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Antibiotics shape microbiota and weight gain across the animal kingdom

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Implications

- The efficacy of antibiotic growth promoters depends on a variety of factors, including time of administration, dietary interactions, and length of growth cycle.
- There is consumer and regulatory pressure to remove antibiotic growth promoters from use, and understanding how modulating the microbiota alters host metabolism could give insights to new production strategies.
- The economic benefits of antibiotic growth promoters should be re-examined for modern agricultural practices.

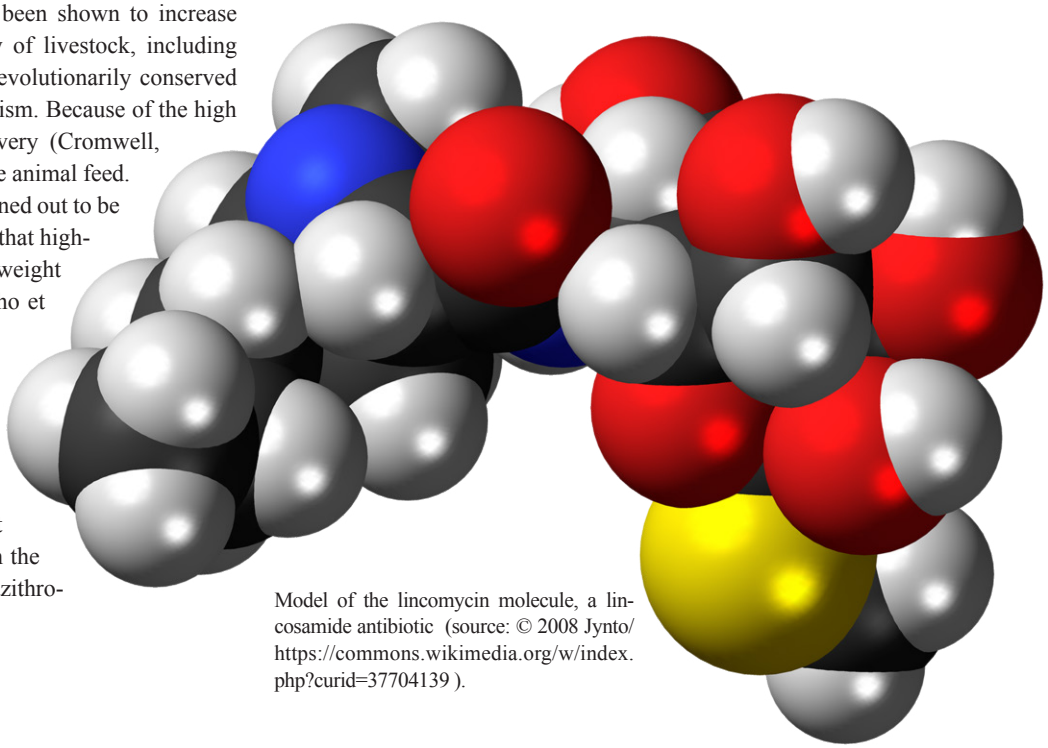
Key words: animal production, antibiotics, microbiota, regulation, weight gain

Early History of Antibiotics in Agricultural Production

Shortly after the discovery of antibiotics and their successful application to treat infectious diseases, researchers discovered the growth-promoting capacity of sub-therapeutic antibiotic treatment (Jukes and Williams, 1953; Taylor and Gordon, 1955; Dubos et al., 1963). For more than 60 yr, sub-therapeutic antibiotic treatment has been shown to increase growth rate and weight gain in a wide variety of livestock, including chickens, pigs, cows, and sheep, indicating an evolutionarily conserved relationship between microbes and host metabolism. Because of the high cost of antibiotics at the time of initial discovery (Cromwell, 2002), antibiotics were provided low levels in the animal feed. This economically constrained dosage choice turned out to be a fortunate one, since later studies demonstrated that high-dose antibiotic treatment could lead to reduced weight gain or weight loss (Dubos et al., 1963; Carvalho et al., 2012).

Many classes of antibiotics are efficacious for growth promotion, including those used to treat human diseases and categorized by the FDA as highly important or critically important for human health, such as β-lactams, macrolides, lincosamides, and tetracyclines (Apley et al., 2012), although the specific antibiotic within the class may differ for human vs. animal use (e.g., azithromycin is a macrolide used for humans, and tylosin a veterinary macrolide). While many antibiotics have been banned in Europe for decades (Millet and Maertens, 2011), their use is only recently being phased out in the United States in response to FDA guidance for a voluntary withdrawal. The antimicrobial dose for growth promotion is often one to two orders of magnitude lower than for therapeutic applications (Apley et al., 2012; Subbiah et al., 2016) and does not have the primary goal of treating disease or preventing infection (Allen and Stanton, 2014). For example, chlortetracycline would be administered at 70 mg/animal/day for growth promotion, at 350 mg/animal/day to for prophylaxis against catching infection, and at 22 mg/kg body weight—approximately 6,600 mg/animal for a 300-kg steer (Cazer et al., 2014).

