The Use and Misuse of Antibiotics in UK Agriculture

Part 2: Antibiotic Resistance and Human Health

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with a preface by Professor Alan Linton

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SUMMARY

It is thirty years since the publication of the last independent advisory committee report into the problem of antibiotic resistance passing from farm animals to humans. The report, by the Swann Committee (Swann et al 1969), set out principles for the regulation and use of antibiotics in British agriculture and also influenced legislation worldwide.

In the UK, successive administrations have claimed to be guided by Swann, but closer examination reveals that in many respects this has not been the case.

The publication of this report from the Soil Association has been timed to coincide with the publication of a report from the Advisory Committee on the Microbial Safety of Food (ACMSF) - the first report from a government advisory committee specifically to look at this issue since Swann.

It is our hope that the committee will make far-sighted and prudent recommendations and that the concurrent publication of our report will help in a small way to draw attention to the subject and provoke wider public awareness and debate. Our principal findings are that:

- antibiotic-resistant bacteria in food pose a substantially greater risk to human health than antibiotic residues. In the UK we have a statutory residue surveillance programme, but no equivalent scheme to monitor resistance
- the threat to human health posed by antibiotic resistance transferring from farm animals is infinitely greater than that posed by BSE. The potential costs to the Treasury and the NHS are enormous and unquantifiable
- multiple-drug resistance is increasing at an alarming rate: in some salmonella from 5% to 95% in 20 years, in MRSA 2% to 40% in 10 years, but the supply of new antibiotics has slowed substantially and no genuinely new classes have been developed for over 20 years
- over-prescribing by veterinary surgeons caused the first multiple-drug resistance in the UK
- the agricultural contribution to the drug-resistance problem has consistently been underestimated
- previous attempts to reduce the use of antibiotics in agriculture have been unsuccessful. New products replace those banned and loopholes are always exploited. This process is continuing
- routine prophylaxis with therapeutic antibiotics poses as great a threat as the use of growth promoting antibiotics and a much greater threat than full therapeutic treatment for short periods
- despite the bans on several growth promoting antibiotics the overall threat they pose has not been reduced
- ways must be found to reduce the overall use of antibiotics in agriculture - ideally to less than half the present level
- deregulation, the introduction of the 'near market' research concept and the semi-commercialisation of the Veterinary Medicines Directorate during the 1980s have left the British government intellectually stranded. It has neither suitable research, surveillance data, nor genuinely independent advice to enable it to analyse, or deal adequately with, the problems caused by antibiotic use on farms
- over the last year the British government has allowed one previously little-used antibiotic growth promoter to come to be fed to virtually every broiler chicken in the country. The growth promoter, avilamycin, is almost identical to Ziracin, widely believed to be the best new life-saving medical drug we will see in the next decade. It is already on trial in British hospitals against three serious superbugs: VRE, MRSA and multiple-drug resistant strains of meningitis and pneumonia. The UK has carried out no research to see if this is safe, but research in Denmark has shown that the two antibiotics are totally cross-resistant and that avilamycin may also be selecting for resistance to vancomycin, currently still the most important antibiotic for treating superbugs. Day-old chicks, with a 42-day life expectancy, which were put on avilamycin following the ban on other growth promoters on 1 July, will be on sale in British shops within a few days of the publication of this report

- unlike some EU Member States, we have given no practical help or advice to our pig and poultry producers to enable them cope with recent antibiotic bans. As a result they have been put at a commercial disadvantage at a particularly difficult time for farming in general. Most are simply using more of the growth promoting and therapeutic antibiotics still permitted, instead of changing their methods of production, as has been the case in Sweden and Denmark

Key recommendations:

bans and restrictions

1 the growth promoting antibiotic avilamycin should be banned immediately, with existing stocks destroyed and farmers compensated

2 an EU exemption should be sought for a limited period (up to a year) to allow the growth promoting antibiotic zinc bacitracin to be again added to broiler rations in order to facilitate an immediate ban on avilamycin. Zinc bacitracin should not, however, be relicensed as a therapeutic antibiotic because it too has a potential use in controlling epidemics of superbugs in hospitals

3 fluoroquinolone antibiotics should no longer be permitted for mass medication. Individual animals of all species should still be allowed to be treated in extreme situations. However, use in poultry production should effectively cease. Vets should record their reasons for selecting fluoroquinolones in the farm medicines book.

