FRI BRIEFINGS

Alternatives to Antibiotic Use for Growth Promotion in Animal Husbandry

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INTRODUCTION

Since the discovery and development of the first antibiotics prior to the Second World War, these drugs have played an important role in curing disease in humans and animals. In 1946 experiments showed that low, subtherapeutic levels of antibiotics could increase feed efficiency and growth in food animals, and the addition of various antibiotics to feed for livestock was initiated. Because prevention of disease transmission and enhancement of growth and feed efficiency are critical in modern animal husbandry, there has been widespread incorporation of antibiotics into animal feeds in many countries (*74, 144*).

Swine feeds in the U.S. often contain antibiotics for purposes of disease prevention and growth promotion. According to data from USDA and Animal Health Institute, antibiotics are currently used in 90% of starter, 75% of grower and more than 50% of finisher feeds for pigs (*34, 37, 38, 55, 173*). Antibiotics have also been widely used in animal feed in many other countries although a number of individual countries and the European Union have recently restricted the subtherapeutic use of some antibiotics (*3, 138, 147, 156, 166*).

Precise figures on the relative amounts of antibiotics used in humans and in animal agriculture are impossible to obtain. Various estimates have been calculated by the Institute of Medicine (*34, 74, 174*), the Animal Health Institute, a trade organization (*172*), and the Union of Concerned Scientists (*174*). Human use of antibiotics has been estimated at 1.36–14.64 million kg/yr while estimated antibiotic use in animal agriculture is 7.36–11.18 million kg/yr. Although estimates from different sources are not directly comparable, it is clear that there is significant use of antimicrobial agents both in human medicine and in agriculture. Currently, the potential for agricultural antibiotics to contribute to the development of antibiotic-resistant bacteria of human concern is the subject of intense debate and research (*3, 74, 163, 166*).

DEVELOPMENT OF ANTIBIOTIC RESISTANCE

Bacteria are very adaptable organisms because of their very short generation time (as little as 15 to 20 minutes for some species under ideal conditions) and their propensity for sharing genetic information—

even among different species of bacteria. The presence of an antibiotic may kill most of the bacteria in an environment but the resistant survivors can eventually re-establish themselves and pass their resistance genes on to their offspring and, often, to other species of bacteria. Both medical and veterinary uses of antibiotics have resulted in the appearance of resistant strains of bacteria. Resistant bacteria which are human pathogens may cause diseases that are difficult to treat; even if the resistant bacteria are not human pathogens, they may still be dangerous because they can transfer their antibiotic resistance genes to other bacteria that are pathogenic (*18, 74, 144, 163, 166*).

Antibiotic-resistant strains of bacteria, including *Salmonella* spp., *E. coli*, and *Campylobacter* spp., have been isolated from farm animals in many countries (*1–6, 14–16, 19, 21, 36, 63, 85, 87, 89, 90, 100, 128, 131, 151, 155, 158, 168*). Fluoroquinoline-resistant *C. jejuni* have recently been detected in chicken following the introduction of fluoroquinolines into feed for chickens (*135, 137*). A draft risk assessment of the threat this may pose to human consumers of chicken has been prepared by the FDA's Center for Veterinary Medicine (*150*).

GROWTH-PROMOTING EFFECTS OF ANTIBIOTICS

Feeding swine with subtherapeutic levels of antibiotics has been documented to increase weight gain by 3.3–8.8% and improve feed efficiency by 2.5–7.0%. The exact mechanisms by which this occurs are not completely understood. Since feed antibiotics provide a relatively greater improvement in farms with poor hygiene, their effectiveness is at least partially due to suppression of some pathogenic bacteria in livestock. Subtherapeutic antibiotics have been shown to reduce the incidence or severity of swine dysentery, porcine intestinal adenomatosis, porcine hemorrhagic enteropathy, and *Clostridium perfringens* infections. Some scientists believe that these effects on pathogens are the primary or only relevant effect of the antibiotics affecting growth promotion (*34, 35, 56, 138, 147, 148*).

