Pediat. Res. *12:* 736–745 (1978)

# Commonality and Diversity in Fetal Development: Bridging the Interspecies Gap

## Presidential Address, Society for Pediatric Research, 1977 Annual Meeting, San Francisco, California

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Today the Society for Pediatric Research is continuing an afternoon dedicated to a series of lectures in various areas of biology. The topics they cover illustrate examples of exciting areas of research, areas with complex and important questions as well as broader ethical issues which need to be addressed. The diversity of the issues and topics serves to remind us that all levels of organization within biologic systems have important questions deserving of our thought and our best effort; questions of sufficient difficulty to challenge the best in each of us, regardless of whether our interests are in subcellular or cellular biology, whether in organ systems or in the biology of the whole organism or, finally, in communal questions, questions relating to societal and behavioral biology.

In that light, I should like to review with you some of my own interests in fetal development, with special attention, perhaps, to the apparent paradox of a commonality in many aspects of fetal metabolism and nutrition despite the striking diversity of mammalian biology apparent in adult biology. In a sense this is an attempt to move from essentially descriptive biology to conceptual biology; a step which cannot be made within the confines of a single species.

In clinical science we are often tempted to search for a more and more appropriate animal "model" of human biology. I believe such attempts to "model" living systems are inappropriate and fraught with the danger of missing exciting clues to general principles in biology elegantly presented by a particular mammalian species. For the purpose of this lecture, I should like to focus upon one specific question, namely, to what extent is there a commonality of metabolic features among fetuses, features not shared among the adults of those same species? Put more bluntly, are the metabolic features of a mouse fetus more those of fetuses generally or more those of the adult mouse?

Reproduction, of course, has been with us for some time and along with it, the hazards of delivery. Figure 1 presents a high risk pregnancy that is 175 million years old, showing the remains of an ichthyosaurus with triplets *in utero* (17). A diversity of size among creatures at that time was even more striking than it is today.

### ADULT SIZE AND METABOLISM

We can begin first by considering the metabolic consequences of the tremendous diversity of size among present day mammals. As many of you know, the classification of mammals into broad subgroups has undergone a number of changes, particularly as it became clear that marsupials as a group did not represent a more primitive or earlier form but rather a parallel development along with that of the eutherian mammals. The marsupials are of great interest in reproductive biology in several ways (15). The adults range in size from this tiny marsupial mouse of approximately 60 g (Fig. 2) to the red kangaroo weighing approximately 40 kg (Fig. 3). In contrast to this diversity among adults, the young at the time of birth are all extremely small, varying from slightly over 10 mg to 750 mg in the red kangaroo. Since the smallest marsupial may have very large litters, up to 20 young, the total weight of fetuses produced is very similar in all marsupials despite 600-fold differences in adult size. Even in the smallest marsupials, the percentage of maternal weight represented by the fetus is still less than 1%, since most of the growth and development of the young which occurs *in utero* in eutherian mammals occurs within the pouch after birth. You will notice, in this photograph of a 2-day-old tammar (Fig. 4), the precocious development of upper limbs and the mouth open for suckling. Obviously, development of the digestive system is also far advanced at birth.

### DIAPAUSE

The diapause phenomenon is another striking characteristic of marsupial development. Essentially, this phenomenon consists of an arrest in development which occurs at the stage in embryogenesis when a unilaminar blastocyst has developed but not yet implanted. The phenomenon is not confined to marsupials, but occurs in some eutherian mammals as well.

The sequence of events in a moderate-sized marsupial, the tammar wallaby, is shown in Figure 5 taken from Tyndale-Biscoe's book (15). As long as there is a pouch young suckling, the development of the approximately 80-cell stage blastocyst is inhibited, presumably through hormonal mechanisms controlled by suckling. This is followed by inhibition which is seasonal and which will not be altered by removal of the pouch young or the suckling stimulus. The sum total of both the inhibition induced by lactation and seasonal inhibition is that development can be arrested for periods as long as 1 year and then be resumed without apparent effect upon subsequent development. Clearly, this phenomenon raises many interesting questions relating to aging and the relationship between gestation length and longevity in different species.

Two aspects of maternal nutrition in marsupial development deserve comment. First, since most of the developmental phase which occurs in the latter half of intrauterine development in other mammals occurs within the pouch, its total nutritional intake can be described completely during this phase of development by analysis of marsupial milk. Unfortunately, there are virtually no data on the composition of marsupial milk during the earliest phase of lactation. However, in the red kangaroo, the milk changes quite markedly in composition from a low fat to a high fat diet during the development of the pouch young. If a drought occurs which kills vegetation and produces both a fasting and thirsting state, the animals continue to breed and produce successive crops of newborns who apparently survive intrauterine development

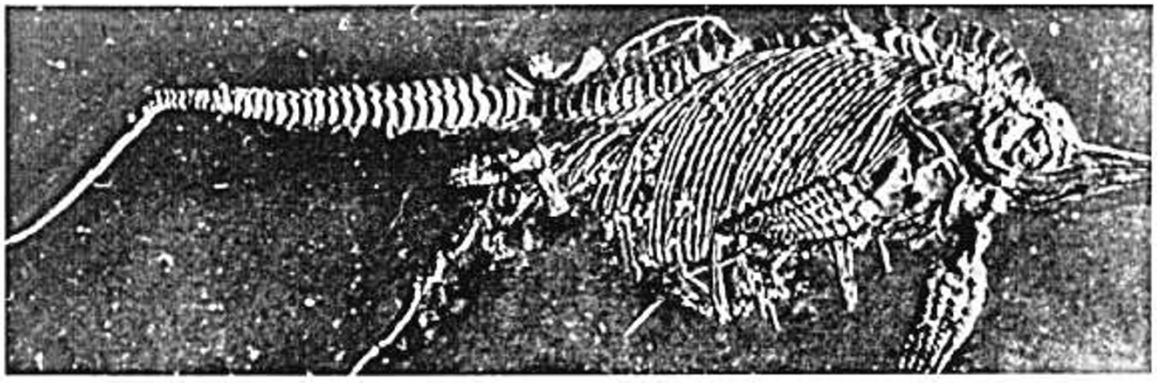

Fig. 1. Photograph showing the remains of an icthyosaurus with triplets *in utero* which is from a high risk pregnancy 175 million years old.