4 fluoroquinolones and third generation cephalosporins should not be permitted against enteric infections in any farm animals. This is to prevent the further development of resistant food poisoning strains

policy

5 EU agricultural policy should be further reformed to encourage livestock production methods with minimum dependency on antibiotics

6 practical and technical help should be given free of charge to producers to encourage them to alter production methods in order to reduce dependency on antibiotics

7 enteric salmonella in all farm animals should become a notifiable disease with a slaughter policy introduced for *S. typhimurium* DT104, rather than treatment with antibiotics

8 evidence to support the ban on antibiotic growth promoters is stronger than that for hormones. Britain should therefore push for the introduction of an immediate unilateral ban on the importation of any livestock products produced with drugs banned in the EU.

9 advertising of any prescription only veterinary medicines, except in the veterinary press, should become illegal

the veterinary profession

10 independent scrutiny of veterinary prescribing practice is needed to rebuild confidence and identify problem farms and practitioners. One single ‘agency’ should be given responsibility for all monitoring of antibiotic use on farms. Farms should receive annual visits and inspectors should prepare reports which are analysed by trained staff. Significant irregularities should be considered anonymously by independent vetting committees. Consistent over-use by farmers should trigger free advisory visits with producers required to implement recommendations. Poor prescribing by vets should lead to retraining, excessive prescribing should result in prosecution

11 veterinary surgeons should retain the right to dispense as well as prescribe veterinary medicines, but should no longer be responsible for checking farm records of these

12 Government should help establish a School of Preventative Veterinary Medicine to be run by vets and other specialists. It should research, collate and disseminate reliable information to farmers, vets and others

Antibiotics have been available for over fifty years and have brought great benefits to man and animals. Foremost has been the saving of lives and the relief of suffering from their therapeutic use. The benefits, however, have not been without certain disadvantages. The most important single factor which in the last analysis decides their success or failure in therapy, is the sensitivity of the causal pathogen to the antibiotic being administered. Parallel to the use of antibiotics has been the simultaneous development of resistance in erstwhile sensitive strains (Linton 1977). The use of what were heralded initially as 'wonder drugs' later resulted in the development of 'superbugs' able to tolerate therapeutic doses of specific antibiotics (e.g. methicillin-resistant Staphylococcus aureus - MRSA); the scenario has been described as 'nature's revenge'. Without doubt this problem, in part, is the outcome of the overuse and misuse of antibiotics in man but it has been compounded by the excessive use of antibiotics for therapy, prophylaxis and growth promotion in domesticated animals. The development of antibiotic resistance in animal strains has even greater significance where these are transmitted to man either directly or in the food chain. Consequently the wide use of antibiotics in animals poses a vital threat to the future therapy of human infectious diseases.

Legislation to control the use of antibiotics has had a chequered history. Based on previous knowledge that bacteria developed resistance to chemotherapeutic agents, e.g. the sulphonamides, the British government initially restricted the use of penicillin under the Therapeutic Substances Act to prescription only (medical and veterinary). This position continued until 1953 when regulations were relaxed to allow small quantities of penicillin and tetracycline to be incorporated into animal feeds to enhance growth. Their benefits were established beyond question and joint committees of the Medical Research Council and the Agricultural Research Council were appointed to monitor the situation. In the 1960s an outbreak of Salmonella typhimurium *phage-type 29 occurred in calves which was multi-resistant to a number of antibiotics and carried extra-chromosomal genes (R plasmids); the R plasmids are transferable to other sensitive strains of the same and different species of gram-negative bacteria within minutes of contact. The seriousness of this phenomenon prompted the Government in 1968 to set up the 'Swann Committee', who reported in 1969 - their recommendations set out good standards of practice and there was political agreement to adopt them. However, not all the recommendations were followed. Among others, Swann distinguished two categories, 'therapeutic antibiotics' and 'feed antibiotics'. In contrast to 'therapeutic antibiotics', 'feed antibiotics' could be purchased without veterinary prescription. Swann, however, allowed veterinary surgeons to prescribe therapeutic antibiotics for therapy, prophylaxis and growth promotion so long as the 'animals were under their care'. Contrary to the 'spirit' of Swann many other loopholes in the legislation were exploited, such as importing feed already incorporating therapeutic antibiotics. At the time of Swann the possibility that*

