THE PUBLIC HEALTH HAZARDS ASSOCIATED WITH THE NON-MEDICAL AND ANIMAL HEALTH USAGE OF ANTIMICROBIAL DRUGS

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ABSTRACT

Antimicrobial drugs are used in many ways. They are used for man's health and as agents to help provide or preserve his food. Similarly they are used for animal diseases and as additives to animal feed in hopes of increasing average daily gain and feed efficiency. There are many variables which determine if the use is an efficacious one supported by scientific observation and documentation or if the use is supported by empirical observations.

The public health hazards associated with the non-medical and animal health uses of antimicrobial drugs are two-fold: (1) hazards produced by direct contact, probably by consuming food containing antimicrobial residues, with the antimicrobial drug resulting in drug sensitization or intoxication, and (2) hazards, real or potential, associated with the development of antimicrobial resistant organisms that facilitate or produce diseases in man which are refractory to therapeutic agents.

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The antimicrobial drugs have been of much benefit to man and his animals; however, they have been employed widely and some of the uses are of questionable efficacy and may contribute to the development of public health hazards. It appears that antimicrobial drugs are of most benefit when intelligently used to treat diseases of animal or man. The benefits are fewer and the hazards greater when these drugs are used indiscriminately as a panacea for animal disease problems or for problems involving the nutrition and management of livestock and poultry. The problem of determining the current status of the non-medical and animal health usage of antimicrobial drugs is one of assessment. For example, assessment of the antimicrobial drug uses that are effective therapeutically and economically, and assessment of the antimicrobial drug uses which contribute little or nothing to the development of health risks to man. We must also assess the uses which may eventually reduce the efficacy of this therapeutically important group of drugs when they are used to treat diseases of man or animals.

Antibiotic drugs are the most common of the antimicrobial agents used for animal purposes. On a chemical basis, the antimicrobial agents with the greatest usage can be classified as follows: the tetracyclines, e.g.

oxytetracycline, chlortetracycline; the penicillins; the aminoglycosides, e.g. streptomycin, dihydrostreptomycin and neomycin; the macrolides, e.g. erythromycin, oleandomycin and tylosin; the polyenes, e.g. nystatin; the polypeptides, e.g. polymyxin B and bacitracin; and assorted structural groups, e.g. chloramphenicol, hygromycin B and novobiocin. The non-antibiotic antimicrobial agents include sulphonamides, nitrofuran compounds and arsenic compounds. Various combinations of the above antimicrobial drugs, sulphonamides and other drugs, are frequently employed.

The addition of antimicrobial drugs to animal feed or drinking water is practiced extensively. During 1966 in the United States, $215,000,000 was spent on animal feed additives and $115,000,000 was spent on animal health pharmaceuticals. More than half of the antibiotics produced in the United States are used in agricultural applications, primarily as animal feed additives. Because of the usage patterns, it is apparent that antimicrobial drug pressures can be exerted on the majority of the livestock and poultry raised in the United States. These pressures may result in the development of residual and ecologial problems.

Low concentrations (less than 100 ppm) of antimicrobial drugs have been added to animal feed with the intent to increase average daily gain and to reduce the cost per unit of body weight gain. Increases in average daily gain and feed efficiency are not always observed following the addition of so-called 'low levels' of antimicrobial feed additives. However, use of these agents under various conditions[1] has shown that the rate of gain in body weight is likely to occur more readily and economically if the drugs are used when:

1. poor quality rations are fed;
2. rations will allow improved utilization;
3. poor sanitation procedures are employed and the premises are unclean;
4. the presence of disease, clinical or subclinical;
5. there are 'runt' or under-size animals in the herd;
6. the animals are in a stage of rapid growth.

The probability of gain and feed efficiency benefits is decreased if the animals are healthy, are fed good quality rations and are past the rapid growth stage. An increase in the rate of gain has been the most consistent finding following the use of 'low level' antimicrobial feed additives; however, it has been observed that animals which are not fed antimicrobial drugs may catch up to antimicrobially treated animals as both groups mature and their rate of gain slows[2]. Antimicrobial agents do not 'stimulate' or 'promote' growth; however, they may permit normal growth to occur in an adverse environment characterized by one or more of the previously listed conditions.