Other researchers believe that the antibiotics alter the normal, non-pathogenic flora of the gut and these changes have a beneficial effect on digestive processes and the utilization of nutrients in feed. It has been estimated that as much as 6% of the energy in a pig's diet may be lost due to microbial fermentation in the stomach and small intestine. Antibiotics added to feed alter activities of microbial populations and may thereby prevent some of this loss to microbial fermentation. Intestinal bacteria also inactivate pancreatic digestive enzymes and metabolize dietary protein with the production of ammonia and biogenic amines, such as cadaverine. Antibiotics inhibit these activities and increase the digestibility of dietary protein. Antibiotics also appear to prevent irritation of the intestinal lining and may enhance uptake of nutrients from the intestine by thinning of the mucosal layer (*10, 35, 138, 148*).

Experiments with a growth promotant containing chlortetracycline, penicillin, and sulfamethazine have shown that treated pigs have higher serum levels of insulin-like growth factor I (*53, 54*). Thus the effects of subtherapeutic antibiotics may extend beyond digestion in the intestine and stimulate metabolic processes throughout the animal.

In addition to positive effects on growth and efficiency, there are reductions in excretion of nitrogen, phosphorus, and manure by antibiotic-treated pigs (*124, 138*). These effects are most probably consequences of the more efficient utilization of feed. When waste disposal from swine operations is considered, these reductions will have a positive economic impact.

Two groups (*55, 160*) have reviewed the potential economic consequences of a ban on the use of subtherapeutic antibiotics in swine production in the U.S. The more recent review estimates that production costs would increase by $5.00–$6.00 per head and this would increase the retail cost of a pound of pork by $0.05 (*55*). However, costs would vary greatly among different swine producers depending on the size and types of facilities and current husbandry practices. Following Sweden's ban on the use of antibiotics as growth promoters, total use of antibacterial drugs in animals has decreased so that by 1998 the total animal usage of antibiotics was only 38% of that used in 1984 (prior to the ban) (*13, 24, 156*). In the first years following the ban there was an increase in postweaning piglet disease and mortality and an increase in antibiotics prescribed to treat disease. However, as producers improved hygiene, sanitary and other husbandry practices, incidence of disease decreased and antibiotic use declined steadily.

In evaluating the possible alternatives to subtherapeutic use of antibiotics, one must consider not only their relative short- and long-term costs but also their ability to produce the same positive effects as the antibiotics. It may well be necessary to adopt changes in the management of livestock and also introduce different feed components in order to compensate for the antibiotics' effects and maximize production. Genetic improvements in animals and vaccinations to prevent establishment of harmful bacteria may also be useful. Therefore, some of the alternatives described below may be part of the solution for decreasing or eliminating antibiotic use in animal agriculture even though they do not mimic all the beneficial effects of antibiotics. One should also always be alert to the possibility that some of these alternatives may also have unintended negative effects that are not immediately apparent.

ALTERNATIVE FEED INGREDIENTS

The three primary effects of the antibiotic growth promoters are:

- increased growth,
- improved feed efficiency, and
- a lower incidence of certain diseases

To be effective, alternative additives for swine feed should generate similar benefits as the antibiotics which are currently used as growth promoters in pig rearing operations.

However, alternative feed additives or supplements may have different mechanisms of action and other positive or negative effects which must be considered. It may be necessary to combine two or more alternative feed ingredients or to combine a new feed supplement with a change in husbandry practices to achieve the best effects. For the most part, the scientific references gathered do not compare relative costs of implementing various changes but rather report data on the efficacy of these supplements as regards pig health and growth. An excellent review of many alternative feed ingredients is presented by Thomke et al. (*149*).

Probiotics and competitive exclusion

Probiotics are live cultures of microbes—often lactic acid bacteria but also some other species—which are fed to animals to improve health and growth by altering intestinal microbial balance. Some authors also consider extracts of these cultures, for example isolated yeast cell walls, to be probiotics even though they do not contain living cells. Some bacterial cultures are used specifically for competitive exclusion (CE): They are fed in one or a few doses to newborn or newly hatched animals in order to quickly establish an intestinal flora that will prevent colonization by pathogenic bacteria. Competitive exclusion preparations are not always pure cultures of bacteria, and their microbial composition may not be completely known. Some CE cultures have proven effective in protecting chicks from *Salmonella* infections.

Results from some experimental trials with probiotics, initiated 20 to 30 years ago, were inconsistent due to variations in bacterial cultures used, age of pigs treated and other factors related to feed composition and husbandry practices. Recently interest in the use of probiotics to improve the growth and health of livestock has been rekindled by current proposals to curtail sub-therapeutic doses of antibiotics in animal feed. Experiments with new probiotic cultures under more controlled conditions have demonstrated beneficial effects of probiotics fed to piglets in many, but not all, cases. Probiotics, like antibiotics, appear to have a more pronounced effect on farms where housing and hygiene are not optimal (*95, 149*).