cross-resistance between 'feed' and 'therapeutic' antibiotics could arise was not fully appreciated. These, and other failures in complying with the recommendations, led to a series of articles seeking to evaluate the situation, ten years after Swann. They included an Editorial, (1980), and articles by Howie (1981), Richmond (1980) entitled 'Why has Swann failed?' and Linton (1981), entitled 'Has Swann failed?' Each concluded that loopholes in the implementation of legislation did not give Swann a chance to succeed. Linton made the point that if Swann succeeded it was by being a failure in that the report highlighted a very important world problem. Nevertheless, despite these warnings no action was taken to control the excessive use of antibiotics, especially as growth promoters. Later work demonstrated beyond doubt that levels of antibiotic as low as 5 p.p.m. select for significant numbers of resistant indigenous strains of Escherichia coli *to therapeutically important antibiotics in the animal gut (Al-Sam et al 1993), thus indicating that the use of low levels of antibiotics for growth promoters can select a reservoir of resistant strains to therapeutic antibiotics.*

Another serious outbreak of salmonellosis in calves, caused by S. typhimurium *phage-type DT 193 and 204, occurred in the 1980s; these strains carried R plasmids and demonstrated resistance to as many as eight therapeutic antibiotics. Later, these strains were transmitted to, and caused infection in, humans. Although antibiotic therapy for salmonellosis in man is not usually indicated, it is necessary in life-threatening situations. The strains were capable of being genetically transformed into other phage types with even wider ranges of drug resistance. These, and other factors, have revived concern over the whole issue of the use of antibiotics for other than therapeutic purposes, and this concern is the subject of the present report.*

Having worked in the field of antibiotic control over many years, and as a former member of the Veterinary Products Committee, I feel honoured to be asked to write the preface to this report. I hope that the issues raised will result in positive action being taken to avoid further erosion into the usefulness of antibiotics in the future.

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ANTIBIOTICS AND ORGANIC FARMING

Helen Browning O.B.E., Chairman, the Soil Association

Antibiotics can be vitally important for saving the lives of farm animals and reducing suffering. As such, the Soil Association recognises not just their value, but their paramount importance in curing once untreatable infections. Any suggestion that they might not be available in the future to treat ill animals would be as alarming to most organic livestock farmers as to those who use conventional methods.

No organic farmer need, or indeed should, think twice about calling in a veterinary surgeon and taking their best advice for the identification and treatment of ill health in their animals. Vets also have a particularly important role to play in helping devise strategies to reduce disease, and under exceptional circumstances antibiotics may even be given prophylactically to individual animals as part of this process.

For several decades, however, the organic farming movement has been sceptical about the excessive and sometimes indiscriminate way in which antibiotics are used in agriculture, and concerned about the wider effects of this on human and animal health and on the environment.

Antibiotics are potent agents capable of killing pathogenic bacteria. In cases of serious ill health their benefits far outweigh their disadvantages, but it is important to realise that they do not eliminate disease, and their overuse can make matters worse by altering the predominant infectious strains. In addition, they can alter the natural ecology of the gut flora in a way not dissimilar to that in which pesticides impact on the wider ecology of a farm and the surrounding countryside.

The free availability of antibiotics has also made it possible to keep farm animals in conditions which many people find morally unacceptable. While their routine use may avoid the welfare problems of disease and death, it nevertheless condemns many animals to an unfulfilling, unnatural and sometimes painful existence.

The general effectiveness of antibiotics has additionally tended to encourage total reliance on drugs as a means of both preventing and curing diseases. As such we appear to have lost confidence in the natural ability of farm animals to fight infection and can even be made to feel that if we do not give antibiotics we are not doing our best for them.

As a result of increasing concern about the development of antibiotic resistance, doctors have recently been urged not to prescribe antibiotics for a number of conditions for which their use was previously frequent. As a result of similar concerns, the Soil Association has, for many years, tried to find ways to keep the use of antibiotics on organic farms to a minimum, whilst nevertheless ensuring that their use is not restricted when they are genuinely needed.

It is has not been an easy balance to get right, but by focusing firstly on the systems under which animals are reared and secondly on the availability of a number of effective alternative therapies, organic farmers are generally able to maintain their animals in a high state of health with minimal reliance on antibiotics; a few organic farmers have even developed their management skills and their use of alternative therapies, such as homoeopathy, to such an extent that antibiotics are either never or only very rarely needed or used on their farms.

