Antibiotic Growth-Promoters in Food Animals

By Peter Hughes and John Heritage, University of Leeds, UK - There has been a developing controversy surrounding the use of antibiotics as growth promoters for food animals. These drugs are used at low doses in animal feeds and are considered to improve the quality of the product, with a lower percentage of fat and a higher protein content in the meat. Other benefits of the use of antibiotic growth-promoters include control of zoonotic pathogens such as *Salmonella*, *Campylobacter*, *Escherichia coli* and enterococci.

Use of any antibiotic is associated with the selection of resistance in pathogenic bacteria and it has been argued that the use of antibiotic growth-promoters imposes a selection pressure for bacteria that are resistant to antibiotics that may be used in clinical or veterinary practice, thus compromising the continued use of antimicrobial chemotherapy. This paper considers the use of antibiotics as growth promoters and then examines some of the alternative methods for achieving meat of high quality.

INTRODUCTION

The term "antibiotic growth promoter" is used to describe any medicine that destroys or inhibits bacteria and is administered at a low, subtherapeutic dose. The use of antibiotics for growth promotion has arisen with the intensification of livestock farming. Infectious agents reduce the yield of farmed food animals and, to control these, the administration of sub-therapeutic antibiotics and antimicrobial agents has been shown to be effective. The use of growth-promoters is largely a problem of intensive farming methods and the problems caused by their use are largely those of developed rather than developing countries.

According to the National Office of Animal Health (NOAH, 2001), antibiotic growth promoters are used to "help growing animals digest their food more efficiently, get maximum benefit from it and allow them to develop into strong and healthy individuals". Although the mechanism underpinning their action is unclear, it is believed that the antibiotics suppress sensitive populations of bacteria in the intestines. It has been estimated that as much as 6 *per cent* of the net energy in the pig diet could be lost due to microbial fermentation in the intestine (Jensen, 1998). If the microbial population could be better controlled, it is possible that the lost energy could be diverted to growth.

Thomke & Elwinger (1998) hypothesize that cytokines released during the immune response may also stimulate the release of catabolic hormones, which would reduce muscle mass. Therefore a reduction in gastrointestinal infections would result in the subsequent increase in muscle weight. Whatever the mechanism of action, the result of the use of growth promoters is an improvement in daily growth rates between 1 and 10 *per cent* resulting in meat of a better quality, with less fat and increased protein content. There can be no doubt that growth promoters are effective; Prescott & Baggot (1993), however, showed that the effects of growth promoters were much more noticeable in sick animals and those housed in cramped, unhygienic conditions.

Currently, there is controversy surrounding the use of growth promoters for animals destined for meat production, as overuse of any antibiotic over a period of time may lead to the local bacterial populations becoming resistant to the antibiotic. This is it not an invariable rule: *Streptococcus pyogenes* remains sensitive to penicillins after over sixty years of clinical use but such examples are, however, very rare. Undoubtedly, the medical exploitation of antimicrobial chemotherapy, particularly to treat human infections, has imposed an enormous selection pressure on formerly sensitive bacteria to acquire genetic elements that code for resistance to antibiotics.

This phenomenon has occurred within our hospitals, where compromised patients and over-use of antibiotics create an optimal environment for promoting resistance in susceptible strains of bacteria. One of the best examples of this is the methicillin-resistant *Staphylococcus aureus*

(MRSA). Most strains of S. aureus produce penicillinases, a class of _-lactamase enzymes that break down penicillins, and so penicillinase-stable _-lactams, such as methicillin, cloxacillin and flucloxacillin, have been used to treat staphylococcal infections. The side chain on these molecules is of such a shape as to preclude binding of the _-lactamase to the antibiotic, thus rendering the drug stable. The widespread use of these drugs in the antibiotic arms race led to the emergence of strains of *Staphylococcus aureus* that resist _-lactamase through an alternative mechanism. MRSA have also acquired resistance determinants to a wide range of antibiotics (Hospital Infection Society, 2001). MRSA isolates often are resistant to a range of commonly used antimicrobial agents, including erythromycin, clindamycin, tetracycline and many aminoglycosides. The only therapeutic options for serious, systemic MRSA infection currently available are antibiotics in the glycopeptide family, including vancomycin. Since 1996, there have been reports of MRSA strains with decreased susceptibility to vancomycin (Centers for Disease Control and Prevention, 2001). Even more worrying is the observation that MRSA can express high-level resistance to glycopeptides when the *van*Agene cassette is experimentally transferred from vancomycin-resistant enterococci (Noble, 1997). Were this to happen outside of the laboratory, this would take us one step closer to a post-antibiotic era where certain bacterial infections can no longer be treated with antimicrobial chemotherapy.