Piglets are born "germ-free" but immediately begin acquiring intestinal microbes, with bacteria such as *Lactobacillus, Bifidobacteria*, and *Bacteroides* often comprising up to 90% of the normal flora. After weaning, there is a large drop in the population of lactic acid bacteria and an increase in coliform bacteria. *Escherichia coli* is the bacterium responsible for most of the diarrhea in newly weaned piglets, and its increase is most likely related to the decrease in lactic acid bacteria. In addition, piglets acquire other bacteria that are opportunistic pathogens, i.e. bacteria which may exist unobtrusively in small numbers and only multiply to cause illness when piglets are stressed by other infections or conditions (*95*).

Probiotic microorganisms added to feed may protect piglets from intestinal pathogens by several possible mechanisms, sometimes referred to as competitive exclusion:

- adherence to intestinal mucosa thereby preventing attachment of pathogens
- production of antimicrobial compounds such as bacteriocins and organic acids
- competition with pathogens for nutrients
- stimulation of intestinal immune responses

In addition, probiotics may affect the permeability of the gut and increase uptake of nutrients (*79, 95, 127, 141, 142, 165*).

Recent research reports that have demonstrated positive effects of probiotics for pigs include the following:

- *Lactobacillus* and *Bifidobacteria* increased weight gain and reduced mortality in young piglets (*7*).
- *Lactobacillus casei* improved growth of piglets and decreased diarrhea and appeared to be more effective than subtherapeutic antibiotics (*32*).
- *Lactobacillus casei* fed to gnotobiotic (germ-free) piglets adhered well to the intestinal mucosa and produced lactic acid, lowering the pH. These piglets consumed more milk and gained more weight than germ-free piglets (*26, 99*).
- Enteracide, a probiotic containing *Lactobacillus acidophilus* and *Streptococcus faecium*, added to feed for weaned piglets stimulated growth and activity of the digestive system (*152*).
- Addition of *Streptococcus faecium* to piglet diets increased weight gain and feed efficiency (*76*).
- Mixtures of *Lactobacillus* spp. and *Streptococcus* spp. increased growth and some measures of immune function in piglets (*154*).
- Digested bacterial cell powder from *Brevibacterium lactofermentum* decreased incidence and severity of diarrhea in piglets (*97, 153*).
- Piglets fed *Bacillus coagulans* had lower mortality and improved weight gain and feed conversion than unsupplemented piglets and did as well as or better than piglets fed subtherapeutic antibiotics (*8*).
- CenBiot, a probiotic containing *Bacillus cereus*, improved weight gain and feed conversion in young weaned piglets and also decreased the incidence of diarrhea as well as the addition of subtherapeutic antibiotics (*169*).
- *Bacillus licheniformis* improved weight gain and feed conversion and reduced diarrhea and mortality in piglets (*77*).
- The probiotic Biomate 2B Plus (*B. licheniformis* and *B. subtilis*) increased feed efficiency and growth of piglets more than an antibiotic (*28*).
- Piglets fed the probiotic *Bacillus toyoi* or a mixture of *Saccharomyces cerevisiae, Lactobacillus acidophilus,* and *Streptococcus faecium* had a significantly greater weight gain as compared to those given antibiotics in feed (*159*).
- *Saccharomyces boulardii* and *B. cereus* var. *toyoi* were found to enhance nutrient transport in pig jejunum (*29*).
- Piglets fed a yeast additive (*Saccharomyces cerevisiae*) tended to consume more feed and gain more weight. In some cases, results for treated piglets were significantly better (*22, 123*); in other experiments, the improved results were not significant (*88*).
- *Enterococcus faecium* 18C23 was found to inhibit the adhesion of enterotoxigenic *E. coli* to the small intestinal mucus of piglets (*69*).
- A mucosal competitive exclusion culture (originating in healthy pigs) and fed to piglets within a day of birth significantly reduced numbers of *Salmonella choleraesuis* (*10, 44*) and *E. coli* (*50*) detected in gut tissues and feces after challenge doses of these pathogens.
- Several other brief reports of positive results from the use of probiotic cultures in pigs have been published (*97*).

