Should Veterinarians Be Allowed to Prescribe Antibiotics?

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The press in recent years has highlighted cases of food poisoning in hospitals and has implied a link with the indiscriminate use of antibiotics in livestock. Professor Richard Lacey, microbiologist at Leeds University, presented a very personal view of why we should be looking more closely at use of antibiotics in man not animals, to the Central Veterinary Society at its winter meeting.

Veterinary surgeons and farmers might experience feelings of intense guilt when they administer antibiotics to animals and birds. This guilt is based on the possibility—or even probability—that such use of antibiotics will endanger the treatment of human infections (Swann Committee Report 1969).

This must assume the premise that man is more deserving of antibiotic therapy than his animals! When the animal receives an antibiotic, it will select resistant bacteria, and these may be pathogenic for man, becoming established in the human host through food, contact in abattoirs, during husbandry or socially. The resistance constitutes a threat even if it is present in bacteria that are not pathogenic to man nor animals because the genes in the bacterial cell that determine resistance are capable of spread to important pathogens.

It is easy in the laboratory to insert the DNA coding for chloramphenicol resistance from a culture of *Salmonella typhimurium* into *Salmonella typhi*—the cause of enteric fever in man. Hence the use of chloramphenicol in cattle is the cause of treatment failure of typhoid in man. Moreover the story suggests the resistance is permanent ('building up') and these resistant bacteria may have increased virulence for man. It is also possible to show that the genes sometimes responsible for resistance are linked to those involved in pathogenicity.

Modern molecular techniques can establish that a unique sequence of DNA is identical to bacteria that colonise animals, that are present in slurry, or in immediate human attendants or in their more remote contacts. It is not unreasonable to propose that the spread of these genes is in the direction from animals to man.

The fear of antibiotic use in animals usually assumes that human use of antibiotics is properly directed towards important bacterial infections, and industry is only just managing to comply with the need for new antibiotics to treat new resistant and virulent strains.

TABLE 1: Conditions in man frequently treated with antibiotics where there is little evidence of benefit

Stick eyes in older children and adults
Otitis media
Otitis externa
Pharyngitis/tracheitis/laryngitis
Chronic bronchitis
Salmonella food poisoning
Campylobacter gastroenteritis
Prophylactically, in dentistry
Some uncomplicated lower urinary tract infections
Varicose ulcers/bed sores

Readers will be familiar with this story; before analysing each of the component steps, I would like to make some suggestions as to why these tenets have received so much publicity. First, the media find this scare irresistible, recently excited by the 'anti-additive' lobby. There is no media mileage in the probability that resistant bacteria may be less dangerous than sensitive, nor in the fact that the resistant bacteria can disappear fairly abruptly in the general community. It is the exceptions to these that are reported.

Some experiments usually appear as accurate observations in the scientific journals and are presented with reasonable objectivity. In the discussion, how ever, extraploation of these findings can be made somewhat hysterically. It is these opinions that are taken by the 'scientific' media aimed at 'educating' the general public. These opinions eventually appear in the general press that is read by politicians.

The second cause of this publicity involves the scientists themselves, partly because of vanity that seduces them to make claims for world wide importance of a few hasty laboratory experiments, and partly because of insecurity of job tenure or finance for experimental work.

British universities, including veterinary colleges, and the Public Health Laboratory Service are all known to be threatened by such restrictions. It is no wonder that these researchers present their work in a form most likely to attract attention and therefore funding. Thirdly, practitioners of human medicine can identify an external source of the problems they have generated by inappropriate antibiotic use. Finally, industry has to an extent a vested interest in antibiotic resistance.

The greater the success of an antibiotic in marketing terms, the greater the potential financial loss on the expiry of the patent. There are, therefore, commercial pressures to promote a new antibiotic instead of an old one. Resistance to the old is a persuasive argument.

It is not my intention to claim that veterinary use of antibiotics does not produce problems of resistance—but that if we really do believe that levels of antibiotic resistance in 'human' pathogens are unacceptably high, then we must primarily look at human, not veterinary use of antibiotics.