Additional information is needed if we are to assess the current economic benefits that antimicrobial drugs can provide when used to increase rate of gain and feed efficiency. Research is needed to quantitate the most beneficial periods of rapid growth in the various classes of livestock and poultry rather than feeding the antimicrobial drugs from birth to death. It would be desirable to use antimicrobial agents for non-medical animal production

purposes when they will be of most benefit and to discontinue their use when the benefit is marginal or disappears, thus reducing antimicrobial drug pressures on environmental bacteria. It also would be desirable to use for non-medical animal production purposes only those drugs that are not used to treat diseases of man. Development of bacterial resistance to antimicrobial drugs appears to be directly related to the extent the drugs are used[3]. Thus, widespread use of valuable therapeutic agents for non-medical purposes seems unwise, especially if other agents are equally effective for the same purpose.

Greater scientific sophistication for measuring the benefits of antimicrobial drugs as non-medical feed additives appears necessary. Numerous factors influence the gross measurements of body weight and feed efficiency. Among these are the variances in subclinical diseases, parasite loads, genetic make-up and nutrient intake. Information to establish the mechanism or mechanisms of action would be of much benefit in helping to remove doubt and inconsistent results from non-medical production practices supported by empirical observations. For most animals, improvement in rate of gain has been reported more frequently and consistently than improvement in feed efficiency[2] and the monetary benefits associated with an increased rate of gain will determine the longevity of these practices.

The benefits of antimicrobial drug treatment of a majority of animal bacterial diseases are well established and documented. Considerable information is available regarding mechanisms of action. There is a dynamic relationship between the choice of antimicrobial drugs for therapeutic purposes and the ability of the microorganisms to resist or remain sensitive to the therapeutic drug. Maximum benefits are obtained when the disease is diagnosed accurately, the pathogen's antimicrobial sensitivity pattern determined and the drug administered in therapuetic doses for a sufficient time. When antimicrobial drugs are so used their benefits are easily established and supported by scientific principles.

If antimicrobial drugs are used at subtherapeutic dose rates for disease prevention or control purposes, their benefits are more elusive and difficult to establish. The literature contains few reports characterized by good experimental procedures and design which support the use of subtherapeutic doses of antimicrobial drugs to prevent or control the prevalence of bacterial diseases. A decrease in the morbidity of bacterial diseases in animals has not been observed since antimicrobial agents have been extensivelty used for disease prevention purposes. To the contrary, some diseases, for example, bacterial enteritis of swine, have experienced increased morbibity since antimicrobial agents have been used for preventive purposes.

In considering the use of antimicrobial drugs for preventive purposes, the risk of doing harm must be weighed against that of doing good. In addition, we must not only consider the ratio of toxicity to positive therapy but we must consider the frequency of the condition being prevented. Thus, if a drug has a ten-fold advantage, when its dose to produce a beneficial effect is compared with the toxic dose, it looks good. But if the drug is used prophylactically or preventively and only 5% of the population will get the disease without the drug, the ratio shifts to 2:1 against its use.

It is possible that the subtherapeutic use of antimicrobial drugs increases

the probability that resistant pathogens will develop. The resistant pathogens may be responsible for zoonotic disease and animal health problems, especially if they become insensitive to therapeutic dosages. Continued administration of antimicrobial drugs in feed may result in tissue residues if withdrawal times prior to slaughter have not been determined or followed. Tissue residues may also occur if meat inspection procedures do not detect contaminated meat.

Antimicrobial drugs have also been added to various foodstuffs for preservation purposes. Poultry have been dipped in solutions of chlortetracycline or oxytetracycline, antibiotics have been applied to vegetables and fruits, and fish have been exposed to antibiotic solutions or ice containing antibiotics. In the United States many food preservative uses have been discontinued, primarily for economic reasons.

