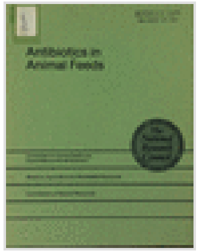

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Antibiotics in Animal Feeds

A Report Prepared by the
Committee on Animal Health and the
Committee on Animal Nutrition

Board on Agriculture and Renewable Resources
National Research Council

NATIONAL ACADEMY OF SCIENCES
Washington, D.C. 1979

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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EXECUTIVE SUMMARY

The food-producing animal and poultry industries have undergone a dramatic change that began around 1950. What was an extensive industry became extremely intensive: units increased in animal concentration, both physically and numerically. Utilization of the beneficial responses of feed-additive antibiotics in improved growth and feed efficiency developed concurrently with the intensification of the animal industry. It has been proposed that feed-additive antibiotic usage was an integral part of this revolution in animal-production technology. It is estimated, at present, that 40 percent of the antibiotics produced are used for feed additives. Estimates allocate 0.5 million kg to the cattle industry, 1.0 million kg to poultry, 1.4 million kg to swine, and 0.4 million kg to other animals such as companion animals.

The animal producer can obtain antibiotics in the form of balanced supplements and premixes that are processed and sold by the feed-manufacturing industry. The producer also has access to and can purchase antibiotic products from farm and veterinary supply centers. Administration of antibiotics in the drinking water is becoming increasingly important in both poultry and swine production.

Feedlot systems for beef cattle and sheep would not change if low-level antibiotic feedings were not permitted, but it is likely that disease problems and therapeutic use of antibiotics would increase.

The discontinuance of low-level (5 to 10 g/ton) usage of penicillin and tetracyclines would have little effect on the poultry industry. However, the elimination of higher levels (100 to 200 g/ton) would make it very difficult to control bacterial disease in young chickens and turkeys. If all tetracyclines and penicillin were banned as feed additives for poultry, the effective alternative antibiotics and sulfa drugs would likely maintain present production and efficiency standards. However, the problem of selective pressure for some multiple antibiotic resistance mediated by plasmids may still persist with alternative antimicrobials.

If only tetracyclines and penicillin were banned as feed-additive antibiotics for swine, there would be little if any effect on swine productivity or efficiency. There are other promising antibacterial agents that could serve the industry well.

If subtherapeutic use of feed additive antibiotics is banned, future changes in disease control will include preventing exposure to infectious agents, treatment of disease after an outbreak has occurred, and control of infectious disease by immunological means. Preventing exposure to infectious agents will be extremely difficult and will result in a slowing down of animal production. Post-outbreak treatment has had variable effectiveness, but would certainly be less effective than the present use of subtherapeutic levels of antibiotics. The control of infectious disease by immunological means would be an ideal way to safeguard against subclinical infection. However, thus far there has been limited success in protecting animals against bacterial pathogens that affect the intestinal and respiratory tracts.

Antibiotics have been effective in improving the rate and efficiency of gain in swine, cattle, and poultry. The responses in poultry and swine are generally greater in younger animals than in those reaching the end of the growing-finishing period. There is some evidence that the improved farrowing rate of swine is associated with the use of antibiotics. Responses in cattle have not been as great as those in swine and poultry. Improvement in rate of gain and feed efficiency in cattle has averaged about 5 percent. Evidence indicates that the effectiveness of antibiotics has not decreased over time.

Antibiotics in feed have also been used in animal production in Europe since 1953. The British have monitored microbial resistance to antibiotics and have conducted some basic and applied research concerning this aspect. Although the use of antibiotics in the United Kingdom has been restricted as a result of the Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (referred to in this report as the Swann Report; Swann et al. 1969), the total tonnage used in animal production in 1975 was at an all-time high. Although the amount used in animals was only about 15 percent of the total usage, the ratio of the human population to the livestock population receiving antibiotics is substantially higher than in the United States.

Ingestion of antibiotics results in the development of resistance in bacteria such as in the *E. coli* and *Salmonella* species. The resistance appears to be related to usage patterns. British research has shown that resistance persists longer following long-term use, compared to short-term use. There is strong evidence that development of resistant strains of bacteria in humans is closely related to antibiotics used in humans. No concrete evidence has been reported in the United Kingdom showing that antibiotic resistance has decreased since the Swann Report, or that antibiotic use has decreased.

The wise use of antibiotics is not a substitute for, but a complement to, good sanitation and husbandry practices. Extensive use of low-level antibiotics in feeds has brought about concern for potential harmful effects due to development of resistant strains of organisms in host animals that might compromise animal as well as human health. Drug resistance in bacteria was observed soon after the introduction of antibiotics. Antibiotics have been used extensively in animal feeds for nearly 30 years. Questions and discussions concerned with the potential human health hazards from subtherapeutic antibiotic feeding to animals have been aired for nearly 30 years. Yet, it is difficult to cite human health problems that can be attributed specifically to meat animals fed antibiotics or that can be associated with contact with animals fed low levels of antibiotics. There have been incidents of salmonellosis in humans involving antibiotic-resistant strains of animal origin but there is no evidence of any relation to low-level antibiotic feeding.

Surveys of the use of drugs for therapeutic purposes indicate that antibacterial agents account for almost 50 percent of drugs used by practicing veterinarians. *In vitro* testing has sometimes been questioned in that infections associated with organisms that seem to be resistant *in vitro* are quite responsive to antibacterial therapy *in vivo* in clinical use.

Scattered reports, published and unpublished, attribute failure in drug therapy to low-level antibiotic feeding. Others claim continued effectiveness of drugs previously fed for long periods at subtherapeutic levels. Carefully controlled studies exploring possible relationships between antibiotic feeding and subsequent drug effectiveness are needed.

Critical experimental studies on the effect of low-level antibiotic feeding on animal therapy and human health are definitely needed. It is proposed that studies be conducted in the following areas:

1. *Does the Feeding of Tetracycline and Penicillin Compromise Animal Therapy?*--This research should be done with swine, poultry, and cattle. In swine and poultry, conditions should be closely controlled. In cattle it would seem essential that research be conducted in commercial-type feedlots.

2. The Relationship of Antibiotic Feeding to Human Health--Although these studies are very complex and time-consuming, it is important that some effort be started in this direction. The incidence of disease-resistant organisms could be determined in humans in industries in which the workers have close contact with animals and animal products and with people who work in industries that have no contact with animals or animal products. Also the incidence of disease and the effectiveness of therapy should be studied. Some information might be obtained by surveys of existing information.

3. Mechanisms of Action of Antibiotics in Growth Promotion--Current evidence strongly suggests that the growth-promoting effect from low-level feeding of antibacterial compounds is not solely related to disease prevention. Knowledge of the mechanisms involved is a vital missing link. If known, the study of other means of eliciting a similar response would become feasible. Thus, such new knowledge would offer the potential for eliminating some or all of the current reasons for using feeding levels of antibacterial drugs.

CHAPTER 1

INTRODUCTION

The use of subtherapeutic levels of penicillin and the tetracyclines in animal feeds has raised the question of the effects of such practices on human health. The Food and Drug Administration (FDA) has proposed a ban on certain antibiotics at subtherapeutic levels in feed because of the potential for compromising the health of humans. A large segment of the regulated industry, including farmers and ranchers, has contended that in nearly 30 years of use, antibiotics at subtherapeutic levels in animals have not compromised human or animal health or influenced the therapy of human disease.

The FDA has contracted with the Assembly of Life Sciences, National Academy of Sciences, for a review and evaluation of human health effects of antibiotics in animal feeds. The Committee to Study Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds has been appointed to:

1. study the human health effects of subtherapeutic use of penicillin and tetracyclines (chlortetracycline and oxytetracycline) in animal feeds;

2. review and analyze published and unpublished epidemiological and other data as necessary to assess the human health consequences of the subtherapeutic use of penicillin and tetracyclines in animal feeds; and

3. assess the scientific feasibility of additional epidemiological studies, and, if needed, to make recommendations about the kind of research necessary, its estimated cost and time requirements, and possible mechanisms to be used to conduct such studies.

Under the terms of the contract, subtherapeutic levels are defined as use of the agent at levels of 200 g/ton or less, and/or use of the agent for 2 weeks or longer. Animal feeds include milk replacers, medicated blocks, and liquid feeds.

The Committee has requested the Board on Agriculture and Renewable Resources (BARR) to prepare a critical review/position paper on certain aspects of the problem. The following list of questions to be answered was submitted to the BARR (the Chapter numbers after each question refer to the chapter in this report that discusses the question):

1. How effective are antibiotics--especially penicillin and tetracycline--in animal feeds? (Chapter 3)

2. Would animal husbandry methods change if antibiotics were eliminated, or if penicillin and tetracyclines were removed? (Chapter 2)

3. Does animal disease decrease as a result of use of antibiotics and would there be an increase in therapeutic use of antibiotics if subtherapeutic use was discontinued? (Chapter 2)

4. What do the data from European countries show with respect to animal health and nutrition where antibiotics have been restricted? Has the restriction of subtherapeutic use led to increased therapeutic use, thus cancelling the benefits of restriction? (Chapter 4)

5. Is it likely that there would be a black market? (Chapter 2)

6. How much therapeutic use is there and has it caused resistance problems? What is the evidence that therapeutic use of penicillin and tetracyclines contributes to resistance and possible health effects? (Chapter 6)

7. What epidemiological studies exist that would be valuable for the committee to consider? Are there epidemiological studies that should be carried out? (Chapter 6)

8. What amounts of penicillin and tetracyclines are used subtherapeutically? (Chapter 2)

9. What amounts of penicillin and tetracyclines are used therapeutically? (Chapter 6)

10. How are animal feeds prepared and how are the antibiotics used in animal feeds mixed and used by farmers or feedlot operators? (Chapter 2)

11. How are antibiotics for therapeutic use in animals regulated? Do veterinarians have guidelines or antibiotic audits? (Chapter 6)

12. Has therapeutic efficacy been compromised by the use of subtherapeutic levels of antibiotics in animal feeds?

Are resistant infections more prevalent in animals? (Chapters 5,6)

13. Critically review the documentation for increase in resistance, pathogenicity, and increase in numbers of pathogens after use of subtherapeutic antibiotics. (Chapters 5,6)

BARR asked its Committees on Animal Nutrition and Animal Health to set up a panel of their members and outside consultants to address these questions. The Panel met on June 11 and July 2 to 3, 1979, and prepared the statement that follows that addresses the 13 questions.

