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The Mammary Gland in Mammalian Evolution: A Brief Commentary on Some of the Concepts

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Current thinking is highlighting the mammary glands and the process of lactation in the evolutionary success of mammals over and above the selective advantages provided by the nutritional and antimicrobial properties of milk. The extended period of contact between mothers and their young, necessitated by the regular and frequent transfer of milk, particularly characteristic of the primate strategy of reproduction and the primate mode of life, has been suggested to afford the offspring the opportunity for more learning and the eventual development of the levels of intelligence present in "higher" primates. Lactation offers the opportunity for maternal effects on development and the eventual phenotype of the offspring in addition to those that occur during pregnancy or from behavioral interactions. Lactation comes with high metabolic costs, which are manifested in parent–offspring conflict, and special physiological adaptations have evolved which match milk supply to demand by the young.

KEY WORDS: evolution; parent–offspring conflict; autocrine control; privilege; maternal effects.

INTRODUCTION

Lactation is the defining characteristic of mammals and their entire way of life. While other animals produce special secretions to nurture their young, for example, some cichlid fish, pigeons, and some insects (1), only mammals have a particular organ devoted to that function and only in mammals is feeding of the young by maternal secretions brought to such a high degree of integration and sophistication. By any measure, the mammalian way of living and passing on an individual's genes has been successful to the point at which one mammalian species effectively determines, by the intentional or unintentional actions of individuals or collections of individuals, the future direction of life on earth. In this commentary, I introduce and discuss briefly the role of lactation in that evolutionary success story, as well as the consequences of using maternal nutrients to fuel a notionally independent organism. Lactation cannot, of course, be considered in isolation from development and growth of the young in utero since the two processes are sequential and part of the whole reproductive strategy of eutherian mammals. But it must be remembered that in metatherians (marsupials), gestation is comparatively very short and lactation very long while in the oviparous prototherians—the duck-billed platypus and echidna—reproduction is similar to that of birds or most reptiles except for the addition of mammary glands and lactation. Mammary glands are the common thread in oviparous and viviparous mammals.

The evolutionary benefits of lactation have usually been interpreted as nutritional. The mother can provide a balanced supply of nutrients to support growth and development isolated from the vicissitudes of providing an immediate supply of food from the environment or the ecological niche of its parents. This isolation from an immediate need is particularly evident in larger mammals with their relatively lower metabolic rate and increased nutrient storage capacity; fat stores can be accumulated and then disbursed hours, weeks, or months later for milk secretion. A newly hatched lizard independent of its parents or a nestling bird depending on its parent bringing

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sufficient insects of the right size and composition almost on a minute-to-minute basis has only its own reserves to depend on with changes in supply. Caroline Pond (2) summed up the benefits of lactation as a conversion buffering mechanism. The mother's food obtained in her ecological niche can be converted to a form suitable for the young, and the mother herself acts as the buffer or reservoir either over the long term (as in some pinnipeds where the mother does not feed during lactation) or short term, even during a daily cycle of food intake. She also made the point that adipose tissue is the opposite side of the same coin, and that the mammalian organization of adipose tissue—the major nutritional buffer—is intimately associated with the evolution of lactation.

In these terms, lactation can be viewed as an extension of the constancy of the maternal internal environment—as in Claude Bernard's famous aphorism *La fixité du milieu intérieur est la condition de la vie libre*—to permit maximal survival and growth of the young, a constancy that enables the supply of appropriate nutrients at appropriate intervals to develop and maintain the constancy of the internal environment of the offspring.

The other benefit of lactation that has been stressed is protection: protection from disease in the form of antibodies and antimicrobials in milk and protection from predation by the presence of the mother for a relatively long period after birth. Indeed the selective advantage of secreting antimicrobial substances has been proposed as a major force in the evolution of mammary glands (3,4). However, the initial evolution of the mammary glands is beyond the scope of this paper (see articles by Oftedal in this issue). What is of more concern are the selective advantages offered by lactation once established in the first mammals.

