PUBLIC HEALTH IMPLICATIONS OF THE USE OF ANTIBIOTICS IN ANIMAL AGRICULTURE — PREFACE

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For more than 35 years, U.S. livestock and poultry producers have used antibiotics in their animals. The drugs sometimes are administered in relatively large (therapeutic) doses to treat sick animals. More common is the use of smaller (subtherapeutic) amounts of antibiotics in animal feeds to prevent or reduce the incidence of infectious diseases and to improve feed efficiency and rate of growth. Approximately 80% of the poultry, 75% of the swine, 60% of the beef cattle and 75% of the dairy calves marketed or raised in the U.S. are estimated to have been fed antibiotics at some time in their lives. Roughly 45% of the antibiotics produced each year in the U.S. are administered to animals (Hays et al., 1981).

Questions regarding safety to animals and humans and continued efficacy have been raised throughout the 35-year history of antibiotic usage. The present debate began, in earnest, more than 15 years ago.

U.S. Food and Drug Administration Task Force Report

Following an NAS/NRC symposium (1969) and the report of the Swann Committee (Swann et al. 1969), the FDA appointed a Task Force to evaluate the animal-health and public-health implications of feed-additive usage of antibiotics. The FDA Task Force (1972) concluded that some antibiotic-sensitive and antibiotic-resistant bacteria of animal origin could be pathogenic to humans, and the available evidence suggested that use of certain antibiotics in animals produced an increase in the animal reservoir of salmonella. As a result of the Task Force study, criteria were established by FDA in which the commercial producers of antibiotics were required to demonstrate that the antibiotics in question did not compromise the treatment of disease in animals or humans or result in an increase in the reservoir of resistant human pathogens, particularly salmonella.

On completion of the studies conducted by drug sponsors, FDA requested an evaluation of the available data by a subcommittee consisting of three members of the National Advisory Committee to FDA and four consultants and asked them to make recommendations to FDA as to whether tetracyclines, penicillin and sulfamethazine should remain as approved feed additives. This subcommittee recommended to the parent FDA advisory committee marked restrictions on the use of penicillin and tetracyclines but no changes in the usage of sulfadiazine. The parent committee accepted the subcommittee's recommendation on penicillin and sulfadiazine, but could not agree that the available evidence suggested a need for change in usage of tetracyclines.

On April 15, 1977, the Commissioner of FDA (Kennedy, 1977) reported to the National Advisory Committee to the FDA that he and his staff had concluded there was sufficient evidence to justify limiting penicillin and tetracycline usage to veterinary prescription only. He acknowledged that there was no direct evidence that disease therapy in humans had been compromised by feed additive usage of these drugs, but he expressed the opinion that such an effect might exist even though it had gone unnoticed.

Subsequently the Food and Drug Administration (1977a,b) published, in the Federal Regis-
ter, proposed rules which would essentially re-
voke all approved subtherapeutic uses of
penicillin, chlortetracycline and oxytetracy-
cline. Justification for these proposed rules is
still being debated, and final action delayed
pending a subsequent congressional mandate
for FDA to arrange for additional research and
to delay final action until research has been ac-
complished and evaluated. Congress appro-
riated $1.5 million to support the research.

The comprehensive study on the flow of sal-
monella and campylobacter in a community
(Nolan et al., 1984) was commissioned as a
result of this congressional action with the ex-
pectation that it would answer some of the ques-
tions regarding the contribution of animal or-
ganisms to human health problems. This study
provided the data for the paper by Harris in this
proceedings.

**Office of Technology Assessment Report**

At the request of Senator Herman Talmadge,
Chairman of the Senate Committee on Agricul-
ture, Nutrition and Forestry, the Office of
Technology Assessment (O.T.A.), Congress of
the United States undertook an assessment of
the use of drugs in livestock feeds. To prepare
the resulting staff synthesized report, O.T.A.
(1979) made use of an assessment advisory
panel, commissioned individual papers dealing
with key issues, reviewed Food and Drug Ad-
ministration documents, sought input through
public participation meetings and invited a di-
verse spectrum of individuals to review the draft
reports.

It was concluded that the health risks from
the development of bacterial resistance to anti-
bacterials in animal feeds is cause for great con-
cern. A direct quote from the conclusions is as
follows:

"The loss of effectiveness of the most
widely used antibacterials (i.e., tetracyclines
and penicillin) and of other antibacterials
with plasmid-mediated resistances poses
risks to both human and animal health.
Therapeutic failure with these antibacterials
would lead to large but unquantifiable mor-
bidity and mortality in humans and ani-
mals."

The authors acknowledged that the economic
consequences of removing these drugs could be
significant over the short term, but were of the
opinion that most of the drugs in question could
be replaced with alternative drugs already ap-
proved by FDA. The balance was interpreted to
be between immediate economic benefits and
future health risks. The authors further con-
cluded that the lack of scientific certainty on
the magnitude of both the probable health risks
and the attributed increases in meat production
makes the formulation of a solution to the di-
lemma most difficult.

