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Trade-offs in evolutionary immunology: just what is the cost of immunity?

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It has become increasingly clear that life-history patterns among the vertebrates have been shaped by the plethora and variety of immunological risks associated with parasitic faunas in their environments. Immunological competence could very well be the most important determinant of life-time reproductive success and fitness for many species. It is generally assumed by evolutionary ecologists that providing immunological defences to minimise such risks to the host is costly in terms of necessitating trade-offs with other nutrient-demanding processes such as growth, reproduction, and thermoregulation. Studies devoted to providing assessments of such costs and how they may force evolutionary trade-offs among life-history characters are few, especially for wild vertebrate species, and their results are widely scattered throughout the literature. In this paper we attempt to review this literature to obtain a better understanding of energetic and nutritional costs for maintaining a normal immune system and examine how costly it might be for a host who is forced to up-regulate its immunological defence mechanisms. The significance of these various costs to ecology and life history trade-offs among the vertebrates is explored. It is concluded that sufficient evidence exists to support the primary assumption that immunological defences are costly to the vertebrate host.

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In recent decades, interest of ecologists and evolutionary biologists in the relevance of parasitism to numerous facets of a host's life history has provided exciting new frontiers of investigation into vertebrate life history (e.g., Hamilton and Zuk 1982, Loye and Zuk 1991, Clayton and Moore 1997). While the study of specific host-parasite relationships have proven insightful, they reflect only a small part of the wealth of parasites and pathogens in an animal's internal and external environment. The immune system is the animal's defense mechanism to fight or control any parasitic or pathogenic infection, and as such, warrants our interest as a focus of study (Lochmiller 1996, Sheldon and Verhulst 1996, Zuk 1996). In addition, immunity is one of the major physiological mechanisms regulating host survival. Survival has long been the most neglected attribute of fitness in part because of the difficulty ecologists have had in quantifying it in the wild. In contrast to this void, reproduction has been the cornerstone of research efforts into life history theory for decades. Reproduction is a clearly defined physiological event both in the field and laboratory, is characterised by having a defined starting and ending point, and can be easily evaluated relative to success, effort, and costs. Ultimately, fitness does not only depend on reproductive success, but on longevity as well.

It has become increasingly clear, however, that mechanisms regulating survival and reproduction are far from mutually exclusive. Apart from survival, mate selection, breeding performance, fecundity, growth, and possibly other life-history traits appear to be associated in various ways with immunity. Mounting an immune response, and even maintaining a competent immune system, is thought by many ecologists to be a nutrition-

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ally demanding process that necessitates trade-off decisions among competing nutrient demands for growth, reproduction, temperature, work, and immunity (Sheldon and Verhulst 1996). In a recent review on nutritional modulation of immunity, however, Klasing (1998) postulates that the nutritional cost of maintaining a normal immune system is minimal relative to tissue growth or egg production. He estimates that the cumulative mass of immune products (cells and molecules) in a chicken does not exceed 5% of total body mass, and that leukopoiesis, even during an immune challenge, accounts for less than 1% of the daily increase in body mass of a growing chick. While such estimates would appear to contradict the assumption that immunity is a costly endeavour that potentially competes with other life-history events for limited nutrients, we suggest that metabolic requirements of immune cells and indirect consequences of mounting an antigen-induced immune response (e.g. acute inflammatory response) are also integral components of the cost equation. Factoring in these additional costs into the equation should provide a more realistic perception of costs of immunity in terms of trade-off decisions, because only a costly immune defence system can provide a relevant explanation of observed parasitism–immunity–reproduction patterns in the wild (Festa-Bianchet 1989, Norris et al. 1994, Richner et al. 1995, Oppliger et al. 1996, Siikamaki et al. 1997, Nordling et al. 1998).

Actual attempts to demonstrate the magnitude of this apparent "cost of immunity" have been limited and no comprehensive ecological review of the subject has been completed, which was the primary motivation for preparing this manuscript. In this paper, the literature is reviewed in an attempt to elucidate the various nutritional costs associated with simply maintaining a normally functioning immune system and to evaluate the costs associated with actually using it. These two physiological traits are not easily addressed quantitatively, particularly with respect to the former, because of the integrated and organisational characteristics of the immune system with other physiological systems. However, enough literature now exists from both the biomedical and animal science arenas to provide some quantitative estimates to these costs. Collectively, these studies demonstrate that considerable nutritional costs (protein and energy) are associated with up-regulation of the immune system. The consequences of such up-regulation to vertebrate survival in the wild appears so significant, that selection should have favoured a level of first-line immunological defence that minimises risk of developing disease (innate immunity) over acquired mechanisms of immunity. Nutritional trade-offs between immunity and other nutrient-demanding processes (e.g., reproduction, growth, thermoregulation) have been an important focus of recent investigations into evolutionary immunology (Sheldon and Verhulst 1996). Trade-offs such as these may be most pronounced within the acquired arm of the immune system as opposed to the more important innate arm (Fearon and Locksley 1996).