Is man more deserving?

It is not possible to answer explicitly the question, is man more deserving of antibiotic therapy than animals? But readers will be familiar with the mutual interdependence of man with other mammals and birds. What we can consider is whether antibiotic use in man is currently appropriate. At present about 45 million prescriptions are issued annually by general practitioners to patients at home (Hawkey 1986). Approaching half this figure is issued within hospitals. On average, therefore, we all receive 2 to 5 g of antibiotic every year. This consumption needs careful scrutiny particularly in general practice where most prescriptions are issued without diagnosis of bacterial infections being established.

In table 1, there is a list of common conditions where antibiotics are frequently used with little evidence of benefit. Many of these conditions are due to viral infections, and the intensity of antibiotic use, represents the success of superb marketing techniques. Most doctors now willingly comply with requests from patients for an antibiotic for a cold. Very little effort from the government, the media or the medical profession has been made to discourage such requests or the issuing of prescriptions by medical practitioners.

The case of chloramphenicol is an important one for the veterinary profession. Most students of veterinary medicine are told of the danger of chloramphenicol in animals on account of the fear of it selection resistance in human pathogens. However, chloramphenicol is available 'over the counter' in many developing countries of Central and South America, Africa and Asia. As near to home as Spain a commonly used antibiotic (for almost all infections in man) is a mixture of a tetracycline, and sulphonamide with chloramphenicol.

In the UK, general medical practitioners issue 1.3 million prescriptions for ophthalmic chloramphenicol annually (data from manufacturers). There is little evidence of benefit from this, and it is inevitable that some of this antibiotic will be absorbed locally, or find its way into the nasopharynx where it may select resistance before being absorbed into the circulation, where bone marrow toxicity may result. It is difficult to see how the use of chloramphenicol in animals can make a substantial contribution to resistance in human bacteria when we are already selecting them by this ophthalmic use.

One other recent development is relevant to this issue. The use of chloramphenicol in man for systemic infections continues to decline. Even typhoid that is caused by infection with *S typhi* (an exclusively human pathogen) does not necessarily require chloramphenicol for therapy. Work in Birmingham shows that trimethoprim (without sulphonamide) gives a cure rate of 90 per cent—as good as that obtained by any agent (Garglianos and others 1986).

In hospitals too, there is good reason to believe that much present antibiotic use is unnecessary. Antibiotics are increasingly being used prophylactically during and after a wide variety of types of surgical procedure. There is a suspicion that such use has been associated with a diminution in quality of surgical technique or environmental hygiene. Certainly, antibiotic consumption in hospitals could be reduced by investment in the provision of new hospitals and improved facilities. At present, it is now almost routine to give all surgical patients two (or more) prophylactic antibiotics for 48 hours or more.

Selection of resistance in animals

It is not the intention here to deny that antibiotics select resistant bacteria in the species to which they are administered; rather, to reconsider some of the dogma portrayed by the Swann report (1969). There is still a widely held belief that low, or subinhibitory, concentrations of antibiotic are particularly prone to select resistance. Is this plausible?

Let us forget this dogma and view the problem from the point of view of the specific mammal or bird who will be colonised by a finite number of microorganisms, mainly bacteria. These numbers result from the interplay of four factors—the colonising space available, the nutrients present, access to the environment and the presence of inhibitory factors produced by the host. Some of these bacteria may be resistant to certain antibiotics, but many, in the absence of antibiotic exposure, will be sensitive.

When this normal flora is exposed to an antibiotic for any length of time, then we can anticipate that changes in the composition of the microorganisms will occur; but only within the constraints that determine the total number of microorganisms that the host can support.

Therefore, depletion of the host of bacteria sensitive to an antibiotic will sooner or later be reflected in an increase in the number that are resistant. So the more profound the depletion in sensitive organisms, the greater will be the increase in the resistance. It follows that the higher the dose (not the lower) of antibiotic, the more likelihood there is of the selection of resistant bacteria.