The panel is indebted to Enriqueta C. Bond and Roy Widdus, of the Division of Medical Sciences, for providing published research documents on the subject, and to Philip Ross and Selma P. Baron for their advice and guidance in the preparation of the report.

CHAPTER 2

SUBTHERAPEUTIC USE OF ANTIBIOTICS

ANIMAL MANAGEMENT

Swine

Pig production in the United States is more diverse geographically than broiler, turkey, and feedlot cattle production. About 90 percent of the nation's pork supply is produced in the 12 north central states plus Georgia, Kentucky, North Carolina, and Texas. The number of pigs slaughtered in the United States has varied from about 73 to 95 million head per year and yielded about 25 to 36 kg (carcass basis) annual per capita consumption for the U.S. citizen during the last 15 years.

The swine industry has changed from an enterprise that historically employed pasture to one that predominantly employs confinement buildings and concrete lots. The swine industry differs from the broiler industry, however, since nearly all the production is by private producers rather than by industrial entities. An appreciation of the change to intensive swine production is evident in Table 2.1. There has been a dramatic decrease in the number of farms which produce pigs, both nationwide and in Iowa, the largest producing state. The total production trend has changed little, except year-to-year responses to feed cost and pig selling price relationships.

Evidence of the continuing intensification since the 1974 census in the swine industry is provided by survey information obtained in 1975 and 1978 from large producers in the United States (Stemme et al. 1978, 1979). The number of producers that market 5,000 head or more and those producing from 2,500 to 4,999 head has increased during the 3-year period (Table 2.2). The annual production of this group of producers would account for more than 20 percent of the total U.S. production. Over 70 percent of the producers in this group have confinement housing facilities. Their worst problem in their farrowing facilities was reported to be *E. coli* scours.

TABLE 2.1 Number of Farms with Pigs in the United States and Iowa and Total U.S. Production

Year	Number of Farms with Pigs, United States	Number of Farms with Pigs, Iowa	Total U.S. Carcass Weight Produced (million pounds)
1954	1,424,000	136,800	12,002
1964	743,000	108,900	14,598
1974	450,000	66,300	14,331

SOURCE: U.S. Bureau of the Census (1974).

TABLE 2.2 Number of Large-Volume Producers and Size of Operation[a]

Year	Number of Operations Producing 2,500 to 4,999 Head/Year	Average Size of Operation	Number of Operations Producing 5,000 Head or More/Year	Average Size of Operation
1975	1,567	2,418[a]	1,168	7,053
1978	1,661	3,196	1,340	10,192

[a]A producer was included in this category if production was 2,500 head or more in any year included in the survey.

SOURCE: Stemme et al. (1978, 1979).

A new organizational form in pork production, the subsidiary sow-farrowing firm or sow-farrowing cooperative, has come into existence since 1970. These firms are organized generally by a group of producers as subchapter S corporations or cooperatives. The purpose of the organization and production unit is to produce feeder pigs (40 lbs) for the members or shareholders who do not want to farrow pigs, but do want to finish them (40 lbs to 220 lbs) on their farms (Hepp 1977, Paulsen and Rahm 1979). In Iowa 63 such firms were identified that began operation since 1974. The breeding herd size of those firms in the second year of production averaged 537 sows with an annual production capability of more than 8,000 feeder pigs each (Paulsen and Rahm 1979).

With intensification the disease problems have also changed. Historically, hog cholera, swine erysipelas, tuberculosis and brucellosis were the disease problems most troublesome. These have largely disappeared due to eradication programs. With concentration and confinement production the enteric diseases and respiratory diseases are the most prevalent problems reported.

As a group, both the large producers and the organized sow-farrowing firms employ an early weaning management system whereby the nursing pigs are weaned at 3 to 4 weeks of age. In 1976 an average investment of $1,176 per sow in the unit was reported (Paulsen and Rahm 1979). Because of the high fixed costs, the management places a high priority on total production. With early weaning the sow can be re-bred within a few days after her pigs are weaned and thereby increase the number of pigs produced per sow per year. Historically nursing pigs were weaned at 8 to 10 weeks of age and the sows were not re-bred until their farrowing date fit expected mild weather and/or the other activities associated with the farm enterprise, such as corn planting or harvesting. In the process of early weaning, natural protection from enteric disease problems in young pigs has been diminished (IgA immune globulins in sow's milk).

It is interesting to note that the introduction and use of feed-additive antibiotics has been concurrent with change in production technology in the swine industry. It is likely that the use of antimicrobial agents has facilitated the development of the concentrated operations.

Poultry

As part of the effort to produce poultry meat and eggs as economically as possible, it is common practice in the United States to maintain broilers, turkeys, and laying hens in large flocks in one location. From 10,000 to 20,000 broilers are typically raised in one house and some operations have as many as a million laying hens in one location. With such a concentration of birds it is essential to have disease control programs that will prevent disastrous losses to the poultry industry. Drugs, including the antibiotics, have played a major role in maintaining the health of poultry flocks since the 1950s.

The management procedures used in today's poultry production have made it possible to provide poultry meat and eggs for consumers very economically. In fact, until very recently the prices of broilers and eggs were similar to those 25 years ago despite a decrease in the value of the dollar through inflation. It is unlikely that future changes in management will result in any reduction in the concentration of poultry. Changes will probably involve upgrading of physical facilities for maintaining the birds, including environmentally controlled housing and the adoption of more automated equipment in the feeding and management of the birds.

Cattle and Sheep

In 1962 feedlots with a capacity of 1,000 head or more accounted for 40 percent of fed cattle marketings, while in 1978 lots of this size marketed 68 percent of the fed cattle (USDA 1979a). Due to the economics of feeding, increases in concentrations can be expected, but at a slower rate. As concentrations of feedlot cattle have increased, there has been increasing need for improved management and management systems.

Penicillin is not used in cattle feeding in the United States. However, the continuous low-level use of other antibiotics in cattle feeding is regional. In the more arid areas of the Southwest, there is no response to antibiotics as growth promotants, and therefore, they are not continuously fed. This lack of response appears to be related to climate. In the remainder of the feeding areas, low-level continuous feeding of antibiotics is routine. An estimated 50 to 60 percent of feedlot cattle are fed low-level antibiotics during the feeding period and a total of 40 percent of the total beef supply has been fed low-level antibiotics (USDA 1979b).

AMOUNT USED AND FEED PREPARATION

Swine

Feed requirement for swine is estimated at about 4.40 kg of feed per kilogram of liveweight sold at market (Van Arsdall 1978). In 1978 about 88 million head were slaughtered in the United States with an estimated average liveweight of 250 lbs. So in total, about 44 billion kg of feed were consumed by swine. The FDA (U.S. DHEW/FDA 1978) from the U.S. International Trade Commission (1974) data estimated the production of feed-additive antibiotics at 3,350,000 kg. About 10,000 feed mills manufacture or mix feeds containing drugs and they supplied about 12 million tons of feed to the swine industry. Several types of products are sold to farmers. Most of the feed-manufacturer tonnage is sold as supplements (protein, minerals, vitamins, and feed additives) to be further mixed or diluted with grain for feeding as a complete balanced diet by the swine producer.

A more concentrated form manufactured is a premix (vitamins, minerals, and feed additives). The premix is further mixed by an intermediate or secondary feed mill or mixed by the producer using grain and generally soybean meal as a protein source. Most pig starter diets used by the producer are purchased from a feed manufacturer as a complete feed. The purchase of complete mixed diets for the other stages of production is not as prevalent. The market structure of the feed industry is presented in Figure 2.1. Antibiotic usage by the feed industry is controlled by periodic inspections and sampling by representatives of the FDA and state feed-control inspectors. Such things as drug inventory control, approved levels of incorporation, product claims, and assay of finished product are monitored.