Other researchers reported that feeding probiotics did not improve performance or decrease incidence of diarrhea:

- piglets given *Enterococcus faecium* (*46*)
- older pigs given a mixture of *Saccharomyces cerevisiae, Lactobacillus acidophilus,* and *Streptococcus faecium* (*118*)
- piglets given Sanobiotic RS (*70*)
- piglets given a yeast-fermented cereal mixture (*72*)

Enzymes

Pigs have a variety of gastrointestinal enzymes to aid in digestion of feed. However, newly weaned piglets may produce inadequate amounts of certain enzymes and even adult pigs cannot digest some plant materials containing complex carbohydrates, such as cellulose, xylans, and β-glucans (*111*). Therefore, the addition of enzymes to feed may be a useful strategy to increase its digestibility. Dietary enzymes may supplement the pig's own digestive enzyme activity or enable the pig to utilize the energy in complex carbohydrates which normally pass unchanged through the gastrointestinal tract. The enzyme phytase can decrease the antinutritional effects of phytate which binds 50–75% of the phosphorus in vegetable matter. Without this enzyme, pig feed must be supplemented with phosphates because pigs can use only 20–40% of the phosphorus in plant foods. The remaining phosphorus in the vegetable matter is eliminated with the fecal material. Phytate also appears to interfere with the digestion and absorption of other minerals such as calcium (*111, 165*). Recent reviews of the currently available enzymes used as feed supplements and prospects for further developments in this area have been published by Bedford and Schulze (*20*) and Thomke and Elwinger (*149*).

Some data indicate that addition of carbohydrate-degrading enzymes (amylase, glucanase, glucoamylase) to a barley-based diet improved feed conversion (but not average growth) and reduced incidence of diarrhea in pre- and newly weaned pigs (*66*). Other experiments demonstrated no growth advantage for inclusion of enzymes to degrade starch, fiber, proteins or fats in a wheat-based diet for weaner pigs (*107*). The efficacy of enzyme additives appears to depend on several factors including the age at weaning, other components of the diet, and the source of the enzymes. Carbohydrate-degrading enzymes, isolated from different bacteria and molds, usually differ somewhat in their activity against specific compounds.

Nutrient utilization and performance of growing pigs fed hulless barley was improved by a mixture of enzymes (cellulase, xylanase, 1,3:1,4 glucanase, amylase and pectinase) extracted from *Trichoderma viride*. Average daily growth and feed conversion were improved by 8.6 and 8.7%, respectively (*17*). Another experiment reported that an antibiotic, avilamycin, and an enzyme, xylanase, increased digestibility of organic matter, protein, fiber, and fat to the same extent in growing pigs fed a diet containing barley, wheat, soy, and wheat bran. Growth rate was slightly increased in both groups fed one additive and was increased significantly in a group fed both enzyme and antibiotic (*120*).

Another issue to consider in feeding enzymes to pigs is whether the enzymes can survive passage through the acidic stomach and then act to digest feed components in the small intestine. Pentosanase, which is inactive under acidic conditions, was found to survive passage through the stomach and aided digestion of rye–soybean dietary material in small intestine (*145*).

Phytase was found to increase weight gain and, in some cases, decrease feed conversion ratios in pigs fed different diets: a barley–maize diet (*48, 58*), a corn–soybean diet (*75, 122, 140, 171*), a low phosphate pearl millet–soy diet (*98*), a pea–barley–wheat–soy diet (*103*), and sorghum–soybean meal diet (*104*). Experiments with cannulated pigs, with a tube inserted for sampling intestinal contents, demonstrated that phytase tripled the pre-cecal breakdown of phytate but much of the liberated phosphate was absorbed by intestinal bacteria. Later this phosphate was absorbed into the pig from the cecum/colon (*132, 133*). Apparent ileal digestibility of crude protein and amino acids was also improved by the addition of phytase to a corn–soy diet (*73*). This may be the result of disruption of phytate–protein complexes.

Phytase enzymes from several sources have been tested and some are more heat-resistant than others and so may be better suited for incorporation into diets which are to be treated with steam (*65, 102, 140*). In addition, phytase activity is affected by the calcium:phosphate ratio in the diet, with higher ratios associated with lower enzyme activity and decreased growth rate (*117, 119*).

Experiments comparing the effects of phytase and supplementary inorganic phosphate indicated that 500 U phytase/kg feed was approximately equivalent to 0.87–0.96 g of inorganic phosphate/kg in improving daily weight gain and phosphate digestibility in growing pigs weighing 18.6 kg

(*52*). In younger pigs (7.8 kg weight), 246 U microbial phytase/kg was functionally equivalent to 1 g inorganic P/kg feed (*75*).