The practice of using low-dose antibiotic growth promotion continues today around the world and is projected to increase in several countries (Van Boeckel et al., 2015). While it has economic benefits associated with increasing weight gain and feed efficiency (the conversion of food to animal mass), results can vary across production facilities, and there is growing evidence and concerns that widespread use of low-dose antibiotics increases the selection for antibiotic-resistant bacteria and their transmission to the human population (Allen et al., 2013). In recent years, there has been both legislative actions and consumer pressure to reduce or eliminate the use of antibiotics for growth promotion (Borron, 2012;



Model of the lincomycin molecule, a lincosamide antibiotic (source: © 2008 Jynto/ https://commons.wikimedia.org/w/index.php?curid=37704139).

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Frontline, 2014; FDA, 2015; Meek et al., 2015), creating a need for new strategies to maximize growth in agricultural production.

Underlying the growth-promoting effects of antibiotics is the intestinal microbiota, which is composed of bacteria, fungi, viruses, and microscopic eukaryotic organisms that inhabit the gastrointestinal tract. These microorganisms are environmentally acquired, and their metabolic functions can shape host physiology. Many classes of antibiotics are effective for growth promotion, with multiple modes of action and spectrums of activity (Table 1), making it difficult to predict which microbial changes are responsible for increases in weight gain or feed efficiency. Greater understanding of how growth-promoting antibiotics alter the microbiota and host metabolism could lead to new insight and strategies for agricultural practices. While the mechanism is not fully understood, it is believed that the antibiotics increase weight gain by selecting for microbes that aid in nutrient extraction; modulate microbial carbohydrate, protein, and lipid metabolism; prevent subclinical infections (Allen and Stanton, 2014); and reduce intestinal and immune cell proliferation and consequential protein loss (Dibner and Richards, 2005).

The Contribution of the Intestinal Microbiota to Host Metabolism

The gut microbiota can influence weight gain in several ways, including increasing nutrient extraction and modulation of immune and metabolic signaling pathways (Cox and Blaser, 2013). Germ-free animals that lack any microbiota weigh less and have less fat than their conventional counterparts (Bäckhed et al., 2004), demonstrating the role of the microbiota in weight gain. Many vertebrate animals, including pigs, chickens, cows, mice, and humans, consume a diet rich in complex nutrients that are indigestible by the animal's own enzymes. Instead, they rely on the diverse biochemical catabolic action of the intestinal microbiota, which is estimated to contain more than 100 times the number of functional genes than genes encoded in the respective host genome. This added metabolic activity can be thought of as a virtual organ, and in addition to increasing caloric harvest from food, the microbiota can also synthesize vitamins and aid in ion absorption, contributing to the overall nutritional status of the host (Nicholson et al., 2012; Cox and Blaser, 2013; Allen and Stanton, 2014; Krishnan et al., 2015).

The intestinal microbiota can both increase and decrease host access to dietary nutrients; while they can increase access to indigestible carbohydrates, they can also decrease calories absorbed from fat (Figure 1). In many monogastric animals, such as pigs, chickens, mice, and humans, the ileum is colonized by facultative anaerobic bacteria, and the cecum and large intestine are colonized by strictly anaerobic bacteria. It is important to consider both the microbe- and host-specific metabolic components to understand how antibiotic growth promoters may function. For example, the majority of the lipid absorption occurs in the small intestine (duodenum, jejunum, and ileum), and bile acids conjugated to fats aid in their transport, and antimicrobial treatment can shift bile acid conjugation and fat absorption (Lin, 2014). *Lactobacillus*, a facultatively anaerobic genus that can often colonize the small intestine in large numbers, has bile salt hydrolase enzymatic activity (Moser and Savage, 2001) that deconjugates bile salts and decreases lipid absorption. In a study of broiler chickens, sub-therapeutic bacitracin increased concentrations of bile salts taurocholic acid and taurochenodeoxycholic acid, increased fat digestibility, and decreased levels of *Lactobacillus salivarius* in the ileum, a bacteria with demonstrated activity for deconjugating bile salts (Guban et al., 2006). Similar reductions in bile salt hydrolase activity and increases in fat absorption have been reported in independent experiments using salinomycin and avilomycin but have been linked to reducing the bile salt hydrolase activity of *Clostridium perfringens* (Knarreborg et al., 2004). Studies like these are important to characterize mechanisms for microbes altering host digestion, physiology, and their applications to agricultural production.