Innate immunity and up-regulation

Infection elicits a complete shift in metabolic priorities within the host to those associated with immunity, including related necessities as the repair of wounded tissues. Because immune challenges are effective at suppressing food intake, the body has evolved a complex mechanism for mobilising reserves of protein and energy to support the initial acute-phase response, characterised by hypermetabolism and protein malnutrition. In fact, immunologic challenges are capable of instilling protein malnutrition in a few days that would take several weeks to develop during simple starvation (Long 1977). So although many of the apparent metabolic adjustments a host undergoes during an infection would at first appear quite counterproductive, overall survival and fitness is undoubtedly enhanced (Kyriazakis et al. 1998). The initial acute response to infection is probably the most important to the fitness and life history of an animal in its natural habitat where one might posit that prolonged disease essentially does not occur because the weakened state of the animal would dramatically increase its risks of predation or starvation. Thus, one might hypothesise that survival in an infectious environment would depend more upon the competence of the innate arm of the immune system, a first-line surveillance and defence mechanism that also involves the acute-phase inflammatory response, than it would depend on acquired facets of immunity. Further, the innate compartment of the immune system would be most important among short-lived prey species under intense selection pressure from predation. In all likelihood, an infection, even a rather mild immune challenge, would not persist for more than a few hours or days before an animal would succumb to predation or starvation. Survival contributes more to fitness in long-lived species relative to short-lived species, because maximum fitness is only attained when a long-lived animal survives through many reproductive seasons. Thus, development of strong innate and acquired arms of immunity would seem an appropriate strategy for long-lived species, while a short-lived species may gamble that it survives until successful (early) reproduction with a less well-developed defence mechanism.

The generalised response to an infection is for the body to redistribute nutritional and energy resources away from anabolic and maintenance processes at the extremities to the vitally important metabolic processes driving immunity and disease resistance. This sequence is orchestrated by a complex cascade of events that

begin with the mononuclear phagocytic system and their release of an array of secondary messengers. While extremely complex, a classic response leads to anorexia, increased degradation and decreased synthesis of protein in skeletal muscle, elevated rates of metabolism, increased glucose utilisation, hepatic acute-phase protein synthesis, increased de-amination of gluconeogenic amino acids, alterations in levels of trace minerals, decreased skeletal development, and increased hepatic lipogenesis. The monokines interleukin-1 (IL-1), IL-6, and tumour necrosis factor-α (TNF-α) are the primary cellular messengers triggering the cascade of metabolic alterations following an immune challenge (Klasing and Johnstone 1991, Tsigos et al. 1997). Several excellent reviews have been published in recent years that provide detailed insights into the physiological mechanisms and pathways involved in the monokine-induced inflammatory response to infection (Klasing and Johnstone 1991, Taylor and Piantadosi 1995, Michie 1996).

Macrophages, like other immune cells, are nutrient-demanding cells as evidenced by their hypermetabolic state and significant rates of glucose and glutamine utilisation relative to other cells in the host. Based on in vitro O_2-consumption rates, elicited macrophages turn over ATP in the cell 10 times per minute, almost comparable to maximally functioning heart muscle (Newsholme and Newsholme 1989). Thus, immunity demands fuel in terms of nutrients and energy at remarkable levels, which reflects the evolutionary importance that has been placed on ensuring host survival. Accelerated lipolysis, proteolysis, and glycolysis supply the fuel necessary for mounting the initial immune responses to infection, resulting in substantial loss of body weight if infections are prolonged and severe.

