Tissue Metabolism and Energy Expenditures of Maintenance and Production

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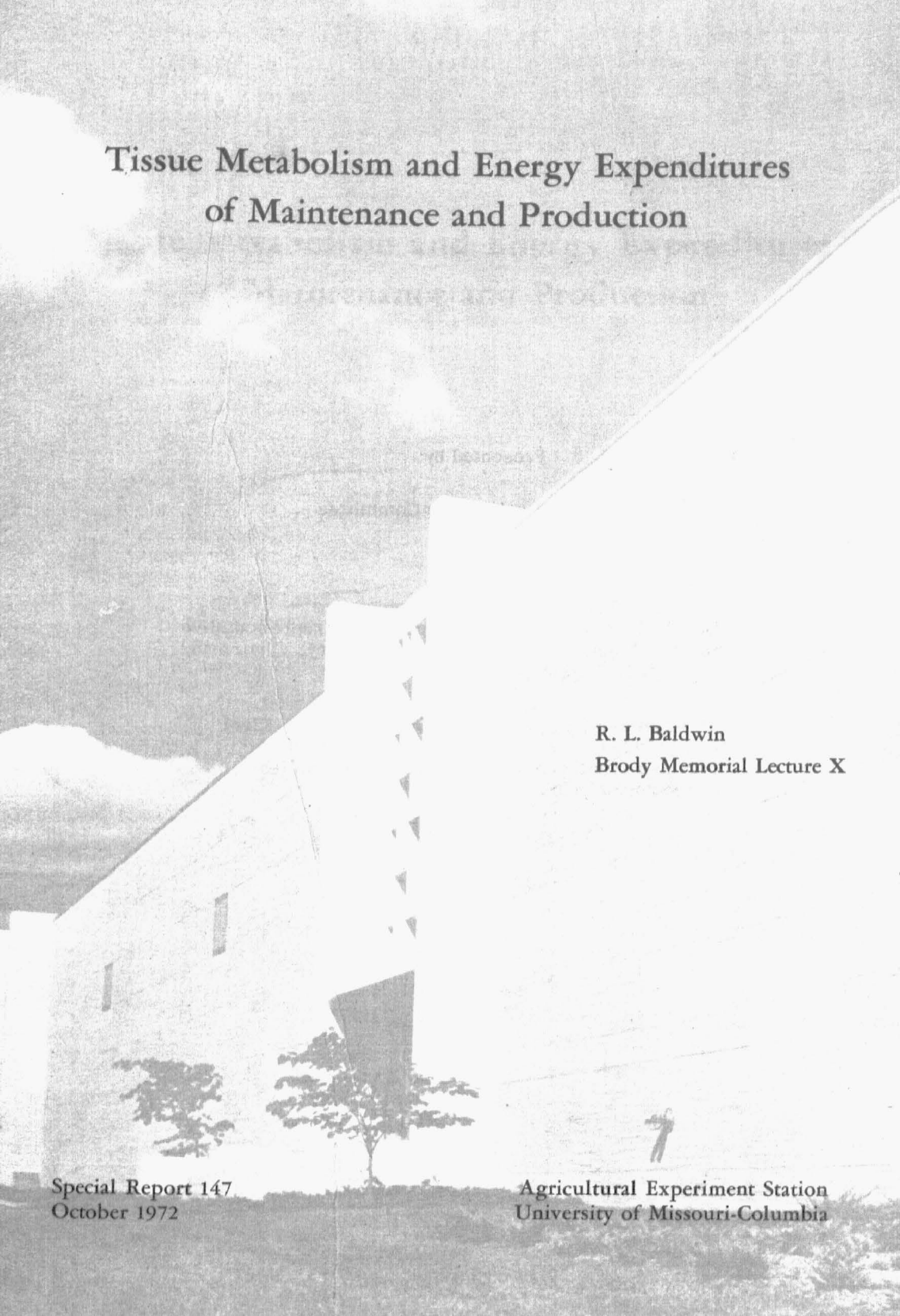
Brody Memorial Lecture X



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Tissue Metabolism and Energy Expenditures of Maintenance and Production

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Nutritionists have long been concerned with evaluation of the energy transformations that occur during the digestion, absorption, storage, mobilization and utilization of feedstuffs for maintenance and production (Armsby, 1917; Lusk, 1922). The efforts of early workers starting with Lavosier and culminating in the efforts of Rubner, Kellner, Atwater and Armsby led to definition of the terms currently utilized by nutritionists conducting energy balance experiments with animals (Armsby, 1917; Lusk, 1922; Blaxter, 1962). Gross energy (GE), metabolizable energy (ME), net energy for maintenance (NE_m), heat increment of maintenance (HI_m), net energy for production (NE_p), and heat increment of production (HI_p) were defined by Armsby as follows:

Gross energy (GE)	"Amount of energy manifested as heat when the feed is completely oxidized."
Metabolizable energy ($ME = GE_{feed} - GE_{excreta}$)	"The energy of the feed minus the gross energy of the excreta." ... "Energy capable of transformation within the body."
NE_m and HI_m ($NE_m = ME - HI_m$)	"The net energy value of a feed for maintenance is measured by the loss of body energy which it prevents. The expenditure of energy by the body which results from the ingestion of feed has been ..., designated as work of digestion ... a collective expression for the energy cost to the organism of all the various processes involved in the digestion and assimilation of feed."
NE_p and HI_p ($NE_p = ME - HI_p$)	"The net energy value of the same feeding stuff may differ according to the species of animal by which it is consumed and the purpose for which it is used."

"... net energy values for growth ... represent that portion of the feed energy supplied in excess of the maintenance requirement which the animal is able to store up in the gain mode" ($NE_g = ME - HI_g$).

