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INTRODUCTION TO THE ROUND TABLE DISCUSSION

Is the use of antimicrobial drugs in agriculture risky for human health?

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In 1997 a network of Polish and Swedish research centres* was established within the "Visby program" (380/4968/19979 no 39) entitled ENVIRONMENTAL IMPACT OF ANIMAL BREEDING, FOOD PRODUCTION AND HUMAN/ VETERINARY MEDICINE.

The intention of the network is to establish an interdisciplinary team of researchers integrating basic research between animal production, ecology, biology and human/veterinary medicine. The additional aims of the programme are to develop new methods and indexes for evaluation of human/animal health impact on the environment. Our idea was to reevaluate the application of feed additives in the aspect of agricultural environment, and human and animal health. Discussion over the use of feed antibiotics seemed to be very up-to-date. Sweden and Denmark have already accumulated considerable experience in managing an "antibiotic free" animal production. In other EU countries there is an increasing debate about the "to be or not to be" for the feed antibiotics. The Central European countries face the problem of uncontrolled use of feed antibiotics. Numerous feed additives have been suggested, which may be suitable to replace feed antibiotics without reducing the high animal performance. Intensive research in this area is warranted. Some alternatives to feed antibiotics, their advantages and their drawbacks, will be discussed during the Satellite Symposium (IV) to the 49th EAAP Annual Meeting and the Round Table Discussion held August 22 and 23, 1998 in Jabłonna near Warsaw.

Antibiotics were approved for use as animal feed additives in 1950 after it was discovered that their use increases animal growth rate, improves feed utilization, and reduces animal mortality and morbidity caused by clinical and subclinical infections. More antibiotics have been used in this manner than in medical applications. In 1969 the Swann report declared that antibiotics of medical importance and those which promote cross-resistance should not be used as growth promoters in animal feeds. Recently, legislation limiting the subtherapeutic use of antibiotics in animal feed has been introduced in some countries. The prevailing use of subtherapeutic doses of antibiotics in animal feed has been responsible for spreading bacterial antibiotic resistance, which ultimately compromises treatment of human bacterial infections. Prolonged oral or parenteral administration of antibiotics has led to the development of resistant strains of microorganisms. Bacteria acquire drug resistance in several ways: through mutagenesis, conjugation, transduction or transfection. Oral antibiotics facilitate the proliferation of resistant variants of bacteria through the process of selection pressure. Bacteria are capable of transfering this drug resistance to other bacteria by spreading plasmid DNA. This can lead to multiple resistance to a vast number of therapeutically useful antibiotics which will, therefore, become ineffective. Transferable multiple drug resistance (MDR) can occur through drug resistance elements (plasmids and transpozons) and can be transfered between pathogenic and non-pathogenic organism. It is also transferable between different species, such as *E. coli*, Salmonella and Shigella. Contamination during slaughter may result in the transfer of antibiotic resistant *E. coli* strains. In the human gut, these strains could transfer resistance to other bacteria existing in the gut, namely *E. coli* or Salmonella strains.

Antibiotic-resistant coliforms have been isolated from the fresh and cooked meat. Many studies indicate that animal-to-man transmission of antibiotic resistant bacteria is possible, and indeed increased levels of drug-resistant organisms have been found in farmers, butchers, etc.

In 1996 the European Committee for Animal Nutrition (SCAN) approved the continued use of avoparcin as a feed additive for farm animals (European Commission suspended the license of avoparcin from April 1997). Avoparcin, a glycopeptide antibiotic, is an analogue of vancomycin and as such it has the same mode of action. It exerts selection pressure for cross-resistance to vancomycin and similar antibiotics in human associated bacteria.

Furthermore, vancomycin-resistant enterococci can invade the human population from the food chain. It is a concern that vancomycin-resistant enterococci have been isolated from samples of minced meat from a number of different butchers, as well as from faecal samples of people living in the same area in Germany in which avoparcin has been commonly used in agriculture. It is possible that the enterococci of animal origin became resistant to these glycopeptides due to the use of avoparcin in animal feed. Vancomycin resistance in Gram-positive bacteria is still one of the most serious problems currently encountered in European hospitals because in many cases vancomycin is the only antibiotic left which is effective against MDR strains of *Staphylococcus aureus*. In 1995, in the UK, *Salmonella typhimurium* phage type DT 104, was found to be endemic in cattle, pigs, sheep, and poultry. More than 3500 human isolates of *Salmonella typhimurium* DT 104 have been obtained of which 98.9% of the isolates were MDR. The risk factors for infection includes sausages, chicken and burger consumption. Resistance to quinolones has emerged among human isolates of *Salmonella* species. In 1995, 3.5% of *Salmonella typhimurium*, 3.9% of *Salmonella virchow*, and 31.1% of *Salmonella hadar* strains were resistant to quinolones. Approximately 80% of *E. coli* isolates from pigs and calves treated with antimicrobial drugs are resistant to more than one antibiotic. These observations lead to the conclusion that the use of similar antibiotics in human medicine (e.g. the quinolones – enrofloxacin or glycopeptides – avoparcin) as animal husbandry creates a selective pressure that encourages the emergence and persistence of resistant strains of bacteria in animal products and may eventually lead to their epidemic spreas in man. The presence of antibiotic residues in meat, milk and their products is potentially hazardous for man, especially for children and their ingestion has resulted in allergic skin conditions, nausea, vomiting, anaphylactic shock. Cooking and freezing have minimal, if any, effect on residues.

Facing the problems listed above, one can ask about the rationale for continuing with subtherapeutical doses of antibiotics in animal nutrition. Two effects of feed antibiotics appear to be still very attractive in animal production: 1. reduction of growth of potentially pathogenic gastrointestinal bacteria and 2. stimulation of the release of the endogenous growth factors (e.g. insulin-like growth factor). These growth factors are crucial for the early weaned animals since supply of the animals with bioactive substances in milk is finished during weaning; however, the mechanism by which the antibiotics stimulate growth factors remains unclear.

It is suggested that there are at present several promising approaches to improve the function of the intestine which may overwhelm the roles played by feed antibiotics. As discussed in the papers in this issue, supplementation with glutamine and its derivatives, biologically active peptides, immunoglobulins, or organic acids may improve intestinal function without having the negative consequences of feed antibiotics.

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