The use of phytase also decreases the amount of phosphate in swine manure by as much as 30% (*52*). High levels of phosphorus are detrimental to lakes and rivers and so a number of European countries have regulations restricting the disposal of manure based on its phosphorus content. In the Netherlands, France, and Denmark, the overall average excretion of phosphorus/pig is 1.0, 1.34, and 1.23 kg. These numbers reflect the widespread use of phytase in feed for Dutch pigs and lower levels of phytase used in other countries (*115, 116*). Although this issue of excretion of phosphorus is not directly related to growth-promoting effects of phytase, economic considerations related to waste disposal may affect the overall cost/benefit evaluation of whether or not to use phytase as a substitute (or partial substitute) for antibiotics in feed.

Immune modulators

Immunologically active compounds affect the working of the immune system and may enhance resistance to disease. These substances include antibodies, cytokines, spray-dried plasma, and other compounds. Some or all of the growth-promoting effects of subtherapeutic antibiotics in feeds may result from their action against sub-clinical infections or competitive intestinal bacteria. Therefore, it has been suggested that addition of antibodies or other immunoactive compounds to feed may accomplish the same purpose. Vaccines may be important in preventing some diseases which may arise when antibiotics are withdrawn. The importance of developing new vaccines and potential benefits of vaccinating sows which would then provide antibodies to piglets in colostrum were discussed in a recent review (*60*). But vaccines may not replace antibiotics as growth promoters because they specifically target pathogens while antibiotics affect general bacterial populations in the gut.

Piglets get protective antibodies from their mothers through colostrum but these last only about a month. Since young pigs do not produce sufficient quantities of their own antibodies until they are about 4 months of age, there is a period of several months when young piglets are particularly susceptible to diseases such as scours (*93*). Antibodies against pig disease organisms have been produced by immunizing hens which secrete antibodies against swine pathogens into egg yolks. These antibodies inhibit the attachment of pathogenic bacteria to the intestine (*97*). Freeze-dried eggs or egg yolks containing antibodies to calf diseases have been used successfully in calf milk replacers and reduced the need for subtherapeutic antibiotics (*111*).

Freeze-dried eggs containing antibodies against porcine rotavirus and some strains of *E. coli* are also available. Lyophilized egg yolks with antibodies to porcine enterotoxic *E. coli* cured 92% of sick piglets when added to one batch of feed. Protimax (hyperimmunized spray dried egg protein) dramatically reduced mortality due to diarrhea and improved weight gain and feed conversion (*93*).

Spray-dried porcine plasma proteins (which contain immunoactive proteins) also reduce mortality and diarrhea and improve growth in piglets. As with antibiotic additives, better results were obtained under more stressful and less hygienic conditions. In experiments with newly weaned piglets, the addition of spray-dried porcine plasma proteins to a corn–soy diet resulted in faster growth than the addition of antibiotics (*31, 33*). However, the feed conversion ratio was better in the group fed the antibiotics. One problem with spray-dried plasma is that it may contain antibodies specific to bacterial strains present on one farm but which are different from those on other farms. On large farms in Latvia, it was noted spray-dried plasma from one farm reduced piglet mortality by 20% on the same farm but was ineffective at another farm (*101*).

More than 12 antimicrobial peptides have been detected in pigs. Most of these compounds kill bacteria by disrupting cell membranes, and it is believed that bacteria may be slower to develop resistance to these compounds. A recent comprehensive review of porcine antimicrobial peptides was presented by Zhang (*170*). These antimicrobial agents in pig husbandry could be added directly to diets, or it may be possible to genetically engineer pigs to produce greater amounts of these compounds. It may also be possible to transfer the genes responsible for synthesis of these peptides into some microbe which could produce large quantities of these antimicrobial compounds at a lower cost.

Experiments with chickens have shown that some cytokines (which are normal regulators of the immune response) can act as growth promoters perhaps by stimulating the immune system to ward off pathogens. As such, it has been proposed that these compounds may be a substitute for sub-therapeutic antibiotics in feed. Avian cytokine genes have been cloned and can be delivered to chickens in a viral vector. With more research, porcine cytokines may also become available for use as growth promoters (*86*).