**Council for Agricultural Science
and Technology Report**

The widely varying opinions among sci-
entists as to the magnitude of the hazard of feed-
additive usage of tetracyclines and penicillin led
the late Senator James B. Allen of Alabama to
request that the Council for Agricultural Science
and Technology (CAST) 'consider appointing a
task force to review the use of these antibiotics
in animal feed and prepare a report on the sub-
ject. . . . CAST commissioned the Task Force
in June 1977 and the report was published in
of that task force were in general agreement
with those of others dealing with the subject. It
was acknowledged that subtherapeutic use of
antibiotics in animal feeds has been questioned
since the introduction of antibiotics because dis-
ease organisms can develop resistance to the
antibiotic being used and perhaps other antibio-
tics as well. Resistance of pathogens to antibio-
tics appeared soon after antibiotic usage began
and such resistance is known to be capable of
compromising antibiotic therapy. According to
the task force "the potential hazard to human
health due to development of bacterial resis-
tance to antibiotics used at subtherapeutic levels
in animal feeds is clear enough, only four
known recorded instances of unfavorable
human health effects due to antibiotic resistant
bacteria have been linked directly to all usages
of antibiotics in the production of many billions
of animals over the past three decades."

The CAST Task Force detailed the economic
aspects of feed additive usage of the antibiotics
and concluded that in the short run, losses to
consumers from banning subtherapeutic use of
antibiotics would be high, perhaps $3.5 billion
or more per year, if no substitutes were to be-
come available. In the long run the impact on
consumers would be reduced to the extent that
effective substitutes were to become available
and adopted.

The tetracyclines and penicillins have been
used extensively in the United States. For exam-
ple, it is estimated that more than 45% of pigs are fed diets containing a combination of these antibiotics during the early stages of production (to about 35 kg body weight) and more than 40% of all pigs receive these antibiotics singly or in combination during the finishing period (35 kg to market weight).

National Academy of Sciences Review

In 1978, the Congress of the United States provided to FDA an appropriation designated for the National Academy of Sciences (NAS) to evaluate epidemiological approaches to the effects on human health of subtherapeutic (189 ppm or less for two weeks or longer) use of antimicrobials in animal feeds. The NAS committee concluded (Stallones et al. 1980) that “the postulated hazards to human health from the subtherapeutic use of antimicrobials in animal feeds were neither proven nor disproven. The lack of data linking human illness with this subtherapeutic use must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk has not been conducted.”

The committee also concluded that “It is not possible to conduct a feasible, comprehensive epidemiological study of the effects on human health arising from the subtherapeutic use of antimicrobials in animal feeds, partly because it is impossible to determine the antimicrobial history of the animal from which a particular piece of meat came” One could also add that it is most difficult or impossible to determine the antibiotic history of the human subjects with respect to direct and indirect exposure to antibiotics or to organisms from other people who had been exposed directly to antibiotics.

The committee did recommend, however, several research possibilities to study certain aspects of the problem, including research on the mechanism by which subtherapeutic levels of antimicrobials promote growth of animals. The committee also recommended continued monitoring and occasional review of the possible effects on humans resulting from the subtherapeutic use of antimicrobials in animal feeds.

The Animal Health Institute is presently sponsoring research which speaks to certain of the research possibilities suggested by NAS. One of the papers in this proceedings (Gustafson) describes the research approaches underway and touches briefly on preliminary results. The studies will not be completed until 1986 or later.

Current Concerns

The current concern about subtherapeutic doses of antibiotics in animal feeds gained impetus from two scientific papers by researchers at the Center for Disease Control (CDC) in Atlanta (Holmberg et al., 1984a,b), a related editorial in New England Journal of Medicine (Levy, 1984) and news articles in Science magazine (Sun, 1984a,b). The CDC studies provide the basis for the paper by Tauxe.

Following the above mentioned CDC papers and resulting publicity, the Natural Resources Defense Council (Ahmed et al. 1984) petitioned the Secretary of Health and Human Services (HHS) to “act immediately to suspend approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds as an imminent hazard to the public health.” The paper by Guest and Frappaolo speaks to sequences of events and the actions taken by FDA regarding the NRDC petition. (Since the Symposium, the Secretary of HHS has denied the NRDC petition.)

Members of the American Society of Animal Science have contributed a voluminous amount of data on the efficacy of the subtherapeutic use of antibiotics in animal feeds and to a somewhat lesser extent on the safety of such practices. The organizers of this symposium sought to emphasize those aspects of antibiotics usage that have generated recent concerns about the advisability of the continued practice of subtherapeutic use.

Only one paper, that of D. R. Zimmerman, deals with the continued efficacy for the purpose of illustrating why and how subtherapeutic levels of antibiotics are used in animal production. The other papers deal with the changes in antibiotic resistance of bacteria in animals and humans, the contribution of animal bacteria to the human flora, and the possible implications of these phenomena on human health.

In choosing the topics for the symposium on Human Health Implications of Subtherapeutic Use of Antibiotics in Animal Feeds, the planning committee was mindful of (1) the 35 year history of their use; (2) the continuing as well as the more recent concerns, about the safety to humans of such use; and, (3) the dedication of the members of the American Society of Animal Science to providing a wholesome as well as a plentiful food supply.
Possibly as a result of these presentations, researchers will become interested in pursuing answers for some of the complex issues relative to this subject.

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Literature Cited