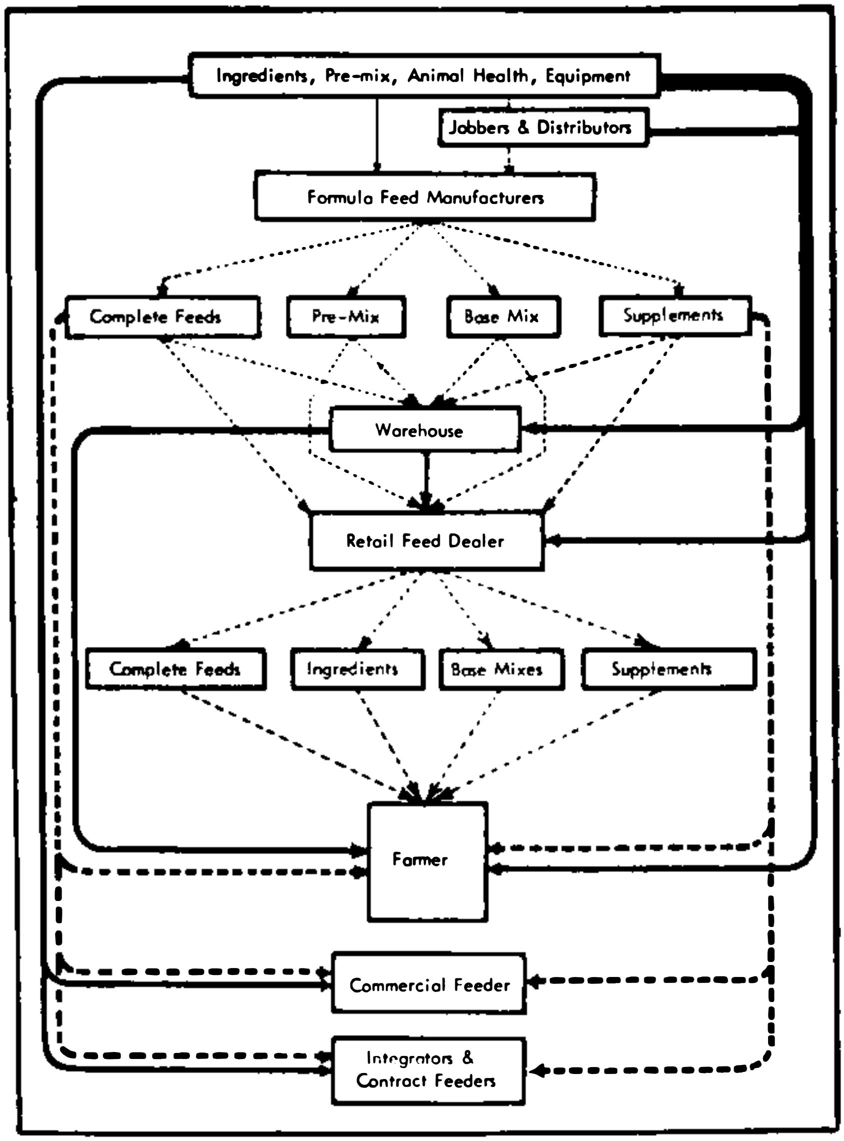
The consumption of feed-additive antibiotics per market pig is estimated in Table 2.3. It is estimated that in 1978, the 88 million pigs marketed consumed 1,408,000 kg of antibiotics or about 40 percent of the feed-additive antibiotics produced.

Poultry

Very little use is made of penicillin and the tetracyclines for low-level feeding (5 to 10 g/ton) for stimulating growth in poultry production. A major reason for this is that these antibiotics are not approved by the FDA for use in combination with monensin ("Coban," an anticoccidial drug). Monensin is used in about 85 percent of the broiler feed prepared in this country. Only the antibiotics lincomycin, bacitracin, and the bambermycins can be used at low levels in combination with this anticoccidial drug (Anonymous 1979c).

Very little penicillin is used in poultry production either for subtherapeutic or therapeutic purposes. Some penicillin is used in the diluent for Marek's disease vaccine, which is injected into day-old chicks. It is also used as a treatment for erysipelas in turkeys at a level of 100 g/ton plus a level injected to provide approximately 5

MARKET STRUCTURE OF FORMULA FEED INDUSTRY



SOURCE: Anonymous (1978).

FIGURE 2.1 Market structure of formula feed industry.

TABLE 2.3 Feed Required to Produce a 250-lb Pig, Recommended Antibiotic Levels, and Consumption of Antibiotics per Pig (estimates)

Stage of Production	Pounds of Feed Required per 250-lb Pig	Recommended Antibiotic Level (mg/lb diet)	Estimated Use (mg/lb diet)	Grams per Pig
Breeding Boar	15	---	Trace	---
Breeding Sow				
Pregnancy	150	---[a]	5.0	0.75
Lactation	60	50[b]	25.0	1.50
Starter	25	100-125	100.0	2.50
Grower	50	50	25.0	1.25
Finisher	800	1-25	12.5	10.00
Total	1,100			16.00

[a]For pregnancy, recommendations would include an antibiotic at a high level (1.0 g/day) during the breeding period, about 20-25 days. Not all sows would be fed an antibiotic.

[b]Since responses to antibiotics fed to the lactating sow are not consistent, no general recommendation is made for their inclusion by experiment stations.

SOURCE: V.C. Speer, Iowa State University, personal communication, 1979.

mg/kg body weight. Apparently little or no penicillin is used for treatment of diseases in chickens.

The tetracycline drugs are used quite extensively for treatment of diseases and for improving suboptimal performance of birds. Frequently, tetracycline (200 g/ton) or a combination of oxytetracycline (50 to 100 g/ton) and neomycin (35 to 140 g/ton) is used in the starter feeds for both turkeys and broilers. These are used in the first 0.23 kg of feed for each bird. In the case of broilers, the anticoccidial drug is removed since the combinations are not permitted by FDA regulations. The antibiotic drugs during this period of time are used to control several bacterial diseases and to get the birds off to a good start. Considerable amounts of tetracyclines are also used in laying hen diets at various times. From 50 to 100 g/ton are used for a 2-to-3-week period to improve shell quality and egg production in laying hens, particularly during the latter part of the laying cycle.

Most of the feed mixed for poultry production in the United States is made by large integrated companies and in large feed mills where careful control of the inclusion of the drugs and other feed ingredients is maintained on inventories. The feed manufacturers, in using drugs in poultry rations, must follow regulations of the FDA and be inspected periodically by this agency and state feed control officials.

A point that should be emphasized is that poultry producers do not indiscriminately use antibiotics in poultry feeds. Poultry operations only use antibiotics when their cost will be more than covered by the improved performance of the birds.

Ruminants

Based on approved claims, tetracyclines serve four purposes in cattle rations: (1) control of liver abscesses; (2) control of respiratory disease related to shipping fever; (3) control of foot rot; and (4) improved gains and feed efficiency (Anonymous 1979c). Cattle finishing diets contain high levels of grain and the incidence of liver abscesses increases as the level of grain feeding increases. Low-level feeding of the tetracyclines may reduce the incidence of liver abscesses by as much as 50 percent (Foster and Woods 1970, Woods 1970, Davis 1978). Daily gains in steers with liver abscesses may be depressed by 5 to 10 percent. No doubt a portion of the increased gain noted because of low-level feeding of the tetracyclines is due to the reduction of liver abscesses. On the basis of 1970 cattle and feed prices, Foster and Woods (1970) estimated a $9.30 loss for each animal with an abscessed liver. This value considered both feed cost and liver loss due to condemnation.

Subtherapeutic use of tetracyclines in cattle feeding may be divided into two categories (Woods 1970, Anonymous 1979c).

1. Incoming cattle may be fed 250 to 1,000 mg/day for a 7- to 28-day period after receipt for control of shipping fever. The highest feeding level would be equivalent to 200 g antibiotic per ton of feed. For incoming cattle, administration of antibiotics via water may also be used. During the feeding period, levels of 250 to 1,000 mg/day may be fed for short periods during outbreaks of respiratory problems. After recovery from shipping fever, the level is reduced to 70 to 80 mg/day for the remainder of the feeding period in areas where continuous feeding of low-level antibiotics is practiced.

2. For growth promotion and improvement of feed efficiency, the recommended levels of feeding are 70 to 80 mg/day (Anonymous 1979c). This may be included in the total feed or the daily supplement in areas where the ration is fed as grain, roughage, and supplement. The combination of chlortetracycline and sulfamethazine has been shown to be effective for control of the shipping-fever complex in cattle (Woods 1970).

The tetracyclines have been used primarily for disease treatment with lambs, although continuous feeding at 20 to 50 g per ton of feed has been shown to be beneficial for growth and aid in reduction of enterotoxemia. However, effective vaccines are available for enterotoxemia. Improvement of growth of suckling lambs occurs when the tetracyclines are included in the creep ration at 20 to 50 g per ton of feed (Beeson 1978).

The tetracyclines up to levels of 100 g per ton in milk replacer and starters for baby calves are effective in growth promotion and control of bacterial scours (Warner 1972).

EFFECTS OF RESTRICTIONS

Swine

The removal of antibiotics as feed additives, while continuing their therapeutic or prescription usage, would not necessarily reduce the total quantity used.

If antibiotics were eliminated as feed additives, it is questionable whether production in confinement swine operations could be maintained at an intensive level. It is likely that weaning age would be increased. Inventory would be reduced, more labor and time would be required to thoroughly clean and disinfect between groups of pigs, and the breeding herd efficiency would be reduced to conform to calendarized farrowings. In the long run, because of the increased cost of operating confinement units, a reversion to extensive or pasture production could take place. The seasonal nature of extensive production would mean large month to month variability in marketings reminiscent of historical patterns and would be disruptive for today's packing industry.

Poultry

The discontinuance of the use of penicillin in poultry feeds would have little effect, since this antibiotic is not used extensively at the present time. The only major problem would be in the treatment of erysipelas in turkeys since this antibiotic seems to be particularly effective against this disease. The complete removal of the tetracyclines, however, would have a much greater impact on the industry. Restriction of the use of these at low levels (5 to 10 g/ton) for growth stimulation would have little effect since they are not used now to any extent for this purpose. The elimination of the use of higher levels of tetracyclines, however, would create problems in the control of bacterial diseases in young chickens and turkeys and in maintaining optimum performance of laying hens. What undoubtedly would happen with the restriction of use of tetracyclines in feeds is a much greater use of these antibiotics in the water. This would lead to increased cost of medication and probably would result in no general reduction in the use of total quantities of tetracyclines in poultry production.