Conjugated linoleic acid has also been shown to affect immune function in laboratory animals by increasing production of T-cells and interleukin-2 (*67*).

Organic acids (Acidifers)

Organic acids contain one to seven carbon atoms. They are widely distributed in plants and animals and are also produced during microbial fermentation. These acids and their salts are often used as food preservatives and, since they are easy to handle, can be used to acidify feed.

Weaned piglets are physiologically immature and may not produce enough hydrochloric acid (HCl) to keep stomach pH at an optimum of approximately 3.5. At this pH, digestion of proteins and populations of beneficial bacteria (lactobacilli) are maximized and harmful bacteria are inhibited. Diets fed to young pigs often have a high buffering capacity, which can further reduce stomach acidity. Therefore, organic acids added to feed can have a beneficial effect in maintaining a low pH (*25*).

A recent meta-analysis of data on growth-promoting effects of organic acids in weaned piglets found that the acids generally improved performance but the magnitude of the effect varied with the amount of acid used and other components of diet. Fumaric acid usually caused a greater weight gain than formic or citric in young piglets while formic acid was more effective in fattening pigs (*110*). Data on several possible mechanisms for growth promotion, including inhibition of undesirable microbes, increased digestibility of proteins, and changes in intestinal morphology, were reviewed.

In fact, although these compounds lower feed and gut pH, their effects are not simply a result of acidification because neither dietary HCl nor phosphoric acid improved growth or feed conversion of piglets. It is likely that the antimicrobial effects of the organic acid ions, which act by controlling bacterial populations in the upper intestinal tract, are responsible for the beneficial effects of these acids (*125*). Fumaric acid was more effective than HCl and the antibiotic tylosin in reducing populations of various bacteria in small intestine of weanling pigs as compared to control pigs consuming feed with no additives (*49*). On the other hand, addition of 1% formic acid reduced feed pH from about 6.2 to about 4.5 but did not decrease diarrhea in weanling pigs (*45*). A recent review (*68*) concluded that data from many experiments showed that the effects of fumaric and formic acids on gut pH and flora are inconsistent. Lactic acid, however, was more consistent in reducing gastric pH and coliforms. Inconsistent results may be due to the variety of diets with different buffering capacities that were used in these experiments. Bacteria are known to develop acid-resistance when exposed to acidic environments for some time. This should be monitored when acids are added to feed over the long term (*113*).

Recent data demonstrating the improved feed conversion ratio and growth-promoting effects of formates (*109*, *126*), citric acid (*119*), and formic acid (*134*) indicated that the effect was greater during growth of young pigs than during the finishing phase of growth.

Several researchers cited evidence that organic acids also improve the digestibility and absorption of proteins, minerals, and other nutrients in the diet (*68, 73, 94, 110, 119, 125*). However, in another feeding study with young piglets neither fumaric nor citric acid additives improved efficiency of amino acid digestion or absorption (*161*).

Organic acids (such as fumaric, formic, lactic) are commonly added to swine feed in many European countries. As the use of antibiotics has decreased, the use of acids in feed has increased. At one pound per ton, organic acids have been approved for controlling mold in feeds; higher concentrations (>6 lb/ton) reduce the pH of feed to 5.0 and help control *Salmonella* and other enteric pathogens. Two problems may occur at higher organic acid levels: (i) palatability may be decreased, leading to feed refusal (*110*) and (ii) acidic feed is corrosive to cement and galvanized steel in swine housing. In order to minimize these effects, the natural buffering capacity of feeds (related to mineral and protein content) should be evaluated to determine the minimum effective amount of acid to use (*23*).

Salts of organic acids, such as formates and diformates, are not as corrosive and can be used to significantly improve growth rate and feed conversion in weanling pigs (*109, 112, 125*). Another strategy to extend the effectiveness of acid supplements and reduce corrosion damage to housing materials is the use of a slow-release form of acid. It consists of organic acids with fatty acids and mono- and diglycerides mixed to form microgranules. Tests show that use of these granules, as compared to use of free acids, results in greater feed intake and growth (*30*).

Fermentation may be a less expensive and equally effective way of acidifying diets. Weanling pigs, fed liquid basal diets of cooked cereal and milk products acidified to pH 4 with lactic acid or by fermentation with *Pediococcus acidilactici*, achieved similar weight gains and feed efficiency (*47*). Several million tons of liquid by-products of food industries, containing sugars and starch, are recycled into pig feed in Europe. These products, including wheat starch, cheese whey, and potato steam peel, are easily fermented to achieve a pH between 3.5 and 4.4. Feeding pigs diets containing these fermented liquid products increases weight gain and improves feed conversion ratio (*129*). Fermented liquid feeds which are high in yeast, high in lactic acid bacteria and high in lactic acid have been found to improve growth performance (*68*).