The widespread use of antimicrobial substances for non-medical animal production purposes and animal health has raised questions about public health hazards and about the reduction of efficacy for the therapeutic use. The potential hazards to man are two-fold: (1) drug sensitization or intoxication and (2) zoonotic problems caused by antimicrobial resistant organisms that are pathogenic to man and animal.

One manner in which drug sensitization may occur is for man to consume food which contains an antimicrobial drug residue. The subsequent use of this drug as a therapetutic agent for a sensitized individual is obviated and if the drug is used, an undesirable allergic reaction may occur. The extensive non-medical use of antimicrobial drugs for animal production purposes and their indiscriminate use in questionable animal health practices has been associated with the development of resistant pathogens, some of which are pathogenic to man and his animals[3, 4].

The direct toxic effects of antimocrobial agents are quite similar to those reactions produced by other residual chemical substances. In addition, the antimicrobial agents may create additional hazards because of their ecologic effect or their ability to render normal bacterial populations insensitive to commonly used therapeutic agents.

Some warn that we must not move too thoroughly on hypothetical dangers associated with the use of feed additives for it would interfere with needed progress in the development of food technology. The best argument for this attitude is that the lack of adverse effects shows how well we have done. However, the primary question is whether adverse effects are lacking or are they being overlooked? One way to 'lack adverse effects' is not to look for them.

The exact number of people sensitive to antimicrobial drugs has not been established; however, it has been estimated that in the United States there are 17–20 million individuals who may experience undesirable reactions following exposure to antibiotics or chemotherapeutic agents[5]. One study of 1,000 consecutively numbered hospital patients was conducted to determine the prevalence of drug allergies or hypersensitivity[6]. Of 1,000 patients, 149 or 15% were found to be hypersensitive to drugs. Seventy-two or 7·2% of the patients were hypersensitive to penicillin. Sulphonamide hypersensitivity was observed in 16 patients, meperidine in 12, codiene in 12, horse serum in 7, barbiturates in 5, morphine in 5, procaine in 4, adhesive

tape in 3, acetylsalicyclic acid in 3 and other compounds in 10. It is possible that allergic or hypersensitive reactions are due to antimicrobial drug residues on or in food. The prevalence of allergic reactions might be more common than would appear from the medical or scientific literature due to the lack of a comprehensive adverse reaction reporting system. If a certain form of sensitization is found to be relatively common in a segment of a population, it would be desirable to avoid contamination of the food with the sensitizing agent. Special attention is required for staple foods such as milk and meat that make up large and consistent portions of the diet.

To evaluate the possible microbiological effects that may develop from the presence of antimicrobial residues in food, the following items should be considered:

1. The likelihood of whether ingestion of antimicrobial residues is consistent or intermittent;
2. The amount and kind of antimicrobial residue consumed;
3. The possible effects that antimicrobial residues may have on the food flora and the effects residues may have on food storage;
4. The possible ecologic effects that antimicrobial residues may have on the normal flora of the consumer;
5. The possible effects on the non-pathogen resident flora and their involvement in the infectious transfer of resistance to pathogens;
6. The possibility that pathogens will acquire resistance as a result of exposure to antimicrobial drug residues and then become a public health problem.

The following questions are pertinent to the use of antimicrobial drugs:

1. Do slaughtered domestic animals contain antimicrobial drug residues?
2. If meat containing antimicrobial drug residues is cooked before consumption, will the heat destroy the drug residues and thus resolve the problem?
3. Do antimicrobial drugs used at 'low levels,' such as 5–15 g/ton or ppm cause the development of resistant bacteria or constitute a health hazard?

Let us consider question 1. Do slaughtered domestic animals contain antimicrobial drug residues? For the past three years our laboratory has been developing methods to detect antimicrobial drug residues. After the methods were established and standardized several classes of domestic animals were surveyed to determine the prevalence of antimicrobial drug residues at the time of slaughter.