Nutritional constraints

An unfortunate consequence of fighting an infection in nearly all species examined is a reduction in feed intake. This sepsis-induced anorexia is striking in the sense that it occurs at a time when the body needs an influx of nutrients to support the increased demands of mounting an immune response (Scrimshaw 1991). Reduced feed intake appears even with rather mild immune challenges such as those associated with simple vaccination (Gandra and Scrimshaw 1961). Consequently, catabolic processes must activate to support the additional fuel requirements of immune cells and protein synthesis (acute-phase proteins, antibodies). Kyriazakis et al. (1998) forward two hypotheses to explain the occurrence of anorexia during sepsis that are consistent with observations during infection. One hypothesis states that the reduced food intake promotes an effective immune response, while the other (non-exclusive?) one asserts that anorexia allows the animal to be more selective in its diet to reduce the risk of further infection. The obligatory reduction in intake of food during infection could be especially important to wild animals during winter when the thermogenic benefits of digestion are critical to maintaining homeostasis. Winter mortality is a common phenomenon for many species in nature, possibly reflecting the futility of trying to satisfy both the excessive nutritional demands of infection and thermoregulation in a food-limiting environment (White 1993, Schetter et al. 1998). Such risks to wild animals are evident from the observation that the combined stress of shivering thermogenesis and illness in human patients can elevate resting metabolism rapidly to nearly 300% of normal (Chiolero et al. 1997).

Malabsorption also can accompany infections leading to additional nutritional constraints on the host. A combination of factors contribute to this syndrome, including physical blockage of absorption sites by bacterial overgrowth in the gut, alterations in villus structure, reductions in transit time such as with diarrhoea, and reductions in blood flow to the gut. During the acute-phase immune response, the metabolism of many nutrients is altered and the requirement for some is actually elevated due to increased catabolic and excretion processes. For example, vitamin A requirements appear to be significantly elevated during infections as a result of urinary excretion during fever (Campos et al. 1987, Stephensen et al. 1994).

Metabolic costs: energy

Metabolic costs of maintaining a competent immune system are extremely difficult, if not impossible, to adequately measure for a variety of reasons. In fact, we know of no study that comes close to truly addressing the question about how costly it is to maintain a competent immune system for any vertebrate species. However, we have gleaned some important insight into this question by observing physiological changes that accompany the down-regulation or up-regulation of the immune system. It is well known that energy restriction in the diet, if prolonged, can lead to suppression of the immune system and increase the risks of infection, especially with opportunistic pathogens (Klurfeld 1993, Lochmiller and Dabbert 1993). The importance of energy in maintaining the immune system has also become clear from the space programme where the minimal energy demands and production manifested by zero-gravity environments can result in declines of 90% in cytotoxic T-lymphocyte function in astronauts (Tanner 1992).

Unlike starvation where the host eventually adjusts physiologically to the reduction of nutrient inputs by decreasing metabolism, infection leads to a hyperme-

tabolic state to support the up-regulation of the immune system (Table 1). Isolated mitochondria of laboratory rats stimulated in vivo with TNF-α or IL-1 can undergo a 30% increase in respiration rate (Jin et al. 1995). Infusions of IL-6 into healthy volunteers will increase resting metabolic rates by 25% (Tsigos et al. 1997). To fuel this up-regulation, immune cells require glucose and glutamine at high levels (Crouser and Dorinsky 1996), which leads to the rapid breakdown of the body's reserves of protein (to provide glutamine), carbohydrates, and lipids (Michie 1996). Moderate infections can easily lead to 150–200% increases in rates of gluconeogenesis in the host, often leading to severe wasting of lean tissue if such infections chronically persist. Animals typically become insulin-resistant as an adaptation to insure glucose concentrations in circulation remain high for the insulin-independent immune cells involved in wound healing and combating infection (Chiolero et al. 1997).

General statements about the metabolic costs of immunity to the whole organism are difficult to assess during an immune challenge. Severity, type, and duration of infection, ambient temperature, and gender, age, and nutritional status of the host all influence the cost of mounting an immune response. However, it is clear from selected studies with humans and laboratory animals that even mild up-regulation of the immune system can be costly metabolically to the host. In general, neonates are buffered from many of the costs that become evident in a fully matured immune system of adults (McIntyre and Hull 1996). In humans, severe infections routinely lead to losses of 15–30% body weight, with 25–55% increases in resting metabolic rates during sepsis compared to healthy subjects (Long 1977, Kreymann et al. 1993). Hypermetabolism approaching two-fold increases in the resting metabolic rate has been observed in some severely ill patients (Frankenfield et al. 1994). About 20% of the protein mobilised from skeletal muscle is used to satisfy these energetic demands (Duke et al. 1970), the remainder is fuelled by carbohydrates and lipids. Borel et al. (1998) estimated that ca 50% of the elevation in metabolic rate during an infection can be attributed to the elevated energetic cost of protein synthesis (acute-phase inflammatory proteins, antibodies). Whole organism use of glucose can increase 68% during the acute-phase immune response (Klasing 1988). Fever, a hallmark of infection, usually elicits a 10–15% elevation in basal metabolic rate for each 1°C rise in body temperature in humans (Roe and Kinney 1965).

