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USE OF ANTIBIOTICS IN LIVESTOCK PRODUCTION AND ANTIMICROBIAL RESISTANCE

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1.   Introduction

The House of Lords Select Committee on Science and Technology undertook in July 1997 an inquiry into the rise in resistance to antibiotics and other antimicrobial agents and its implications for the UK and international public policy.   The report "Resistance to Antibiotics and other Antimicrobial Agents" was published on 23 April 1998.

The Committee was primarily concerned with human infections and was aware that the use of antibiotics as growth promoters in livestock was under consideration by the Advisory Committee on the Microbiological Safety of Food while the use of antibiotic resistance markers in genetically modified organisms was under consideration by the Advisory Committee on Novel Foods and Processes. Hence those issues were not the main focus of the enquiry. Nevertheless there has been much attention directed to the section of the report dealing with antibiotic use in livestock, albeit a minor part of the report. The rôle of animal use of antibiotics both for clinical treatment illness and for "growth promotion" has generated much discussion and in some cases legislative action to curb the use of antibiotics in livestock production. Most recently the European Commission has proposed phasing out (banning) certain antimicrobials (where there is a medical equivalent antimicrobial in current or planned use) including virginiamycin, spiramycin and tylosin phosphate and also bacitracin zinc. The British Government have agreed with this proposal.

Other reports include the UK Industry of Agriculture, Fisheries and Food Technical Report, "A Review of Antimicrobial Resistance in the Food Chain" (July 1998), where extensive accounts analyse the evidence for and against the relationship between resistance in animals and in man.

In the USA a signal publication provides important reading on antimicrobial resistance, namely, the National Research Council and Food and Nutrition Board publication *The Use of Drugs in Food Animals: Benefits and Risks* (National Academy Press 1998).

Other initiatives include Danish Ministries of Health and of Food Agriculture and Fisheries conference on "The Microbial Threat" and the World Health Organisation's recommendations on antimicrobial resistance.   Hence, the topic of antimicrobial resistance has generated much debate and discussion, nationally and internationally.

However, it should be recalled that the issue of antibiotic resistance in animals and the possibility of its transfer to humans was addressed some 30 years ago in the report

which has become know as the Swann Report (1969). A number of recommendations were made by this Report and it is generally believed that had they been rigorously pursued the situation, with respect to antibiotic resistance, would be much less serious than it is today, 30 years on.

2.   Resistance to Antibiotics

Antibiotics have been in use for over 50 years. They are the wonder drugs and have changed the practice of human and animal medicine across the world. The ravages of bacterial infections, which continued until the late 1950s, are now very much a thing of the past. At least so it was thought until recent evidence demonstrated a world wide alarming growth in the number of cases where humans being treated for infections with antibiotics failed to respond to the therapy. The situation in the animal field is not as serious as that in human medicine but it is of growing concern and a major aspect of this concern is the relationship between antibiotic use in animals (especially antibiotics used as growth promoters in intensive livestock production) and the development of antibiotic resistance in man.

The concept of resistance of an organism to an antibiotic is not new and shortly after the development of penicillin, penicillinase was identified and it was predicted that resistance would become a problem. Indeed resistance has followed each new antibiotic, though with varying time and intensity.

Many soil fungi and bacteria produce antibiotics to control and kill competing organisms that challenge their ecological niche. These antibiotic-producing organisms carry a gene responsible for producing the antibiotic but also carry genes responsible for resistance to the antibiotics so the organism itself is not killed by the antibiotic. Thus for each antibiotic there is a naturally occurring resistance mechanism. (Harris et al., 1995)

3.   Nature of Resistance

The biochemical processes responsible for antibiotic resistance arise from five mechanisms: (1) the organism can inactivate the drug before it reaches its target within the cell; (2) the surface of the cell may be impermeable and prevent the drug from entering; (3) the drug enters the cell but is pumped out again; (4) the target in the cell is altered so that it is no longer recognised by the antibiotic, or (5) the bacteria acquire an alternative metabolic pathway rendering the antibiotic ineffective.