Table 1. Antimicrobials used for growth promotion in the United States.

Antibiotic	Class	Mode of Action	Cattle	Swine	Chickens
Bacitracin	Cyclic peptide	Inhibition of cell wall synthesis	L	L	L
Bambermycin	Glycolipid	Inhibition of cell wall synthesis	L	L	L
Carbadox	Quinoxaline	Inhibition of DNA synthesis		L	L
Chlortetracycline	Tetracycline	Inhibition of protein synthesis	L	L	L
Laidlomycin	Ionophore	Disintegration of cell membrane	L		
Lincomycin	Lincosamide	Inhibition of protein synthesis		L	L
Monensin	Ionophore	Disintegration of cell membrane	L		
Neomycin	Aminoglycoside	Inhibition of protein synthesis	L	L	L
Penicillin	Beta-lactam	Inhibition of cell wall synthesis	L	L	
Tylosin	Macrolide	Inhibition of protein synthesis		L	L
Virginiamycin	Streptogramin	Inhibition of protein synthesis	L	L	L

Adapted from Allen and Stanton (2014) and Butaye et al. (2003).

In ruminants, such as cattle and sheep, the structure of the gastrointestinal tract alters their metabolic relationship with their microbiota. The rumen is the primary fermentation chamber and is toward the beginning of the digestive tract. These foregut fermenters may get up to 50% of their energy from microbial metabolites (Callaway et al., 2003), including short-chain fatty acids, whereas hindgut fermenters (pigs, chickens, horses, mice, and humans), in which most fermentation takes place in the cecum and large intestine, receive only 5 to 10% of energy demands from microbial fermentation products (Bergman, 1990). Ionophore antibiotics are the most common class used for growth promotion in ruminants, including antibiotics monensin, lasalocid, and laidlomycin (Callaway et al., 2003), and their efficacy depends on feeding practices and whether other growth-promoting technologies are utilized (Bretschneider et al., 2008)

The Influence of Microbial Metabolites

In mouse models, high-dose antibiotic treatment that results in a substantial, multi-log fold reduction of microbial populations can lead to weight loss (Murphy et al., 2013) while lower doses can lead to weight gain (Dubos et al., 1963; Cox et al., 2014), suggesting that the modulation of the composition of the microbiota is more important than removing the bulk of the microbiota. Weight gain induced by antibiotics could be, in part, due to modulating specific metabolic pathways since several microbial metabolites can stimulate growth, including acetate, butyrate, and propionate, or repress growth, such as toxic amines or indoles. Conversely, antibiotic-