Mild immune challenges such as those associated with vaccination with protein antigen (e.g., keyhole limpet hemocyanin; Demas et al. 1997, Svensson et al. 1998) or avirulent organisms (typhoid vaccine; Cooper A. L. et al. 1992) can result in 15–30% increases in the metabolic rate of a host. Additionally during the recovery period, an animal may be faced with substantial nutritional costs associated with replenishing body tissue reserves that were depleted during the catabolic processes accompanying a typical immune challenge. The energy cost of synthesising new proteins to replace those lost in skeletal muscle must be added to the overall cost of mounting an immune response. An estimated 24 kcal is required by the host to deposit a single gram of protein (Scrimshaw 1991). It may be that the negative nitrogen balance persisting during an immune challenge becomes a more critical factor than elevated energy requirements to survival of animals in natural populations where protein resources in the available food supply fall short of meeting requirements (White 1993, Schetter et al. 1998).

Metabolic costs: protein

Negative nitrogen balance is a classic response during an immune reaction and varies in proportion to severity of infection (Table 2). Inflammatory cytokines and glucocorticoids mediate this energy-dependent proteolytic response in skeletal muscle (myofibril proteins). So, not only does this lead to a negative nitrogen balance, but the accelerated breakdown of proteins places additional energetic demands on the host (Hasselgren and Fischer 1998). The obligatory reduction in

Table 1. Estimated energetic costs (percentage increase in resting metabolic rate as compared to controls) to the vertebrate host when mounting an immune response during vaccination or sepsis.

Species	Immune challenge	Cost	Reference
Human	Sepsis	30%	Kreymann et al. (1993)
	Sepsis	30%	Carlson et al. (1997)
	Sepsis and injury	57%	Clark et al. (1996)
	Typhoid vaccination	16%	Cooper A. L. et al. (1992)
	Sickle cell disease	15%	Borel et al. (1998)
Laboratory rat	IL-1 infusion	18%	Tocco-Bradley et al. (1987)
	Inflammation	28%	Cooper et al. (1994)
Laboratory mouse	KLH challenge[a]	30%	Demas et al. (1997)
Sheep	Endotoxin	28%	Fewell et al. (1991)
	Endotoxin	10–49%	Baracos et al. (1987)

[a] Keyhole limpet hemocyanin injection.

Table 2. Estimated alterations (percentage change compared to controls) in feed intake, body weight (BW) gain, urinary nitrogen excretion, rates of protein catabolism (RPC), rates of protein synthesis (RPS), and total body protein (TBP) levels in vertebrate hosts with an up-regulated immune system.

Host	Reference	Condition	Parameter	Percent change
Pig	Spurlock et al. (1997)	PRRS vaccine[a]	BW gain	−21%
			Feed intake	−15%
Chicken	Lee and Reid (1977)	HVT vaccine[b]	Feed intake	−3%
	Henken and Brandsma (1982)	SRBC[c]	Feed intake	0%
			BW gain	0%
	Klasing et al. (1987)	SRBC	BW gain	−13%
		Endotoxin	BW gain	−18%
Human	Borel et al. (1998)	Sickle cell disease	RPC	+32%
			RPS	+38%
	Carlson et al. (1997)	Sepsis	N excretion	+160%
	Clark et al. (1996)	Sepsis and injury	TBP	−12%
Laboratory rat	Hobler et al. (1998)	Sepsis	RPC	+40%

[a] Porcine respiratory and reproductive syndrome.
[b] Herpes virus of turkeys.
[c] Challenge with sheep red blood cells.

cell mass that occurs from this wasting syndrome, if prolonged, can result in tremendous reductions in body mass. The demands for amino acids to support protein synthesis, elevated metabolic rates, and increased gluconeogenesis are so great that the host has evolved a radical physiological mechanism for responding to an immunological challenge from infecting organisms. Nearly every defensive mechanism available in the immunological arsenal of the host requires significant supplies of amino acids for production of proteins (Beisel 1977).