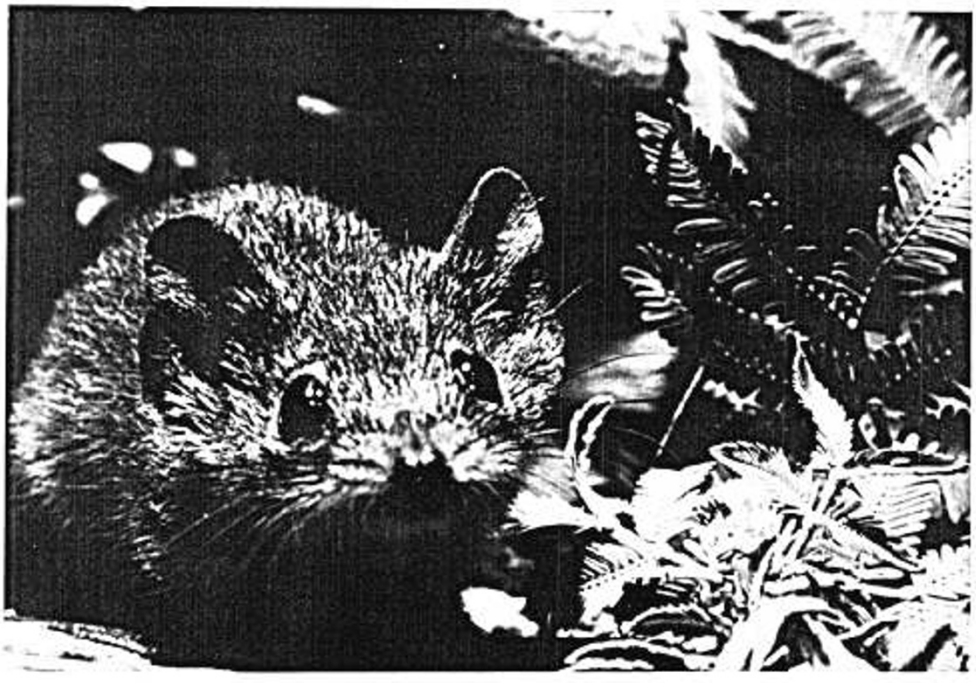

Fig. 2. Photograph of a marsupial mouse of approximately 60 g.

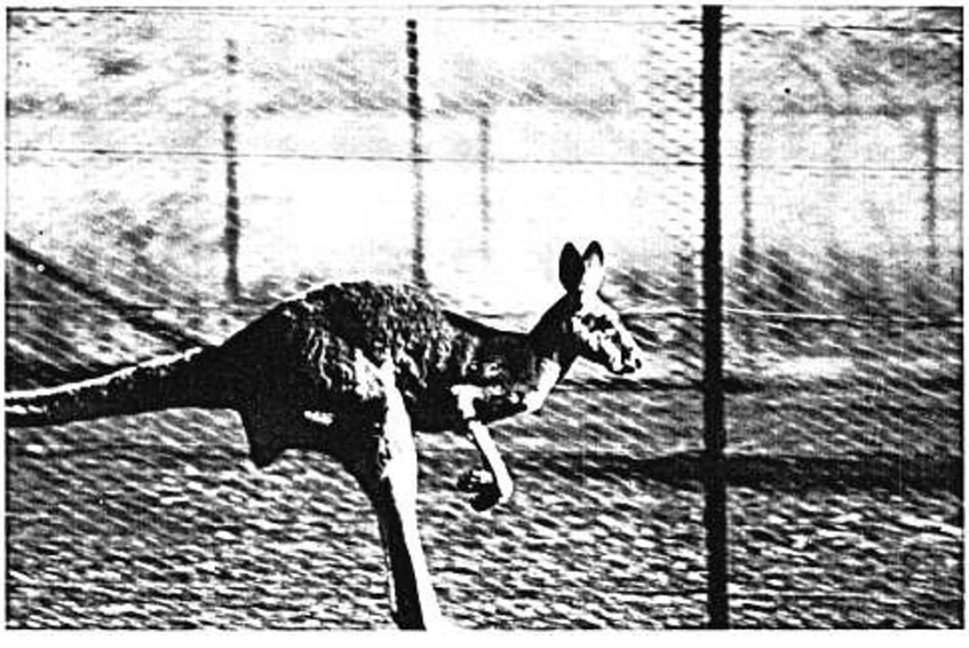

Fig. 3. Photograph of a red kangaroo weighing approximately 40 kg.