"... net energy value of a feeding stuff for milk production ... is that part of the feed energy supplied in excess of the maintenance requirement which is recovered in the product."

Among early workers there were differences in terminology applied to the collective terms herein referred to as heat increments of maintenance and production. However, as Armsby stated, "Rubner's specific dynamic action, or Kellner's thermal energy, is equivalent to the 'work of digestion' in this (Armsby's) broad meaning." The difference was in terminology and not in intent. All of the terms utilized represented the differences between metabolizable energy and net energy and were presumed to reflect costs of digestion, assimilation and utilization of nutrients for maintenance and productive processes.

Early workers frequently speculated about the nature of the "intermediary" processes for which body energy and/or feedstuff NE_m were utilized and about other energy transformations in animals and suggested that the energy transformations they investigated utilizing energy balance (calorimetric) techniques would someday be defined in terms of specific physiological functions and "intermediary" processes (Lusk, 1922). Advances in our understanding of energy and intermediate metabolism of the energy costs of various physiological functions, and of regulatory systems accomplished over the past fifty years are now sufficient to support calculations directed at describing and defining energy transformations in animals in specific metabolic and physiological terms. Several workers including Brody (1945), Barcroft (1947), Krebs (1957, 1964), Kleiber (1961) and Blaxter (1962) made major contributions in advancing our understanding to the point where animal energy transformations can be accounted in specific metabolic terms as will be attempted in this presentation. One of the most significant contributions was by Brody (1945). Bioenergetics and Growth (1945) was one of the primary reference works utilized in formulating many of the calculations presented in this paper.

Energy Transformations during Digestion and Assimilation

An important advance in our knowledge of intermediary metabolism which is essential to calculations of "intermediary" energy

transformations was recognition of the fact that the chemical energy resident in the high energy phosphate bond of ATP provides the means for transfer of chemical energy from sites of nutrient utilization and oxidation to sites of energy utilization for vital processes. Because ATP fulfills a central role in linking catabolic and anabolic functions, calculations of energy release associated with many metabolic and physiological processes can be accomplished by simply determining the amount of ATP formed and expended in a process and multiplying by the total heat loss associated with the formation and utilization of one mole of ATP. For the simplest case wherein the energy resident in the pyrophosphate bond of ATP is not transferred to a product, i.e., all the energy transformed during the formation and utilization of one mole of ATP is converted to heat, the heat loss associated with the turnover of one mole of ATP can be calculated by dividing the heat of combustion of the nutrient catabolized to form the ATP by the net ATP yield expected from oxidation of the nutrient as follows:

$$\frac{\text{- 673 kcal heat/mole glucose oxidized}}{\text{38 moles ATP formed/ mole glucose oxidized via standard pathways}} = \text{-17.7 kcal/ mole ATP}$$

It must be emphasized that the value (-17.7 kcal/mole ATP) calculated in this manner represents heat loss during both the formation ($\backsim$ 10 kcal) and utilization ($\backsim$ 8 kcal) of ATP. Estimates of the heat release associated with the formation and use of ATP formed from glucose, stearate, acetate, propionate and butyrate are presented in table 1.

The primary, identifiable energy costs of digestion and assimilation of a meal are bond breakage, absorption, synthesis of digestive proteins and assimilation or storage of nutrients (table 2). These energy costs correspond to the heat increment of maintenance and represent the difference between utilization of body stores for maintenance processes by fasted animals (equivalent to NE required for maintenance) and metabolizable energy required from food for maintenance. The bases for the estimates tabulated in table 2 have been discussed and justified in detail elsewhere (Baldwin, 1968, 1970; Baldwin and Smith, 1971b) and will not be reiterated in detail here. The percentage heat loss due to bond breakage during digestion was calculated by dividing the heats of hydrolysis of glucosidic, ester and peptide bonds by the heats of combustion of starch, triglyceride and protein, respectively. The energy costs of absorption of carbohydrate, lipid and amino acids, respectively, were calculated on the bases of one ATP expended per glucose absorbed, four ATP expended per triglyceride resynthesized from monoglyceride and two fatty acids, and 0.5 ATP used for each mole of amino acid absorbed. The energy cost of synthesis of most digestive secretions is relatively minor excepting digestive proteins. The cost of synthesis of digestive proteins was calculated on the basis of an estimate of the increase in the rate of protein secretion (and synthesis) that occurs during eating and digestion and the estimate that five ATP are expended in

the synthesis of 110 g of protein containing one mole of amino acid. Estimates of costs of assimilation and/or storage were calculated on the assumption that 20% of the calories provided are utilized directly by meal-eating animals; that the remaining nutrients are stored; that up to 30% of calories provided can be stored as glycogen; that the remaining calories are stored as triglyceride; and, that glucose is stored as glycogen in preference to conversion to triglyceride (table 2). The estimates of cost of storage are based upon balance equations for glucose conversion to glycogen (2 ATP/mole glucose), glucose conversion to tripalmitin (energy in tripalmitin - energy in glucose converted), and triglyceride hydrolysis and resynthesis (8 ATP/mole triglyceride).

Examination of the estimates in table 2 indicates that essentially all of the processes contributing to the heat increment of maintenance have been identified, in that, the theoretical estimates of HI_m agree quite closely with observed heat increments. The major components of HI_m appear to be absorption and assimilation. As will be discussed in a subsequent section, the major components of heat increments of production are costs of biosynthesis and, hence, calculated costs of digestion and assimilation of diets provided above maintenance account for only a small portion of observed heat increments of production (table 3, column 3).