Acquired resistance can arise by a number of mechanisms, for example by mutational resistance where random mutation in a bacterial population is then selected for

by the use of a given antibiotic, and the resistant organism then constitutes the dominant population. An alternative mechanism is by horizontal transfer of resistance genes from
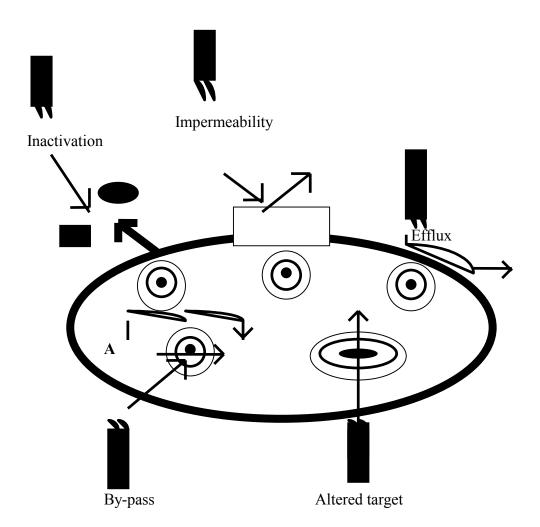
Figure 1: Antibiotic Resistance

Inactivation

Impermeability

Efflux

A

By-pass

Altered target

one organism to another, either by conjugation or direct transfer of genetic material carried on plasmids, or introduced on a bacterial virus or by direct transfer of naked DNA.

Recent studies have shown that the exchange of genetic material between bacteria is frequent and flexible. There is genetic interchange between diverse groups of organisms and this constitutes a global pool of resistance genes, which can rapidly spread between different bacterial populations in different habitats of man, animals and the

environment. The presence of an antibiotic in the environment of a bacterium imposes selection pressure and encourages the spreading of resistance. However, there are no specific studies to determine the prevalence of resistant commensal organisms.

Anderson (1999) in considering the development of antimicrobial resistance comments that knowledge of pesticide resistance in insect population and antimicrobial compounds has been little applied in the antibiotic field. The evolution of a new genotype with a selective advantage over the most abundant genotype will increase in a sigmoid pattern but the speed of development depends on the magnitude of the selective advantage and on the intensity of the selective pressure. The period of low frequency of the variant may be of long duration while the development of the sigmoid curve may occur quickly with a subsequent period of slower change as the frequency approaches its steady state. This sigmoid pattern arises despite the fact that the selective pressure may be constant. (Anderson, 1999).

3.1   How Serious is Antibiotic Resistance?

The major concern in antibiotic resistance is the threat to human health and, in the absence of action to reduce the prevalence of resistance, there is the prospect of returning to the pre-antibiotic era. The reasons for this lie mainly with the medical profession by over prescribing antibiotics, especially the inappropriate use of antibiotics for mild to moderate viral infections such as common colds, earache, sore throat and others. In fact, depending on the geographical area in the UK it has been estimated that from 5% to 50% antibiotic prescriptions are unjustified. In some countries antibiotics are available "over the counter" and this further adds to the development of resistance. In some countries also routine self-medication with "over the counter" antibiotics is common place for medical entities for which antimicrobial therapy is unnecessary.

It is generally held that the onset and maintenance of antibiotic resistance is dependent on the volume of drug use. Austin et al. (1999) note that it has been difficult to establish a quantitative relationship between resistance and drug use in man. In a recent analysis of antibiotic resistance they conclude that the time scale for the emergency of resistance under constant selective pressure is typically much shorter than the decay time following cessation or decline in the volume of drug use. Nevertheless significant reductions in resistance require equally significant reduction in drug consumption.

Examples of the importance of antibiotic resistance include the following: multi-drug resistance occurs in the *Salmonella* species (8 to 10 antibiotics) (Table 1). Resistance to many antibiotics has left ciprofloxacin as the only effective antibiotic for typhoid fever—now ciprofloxacin-resistant typhoid has emerged. *Pneumococcus* as a cause of pneumonia and meningitis has been regularly treated with penicillin but there is

an increase in penicillin resistant strains, some showing multi-drug resistance and few options remain and in countries where the effective agents are unavailable or too expensive meningitis has become untreatable.

Staphylococcus aureus, a common commensal on the skin, is normally benign, but can cause life-threatening septicaemia due to methicillin resistance (MRSA). This "killer bug" has become prevalent in hospitals and nursing homes (nosocomal infections). In the UK resistance frequency was 2% in 1975 and 35% in 1996 while the number of hospitals with epidemic MRSA increased from 40 a month in 1993 to 110 per month in 1996 (Austin et al., 1999).