To avoid entering a post-antibiotic era, agencies around the world are examining our use and abuse of antimicrobials (House of Lords 1998; Commission of the European Communities, 2001). Most antibiotics, around 60 *per cent*, are used for therapeutic purposes in humans, although an increasing amount is administered as prophylaxis to prevent infections. The farming industry is the second largest consumer of antibiotics after medical practitioners. About 40 *per cent* of antibiotics are used as growth promoters although antibiotics are also used therapeutically for animals. To reduce the risk of selecting resistant bacteria, the use of antibiotics must be restricted. The most attractive area for reducing the use of antibiotics is to ban their use as growth promoters in food animals. This review examines the consequences of the use of antibiotics as growth promoters and looks at alternatives aimed at reducing the pressure for the selection of resistance in bacteria that cause disease in both humans and animals.

CURRENT USE OF ANTIBIOTIC GROWTH PROMOTERS

On a world scale, the use of antibiotics as animal growth promoters differs dramatically. Sweden now makes no use of antibiotics for growth promotion purposes; the USA uses a wide range of antibiotics, including some considered to be "medically important". The following information is taken from the Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR, 1999) on the use of antibiotics in food producing animals. Pigs are exposed to the greatest range of growth promoters. In the USA, for example, pigs are exposed to _-lactam antibiotics, including penicillins, lincosamides and macrolides, including erythromycin and tetracyclines. All these groups have members that are used to treat infections in humans. Pigs in the USA are exposed to a range of other compounds intended for growth promotion. These include bacitracin, flavophospholipol, pleuromutilins, quinoxalines, virginiamycin and arsenical compounds. In the USA, compounds used as growth promoters for cattle include flavophospholipol and virginiamycin, both also used as growth promoters in poultry. Cattle are also exposed to ionophores such as monensin to promote growth. Poultry are given arsenical compounds. The Animal Health Institute of America (AHI, 1998) has estimated that, without the use of growth promoting antibiotics, the USA would require an additional 452 million chickens, 23 million more cattle and 12 million more pigs to reach the levels of production attained by the current practices.

In Australia a range of growth promoters are employed. Pig farmers use arsenical compounds, flavophospholipol, the macrolides kitasamycin and tylosin, the quinoxaline olaquindox, and also

virginiamycin, a streptogramin. Poultry producers use arsenical compounds, flavophospholipol, bacitracin and virginiamycin. Australian cattle farmers employ a range of ionophores, namely lasalocid, monensin, narasin and salinomycin. They also employ flavophospholipol and the macrolide oleandomycin. The glycopeptide avoparcin is still used in pig and poultry farming and in rearing cattle in Australia. Use of this compound is discussed more fully below.

The use of growth promoters in the European Community is more limited. The oligosaccharide avilamycin is used in pig and poultry farming, ionophores, namely monensin and salinomycin are used for cattle and pigs and flavophospholipol is used with a range of livestock, including cattle, pigs, poultry and rabbits. In pig production, feed conversion efficiency is improved, along with daily growth rates, by approximately 2.5 *per cent*. Mortality rates, associated with scouring and proliferative enteritis, are 10-15 *per cent* lower than in countries, such as Sweden, who do not use antimicrobial growth promoters. In poultry, growth promoters, such as bacitracin, virginiamycin and avoparcin, control *Clostridium perfringens* infections, which are potentially fatal, in addition to improving feed conversion efficiency. It is estimated that this translated into an improvement of 1.5 *per cent*, with added economic benefits from the reduction of *C. perfringens* infections (JETACAR, 1999).

The cattle industry in the USA is, perhaps, the most dependent on growth promoters as cattle have energy requirements that are high and that cannot be met easily without the use of growth promoters. High energy rations increase muscle growth and fat deposition in beef cattle, and help to improve milk productivity in dairy cattle. Unfortunately, the use of such rations is associated with side-effects, such as bloat and lactic acidosis, which can be debilitating or even fatal. These conditions are not a problem in Europe, where cattle diets contain more forage. To counteract this, monensin is used and, in addition to preventing the aforementioned conditions, it also significantly reduces ammonia and methane emissions (Mbanzamihigo *et al.*, 1995). It does not belong to a class of medically important antibiotics and is not associated with any major resistance problems. In an investigation to discover the long-term effects of monensin therapy, Rogers *et al.* (1997) concluded that there is no real adaptation of rumen microbes after a period of 96-146 days of monensin treatment and that most effects disappear within a few hours following monensin withdrawal.