Energy Requirements for Several Maintenance Functions

The nutrients required to provide energy or ATP for the performance of maintenance functions are obtained from body stores in fasting animals and from absorbed nutrients in fed animals. The amount of energy expended in the performance of vital maintenance functions corresponds to the basal energy expenditure which can be calculated from the interspecies relationship -

$$\text{basal energy expenditure} = 70\ W^{3/4}\ -$$

established by Brody (1945) and Kleiber (1961). Energy expenditures for specific maintenance functions are usually calculated in absolute terms (kcal), but are most conveniently expressed as a percentage of basal energy expenditure (70 $W^{3/4}$) because this allows ready assessment of the relative energetic significance of each process.

Brief consideration of the "vital" processes that must be performed in order to maintain an animal leads to the intimidating conclusion that the number of specific functions that must be identified and evaluated must be very large. This conclusion is, likely, quite valid and it will probably be a long time before the identities and energetic significances of all maintenance functions are established. In attempting to identify and assess the significances of a few maintenance functions, two general approaches have been utilized. The first has been to evaluate energy expenditures for specific functions

on a whole animal basis. Typical results obtained utilizing this approach are presented in table 3. The estimate of kidney work in Na transport was calculated from an estimate that 24-26 moles of Na^+ are reabsorbed per day (based on blood flow rates to the kidney and glomerular filtration rates (Bard, 1961)), the observation that 65% of sodium resorption requires active transport (Bard, 1961) and the observation that about 2.5 moles of Na^+ are transported per mole of ATP expended in kidney in active Na^+ transport (Caldwell, 1966 and 1968). These indicate that 6.5 moles of ATP or approximately 124 kcal (6.5. moles ATP x 19 kcal/mole ATP) are expended in kidney per day for Na^+ transport. This calculation indicates that 6-7% of the basal energy expenditure can be attributed to kidney work. Data summarized by Neuberger and Richards (1964) indicate that in the order of 200 g of protein are resynthesized per day in a typical human subject. On the basis that five ATP (Baldwin, 1968) are expended in the synthesis of a peptide bond, it can be calculated $\left(\frac{200 \text{ g protein} \times 5 \text{ ATP} \times 19 \text{ kcal/ATP}}{110 \text{ g/mole amino acid in protein}}\right)$ that 173 kcal heat are released per day due to protein resynthesis. This amounts to approximately 10% of basal energy expenditures (table 3). The estimate of heat release attributable to triglyceride resynthesis (table 3) was calculated on the basis of rates of glycerol turnover (Havel, 1965; Bjorntorp et al., 1969) and the ATP expenditure required for triglyceride resynthesis (Ball, 1965; Baldwin and Smith, 1971b). The estimates of energy expended in heart work, nervous functions and respiration were obtained from Bard (1961). It is evident from the estimates presented in table 3 that service functions such as heart work, respiration and kidney ion transport require significant energy expenditures. The requirement for resynthesis of specific body substances continuously catabolized in the body may (protein resynthesis) or may not (triglyceride resynthesis) result in large energy expenditures (table 3).

A second approach which has been utilized in attempts to assess the costs of specific maintenance functions involves consideration of the energy expenditures of individual tissues followed by evaluation of the energy costs of specific processes occurring within each tissue. A summary of the energy expenditures of individual tissues in a ruminant, 24 hours post-feeding is presented in table 4. A wide range of data was drawn upon in developing these estimates (Smith, 1970). The values in table 4 are estimates derived from available data for several species and are not all based upon direct determinations with ruminants. The estimates are probably within the correct range but the existence of considerable individual variance must be recognized. Comparison of the estimates presented in tables 3 and 4, with due recognition of species differences and especially the fact that the proportionate energy expenditures in brain and nervous tissues are considerably higher in humans than in ruminants, indicates clearly that the major energy expenditures of kidney and heart are for Na^+ transport and heart work,

respectively. Milligan(1971) and Baldwin and Smith(1971b) discussed several data indicating that significant proportions of the energy expenditures of various tissues including nervous tissue are attributable to costs of ion transport in the maintenance of membrane potentials and required intra- and extracellular distributions of cations. The larger, relative energy expenditure of muscle is due to its large mass (41% of empty body weight) rather than high activity per unit mass. A significant proportion of muscle energy expenditure can be accounted for on the bases of protein resynthesis (15-20%), ion transport (15-20%), work associated with activity (in excess of basal or 70 $W^{3/4}$) and the maintenance of muscle tone.

A summary of processes contributing to the energy expenditures of the gastrointestinal tract is presented in table 5. The result of the calculations summarized in table 5 indicating that 100% of the heat release by the gastrointestinal tract can be accounted for in terms of specific processes is considered a fortuitous, misleading artifact. Surely additional, unaccounted energy requiring processes must be accommodated. It is more than likely that either the estimated energy expenditure of 241 kcal/day for the gastrointestinal tract is too low or some of the processes accounted were overestimated. The calculations do indicate, however, that all of the major energy requiring functions of the gastrointestinal tract have been identified. Calculations of the results presented in table 5 were quite straightforward. The heat release due to conversion of butyrate to ketone bodies by the rumen epithelium is based upon the rate of butyrate β-absorption (corrected for butyrate oxidation to CO_2) from the rumen expected 24 hours post-feeding (rate at 24 hours = 450 mmoles/24 hours) and the difference in heats of combustion of butyrate and hydroxybutyrate (31.1 kcal/mole). The estimates of costs of triglyceride synthesis (via α-glycerol-P and monoglyceride pathways) and of absorption of a small quantity of glucose and of amino acids are based on passage of dietary nutrients (fatty acids) and digestion of microbes passing to the lower tract (carbohydrate, protein, triglycerides) (Baldwin et al., 1970; Baldwin and Reichel, unpublished). The energy cost of resynthesis of digestive enzymes secreted into the digestive tract was calculated from an estimate that 60 g of protein (0.55 moles average amino acid) are secreted per day requiring the expenditure (@ five ATP/peptide bond) of 2.78 moles of ATP or 58.3 kcal (Baldwin, 1968; Smith, 1970). The heat release due to replacement of mucosal and other GI proteins was similarly calculated from estimates of mucosal cell turnover rates and turnover rates of other GI proteins. The bases for estimating costs of ion transport were discussed by Milligan (1971) and Baldwin and Smith (1971b).