THE CONCEPT OF PRIVILEGE

The mammary gland clearly provides the mammalian mother the opportunity to give her offspring a flying start from the view point of nutrition and chemical protection against pathogens. In addition, the relatively long periods of parental care and close contact entailed by lactation bring other maternal influences to bear—both behavioral and chemical through the components of milk.

The whole gamut of advantages afforded by intimate contact between mother and offspring and a long period of parental care has been encapsulated in a single concept by Jack Cohen (5), that of enabling parents to confer *privilege* on their offspring. This direction of thought extends the importance of parental care beyond the physiological or protective elements to make maternal influences on the young the greatest advantage of the mammalian reproductive strategy, one which has enabled the appearance of man and this species' sophisticated (if that is the appropriate word) culture.

Stewart and Cohen (5) explained "privilege" starting with the evolutionary step of parental care, which reaches its apotheosis in mammals, with the uterus providing an incubator for embryonic and fetal development followed by the provision of milk for a relatively long period. The young are therefore privileged because they are given special care at the parents' expense. Because of this continuing intimate association, more complex developmental routes could be adopted as reliable and could be learnt. They continued,

> By a whole series of gradual becomings, which are now moderately well understood, parental privilege led to a whole new kind of intelligence, involving new tricks of *learning* and *teaching*. Parents became part of the behavioural context of their offspring... Rats and wolves, cats and dolphins are born into a parental environment in which they pick up tricks "in the nest"—new alarm cries, new ways of catching fish, new ways to cadge food from people.... And that is where mind comes into the picture. It is from this kind of cultural transmission of special forms of behaviour, we shall argue, that the specifically human mind has evolved.

It is in this context that the different reproductive strategies employed by the different groups of mammals come into play (reviews in 6). Primates in particular have evolved a strategy that comprises the production of a small number of offspring by a process that involves a relatively long period of lactation (with low daily energy costs) following a long gestation (7,8). It is tempting to speculate that the long period of parental control of the offspring's development in primates had such great selective advantage in the particular environments in which they evolved that a positive evolutionary feedback loop operated such that the duration of gestation increased to the point at which birth through the ancestral pelvic route became the limit to fetal growth. Thus, the offspring was born at a stage when its neural development permitted plasticity in its future behavior; the length of lactation increased and parental care was extended beyond weaning. Somehow these processes appear to have produced organisms that can write papers for *Journal of Mammary Gland Biology and Neoplasia* and speculate about the origins of their own behavior.

MATERNAL EFFECTS

The influence and control a mother has on her offspring during pregnancy and lactation are examples of *Maternal Effects* defined, for example, by Mather and Jinks (9):

> Maternal effects arise where the mother makes a contribution to the phenotype of her progeny over and above that which results from the genes she contributes to the zygote.

Evidence of maternal effects in all sorts of organisms has been accumulating for many years. Very recently, there has been a resurgence of interest in diverse areas, from the ecological and evolutionary standpoint (reviews in 10) to their role as possible mediators of human disease in later life (11). In earlier years, maternal effects were actually studied more by applied plant and animal geneticists to eliminate environmental variables from animal breeding studies designed to determine purely genetic effects on phenotype and to improve farm livestock or crops. One might be tempted to wonder whether elimination of maternal effects resulted in the baby being thrown out with the bath water.

The great advantage of nongenetic, maternal influences on her offspring is that it allows the phenotype to be switched to match prevailing environmental conditions. Maternal effects permit, in the terminology of Bateson and Martin (12), mothers to pass a weather forecast to their offspring that alters the phenotype either temporarily or permanently. Developmental paths are switched by the mother, sometimes for more than one generation, even though the offspring have never been exposed to the stimulus that evoked the maternal effect initially. There are no dramatic morphological changes induced by maternal effects in mammals but in locusts, the change between the migratory and solitary form is determined by the mother (13,14). Wide-ranging examples (in terms both of species and of importance to different biological disciplines and social concerns) of maternal effects in mammals (and much of recent interest has not been derived from mammalian studies) are shown in Table I.