Urine, faeces and/or tissues were collected from swine, sheep, veal calves, beef cattle and poultry at slaughter houses subjected to federal or state inspection. The samples were collected from apparently normal animals sent to the abattoir for slaughter and subsequent use for human consumption.

A microbiologic *Bacillus subtilis* disc assay method was used to detect the presence of antimicrobial substances[7]. The disc assay method for fluid milk[8] was modified to test urine, faeces and tissues. A method involving electrophoresis of agar gel[9] was modified and used to identify the antimicrobial substances.

Swine

Seven groups of swine were tested in the State of Illinois during winter, spring, summer and autumn. Twenty-five per cent of the 1,224 slaughtered hogs had urine which contained antimicrobial substances. Thirty-one or 10 per cent of the 309 positive antimicrobial samples of the swine had penicillin residues. (*Table 1*)

Table 1. The prevalence of antimicrobial substances in swine

Group	*Number tested*	*Positive urine*	*Per cent*
1	233	88	38%
2	185	53	30%
3	118	45	37%
4	281	33	12%
5	149	12	8%
6	100	36	36%
7	158	42	26%
	1,224	309	25% (av.)
	10% Penicillinase Positive		

Comparison of faeces and urine

Number tested	*Positive urine*	*Positive faeces*
118	45/118 (37%)	34/118 (29%)

In an attempt to determine whether antimicrobial residues were the result of drugs injected parenterally or attributed to medicated feed not withheld the necessary time before slaughter, swine faeces collected from animals showing a positive urine test were assayed for the presence of antimicrobial substances. Animals which had positive penicillinase urine tests were also found to have positive penicillinase faecal tests. The large number of animals with both positive urine and faecal tests, the lack of visible injection sites, the numbers of animals involved and the metabolic and excretory patterns of the commonly used antibiotics all indicate that many of the antimicrobial residues are probably the result of oral administration rather than parenteral administration.

Beef Cattle

Mature beef cattle had the lowest prevalence of antimicrobial residues. In four groups of cattle tested, 6% of the 418 animals revealed the presence of antimicrobial substances; 2% of the cattle had penicillin residues (*Table 2*)

Table 2. The prevalence of antimicrobial substances in beef cattle

Group	*Number tested*	*Positive urine*	*Per cent*
1	33	5	15%
2	150	2	1%
3	177	12	7%
4	58	7	11%
	418	26	6% (av.)
	2% Penicillinase Positive		

Veal Calves

Tests on urine samples collected from 756 veal calves consisting of five groups showed that 16% of the samples contained antimicrobial residues, of which 7% or 53 of the veal calves were found to have penicillin residues. (*Table 3*)

Table 3. Prevalence of antimicrobial substances in veal calves

Group	*Number tested*	*Positive urine*	*Per cent*
1	216	18	8%
2	337	78	23%
3	82	18	22%
4	70	6	9%
5	51	1	2%
	756	121	16% (av.)
	7% Penicillinase Positive		

Fat Lambs

Four groups of fat lambs were tested. Twenty-one per cent or 68 of the 328 animals tested contained antimicrobial substances. Four per cent of the animals were positive for penicillin residues. (*Table 4*)

Table 4. The prevalence of antimicrobial substances in sheep

Group	*Number tested*	*Positive urine*	*Per cent*
1	121	27	22%
2	114	14	12%
3	45	18	40%
4	58	9	16%
	328	68	21%
	4% Penicillinase Positive		

Chickens

Three groups of laying hens or a total of 798 were tested after slaughter. Seventeen per cent or 132 chickens were found to have antimicrobial substances present in their gastrointestinal tract. Six per cent of the positive tests were penicillin positive. (*Table 5*)

Table 5. The prevalence of antimicrobial substances in laying hens

Group	*Number tested*	*Positive faeces*	*Per cent*
1	214	53	25%
2	200	32	16%
3	384	47	18%
	798	132	17% (av.)
	6% Penicillinase Positive		

Urine and tissue samples were assayed by both the microbiologic *B. subtilis* screening test and the electrophoretic test to identify the antibiotics. The results are recorded in *Table 6*. The electrophoretic test was used to identify penicillin, dihydrostreptomycin or streptomycin, tylosin, the tetracycline group and neomycin. Other antibiotics and chemical antimicrobials such as erythromycin, sulphonamides, nitrofuran compounds, etc. were not included in the electrophoretic analytical procedures.