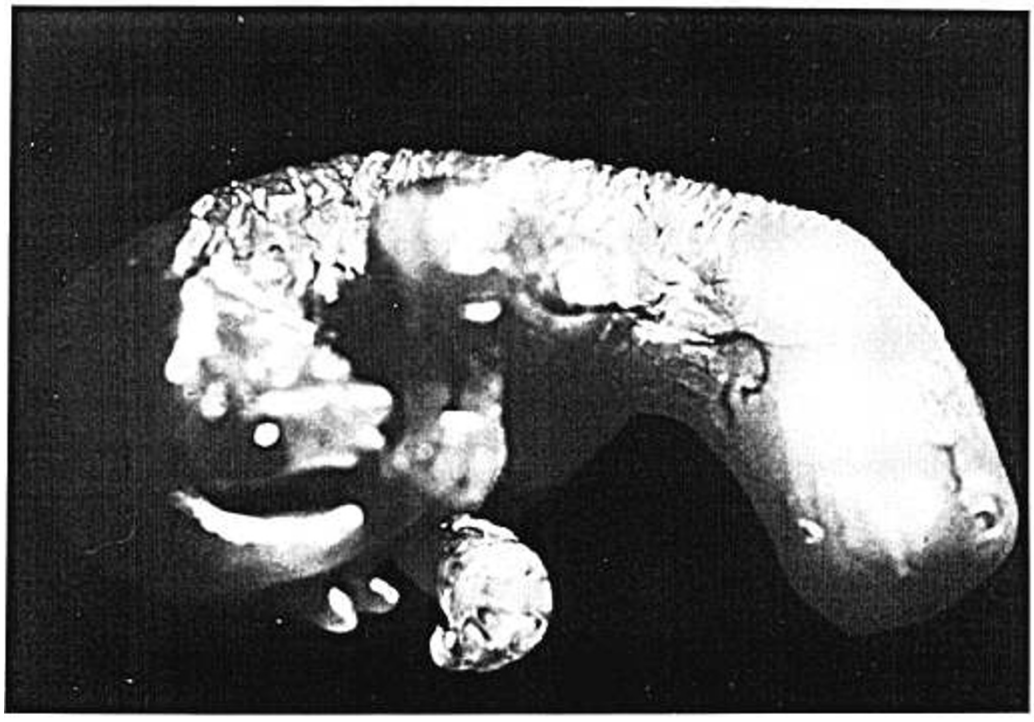

Fig. 4. Photograph of a 2-day old tammar showing the precocious development of upper limbs and open mouth for suckling.

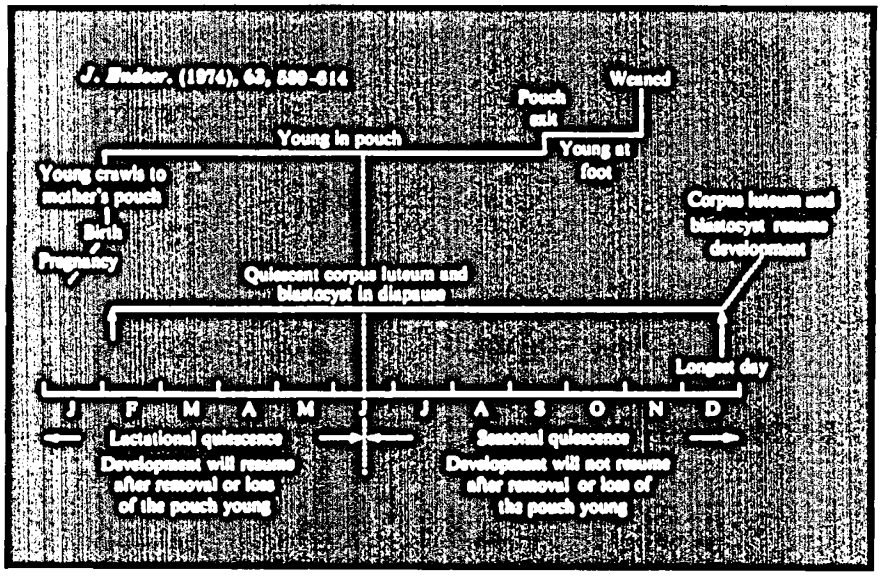


Fig. 5. The sequence of events in a moderate-sized marsupial, the tammar wallaby.

only to die of malnutrition within the pouch. Thus, the phase of intrauterine development is preserved despite severe maternal malnutrition, while the phase of lactation and pouch development is curtailed, leading to the high mortality of the pouch young.

## SIZE IN EUTHERIAN MAMMALS (9)

The size of eutherian mammals, including man, varies far more greatly, with a difference of more than 14 million-fold between the smallest mammals, such as this creature, the fruit bat (Fig. 6), a close relative to the lesser horseshoe bat, weighing approximately 6.0 g, and the blue whale, weighing approximately 100,000 kilos. Similarly, the variability in the metabolic demand imposed upon the mother by pregnancy is very great. The bat and the bear represent two mammals at either extreme in the metabolic demands imposed upon the mother by pregnancy. In the bat, for example, the newborn of 2 g is equal to approximately 30% of the maternal weight. You will recall that in the marsupial mouse or other small maruspials the maximum percentage of maternal weight represented by newborn weight is approximately 100 times less than the bat. Despite this demand, the bat continues to fly and carry on considerable muscular work in addition to maintaining a very high basal metabolic rate.

The pressures of metabolic demand upon pregnant females has led to a reversal of the usual sexual dimorphism in bats. Dr. Philip Myers of the Museum of Zoology at the University of Michigan has pointed out that several factors related to reproduction favor "big mothers," particularly in bats, with such a large fetal tissue mass to produce (13). Among the little brown bats, the females are larger in total body weight and in wing span than males. Dr. Meyers showed that there was a striking correlation between the degree of sexual dimorphism, that is, how much bigger the female