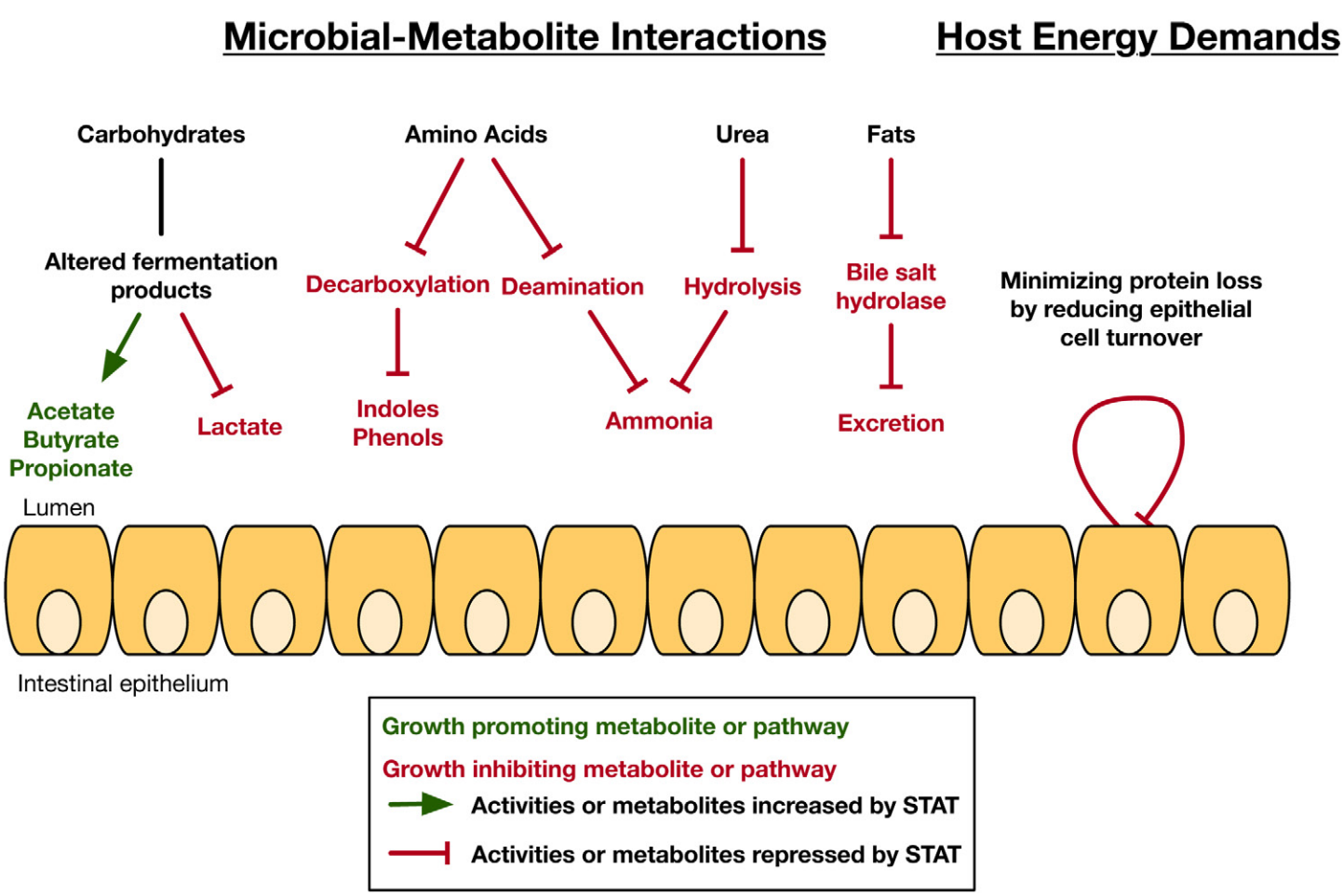


Figure 1. Influence of sub-therapeutic antibiotic treatment on microbiota and host metabolism. Low-dose antibiotics can modulate microbial metabolic pathways to increase metabolites that promote growth (e.g., acetate, butyrate, and propionate) while reducing metabolites that can repress animal growth (e.g., lactic acid for ruminants and indoles, phenols, and ammonia). Sub-therapeutic antibiotic treatment (STAT) also reduces intestinal epithelial cell turnover and immune cell proliferation, sparing the animal protein losses associated with regenerating this tissue.

mediated weight loss could be due to the removal of key nutritional requirements that the microbiota provide. In an elegant example from Rene Dubos, it was found that mice fed a diet with its protein source limited to gluten lost weight when given the antibiotic terramycin (oxytetracycline) (Dubos et al., 1963). The gluten protein diet was deficient in lysine and threonine, and the mice were relying on microbial production of these amino acids for normal growth and development. Knockdown of the intestinal microbiota with high-dose antibiotic treatment resulted in weight loss. Addition of these amino acids back to the gluten diet blunted the weight loss although antibiotic-treated mice still showed slower growth than their untreated counterparts. Finally, when a complex protein mixture was included in the diet, mice given terramycin had increased weight gain compared with untreated controls. In total, these experiments demonstrate the need to consider microbial interaction with individual dietary components and how antibiotics might influence overall host digestion and growth. These studies may also explain why the effect of antibiotics may vary between farms and over the years as animal nutrition regimens have changed.

Another primary way that the intestinal microbiota can alter calories extracted from the diet is the digestion of complex carbohydrates and conversion to metabolites that can be absorbed by the host, such as monosaccharides and short-chain fatty acids. The several species of the microbiota can convert carbohydrates to short-chain fatty acids (Macfarlane and Macfarlane, 2003), predominately acetate (vinegar), butyrate, and propionate, which can directly contribute to host caloric intake, and the amount of energy contribution depends on host species (i.e., cow, sheep, pig, human, and mouse) (Bergman, 1990). In addition to providing calories, short-chain fatty acids can also signal through free fatty acid receptors (**FFAR**) to alter digestion, appetite, and immunity (Ichimura et al., 2009). Enteroendocrine cells in the intestine can respond to short-chain fatty acid binding to FFAR3, which stimulate the secretion peptide YY, an appetite-suppressing hormone. Peptide YY acts on host digestion by slowing down intestinal transit rate, resulting in an increase nutrient absorption from the diet. Adipocytes (fat cells) can also respond to acetate and propionate through FFAR2 and FFAR3, which results in reduced lipolysis (the destruction of fat cells), and the secretion of the metabolic hormone leptin (Ichimura et al., 2009). Microbial short-chain fatty acid metabolism is complex, with many specialist and generalist pathways, resulting in secreted compounds that can affect growth and development by a variety of mechanisms.