In some cases only vancomycin and antibiotics related to it remain for treatment of MRSA, those being expensive and more toxic. Even vancomycin-resistant strains are now appearing, placing deep surgery at risk in Japan and the USA. Other infections similarly carry serious risks because of resistance, gonorrhoea and human tuberculosis being examples.

Table 1: Examples of Valuable Antimicrobial Therapies now Lost or Imperilled by the Spread of Resistance

Organism	*Disease*	Agents lost or threatened
Pneumococcus	Pneumonia, otitis, meningitis	Penicillin; many others
Meningococcus	Meningitis, septicaemia,	Sulphonamides; (penicillin)
Haemophilus influenzae	Meningitis	Ampicillin, chloramphenicol
Staphylococcus aureus	Wound infection, sepsis	Penicillin, penicillinase-resistant penicillins, others
Salmonella typhi	Typhoid Fever	Most relevant agents
Shigella spp.	Bacillary dysentery	Most relevant agents
Gonococcus	Gonorrhoea	Sulphonamides, penicillin, tetracycline; (ciprofloxacin)
Plasmodium falciparum	Severe malaria	Chloroquine, pyrimethamine; (mefloquine, quinine)
Escherichia coli (Coliforms)	Urinary infection, septicaemia	Ampicillin, trimethoprim, others

(From House of Lords Select Committee on Resistance to Antibiotics)

4. Antibiotics in Livestock: Relation to Human Health

The progressive increase in antibiotic resistance in human infections is largely the result of imprudent use of antibiotics in the human medical field. Why then should veterinarians and livestock producers be concerned that they have a rôle to play in this and why should they be accused of contributing to the problem?

To answer these questions it is important to recognise that two major mechanisms constitute the hazard. One is the transfer of antibiotic-resistant zoonotic organisms, the second is the selection of antibiotic resistance in non-pathogenic commensal bacterial populations and the transfer of this to the commensals of the human gut, eventually with transfer to human pathogenic forms.

As has been mentioned in the introductory comments, the potential threat to human health posed by the use of antibiotics in livestock farming was addressed some 30 years ago by the Swann Report. Many of the recommendations of Swann were not acted upon and many believe that had action taken place then the present concerns would be much less in the United Kingdom and possibly also in other countries.

To appreciate the rôle of animal use of antibiotics in the issue of antimicrobial resistance in man, it is necessary to have a clear picture of how antibiotics are used on the livestock field. The clinical use of antibiotics for therapeutic purposes is a well accepted and legitimate application. It is not possible to envisage modern veterinary practice without them and they play an important rôle in animal welfare in controlling disease which may constitute 80% of welfare problems in intensive livestock production units.

The House of Lords Select Committee on Science and Technology was anxious to assure the livestock industry that there was no call to ban the use of antibiotics for clinical use in the treatment of the individual animal. Indeed the aim must be to maintain thus potency.

Disease prevention use of antibiotics is also a legitimate and appropriate use of antibiotics. This may apply to groups of animals where some of a group show signs of disease but others do not, but it is prudent to treat the whole group. Instances of such use occur when groups of young animals are weaned and coliform diarrhoea is a common sequel; a further example is the use of antibiotics in non-lactating cows to control mastitis in subsequent lactations.

In both the above instances, therapeutic use and disease prevention, the use of antibiotics is under veterinary direction and requires a veterinary prescription.

The area where concern exists particularly is the use of antibiotics in animals as "feed additives", "growth promoters" or "digestive enhancers", the variety of names possible being indicative of the full lack of understanding of how these act.

4.1   Antibiotics as Growth Promoters

As early as 1946 American workers demonstrated that streptomycin and sulphasuxidine increased the weight gain of chicks, an observation largely ignored at the time. Later the waste products of tetracycline fermentation were shown to increase growth, a response initially attributed to vitamin B12.

The greatest effects of growth promoters occur in early life but not all antibiotics produce the same effect in different species. Thus penicillin will promote growth in pigs and poultry, but not calves, whereas tetracyclines increase growth in all these species. The growth promoters (digestion enhancers) in common use include; Carbodox, Olaquindox, Avilamycin, Avoparin, Efrotomycin, Flavophospholipol, Oleandamycin, Spiramycin, Tylosin and Virginiamycin.