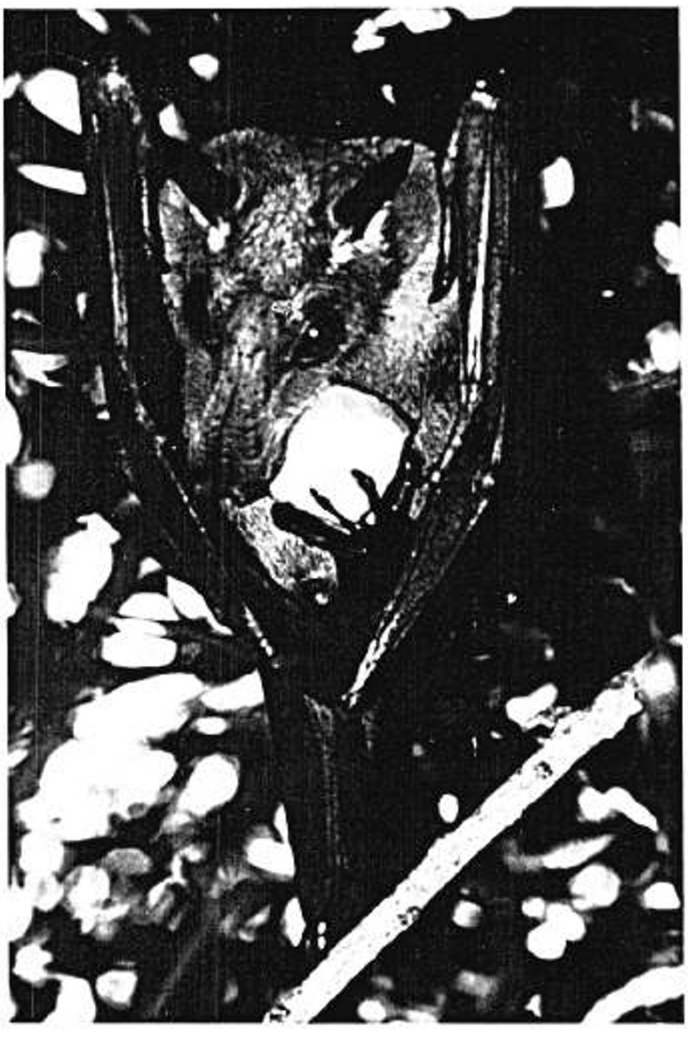

Fig. 6. Photograph of a fruit bat, weighing approximately 6.0 g.

is than the male, and the number of young per pregnancy. This provides strong evidence against the Darwinian hypothesis that it was competition of one sex for another that determines size differences.

In contrast, the polar bear (Fig. 7) weighs 260 kg, with a proportionately lower adult metabolic rate, and yet produces a newborn of only 0.6 kg representing 0.3% of maternal weight, 100 times less than the bat.

## SIZE OF PRIMATES

These size differences and metabolic rate differences apply to primates as well. The small primate in Figure 8, the pygmy marmoset, weighs only 70 g, with a newborn weight equal to 13% of maternal weight. In contrast, the gorilla, weighing about 60 kg, produces a newborn only equal to 3.0% of maternal weight.

## METABOLIC RATE VERSUS SIZE (8, 11)

However, what is overlooked in consideration of size is the relationship between size and metabolic rate; a relationship which holds for both marsupials and eutherian mammals.

Metabolic rate, that is, basal $O_2$ consumption, is a function of the 3/4 power of body weight, a relationship that has been confirmed in animals as different in size as the bat and the elephant. Thus, a small mammal may have a metabolic rate of approximately 10 times that of man. It should be emphasized, particularly to clinical scientists, that the relationship between size and metabolic rate is no different for primates than other mammals. A rhesus monkey of approximately 7 kilo, for example, has a metabolic rate 80–100% greater than man and equal to that of other 7-kg mammals.

Figure 9, taken from the report of Ballard *et al.* (1) points out that this relationship between size and metabolic rate applies not only to oxygen utilization but to glucose turnover rate as well. Thus, depending upon the questions asked in metabolism, the choice of the size of animal studied both in terms of the adult animal and the size of the newborn produced becomes critical in attempting extrapolations back to man. These differences in metabolic rate of the whole organism apply to the metabolic rate of individual tissues studied *in vitro*. Thus, the $O_2$ consumption *in*

Fig. 7. Photograph of the polar bear, weighing approximately 260 kg.

Fig. 8. Photograph of the pigmy marmoset weighing approximately 70 g.

*vitro* of liver from a rat is higher than that of a sheep or of man, two mammals of comparable size and comparable metabolic rate (8, 11).

## DIVERSITY OF DIET: VARIABILITY OF DIGESTIVE SYSTEM

The second characteristic of diversity among mammals, even of the same size, is the striking differences in the kinds of foodstuff used to meet metabolic requirements, both as sources of fuel and as building blocks for growth.

The fuel requirements are what the late Max Kleiler called "The Fire of Life" (6). Those needed for growth are often overlooked and represent the calories deposited as new tissue in a growing organism. These latter requirements can be determined by bomb calorimetry studies at different stages of growth (3, 14).

Figure 10 presents the caloric requirement in the latter one-third of pregnancy in the sheep calculated from data on fetal $O_2$ consumption (2) and body composition (3, 14). Approximately 50% of the total caloric requirements of a sheep fetus are needed for new tissue accretion, a requirement that would be much larger in some smaller mammals. The large contribution of new tissue

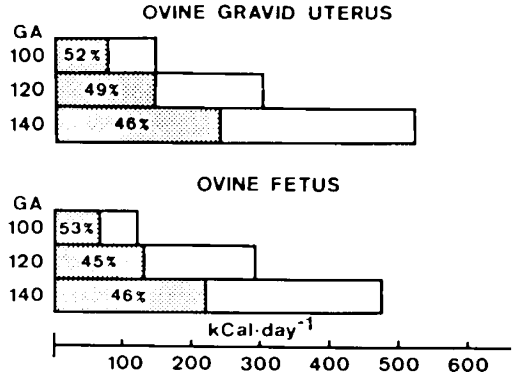


Fig. 10. The caloric requirement in the latter of one-third of pregnancy in the sheep calculated from data on fetal $O_2$ consumption and body composition.