At this point it may be worth stressing that biologists in the laboratory or on the farm tend to study animals in good environmental conditions and good health. But many populations of animals are not in good or optimal environments or do not have optimal diets. This stipulation likewise applies to many human populations throughout the world, to domestic animals improperly maintained and to wild animals in degraded habitats or where there is extreme competition. These poor environments would be expected to induce maternal effects that could be crucial to survival of the young and to their successful reproduction in the future.

The question then arises of whether a particular maternal effect is adaptive. Some modifications of the offspring are probably simple consequences of

Table I. Examples of Maternal Effects in Mammals

- When food intake by female hamsters was restricted during first 50 days of life, sex ratio of litters and growth were affected in the third generation (15)
- The daughters of mothers exposed to the Dutch famine of 1944–45 during the first two thirds of pregnancy had children with low birthweights (16)
- In female rats on restricted food intake, impaired antibody responses were evident in two succeeding generations (17)
- Offspring of female rats fed a low-protein diet for 1 month before and during pregnancy; brain weight and total DNA were reduced (18)
- In white-tailed deer, maternal and grandmaternal condition affects bodyweight and vulnerability to predation by wolves (19)
- When cats were restricted to 80% of ad-libitum intake during lactation, play in the kittens increased: reprogramming the young to catching their own food earlier (20)
- Photoperiodic information is passed from mother to young in utero in rodents (21)
- Flavor of food eaten during pregnancy and lactation influences flavor preferences of young after weaning (reviewed by 22)
- In rabbits, rank of females in pecking-order is passed to females. High-ranking females have higher milk yields and young have faster growth rates; the young get bigger sooner and outcompete offspring of subordinate mothers (23)
- Energy level of maternal diet alters sex ratio at birth in fallow deer (24)
- Maternal undernutrition, during preimplantation period of rat development, evokes abnormalities in blastocyst and programming of hypertension in young (25)
- Maternal diet alters expression of glucocorticoid receptor and 11B-hydroxysteroid dehydrogenase type II in young, relevant to programming of hypertension in utero (26)

maternal experience rather than adaptations to enhance the fitness (in the evolutionary sense) of offspring (27). This category might be summed up by the English phrase "making do." In other maternal effects there is good evidence that the response is adaptive, i.e., the fitness of the offspring in that environment is increased. In other words, not just "making do" but altering some process to optimize performance in that particular environment—"making the best of a bad job." In both nonadaptive and adaptive maternal effects, there is the possibility of permanent change. For example, the absence of nutrients at a key stage of development may mean that the animal would miss a critical growth "window" and remain stunted for the rest of its life. The effects of adaptive maternal effects are also far-reaching in terms of policies to improve human health in deprived populations. In discussing the effects of maternal malnutrition on the offspring, Hales *et al.* (28) have pointed out the possibility of adaptations in the offspring which *permanently alter adult metabolism in a way that is beneficial to survival under continued conditions of malnutrition but detrimental when nutrition is normal or supranormal.* Any such adaptations have major implications in trying to reverse the effects of malnutrition in human populations—morbidity and mortality may increase in times of plenty after malnutrition in earlier generations until the intergenerational effect is lost. Experiments on reversal from poor environments show the process can be slow. For example in an inbred strain of rats kept on a low-protein diet for 10–12 generations, males were 40% and females 30% lighter than ad-lib-fed controls. Relative organ weights, the endocrine system, exploratory behavior, reaction to noise, and learning ability were all affected. When a normal diet was introduced, two generations were needed for the recovery in body size while more than two generations were needed for the recovery of learning ability (29). Similarly, in rats kept and bred at low temperatures and then returned to normal, nonshivering thermogenesis took three generations to return (30)—a real case of a long-range weather forecast.