A summary of estimates of the energetic significances of several liver functions is presented in table 6. Expenditures for protein synthesis were calculated from estimates of turnover times of liver and plasma proteins indicating rates of synthesis of approximately

14 g/day, respectively. Expressed as a percentage of total liver heat production, protein synthesis accounts for only 4-6% of liver energy costs; less than was estimated for human liver (Baldwin and Smith, 1971b). The estimate of energy costs of glycogen turnover was based upon the following formulation:

Glucose + ATP	→ glucose-6-P + ADP
Glucose-6-P	→ glucose-1-P
Glucose-1-P + UTP	→ UDPglucose + $2P_i$
UDPglucose + $glycogen_{(n)}$	→ UTP + $glycogen_{(n+1)}$
UDP + ATP	→ UDP + ADP
$Glycogen_{(n+1)}$	→ $glycogen_{(n)}$ + glucose
2 ATP	→ ADP + 2 P_i

and a turnover rate of 20 g/day which, if anything, is probably a high estimate for an animal 24 hours post-feeding. Glycogen turnover is apparently a minor energy requiring process. The estimates of energy expenditures in gluconeogenesis are based upon rates of turnover and incorporation into glucose of the several precursors determined, largely, in radioisotope tracer studies. Details and justifications of these estimates were presented by Smith (1970). A total of about one-third of liver energy expenditures appear to be associated with gluconeogenesis. The estimate of energy expenditures in ketogenesis from acetate and fatty acids, justified by Smith (1970) and Baldwin and Smith (1971b), indicates that this is a minor energy requiring process. Incorporation of acetate and blood fatty acids (NEFA) into triglycerides by the liver of ruminants is a minor function 24 hours post-feeding. The energy cost of urea synthesis was estimated based upon nitrogen excretion by animals in nitrogen balance on a normal ration fed once daily and reported rates of urea secretion into the digestive tract (Baldwin et al., 1970). The estimate may be high in that it represents a whole day estimate for an animal fed once daily and is not based on actual rates at 24 hours post-feeding. Even so, it is clear that urea synthesis is a significant contributor to liver energy expenditures. Estimates of energy costs of ion transport in liver discussed elsewhere by Milligan (1971) and Baldwin and Smith (1971b) indicate that in the order of 20-30% of the energy expenditure of liver can be attributed to ion transport. A number of additional liver functions including nucleic acid synthesis and other synthetic functions have been considered and found to be minor contributors to liver energy expenditures.

Various investigators including Ball (1965) and ourselves (Baldwin, 1970; Smith, 1970; and Baldwin and Smith, 1971ab) have attempted to account for the energy expenditures of adipose tissue in several physiological states. It appears that costs of fatty acid

synthesis contribute significantly to adipose energy expenditures immediately after feeding in rats and that costs of triglyceride turnover can be significant (Ball, 1965). In the ruminant 24 hours after feeding, it appears that about 30% of adipose tissue energy expenditures can be accounted for on the bases of fatty acid synthesis from acetate (15%) and ketone bodies (5%), and triglyceride turnover (10%). Ion transport may account for an additional 10-20% of adipose energy expenditure (Posner and Baldwin, unpublished). The remaining 50-60% of adipose energy expenditures in basal ruminants remains a mystery and can only be identified through further experimentation and analysis.

Energy Requirements for Productive Functions

As indicated in the introduction, the basic nutritional energetic formulation defining the utilization of metabolizable energy provided above maintenance for production is

$$ME = HI_p + NE_p$$

where net energy of production (NE_p) is defined as work performed or energy in product (growth, milk) and HI_p is defined as energy not converted to work or the cost of biosynthesis of the product. Efficiencies can be expressed as $NE_p \times 100/ME$. In evaluating productive processes such as growth and milk production, the objective is to identify functions contributing to the costs of synthesis of the product, i.e., account for HI_p. The results of several attempts at identification of the costs of biosynthetic processes have been summarized in detail elsewhere (Baldwin, 1968; Baldwin and Smith, 1971b; Baldwin et al., 1970), and only an example estimate of the costs of milk synthesis will be presented here.

Propionate, a major precursor of milk lactose, must be converted to glucose in the liver. The glucose formed must be transported to the mammary gland and incorporated into lactose according to the formulation presented in table 7. The estimated efficiency of lactose synthesis from propionate is 78%. Similar formulations of energy transformations associated with milk protein and fat synthesis, indicate efficiencies of 84 and 72%, respectively. These estimates can be combined, as in table 8, to obtain a theoretical estimate of the efficiency of milk synthesis. It is considered that the estimated efficiency of milk synthesis of 79% obtained in table 8 compares favorably with real efficiencies of up to 72% (Baldwin, 1968), especially when it is recognized that only the major milk components were considered.

The major problem in theoretical and experimental analysis of the energy costs of lactation (and other productive functions) is encountered in attempting to identify and account for functions which reduce apparent productive efficiencies in average and below average

animals to 50-65% as compared with above average animals synthesizing milk with efficiencies of 70% or better.

In this, and previous sections, an attempt was made to summarize with some documentation, the results of our attempts at identifying and evaluating the significances of energy requiring processes associated with maintenance and the heat increments of maintenance and production. It must be noted that these estimates are not always based upon exact and complete data and theory and are subject to continuous correction and revision. However, we hope that it is clear that current data and knowledge provide a sufficient base for identification and quantitative evaluation of many of the physiological and metabolic processes which contribute to animal energy expenditures. There are definite gaps to be filled and many refinements required, but in many cases these only require further study and more effective utilization of existing data and knowledge. It is considered that the estimates presented above are useful in contributing to our understanding of energy transformations in animals. It is also recognized that these estimates suffer from, at least, two major disadvantages as follows:

1. The formulations are directed at idealized animals in prime physiological states - excess energy expenditures by individual animals performing at less than optimal efficiencies are not accommodated.