Quantitative estimates of protein costs to the host for mounting an immune response are difficult to derive and so few exist in the literature. Even less is known of the protein costs for just simply maintaining baseline immune function. Nitrogen excretion in the form of urea can elevate to 160% above normal during sepsis in humans (Carlson et al. 1997). Although synthesis of selected acute-phase inflammatory proteins and antibodies can be elevated, synthesis of other less-vital proteins are reduced during an immune challenge (Biolo et al. 1997). Protein synthesis does not keep pace with accelerated rates of protein loss from skeletal muscle, resulting in losses in total body protein of 20% in septic patients (Biolo et al. 1997). Even intensive intervention by supplying amino acids and glucose to an ill patient is generally unsuccessful at obviating the loss of lean body mass. Septic laboratory rodents have rates of muscle protein breakdown approaching $>40\%$ and significant reductions in rates of protein synthesis (Hobler et al. 1998). Even mild challenges of the immune system such as those induced by vaccinations can reduce nitrogen retention by as much as 30% in the vertebrate host (Gandra and Scrimshaw 1961, Hentges et al. 1984).

It appears that even rather mild, subclinical challenges of the immune system can result in negative nitrogen balance persisting for several days or weeks and requiring nearly four times as long to replenish body reserves (Scrimshaw 1977). The consequences to animals in the wild appear obvious, and one would predict that selection has favoured an immune strategy that minimises the risk of developing a full-blown, clinical infection. Survival for most diseased animals in the wild would quickly approach zero under the natural forces of predation and nutritional stress (Wobeser and Wobeser 1992).

Trade-offs between production and immunity

Energy and nutrients required for growth (cellular proliferation leading to an increase in body size) are often expensive because of inherent inefficiencies in the process as well as dietary imbalances. These "overhead costs" can make the process of growth particularly sensitive to alterations in immune status. In general, stimulation of a host's immune system equates to proportional declines in growth as endogenous strategies of resource allocation shift towards survival and away from nonessential processes such as growth. Even mild up-regulation of the maternal immune system can have suppressive effects on foetal growth and development as a consequence of direct and indirect mechanisms (Rivera et al. 1998). This reallocation and ultimate growth suppression that results demonstrates the costly nature to the host of maintaining a competent immune system and mounting an immune response against infectious agents. This reallocation is another reflection of the major metabolic and nutritional adjustments that can occur following up-regulation of the immune system.

Some of the most interesting insights into the trade-offs between growth and immunity have come from studies in germ-free and antigen-free environments (Tables 3, 4) and with the use of antibiotics in meat-animal

production systems (Table 5). The antigenicity of environments varies greatly and includes everything from food antigens to microbes and collectively calls upon the immune system to work. Considerable research has focused on the consequences of a germ-free existence, primarily in an attempt to ascertain the role of gut microflora on nutrient dynamics in the host (Muramatsu et al. 1994). It is difficult to separate out the positive effects that gut microbes have on nutrient digestion and metabolism from those negative effects on nutrient balance because their presence in the gut effectively stimulates the immune system as well. Despite these difficulties, numerous studies of this type have provided interesting clues and insights into how exposure to normal aseptic environments challenges the physiology of vertebrate hosts (Table 3). Concentrations of monokines such as IL-1 are greater in laboratory animals raised under unsanitary conditions even when clinical symptoms of infection are not present (Klasing et al. 1987, Klasing 1988, Roura et al. 1991). Similarly, IgG and IgA-secreting lymphocytes in immune organs are substantially increased (ca. 100-fold) in conventional husbandry conditions when compared to germ-free, antigen-free, or specific pathogen-free practices (Hooijkaas et al. 1984, Pereira et al. 1986, Bos et al. 1988, Bakker et al. 1995). Bacteria, especially the normal streptococci inhabitants of the gut, inoculated into germ-free chicks cause a 5–15% depression in growth, which can be ameliorated with antibiotics (Huhtanen and Pensack 1965, Fuller et al. 1979). Germ-free chicks fed diets adequate in energy have lower metabolisable energy intakes, greater rates of protein and energy retention, lower maintenance energy requirements, and ultimately greater rates of growth (5–30%) when compared to conventionally reared chicks (Table 3). Greater efficiency of converting metabolised energy and protein into production in germ-free chicks and maintenance energy requirements that are 20% greater in conventional chicks both contribute to observed differences in body growth (Furuse and Yokota 1984a, 1985).

