THE ENERGY COST OF ILLNESS IN SWINE

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Summary
Dirty, less hygienic environments increase the level of immunological stress and depress growth and performance of pigs. In response to challenge by bacterial or viral pathogens, the pig's immune system responds by secreting cytokines. These molecules which promote inflammation were originally described for their ability to orchestrate the immune response against the infectious pathogen. It is now recognized that cytokines also act on other targets outside of the immune system. The cytokines released by activated macrophages have been found to alter the metabolism of carbohydrate, fat and protein substrates, regulate certain endocrine secretions, and reduce food intake. In short, many findings converge to suggest that a major component of the growth inhibition observed in immunologically challenged pigs is mediated by pro-inflammatory cytokines. The goal of this short paper is to provide an integrated view of how immunological stress through the secretion of cytokines depresses growth in pigs.

Introduction
Disease and growth have long been two of the most important issues in pig research. Although animal scientists and husbandmen alike have long recognized that sick pigs fail to eat and therefore grow, only recently have they begun to understand the relationship between growth and disease. Disruption of a pig's internal milieu by infection or injury threaten its integrity and require immunological, behavioral and physiological responses so that a relative homeostatic state may be achieved. These responses may be subtle, as is probably the case for pigs with a subclinical, chronic, low-grade infection. Other instances, however, require a more extensive response. In any case, there is a reduction in food intake and a deliberate shift in the partitioning of dietary nutrients away from lean muscle accretion towards metabolic responses that support the immune system. It makes sense that the pig would readily sacrifice growth in order to contend against pathogens that may otherwise lead to disease and perhaps death. This complex which is commonly referred to as immunological stress (Klasing and Johnstone, 1991), also accelerates breakdown of muscle protein. Thus, the shift in the balance between anabolic and catabolic processes forms the basis for impaired growth and feed utilization in pigs subjected to infectious and noninfectious agents.

Immunological Stress Re-Partitions Nutrients
Dirty, less hygienic environments increase the level of immunological stress and depress growth and performance. The concept that immunological stress diverts nutrients from productive processes (e.g., lean tissue accretion and lactation) is not new. More than 20 years ago Bruce Young devised a graphic scheme depicting the partitioning of dietary energy (Figure 1; see Curtis, 1983). It shows that as the energy required to maintain body integrity and combat stress increases, the energy available for production decreases. What is important in the area of immunological stress and growth is the newly acquired appreciation for how the pig's immune system communicates with other physiological systems to orchestrate this shift in priorities.
The old idea was that the reduction in feed intake, growth and efficiency seen in immunologically challenged pigs were caused directly by infectious pathogens which disabled or impaired cellular function. Although still valid to some extent, we have proposed that an immunological mechanism is at least partially responsible for this phenomenon (Kelley et al., 1994). To fully appreciate why or how the immune system regulates growth, one must first understand how cells of the immune system behave when challenged by a pathogen. As shown in Figure 2, when exposed to lipopolysaccharide (LPS) which is a molecule found on the surface of gram-negative bacteria (e.g., *Escherichia coli*), the macrophage responds by secreting at least three cytokines; interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Figure 2). These cytokines up-regulate the immune response (Figure 2) so that the host can better contend against the invading pathogen. Interestingly, these pro-inflammatory molecules also act "outside" the immune system. In essence they are important messengers used by the immune system to inform the rest of the body of an ongoing challenge. This cytokine signal from the immune system re-organizes the animal's priorities, and metabolic changes that serve the immune system at the expense of growth ensue. An example of how this re-organization might influence protein metabolism is described below.

**How Does the Immune System Antagonize Growth?**

Cytokines inhibit growth in many ways and some of these are summarized in Figure 3. It should be noted that the current understanding of the metabolic effects of cytokines is largely based on studies conducted in small rodent animals. However, several recent studies in pigs indicate similarities between species and therefore suggest that many of the well-described effects of cytokines in rodents can be extended to pigs. With this precautionary note in mind, upon examination of the effects of pro-inflammatory cytokines on protein metabolism, it is easy to appreciate the broad implications of immunological stress for pig growth.