In this sense, monensin is probably one of the safest and most effective antibiotic growth-promoters with regard to human and animal health and associated bacterial resistance problems. Virginiamycin is used for similar purposes, such as the prevention of acid lactosis in cattle and poultry, but use of this compound has led to the selection of bacteria that are resistant to its effects. It is related to pristinamicin and quinupristin, both of which are used in human medicine and so there are fears that its continued use may compromise human therapy. Its use as a growth promoter has now been banned in the EU (Butaye *et al.*, 2000).

HUMAN HEALTH AND THE CONSEQUENCES OF USING ANTIBIOTIC GROWTH PROMOTERS

Human health can either be affected directly through residues of an antibiotic in meat, which may cause side-effects, or indirectly, through the selection of antibiotic resistance determinants that may spread to a human pathogen. A drug that illustrates both potential problems is chloramphenicol. Gassner & Wuethrich (1994) have demonstrated the presence of chloramphenicol metabolites in meat products and have concluded that a link with the presence of these antibiotic residues in meat and the occurrence of aplastic anaemia in humans cannot be ruled out. Banned for growth promotion use in America over a decade ago and in the EU since 1994, chloramphenicol remains a drug used in treating typhoid fever. Over-use in animal husbandry is believed to have led to an increase in resistance to the drug in bacteria of the genus *Salmonella*, including *Salmonella typhi*, the causative bacterium of typhoid. It should be noted that the link between the use of antibiotic growth-promoters and increasing resistance remains unproven and that typhoid rates of infection and cure have not changed significantly since the introduction of the ban in 1994. There were 153 cases of typhoid fever in England and Wales in 1999, compared with 227 in 1994 and 132 in 1991 (Public Health Laboratory Service, On-Line). An alternative explanation for the increase in resistance to chloramphenicol is its availability as an over-the-counter drug in developing nations. It is cheap and relatively easy to

produce.

In general, the effect of antibiotic residues in meat is insignificant when compared with the issue of selection and amplification of antibiotic resistant strains of bacteria. Antibiotic resistance determinants selected in this manner may have various routes by which they may compromise the therapeutic use of antibiotics. Selection may occur in microbes that are pathogenic for humans. Alternatively, resistance may be selected in zoonotic bacteria that subsequently cause human disease. On another level, the resistance determinant may be selected in a bacterium that is a member of the commensal flora of the animal being fed a growth promoter. If such a resistance determinant is mobilisable, it may subsequently transfer to human or animal pathogens. The consequences of selection of resistance can range from prolonged illness and side effects, due to the use of alternative, and possibly more toxic, drugs, to death, following complete treatment failure. Modern medicine has furnished us with a wealth of antibiotics but, as the MRSA example discussed above illustrated, alternatives are starting to run out. The four types of bacteria most commonly associated with resistance due to use are *Salmonella*, *Campylobacter*, *Escherichia coli* and the enterococci; these bacteria are likely to be transmitted frequently from animals to humans.

Salmonella sp.

Bacteria of the genus *Salmonella* are responsible for many human diseases. *Salmonella typhi* is the causative agent of the potentially lethal typhoid fever. This infection is exclusively of human origin, spread via human faecal contamination of food or water and has a high mortality rate if left untreated. As it is mainly spread through insanitary conditions, and from human carriers, it is not within the scope of this review. Other species of *Salmonella* are zoonotic and are usually acquired from contaminated food sources, such as poultry. They commonly cause gastroenteritis. Symptoms can range from mild diarrhoea and nausea to severe vomiting, fever and violent diarrhoea. Most infections are confined to the gut but with people at the extremes of the age range, *Salmonella* may cause invasive disease. Such cases can require hospitalisation due to extreme dehydration coupled with endotoxic shock and may even result in death. The most common causative agents of salmonellosis are *Salmonella enterica var.* Enteriditis and *Salmonella enterica var.* Typhimurium and these bacteria are often found as contaminants in poultry and eggs. Recent measures to control *Salmonella* infections have proved very successful in controlling the incidence of infection, particularly by *Salmonella enterica var.* Enteriditis (Advisory Committee on the Microbiological Safety of Food, 2001).