2. The formulations are based upon static and simplified assumptions whereas, in contrast, animal functions are dynamic and complex.

Our research objectives as nutritionists and animal scientists are to advance understanding of animal energy metabolism and on the bases of greater understanding to devise means of improving productive efficiencies. In order to provide an additional means of enabling more efficient utilization of information in advancing our understanding of animal function, we feel that a means for dynamic analysis of energy metabolism should be developed. We have elected to use computer simulation modeling techniques to fulfill this need.

Application of Computer Simulation Modeling Techniques in Analyses of Animal Energy Metabolism

The decision to utilize computer simulation modeling techniques in further analyses of animal energy transformations was based upon an estimate that the following advantages could be gained:

1. Unification and summarization of data and concepts in explicit form in models constructed;
2. More effective utilization of existing data in support of experimentation;

3. Reduction in conceptual difficulties in analyses of complex systems;
4. Explicit and quantitative consideration of greater numbers of relevant data in formulations of hypotheses and analyses of experimental data; and,
5. Dynamic - as compared to static - analyses of variable and interacting processes.

The kinetic simulation language developed by Garfinkel (1968) and described elsewhere (Garfinkel, 1969; Baldwin et al., 1970; Baldwin and Smith, 1971a) was selected as the primary simulation technique to be employed because the language is simple and user-oriented, the model formats are explicit in representing biochemical and physiological data and processes, the basic mathematic (simultaneous linear differential equations) is familiar to biologists, and the basic programs are readily available to interested investigators. The basic input to the Garfinkel system is in the form of "chemical" equations such as:

$$A - B \quad /10.0$$

where A and B are chemicals, the minus sign (-) denotes an irreversible reaction and /10.0 denotes the rate constant for the reaction. The irreversible conversion of A to B may represent either a chemical conversion or a physiological process such as transport of a metabolite to a tissue by blood. The simulation programs convert the "chemical" equations to rate or flux equations (flux 1 = k[A]) and differential equations ($\frac{dA}{dt}$ = - flux 1) and solve these for a specified time period. The system is quite flexible and offers a number of useful options which facilitate modeling.

The general approach we have adopted for use in our analyses of animal systems has been to model tissue, cellular and sub-cellular functions in detail (up to 300 chemical and other transformations specified) and to simplify these - retaining appropriate regulatory and overall metabolic and physiological functions - for inclusion in whole animal models (4-500 processes explicitly represented). In constructing tissue and whole animal models, a wide range of biochemical, nutritional and physiological data are utilized including data on blood and tissue metabolite levels and pool sizes, blood flow rates to and weights and energy expenditures of individual tissues (table 4), metabolite turnover and utilization rates, patterns of metabolite uptakes and utilizations by tissues (table 4), metabolite turnover and utilization rates, patterns of metabolite uptakes and utilizations by tissues, tissue and cellular regulatory systems, and animal metabolic and energetic responses to changes in physiological states.

An example formulation from a model of ruminant metabolism 24 hours after feeding is presented in table 8 in input format compatible with the Garfinkel simulation system. The model for regulation of insulin secretion in table 8 is based on the premises that insulin secretion is highly correlated with pancreatic glucose-6-P levels (Montague and Taylor, 1969) which are determined by glucose availability, hexokinase activity and rate of glucose-6-P utilization; and, that propionate and butyrate, when available, decrease glucose-6-P utilization by acting as alternate energy sources. The first two equations (reactions 1-4) in table 8 are a minimal representation of the effects of glucose availability to the tissue and hexokinase activity upon rate of glucose-6-P formation. Reaction 5 represents the conversion of insulin precursors to insulin and insulin release as affected by glucose-6-P concentration. Reactions 6-9 represent the mingling of metabolic intermediates formed from propionate and butyrate which are common with intermediates of glucose-6-P utilization. It should not be implied from these equations that propionate and butyrate are converted to glucose-6-P, but rather that they exert a glucose-6-P sparing action which results in the accumulation of glucose-6-P when propionate and butyrate concentrations are high. Destruction of arterial insulin is represented in reaction 10. A primary determinant of rates of oxidation of propionate, butyrate and glucose-6-P utilization is the requirement for ATP resynthesis from ADP formed during ATP utilization for cellular functions. These processes, which effectively provide a means whereby propionate and butyrate can decrease rates of glucose-6-P utilization and increase insulin release, are presented in reactions 11-14. It must be emphasized that the formulation represented in table 8 is extremely speculative and is not considered to be in final form. This particular formulation was selected for presentation as an example because it represents, concisely a number of different types of functions that can be readily formulated and illustrates the flexibility of the Garfinkel simulation system. Additional, less speculative and more thoroughly documented models were presented by Smith (1970) and Baldwin and Smith (1971a). Despite the speculative nature of the model of insulin regulation presented in table 8, when incorporated into a whole animal model, the simulation results obtained agreed quite well with the experimental data of Horino et al. (1968) (figure 1).

As a further example of the capacity of simulation techniques for simulation of dynamic aspects of animal metabolism, the results obtained in a simulation of muscle work using a model of ruminant muscle are summarized in figure 2. With the onset of work (figure 2) the rate of oxygen utilization and rates of lactate and heat release from muscle increased markedly (lactate and heat production are represented as cumulative functions in the figure). Muscle glycogen decreased during work and was restored to normal during the period where the oxygen debt in muscle, after work, was evident. These simulation results agree well with experimental results summarized in physiology texts.