Ruminants

Unless the tetracyclines are completely restricted for use as a subtherapeutic low-level feeding, the resident veterinarian might prescribe them for low-level feeding to prevent certain disease problems.

Feedlot systems for beef cattle and sheep would not change if low-level feedings were not permitted. Disease problems and carcass condemnations would increase, and therapeutic use of antibiotics would increase.

ECONOMIC EFFECTS OF A BAN ON THE USE OF ANTIBIOTICS

Potential economic effects of a ban on antibiotic feed additives for 1973 livestock output, price, and cost conditions were examined by Gilliam and Martin (1975). They considered two hypothetical ways in which producers might react to such a ban: (1) by feeding additional numbers of beef cattle, veal calves, and hogs to achieve pre-ban output levels; and (2) by feeding the same number of animals on the same schedule, with the result of reduced output.

In situation (1), increased costs of production would be $801.7 million, assuming no change in mortality and no change in the cost of feeder cattle and pigs. If the costs were borne by consumers, annual per capita red meat costs would increase $3.85.

In situation (2), the annual expenditures for red meat would increase $2,134.5 million annually or $10.26 per capita.

If mortality increased in either situation, costs would be estimated to increase $0.36 to $1.25 per capita for each 1-percent increase in death rates.

A U.S. Department of Agriculture study (USDA 1978) considered the effects of a total ban on feed-additive antibiotics for each species of food-producing animals, assuming moderate drug efficiency and high drug efficiency. They considered the impact on total farm income and changes in consumer food costs during the first year of a total ban, and then the adjustments that would occur in 5 years. Their conclusions are summarized in Table 2.4. It is interesting to note that total farm income is projected to rise the first year. This is because of the inelastic relationships between price and supply for meat products.

Headley (1978) reported the results of an econometric analysis on the meat-animal industry as a result of banning different drug combinations. The consumer and national costs are presented in Table 2.5. The estimates of the economic impact to the industry and consumers appear to be realistic.

FUTURE CHANGES IN ANTIBIOTIC USE

As research in the control of diseases and the maintenance of optimum health continues, the use of antibiotics in the future will undoubtedly change. Producers will use the most economical means of preventing diseases to attain the lowest cost of production per unit of meat or eggs. If new vaccines, alternative drugs, and total eradication programs become more effective and/or more economical than the use of tetracyclines, these methods will replace the use of tetracyclines.

TABLE 2.4 Summary of Changes in Net Farm Income and USDA Food Market Basket from Banning All Subtherapeutic Use of Animal Drugs, First and Fifth Year after Ban

	First Year	Fifth Year
Farm Income		5
Moderate Drug Efficacy		
Change in billion dollar	+ 1.2	- 0.5
Change in percent	+ 4.7	- 2.1
High Drug Efficacy		
Change in billion dollars	+ 2.8	- 0.9
Change in percent	+10.8	- 3.81
Food Market Basket:[a]		
Base (dollars)	2,132	2,530
Moderate Drug Efficacy		
Change in dollars	+32.0	+ 5.0
Percent change from base	+ 1.5	+ 0.2
High Drug Efficacy		
Change in dollars	+99.0	+16.0
Percent change from base	+ 4.6	+ 0.7

[a]The market basket is the average quantities of domestic farm-origin foods purchased annually in retail food stores per urban household.

SOURCE: USDA (1978).

TABLE 2.5 Effects of Banning Selected Antibiotic and Drug Feed Additives on Annual Consumer Expenditures for Meat

Option	Estimated Annual Consumer Costs	
	Per Capita ($)	Nationally (billion $)
Ban tetracyclines and penicillin[a]	5.70	1.2
Ban nitrofurans and sulfa	12.00	2.6
Ban all of above	19.00	4.1

[a]It is assumed that substitute antibiotics will be available, mainly tylosin and bacitracin.

SOURCE: Headley (1978).

The concentrated raising of cattle, swine, and poultry has brought about new problems in control of infectious disease. Conditions have changed: the number of farms raising livestock has decreased 80 percent since 1940, and yet the number of animal units has doubled. The control of infectious disease has been responsible for the success of these concentrated enterprises. Such control is particularly important for young susceptible animals during the rapid growth phase. The main methods of controlling infectious disease are:

1. Preventing Exposure to Infectious Agents--Attempts to raise swine under specific pathogen free conditions in strict isolation have been tried, but found to be expensive and impractical. Cattle can be raised successfully and disease controlled through range-type rearing. However, this system would result in reducing total beef production by approxiamtely 50 percent as feedlot production would be lost. Isolation of dairy animals has been partially successful where calves are fed ample levels of colostrum and herds are confined. Some success has been achieved at raising poultry in isolation, but this is not a practical procedure by itself.

2. Subtherapeutic Use of Antibiotics--This approach has made possible the disease control and production gains known today. However, it has created an antibiotic-resistant bacteria problem that may affect the use of these drugs in both man and animals.

3. Treatment of Disease After Outbreak has Occurred--This technique is difficult and impractical especially in young stock because losses occur rapidly and morbidity and mortality during the growing period have major unrecoverable effects on production.

4. Control of Infectious Disease by Immunological Means--The main concerns in controlling infectious diseases in cattle, swine, and poultry are immunizing young animals and protecting the portals of entry, such as the respiratory and intestinal tracts. Under the present conditions of concentrated production, the natural protection afforded by maternal antibodies should be utilized by allowing the young to suckle for as long as possible.

There has been little success thus far in protecting animals against bacterial respiratory and intestinal pathogens. Certainly strides are being made in developing immunogens for certain coliform organisms, but solid long-term protection against pathogens of the respiratory and intestinal tracts may be difficult to produce. The immunological approach to disease control will not replace the use of antibiotics in the near future.

ALTERNATIVES

Resistance characteristics similar to those from tetracyclines and penicillin evolve when most other approved feed-additive antibiotics for swine are fed (Fagerberg and Quarles 1979). Certain sulfa drugs may be eliminated as feed additives because of residue problems, and carbadox and furazolidone are possible carcinogens. Bacitracin and Flavomycin (bambermycins) are not viable alternative feed additives, since they lack efficacy for the young pig (Hays 1978). Virginiamycin is the only approved feed-additive antibiotic that would then remain that would be efficacious for the young pig and growing-finishing pigs. Similar microbial defense mechanisms are likely to emerge against virginiamycin or against new antibiotics developed specifically for animal use.

In some situations, antibiotics other than the tetracyclines or penicillin could be used for the treatment of diseases in poultry. With few exceptions penicillin could be replaced by other antibiotics presently available. Elimination of tetracyclines would create more of a problem because these appear to be the most economical and effective for certain purposes in poultry production.

A detailed description of the approved subtherapeutic use and levels of the tetracyclines for cattle is given in the Feed Additive Compendium (Anonymous 1979c). At the present time, besides the tetracyclines, only three antibiotics (tylosin, bacitracin, and erythromycin) are available for subtherapeutic use in feedlot cattle. The only approved claim for tylosin is as an aid in reducing liver abscesses. Tylosin costs three times as much as the tetracyclines. While there is an approved claim for erythromycin for growth promotion and feed efficiency, it has not been used in the field. Very little field information has been developed for the use of bacitracin in cattle feeds. There is no approved substitute for chlortetracycline-sulfamethazine combination used for control of the shipping-fever complex.

If feed-additive drugs were available therapeutically via prescription, there probably would be little or no reduction in usage in swine, poultry, and ruminants.

If feed additives were not available through approved channels, violations by segments of the industry would be likely. Examples would include the use of chloramphenicol, dimetridazole, and high levels of copper sulfate.

Alternatives to feed-additive drug usage, discussed in more detail below, might include the following: (a) environmental and management changes, (b) selection for genetic resistance, (c) development of vaccines, (d) adoption of minimal disease programs, and (e) development of new feed additives that do not promote bacterial resistance relevant to human and animal health.

Environmental and Management Changes

Reducing the production intensity of facilities would reduce the enteric problems commonly encountered in farrowing and baby pig facilities, and would reduce respiratory problems in cattle feedlots. A time lapse between groups would allow adequate time for more thorough cleaning and sanitation of the facilities. As new facilities are constructed for swine, knowledgeable producers are building modified isolation rooms with reduced capacity to allow the opportunity for better sanitation between farrowings. In the case of broilers the use of cages would also allow for improved sanitation. A recent innovation has been the use of small wire-penned enclosures for young pigs which reduces the chance of contamination from one pig to another.

Progressive swine producers are becoming more appreciative of herd isolation to reduce disease problems. Many of the more intense units are applying artificial insemination as a means of introducing new blood lines into the herds. By raising their own boars and gilts for breeding herd replacements, producers avoid the risk of introducing new animals, possibly bearing new diseases, into the herds.

Selection for Genetic Resistance in Natural Immunity

Although information on this topic is limited, there are indications that older animals are more resistant to respiratory problems than younger ones. Usually, older, lactating sows confer an immunity to their offspring not present in pigs from young sows. Also some strains or breeds of animals may be more susceptible to respiratory and enteric problems.

Development of Vaccines

The need for disease control by antibiotics could be reduced by vaccinating animals for certain disease conditions, commonly the most troublesome in production. A bacterin was recently developed to control atrophic rhinitis in swine, and was sucessfully demonstrated in the field. Research is in progress on similar approaches for control of mycoplasma and _E. coli_ organisms and the agent for porcine pleuropneumonia.