The consequences of a germ-free existence appear to differ between rodents and poultry, as well as being strain-dependent (Table 4). Under optimum dietary conditions, the benefits derived from microbial populations in the gut can result in greater body size in conventional rats compared to those reared under germ-free conditions, but an opposite response develops when animals are raised with restrictions in dietary intake (Levenson 1978, Snyder and Wostmann 1987). Most studies have revealed that germ-free rodents have metabolic demands for energy that are 10–30% below levels required by conventional animals which appears to be linked somehow to caecal enlargement (Levenson et al. 1966, Sewell et al. 1975, Yamanaka et al. 1977). However, other studies have demonstrated no such relationship under ad libitum feed conditions (Wostmann et al. 1983).

Negative effects of gut bacteria on animal growth become most remarkable when diet quality is less than optimum (Levenson 1978, Furuse and Yokota 1984a, b). This suggests that maintenance of immunity in the gut has considerable priority over body growth when nutrients, especially protein, are limited in the diet. Such nutrient limitations probably come closer to reflecting the dietary conditions that exist in the habitat of natural vertebrate populations (White 1993). The magnitude of growth suppression in birds under nutritional stress can be dramatic as evidenced by a 78% greater rate of growth in germ-free chicks compared to conventional-reared chicks fed a low-protein diet (Furuse and Yokota 1984a).

Table 3. Metabolic and developmental characteristics of chickens reared in germ-free (GF) or conventional (CV) environments and fed nutritionally adequate or inadequate diets. Differences in body weight (BW) gain, food intake, metabolizable energy (ME), and nutrient retention rates between these two models were obtained from published literature.

Reference and experimental conditions	Parameter	Response measured
Furuse and Yokota (1985)	BW gain	27% > in GF
Chicks feed adequate protein diets	Food intake	similar
	Protein required for growth	23% > efficiency in GF
	Energy required for growth	27% > efficiency in GF
Furuse et al. (1985)	ME intake	CV > GF
Chicks fed adequate energy in diets	BW gain	7% > in GF
	Protein retention	7% > in GF
Furuse and Yokota (1984a)	ME retention	78% > in GF on low protein diets
Chicks fed dietes that differed in protein	Maintenance energy costs	20% > in CV
Furuse et al. (1991)	Protein retention	15% > in GF
Chicks fed complete diets with sorbose	ME retention	17% > in GF
	BW gain	31% > in GF
Fuller et al. (1979)		
GF chicks were innoculated with bacteria	BW gain	5–15% decline in gnotobiotic
Freeman et al. (1975)		
Chicks fed a complete basal diet	BW gain	17% > in GF
Huhtanen and Pensack (1965)	BW gain	CV gain was 62–68% of GF

Table 4. Metabolic and developmental characteristics of mammals reared in germ-free (GF) or conventional (CV) environments and fed nutritionally adequate or inadequate diets. Differences in body weight (BW) gain, maintenance energy (ME_m), efficiency of gain (BW/ME intake), and metabolizable energy (ME) intake and requirement between these two models were obtained from published literature.

Reference and experimental conditions	Parameter	Response measured
Snyder and Wostmann (1987)		
Wistar rats fed ad lib or 70% ad lib for 2 yr	BW growth (ad lib)	CV and GF similar
	BW growth (70%)	GF 12% > than CV rats at 2 yr
Eggum and Chwalibog (1983)		
Gut microflora reduced 90% in Wistar rats using antibiotic (GF_r)	BW gain and ME_m	No difference with control.
	Efficiency of gain	GF_r 19–22% > CV rats
Wostmann et al. (1983)		
Adult Wistar rats in a food balance trial	ME utilization	GF and CV rats similar
	Energy absorption	CV > GF rats
Yamanaka et al. (1977)		
ICR strain mouse in energy balance trials	ME requirement	44% more in CV mice
	ME intake	GF mice inoculated with *Staphylococcus* had > intake
Sewell et al. (1975)		
Wistar rats fed a complete diet	Metabolic rate	20–30% lower in GF rats
Levenson et al. (1966)		
Fischer rats compared by indirect calorimetry	Rectal temperature	Lower in GF rats
	Metabolic rate	15–20% lower in GF rats