In a mouse model we developed to further study the effect of antimicrobial growth promoters in a laboratory setting, sub-therapeutic antibiotic treatment altered microbial short-chain fatty acid metabolism. In a set of experiments, we administered low-dose antibiotics to mice and character-

ized changes in microbiota and host physiology (Cho et al., 2012; Cox et al., 2014). Initially, different classes of sub-therapeutic antibiotics, including penicillin, vancomycin, and chlortetracycline, were administered to 3-wk-old female mice fed normal chow (Cho et al., 2012). While there was no change in weight gain, there was a significant increase in fat mass. We measured short-chain fatty acids in the cecal lumen by gas chromatography and observed a significant increase in acetate in mice given vancomycin and a trend of increased acetate in mice given penicillin and chlortetracycline. Butyrate was significantly increased in mice given vancomycin and chlortetracycline. We also observed altered levels of microbial short-chain fatty acid production genes by quantitative PCR, suggesting that the antibiotic treatment altered the microbial genetic potential for short-chain fatty acid production. Using bomb calorimetry, we detected fewer calories in the feces, which indicates that the antibiotic treatment increased energy extraction to the diet. Since enterohepatic circulation delivers microbial metabolites to the liver, one possible mechanism of antibiotic-mediated increases in body fat could be altered short-chain fatty acids reaching the liver and promoting fat production. We next examined changes in the liver and detected altered hepatic gene expression in lipogenic pathways, which supports this theory. To identify key microbes associated with the antibiotic-induced adiposity, we performed 16S rRNA sequencing of fecal and cecal samples. While we did not observe a set of bacteria that were consistently lost across the different antibiotic regimens, we did observe an increase in the microbial family *Lachnospiraceae*, which contains many species with a wide array of enzymes capable of digesting complex carbohydrates (Cotta and Forster, 2006). It is possible that this expansion of *Lachnospiraceae* and other microbes assisted in energy harvest from the diet in the form of fermentation to short-chain fatty acids.

Certain microbial metabolites may repress growth and can be modulated by low-dose antibiotics. Proteins from the diet or host tissues are hydrolyzed to amino acids and further converted to bioactive compounds (Nyangale et al., 2012). Aromatic amino acids, such as tryptophan, can be converted to phenolic and indolic compounds that can impair growth. Toxic amines can be produced from the decarboxylation of amino acids while ammonia is produced from deamination. Ammonia can also be produced from the hydrolysis of urea and can stunt growth at high levels (Dibner and Richards, 2005). In addition to microbial metabolites from protein degradation, carbohydrate breakdown in ruminant by homolactic acid producers (such as *Streptococcus bovis*) can result in excessive levels of lactic acid that decrease the pH of the rumen, which can negatively impact growth or even lead to acidosis and fatal indigestion (Hungate, 1966). Ionophore antibiotics can reverse some of these negative microbial metabolites, decreasing lactate and ammonia while increasing propionate (Callaway et al., 2003). It is important to note that these biochemical reactions depend on having microbiota that contain the functional ability to produce specific metabolites. Identifying which microbes are responsible for physiologically relevant levels of growth-suppressing metabolites could provide new strategies for optimal animal production.

The Energy Demands of the Immune System

The intestinal microbiota contributes to the development of the immune system, and mounting an immune response to prevent invasion of the commensal microbiota can be energy intensive (Kau et al., 2011). These actions include a continual sloughing off of intestinal epithelial cell lining, production of mucus, proliferation of immune cells, and secreting protein antibodies, which result in a total protein loss. It is estimated that renewal of the gut lining can account for 20 to 30% of the total energy expenditure (Dibner and Richards, 2005). The use of a sub-therapeutic antibiotic treatment can substantially change the intestinal architecture and lead to the thinning of the gut wall (Gaskins et al., 2002), which could result in a greater availability of nutrients to go toward overall growth. Other means of limiting cell cycle turnover in the gut could be a complimentary or alternate approach to maximize growth in livestock.