First, it is evident that a pig experiencing a "high level" of immunological stress has a lower motivation for food and eats less than a pig experiencing a lower level of immune stimulation. This is evidenced by the numerous studies showing that pigs kept under all-in, all-out management eat more, grow faster and are more efficient at converting feed to gain compared to pigs kept under continuous flow management. Of course, the efficacy of all in, all out management to improve growth performance of pigs is attributed to the ability to appropriately disinfect the environment between groups of pigs. In doing so, immunological stress is reduced. It is important to note that the pro-inflammatory cytokines are well known for their ability to reduce appetite and alter the utilization of protein, fat and carbohydrate substrates.

Second, during the inflammatory response there is an increase in synthesis by the liver of acute phase proteins. Synthesis of some acute phase proteins may increase several 100-fold. It has been estimated in humans that during an inflammatory response the acute phase proteins increase in concentration by about 850 mg protein/kg body weight (Reeds et al., 1994). The synthesis of acute phase proteins is an important component of the inflammatory response since some proteins both activate complement to lyse bacteria and opsonize bacteria to help the immune system clear it. Nonetheless, this increased demand for hepatic protein synthesis can impose a substantial "tax" on growth. For instance, if the pig is consuming less protein (i.e., its appetite is reduced) but must increase hepatic synthesis of acute phase proteins, from where are the amino acids which fuel this process derived? Of the amino acids used in protein synthesis, at least 60% are derived from body protein degradation. And because skeletal muscle protein represents the largest available pool of
amino acids, it seems reasonable to postulate that this is the principal source. Indeed, by comparing the amino acid composition of the acute phase proteins to that of skeletal muscle protein, Reeds et al. (1994) estimated that to provide enough phenylalanine (the limiting amino acid for acute phase protein synthesis) to synthesize 850 mg of acute phase protein, 1980 mg of skeletal muscle protein would have to be degraded. Because many of the other amino acids liberated by degradation of skeletal muscle are in excess, they are excreted. Again, it is important to note that the pro-inflammatory cytokines not only stimulate hepatic acute phase protein synthesis, but also induce degradation of skeletal muscle protein. Thus, the cytokines are part of a network which seems to inherently link muscle protein synthesis/degradation with hepatic acute phase protein synthesis.

From a practical standpoint this may explain why in a recent study conducted by Tim Stahly's group at Iowa State University, pigs kept under a management scheme that presumably provided fewer immunological challenges (e.g., Medicated Early Weaning) consumed more feed, grew faster, and retained more nitrogen for proteinous tissue growth (Williams et al., 1993). In this study, pigs maintained in an environment that presumably imposed a high degree of immunological stimulation, also had high plasma levels of the acute phase protein, α₁-acid glycoprotein. From this and other studies it is simple to see why the emerging view is that sickness in pigs, manifesting as reduced feed intake and lowered lean muscle growth, is the result of increased biosynthesis of certain cytokines. However, the evidence for such a connection is only now emerging.

To more directly address this issue, in a recent study we injected pigs with lipopolysaccharide to induce immunological stress so that the relationship between plasma cytokines and protein and lipid metabolism could be evaluated (Webel et al., in press). Some of the results of this study are summarized in Figure 4. It is interesting to note that only after the marked increase in TNF-α, IL-6 and cortisol (a catabolic hormone released in response to stress), was there an increase in plasma urea nitrogen. Because the pigs were fasted beginning 12 hours prior to injection, it seems reasonable to postulate that the 3-fold increase in plasma urea nitrogen was the end result of muscle protein degradation. Thus, these results corroborate the idea that secretion of pro-inflammatory cytokines increases muscle protein degradation. Whether these same concepts can be used to explain the chronic depression in feed intake and growth in seemingly healthy pigs is an important question.

Implications
The best strategy for inhibiting the costly effects of increased cytokine activity is obvious: reduce disease and immunological stress. Maintaining a clean hygienic environment and incorporating "growth-promoting" levels of antibiotics into the diet are common practices which help control this complex. Unfortunately, even pigs reared under the best management experience some degree of immunological stress which prevents them from growing at their true genetic potential. Because this depression in growth and efficiency is probably mediated by cytokines, understanding how these products of the immune system alter metabolic processes is important. This type of information is critically needed to design diets and management schemes which improve growth and performance of pigs experiencing farm-level immunological stress.

References


