webster (1989). The rate of increase in F may be calculated as 3·4 MJ/kg per d increase in mass of liver + gut. By cross reference to measurements made with sheep (Burrin *et al.* 1990) one may estimate that this is more than twice the direct contribution of these visceral tissues to total heat

Table 5. *Growth and body composition in pigs given free access to low (130 g/kg)- and high (280 g/kg)-protein diets from 9 to 16 kg body weight (from Kyriazakis & Emmans, 1991)*

Diet . . .	Low protein	High protein
Time-period to reach 16 kg (d)	17	11
Food intake (g/d)	749	666
Total ME (MJ)	203	118
Total protein (kg)	1·75	2·12
Body composition at 16 kg:		
Protein (kg)	2·73	2·80
Fat (kg)	2·97	1·92

ME, metabolizable energy.

Table 6. *Growth and body composition in pigs fed on low (130 g/kg)- and high (280 g/kg)-protein diets to 16 kg then allowed choice of diets thereafter (from Kyriazakis & Emmans, 1991)*

Diet . . .	Low protein		High protein	
	Male	Female	Male	Female
Time-period (d) for wt change:				
16–33 kg	12	13	17	18
9–33 kg	29	30	28	29
Food intake during wt change 16–33 kg (kg/d)	1·26	1·57	1·24	1·39
Protein intake (g/d) during wt change				
16–33 kg	332	319	238	220
Selected protein concentration during wt				
change 16–33 kg (g/kg)	263	203	192	158
Body composition at 33 kg:				
Protein (kg)	5·13	4·89	5·27	5·16
Fat (kg)	3·82	5·77	3·58	5·21

production. This implies that approximately half the observed increase in F can be attributed to increasing proportional mass of metabolically active tissues and half to increases in metabolic rates per unit tissue mass.

The studies of Koong *et al.* (1985) and Taylor *et al.* (1991) describe the effect of varying nutrient supply on tissue growth when supply is regulated by man rather than by the animal. In the studies of Fisher *et al.* (1986) and Campbell *et al.* (1988) the nature of growth was varied hormonally and the animal was able to control nutrient intake but not quality. In elegant recent experiments by Kyriazakis & Emmans (1991), however, young pigs have been allowed to express their impetus for growth by regulating both the quantity and quality of nutrient intake. Kyriazakis & Emmans (1991) initially allowed pigs to grow from 9 to 16 kg on a low (130 g/kg)- and high (280 g/kg)-protein diet offered *ad lib.* On the low-protein diet pigs ate more ME daily, but took much longer (17 *v.* 11 d) to reach 16 kg and were much fatter (2·97 *v.* 1·92 kg). These pigs were overeating for energy but failing to achieve their protein requirements (Table 5).

After reaching 16 kg all pigs were then offered free access to both rations (130 and 280

g protein/kg). The pigs previously restricted by the low-protein diet showed extreme compensatory growth and effectively caught up with the high-protein-fed pigs at a body weight of 33 kg. The males (in particular) achieved this not by consuming more food energy but by selecting food of a higher protein concentration. As their weights and their weights-for-age converged so too did their choice of ration. Females, having a higher propensity to lay down fat than males showed similar, but less marked, trends in choice of protein concentration and an increase in ME intake following growth restriction, presumably because they were physiologically programmed for a greater ratio of fat:protein deposition than males and so had to consume more energy in order to meet their primary target for lean tissue growth. I interpret these experiments as being entirely consistent with the original hypothesis from the results of Radcliffe & Webster (1978, 1979), i.e. that the optimal partition of nutrients between protein, fat and heat is genetically and physiologically pre-ordained but that appetite for specific organic nutrients for energy and protein metabolism is dominated *during growth* by the impetus for protein deposition. When the protein:energy ratio in the food is fixed, rats and pigs adjust intake in an attempt to regulate protein deposition and allow fat deposition to vary over a wide range, implying that they are prepared to consume energy to excess in order to achieve sufficient protein. When pigs can regulate energy and protein supply independently they achieve optimal rate of lean tissue growth and, presumably, their physiological target for partition of retained nutrients between protein and fat. This implies, I think, that in these circumstances they may both transduce and regulate rate of fat deposition but that in circumstances where the quantity or quality of food is restricted this regulator is overwhelmed by the impetus for protein deposition.

It must finally be stressed that the requirement for nutrients to support protein deposition does not simply equate to a requirement for protein in food. Rao & McCracken (1992) varied the supply of ME and protein to very fast growing lean pigs. When ME supply was reduced from 30 to 25 MJ/d but protein supply held constant at 500 g/d by increasing protein concentration from 250 to 310 g/kg, growth rate and the efficiency of utilization of food protein both fell significantly. In this experiment protein growth was restricted by lack of ME. The pigs were fashionably lean but could have grown faster.

What implications has this useful approximation to the truth in terms of our ability to control growth and body composition in animals including man? The results suggest that if pigs, and probably rats, are given the opportunity to control both quantity and quality of nutrient supply from a choice of sound but not seductive materials they will eat wisely to meet targets for both protein and fat deposition. If they are unable to control food quality then the target for protein deposition dominates and they don't care how fat they get.

At present most farm animals are fed on a single pre-ordained compound ration devised by a nutritionist from tables of requirements that may not have kept pace with genetic progress. It may be more profitable to allow growing animals to choose their own ration from, for example, straight cereal plus a compound balancer ration. If this leads to an animal that is too fat for commercial purposes we can in theory reduce fat deposition without reducing protein deposition by physiological means (avoidance of castration, exogenous hormones if permitted). If this is disallowed, or insufficient, it may be necessary to restrict access to one or both food sources. In this case one would anticipate a reduction in lean tissue growth rate.

The hedonistic component of appetite in man is so great that it would be dangerous in the extreme to extrapolate this hypothesis beyond the food animals. However, it may be both fair and kind to recognize the possibility that children with a predisposition to deposit excess fat may have a genuine extra hunger to achieve their target for lean tissue growth. If so, both body composition and hunger (if not greed) should be amenable to dietary control.

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