Adaptation of Minimal Disease Programs

Swine herds free of respiratory problems can be maintained in that condition for some reasonable period of time. This state can be attained by hysterectomizing pregnant sows and raising the young pigs in isolation in the first generation. Subsequent generations are obtained naturally. The largest problem has been the accidental reintroduction of respiratory diseases. For this approach to be successful over long periods of time, complete isolation from man, pets, birds, and rodents is essential, which would be impractical.

Development of New Antibiotics

There are new experimental antibiotics effective for swine that are not being used in human medicine. Whether they have all the desirable attributes by present-day standards is not known. The goal of research should be the development of such compounds that avoid the characteristics that are thought to pose health hazards of men and animals as recognized by today's standards.

CHAPTER 3

EFFICACY OF ANTIBIOTICS IN ANIMAL FEEDS

SWINE

Several compilations of the average weight gain and feed efficiency improvements from feed-additive antibiotic additions to swine diets have been reported since the discovery of antibiotic growth stimulation (see Table 3.1). These reports represent mainly research or experiment-station trials, and it has been suggested that the improved performance observed in research facilities because of better sanitation and disease control is a conservative estimate of the response of animals fed in commercial production facilities. The percentage of responses in the young animal are great, but decrease as the animal nears market weight (Hays 1978). This is explained by the performance of the control animals and their increasing daily gain as they mature.

Hays (1978) compared present-day efficacy of antibiotics to their past effectiveness. The liveweight gain response of young pigs fed tetracyclines during the 1967 to 1977 period was greater than during the 1950 to 1956 period. Feed efficiency response was not as great, but the initial weights of the experimental pigs used in the 1967 to 1977 comparison was considerably greater (7 vs. 11 kg liveweight). The percentage of responses during the growing and finishing phases of production were not as great, but the liveweight gains of the growing pigs fed tetracyclines were essentially the same, while the rate of gain of the controls in the 1967 to 1977 group improved more than 11 percent for growing pigs and 3 percent for growing-finishing pigs compared to groups of animals used in the 1950 to 1956 comparison groups.

Beneficial effects of antibiotics on farrowing rates of sows have been summarized (Speer 1979c) in Table 3.2. In most cases the antibiotic or chemotherapeutic was fed at the rate of 1.0 g/sow/day for a short time before and after mating (about 20 days). Sows fed the control diets averaged 68.4 percent and sows fed the control diets plus drug averaged 77.4 percent farrowing rate.

An increase in the number of pigs farrowed by sows fed antibiotics before mating has been reported in a few experiments, but there is not enough evidence on this

TABLE 3.1 Experimental Antibiotic Responses for Swine

Years	Number of Experiments	Feeding Period	Percent Improvement		Author
			Rate of Gain	Feed/Gain	
1960-1967	8	Baby pigs (<100 g/ton antibiotic)	36.0	13.5	Zimmerman (1965)
1960-1967	7	Baby pigs (>100 g/ton antibiotic)	49.5	13.2	Zimmerman (1968)
1965-1970	20	Baby pigs (8-20 lbs)	35.7	15.6	Teague (1971)
1965-1970	6	Young pigs (22-42 lbs)	5.1	9.0	Teague (1971)
1950-1977	378	Young pigs (<35-80 lbs)	16.1	6.9	Hays (1978)
1950-1953	165	Growing pigs (30-50 lbs)	8.7-15.0	2.6-7.8	Braude et al. (1953)
1965-1970	7	Growing pigs	9.0	1.4	Teague (1971)
		Finishing pigs (same pigs)	6.7	0.1	
1950-1977	276	Growing pigs (35-80 lbs)	10.8	4.5	Hays (1978)
1950-1963	9	Growing-finishing	9.0	2.9	Melliere and Waitt (1971)
		Growing-finishing (no antibiotic during finishing)	6.2	1.2	
1950-1977	279	Growing-finishing (32-207 lbs)	4.0	2.1	Hays (1978)

TABLE 3.2 Effect of Antibiotics on Farrowing Rate

Drug	Number of Sows	Farrowing Rate (%)	
		Control	Treated
Chlortetracycline	179	62	79
Chlortetracycline	198	74	86
Aureo SP-250	96	81	96
Aureo SP-250	126	53	56
Aureo SP-250	79	30	36
Tylosin	192	75	77
Tylosin	143	81	84
Tylosin-Sulfamethazine	197	70	83
Furazolidone	87	63	93
Chlortetracycline	249	67	75
Chlortetracycline	239	71	72
Aureo SP-250	184	61	70
Chlortetracycline	101	90	94

SOURCE: V.C. Speer, Iowa State University, personal communication, 1979.

production trait to demonstrate that it has had a real effect.

POULTRY

It is generally conceded that management, housing, disease elimination, disease control, isolation, and genetic improvement is far more sophisticated in the poultry industry than any of the other industries. Poultry production facilities can be completely vacated between groups of birds, the facilities thoroughly cleaned, and then the whole production unit filled with birds of the same age and at the same time. Yet, improvements in production traits as a result of antibiotic administration are clearly evident from the summary data presented in Table 3.3. The only production criterion that was not improved was percent hatchability for turkey breeders. A comparison of the responses to antibiotics reported in the literature since 1970 compared to the period 1950 to 1977 was examined by Hays (1978). It can be concluded that the antibiotics continue to be as effective as they were originally.

CATTLE AND SHEEP

Feedlot cattle rate of gain and feed efficiency responses to antibiotics are both improved about 5 percent (Table 3.4). The tetracyclines have been the most widely used antibiotics in the beef cattle industry. (Recently monensin has been approved for use for improved feed efficiency in feedlot cattle. General use by the industry has been rapid. Only tylosin in combination with monensin has been approved for use at this time.) The response seems to be greater on high-roughage rations than low-roughage rations. A marked reduction in the incidence of liver abscesses in feedlot cattle fed antibiotics, particularly the tetracyclines or tylosin, is economically significant both from improved performance in the feedlot and increased carcass value. Responses in calves, both dairy and veal, are greater than with older cattle (Table 3.5). Feed-additive antibiotics have no recognized beneficial effects for the milking dairy cow.

Like other farm species, the young lamb responds to low levels of antibiotics (10 to 25 g per ton of diet). The response of western feeder lambs seems to be more variable. The tetracycline antibiotics are more commonly used in feeder lamb diets. Low levels of these antibiotics reduce the incidence of enterotoxemia in feedlot lambs.

TABLE 3.3 Experimental Antibiotic Responses for Poultry

Species or Type of Bird	Stage of Growth or Production	Number of Comparisons	Comparison: Control	Comparison: Antibiotic	Percent Improvement	Number of Comparisons	Comparison: Control	Comparison: Antibiotic	Percent Improvement
			Weight (grams)				Feed/Gain		
Chick	Hatch to about 4 weeks	565	382.0	407.7	6.72	313	2.03	1.94	4.43
Chick	Hatch to about 8 weeks	286	1,313.0	1,351.6	2.94	219	2.42	2.36	2.48
			Egg Production (%)				Feed/Dozen Eggs (lbs)		
Hens	Egg production	244	59.9	62.3	4.01	122	5.30	5.05	4.72
			Hatchability (%)						
Hens	Breeders	69	76.2	78.8	3.41				
			Weight (grams)				Feed/Gain		
Turkeys	Hatch to about 4 weeks	166	489.0	554.0	13.29	76	1.86	1.73	6.98
Turkeys	Hatch to about 8 weeks	126	1,963.0	2,101.0	7.03	100	2.08	2.00	3.85
			Weight (lbs)						
Turkeys	Hatch to market weight	85	19.80	21.22	7.17	77	3.18	3.12	1.89
			Egg Production (%)				Feed/Egg (grams)		
Turkeys	Breeders	15	44.2	44.8	1.36	9	516.00	483.00	6.40
			Hatchability (%)						
Turkeys	Breeders	16	70.0	70.0					

SOURCE: Adopted from Hays (1978).

TABLE 3.4 Cattle Feeding Trials with Chlortetracycline

Number of Trials	Comparisons Control	Antibiotic	Percent Improvement	Source
	Daily Gain (lbs)[1]			
16	2.17	2.29	5.82	U.S. DHEW/FDA (1972)
	Feed/Gain*			
21	10.2	9.7	4.22	U.S. DHEW/FDA (1972)
	Liver Abscess Incidence (%)[1]			
8	41.5	15.9	-61.8[2]	U.S. DHEW/FDA (1972)
	Daily Gain (lbs)			
34	2.33	2.43	4.3 Rapid gaining animals	Burroughs et al. (1959)
31	1.42	1.50	5.6 Slower gaining animals	Burroughs et al. (1959)
	Feed/Gain			
34	10.34	9.96	3.7 Rapid gaining animals	Burroughs et al. (1959)
31	12.31	11.45	7.0 Slower gaining animals	Burroughs et al. (1959)

[1]Only trials in which <100 mg CTC/head/day was fed.
[2]Reduction

TABLE 3.5 Calf Feeding Trials with Chlortetracycline[a]

Number of Trials	Comparison		Percent Improvement
	Control	Antibiotic	
	Daily Gain (lbs)		
16	1.16	1.38	19.0
	TDN/Gain (lbs)		
10	2.16	1.96	9.3

[a]Only trials in which <100 mg CTC/head/day was fed.

SOURCE: U.S. DHEW/FDA (1972).

CHAPTER 4

RESTRICTIONS ON ANTIBIOTICS IN EUROPE

BACKGROUND

Most of the activities concerning restriction of antibiotic use were initiated in the United Kingdom following the Swann Report (1969). Action in other European countries followed that of the United Kingdom. The British were among the first in Europe to use antibiotics extensively as growth promotants.