Table 6. Antimicrobial substances found in urine and tissues when both the microbiologic and the electrophoretic methods were used

	Microbiologic assay			*Electrophoretic assay*					
Urine	*Number tested*	*Neg*	*Antimicrobial activity*	*PEN*	*DHS*	*TYL*	*TET. GR.*	*NEO*	*Not identified*†
Swine	281	248	33 (13%)	2	0	0	47	0	0
Swine	100	64	36 (36%)	2	0	0	35	0	0
Swine	145	75	70 (48%)	1	0	0	83 (+13)	0	0
Calf	51	50	1 (2%)	0	0	1	0	0	0
Calf	75	70	5 (7%)	0	0	0	4	0	1
Lamb	58	49	9 (16%)	0	0	0	9	0	0
Lamb	75	48	27 (36%)	0	0	0	29 (+2)	0	0
	785	604	181 (23%)	4	0	1	207	0	1
Tissue									
Chicken Livers	231	204	27 (12%)	5	2	3	2	0	15
Lamb Livers	200	168	32 (16%)	3	4	1	0	0	24
Swine Kidneys	101	94	7 (7%)	1	0	0	0	0	6
	532	466	66 (12%)	8	6	4	2	0	45

† Assay limited to 5 listed antibiotics.

Urine samples from three groups of swine were tested by both methods. In the first group of 281 pigs, 48 or 13% contained antimicrobial substances. The 48 positive samples were assayed by the electrophoretic method. The following antibiotics were identified: 2 penicillin residues and 47 tetracycline residues. The urine assayed from the second group containing 100 pigs had 36 or 36% positive microbiologic tests. Electrophoretic assay identified the following: 2 penicillin and 35 tetracycline residues. In the third group of 145 swine tested, 70 or 48% were positive microbiologic reactions. One animal contained both penicillin and tetracycline residues and 82 contained tetracycline residues. The electrophoretic assay detected 13 additional positive tests that were not detected by the *B. subtilis* microbiologic disc assay.

Two groups of calves or 126 animals were tested by both methods. Six positive microbiologic tests were identified by the electrophoretic method. One tylosin and 4 tetracycline residues were detected. One animal had an antimicrobial substance not identified.

Urine was obtained from 2 groups of lambs, involving 133 animals. Thirty-six of the lambs contained antimicrobial substances in the urine which were all identified as tetracycline antibiotics. In addition, the electrophoretic method detected 2 additional positive samples not detected by the *B. subtilis* microbiologic test on the urine.

In this study the residues identified according to frequency of occurrence were as follows: tetracycline residues 207, penicillin 4, tylosin 1 and 1 not identified.

Chicken and lamb livers and swine kidney tissue samples were assayed using the *B. subtilis* microbiologic method and the electrophoretic method. Of the 231 chicken livers assayed, 27 (12%) were found to contain antimicrobial substances. All 231 samples were subjected to electrophoretic assay. Five livers were found to contain penicillin, 2 dihydrostreptomycin, 3 tylosin and 2 tetracyclines. Fifteen of the positive reactions were not identified.

Sixteen per cent or 32 of 200 lamb livers were found to contain antimicrobial substances. Electrophoretic assay identified 4 livers containing dihydrostreptomycin, 3 penicillin and 1 tetracycline. Twenty four positive reactions were not identified.

One hundred and one swine kidneys were assayed with microbiologic tests and 7% were positive for the presence of antimicrobial substances. One liver was found to contain penicillin and in 6 samples the antimicrobial agent was not identified.

The category of antimicrobial agents not identified requires explanation. Five of the antibiotics commonly used in animal health production were tested in the electrophoretic assay. Other drugs such as erythromycin, nitrofuran compounds, etc., could have been included but only at the expense of excluding the gathering of information on the 5 antibiotics which were used.