Livestock and chickens fed selected antibiotics in their feed, especially those residing in unsanitary environments, often show improved growth performance, feed efficiency, and reduced oxygen consumption (Coates et al. 1952, Lev and Forbes 1959, Huhtanen and Pensack 1965, Freeman et al. 1975, Yen et al. 1985). Germ-free chickens do not respond to orally administered antibiotics, while conventional-reared birds can demonstrate a remarkable increase in body mass gain (Freeman et al. 1975). Autoimmune disorders are also capable of impairing growth performance in animals for many of the same reasons (Halliday 1980). Livestock producers have long noted the benefits to body mass gain that can be realised if animals are reared in an environment where microbial challenges are minimised through the use of disinfectants, even when clinical diseases or pathologies do not exist (Klasing and Barnes 1988). Klasing and Barnes (1988) have referred to this continual activation of the immune system as "chronic immunologic stress". Although the exact mechanisms responsible for the observed antibiotic-induced improvements in growth performance are speculative and have included alterations in microbial metabolism and urease production, it has also been proposed that antibiotic-induced reductions in antigenic challenges allows protein and energy destined for immune surveillance and response (prevention of the catabolic action of immune cytokines) to be reallocated into host production (Roura et al. 1991). It has been suggested that selection for greater body size in poultry may have been achieved in part through trade-offs with the immune system, as heavier breeds respond less to some immune challenges (Cook et al. 1993).

The pathophysiological consequences of infectious disease and parasitism in a vertebrate host can be readily seen with a quick examination of the literature. Several excellent reviews of the subject can be found as it pertains to human health and livestock production (Cooper et al. 1992, Fox 1997). These studies reveal that one of the most widely reported effects of disease (to include parasitism) is suppressed growth, which can lead to reductions in reproductive fitness (Goossens et al. 1997). Catabolic wastage via activation of the acute phase immune response, malabsorption and digestive problems, and nutrient competition with gastrointestinal parasites interact to create a growth-suppressing environment in the host (Elsasser et al. 1988, Nesheim 1993, Solomons 1993). Parasite control in cattle, especially those harbouring substantial loads of parasites, can lead to vast improvements in feed efficiency, weight gain, immunity, carcass quality, reproductive performance, and survival (Hawkins 1993). Similar observations have been made in children from impoverished areas when they are provided antihelminthic treatments (Stephenson 1994).

It is apparent that immune system challenges do not have to be remarkable to alter nutrient dynamics in the host because even rather mild immune reactions like those associated with vaccination can suppress feed intake and development. Pigs vaccinated against porcine respiratory and reproductive syndrome or endotoxin showed a 15% decline in feed intake and 21% decline in daily weight gain during the challenge period (Spurlock et al. 1997). Similarly, lambs vaccinated with irradiated nematode larvae demonstrate a negative correlation between antibody titre and body weight gain

(Wagland et al. 1984). However, not all immune challenges of this type elicit hypermetabolic responses that lead to suppressed growth. Henken and Brandsma (1982) observed essentially no change in maintenance energy requirements or growth in extremely young poultry challenged with an injection of sheep red blood cells (SRBC). It is possible that more developed birds may respond more classically to such a challenge as indicated by Klasing et al. (1987) who observed about a 10% growth suppression in SRBC challenged chicks 3 weeks of age.

The degree to which immunological challenges elicits reductions in fitness among wild vertebrates has not been adequately explored, but the wealth of literature for livestock strongly suggests that such costs could be substantial. We would like to draw attention to the general observation that fitness returns as a function of a physical or physiological factor, such as growth rate or energy expenditure, are rarely linear. Therefore, reported changes in such factors as a result of variable investment in the immune system may over- or underestimate the fitness costs, depending on the shape of the fitness curve. The above observations are extremely relevant to life-history theory where species differ considerably in the pathogenicity of their environments. For example, species with more colonial than solitary social systems may be expected to have evolved mechanisms for devoting more nutrients to immune surveillance and response given the greater likelihood for disease transmission. Such species may benefit greatly from natural reductions in the pathogenicity of their environment or improvements in their nutritional status. Relative growth and reproductive performance would be predicted to be greater in populations residing in less pathogenic environments, as suggested from the livestock literature. Interestingly, rodents raised in germ-free environments outlive their conventionally raised counterparts in the laboratory (Wostmann et al. 1983).

