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Antibiotics - Yes or No?

Abstract

From January, 1976, to January, 1977, I served as chairman of a subcommittee of the National Advisory Food &Drug Consultants charged with examining several issues concerned with the "Use of Antibiotics in Animal Feeds". It was through the activities of this subcommittee that I have had the opportunity to review papers and to hear presentations and discussions by many knowledgeable people concerning such use. Most of you are fully cognizant that the use of antibiotics in animal feeds originated from the observations of Jukes and Stokstad in 1949. Subtherapeutic levels are used for increasing weight gain, improving feed efficiency, and preventing or controlling animal disease. In 1973 in the United States, 20.8 million pounds of antibiotics were produced--12.6 million destined for medicinal use and 8.2 million pounds for nonmedical use, primarily in animal feeds.; Swine Day, Manhattan, KS, November 10, 1977

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Antibiotics - Yes or No?

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Most of you are fully cognizant that the use of antibiotics in animal feeds originated from the observations of Jukes and Stokstad in 1949. Subtherapeutic levels are used for increasing weight gain, improving feed efficiency, and preventing or controlling animal disease. In 1973 in the United States, 20.8 million pounds of antibiotics were produced--12.6 million destined for medicinal use and 8.2 million pounds for nonmedical use, primarily in animal feeds.

During the period 1949 to 1976 the benefits and risks of the use of antibiotics in animal feeds have been reviewed several times.

The first conference to review the use of antibiotics was sponsored by the National Academy of Sciences in 1955. One paper by Dr. Maxwell Finland of Boston City Hospital reviewed the emergence of resistant organisms following chronic intake of antibiotics. Dr. Finland did not foresee hazard to either animal or man. Over the next 5 years concerns continued to surface.

In 1960 the Netherthorpe Committee was established in Great Britain to examine the possible consequences of feeding antibiotics to farm animals and to consider whether this use constituted any danger to human or animal health. In its initial report, the committee said that it saw no need to discontinue the permitted usage of feed additives but that should new antibiotics be developed with comparable efficacy in growth promotion but with little or no therapeutic application, the continued use of therapeutic antibiotics should be reconsidered. Later, continued investigation of transferable antibiotic resistance and the phenomenon of multiple resistance caused the committee to renew its inquiry.

In 1965 and 1967 FDA committeees considered the veterinary medical and nonmedical uses of antibiotics and expressed their concern relative to emergence of resistant organisms in animals receiving antibiotics in feed.

Then in 1968, on recommendation of the Netherthorpe Committee, the Swann Committee was formed to obtain information about current and prospective uses of antibiotics in animal husbandry and veterinary medicine, and to study the extent to which the reservoir of resistant bacteria resulting from such uses poses a potential danger to human health.

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The Swann Committee concluded that administering antibiotics to farm livestock, particularly at subtherapeutic levels, posed certain hazards to human and animal health. Grouping antibiotics into Feed Antibiotics and Therapeutic Antibiotics, the committee recommended that those antibiotics used for therapy be banned from low-level use in animal feeds for growth promotion and further recommended that they be used for disease prevention only on prescription by veterinarians. Feed antibiotics approved for use for growth promotion were not restricted to prescription; those approved have not been used to treat disease, do not usually produce multiple drug resistance, and are not thought to cause transfer of resistance.

In 1970 an FDA Task Force was convened to review and to make recommendations on the use of antibiotics in animal feeds. In 1972 the Task Force grouped its concerns into three areas: human health hazards, animal health hazards, and antibiotic effectiveness.

In its report, the Task Force noted that food-producing animals constitute a major reservoir of certain bacteria (notably Salmonella) pathogenic for man. Subsequently, the FDA proposed that an antibiotic in animal feeds should not produce an increase in quantity, prevalence, or duration of shedding of Salmonella, nor an increase in the proportion of drug-resistant Salmonella. The Task Force noted that antibiotic use does promote drug resistance in bacteria, that this resistance could be transfered to other bacteria, and that a potential hazard existed in that the resistant bacteria might be transmitted to man. The Task Force expressed concern that the use of antibiotics in feed might compromise subsequent treatment of clinical disease and suggested the need for additional information.

In 1973 the FDA published in the Federal Register the order implementing the recommendations of the Task Force, thus notifying drug sponsors of the necessary step to be taken if marketing of antibacterial drugs for use in animal feeds was to continue. Certain deadlines were established.

In 1976, as a result of discussions in the National Advisory Food and Drug Committe, the Subcommittee on Antibiotics in Animal Feeds was formed. The subcommittee was asked to consider the risks and benefits involved with the use of a number of antibiotics and sulfonamides (Tetracyline, Penicillin, Sulfaquinoxylin), and to reach judgments as to whether or not the use of those drugs was worthwhile.

Three major questions were posed for subcommittee consideration:

1. Is there a risk? If so, what is the extent and nature of that risk, and should it be accepted by consumers?
2. What are the alternatives to the use of these drugs, either in the use of other drugs or in the use of nondrug methods?
3. If we should accept the use of these drugs and the risks involved, are there restrictions that should be imposed and what are those restrictions?

In table 1 the recommendations of the subcommittee are compared with those of the parent committee and FDA's proposals as published in the federal register.

Table 1 . A comparative study.

