Growth-Promoting Antibiotics

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Antibiotics are often used in animal feed to promote growth. But indiscriminate use of antibiotics could lead to antibiotic resistance even in humans. There is, therefore, a need to look for suitable alternatives.

ANTIBIOTICS are one of the major gifts of modern science that have changed the history of the human civilization. The mortality and morbidity caused by infectious diseases in the pre-antibiotic era were substantially reduced following the discovery of antibiotics in the last century. Antibiotics have significantly improved the quality of our life.

Antibiotics are also known to speed up growth in animals. If small doses of antibiotics are added to the animal feed, the daily growth rate is improved by 1 to 10%. The meat obtained from the antibiotic-fed animals is also of better quality with more protein and less fat. Growth-promoting effects of antibiotics were first reported in the late 1940s, based on observations on chicken, pigs and other species, fed with the by-products of fermentative production of chlortetracycline. Today, it has become a global practice.

Needless to say, the approach makes business more profitable. Pigs fed with antibiotics require 10-15% of less feed to achieve the desired weight. Cost of feed contributes a major fraction (70%) of the total cost of animal production. That is why, addition of sub-therapeutic doses of antibiotics (including those therapeutically useful to humans and animals) to feed is a standard practice followed in animal farms and poultries all over the world.

More than 80% of the antibiotics sold in the US and at least 50% of the antibiotics manufactured in China are used in animals and a major portion of these antibiotics are used as growth promoters. Examples include Beta-lactams (penicillins), lincosamides, macrolides, tetracyclines, bacitracin, flavophospholipol and virginiamycin.

The rationale for adding antibiotics to animal feed is evident from an estimate that reveals that if the use of antibiotics as growth promoters was banned, the production of feed animals (pigs, cattle) and birds (chicken) would have to be increased substantially to match the production that was achieved using antibiotics as growth promoters (Animal Health Institute of America, 1988).

Mechanism of Growth-promoting Effect

According to the National Office of Animal Health (a British organization consisting of members from the animal medicine industry in the UK and Northern Ireland) antibiotics used as growth promoters "help growing animals digest their food more efficiently, get maximum benefit from it and allow them to develop into strong and healthy individuals". The underlying mechanism behind the growth-promoting effects of antibiotics however is not clearly known.

Food materials contain bacteria, which destroy some of the nutrients of the food materials, inhibit absorption of nutrients from the intestine and produce toxin that inflicts adverse effects on the health of the animals. It is known that as much as 6% of the energy in the diet could be lost due to microbial fermentation in the intestine of the pigs. The growth-promoting effect of antibiotics is believed to stem from their ability to suppress growth of the food-borne bacteria.

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It is also postulated that in the unhygienic environment of the farms and poultries, animals and birds always harbour some latent infections, which trigger immune responses in their body. During immune response, a group of immunomodulators (chemicals which induce, enhance or suppress immune response) called cytokines is released. It is believed that cytokines might stimulate the release of catabolic hormones thus resulting in wastage of muscles.

Similarly, in animals with low-grade infections, a substantial portion of the nutrients, which could otherwise be used for growth, is used up by the immune system of the body. By suppressing the infections, antibiotics appear to spare the resources, leading to improved growth.

It is relevant to recall an interesting hypothesis, also called the Dirty Chicken Hypothesis, proposed by Dr. Noel W. Solomons of the Centre for Studies of Sensory Impairment, Aging and Metabolism (Guatemala) in 1993 (Nutrition Reviews, 51: 327-332). Based on the observation that poor growth of chickens in overcrowded poultries with

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unhygienic conditions could be reversed by supplementation of antibiotics in their diet, he proposed that children who are brought up in unhygienic environment grow to small-sized adults with low body weight. Even though they are apparently healthy (bearing no symptom of illness) their immune system is always challenged with low-grade infections and they bear high level of some immunological indicators.

In analogy with the chickens reared in unhygienic poultries, a lot of nutrients are spent up in these children in keeping the infections under control. Hence they fail to grow as healthy adults.

Antibiotic Resistance

Resistance of microorganisms to antibiotics is a major problem that could undo the beneficial effects of antibiotics. The problem has assumed monumental proportions on a global scale leading to the apprehension of some scientists that we might be pushed back to the pre-antibiotic era with almost no antibiotics available to control the infections. The concern does not appear to be grossly over-blown in view of the reports of the emergence of bacterial strains resistant to methicillin and vancomycin, the two antibacterial antibiotics which were believed to be invincible when they were introduced into clinical practice.

An enzyme, called New Delhi metallo-beta-lactamase-1 (NDM-1), produced by some bacteria that are believed to originate from the Indian subcontinent, has been found to make the producer organisms resistant to a broad range of therapeutically useful antibiotics. The emergence of multidrug-resistant *Mycobacterium tuberculosis*, the causative organism of tuberculosis, has raised serious concern all over the world.

Indiscriminate and imprudent use of antibiotics is believed to promote the emergence of antibiotic-resistant strains of bacteria. The postulation, called Antibiotic Paradox, has earned credence since increase in the frequency of resistance to an antibiotic has been found to have a close association with the increase in its use in many cases. The animal body is inhabited by a large number of harmless bacteria sensitive to antibiotics. The antibiotic-resistant bacteria, which occur in small number, are outnumbered and suppressed by the sensitive bacteria.