There is still doubt as to precisely how growth promoters exert their action. They are used at low concentrations (2.5 ppm to 50 ppm according to compound) and increase average daily growth and food conversion ratios by 3% to 11% percent. Three commonly accepted explanations are that the sub-therapeutic doses of antibiotic also suppress disease, another explanation is the maintenance of a more effective and absorption gut lining and a further one is the suppression of commensal bacteria which would divert nutrients from the host to microbe. Other explanations offered are a decrease in bacterial growth depressing toxins including ammonia or monoamines, increased synthesis of vitamins and the growth factors reduced intestinal mucosal epithelial cell turnover and reduced intestinal mobility. It is interesting to note that the effects of some antibiotics on growth are more marked under conditions of poor hygiene than when animals are kept in new accommodations or in thoroughly cleaned facilities, suggesting that the suppressive effect intestinal microbes is an important effect.

4.2   Antibiotic Resistance in Animals

Antibiotic resistance occurs widely in bacteria in farm animals and varies greatly depending on management practices, antimicrobial usage and the degree and nature of diseases present in the livestock units. In general veterinarian and livestock producers co-operate to monitor and ensure that resistance does not reach a level to cause disease. Whereas resistance levels (MICs) are frequently determined for animal pathogens (e.g., *Salmonella*) there is a paucity of information on resistance in commensal or background bacteria.

The major pathogens for animals are *Salmonella, Staphylococci, Escherichia coli* and *Pasteurella* and resistance has been reported in all. Salmonella cause a variety of illnesses but also may occur in the intestine of animals without obvious disease. *Salmonella typhimurium* DT 104 is a particularly important serotype. Resistance is on the increase. Thus in 1995 of 11,083 salmonelas tested at the UK Central Veterinary Laboratory 38.8% were sensitive to all microbials tested while 51% were so sensitive in 1994. Similar trends in a range of antibiotic resistances have been noted (Anon, 1996).

Escherichia coli is a major pathogen of farm animals, especially in the neonate and in growing poultry. Single and multiple resistances has been present on UK farms since 1956 and has developed world-wide.

Whereas most concern is expressed about antibiotic resistance in food producing animals, nevertheless resistance also occurs in companion animals. Thus multi-resistant and *E. coli* are found in dogs and fluoroquinolone resistance has also been identified in these.

In some instances the resistance in companion animals reflects the resistance in the agricultural community and the food chain.

Other companion or display animals such as reptiles and fish may exhibit resistance and may be sources of resistance organism for a household. For example, gentamycin resistance is common in Salmonella isolated from the eggs of red-eared turtles intended as pets. Turtles can shed Salmonella into tank water for up to 11 months.

With respect to farmed fish, resistance in *Aeromonas salmonicida* (furunculosis) has been identified and plasmid transfer of resistance between Aeromonads and organisms in the environment is possible (Kruse and Sorum 1994; Smith et al 1994). In the Far East antimicrobials are used discriminately for cultured shellfish, prawns and farmed fish, while the waste from poultry and pig units is used to feed fish and this may contain resistance organisms.

The survival of antibiotic resistant organisms in the environment is the same as for susceptible organisms. Hence, Salmonellas, coliforms, etc., can survive in farmyard manure, slurry, dust and water.

4.3   *Antibiotic Use in Animals in Relation to Resistance in Man*

The contribution of antibiotic use in animals to antibiotic resistance in man is of long-standing controversy. However, increasingly, various consultative committees have

emphasised the potential danger to human health of this use. For example, the Expert Group on Animal Feedstuff (The Lamming Committee) (1992) recommended that prophylactic used should be reconsidered. In 1997 the World Health Organisation convened a major multi-disciplinary committee (Medical Impact of the Use of Antimicrobials in Food Animals, Berlin, October 1997) and concluded amongst several points that "low-level long term exposure to antimicrobials may have a greater selective potential than short-term full dose therapeutic effect and recommended prohibition of growth promoters which are used in human therapeutics, or known to select for cross resistance to antimicrobials used in human medicine". More recently the UK House of Commons Select Committee on Agriculture has recommended that the use of antibiotics as growth promoters should be banned.