In 1947 a Penicillin Act was passed by the British Parliament prohibiting the sale of antibiotics except for medical and veterinary use (Braude 1978). In 1953 the Therapeutic Substances Act was passed following research in the United States and the United Kingdom showing substantial economic advantages from including penicillin or chlortetracycline in the diets of young animals, and advice from the Medical Research Council that no adverse effects were observed in humans eating meat from antibiotic-fed animals. The regulation allowed inclusion of penicillin or chlortetracycline at a maximum of 100 g/ton to diets of growing pigs and poultry. Later, oxytetracycline was approved. Use of antibiotics in ruminant feeds was not approved.

In 1956 workers convened by the Agricultural Research Council concluded that the only potential danger from feeding antibiotics was the possible establishment of resistant strains of pathogenic microorganisms. In 1960 a Joint Committee was appointed by the Agricultural and Medical Research Councils, under the chairmanship of Lord Netherthorpe. In the first report this committee recognized that continued exposure of a bacterial population to an antibiotic leads to a progressive reduction in sensitivity to that antibiotic. They indicated that there was firm evidence that antibiotic-resistant strains of certain microorganisms such as E. coli and Salmonella species became established in animals that had received antibiotics as feed additives or therapeutically. However, there were no substantial indications that bacterial resistance had interfered with therapy by a particular antibiotic.

Following agitation in the popular press and media, the Netherthorpe Committee met in January of 1966 and recommended that "an appropriate body with sufficiently wide terms of reference should consider the evidence about the use of antibiotics in both animal husbandry and veterinary medicine and its implications in the field of public health" (Braude 1978). In July 1968 the Ministers of Health and Agriculture, Fisheries, and Food appointed a joint committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine under the chairmanship of Professor M.M. Swann. In November 1969 the Swann Report was published. The main recommendations were that:

1. the supply of penicillin, chlortetracycline, and oxytetracycline without prescription should be revoked, and that of tylosin, nitrofuran, and sulfonamides should be available only on prescription;

2. "feed" antibiotics as defined by the Netherthorpe Committee should be available without prescription for pigs and poultry, and for calves up to 3 months of age, but not to laying poultry and adult breeding stock (the latter restriction was subsequently removed); and

3. "therapeutic" antibiotics should be available for use in animals only if prescribed by a member of the veterinary profession who has the animals under his care.

ANTIBIOTIC USE

The Swann Report noted that in 1967, 240 tons of antibiotics were used in the United Kingdom for medical use and 168 tons for veterinary use, a 6:4 ratio (Braude 1978). If penicillin and tetracyclines were removed, the ratio was 8:2. In an independent survey the same year a ratio of 8.5:1.5 was obtained (Braude 1978). In the latter survey two-thirds of the 15 percent used by veterinarians was for therapeutic purposes (10 percent of total) and one-third for growth promotion (5 percent of total). The ratio between medical and other uses of antibiotics was about 7.5:2.5 in 1975 (Braude 1978). The 25 percent used for nonmedical purposes was divided 70:30 for veterinary and growth promotion, respectively.

There is little indication that overall sales of antibiotics for veterinary use has decreased as a result of the Swann Report (Linton 1977a). The total usage of antibiotics in the United Kingdom has increased since the Swann Report (Table 4.1). There was no substantial increase from 1963 to 1967, but the amount essentially doubled (penicillins, tetracyclines, and feed antibiotics) by 1975 (Braude 1978). "Feed" antibiotics include those that are allowed to be used in the feed and include flavomycin

TABLE 4.1 Usage of Antibiotics as Feed Additives (kg of active ingredients)

Year	Penicillins and Tetracyclines	"Feed" Antibiotics
1963	40,983	
1964	37,188	
1965	35,205	
1966	36,460	
1967	41,680	
1971		20,000
1973	19,000	
1974	22,000	
1975	26,500	55,000

SOURCE: Braude, R. (1978) Antibiotics in Animal feeds in Great Britain. Reprinted by permission of Journal of Animal Science 46:1425.

(bambermycins), virginiamycin, and zinc bacitracin. In a recent controversial BBC program, "Brass Tacks," misuse of antibiotics by farmers was alleged (Anonymous 1979a). It was suggested that veterinary surgeons may over-prescribe.

PERFORMANCE

There is no evidence that performance has been decreased as a result of the implementation of the recommendations of the Swann Report. However, antibiotics are still used in large amounts (Table 4.1) and substitutes such as copper sulfate have been introduced.

RESISTANCE

Low-level antibiotic feeding has resulted in bacterial resistance (Linton 1977 a,b; Smith 1977a; Braude 1978; Richmond and Linton 1979). Large differences have been found in drug resistance of E. coli between animals fed and those not fed antibiotics. The resistance to antibiotics is transmissible. In many instances the resistance is due to the presence of R-plasmids. These R-plasmids are able to mediate their own conjugal transfer in addition to specifying resistance to certain antibiotics.

An outbreak of Salmonella typhimurium phage type 29 occurred in calves in Britain from 1963 to 1969 (Linton 1977b). Evidence was obtained indicating that the emergence of resistant S. typhimurium correlated closely with the increasing range of antibiotics used, and that resistant strains also caused infections in man. The evidence concerning antibiotic-resistant E. coli of animal origin reaching man is not complete. It was concluded that antibiotic-resistant E. coli in animals cannot be distinguished from those found in man. Transferable drug resistance was demonstrated in chickens and calves, but not in pigs, by feeding large numbers of donor strains to these animals. Transfer of drug resistance to humans by feeding donor cells from animals or humans has not been substantiated.

Persistence of drug resistance has been related to the usage pattern of antibiotics (Linton 1977 a,b). Use of antibiotics in dairy herds for treating mastitis or as a prophylactic at the end of lactation had little or no effect on drug resistance in E. coli. In pigs, calves, and poultry, administration of antibiotics by the oral route for short periods resulted in high levels of drug resistance which soon decreased. Conversely, when antibiotics were fed continuously at subtherapeutic levels incidence of drug resistance was greater and persisted for a long period after the drug was discontinued. Continuous exposure appears to stabilize the resistant organisms, which become part of the flora of the gut.

Richmond and Linton (1979) recently conducted studies to determine if the animal or human use of tetracyclines was quantitatively the more important source of resistant E. coli for man. They studied the amount of tetracycline prescribed in the County of Avon, England. By extrapolation they found that 3 percent of all prescriptions were for tetracyclines. They found that in hospitals tetracycline was used in 26 percent of all acute beds and 55 percent of all long-stay beds. It was concluded that at any one time 0.75 percent of the county's approximately 1 million inhabitants will be excreting tetracycline-resistant organisms as a direct result of tetracycline treatment. This figure compares favorably with the value of 3 percent of the coliforms in Bristol sewage found to be resistant to tetracycline. Furthermore, sewage from hospitals was found to contain a higher proportion of resistant R-factor-carrying strains of E. coli with multiple resistance than did domestic sewage (Linton 1977b). Richmond and Linton also obtained evidence that use of other antimicrobial agents such as sulfonamide may select indirectly for tetracycline resistance.

Richmond and Linton (1979) stated "overall, therefore, it seems as though we must look to the medical, as opposed to the veterinary, use of tetracycline as the main selective pressure for the high incidence of tetracycline-resistant organisms in the human population, and the source of such organisms in human beings not receiving antibiotics is more likely to lie in human beings who are being treated than in the farm animal population." It has been suggested that "those doctors who criticize their veterinary colleagues for the indiscriminate and inappropriate use of antimicrobial agents in animals should pause awhile before casting their stones" (Anonymous 1979b).

It has been reported that tetracycline-resistant Salmonella species in swine and humans have decreased in the Netherlands since 1973 (van Leeuwen et al., National Institute for Public Health, Bilthoven, the Netherlands, personal communication, 1979). This decrease coincides with the discontinued use of tetracycline as a feed antibiotic. However, in calves the number of type 505 isolates of S. typhimurium has remained constant and the number of multiple resistant phage type 201 has increased.

In the United Kingdom there has been no change in the incidence of pigs excreting tetracycline-resistant E. coli (Braude 1978). No decrease in oxytetracycline-resistant E. coli in pigs was found in the United Kingdom from 1956 to 1975 (Smith 1977a). M.R. Richmond (University of Bristol, personal communication, 1979) stated that no reduction had occurred in the incidence of antibiotic-resistant E. coli in Europe following the implementation of regulations recommended in the Swann Report.

The Scientific Committee for Animal Nutrition was set up by the Commission of the European Communities to provide informed opinions on matters pertaining to animal nutrition and effects of production methods on food quality and the environment. A series of reports was prepared by the Scientific Committee for Animal Nutrition (1978) related to antimicrobials. Three of the reports concerned antibiotics. The reports covered (1) The Use of Macrolides and Related Products in Feedingstuffs, (2) The Conditions of Use of Certain Antibiotics in Feedingstuffs, and (3) Use of Zinc Bacitracin and Flavophospholipol and Feedingstuffs for Laying Hens. The antibiotics covered in the reports were: oleandomycin, spiramycin, erythromycin, tylosin, lincomycin, virginiamycin, zinc bacitracin, and flavophospholipol. Use of penicillin and tetracyclines was not addressed.

CHAPTER 5

EFFECTS ON ANIMAL DISEASE OF SUBTHERAPEUTIC USE OF ANTIBIOTICS

During the last 30 years, subtherapeutic levels of antibacterial drugs have been fed extensively in every major livestock and poultry producing country. The wide acceptance of antibiotics in low levels is attributed to their established benefits of improving feed conversion and growth rate and reducing the morbidity and mortality from subclinical and clinical diseases. During this same period, the poultry, swine, and beef cattle industries were able to develop large, highly intense production units by the use of antibiotics to control disease problems or to increase performance.