Conclusions

It is apparent from the above review of the literature that substantial nutritional and energetic costs are associated with immunological stress and maintenance of the system. Host protein metabolism during infection and the nitrogen-limited environments in which they reside may be the most important determinants driving life-history trade-offs among growth, reproduction, and host immunocompetence (Beisel 1977, Lochmiller and Dabbert 1993). Although no single quantitative estimate can be provided for these costs that would be relevant for all vertebrates, it is probably justified to hypothesise that these costs are comparable in magnitude to those for reproduction and growth. We would further predict that life history is as much a reflection of an organism's pathogenic environment as it is any other facet that may be driving complex evolutionary changes within a species, as suggested by Piersma (1997). Consequently, the physiological trade-offs that are necessary in a nutrient-limiting environment involve the seasonal balancing of reproductive, developmental, and immunological costs as dictated by seasonal environmental constraints. Such life-history trade-offs between fitness components are undoubtedly stochastic across seasons as suggested by Nelson and Demas (1996), who offered the "winter immunoenhancement hypothesis" to explain observed declines in reproductive activity and increased immune function in small mammals during stressful winter conditions (Lochmiller and Dabbert 1993, Lochmiller et al. 1994). Given the suggestions of Piersma (1997), one must wonder how much of the geographic variation in life-history attributes such as body size, rates of growth, and reproductive traits (Cameron and McClure 1988, Ims 1997) is attributable to trade-offs with immune function.

It is apparent that we advocate a viewpoint remarkably different from that of Klasing (1998) who suggested that costs of having and maintaining an immune

Table 5. Selected examples of studies examining the responses of avian and mammalian models to the growth-promoting influences of antibiotics that were supplemented in the diet of young growing animals. Percent change reflect comparisons of supplemented animals to a control group and studies reflect considerable variation in types of antibiotics, doses, and exposure duration.

Species	Measurement	Change	Reference
Chicken	Weight gain	+10–34%	Feighner and Dashkevicz (1987)
	Weight gain	+23%	Stutz et al. (1983)
	Efficiency of gain	+10–12%	Begin (1971)
Guinea fowl	Weight gain (12 weeks)	+11–14%	Oguntona (1988)
	Nitrogen retention	+26%	Oguntona (1988)
Swine	Weight gain	+5–9%	Foster et al. (1987)
	Weight gain	0%	Brumm et al. (1989)
	Weight gain	5%	Schrijver et al. (1990)
	Efficiency of gain	10%	Schrijver et al. (1990)

system are minimal to a host. While in terms of absolute mass the immune system appears to be a minor contributor to body mass, such a comparison fails to incorporate the plethora of costs associated with indirect effects of acute-phase responses, anorexia, cellular metabolic rates, and cellular-molecular turnover. To provide an example with another organ system, the gut tissues comprise about 3.7% of body mass in a non-lactating cow, yet because of its high rate of metabolic activity, the liver and gut collectively produce 40% of total heat production in a resting animal (Parker 1990). It may be more appropriate to look at the immune system using an analogy of the female reproductive system where the costs of maintenance are minor compared to the costs of actually using it. Given the antigenicity of environments, having a functional immune system may invariably mean using it upon challenge (''chronic immunologic stress''). If this is true, the benefits to the host of a reduced investment in maintenance of the immune system do not come from the actual economisation of nutrients required to maintain the system, but from avoiding the more costly up-regulation that results from immune challenges. Evolutionary theory predicts that the risks and costs of becoming infected are to be balanced against these benefits. Even if the risk of infection is low, the cost (for example death) may be such that it does not offset the benefits of avoiding the complex and nutritionally costly chain of events invoked by an immune challenge or infection. Similarly, the cost of up-regulation of the system during a response, whether to a benign or potentially deadly infection, may push the animal beyond the minimal levels of bodily reserves to survive. In the first example, the costs of failing to respond (death) is much higher than the nutritional costs of a functional immune response. This in contrast to the second example, where the immune response itself is deadly, independent of whether the pathogen evoking it is lethal or controllable. Thus, the optimal evolutionary strategy concerning the maintenance or down-regulation of the immune system will depend on the pathogenicity of the current environment of the animal, as well as on its body condition and the costs and success of mounting an immune response.

Unravelling the mysteries of life-history evolution can clearly benefit from further studies in the realm of ecological immunology (Sheldon and Verhulst 1996). The primary assumption that immunological defences are costly to the host appear well justified for providing the basis of myriad hypotheses that have been formulated to explain observed patterns in mate selection (Hamilton and Zuk 1982), reproductive strategies (Møller and Erritzøe 1996, Klein and Nelson 1998), sex-specific and seasonal survival rates (Nelson and Demas 1996), habitat use (Piersma 1997), and population regulation (Lochmiller 1996) among vertebrates. Thus, it is becoming increasingly clear that in addition to growth and reproduction being inherently related life-history traits in vertebrates (Roff 1992), these traits are also inherently related to immunity (hence survival). Understanding of the significance of life history attributes will benefit from further research into ecological immunology.

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