As a result of our studies, we hold a firm belief that computer simulation modeling techniques are a valuable and powerful tool which can be utilized efficiently in support of theoretical, interpretative and experimental studies relevant to nutritional energetics and animal science.

Table 1. Heat released during turnover of ATP formed from several common nutrients

	ATP formed per mole substrate	Heats of combustion	Heat release per mole ATP turned over
Glucose	38	673	17.7
Stearate	146	2712	18.6
Acetate	10	209	20.9
Propionate	18-19	367	20.4
Butyrate	27	524	19.4

Table 2. Estimated heat increments of two meals fed at maintenance and of corresponding heat losses associated with the utilization of metabolizable energy provided above maintenance for production[1]

Process	Carbohydrate meal	Mixed meal	Above maintenance
	%	%	%
Bond breakage	0.5	0.3	0.3-0.4
Absorption (active transport)	2.6	1.3	1-2.5
Digestive secretions[2]	2.0	2.0	1-2
Assimilation and/or storage[3]			1-2
Glucose as glycogen (0.3 x 5%)	1.5	1.5	
Glucose as fat (0.5 x 8.2%)	4.2	-	
Fat as fat (0.5 x 3.0%)	-	1.5	
Theoretical HI	10.8	6.6	3.3-7.0
Observed HI	9-12	5-7	25-45

[1]Values expressed as percent of metabolizable energy fed at maintenance as carbohydrate or carbohydrate plus fat (50:50 mixed meal) or an increment of balanced ration fed above maintenance for production lost as heat during digestion and assimilation.

[2]Includes cost of synthesis of the portion of digestive proteins replenished in the period after feeding during which heat increment is evident.

[3]Assumes in case of diets fed at maintenance, that 80% of calories provided in diet are stored as glycogen (30%) or triglyceride (50%). Estimated energy expenditures for conversions of glucose to glycogen, glucose to storage triglyceride and dietary triglyceride to storage triglyceride are 5.0%, 8.2% and 3.0%, respectively (Baldwin, 1968).

Table 3. Energy expenditures in several major maintenance functions[1]

Functions	% basal energy expenditure
Kidney work (Na transport)	6-7
Protein resynthesis (muscle, liver, intestine)	8-12
Triglyceride resynthesis (adipose, liver)	1-2
Heart work (cardiac output)	9-11
Nervous functions	15-20
Respiration (muscle work)	6-7
Other	30-40

[1]Calculated for 70 kg man at basal (1700 kcal/da).

Table 4. Estimated mass, blood flow through and energy expenditures in tissue and organ systems of a ruminant 24 hour post-feeding[1]

Tissue system	Mass % of empty body weight	% of cardiac output	Energy expenditure	
			% of total	kcal/24 hr[2]
Kidney	0.3	13.4	7.0	188
Skin	6.3	8.0	2.7	72
Nervous tissue	2.0	10.0	12.0	322
Adipose tissue	15.0	9.6	8.0	214
Gastrointestinal	6.5	23.0	9.0	241
Liver	1.6	27.0[3]	22.5	603
Heart	0.6	4.1	10.0	268
Muscle	41.0	18.0	23.0	616
Other (skeleton, etc.)	27.7	9.9	5.8	156
Total	100.0	100.0	100.0	2680

[1]Adapted from Smith (1970). Data sources included Brody (1945); Wade and Bishop (1967); Bard (1961); Dukes (1955); Smith and Baldwin (unpublished); and others.

[2]Calculated for a 100 kg ruminant with empty body weight of 95 kg.

[3]Includes both arterial (4%) and venous (23%) flow to liver.

Table 5. Evaluation of processes contributing to heat release by the gastrointestinal tract of a ruminant[1]

Process	% of total GI heat production	Kcal/24 hr
Ketone body formation from butyrate	5.8	14.0
Triglyceride synthesis	0.8	1.9
Digestive enzyme secretions	24.2	58.3
Protein turnover		
Mucosa	28.8	69.5
Other	13.2	31.8
Active transport in absorption	18.0	41.3
Ion transport	10.0	24.2
Total	100.0	241.0

[1]Calculated for a 100 kg ruminant 24 hours post-feeding with an empty body weight of 95 kg and estimated total energy expenditure of 241 kcal/day (see table 4).

Table 6. Estimated energy expenditures for several liver functions[1]

Process	Kcal/24 hr	% of total liver heat production
Protein synthesis		
Liver proteins (14 g/da)	12	1.5-2.5
Plasma proteins (20 g/da)	17	2.5-3.5
Glycogen turnover (20 g/da)	5	0.5-1.0
Glyconeogenesis[2]		
From lactate (144 g/da)	70	9-14
From propionate (68 g/da)	45	6-9
From amino acids (10-13 g/da)[3]	74	10-13
From glycerol (36 g/da)	12	2-3
Ketogenesis (acetate, FA)[2]	10	1-2
Triglyceride synthesis[2, 4]	15	2-3
Urea synthesis (65 g/da)[5]	78	11-15
Ion transport	150	20-30
Total	488	80

[1]Calculated on same basis as estimates in table 5.

[2]Calculations based upon data summarized by Smith (1970). Estimates of amounts of glucose synthesized from various substrates expressed as g glucose produced per day at basal rate.

[3]Calculation for gluconeogenesis and ketogenesis from amino acid mixture comparable to meat protein. Estimate includes cost of synthesis of 0.367 moles of urea (27.7 kcal).

[4]Includes costs of fatty acid synthesis from acetate and incorporation of fatty acids into triglyceride.

[5]Based upon determinations of urea excretion and secretion. Estimate corrected for urea synthesis accounted for under gluconeogenesis from amino acids.