Numerous surveys on the incidence of antibiotic

resistance do show that the more an antibiotic is used, the greater the selection of resistance. It follows from this that if an antibiotic feed additive enhances weight gain through a microbiological mechanism, eg, by reducing the numbers of toxin-producing clostridia, there will be an inevitable increase in the number of other bacteria resistant to it, evidently of no consequence to the animal on account of the beneficial effect on growth.

Thus effective use of antibiotics will be expected to increase resistance in the commensal flora. This reflects the mechanisms of benefit and is not itself reason for concern.

Spread of resistant bacteria

In recent years, a number of workers have attempted to prove that resistant bacteria found initially in animals can colonise man (eg, Linton 1986). Of course, this does happen, albeit transiently. No doubt, there is continual exchange of microorganisms between different mammals and birds that are involved with social or other contact. Most studies on possible transfer of microorganisms from animals to man concentrate on the success of this transfer without consideraton of transfer in the other direction nor is their contemplation in general biological terms that such transfers are potentially desirable.

This possibility is based on the premise that the microbial flora colonising a mammal is generally desirable, and for it to successfully persist in a host that is confronted with a changing environment it must acquire new constituents (either whole bacteria, or part of their genetic makeup) in order to survive. If this is the case then, from the point of the general biological symbiotic relationship between a mammal and its microorganisms, such transmission is desirable. Expressed another way, the continual symbiosis of man and his microorganisms is necessary for both host and parasite. Antibiotic resistance is easy to quantify and analyse and has achieved publicity; where are the considerations of these other issues in the scientific literature?

Consider the specific risk that a resistant organism or its genetic component from animals is the cause of therapeutic problems in man. It is well known that salmonella and campylobacter can spread from animals to man. However, is antibiotic resistance in these important, at least as far as man is concerned? Rarely, if at all, is the answer.

Campylobacter species cause an acute (and unpleasant) enteritis in man, but it is self-limiting, and no evidence has been presented that antibiotics are of value. Similarly, salmonella food poisoning is unpleasant even fatal in the very young, old and debilitated but does not require antibiotics.

Salmonella in hospitals

Recent publicity concerning salmonella food poisoning is well illustrated by the incident at the Stanley Royd Psychiatric Hospital at Wakefield at the end of August 1984. Nineteen long stay, geriatric patients died, giving a mortality of about 5 percent, typical of this type of episode. What is not clear, even from reading the report of the public inquiry, is that this was essentially a single point incident of food poisoning resulting from dangerous kitchen procedures. It is not known (nor is it important) how this food became contaminated by salmonella. The organism was *S typhimurium* type 49 and was fully sensitive to all relevant antibiotics. Despite the evident lack of relevance of antibiotic resistance, claims in the media have stated that antibiotics in animals were responsible for these deaths. This is not true.

As for the risk that specific genes coding for antibiotic resitance from an animal source might become established in human pathogens, it is unlikely to be important for the following reasons. If those genes confer resistance to antibiotics that are not used in human medicine, then there would be no advantage for human bacteria to possess them. As bacteria have the ability to lose 'unwanted' genes, then there would be no benefit from such possession, and such genes would tend to be lost.

Consider two antibiotics used specifically in animals, tylosin and apramycin. Resistance to these occurs in bacteria isolated from animals, but acquired resistance to these in cultures from human sources is rare.

Alternatively, if resistance to an antibiotic used in both veterinary and human medicine was found in human bacteria, surely the main pressure selecting resistant human bacteria would be the use of the antibiotic in man. These arguments do not deny that the input of resistant genes from animal bacteria with human pathogens or potential pathogens is zero. However, the commonsense view suggests it is small. Those workers who believe that such animal contribution is substantial must show it to be the case in properly constructed experiments that can separate the effects of the various selection pressures of antibiotics in different species. At present no such data have been published.

Are resistant bacteria more pathogenic?

In recent months, considerable prominence in the media has been given to so-called MRSA (methicillin resistant *Staphylococcus aureus*) in hospitals, with certain units even having to be closed. The *Daily Tleegraph* of December 19, 1986 described these as 'super bacteria' and reported that 'all routine surgery had been halted at Addenbrooke's Hospital, Cambridge, after the discovery of deadly bacteria resistant to antibiotics in the intensive care unit.'