Antibiotics have to be used for prevention and clinical management of various types of infections in the livestock and birds in animal farms and poultries. Besides being used for therapeutic purpose, they are also used in a large scale as growth promoters. These antibiotics kill or suppress the sensitive bacteria in the animals. The resistant bugs get an opportunity to grow freely in absence of any challenge posed by the sensitive bacteria. Thus the food animals and birds become a reservoir of antibiotic-resistant bacteria. The antibiotic- defying organisms are excreted by them into the soil, washed by rain, carried to the ponds, lakes and rivers and enter into the bodies of the aquatic animals (e.g. fishes) which we use as food.

Resistant bacteria are selected into the body of the fishes also because of widespread use of antibiotics in aquaculture. There is enough literature on the occurrence of antibiotic-resistant bacteria in meat, eggs, fishes and shell-foods. Thus, use of antibiotics in animals promotes emergence and dissemination of resistant bacteria.

Even use of a non-therapeutic antibiotic as a growth promoter could promote the emergence of bacterial strains, resistant to a therapeutically useful antibiotic. For example, avoparcin is a glycopeptide antibiotic, not used in humans. But its use as a growth-promoting agent in animals and birds has been implicated behind the emergence of bacterial strains resistant to vancomycin, which is also a glycopeptide antibiotic.

Antibiotic-resistant bacteria are transmitted from animals to humans also by direct contact. Though many of them are harmless, they may lead to serious health hazards in persons with weak immunity. They also bear the potential to disseminate copies of the resistance conferring genes to the bacterial flora of humans by horizontal gene transfer. Thus use of antibiotics as feed additive is associated with far-reaching consequences.

Remedial Measures

1) Use of friendly bacteria: In view of the problem of antibiotic-resistance being furthered by the use of antibiotics as growth promoters, scientists are looking for non-antibiotic growth promoters like feed bacteria that colonize in the intestine

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of the animals and prevent the growth of pathogenic bacteria. Bacteria used for this purpose are known as probiotics. Besides colonizing in the intestine and suppressing the pathogenic bacteria, they are also believed to stimulate the immune system. Some of them are known to have tumour-suppressing effect. However, the use of live bacteria is also associated with dangerous possibilities. Use of enzymes, which break down complex food materials and promote nutrition, appears to be a suitable alternative.

2) Use of safe antibiotics: Flavophospholipol, a glycolipid antibiotic, is not absorbed from the intestine of the animals. Besides improving the efficiency of feed conversion in the intestine, it also alters the microflora in the intestine in such a way that growth of the beneficial microorganisms (involved in the synthesis of vitamins, amino acids, and enzymes) is promoted. Flavophospholipol also accelerates the synthesis of volatile fatty acids, decreases the formation of ammonia and methane and promotes the degradation of cellulose. It does not induce cross-resistance to any antibiotic. It selectively inhibits the growth of some bacteria that play a significant role in transmission of antibiotic-resistance. Hence, it appears to be a safe alternative to the therapeutically important antibiotics used as growth-promoters.

Ionophores, fermentation products of microorganisms, disrupt the transmembrane ion concentrations required for proper functioning of the membrane and survival of the microorganisms. Hence they have antibiotic properties. Some of the ionophores (monensin, lasalocid, salinomycin, narasin) are used as growth promoters. The mechanism of microbial resistance to ionophores is complex and specific. Hence use of ionophores is not likely to contribute to the problem of antibiotic-resistance.

3) Ban on the use of antibiotics: Since use of antibiotics as growth promoters is likely to promote the emergence of antibiotic-resistant bacteria, strictures on the addition of therapeutically useful antibiotics to the feed were imposed by a number of regulatory authorities all over the world from time to time.

In the UK, the Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by Professor M.M. Swann, was appointed in July 1968 following an epidemic of the antibiotic-resistant food-borne pathogen Salmonella typhimurium in 1963-65. The report of the committee published in November 1969, recommended a ban on the use of some therapeutically useful antibiotics (chlortetracycline, oxytetracycline, penicillin, tylosin and the sulphonamides), as growth promoter. The recommendations were mostly accepted by the government. However no restriction was imposed on the use of such antibiotics for therapeutic and prophylactic purposes in animals.

Subsequently, in 1992, the Lamming Committee recommended reconsideration of the use of antibiotics for prophylactic purpose. Accordingly, the Veterinary Products Committee decided to discourage such use and to consider each case individually by merit. Similar prohibitive measures were adopted in some other countries of Europe. Use of all growth-promoting antibiotics was banned in Sweden (1986) and Switzerland (1999).

Use of avoparcin and virginiamycin was banned in Denmark in 1995 and 1998 respectively. A ban on the use of bacitracin, tylocin, spiramycin and virginiamycin was imposed by the European Union in 1999 and a total ban on the use of antibiotic as feed additive was completed with effect from 1 January 2006, when four substances (monensin sodium, salinomycin sodium, avilamycin and flavophospholipol) were removed from the EU Register of permitted feed additives.

In 1977, the US Food and Drug Administration (FDA) imposed a ban on some agricultural uses of antibiotics. But subsequently it had to remove the ban since the Congress passed resolutions forbidding the ban. Many poultry and meat producers in the US are not convinced that use of antibiotics in animals has any link to the occurrence of drug-resistant bacteria in humans.

Following the ban, a decrease in antibiotic-resistance was noticed in some cases. However, in absence of the protection obtained from the prophylactic use of antibiotics, an overall deterioration in animal health (indicated by diarrhoea, weight loss, mortality) was observed.

There is no doubt about the advantages that antibiotics as a feed additive offer and also about the problems they contribute to. It appears that search for suitable alternatives and periodic evaluation of the performance and side effects of the compounds which are in use are the only measures that we could adopt to contain the problem. Concerted efforts involving the government and private agencies are the need of the hour to deal with the issue.

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