Firm evidence of the contribution of antibiotic resistance in animals to humans has always been difficult to obtain. Nevertheless there is an increasing number of reports which do provide evidence of transfer from animals to man.

Foodborne bacterial zoonoses have been well documented and where the bacteria are resistant to antibiotics then resistance is transferred with them. It is assumed but not proven that resistant bacteria are no less or more infective or pathogenic than their nonresistant counterparts though then pathogenic effects may be more prolonged due to the lack of effective therapy.

Some 20 years ago Smith (1969) and Linton (1977) demonstrated that antimicrobial resistance *E. coli* could transfer their resistance to normal human gut organisms but further evidence for this is slow in coming.

Glycopeptide resistant enterococci were detected in man in 1988 (Uttley et al., 1988) and others. The isolates were obtained from animals and raw meat and were indistinguishable from glycopeptide resistant enterococci isolated from turkeys and farmers raising them (Van den Bogaard et. al., 1997). The use of avoparcin (a growth promoter in the poultry and pig rearing industry) is likely to glycopeptide resistances in man, resistance being transmitted by transposon TN 1546. Van de Bogaard et al (1997) reported that vancomycin resistant enterococci in turkeys not receiving avoparcin was 8% while it was 60% in flocks fed avoparcin as a growth promoter.

The danger exists that human glycopeptide resistant enterococci could transfer the vancomycin resistant gene to methicillin resistant *Staphylococcus aureus* (MRSA), these being life threatening infections which can be treated effectively only with vancomycin.

Wray (1997) reported the detection of the enzyme ACC (3) iv which mediates apramycin resistance in enterobacteria in man, in animal bacteria. Werner, Klane and

Witte (1999) reported the occurrence of *Sat* A mediated virginiamycin resistance in strains of *Enterococcus faecium* of clinical origin which were collected before any use of streptogramines in German hospitals and suggest an animal source. Witte (1998) discussed the spread of nourseothricin resistance in animal and human isolates in Germany. This compound, which was used as a growth promoter is unrelated to any drug used in man yet resistances was seen in human *E. coli* isolates and shigellae which are exclusive to man and primates. *Sat* A is carried on plasmids and further spread among *E. faecium* and to humans seems likely especially via meat products.

Zervos (1997) found 100% of animals at the time of processing from three large turkey flocks fed virginiamycin had quinapristin-dalfopristin resistant strains. This is the only available treatment for some patients with vancomycin enterococcal infections.

The House of Lords Report on "Antibiotic Resistance" did not call for a ban on all growth promotion and long-term mass prophylaxis. However, it did recommend that "antibiotic growth promoters such as virginiamycin which belongs to classes of antimicrobial agent used (or proposed to be used) in man and are therefore most likely to contribute to resistance in human medicine, should be phased out, preferably by voluntary agreement, between the professions and industries concerned, but by legislation if necessary".

It was noted that other antibiotics of importance to human health, such as the fluoroquinolones, deserved "extreme economy of use" in veterinary practice. While their use as medicates for the short time treatment of animal illnesses would be justified their use on long term or mass treatment "cannot be best practice from the point of view of human health". Much concern is with the Salmonellas and Campylobacters and poultry which is a significant source of resistant organisms. Fluroquinolone resistance in Campylobacters is well documented in Spain and in *Salmonella virschon* in the UK and hence may become more common and complicate treatment.

4.4   Effects of Discontinued Use of Antibiotics as Growth Promoters

It is held by some (e.g National Office of Animal Health - NOAH) that apart from the economic benefits of the use of growth promoters, there also are animal health and welfare and environmental benefits. The last can be estimated by the increased number of livestock units required producing the equivalent amount of meat, milk, eggs, etc. were antibiotic growth promoters discontinued. Reflected also in this consideration is the increase in effluent from farms and the greater production of methane.

The Fédération Européene de la Santé Animale (FEDESA) in a 1995 memorandum on "Responsible use of antimicrobials to control disease in farm animals"

emphasises that antimicrobials are no substitute for bad farm management. It is considered by some that antibiotic growth promoters are in fact used as a crutch to poor livestock husbandry. Hence the experience of banning their use in Sweden generated substantial interest.