Salmonella enterica var. Typhimurium can usually be treated with fluoroquinolones, chloramphenicol and ampicillin. Molbak *et al.* (1999), however, reported that isolates of *Salmonella enterica var.* Typhimurium DT104, which is already resistant to multiple drugs including ampicillin and tetracycline, was showing resistance to quinolones. Consequently, some infections caused by DT104 can be very difficult to treat.

In 1998, Bonner reported that, in 1983, an outbreak of food poisoning caused by a resistant strain of *Salmonella* was linked to hamburgers made from cattle fed with chlortetracycline. Spika *et al.* (1987) traced a chloramphenicol-resistant strain of *Salmonella enterica var.* Newport from beef burgers to herds that had been dosed with chloramphenicol. Tacket *et al.* (1985) reported an outbreak of multi-drug resistant *Salmonella enterica var.* Enteriditis following consumption of raw milk. All of these reports originated in North America but this is not just an American problem; bacteria do not respect national boundaries. *Salmonella enterica var.* Typhimurium DT104 was isolated in the UK in 1988 and has subsequently migrated around the world.

Using medically important drugs, such as chloramphenicol and tetracycline, as growth promoters would seem to be the most obvious route towards resistant strains that pose a threat to human health, but the selection of resistance is not necessarily that simple. JETACAR (1999) report a significant correlation between the use of the aminoglycoside apramycin as a growth promoter and the isolation of resistant *Salmonella*, especially *Salmonella enterica var.* Typhimurium DT104, in cattle. Aminoglycoside resistance in these bacteria is due to the

acquisition of an acetylating enzyme. This enzyme also confers resistance to gentamicin, an important drug in human medicine.

Some scientists believe that antibiotic growth-promoters may contribute indirectly to the spread of *Salmonella* by allowing animals to be kept in unhygienic conditions. Growth promoters may act as masking agents for proper sanitation by reducing the pathogen load. The fundamentally unhygienic conditions of intensive broiler chicken production have been criticised. Broilers are reared in confined housing: this allows any pathogen to spread through the cohort rapidly.

Campylobacter sp.

Campylobacter, particularly *Campylobacter jejuni* and *C. coli*, is the most common cause of bacterial food poisoning in developed countries, such as the UK and USA. The Public Health Laboratory Service in the UK reported 53,858 faecal reports of *Campylobacter* in the year 2000, compared with only 14,844 faecal reports of *Salmonella* (Public Health Laboratory Service, On-Line). Gastrointestinal disease caused by *Campylobacter* shares many of the clinical symptoms of *Salmonella* infection, including diarrhoea, vomiting and fever. Hospitalisation is uncommon, affecting mostly those individuals at the extremes of age; death due to *Campylobacter* infection is even less common.

C. jejuni, the commonest species to cause of human *Campylobacter* infection, is sensitive to a range of agents, including erythromycin, chloramphenicol, tetracyclines, aminoglycosides and quinolones. Unusually for a Gram-negative bacterium, the agent of choice in infections requiring therapy is the macrolide erythromycin, which is also used as a growth promoter for pigs in America. This use is not believed to have compromised therapy. Due to the relative unimportance of *Campylobacter* in animal health, however, few studies on the resistance of animal isolates have been completed. The widespread use of macrolides in the food industry is of concern, because of the clinical importance of this family of antibiotics. Thus, investigations into the occurrence of antibiotic resistance determinants in animal isolates are required.

If growth-promoting macrolide antibiotics have had little or no effect, then the therapeutic use of fluoroquinolones has had been associated with increased resistance. Fluoroquinolone-resistant strains are emerging around the world. Engberg *et al.* (2001) reviewed in vitro macrolide and quinolone resistance prevalence and trends in *Campylobacter* isolated from humans, showing a temporal relationship between use of quinolones in food animals and resistant isolates in humans. Endtz *et al.* (1991) reported that the use of fluoroquinolones to treat respiratory diseases in poultry seems to have led to the development of fluoroquinolone-resistant *Campylobacter* in the gut of treated birds. It is worth noting that the use of therapeutic drugs is often at doses that are orders of magnitude larger than the dose administered for growth promotion purposes. Such a high dose exerts a huge selection pressure and, in the case of *Campylobacter*, has allowed resistant strains to emerge and even dominate.