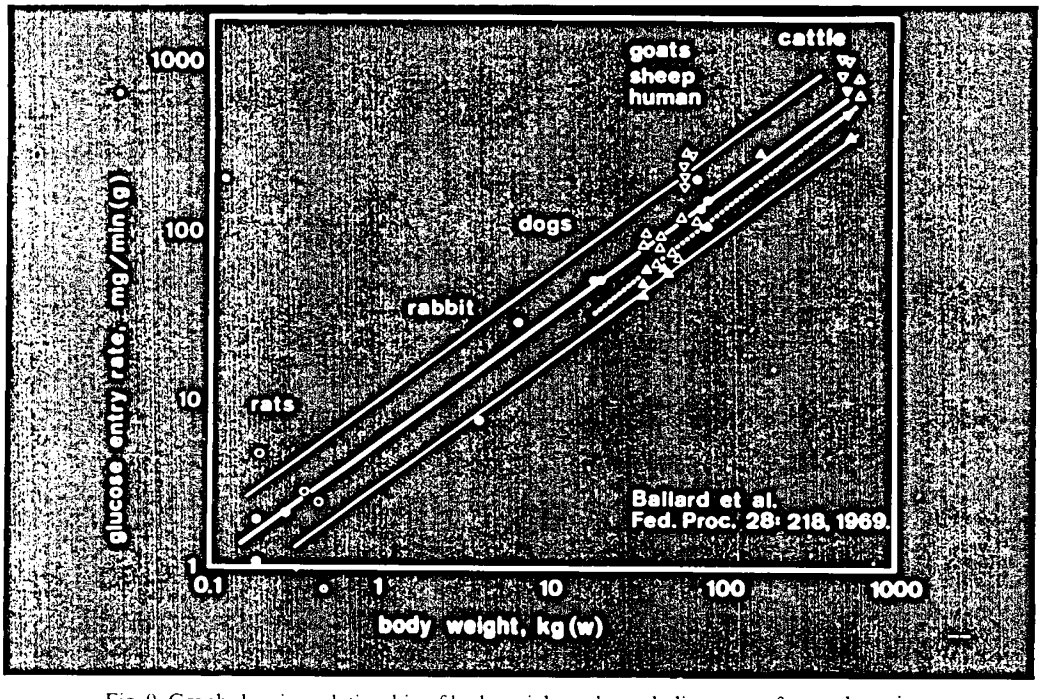


Fig. 9. Graph showing relationship of body weight and metabolism rate of several species.

accretion to the total caloric requirements helps explain how the growing infant can adapt to a restriction in nutrition, namely, by reducing its growth rate by 50%. The fetus can reduce its total caloric requirement by 25%.

These total requirements, that is, the need to meet both fuel and growth demands, are there for all creatures. The magnitude of the requirements and how they are met, vary markedly among mammals. For example, the vampire bat lives on an essentially all protein diet, the hibernating black bear upon body fat, the ruminant, including a ruminant primate such as the leaf-eating monkey, on a cellulose diet which is broken down by bacterial fermentation into short chain fatty acids, and man upon a variety of food sources. These diets vary markedly in the percent of calories represented by protein, fat, and carbohydrate. Not surprisingly, the digestive tracts and specifically liver function of the various animals reflect these differences.

In all species, some of the carbon in fats and amino acids are used for gluconeogenesis in the adult liver. I should like to suggest, however, that we have focused far too much attention in comparative physiology upon the variability among species in the function of the digestive tract and overlooked the commonality among mammals in the metabolism of organs outside the digestive tract.

## SIMILARITY OF ORGAN METABOLISM (2)

These striking metabolic differences among species disappear when one considers the metabolic profile of individual organs such as the brain or the heart, unconnected with the digestive tract. There is no apparent reason why one should assume, for example, that the brain of a ruminant such as the sheep or goat might metabolize short chain fatty acids such as acetate and propionate instead of relying upon hepatic gluconeogenesis for a supply of glucose.

As you see from Table 1, the brain of these mammals and that of non-ruminant mammals, such as the dog or rat, is characterized by a reliance upon glucose metabolism. A high rate of cerebral oxygen and glucose utilization appears to be a general characteristic of cerebral tissue regardless of the stage of development or of the size of the organ. In like manner, in all species studied, rat, sheep, and man, its metabolism can be shifted to the utilization of ketoacids when the arterial ketoacid concentrations are elevated.

Adult myocardial metabolism has been best studied in the rat, dog and man. Again, in several species widely different in food intake and liver function, the metabolic profile of the heart is similar, with most of the $O_2$ consumption met by the metabolism of free fatty acids. Thus, one could not tell by knowing the substrates used as fuels whether a brain or a heart had come from one or another species. The metabolic profile of these organs bridges species differences.

## FETAL METABOLISM (2)

Similarly, the metabolism of the fetus has features demonstrating its commonality quite apart from whether it is a rat fetus, a fetus of man or of other mammals. Certainly, differences in fetal metabolism do exist and have been well established among species. But I believe we have been distracted by relatively minor differences and have thus failed to search as diligently as we might for a conceptual basis to fetal nutrition and metabolism, bridging apparent interspecies differences.

Table 1. *Metabolic requirements of brain*

| | $Q_{O_2}$, ml/100 g/min | $Q_G$, mg/100 g/min |
|---|---|---|
| Fetal sheep | 4 | 5.5 |
| Lamb (2–14 days) | 5.7 | 7.7 |
| Child (0.6–2 years) | 5.1 | 6.8 |
| Adult sheep | 3.7 | 4.95 |
| Adult man | 3.5 | 5.5 |

Table 2. *Oxygen consumption rates per kilo body weight of adults and fetuses in species of different size: Adult values calculated according to Equation 2*[1]

| | $O_2$ consumption (ml/min·kg) | | |
|---|---|---|---|
| Animal | Adult | | Fetus |
| Horse | 2.0 | | 7.0 |
| Cattle | 2.2 | | 7.4 |
| Sheep | 4.0 | | 6–9.4 |
| Rhesus monkey | 7.0 | | 7.0 |
| Guinea pig | 9.7 | | 8.5 |
| Rat[2] | 14.1 | 23.4[3] | 10.4[4] |

[1] $O_2$ consumption in the adult and newborn rat calculated from the data of DeMeyer *et al.* (5).

[2] In: F. C. Battaglia and G. Meschia: Principal Substrates of Fetal Metabolism (2).

[3] Forty-eight hours old.

[4] Newborn.

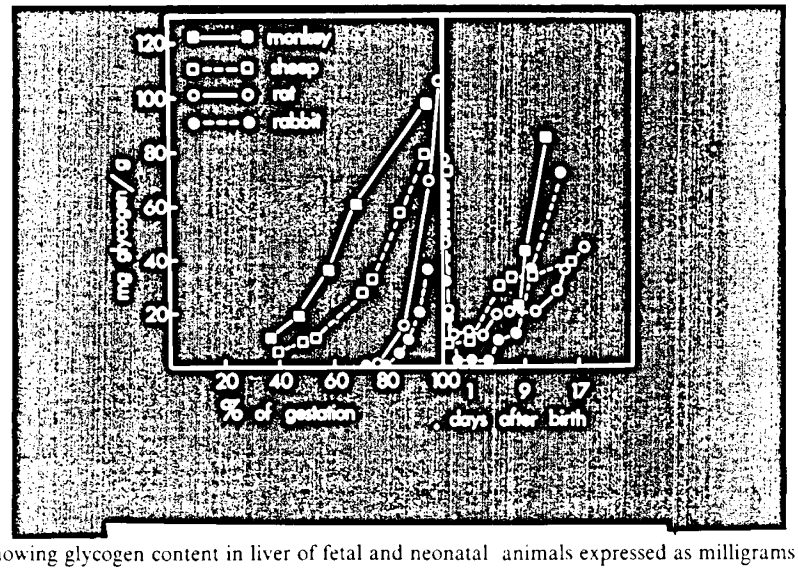


Fig. 11. Graph showing glycogen content in liver of fetal and neonatal animals expressed as milligrams per g liver (108).