The Weight of Early-Life Interactions

In addition to dosage, timing of antibiotic administration is an important factor in shaping host metabolism. Antibiotics have the greatest growth promotion effect when administered to young, developing animals. Summarizing data from 1,194 experiments conducted on a total of 32,555 pigs between 1950 and 1985, sub-therapeutic antibiotic treatment increased weight gain and feed efficiency in swine regardless of growth phase introduction; however, there was a substantially greater effect during the starting phase (16.4% increase in weight, 6.9% increase in feed efficiency) than in the growing phase (10.4% increase in weight, 4.5% increase in feed efficiency) with diminishing returns in the growing-finishing phase (4.2% increase in weight, 2.2% increase in feed efficiency) (Cromwell, 2002). This suggests that perturbation of the microbial ecosystem during a critical developmental time period can permanently shape host metabolism and weight gain.

To investigate the effect of timing, we administered low-dose penicillin to mice either at weaning, or at birth by giving antibiotics to the pregnant mothers in the last week of pregnancy, maintaining them on penicillin through the nursing period and weaning the pups onto penicillin water (Cox et al., 2014). Antibiotics from birth, but not at weaning, significantly increased total weight compared with controls, which suggests that the host is more metabolically vulnerable to microbiome changes during the time of late gestation through nursing. The transfer of maternal microbiota initiates microbial colonization and development, and epidemiological studies have demonstrated a risk of increased weight in children born by Caesarian section rather than by vaginal delivery (Blustein et al., 2013). Thus, the antibiotics may work by disrupting the maternal microbiota that colonizes the offspring by altering development during gestation or by directly disrupting the infant microbiota. Further studies are needed to address this issues.

Next, we wanted to see how the phenotype developed over time in both male and female mice. Consistent with other models of obesity, male mice gained weight faster and showed differences in weight and adiposity sooner (at 16 wk). Female mice also showed increases in total weight and fat mass, but took longer to show the effect of antibiotics (20 wk). This gender-dependent microbiome effect may be useful when examining the utility of antibiotic growth promoters on a fast-paced production schedule. While antibiotics may accelerate weight gain, substantial effects might not be seen before the animal reaches market weight.

Continuing to examine early-life microbiome perturbations, we next asked whether the effect could be amplified by dietary changes. We administered low-dose penicillin to male and female mice from birth; control mice did not receive antibiotics, and in adulthood, half of the mice were switched to a high-fat diet. While both control and sub-therapeutic antibiotic treatment mice gained weight on a high-fat diet, those receiving penicillin gained the most weight and fat mass. Female mice had approximately 100% increase in fat mass, from 5 g (control, high-fat diet) to 10 g body weight (sub-therapeutic antibiotic treatment, high-fat diet), indicat-

ing that there was a synergistic effect between sub-therapeutic antibiotic treatment and caloric excess. We also observed significant elevations in fasting insulin in sub-therapeutic antibiotic treatment male mice fed high fat diet but not in female mice. These experiments provide evidence that antibiotics can have a greater effect on metabolism when combined with diets that select for weight gain and adiposity.

At this point, it was unknown if sustained antibiotics were necessary to induce changes in metabolism and body composition or if limited exposure could lead to lasting effects. We administered penicillin to mice for either the first 4 wk (nursing period), the first 8 wk (juvenile), or lifelong (28 wk, mid-adult). Regardless of length of antibiotic exposure, we observed significantly increased total and lean mass through middle age (until week 20 of life) and increased fat mass later on (from weeks 24–28 of life). To discover key microbial changes, we characterized the microbiome with high-throughput sequencing. We discovered that the microbiota is significantly altered by antibiotic treatment but recovers 4 wk after antibiotics are stopped. Despite microbiota recovery, the mice later go on to develop increased fat mass at 24 wk, even when their microbiota appear normal, which indicates that the early-life microbes participate in programming long-term host metabolic outcomes.

To better characterize the early-life physiologic effects of antibiotic treatment, we examined changes in the intestine by histopathology and gene expression analysis. We detected significant ileal atrophy (shortened intestinal villi) in 4-wk mice treated with antibiotics and a significant downregulation of genes involved in intestinal immune responses in antibiotic-treated mice compared with controls. This is consistent with the hypothesis that one mechanism of sub-therapeutic antibiotic treatment is to reduce the energy demands of the immune system and rapidly renew gut tissue. We also examined markers of systemic inflammation as reduced barrier function has been associated with low-grade inflammation driving obesity (metabolic-endotoxemia) (Cani et al., 2008); however, we did not detect any changes in serum markers of inflammation.