Escherichia coli

When they are located in the gut, *Escherichia coli* strains are regarded as non-pathogenic, Gram-negative members of the commensal flora of humans and animals. They are, however, the frequent cause of a variety of human infections. Pathogenic strains are most commonly associated with urinary tract infections but strains are also the cause of traveller's diarrhoea. This bacterium is also involved frequently in abdominal infection, such as perforated bowel or appendicitis. It is also one of the most common causes of septicaemia. Rarely, it is the causative agent of neonatal meningitis. In summary, *E. coli* is capable of causing problems at almost any site of the body.

Some strains, the most notorious being *E. coli* O157, produce Vero cytotoxins and are referred to as *Vero-Toxigenic Escherichia coli* (VTEC) strains. These bacteria may cause haemorrhagic colitis and about 5 *per cent* of cases progress to the haemolytic uraemic syndrome, with a case fatality rate of about 10 *per cent*. This is the major cause of acute renal failure for children in the UK. In adults, symptoms of haemolytic uraemic syndrome are seen along with neurological complications. The natural reservoir for VTEC strains is the gastrointestinal tract of cattle and

possibly other domesticated animals and so these bacteria may be subject to selection pressure from antibiotic growth promoters.

Antibiotic resistance in *E. coli* is widespread globally, with agents such as the penicillins found to be of decreasing efficacy against it (Heritage *et al.*, 2001). LeClerc (1996) warns about the dangers of complacency by reporting high rates of mutation in *E. coli* O157, following observations that they could acquire resistance determinants easily by horizontal gene transfer. It was noted that this was a possible route via which antibiotic resistance, from a pool of environmental pathogens, could be conferred. Even if antibiotic growth-promoters were not directly targeted against the bacteria, it remains possible that strains of this bacterium may acquire resistance from the gut microflora of the food animal. For this reason, and for the sheer volume and severity of disease it causes, it would be sensible not to ignore *E. coli* when considering the risks associated with the use of antibiotic growth-promoters.

Enterococci

The enterococci, such as *Enterococcus faecalis*and *Enterococcus faecium*, are of increasing concern, since they cause illness and death, especially in severely compromised patients in hospitals. Unlike the bacteria discussed above, the enterococci are Gram-positive and so are susceptible to most of the antibiotics used as growth-promoters. (Over)-use of antibiotics in a clinical setting has resulted in the selection of multi-resistant enterococci, including vancomycin-resistant enterococci. Such isolates are resistant to all conventional systemic antimicrobial therapies. Vancomycin-resistant enterococci were first isolated in Europe in the mid-eighties but quickly spread to the USA. Edmond *et al.* (1996) found that patients with blood-borne infections caused by vancomycin-resistant enterococci had over double the mortality of patients who were infected with enterococci susceptible to amoxycillin and vancomycin.

It has been suggested that the use of antibiotic growth-promoters, in particular the drug avoparcin, has contributed to the emergence of vancomycin-resistant enterococci. Both drugs are glycopeptides and the van genes found in enterococci confer resistance to both drugs. Use of avoparcin as a growth promoter increases the selective pressure for resistance within the animal. There is thus a risk that, subsequently, resistant bacteria may colonise humans. These resistant bacteria have the potential to cause disease, either in the colonised host or after spreading to another, susceptible host, such as an immunocompromised patient. Alternatively, organisms passing through the gut on meat may be able to transfer resistance genes to the resident microflora, via mobile genetic elements including transposons and plasmids.

Although avoparcin is not used in human medicine its analogues, vancomycin and teicoplanin are. Khachatourians (1998) noted that vancomycin-resistant isolates from Denmark and Germany are cross-resistant to avoparcin, illustrating that avoparcin-resistant bacteria in animals pose a potential threat to humans. The work of Das *et al.* (1997) shows that this potential may be a reality. A truck driver suffered a compound fracture of the femur whilst working in a chicken packing factory. He later developed a localised infection at the wound site. A wound swab yielded a mixture of *Proteus* sp. and *Enterococcus faecalis*. The *Proteus* was sensitive to the cefuroxime, with which the patient was treated. Subsequent swabs revealed a pure culture of vancomycin-resistant *Enterococcus faecalis*. Resistance in this bacterium resulted from expression of the *van*Acassette. The factory was investigated and, out of 21 samples taken from surfaces and chickens, eight contained vancomycin-resistant enterococci that carried the *van*Acassette. As the patient did not carry VRE in his faeces and had not been hospitalised or taken antibiotics within a recent period, it was concluded that the patient most likely became infected at the factory. If this was the case, it demonstrates the potential for avoparcin used as an animal growth promoter to compromise human health.