Subtherapeutic levels of antibiotics have been defined by the FDA as lower than the therapeutic levels needed to cure disease. This has arbitrarily been set at 200 g per ton of feed for chickens and/or swine and 11 mg/kg bodyweight per day for cattle (U.S. DHEW/FDA 1978).

It is unknown whether the activity of antibiotics used in low levels in animal feeds exerts its influence by: (a) metabolic effect, (b) nutrient sparing or increased absorption and utilization of nutrients, (c) activity against microorganisms, or (d) a combination of these activities.

Data presented by Hays (1978) indicated that the wise use of antibiotics is not a substitute for, but a complement to, good sanitation and husbandry for disease control.

Soon after the introduction of antibiotic agents, drug resistance in bacteria was observed. This phenomenon was also observed to occur spontaneously and in other stress situations. Under continuous antibacterial pressure such resistant organisms will become predominant (Smith 1967).

After 30 years of extensive use of antibiotics in animal feeds, discussions still deal with potential public health hazards. It is difficult to cite human health problems that can be attributed specifically to meat from animals fed antibiotics or that can be associated with direct or indirect contact with animals fed low levels of antibiotics. The evidence that resistant organisms in animals compromise the treatment of diseases in man or animals is sparse, indirect and difficult to evaluate.

A general decrease in the cost of antibiotics has encouraged the use of higher levels than were commonly used several years after the growth promoting effects of antibiotics were first discovered. The levels selected at that time were not levels that elicit maximum response. Generally they were compromised levels based upon a cost/benefit ratio.

The possible hazards to animal health from using antibiotics in low levels are: (1) adverse or toxic reactions in the animal, (2) development of resistant strains of pathogenic organisms, and (3) increased susceptibility to some infections through immunosuppression or alteration in the microflora.

Toxicity is usually not a problem in food animals from the use of antibiotics. When such problems occur, they are usually traced to human error, i.e., the misuse of the drug for purposes not included on the label or mixing errors.

There is likelihood that antibiotic utilization has been abused both in animal and human medicine. It has been shown that the use of subtherapeutic and therapeutic levels of antibiotics does in fact cause resistant strains of organisms to emerge. This may make it necessary to change drugs when treatment is not effective for the first drug of choice. As in man, there is no way to know what role the use of antibiotics in animal feeds at the subtherapeutic level has on the establishment of resistant populations of bacteria when compared to the therapeutic use of antibiotics.

Salmonella species are widespread in nature and frequently cause food poisoning in humans. Epidemiological studies show that foods of animal origin are frequently involved. Salmonellosis in humans involving antibiotic-resistant strains of bovine origin has occurred (Anderson 1968, Threlfall et al. 1978). Although the disturbances occurred under conditions of widespread antibiotic use, there is no evidence of any relationship to subtherapeutic feeding. These studies are not generally complete enough to determine the source of contamination. It is difficult to determine whether or not these foods were contaminated before or after slaughter or if the last vector was a food handler. It is doubtful that restricting antibiotic levels in animal feeds will cause a reduction in food-borne infections of humans.

Up to the mid-1960s, before antimicrobial resistance became recognized as a result of widespread use of antibiotics, the compromising effect of subtherapeutic antibiotic administration was repeatedly registered. Smith (1967) wrote "it is becoming increasingly apparent that the frequent prophylactic and therapeutic use in a pig herd of any of the available antibacterial drugs eventually results in penicillin drugs becoming largely ineffective in the treatment of E. coli infections." He also documented the development of penicillin resistance in 60 percent of staphylococcal strains in arthritis in chickens on diets containing penicillin and tetracyclines. Arthritis outbreaks in years prior to antibiotic feeding yielded strains susceptible to penicillin. More recently, Hjerpe (1976) reported a decline in response to tetracycline therapy by pneumonic cattle simultaneous with a rise in prevalence of tetracycline, penicillin, and sulfonamide-resistant strains of Pasteurella species after feeding of subtherapeutic levels (100 g/ton) of chlortetracycline was initiated in a feedlot.

The general rise in antibiotic resistance among bacteria during the past 30 years of intensive antibiotic use has undoubtedly curtailed the usefulness of some previously effective drugs. Documentation concerning this development is scarce, and the extent of it ascribable to subtherapeutic use of antibiotics is impossible to determine.

CHAPTER 6

THERAPEUTIC USE OF ANTIBIOTICS

BACKGROUND

Infectious diseases constitute the largest single category of medical problems in the several species of domestic animals. As a result, veterinarians have had a critical need for the anti-infective drugs in the course of everyday practice. Prior to the introduction of modern antibiotics, metallo-organic compounds, various antibacterial dyes, and other chemotherapeutic agents were employed. Shortly after sulfonamides were introduced in the late 1930s, they were recognized as being effective against bovine mastitis, and soon after against a wide spectrum of other bacterial infections of animals. Similarly, introduction of the various forms of penicillin soon led to their broad application in all species of domesticated and zoo animals. As the antibiotic era developed, each new addition to the antibiotic roster, such as the tetracyclines, chloramphenicol, bacitracin, streptomycins, neomycin, kanamycin, gentamicin, polymyxin, griseofulvin, nystatin, amphotericin B, erythromycin, tylosin, lincomycin, clindamycin, cephalosporins, and the semisynthetic penicillins soon found a valued position in veterinary medicine.

In-depth surveys (1967, 1972 to 1975) of the therapeutic usage of various classes of drugs in veterinary medicine have been reported from the University of Minnesota College of Veterinary Medicine. There, workers have, over the past years, surveyed the frequency of total drug usage in both large and small animals, including the categories of companion, zoo, and food-producing species (Stowe 1975). These studies clearly revealed that antibiotic drugs were the most frequently used agents in the treatment of animal disease. The studies involved the sampling of 5 percent of the clinical cases that were presented to the Veterinary Teaching Hospitals, including the out-patient and in-patient Large and Small Animal Hospitals and a rural outlying food-animal practice. In terms of the total number of drug treatments (many animals received more than one drug) the most frequently employed classes of drugs were as follows: antibiotic agents, 48 percent; anthelmintics, 15 percent;

corticosteroids and other endocrine agents (exclusive of diethylstilbestrol), 12 percent; fluids and electrolytes, 7 percent; analgesics, anesthetics, and tranquilizers, 6 percent; and gastrointestinal agents, 5 percent; with the remainder scattered among the autonomic, cardiac, antihistamine, topical, and miscellaneous categories. While this survey dealt only with one large teaching hospital in the upper Midwest, frequent contacts with comparable institutions elsewhere and with both large and small animal practitioners leaves little doubt that infectious diseases constitute the largest single category of disease problems, and that antibiotic drugs are the most frequently employed agents.

Within the category of antibiotic agents, the most frequently employed drugs are the penicillins (including the broad spectrum derivatives such as ampicillin and the penicillinase-resistant penicillins such as cloxacillin, dicloxacillin, etc.) and the tetracyclines, particularly oxytetracycline. In addition to these "mainstays" which continue to be effective and serviceable in the majority of cases, the sulfonamides continue to be heavily used because of their efficacy in the frequently encountered pasteurellosis infections in cattle and sheep. Tylosin, a nonhuman antibiotic, is also very heavily employed. In general, the economics of livestock production is a significant determinant in deciding which antibiotic agent to employ: the newer antibiotics tend to be more costly, a fact that makes their routine use in food animals uneconomical. In companion animals, on the other hand, including horses, the cost of medication is often not a major consideration, and thus erythromycins, cephalosporins, gentamicin, and sulfonamide-trimethoprim combinations are more frequently employed.

In terms of efficacy and safety, there can be little doubt that the antibiotic drugs are essential therapeutic agents in the diseases of domestic animals.

The widespread usage of veterinary services in the livestock industry points to a very real economic gain to the producer when veterinary services are utilized. In a series of studies sponsored by the Minnesota Agricultural Experiment Station, the World Bank, and the U.S. Department of Agriculture, it was found that there is a strong positive correlation between the use of veterinary services, the health of livestock, and the net income from the farm operation (McCauley 1974 a,b). In view of the major use of antibiotic drugs in veterinary practice, it would seem reasonable to infer that these drugs constitute a significant contribution to livestock production and economics.

From time to time, infectious diseases do not seem to respond to treatment with a particular antibiotic drug. In such instances either the dosage is increased, or another antibiotic agent is selected. In most cases, when therapy with an appropriate drug is initiated early in the course of the disease, the outcome is ultimately successful. However, when faced with therapeutic failure, some veterinarians conclude that their initial selection was unsuccessful because of prior use of low-level feeding of antibiotic substances to a herd or flock. A few practitioners declare that the problems they perceive as drug failures can be attributed to low-level antibiotic feeding. When queried in detail about their justification for such statements, proof is lacking. Carefully controlled studies regarding the cause-and-effect relationships between antibiotic feeding and subsequent therapeutic failures are lacking. Certainly veterinary practitioners, whether rural or urban, are not equipped to undertake the in-depth studies required to establish or refute the point at issue and consequently their opinions, no matter how firmly expressed, have to be rejected due to lack of scientific evidence. It is self-evident that perceived therapeutic failures could be due to factors such as misdiagnosis, inadequate dosages, antibiotic drug antagonisms, and others.