## FETAL METABOLIC RATE AND RESPIRATORY QUOTIENT (RQ)

The metabolic rate of the fetus has been measured in a number of mammals of different size. Table 2 presents fetal $O_2$ consumptions in those mammalian species for which they have been measured. I have calculated the adult $O_2$ consumptions as the ¾ power of body weight. As you see in this comparison of adults varying in size with their fetuses, although the adults have quite striking differences in $O_2$ consumption reflecting their differences in size, the fetuses have approximately the same $O_2$ consumption, despite their different birthweights.

There have been a few instances where $O_2$ consumption has been estimated immediately after birth. I have included observations of DeMeyer *et al.* (5) in the newborn rat. When such measurements have been made, it would appear that the newborn infant quickly adopts the metabolic rate characteristic of that species' size. Thus, in the very small mammals, $O_2$ consumption may rise after birth and in the very large mammals may fall, the variability residing in the adult metabolic rate, not in the fetal.

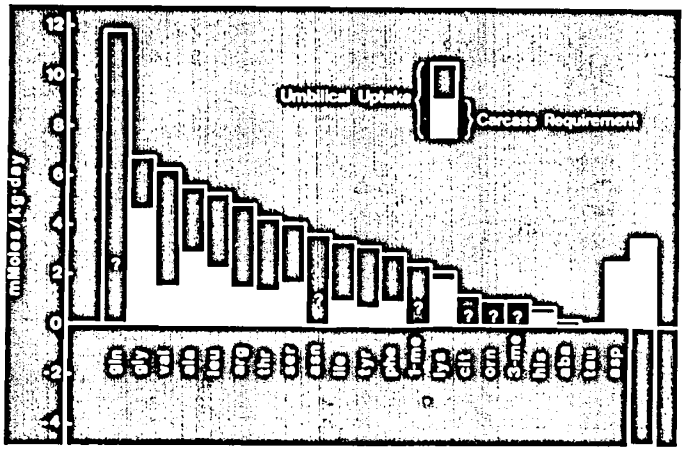


Fig. 12. Graph showing the transfer of amino acid across the sheep placenta during the latter part of gestation.

The RQ of the fetus has been estimated in several mammalian species as well. Unfortunately, such measurements were often made to determine whether carbohydrates, fats, or amino acids were used as fuels. Such an interpretation can never be made from the RQ in a rapidly growing organism where the quantity of carbon incorporated into the carcass as new tissues is a significant percentage of total carbon utilized.

Theoretically, the RQ could vary from 0–8 depending on the

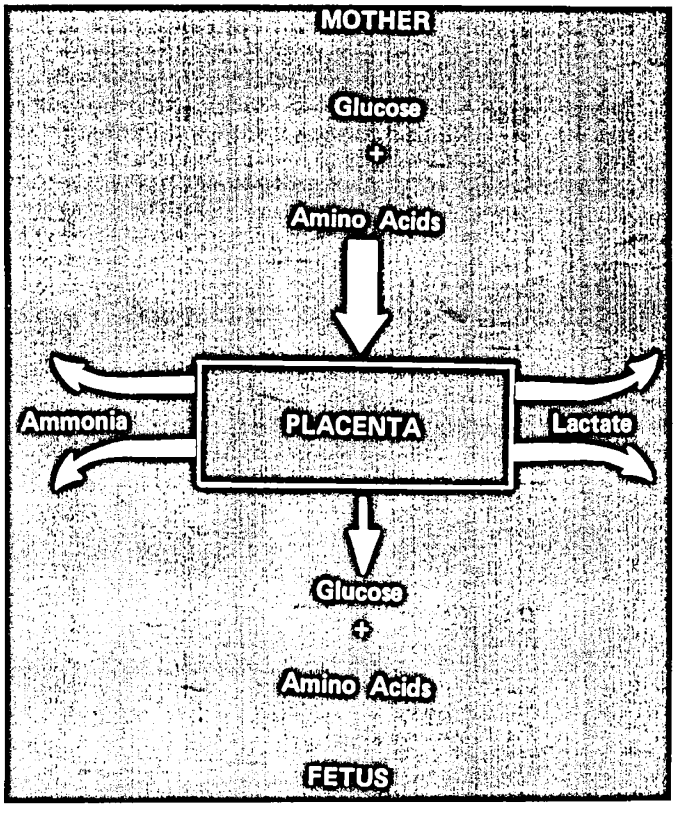


Fig. 13. Chart demonstrating placental lactate production.

Fig. 14. Photograph of aquatic mammal, the elephant seal.