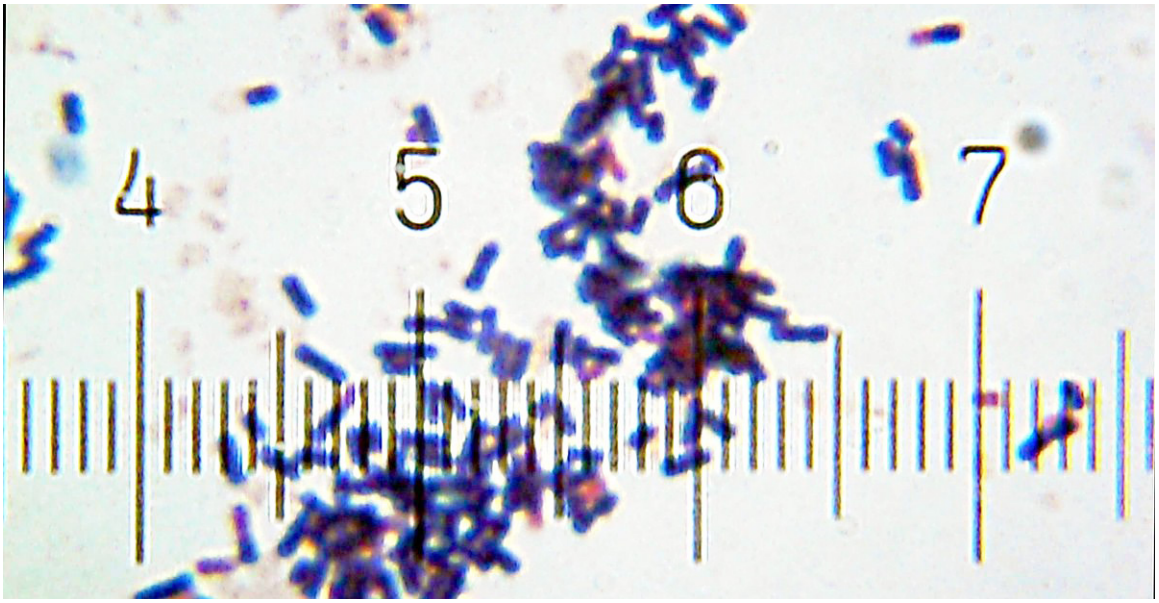
Three-dimensional map of part of one of the crystal salts of penicillin based on X-ray crystallography work by Dorothy Hodgkin and Barbara Low (Oxford) and C.W. Bunn and A. Turner-Jones (I.C.I. Alkali Division, Northwich). The work has been made available by the Museum of History of Science, University of Oxford under Wikimedia Commons for Ada Lovelace Day 2013 (source: © 2008 commons.wikimedia.org).

Finally, to test whether the effect was dependent on antibiotics or could be mediated by the microbiota alone, we performed a microbiota transplant (Cox et al., 2014). Young (3 wk old) germ-free mice were colonized by microbes from either control or sub-therapeutic antibiotic treatment mice and continued on a high-fat diet as in prior studies. In just 5 wk, we observed a significant increase in total and fat mass as well as a reduction in the expression of ileal genes associated with intestinal defense. This demonstrated that the microbes could transfer both the growth promotion and the immunologic phenotypes and were directly responsible for the effect. To identify key microbes, we examined more than 1,000 samples from four independent experiments including multiple time points. It is important to remember that there is a great deal of variability in the microbiota over time, and it is possible to detect changes that do not have any biological relevance. While each of the 4 experiments had approximately 20 different types of bacteria altered in early-life, only 4 bacteria were consistently reduced, and none were consistently elevated. These microbes included the genera *Lactobacillus*, *Allobaculum*, the family Rikenellaceae, and *Candidatus* Arthromitus [also known as segmented filamentous bacteria (SFB)]. While these bacteria represent widely different taxonomic lineages, both *Lactobacillus* and SFB are associated with stimulating specific intestinal immune responses. We also detected a significant positive correlation with *Allobaculum* and markers of intestinal defense. Further work is needed to characterize the role that the microbes might play in shaping host metabolism, and better understanding could help uncover new pathways of microbe–host metabolic interaction.

The goal of these experiments was to examine the effect of early life, and thus focused on time as variable, rather than antibiotic class. Penicillin was selected as a model antibiotic based on earlier studies (Cho et al., 2012), in which there was marginally higher fat mass from administering penicillin. While other antimicrobials, in addition to penicillin, are used in agriculture, the concept that early-life microbiota disruption can maximize growth-promoting effects is applicable to farming. In addition, we observed significant elevations in lean mass in young adult animals and a later increase in fat mass in multiple experiments, consistent with the goals of increasing muscle mass in addition to overall market weight in animal production.