In some of the larger group practices and at the veterinary teaching institutions, antibiotic drug sensitivity tests are employed quite routinely. Lack of susceptibility or resistance to standard concentrations of various antibiotic drugs is encountered to a varied degree with all drugs, including those that have not been used at all, or used only to a minimal extent for low-level antibiotic feeding (i.e., cephalosporins, chloramphenicol, gentamicin, kanamycin). Moreover, the validity of _in vitro_ sensitivity testing has sometimes been questioned. Clinicians have reported therapeutic successes in treating infections due to agents shown to be resistant by laboratory tests (C.M. Stowe, University of Minnesota, College of Veterinary Medicine, personal communication, 1979). This general observation is further buttressed by comparing the apparent frequency of _in vitro_ nonresponsiveness in the hospital-clinic setting to that which one obtains in the farm setting, where the frequency of nonresponsive organisms seems to be lower despite the juxtaposition in the latter case to low-level antibiotic feeding.

The use of data gathered from veterinary teaching hospitals and clinics regarding the frequency of resistance among pathogens may not be an accurate reflection of the true level of resistance in specific regions of the country or in the nation at large. Before any inferences are drawn regarding the degree or frequency of resistant animal pathogens, we need to have more in-depth knowledge of the spectrum, scope, and degree of antibiotic resistance that is representative at least in the domestic animal population. At present there simply is no body of incontrovertible evidence regarding the relative importance of the human as a source of resistant organisms in animals or of animals as a source of resistant organisms in man. Furthermore, it would be impossible at the present time to say whether the resistant organisms arose as a result of subtherapeutic antibiotic feeding, prophylactic use, or therapeutic use for the treatment of a specific disease outbreak.

CONTROL AND REGULATION

Control and regulation of the therapeutic use of antibiotic drugs is under the purview of the FDA, particularly the Bureau of Veterinary Medicine and the Bureau of Foods. Control is exercised through the mechanism of the New Animal Drug Application (NADA). Once approval is granted and the drug is marketed, therapeutic use by veterinarians and in some cases by livestock producers follows. Such usage is based on the indications of the drug; the experience of the practitioner; and the inherent constraints of the dosage, route of administration, and the residue or withdrawal times. In the overwhelming majority of cases care is taken to observe the requirements of proper withdrawal times for either milk or meat.

From time to time, the question of auditing antibiotic drug usage arises, primarily within the setting of human hospitals. Other than in an institutional setting, the auditing of drug usage would be very time consuming, costly, and difficult to control.

EPIDEMIOLOGICAL CONSIDERATIONS

There is general agreement that the use of antibiotics in both animals and humans leads to increased frequency of antibiotic resistance. Furthermore, there is little doubt that resistance can be transferred through plasmids from certain resistant microorganisms to others that were originally sensitive. These in turn have been shown to be transmissible to other animals and, in isolated cases, to humans (Levy et al. 1976 a,b; Hirsh 1977). This resistance transfer or "infectious drug resistance" has led on the part of some individuals, to the fear that resistant strains could be transferred to other animals and humans, thereby creating a reservoir of pathogens, which when involved in clinical infections, would be unresponsive to antibiotic treatment. While such fears may seem to be a logical extension of current knowledge regarding resistance, there is practically no information on the extent to which this is happening, nor is it clear in the case of the few such instances known whether they were due to low-level antibiotic feeding, therapeutic use of antibiotics in domestic animals (including companion and pet animals), or therapeutic or prophylactic use of antibiotic drugs in human beings. These vexing questions are not easily resolved, particularly in view of the fact that both humans and animals often share the same pathogens.

CHAPTER 7

VOIDS IN KNOWLEDGE AND SUGGESTED RESEARCH

Although voluminous research has been conducted regarding the effects of feeding antibiotics on performance, research has been very limited in certain other areas. Research results have shown that resistance of microorganisms exists in animals fed antibiotics and that this resistance can be transferred (Linton 1977 a,b; Smith 1977a). However, there is inconclusive evidence that the use of antibiotics as growth promotants compromises therapy of humans and animals. Few well-designed experiments have been reported, and clearly there is a need for well-designed intensive investigations of this important issue.

The main objectives of the proposed research to fill in the primary voids concerning antibiotics are to determine: (a) if the feeding of tetracyclines and penicillin compromise animal therapy, (b) the relation of antibiotic feeding to human health, and (c) the mechanism of action of antibiotics in growth promotion.

It is suggested that the research described in the following pages be undertaken.

EFFECT OF TETRACYCLINE FEEDING ON ANIMAL THERAPY

Poultry and Swine

The possibility that administration of subtherapeutic levels of antibiotics may compromise therapy has not been adequately investigated. Most previous studies have given negative results with respect to this question, but according to the FDA (U.S. DHEW/FDA 1978) experiments generally were poorly designed. Carefully planned and controlled experiments conducted with poultry and swine should be conducted to attempt to answer this question with organisms such as _Salmonella typhimurium_. This organism should be used in these animals to determine whether development of resistant organisms will compromise treatment of a severe infection in the species. Chicks and swine should be inoculated with _S. typhimurium_ to induce a low-level, nonlethal infection, and be fed diets with and without tetracycline. After a few weeks the animals will be challenged with an inoculum calculated to cause a severe infection resulting in considerable mortality. This inoculum should be isolated from animals fed antibiotic and should be documented to contain antibiotic-resistant organisms. The effectiveness of therapeutic levels of tetracyclines and other antibiotics against this infection should be determined. To avoid the problem of possible development of immunity, animals unexposed to the organism should also be inoculated with the dose to cause a severe infection, and the effectiveness of antibiotic therapy in these animals should also be investigated. Careful laboratory work to monitor development of antibiotic-resistant organisms in the animals and immunity development would be needed.

Cattle

Cattle in commercial feedlots should be studied that (a) have not received antibiotics; (b) have received a high level of antibiotic during the first 3 to 4 weeks, followed by a low level during the remainder of the period on feed; and (c) have received a high level of antibiotic during the first 3 to 4 weeks, followed by withdrawal of the drug. Comparisons should be made of tetracycline therapy on sick animals from the lots on the various treatments. Response to therapy should also be monitored by the number of animals treated, the length of stay in the sick pens, and mortality. Measurements should also include antibiotic susceptibility of organisms in treated animals and samples of healthy animals from all lots at periodic intervals.

This type of experiment will need to be performed in cooperation with university or USDA scientists and feedlots. It would be ideal for most of the feedlots to be in the California and Arizona area where antibiotics are not normally used. However, it would be important that some feedlots, at least those that are treated, be located in the Colorado or Kansas area, where a continuous level of feeding of tetracyclines is routinely practiced. It will be essential that the cooperating feedlots use only tetracycline as the subtherapeutic and therapeutic drug. It will be essential to reimburse the feedlots for death losses above the normal mortality rate caused by the experimental treatments. Also, some compensation will have to be made for the extra labor involved in handling the cattle, such as monitoring the normal animals for antibiotic-resistant organisms. The organisms used to monitor resistance will likely be a common species of *Salmonella* and *E. coli*.

RELATION OF ANTIBIOTIC FEEDING TO HUMAN HEALTH

The information which would be required to answer the controversial question will necessitate investigations of staggering complexity and cost. It is likely that broad-based studies will involve monitoring of health-related problems among human populations involved in and isolated from low-level antibiotic feeding programs. Of course, when studying people involved with animals and animal products, animal health should also be monitored. Baselines must also be established by determining the history of the subjects with regard to antibiotic exposure and the susceptibility of the microflora species to antibiotics.

Recent experiments with animals have shown that randomly selected individuals already carry some resistant enteric microorganisms. It may be necessary to study respiratory bacterial flora instead of, or in addition to, the changes or lack of changes in susceptibility by species over a period of time and the nature of any disease episode particularly if suggestive of microbial etiology. The susceptibility of any agent thought to be involved would have to be established and the success of antimicrobial therapy determined clinically and microbiologically. The logistics and mechanics of this type of study will be extremely demanding in time and labor. Some aspects, especially those involving humans, would require several years, a large population, or both, for the collection of adequate data. If the microflora present at the onset is already predominantly resistant to the antimicrobials of interest, this study would be pointless.

MECHANISMS OF ACTION OF ANTIBIOTICS IN GROWTH PROMOTION

"Growth promotion" from the low-level feeding of antibiotics refers to an improvement in both rate of gain and efficiency of feed conversion. Improvement normally occurs in both measures of performance but not necessarily to the same degree. In view of known factors that influence rate and efficiency of gain, antibiotic action affecting each measure of performance should prove to be, at least in some respects, different.

The different chemical nature, absorbability, and bacterial spectrum of growth promoting antibiotics suggest that the mode of action in growth promotion cannot be the same for all of the antibiotics that have proven efficacious. There is also good evidence that antibiotic action affecting growth in the different species is not entirely from the same mode of action. Factors involved are the complex mechanisms related to disease, feed intake, digestion, absorption, and metabolism of nutrients, as well as antibiotic effects on enteric flora and the systemic bacterial population.

In swine, frequent measurement of rate and efficiency of gain in control and antibiotic-fed animals reveals that a response to the antibiotic is not consistent but occurs only occasionally, and for what is usually a short period of time. Such an effect over an extended period promotes "average" performance above controls.

In view of this important temporary effect, studies are suggested in which short-term performance measurements (feed intake and rate of gain) are correlated with similar short-term measurements related to the microbiology and biochemistry of the different physiological systems in control versus responding animals. Intestinal cannulation to permit sampling of ingesta at different points in the tract, together with simultaneous blood measurements, are needed for such an approach.

Experiments designed to uncover mechanisms related to the growth-promotant effect might provide a means of exploiting these mechanisms other than by the use of feeding levels of antibacterial compounds.

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