Sweden banned the use of antimicrobials for in-feed use without prescription in 1986. Various bodies have commented that the ban has resulted in low production efficiency and increased costs. There was an increase in post-weaning scour, mortality and longer growth rate. In fact it was reported that the husbandry system without growth promoters may even use more antimicrobials because of their need for therapeutic use. These points were stated in the House of Lords Report. However, the Swedish authorities vigorously contest the statement and maintain that after initial problems the Swedish pig industry is flourishing, is as efficient as that in any other EU Country and does not benefit from any greater subsidy than that in any other country of the European Union.

5. Summary and Conclusions

The House of Lords Report on "Resistance to Antibody and other Antimicrobial Agents" concluded in a press inference that: "Our enquiry has been an alarming experience. Misuse and overused of antibiotics are now threatening to undo all their early promises and success in curing disease. But the greatest threat is complacency, from Ministers, the medical profession, the veterinary service, the farming community, and the public at large. Our report is a blueprint for action. It must start now, if we are not to return to the bad old days of incurable diseases before antibiotics were available".

The response to the Report has been very satisfactory from both the medical and veterinary profession, with a recognition of the need to develop the concept of prudent use of antibiotics in a positive way. Various conferences have been held to discuss the issue and voluntary guidelines or codes of conduct are to be elaborated to avoid the need for control by legislation.

The United Kingdom Government has responded positively to the Report and all major recommendations have been accepted and action is promised—a very satisfactory result.

6. Recommendations

1.   There is need to develop quick adequate diagnostic tests for surveillance of antibiotic resistant organisms.

2.   Surveillance of antibiotic resistance should be increased and correlated at some central agency, e.g., PAHO.

3.   All antibiotic use in animals should be under veterinary prescription.

4.   Antibiotics used as growth promoters and which also are used or are proposed to be used in man should be discontinued.

5.   An over arching committee should be responsible for the use of antibiotics in medicine, and veterinary medicine.

6.   Pharmaceutical companies should increase their development efforts to produce effective alternatives to growth promoters and digestion enhancers in livestock.

REFERENCES

Anderson R M (1999), The Pandemic of Antibiotic Resistance, Nature Medicine 5, 147-149.

Anon (1996), Salmonella Livestock Production, 1995, Veterinary Laboratories Agency.

Austin D J Kristinsson K G and Anderson R M (1999), The Relationship between the Volume of Antimicrobial Consumption in Human Communities and the Frequency of Resistance, Proceedings National Academy of Science, USA.

Harris F, Chatfield L and Phoenix D (1995), Antibiotics: the Bacterial Resistance Movement Sunken Back, Biologist 42 62-64.

Kruse H and Sorum (1994), Transfer of Multiple Drug Resistant Plasmids Between Bacteria of Disease Origins in Natural Microenvironments, Applied and Envchemicals Microbiology, 60, 4015-4021.

Linton A H (1977), Animal to Man Transmission of Enterobacteriacea, Royal Society of Health Journal, 97, 115-118.

Smith H N (1969), Transfer of Antibiotic Resistance from Animal and Human Strains of Esherichia Coli to Resident E.Coli in the Alimentary Tract of Man, Veterinary Record 85, 31-33.

Smith P, Hiney M P and Samuelson O B (1994), Bacterial Resistance to Antimicrobial Agents Used in Fish Farming: a Critical Evaluation of Method and Meaning, Animal Review of Fish Diseases 4, 273-313.

Uttley A A, Collins C H, Naidoo J and George R C (1988), Vancomycin Resistance Enterococci, Lancet 1, 57-58.

Van den Bogaard, A E Jensen and Stobberingh E E (1997), Vancomycin Resistant Entercocci in Turkeys and Farmers, New England Journal of Medicine 337 1558-1559.

Wernor G, Kline I and Witte W (1999), Quinpristin Dalfopristin Resistance in Glycopeptide Resistant Enterococcus Faecuim - the Link to Animal Husbandry, European Journal of Clinical Microbiology and Infectious Diseases (in press).

Witte W (1998), Medical Consequences of Antibiotic Use in Agriculture Science 279, 949-1096.

Wray C (1997), Development of Antibiotic Resistance: A Vets Tale, Journal of Medical Microbiology 46 26-33.

Zervos M J, Occurrence and Epidemiology of Resistance to Virginiamycin and Streptogramins.