Following molecular genetic analysis of vancomycin-resistant enterococci from the faeces of poultry, pigs and humans, McDonald *et al.* (1997) found that there was evidence of transmission of the Tn*1546* transposon, which codes for resistance to glycopeptides, between farm animals and humans. Van den Bogaard *et al.* (1997) used similar analyses to examine the prevalence of vancomycin-resistant *Enterococcus faecium* in faeces from turkeys and those involved in their cultivation. They discovered that at one of the 47 turkey farms tested, the

isolates from the turkeys were identical to those of the farmer. Polymerase Chain Reaction (PCR) amplification and analysis and Pulsed-Field Gel Electrophoretic studies on *van*Aand other cassettes showed identity between the animal and the human isolates. Critics of this study have pointed out, however, that there was no evidence that the farmer was colonised with the bacterium and that reproducible observations in this case are lacking. The impact of avoparcin on the resistance problem is difficult to evaluate, but as the evidence from various studies accumulates, it would appear that there exists a theoretical risk of selection of glycopeptide resistance through use of avoparcin as an animal growth promoter and that resistant bacteria selected in this manner may subsequently compromise human health.

The European Commission banned the use of avoparcin as a growth promoter on the grounds of unknown risk. Del Grosso *et al.* (2000) found that, after the ban, a decrease was observed in contamination of meat products by vancomycin-resistant enterococci. The reduction was statistically significant in poultry (from 18.8 *per cent* to 9.6 *per cent*) but not in pork products (from 9.7 *per cent* to 6.9 *per cent*), allowing the conclusion that avoparcin withdrawal has been successful in reducing VRE contamination in meat products.

There are those who argue that antibiotic growth-promoters cause resistance that can be transferred to humans, or that antibiotic growth-promoters pose a threat to human health. To support this argument, it has been said that evidence to demonstrate the threat is non-existent because of methodological inadequacies, lack of reproducibility and limited data comparability. Critics also point out that the greatest threat to the continuing use of antibiotics in human medicine comes from the use of these agents in the treatment of infections in humans. What cannot be dismissed, however, is the fact that antibiotics foster resistance and that antibiotic growth-promoters are strongly implicated as a probable selective agent. The European Commission no longer permits "medically important" antibiotics to be used as antibiotic growth-promoters, due to possible risks of compromise of therapy. However, this needs to be a global effort. As Fidler (1996) noted, bacteria do not respect international borders.

In the early 1970s, the UK banned the use of tetracycline and penicillin for growth promotional purposes, spurring other European countries to take the same precaution shortly after. In the mid 1970s, the Food and Drug Administration (FDA) proposed a similar ban in the USA, but Congress intervened and required the FDA to do more research before instituting a ban. Today, the European Commission, the World Health Organisation, the Centers for Disease Control and the American Public Health Association all support the immediate prohibition of antibiotic growth-promoters that are the same as, or closely related to, antibiotics used in humans. In March 1999, the Center for Science in the Public Interest, the Environmental Defense Fund, and others petitioned the FDA to ban, for purposes of growth promotion, six antibiotics used in or related to those used in human medicine, including penicillin, tetracycline, erythromycin, lincomycin, tylosin, and virginiamycin. The FDA has recently launched a Task Force (FDA, 2001) to tackle the subject of the use of antimicrobials in agriculture but many politicians have greeted it with negativity. It is worth noting that the Framework Document simply laid out a program for assessing the risk of antimicrobials on human health. In itself, it did not represent any form of legislation, yet still was met with many negative comments that threatened its success. The most common criticism was that it lacked evidence.

THE ALTERNATIVES TO ANTIBIOTIC GROWTH PROMOTERS

In considering phasing out or banning antibiotic growth promoters, the quality of any alternatives, either on the market, that could be developed or that are available illegally, must be assessed. Essentially, there are two main ways in which we can reduce our dependence on antibiotic use in animals. An obvious choice is the development of alternatives to antibiotics that work via similar mechanisms, promoting growth whilst enhancing the efficiency of feed conversion. A more difficult route would be to improve animal health. Growth promoters have been shown (Prescott & Baggot, 1993) to perform best when conditions are worst: i.e. when the animal is in poor health and the living conditions unhygienic. If their local environment is improved, with overcrowding reduced and infection control techniques introduced, then the actual need for growth promoters may be removed.