Regarding the question of drug residues in meat, these results verify that some animals containing antimicrobial drugs in the tissues and body fluids are shipped to market and slaughtered. The exact antibiotic residue prevalence on a nationwide scale is not known. Our results are limited to animals slaughtered in the state of Illinois. The prevalence may vary considerably in animals from one farm to another and from one class of livestock to another. In this study, the prevalence of antimicrobial residues in the urine of domestic animals exceeds that reported for fluid milk in the United States during the 1950's before a successful milk monitoring programme was employed. Reports in the European literature[10, 11, 12] of studies using similar assay methods demonstrated that European veal calves had the highest prevalence of antimicrobial residues in meat (77%), whereas in our study a 20% prevalence was recorded. Fat cattle had the lowest prevalence as reported in our work and in the European reports. The prevalence of antimicrobial residues in swine was higher in the United States (25%) than in Europe. The major factor responsible for the presence or absence of a residue is one of animal management which requires that animals be retained at the farm until the drugs are completely excreted.

The second problem presented was the question of whether or not cooking will destroy residues in contaminated meat. The temperatures attained during cooking may partially degrade some of the antibiotics such as a tetracycline or penicillin. However, cooking has very little effect on the degradation of other antibiotics such as streptomycin or dihydrostreptomycin. Furthermore, the degradation products or metabolites of the commonly used antibiotics may have a toxic impact equally as harmful as the

original compound, e.g. penicillanic acid may have sensitizing properties as great as its parent compound, procaine penicillin G. Similarly, tetracycline metabolites may have a greater hemolytic or hepatoxic effect than the parent compounds. Thus, the temperatures incident to the process of cooking cannot be relied on to completely and effectively inactivate antibiotics and chemotherapeutic agent residues because (a) some drugs are very stable and resist heat; (b) those drugs sensitive to heat may be only partially inactivated; and (c) degradation products and metabolites may be as important toxicologically as the original antibiotic or chemotherapeutic agent.

The third question—Do antimicrobial drugs used at 'low levels,' such as 5–15 gm/ton or ppm, cause the development of resistant bacteria or constitute a health hazard?—might have been considered extremely unlikely a few years after the antimicrobial agents were used on a widespread basis for animal purposes. However, there is evidence that the addition of antibiotics or chemotherapeutic agents to the feed at 2 g/ton or 2 ppm may produce undesirable effects[13]. In 1965 it was reported that animals fed antibiotics at the rate of 2–10 ppm had a greater prevalence of antimicrobial multi-resistant organisms which persisted for a longer period of time than did animals not fed antibiotics. The administration of subtherapeutic amounts of various antibiotics increased the number of animals from which multi-resistant *Salmonellae typhimurium* could be isolated[14]. In our laboratory we have found that drug resistance can be produced more rapidly and more easily if organisms are exposed to small concentrations or subtherapeutic amounts of drugs over a long period rather than being exposed to therapeutic concentrations for a short time.

Along with the discovery of infectious drug resistance or the transference of drug resistance, we must also consider the effect that antimicrobial drugs have on non-pathogenic organisms. It has been demonstrated that drug resistant non-pathogens can transfer their resistance to unrelated pathogens. For example, drug resistance may be transferred from a non-pathogenic *Escherichia coli* to a pathogenic *Salmonella*.

It has been demonstrated that small amounts or low levels of antimicrobial drugs may result in the development of drug resistant organisms. It appears that antimicrobial drugs administered at 2 ppm and up have an ecologic effect as a result of the development of resistant pathogens. A withdrawal period of 24 hours prior to slaughter was not sufficient when the antibiotic was administered at 100 ppm.