Other feed supplements

Minerals

Zinc (3000 ppm) or copper (250 ppm) added to piglet diets containing antibiotics significantly improved average daily weight gain, feed intake and feed efficiency. When the minerals were added together, their effects were not additive (*59, 136*). Use of zinc oxide in Denmark has led to decreased use of antibiotics in swine feed. Zn not only improved performance of piglets but also reduced incidence and severity of diarrhea in piglets (*61*).

Rare earth elements have been described as performance-enhancing feed additives in Chinese literature for some time. Recently, a rare earth mixture (containing lanthanum, cerium, and praseodymium) was tested in swine grown under "western" conditions and was found to significantly improve weight gain and feed conversion (*57*).

Vitamins

Vitamin E supplements did not appear to improve feed intake or weight gain in growing pigs (*48*) but did have a statistically significant effect on reducing weanling diarrhea (*78*).

Conjugated linoleic acid

Conjugated linoleic acid (CLA) refers to a mixture of positional and geometric isomers of linoleic acid with conjugated double bonds in the region of carbon atoms 8–13. It has been demonstrated to have anticarcinogenic effects and, in laboratory animals, reduces the proportion of body fat and increases lean tissue. In experiments with pigs fed isoenergetic, low fat diets containing 1–3% CLA or vegetable oil, CLA did not affect total energy metabolism but nonsignificant increases in lean tissue and weight gain were observed in some groups of animals (*96*). In several other experiments with pigs fed up to 1% CLA in the diet, small improvements were seen in average daily weight gain and feed efficiency during some stages of growth but these increases were not always significant (*41, 42, 67, 105, 106, 108, 146*). Two recent reviews (*42, 67*) summarize the earlier work and compare differences in methodology.

Phospholipids

Lysoforte, a phospholipid product, can aid in nutrient uptake from digestive tract. Addition of lysoforte significantly improved growth and feed conversion of piglets but not of older, growing pigs (22 kg) (*130*).

Amino acids

Swine diets may be deficient in one or more amino acids, and this can limit growth rate of pigs and resistance to disease. Simply adding more protein to the diet may increase the absolute amounts of these limiting amino acids but will not provide an optimum mix of amino acids and may increase intestinal disorders. Much of the additional protein may be "wasted" because it contains excess amounts of more common amino acids. Therefore, supplements of the limiting amino acids have been added to diets to improve performance of pigs (*149*).

- Supplementation of a barley, wheat, soybean diet containing 13.5% crude protein with the amino acids lysine, methionine and threonine resulted in a greater growth rate and feed conversion ratio in growing pigs than feeding an unsupplemented diet containing 15.8% crude protein (*12*).
- Addition of threonine to a maize, soybean, rapeseed and cottonseed meal diet increased weight gain and feed conversion in growing pigs and also improved immune function (*73*).
- In another experiment with finishing pigs fed a low protein corn–soybean diet, the addition of individual amino acids did not improve growth (*135*).

Carnitine

Carnitine is synthesized in the body from lysine and methionine but the enzymes needed to do this may be at low levels in piglets. Trials adding carnitine to piglet diets usually improve daily growth, and supplements to sows increase piglet survival and weight gain. However, results from field trials are not always statistically significant (*82*). When carnitine (25 or 50 mg/kg feed) was added to feed for 10 kg pigs, no improvement was noted in incidence of diarrhea or in ADG or feed efficiency (*71*).

Carbohydrates (Polysaccharides; Fiber)

The incidence of swine dysentery is related to diets fed to pigs: In experiments with weanling pigs, cooked rice (which is expensive) completely prevented dysentery while pigs fed steam-flaked corn and steam-flaked sorghum had significantly less sickness than those fed hammer-milled and extruded wheat. The steam flaking process makes these feeds more digestible and so there is less non-starch polysaccharide passing through into large intestine. Fermentation of these polysaccharides in the colon apparently encourages growth of dysentery-causing bacteria (*114*). Heat treatment of barley and maize for swine diets also increased weight gain and feed efficiency in piglets (compared to diets with no heat treatment) (*92*). Non-digestible oligosaccharides added to diets of 9-week-old pigs did not improve performance but rather temporarily decreased feed intake (*62*).