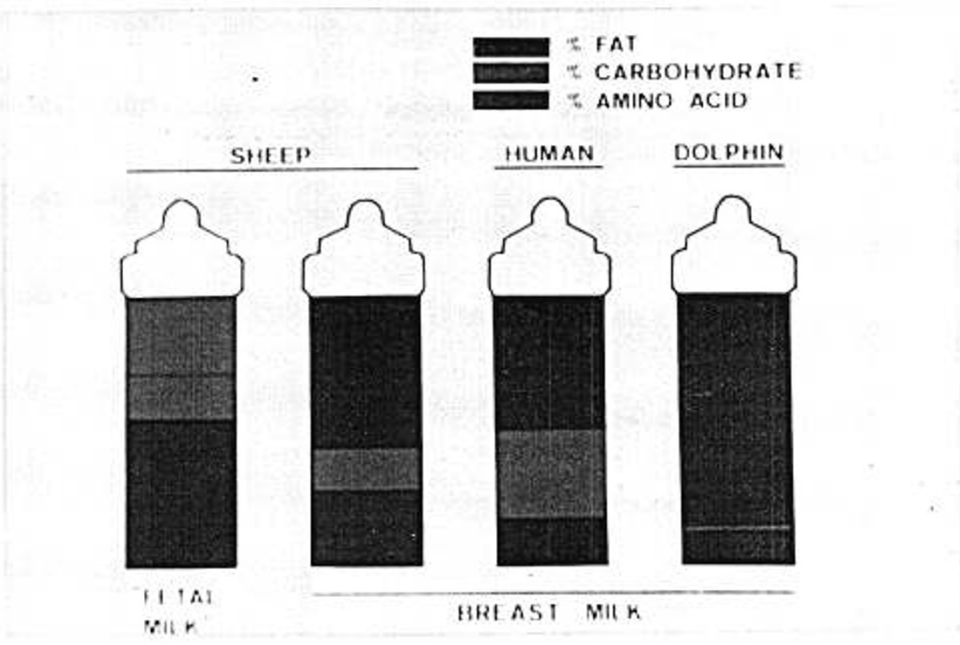


Fig. 15. The diet of the fetus and the newborn.

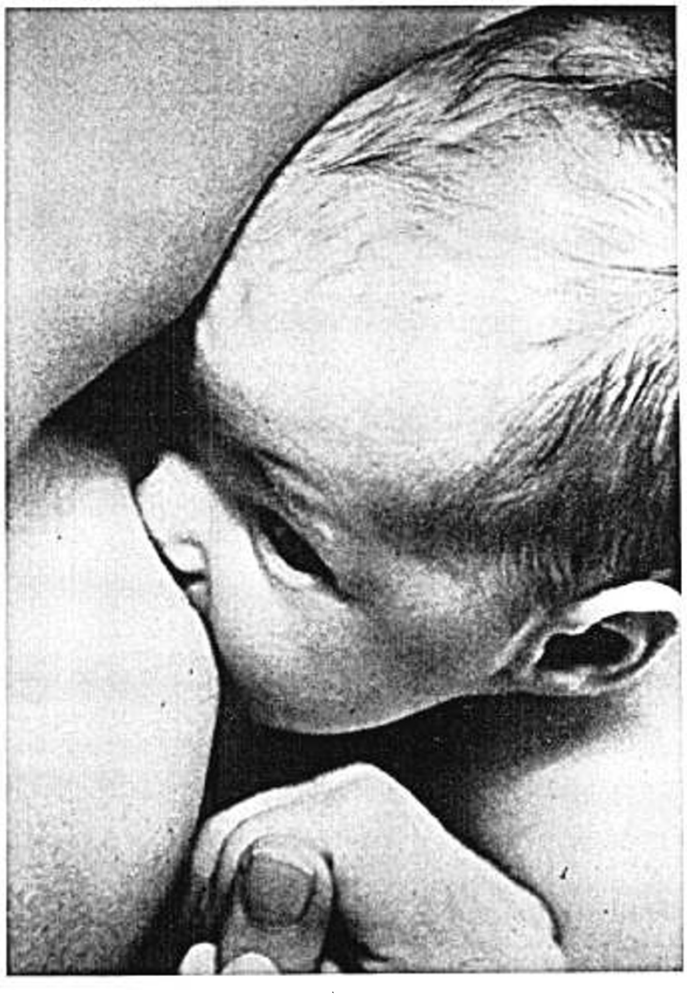

Fig. 16. Photograph of a baby nursing.

extent to which carbohydrate is being used to synthesize fat or fat used to make carbohydrate. In adult rats, stimulating one or the other pathway in metabolism has varied the RQ between 0.2 and 2.0.

## PRINCIPAL CARBON AND NITROGEN SOURCES

Let us consider next the principal carbon and nitrogen sources of the fetus. The role of glucose in fetal metabolism has been better established in the last few years. In a few instances, the utilization rate of glucose by some individual organs of the fetus and/or newborn have been measured and the glucose uptake by the fetus as a whole determined. Glucose provides sufficient carbon to account for approximately 50% of the fetal $O_2$ consumption and 25–30% of the total carbon requirements of the lamb fetus. In all mammals studied, the fetus stores liver glycogen in the latter part of gestation and mobilizes it immediately after (Fig. 11) (1). Again, the similarity among fetuses of different species is apparent.

## LACTATE

A second carbohydrate of importance in fetal metabolism is lactate. Nutrition *in utero* is provided by an organ, the placenta, at least as complex metabolically as any organ in the body. One of its more striking characteristics is the production of lactate under aerobic conditions. This phenomenon was first described in 1925 for the placenta of the rat (12). Subsequently, Villee demonstrated the aerobic production of lactate for human placental tissue *in vitro* (16) and more recently we have shown that this occurs *in vivo* in the sheep placenta and have demonstrated that lactate accounts for approximately 25% of the fetal $O_2$ consumption and approximately 13% of the total carbon required by the fetus (4). Again, it deserves emphasis that this phenomenon of a high rate of placental production of lactate under aerobic conditions was found in animals varying greatly in size and in adult nutrition (*i.e.*, in man, sheep, and rats).