Drug	Subcommittee	NFDA Committee	FDA
Penicillin			
Growth Promotion	Discontinue	Discontinue	Discontinue
Disease Prevention	Discontinue where effective substitutes are available	Discontinue where effective substitutes are available	Discontinue where effective substitutes are available
Sulfaquinoxylin			
Growth Promotion	No approved use	No approved use	No approved use
Disease Prevention	Continue as currently approved	Continue as currently approved	Continue as currently approved
Streptomycin, DHS			
Growth Promotion	No approved use	No approved use	No approved use
Disease Prevention	No approved use	No approved use	No approved use
Tetracycline			
Growth Promotion	Discontinue where effective substitutes are available	No change in current use	Restrict to minor animal species
Disease Prevention	Continue with limitation where effective alternates are not available	No change in current use	Continue with limitation where effective alternates are not available
Recommendations	App. med. feed application OR Presc. by veterinarian	App. med. feed application OR Presc. by veterinarian	App. med. feed application AND Presc. by veterinarian

In addition to the recommendations regarding subtherapeutic use of antibiotics in feeds, the subcommittee presented the parent committee with a number of general recommendations that they believed should constitute commitments by the Food and Drug Administration. These recommendations were accepted by the National Advisory Food and Drug Committee and forwarded to FDA:

1. Monitor, perhaps in collaboration with CDC, the development and transfer of antimicrobial resistance in those organisms capable of inducing disease in man and animals, and establish a baseline on current antibiotic resistance for use in future evaluations.
2. Continue to evaluate the effect of implementation of national recommendations in other countries.
3. Re-evaluate the effect of the subtherapeutic uses of antimicrobial products in animal feeds in this country within 5 years.
4. Affirm that the long-term goal of the FDA is the elimination to the extent possible, from low-level animal feed use, of those drugs also used for therapy of disease in man. This should be accomplished as satisfactory alternative measures for disease prevention in animals become available--including use of substitute drugs, vaccines, new husbandry practices, and genetic improvements.
5. Promote research regarding the mechanism of growth promotion and disease prevention in food-producing animals.
6. Foster the creation of a highly scientific and specialized committee to attempt to establish the magnitude and to define the future significance of the human-health risk that has evolved from the increasing bacterial resistance to antibiotics in man and animals.

It is apparent that the major issue of risk rests on judgments regarding the development of resistant organisms, the transfer of resistance from one bacterium to another, the transmission of resistant bacteria from animal to man, and the existence of multiple resistance. There is no question but that all four exist. The pertinent question is: Do the resistant organisms in animals pose a threat to man? Proponents for action banning the use of antibiotics in animal feeds will argue that the mere existence of resistant bacteria, coupled with the ability to transfer that resistance to other bacteria, either pathogens or nonpathogens, constitute a serious risk. Some will maintain that we have already created the monster and that it is only a matter of time until serious problems unfold. Current information indicates that human E. coli and those of other mammals are not separate and distinct strains, but interchangeable between man and other species. The resistant plasmids cannot be distinguished as human and animal types; rather, all evidence points to a common pool of plasmids. R. plasmids can be exchanged between enteric pathogens and some nonenteric pathogens.

There is little argument but that resistant E. coli arise from the use of antibiotics and that resistance transfer increases under antibiotic pressure; therefore, one must consider the possibility that these resistant factors to pathogenic organisms will spread and how to minimize that hazard.

Diagnostic laboratories report that they are isolating an increasing number of resistant organisms from specimens submitted to them.

However, most of the specimens they have examined probably are from animals that have received antibiotic treatment. Penicillin resistance and tetracycline resistance are rapidly increasing in animal strains of Pasteurella multocida. In man the use of antibiotics in therapy has most assuredly resulted in the emergence of penicillinase-producing gonoccii. Similarly, a considerable increase in resistance has resulted in Haemophilus influenza. Salmonella of animals and man have shown a marked increase in their resistance gene pool, and one must contemplate the source of their plasmid mediated resistance.

The best estimate is that Salmonella receive their R. plasmids from the resistant E. coli flora. Recent reports of multi antibiotic resistance in Salmonella dublin are particularly distressing.

Proponents for continued use of antibiotics in animal feeds argue that their use over 25 years has not produced serious health problems and that while transfer of resistance is possible, it primarily occurs in the laboratory situation and the transfer from animal to man is a rare event.

Solving the problem would be relatively simple if we were confident of suitable alternatives to currently-used antibiotics--alternatives that would be efficacious, economically acceptable, and safe; and would not be used for therapy nor produce multiple drug resistance or result in transfer of resistance.

Several alternatives have been suggested and indeeed may provide partial answers to the dilemma. Dr. Kennedy, head of FDA, is apparently satisfied that satisfactory alternatives have been identified. At least the proposals posted in the Federal Register would lead one to that conclusion. It is important that authorities designating alternative drugs consider the assurance that currently-used products are not replaced with substances endowed with lesser benefits and unexplored hazards. The alternatives must satisfy the animal and human health criteria specified by the Antibiotics in Animal Feeds Task Force.

It isespecially important that all persons who use antibiotics or who cause antibiotics to be used recognize the potential hazards associated with their use. We cannot involve ourselves in the indiscriminant use of antibiotics. We must redouble our efforts to learn more about the dangers inherent in the misuse of antibiotics and in their uncontrolled or illegal sale, improper prescription, and unjustified prophylactic use.

It is through the combined concern of the physician, the veterinarian, the animal scientist, the microbiologist, the research worker, the manufacturer, the regulatory official, and the consumer that we will maximize the benefits and minimize the risks of antibiotics in feeds.

In response to the question, Antibiotics - Yes or No? I would offer these predictions:

1. Antibiotics will continue to be an important and accessable tool in livestock production; however, there will be continued pressure to restrict subtherapeutic use to those antibiotics not used for therapy in man.
2. All parties will become ever more appreciative of the hazards (real and potential) of the subtherapeutic as well as the therapeutic use of antibiotics.
3. Availability of antibiotics for purposes of growth promotion, feed efficiency, and disease prevention will be restricted to use conditions that permit controlled access and monitored use.