In-feed enzymes

In-feed enzymes are routinely added to pig and poultry feeds and work by helping to break down certain components of the feed, such as _-glucans, proteins and phytates, that the animal may have problems digesting. They are produced as fermentation products from fungi and bacteria and seem to only have a positive effect on the animal. Some ethicists, however, have argued that adding enzymes to animals merely shows that we think of them as "factory beasts". Apart from ethical objections, in-feed enzymes are very effective at maximising feed conversion efficiency and have few drawbacks. As a result, current research is focussed on improving the quality of existing enzymes, whilst broadening the range of feed ingredients that they may be used to digest. The Scientific Committee for Animal Nutrition (2001) concluded that conditions of use evaluated so far are acceptable as regards to consumers, users and animals.

Competitive exclusion products

Competitive exclusion products are in-feed microbes consisting of a variety of species of bacteria that are marketed as being "friendly". The mechanism of action is believed to be that, by allowing such bacteria to colonise the gastrointestinal tract, potential pathogens are prevented from colonising the gut and thus causing infection. This is the competitive exclusion principle. These products are often administered to newborn animals, especially poultry, to colonise the gastrointestinal tract and prevent *Salmonella* and *Campylobacter* infections. It is not known how effective the treatment is but it is believed to reduce diarrhoea and reduce levels of mortality. These products are also given to animals that have been treated therapeutically with antibiotics, to re-colonise a gut that may have been depopulated by the antimicrobial action of the drugs.

Probiotics

Probiotics are similar to competitive exclusion products. They are believed to improve the overall health of an animal by improving the microbial balance in its gut. The way they work has not been established, although it has been hypothesized that their action can be summarised in three ways. The first proposal is a reiteration of the competitive exclusion principle: by colonising the gut in large numbers, the probiotic bacteria exclude pathogens and thus prevent them from causing infection. The second possibility is that they act as a stimulus for the immune system. As the immune system is engaged following exposure to probiotic bacteria, any hostile bacteria are also noticed, following increased surveillance by leukocytes, and thus potential pathogens are eliminated. The third suggestion proposes that probiotics have a strong, positive influence on intestinal metabolic activities, such as increased production of vitamin B12, bacteriocins, and propionic acid. Other mechanisms have been proposed but remain to be confirmed.

The problem with probiotics is the lack of evidence as to their mechanism of action and of the effects on host animals. Shahani *et al.* (1983) demonstrated that the growth of experimentally induced tumours could be inhibited in mice fed with fermented colostrums, but only in animals dosed before tumour growth started. Kato *et al.* (1985) confirmed these experiments, showing that intraperitoneal administration of Lactobacillus casei inhibited tumour growth. Following these experiments, it was suggested that L. casei had immunopotentiator properties similar to those of BCG: in effect, a vaccine to tumours and a stimulus to the immune system. Unfortunately, these results could not be replicated on farms. Most probiotics would not be administered via the intraperitoneal route on a working farm. Disturbingly, it was also discovered that some strains could be harmful: Sharpe *et al.* (1973) found that L. casei subspecies *rhamnosus* could produce endocarditis or abscesses in host animals.

For probiotics to be used as immunopotentiators, as many studies have suggested, there remain a number of questions that must be answered. What are the most active strains and do they have the potential to be pathogenic? What is the maximum dose? When and how should the probiotic be delivered? The easiest option is an in-feed delivery system.

Probiotics are effective in certain cases, notably in newborn animals or those that have been treated with antibiotics, where they have the same effect as competitive exclusion products. They may also be useful in helping to boost weight gain and feed conversion rates. Antibiotic growth-promoters have a lot of evidence, supported by excellent field results, to prove their efficacy. The usefulness of probiotics, however, remains unproven: they do have some strong supporters in the scientific community, but these are matched by an equal number of detractors. The beneficial effects of probiotics have been demonstrated, almost exclusively under defined experimental conditions. There have only been a small number of well-designed, double-blind, controlled trials to support the health-promoting claims of probiotic therapy.