## AMINO ACIDS AND NITROGEN METABOLISM

The transfer of a net quantity of amino acids across the placenta occurs for most of the individual amino acids. We have studied the quantity of each amino acid transferred across the sheep placenta during the latter part of gestation (10). So far as I know, these are the only data for net amino acid uptake by a fetus (Fig. 12). You will note the wide differences among the amino acids in the quantity transferred versus that required for carcass growth. For example, glutamine and gycine were delivered to the fetus in amounts far greater than that required for growth, whereas lysine and histidine transfer was approximately equal to that required

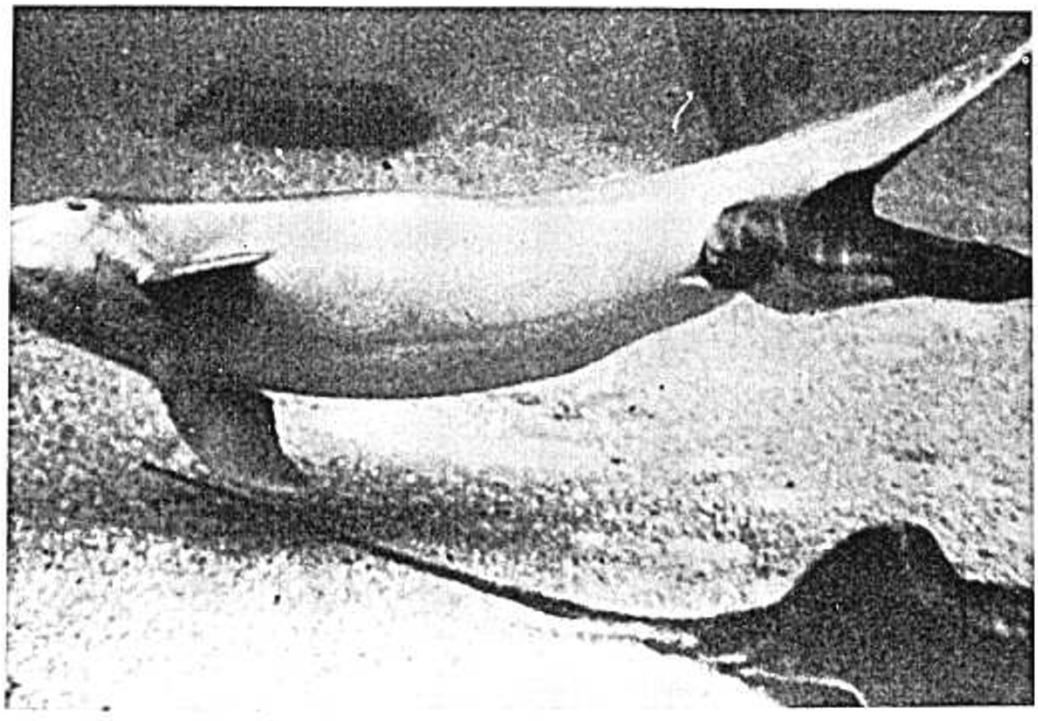

Fig. 17. Photograph of a whale.

for growth. These data suggest strongly that there is little catabolism of lysine and histidine in the fetus. The quantity of amino acids used as fuel by the sheep fetus has been estimated from the urea production rate (6). The observation that the net umbilical uptake of amino acids is considerably greater than the total nitrogen requirement for growth provides additional support to the observations of a high urea production rate during fetal life. Recently, Dr. Holzman and others in our laboratories demonstrated a high rate of $NH_3$ production by the sheep placenta (7). $NH_3$ production could be demonstrated by Dr. Holzman and Dr. Philipps in our laboratories for human placental tissue *in vitro*, as well as for the sheep placenta *in vivo*, similar to comparable studies for placental lactate production (Fig. 13), suggesting another common feature of nitrogen metabolism in early development. Thus, in those mammalian fetuses which have been studied, there has been a net transfer of glucose, lactate, and amino acids to the fetus.

These substrates account for over 90% of the carbon and an excess of the nitrogen required by the ovine fetus both as fuels and as materials for new tissue growth. Collectively, they may be regarded as the "fetal milk" in mammals. After birth, the higher the fat content of the breast milk, the more water is spared for the mother in feeding the young. Thus, the desert mammals or aquatic mammals such as the elephant seal (Fig. 14), for whom water is in short supply, have the fattiest milks. In contrast, "fetal milk" in the ovine fetus consists essentially of the two carbohydrates, glucose and lactate, and amino acids (Fig. 15). Once milk is produced by the mammary gland, fat is introduced in large amounts into the diet and the proportion of fat increases as the need for $H_2O$ conservation by the mother increases. As you can see from this baby's expression (Fig. 16), he certainly gives a three-star rating to what may well by his first fatty meal.

To summarize, I have offered the hypothesis that many of the differences in mammalian metabolism reflect differences in diet and thus are confined to the organs associated with the digestive tract. For other organs of the body which "see" arterial, not portal venous concentrations of solutes, there is a commonality to the metabolism of an organ among mammals. This characteristic is shared by the uterus, and specifically by fetal metabolism.

In closing, I should like to reverse the usual order and thank those colleagues who have encouraged me in the preparation of this address and who have provided much of the visual material I have used. These include Dr. Kurt Benirschke, Scientific Director of the San Diego Zoo and Chairman of the Department of Pathology at the University of California, San Diego; Dr. Marilyn Renfree, School of Environmental and Life Sciences, Murdoch University in Western Australia, and Dr. Philip Myers from the Museum of Zoology at the University of Michigan and Dr. Conrad Riley, a member of our societies and a member of the Denver Zoologic Societies. I should especially like to thank all of you for giving me this opportunity to speak with you.

I hope this brief review will stimulate some of you as it has me during its preparation; that it will nudge us, however gently, to view the remarkable beauty and diversity of mammals (Fig. 17) and of mammalian development not as an obstacle to be overcome by a search for a more perfect model, but rather as an entrée to answers for important questions in biology, questions whose importance should be judged not only by their applicability to the biology of man but to the biology we share around us. Thank you.

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17. Figures 1, 8, and 18 were provided through the courtesy of Dr. Kurt Benirschke, Professor and Chairman, Department of Pathology, University of California, San Diego and Scientific Director of the San Diego Zoologic Society. Figures 2, 3, and 4 were provided through the courtesy of Dr. Marilyn Renfree, Lecturer, School of Environmental and Life Sciences, Murdoch University, West Australia. Figures 6 and 7 were provided through the courtesy of Dr. Conrad Riley, Professor Emeritus, Department of Pediatrics, University of Colorado Medical Center.


0031-3998/78/1206-0736$02.00/0

*Printed in U.S.A.*