Translation to the Human Population

The evidence of antibiotic-mediated weight gain in animals raises two questions. First, could a similar growth promotion effect occur in people directly receiving antibiotics? And second, could low level of antibiotic exposure through the food or water supply lead to weight gain in the human population? In the United States, antibiotic use is widespread, with the highest use in children under 2 (Hersh et al., 2011). Several studies have measured a significantly increased risk of being overweight later in childhood if the child received antibiotics within the first year of life (Azad et al., 2014; Bailey et al., 2014; Trasande et al., 2012). In animals, we modeled the typical antibiotic exposure in children by giving therapeutic level of antibiotics to mice and observed an accelerated weight gain and early elevations in lean and total mass, which were smaller than our sub-therapeutic antibiotic treatment effects (Nobel et al., 2015). Together, the experimental and epidemiological data suggest that humans might also have lasting changes in growth and weight from early-life prescribed antibiotics. Whether or not low-level of antibiotics inadvertently ingested through environmental and dietary exposure has any effect in the human population has not been addressed. The FDA has limits on antibiotic residues in meat, and these levels are substantially lower than the



Lactobacillus acidophilus (source: © 2012 Bob Blaylock/commons.wikimedia.org).

growth-promoting doses used on the farm. Nevertheless, this is an important topic of study with broad translational implications.

Economic Considerations

There is a widespread belief that antibiotics used for growth promotion are economically beneficial, which is rooted in studies that were conducted more than 60 yr ago. However, many aspects of animal production have changed over the years, including housing conditions, selective breeding, and dietary supplementation; thus, the effect of antibiotics today might not be the same as when it was initially discovered (Graham et al., 2007). To address this issue, the economic impact of removing antibiotics as growth promoters was calculated from more than 7 million chicks in 158 paired control-trial chicken houses from the Purdue company from 1998 to 2001 (Graham et al., 2007). The antibiotics used in the trial houses were bacitracin methylene disalicylate, zinc bacitracin, flavomycin, and virginiamycin, and control houses did not receive antibiotics for growth promotion. Removing the antibiotics did result in a decreased market weight and feed efficiency. However, the extent of change was not substantial enough to offset the added cost of adding antibiotics to the feed. Stopping antibiotic use for growth promotion increased the net value of a flock in both the Del Marva Peninsula (Delaware, Maryland, and Virginia) and in North Carolina by 0.9 to 1.35 cents per chicken. In total, the authors calculated that using antibiotic growth promoters resulted in a loss of value of approximately 0.45%. While antibiotic growth promoters were removed, both trial and control houses received the coccidiostat therapy (an anti-parasitic treatment targeting the class Coccidia), which may impact the microbiota and potentially confound this study. Nevertheless the authors raise the important point to reconsider current practices from recently obtained data and provide a framework for conducting an economic analysis to evaluate production in a real-world setting.

Alternative Strategies for Growth Promotion

Though sub-therapeutic antibiotic treatment has long been used to increase growth and feed efficiency in production animals, changing regulatory and consumer pressure, as well as the risk of selecting for antimicrobial resistant bacteria, creates a need to develop alternate strategies. New production approaches could include administering live bacteria (probiotics), administering compounds to stimulate the growth of beneficial bacteria (prebiotics), giving small molecules (e.g., short-chain fatty acids) to directly influence host physiology, or by administering enzymatic inhibitors (e.g., inhibitors for bile salt hydrolase) (Allen et al., 2013; Lin, 2014). Management of housing conditions could also improve net profits. In the Purdue study described above, litter change in the chicken houses was associated with a drop in mortality although it had no effect on growth rate (Graham et al., 2007). While alternate strategies exist, their efficacy can be variable depending on the species, diet, gender, age, and health status, and there are several challenges, which have been well reviewed (Allen et al., 2013). Nevertheless, it is important to continue to undertake studies that can reveal new mechanisms of microbe–host metabolic interaction and apply these new findings to modern agricultural practices.

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About the Author

Dr. Laura Cox completed her Ph.D. in Martin Blaser's laboratory at NYU Sackler Institute of Graduate Biomedical Sciences where her work demonstrated that early-life microbiota disruption with sub-therapeutic antibiotics resulted in lasting changes in metabolism. She is now a post-doctoral fellow in Howard Weiner's lab at the Brigham and Women's Hospital and Harvard Medical School. Her current work examines the influence of intestinal microbiota on immunity and neurodegenerative diseases throughout aging.

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