It is true that these are resistant to several antibiotics

(although usually sensitive to at least three recognised drugs for treating *S aureus*, namely vancomycin, rifampicin and fusidic acid). It has been found that some *S aureus* cultures are unable to synthesise three products associated with pathogenicity; lipase, cell found coagulase and protein A. We have observed the presence of these cultures over the past few years in patients (colonising rather than infecting) in a burns unit, and believe them to be of low virulence (Lacey and others 1986). The properties seem to reflect events in vitro when, associated with the construction of a culture of *S aureus* resistant to many antibiotics, loss of virulence also occurred.

Most microbiologists do not consider the possibility that multiresistant bacteria have reduced pathogenicity. However, the speed of bacterial change is so great that names of species associated with uniform and predictable properties may now include a large variety of both commensal and pathogenic bacteria.

The important aspect of the relationship between virulence and resistance is that it cannot be assumed that all resistant bactria are pathogenic. Some may be, perhaps more will not be for the equivalent host. It is true that if, for example, a plasmid carries genes determining resistance and a virulence factor, this will be reported in the scientific journals. But if, as is usually the case, no such association exists (or even an inverse one), will any report be made? Probably not.

We can also view virulence from the point of view of the organism. Biologically how does a bacterium give itself the best chance of survival? First it possesses mechanisms able to resist antibiotics within the host. It must also strive to utilise the nutrients from the host without damaging the provider. The most successful bacteria or other microorganisms seem to be those that resist antibiotics, yet live symbiotically with their host, ie, are not pathogenic. Evolution would not seem to favour the appearance of resistant and virulent organisms. The most successful microorganisms are not pathogenic and, particularly today, do not attract persecution by man. It is reasonable to infer that if, generally, there is any relationship between resistance and virulence, it is inverse.

Is resistance permanent?

Populations of bacteria require to be resistant to an antibiotic in order to survive in the presence of it. This survival is mediated through the expenditure of considerable energy needed to synthesise specific proteins to counteract the effects of the antibiotic. In the absence of the antibiotic, the genetic make up of the cell usually enables the gene responsible for this mechanism to be lost. Thus in antibiotic-free environments, resistance is lost and then sensitive derivatives tend to replace the resistant (Lacey 1975). Thus antibiotic resistance is reversible. The incidence of resistance tends to reflect the intensity of antibiotic use in the corresponding host.

In man, at present, the excessive use of amoxycillin and other ampicillins is evidently responsible for the fact that 50 to 60 percent of bacterial cultures from patients referred to microbiological laboratories are amoxycillin (ampicillin) resistant. To return to the central theme, if we are concerned about this, then we should endeavour to reduce the amount of ampicillin in man, rather than look at the veterinary use of these antibiotics.

Conclusion

The notion that resistant bacteria selected by veterinary or agricultural use of antibiotics is a danger for the treatment of human infections has been widely broadcast. The publicity given to this fear is not commensurate with the supporting scientific data.

At present there is massive irrational use of antibiotics in man, including that of chloramphenicol.

Resistant bacteria in animals are an inevitable consequence of antibiotic use in those species. If growth promoters act by elimination of toxigenic sensitive species, then the selection of non-toxigenic resistant species is a necessary corollary of this.

Resistant bacteria from animals are exceedingly rarely a cause of antibiotic failure in man, such genes are not isolated from animal bacteria commonly assimilated into human pathogens.

Resistance is not associated with enhanced virulence. The inverse may be true. Bacteria tend to lose their resistance in the absence of the antibiotic; resistance is therefore potentially reversible. The incidence of resistance correlates with total antibiotic consumption in the target species.

The whole field of this work has been marred by a lack of objectivity from scientific workers, the media and regulatory authorities.

At present, the veterinary use of antibiotics is essentially irrelevant to problems of resistance to antibiotics in bacteria that cause problems in human medicine.

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