Some other polysaccharides appear to have beneficial effects when added to swine feed (*149*). Some of these compounds are sometimes called probiotic chemicals because they enhance the growth of probiotic bacteria. Feeding of Jerusalem artichoke meal (rich in fructans which act as bifidogenic factors) increased weight gain and feed intake of piglets (*43*). Feeding of fructooligosaccharides decreased shedding of *S. typhimurium* in a trial in Canada (*80*). A preparation of sugar beet fiber with lactose, termed Cellulac, may aid piglets in resisting pathogenic bacteria by increasing lactic acid levels in the intestine. This would encourage the growth of lactic acid bacteria which could prevent the establishment of pathogens (*121*).

Herbs

The quest for alternatives to sub-therapeutic doses of antibiotics in swine feed has recently included the testing of a number of herbs or herbal mixtures. The rationale for using these "natural remedies" is that many herbs and spices are known to have compounds with anti-bacterial effects (which may protect pigs against pathogens). Herbs may also increase the palatability of diets and thereby increase feed intake.

In most cases, these studies have been conducted in Europe and a number of reports are published in journals which are not available. However, I will mention below studies which reported positive effects. If there is further interest in some of these reports, it should be possible to contact the authors directly.

- An herbal mixture containing great nettle, garlic, and wheat grass was reported to improve growth and feed efficiency in growing pigs (*51*).

- An herbal preparation called "Nebsui" was reported to improve growth and reduce dysentery (*164*).
- Homeopathic remedies were reported to reduce incidence of disease in pigs (*9, 91*).
- Oregano and a mixture Aromex (a mixture of essential oils, spices and herbs) were reported to increase growth and in some cases reduce diarrhea in pigs (*93*).

Alternative Husbandry Practices

Although alternative feed supplements may compensate to some extent for the reduction or elimination of antibiotics in feeds, some changes in swine husbandry practices may also be important. Only a brief overview with some recent reviews as references is presented here. In addressing a problem such as the elimination of antibiotics in animal feeds, one should reconsider many aspects of swine rearing operations to determine whether changes in breeding and husbandry practices as well as changes in feed composition will be important parts of the solution.

Good hygiene is, of course, very important for preventing the spread of disease among livestock. If the routine use of antibiotics in feeds is discontinued, it may be necessary to be even more rigorous in maintaining clean environments for livestock (*13*). Improvements in the pig-rearing environment which have demonstrated effectiveness include (*34, 139*):

- attention to efficient cleaning methods and effective sanitizer use to minimize spread of disease
- maintenance of an appropriate ventilation rate since pathogens may be spread through the air
- appropriate environmental temperatures
- stocking rates appropriate for size of the farm
- careful record keeping to identify problem areas

Weaning is a particularly stressful time for piglets, with new foods and social groupings and interactions being introduced. The piglets' normal intestinal bacterial populations are not well established, making them more susceptible to pathogens in the environment. There are trade-offs between early weaning, which can reduce exposure to pathogens, and a later weaning, which allows a greater development of intestinal function and normal bacterial populations. Segregating newly weaned piglets with age-mates in clean facilities (all-in-all-out) can reduce exposure to pathogens which may be shed by older pigs (*39, 90, 143*). However, data from U.S. swine producers indicate that early weaning (before 28 days) was associated with increased mortality (*84*).

Feeding practices may also affect spread of disease. Automated liquid feeding systems were associated with a decreased risk of infection with *Salmonella* as compared to trough feeding in a study in the Netherlands (*167*). Improved feed conversion ratios were observed in swine herds in the U.S. that used three or more different rations during the growing-finishing phase (*40, 83*).

Biotechnology may lead to improvements in the genetic background of pigs, making them more resistant to diseases such as edema (*11, 97*). Other possibilities, which will require considerable time and investment to develop, include pigs that can utilize feed more efficiently because of an altered expression of gut enzymes or nutrient absorption potential in the gut lining. New techniques in biotechnology may also lead to improved vaccines, more effective probiotic preparations, feed plants with lower concentrations of antinutritional factors or increased amounts of useful nutrients, and other genetic changes in pigs which allow them to grow faster or be more resistant to various pathogens. Many of these possibilities were discussed in recent reviews (*27, 64*).

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