Table 7. Summary formulation of the energy cost of lactose synthesis from propionate

1. Conversion of propionate to glucose in liver

2 propionate + 2 ATP + 2 CoASH	→ 2 propionyl-CoA + 2 AMP + 4 P_i
2 propionyl-CoA + 2 CO_2 + 2 ATP	→ 2 succinyl-CoA + 2 ADP + 2 P_i
2 succinyl-CoA + 2 ADP + 2 P_i	→ 2 succinate + 2 ATP + 2 CoASH
4 ADP + 4 P_i + O_2 + 2 succinate	→ 2 fumarate + 4 ATP + 2 H_2O
2 NAD + 2 fumarate + 2 ATP (equivalent)	→ 2 phosphoenolpyruvate + 2 $NADH_2$ + 2 CO_2 + 2 ADP
2 ATP + 2 phosphoenolpyruvate + 2 $NADH_2$	→ glucose + 2 NAD + 2 ADP + 4 P_i
Sum: 2 propionate + O_2 + 4 ATP	→ 1 glucose + 4 ADP + 4 P_i

2. Synthesis of lactose in the mammary gland

2 liver glucose + 2 ATP + 2 H_2O	→ 2 glucose (mammary) + 2 ADP + 2 P_i (estimated transport costs)
glucose + ATP	→ glucose-6-phosphate + ADP
glucose-6-phosphate + UTP + H_2O	→ UDPglucose + 2 P_i
UDP glucose	→ UDPgalactose
UDPgalactose + 1 glucose	→ lactose + UDP
UDP + ATP	→ UTP + ADP
Sum: 2 liver glucose + 4 ATP	→ 1 lactose + 4 ADP + 4 P_i

Net ATP requirement for the conversion of 4 propionate to 1 lactose = 12 ATP.

3. Conversion of propionate energy to provide ATP requirements

2 propionate + O_2 + 4 ATP	→ 1 glucose + 4 ADP + 4 P_i (from above)
1 glucose + 6 O_2 + 38 ADP + 38 P_i	→ 6 CO + 6 H_2O + 38 ATP
Sum: 2 propionate + 7 O_2 + 34 ADP + 34 P_i	→ 6 CO_2 + 6 H_2O + 34 ATP

Net ATP yield per mole of propionate = 17.

At 17 moles ATP/mole propionate oxidized (12/17) 0.70 mole of propionate must be oxidized to provide the ATP required for the synthesis of lactose.

Input: 4.70 moles of propionate @ 367 kcal per mole = 1730 kcal.

Ouptut: 1 mole of lactose @ 1350 kcal per mole = 1350 kcal.

$$\text{Efficiency} = \frac{\text{output}}{\text{input}} \times 100 = 78\%$$

Table 8. Example representation of the regulation of insulin secretion in the ruminant

Reaction numbers	Chemical equation [1]	Fluxes in steady state	
1, 2	GLU + ATP + HK = HKGLUATP	(2.5 E 2	(2.5 E 2
3, 4	HKGLUATP = HK + G6P	(2.5 E 2	(2.5 E 2
5	PI + G6P - AI	(1.0 E 3	
6, 7	PROP + INTERMEDIATES = G6P	(3.0 E 3	(3.0 E 3
8, 9	BUT + INTERMEDIATES = G6P	(5.0 E 2	(5.0 E 2
10	AI - DAI	(1.0 E 3	
11	PROP + ADP - ATP + ----	(8.0 E 2	
12	BUT + ADP - ATP + ----	(2.0 E 3	
13	G6P + ADP - ATP + ----	(1.0 E 2	
14	ATP - ADP (a series of ATP utilizing functions)		

[1]Abbreviations include GLU (pancreatic glucose), HK (hexokinase), G6P (glucose-6-P), PI (precursors of insulin), AI (arterial insulin, PROP (propionate), BUT (butyrate), INTERMEDIATES (intermediary metabolites propionate and butyrate have in common with glucose-6-P) and DAI (degraded insulin).

References

Armsby, H. P. 1917. The Nutrition of Farm Animals. The MacMillan Co., New York.

Baldwin, R. L. 1968. Estimation of theoretical calorific relationships as a teaching technique. A Review. J. Dairy Sci. 51:104.

Baldwin, R. L. 1970. Metabolic functions affecting the contribution of adipose tissue to total energy expenditure. Fed. Proc. 29(3):1277.

Baldwin, R. L., H. L. Lucas and R. Cabrera. 1970. Energetic relationships in the formation and utilization of fermentation end-products. In: Third International Symposium on the Physiology of Digestion and Metabolism in the Ruminant. A. T. Phillipson, Ed. Oriel Press, Cambridge.

Baldwin, R. L. and N. S. Smith. 1971a. Application of a simulation modeling technique in the analysis of dynamic aspects of animal energetics. Fed. Proc. 30:1459.

Baldwin, R. L. and N. E. Smith. 1971b. Molecular control of energy metabolism. In: Symposium on Control of Energy Metabolism. J. D. Sink, Ed. (In press).

Ball, E. G. 1965. Some energy relationships in adipose tissue. Ann. N. Y. Acad. Sci. 131:225.

Barcroft, S. J. 1947. Researches on pre-natal life. Charles C. Thomas, Illinois.

Bard, P. 1961. O_2 uptake and tissue energy expenditure. In: Medical Physiology. P. Bard, Ed. C. V. Mosby Co., St. Louis, Mo. p. 239.

Bjorntorp, P., H. Bergman, E. Varnauskas and B. Lindholm. 1969. Lipid metabolism in relation to body composition in man. Metabolism 18:840.

Blaxter, K. L. 1962. The Energy Metabolism of Ruminants. Charles C. Thomas, Illinois.

Brody, S. 1945. Bioenergetics and Growth. Reinhold Publishing Corp., New York.