MESSAGES IN MILK

Lactation extends the period of chemical communication between mother and offspring that is characteristic of pregnancy but restricts the flow of information to one direction. Milk is therefore a potential means of conveying maternal effects. The amount of milk (and whether it satisfies the demands of the young) is itself a message and could form an important signal to the young on the state of the nutritional environment it can expect when weaned. This might be mechanism responsible for the example in Table I of play increasing in kittens when their mothers are restricted to 80% of ad-libitum intake during lactation (20), play in this case being practice and rehearsal for catching prey, with the maternal signal perhaps suggesting early weaning or an immediate need of an enhanced ability to increase predatory skills during shortage of prey. Hunger, or some other form of signal, might then drive the adaptive increase in play behavior in the young.

However, milk also contains a vast array of substances known to be involved in signaling between cells in biological systems (31). Therefore, there is the possibility that these substances may be involved in signaling to the suckling. But as evidence for the presence of factors increased from the 1970s on, it was assumed by many that evidence of presence meant evidence of action in the young. Many of those notions were fanciful and entirely unsupported by experimental evidence. In short, many authors were falling into the trap of the "adaptationist programme" (32) which assumes that all existing characters are adaptive. The alternative view in each case, of course, is that the hormone is in milk simply because it has no biological effects in the young and involves no significant loss to the mother; therefore, no mechanisms have arisen during evolution to exclude it from milk. Hormones in milk may also or alternatively be involved in signalling within the mammary gland of the mother (33).

In an attempt to establish whether or not a biologically active substance in milk has effects in the suckling neonate, Peaker and Neville (34) proposed a set of four criteria, similar in many ways to Koch's postulates for infectious diseases, that need to be fulfilled before hypotheses on the transmission of regulatory information via milk can be considered acceptable. The criteria are as follows: (i) an effect in the offspring must be obtained in response to exposure to the substance in milk; (ii) the effect in the offspring must be abolished by removal of the substance from milk and restored when that specific component is restored; (iii) the substance must be shown to be present and active in milk; and (iv) the substance must be shown to retain its biological activity in the offspring to the point at which it is postulated to act or to be activated by partial digestion within the digestive tract.

The criteria are not easy to fulfill experimentally especially since some hormones could cause programming events in the young whose effects are only manifested at some later stage of life. However, more than 10 years later, it is fairly clear that there are two categories of biologically active substances in milk. The first type is supplied by the mother in milk until the suckling reaches a stage in development when it can produce its own supply; an example is epidermal growth factor (EGF) in altricial mammals. Success in determining this role is attributable to the late Otakar Koldovsky's group (35). The second type is the programming of the young by a hormone in milk at a critical period of development; an example is the control of pituitary mammotrope differentiation in rats by two factors in milk, one of which is prolactin. The definitive study in this area was achieved by the late Steve Frawley's group (36). Even after these demonstrations of important maternal effects exerted through milk, the key question remains: is adaptive as opposed to constitutive information passed from mother to offspring in terms of a "weather forecast"? The sort of hypothesis that might be tested can be framed as a question—since adrenocorticosteroid concentrations in milk increase when a mother is stressed, do these increased concentrations convey information to the young that invokes some adaptive response?

THE COSTS OF LACTATION AND ITS CONSEQUENCES

It would not be surprising if the reader had the impression at this stage of the review of the biological process of lactation as mother bountiful. Picasso's 1963 cartoon, *Maternité*, captures this romantic and classical view of lactation between mother and child that can be summed up in the following two sentences. The mother devotes all her energies, except those necessary to maintain her own life, to care for her young in order for the young to survive and reproduce. Mother bountiful gives her young the best of everything until they are old enough not to want any more milk. Before Robert Trivers (37) analyzed parental care, if asked the question of whether this was a correct view of lactation, most of us would probably have said *yes*. After Trivers most of us would say *yes*—but only bountiful up to a point.