An additional problem caused by the use of live bacterial products is that there may be potential dangers concerning antibiotic resistance and cryptic virulence factors. The Australian government is considering introducing legislation on probiotics, to require monitoring for the presence of resistance plasmids and the resistance patterns associated with antimicrobials of every strain of bacterium within a preparation, as part of the registration procedure. A recent report from the Scientific Committee for Animal Nutrition (2001) concerning the safety of a probiotic product found that two of the principal strains within the product, *Pediococcus acidilactici* and *Lactobacillus plantarum*, were resistant to tetracyclines. Resistance was found to be coded for by the *tet*(S) gene, which is often located on highly mobile genetic elements. As a result, it was concluded that because of the possible dissemination of tetracycline resistance genes in animal bacterial populations, the food chain and the environment, the use of that product poses a risk when used in animal nutrition.

Infection control measures

The use of antimicrobials as growth promoting agents rests on their role in controlling infection in growing animals. Similarly, many of the alternatives are aimed at controlling infection, often indirectly. But what of direct measures used to control infection in farm animals? The Australian Pig Farming Industry pioneered the "all-in-all-out" method of pig production. This is a new system, used to replace the older technique of having a constant stream of pigs moving through the farm. Instead of having a range of ages, all the pigs weaned within a week are designated into a single cohort and are housed together in one shed. They are not allowed to mix with pigs from other cohorts and so cross-infection between groups is prevented. "Segregated early weaning" takes note of the observation that the sow is an important source of pathogens. If piglets are weaned early, they are less likely to come into contact with pathogens from their mothers. Care must be taken not to create welfare problems by weaning animals too early, however.

The "specific pathogen-free" system is used to prevent pigs from acquiring many of the diseases that require antibiotic intervention, especially respiratory disease. To achieve this, they are born by hysterectomy and hand reared. This will only be cost-effective for valuable breeding stock.

Finally, vaccination is used to offer protection against certain pathogens, such as enterotoxigenic *E. coli* and various mycoplasma infections. One of the major drawbacks to all these schemes is the huge cost involved. In Australia, many of the farms are very large, by European standards, so they can afford to implement these measures. Some UK farmers have started to adopt infection control methods, in particular "all-in-all-out" husbandry.

The Swedish model

Sweden posed the question of suitable alternatives to antibiotics in 1985, when its Parliament passed the Feedingstuffs Act and banned the use of antibiotics for growth promotion. Calves, turkeys and fattening pigs did not appear to be affected significantly by the ban: growth rates may have decreased slightly, but there were no major increases in mortality. Efforts were made to establish new feeds and housing for broiler chickens and, after an initial "unsettled" period of outbreaks of necrotic enteritis, were considered successful. Animal Welfare groups were also happy to note that the new conditions were much better for the birds. Weaner pigs did not, however, enjoy the same level of success. JETACAR (1999) reported that scouring increased

and there was an increase of 1.5 *per cent* in mortality, roughly fifty thousand pigs. Furthermore, the time taken to reach 25kg increased by 5-6 days. Housing and hygiene were improved, livestock buildings were partitioned to help slow the spread of disease, "all-in-all-out" measures were introduced and the feed was changed. This resulted in a 50 *per cent* reduction in the use of antibiotics by 1993 and was followed by further reductions each year. In 1995-96, only 11 *per cent* of weaners were treated with antibiotics in their food.

The ban stimulated new ideas and technologies and successfully achieved its goal of an agricultural industry independent of growth promoting antibiotics. In addition, animal welfare was improved overall. The Swedish experience shows that antibiotics are not necessary to produce healthy animals, provided their living conditions, rearing and foods are improved. This did come at a cost: thousands of pigs and chickens probably died as a direct result of the ban, despite the overall improvement in animal welfare. Swedish produce is more expensive, and so less competitive on the market, and the costs of the venture are expensive. It may be argued, however, that the problems encountered by adopting the Swedish model have been justified by the outcome. Sweden has shown the rest of the world that it is possible to have modern farming without the use of antibiotics as growth promoters.

CONCLUSIONS

The best alternative to Antibiotic growth-promoters is a general improvement of conditions for animals that produce our food, following, for example, the Swedish model. Medically important antibiotics must be prohibited from use in a growth promotional role as a matter of immediacy. Unfortunately, reform can be slow and extremely costly, as Sweden showed. In order to start a reformation of the Industry as a whole, it is essential that attitudes to the use of antibiotic growth promoters be changed. While the greatest threat to the continued use of antibiotics comes from human medicine, selection of resistance is a problem that affects everyone. It matters very little to someone whose antibiotic treatment is failing if selection of the resistant strain resulted from clinical overuse of the antibiotic or from other sources.

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