Caldwell, P. C. 1966. Energy relationships and the active transport of ions. In: Current Topics in Bioenergetics. D. R. Sanadi, Ed. Acad. Press, New York. p. 251.

Caldwell, P. C. 1968. Movement and distribution of inorganic ions. Physiol. Rev. 48(1):13.

Dukes, H. H. 1955. The Physiology of Domestic Animals. Comstock Publ. Assoc., New York.

Garfinkel, D. 1968. A machine-independent language for the simulation of complex and biocnemical systems. Comp. Biomed. Res. 2:31.

Garfinkel, D., L. Garfinkel, M. Pring, S. B. Green and B. Chance. 1970. Computer applications to biochemical kinetics. Ann. Rev. Biochem. 39:473.

Havel, Richard J. 1965. Some influences of the sympathetic nervous system and insulin on mobilization of fat from adipose tissue: Studies of the turnover rates of free fatty acids and glycerol. Ann. N. Y. Acad. Sci. 131:91.

Horino, M., L. J. Machlin, F. Hertelendy and D. M. Kipnis. 1968. Effect of short-chain fatty acids on plasma insulin in ruminant and non-ruminant species. Endocrinology 83:118.

Kleiber, M. 1961. The Fire of Life. John Wiley and Sons, New York and London.

Krebs, H. A. and H. L. Kornberg. 1957. Energy transformations in living matter. Ergeb. Physiol. 49:212.

Krebs, H. A. 1964. The metabolic fate of amino acids. In: Mammalian Protein Metabolism. H. N. Munroe and J. B. Allison, Eds. Acad. Press, New York.

Lusk, G. 1922. A history of metabolism. In: Endocrinology and Metabolism. L. F. Barker, Ed. D. Appleton and Co., Vol. 3, p. 3.

Milligan, L. P. 1970. Energy efficiency and metabolic transformations. Fed. Proc. 30:1454.

Montague, W. and K. W. Taylor. 1969. Islet-cell metabolism during insulin release. Effects of glucose, citrate, octanoate, tolbutamide, glucagon and theophylline. Biochem. J. 115:257.

Neuberger, A. and F. F. Richards. 1964. Studies on turnover in the whole animal. In: Mammalian Protein Metabolism. H. N. Munro and J. B. Allison, Eds. Acad. Press, New York, p. 243.

Smith, N. E. 1970. Quantitative simulation analyses of ruminant metabolic functions: basal; lactation; milk fat depression. Ph. D. Thesis. Univ. Calif.

Wade, O. L. and J. M. Bishop. 1962. Cardiac Output and Regional Blood Flow. Blackwell Scientific Publications, Oxford.

Fig. 1. Insulin secretion in response to propionate infusion in ruminants. Experimental data from Horino et al. (1968). Simulation data from Smith (1970).

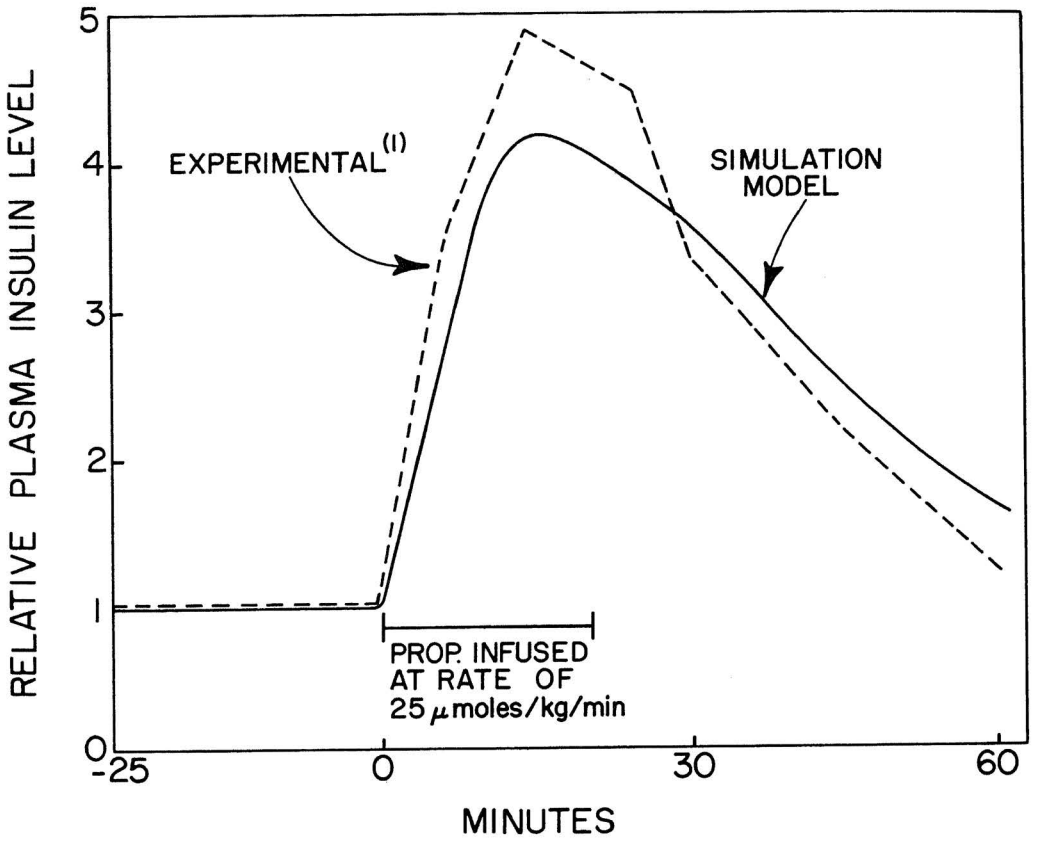

Fig. 2. Simulation of work in ruminant muscle model. (Adopted from Smith (1970).