Trivers (37) introduced the concept of parent–offspring conflict into considerations of parental investment. He analyzed the costs and benefits of lactation from the point of view of the two participating organisms because he had observed langur monkeys about the time of weaning. At that time there was behavioral conflict between mothers and their young; the young demanded to be fed but the mother was trying to stop them getting milk—not the mother bountiful image in the classical view. The key to the analysis was the appreciation that in most animals, including mammals, that the mother and her offspring are not genetically identical. The mother is related to her offspring only, on average, by one half in an outbreeding system. The interests of a mother in passing on her genes are not, therefore, identical to those of the offspring, with half its father's genes, even though there is clearly an overlap of self-interest. Selection pressure on the mother is the drive to maximize the number of offspring surviving to reproduce successfully—selection for lifetime reproductive success. The benefit to the mother is the extent to which the mother's expenditure increases the survival of the present offspring; the cost is the extent to which the expenditure decreases her ability to invest in other offspring, including those not yet born. Therefore, selection pressure on the mother will act to maximize the difference between benefit and cost and is against overinvestment in a particular offspring, since that course would impair the mother's ability to raise successful offspring in the future.

On the other hand, selection pressure on the offspring is for it to devalue the costs it inflicts on its mother. It is in competition with its siblings and potential siblings (which may have half its genes from a different father). There is, therefore, an inherent conflict between mother and offspring and, although the extent will vary with the reproductive strategy and life history of different mammals, the young are selected to demand more than the mother is selected to provide. Once the common self-interest phase, in this case full lactation, has passed and the continuing cost–benefit analysis yields odds for the mother to favor cutting off investment to the present offspring, the young may deploy behavioral patterns and false signaling to try to inveigle more resources from their mothers. Mothers are selected to be wise to such wiles (but human experience makes grandmothers worth an approach).

The theoretical predictions on parental investment by Trivers have been considerably extended and have been the subject of a great number of observational and experimental studies as well as arguments on theoretical grounds in organisms with different life histories and reproductive strategies. It is also worth pointing out that before lactation the placenta is a battleground for overlapping but competing self-interest of mother and offspring, and that too is an active area of research in the overall context of parent-offspring conflict (38).

GETTING THE LEVEL OF INVESTMENT RIGHT

As remarked earlier, lactation is an expensive process for the mother in terms of the direct and transactional costs of nurturing the young with milk. It is not surprising that sophisticated controls have evolved over the rate of milk secretion—to match demand by the young (when the overlap of self-interest between mother and offspring favors that demand being met by the mother) and to limit the rate of secretion to the current rate of demand. Such a control system operates within each mammary gland (39–42).

MAMMALS SUCKLE THEIR YOUNG

It is worth pointing out the reason why mammals came to be called mammals. Londa Schiebinger (43) has produced convincing arguments that Carl Linnaeus coined the term *Mammalia* in 1758 (when other equally suitable anatomical terms, denoting hairiness, for example, were available) because he was an active supporter of breast-feeding and an opponent of wet nursing then rife amongst the Swedish well-to-do. This argument raises pertinent questions: why, when lactation is central to the successful passing of a mother's genes to the next generation, has breast-feeding been unpopular to that extent that wet nursing was preferred even though the high death rate of babies so treated was known; why has the greatest uncontrolled experiment in human history—the provision and choice of artificial formula for babies over breast-feeding—become and remains popular? Does the answer lie in parental investment and life history theory or was desertion of breast-feeding an emergent, cultural phenomenon enabled by the very same process that started off the success of mammals, culminating in the development of the mind, in evolutionary history?

CONCLUDING REMARKS

In this commentary I have attempted to give a flavor of how mammary gland biology and the process of lactation are considered in an evolutionary context. My reason for so doing is best explained by Medawar and Medawar (44);

> For a biologist the alternative to thinking in evolutionary terms is not to think at all.

However, from these considerations at the level of ultimate causation cogent research agendas can be derived for the proximate, explanatory reductionist approach. For example, how are the various non-behavioral maternal effects exerted physiologically; what is the route; what are the signalling pathways; how is sex ratio at birth in some mammals influenced by maternal conditions; how does an organism store adaptive information to pass to its own offspring from its own mother?

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