When using antimicrobial drugs we have a definite responsibility to use them most effectively and with an awareness that meat and products must be kept free of potential health risks to the consumer. It also seems logical that regulatory agencies would want to insure a meat supply as unadulterated as the current milk supply in many countries. Several years ago in the United States, 12–14% of the milk contained antimicrobial drugs. Currently, less than 0·5% of the milk is contaminated because an effective monitoring system has been established. Research in the United States[7, 15 16] and Europe[10, 11, 12] indicate that the prevalence of antimicrobial drug residues in meat and animal products is sufficient to constitute a health hazard to certain individuals.

There is an urgent and growing need to monitor ecologic changes due to pressures created by the widespread use of antibiotics and chemotherapeutic agents for animal production purposes. The results of research conducted in England and Japan has been interpreted by some as alarming[3, 4, 17].

Many bacteria have developed resistance to more than one antimicrobial drug. The rate of resistance development is dependent on the existant antibiotic pressures and the species of bacteria. Low concentrations of antimicrobial drugs over a long period may produce greater ecologic effects than use of the drugs at therapeutic concentrations for short periods.

Watanabe[17] in 1967 identified the resistance problem well when he wrote, "The public health threat posed by infectious drug resistance is measured by the range of bacterial hosts it affects, the number of drugs to which it imparts resistance and the prevalence of certain practices in medicine, agriculture and food processing that tend to favour its spread."

"In many parts of the world, antibiotics are routinely incorporated into livestock feed to attempt to promote growth and are also used to attempt to control animal diseases. Anderson and Datta[18] have shown clearly that the presence of antibiotics in livestock exerts a strong selective pressure in favoured organisms—particularly Salmonellae—with resistance factors and plays an important role in the spread of infectious drug resistance."

The rate of development of bacterial resistance through mutation, selection, adaptation or infectious drug resistance will determine how long we will have effective antibiotics, sulphonamides and other chemotherapeutic drugs. The antimicrobial drugs should be used with scientific discretion because treatment of bacterial diseases has now reached the point where many formerly sensitive pathogens are now resistant to many antimicrobial drugs. The current chances for successful treatment of a bacterial disease in a herd or flock are quite small unless the causative organisms can be identified and the sensitivity pattern determined. The gap between diagnosis and treatment has become wider and more complex as pathogens have developed resistance to the pressures of antimicrobial drugs. Thus, sophisticated treatment is mandatory to deal with bacterial pathogens, the host and the environment.

There should be a balance between the scientific use of antimicrobial agents so that they can be beneficially used with a minimum probability of creating a health risk to man. At this time it is impossible to make an accurate measurement of all benefits and public health hazards. It has been well established that the antimicrobial drugs have been most beneficial when they are administered in therapeutic amounts to treat many bacterial diseases. In this capacity they are truly magnificent. However, benefits ascribed to their use as feed additives for increasing rate of gain and feed efficiency and to their use in subtherapeutic amounts to attempt to prevent or control certain diseases require further critical investigation employing sophisticated scientific procedures.

Information is needed to determine the time or periods during the animal's life when benefits are most likely to occur. Many questions have not been answered completely. Are there differences in the activities of the various antimicrobial agents for animal production purposes? Can antimicrobial drugs that are not used to treat diseases in man be used for non-

medical animal purposes? Similarly, more information is needed to minimize potential hazards of these drugs. Can a satisfactory meat inspection programme reduce the likelihood that food will contain antimicrobial drug residues? Can man tolerate small amounts of antimicrobial drugs in his diet on a continuous or intermittent basis? May increased bacterial resistance lead to increased pathogenicity? Can effective ecologic monitoring programmes be established to determine if antimicrobial drugs are being used indiscriminately?

The chemical control of animal health with antimicrobial drugs has been most effective when drug use is scientifically justified. Can we afford the luxury of thinking that disease control has been complete and permanent? Bacterial pathogens, their animal hosts and their environments are in a constant state of dynamic flux which demands that new antimicrobial agents be sought and that we obtain additional information about mechanisms of action. We must seek the most effective use of drugs, but not at the expense of endangering man's health.

ACKNOWLEDGMENT

The research conducted at the University of Illinois has been supported by a grant from the U.S. Public Health Service, National Centre for Urban and Industrial Health (UI 00200).

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