(See appendix VI for details of Soil Association standards and further information on antibiotics and organic farming)

INTRODUCTION

This is the second in a series of reports from the Soil Association on *The Use and Misuse of Antibiotics in UK Agriculture*. The first report - *Current Usage* - detailed how and why antibiotics are used in the rearing of farm animals and gave some examples of their misuse (see appendix I). This report examines the extent to which the use of antibiotics in agriculture is contributing to the development of antibiotic-resistant strains of bacteria which compromise human health or may do so in the future.

Worldwide, we are facing an epidemic of antibiotic resistance. Serious bacterial diseases, which little more than a decade ago were still treatable with penicillin, are today resistant not just to penicillin but to almost every other antibiotic available. The incidence of multiple drug resistance in infections which can strike down perfectly healthy people who go into hospital for even minor surgery has risen dramatically. Food poisoning bacteria, which affect as many as one million people in the UK each year, are increasingly resistant to the very antibiotics needed to treat the most severe cases.

The problem of antibiotic resistance is not new, but it is now snowballing out of control. And while resistance is escalating, the supply of new drugs - which in the past could be relied upon to rescue us from resistance problems - has slowed dramatically. No new classes of antibiotics have been introduced for over twenty years and there are none on the horizon.

The focus of the report remains the production of livestock and the situation in the UK, but due to the noticeable lack of data in some areas it has been necessary to include evidence from other countries in a number of cases. The science is complex and technical, but this report aims to provide basic information, scientific evidence and an historical dimension in order to inform the choices that must now be made if we are to avoid still more serious problems in the future. Other effects of the farm use of antibiotics are dealt with briefly in appendix V. Resistance issues relating to the genetic modification of crops and the use of antibiotics in crop production are covered in appendices III and IV.

In October 1997, the World Health Organisation drew attention to the problem of antibiotic resistance arising in farm animals and passing to the human population. It concluded that 'the magnitude of the medical and public health impact of antimicrobial use in food animal production is not known' (WHO 1997). Despite the establishment of a number of new committees and working parties, both in the UK and elsewhere within the EU, a steady stream of new research papers and the publication of a large number of reports over the last two years, the WHO conclusion is still broadly true today.

However, while there are still large gaps in the scientific knowledge, there is already ample evidence that the use of antibiotics in agriculture is the principal source of resistance in a number of serious infections. Taken together they cause ill health in large numbers of people each year and are occasionally, but increasingly, untreatable.

In April last year a House of Lords' committee attracted national publicity when it warned of 'the dire prospect of revisiting the pre-antibiotic era' (House of Lords 1998b) and recommended among other things that the use of certain growth promoting antibiotics should be phased out. On 1 July this year, a ban (or more accurately a suspension) was introduced throughout the European Union on four of these antibiotic growth promoters (AGPs). These have been included in the feed of almost all pigs and poultry and also used to a limited extent in the rearing of cattle. For last two years these four antibiotics have accounted for over 80% of the growth promoting market in Britain and most other EU countries. Scientific

evidence has linked each with actual or potential resistance problems in human medicine, although the strength of the case against the individual antibiotics varies.

Britain has opposed a similar ban in the past, but on this occasion supported the proposal. As such, it is easy to assume that the British government and regulatory bodies have reacted swiftly and responsibly to deal with the human health problems arising from the farm use of antibiotics. Sadly the reality is very different. The overall use of antibiotics for growth promotion in pigs and poultry has not been reduced in any significant way during the last two years and in some respects the situation has been made considerably worse. One previously little-used AGP which is cross-resistant with an important new drug of last resort already on trial in two UK hospitals, is now being fed on a daily basis to virtually every broiler chicken in the country (see section 6).

Moreover, the use of antibiotics for growth promotion accounts for only half of the story told by this report. There are further and equally serious problems associated with resistance caused by the agricultural use of prescribed therapeutic antibiotics, particularly those routinely used at low doses in feed and sometimes for long periods in intensively-farmed animals. These problems have appeared less urgent than those associated with the growth promoters because until recently, where therapeutic antibiotics encouraged resistance in bacteria which then infected humans, there were antibiotics left which could still be used to save life, whereas with some of the problems associated with certain growth promoters we had already reached the end of the line in terms of currently licensed medical drugs. However, the continuing rise in resistance to a wide range of antibiotics, especially in some common forms of food poisoning, is now severely limiting the choice of effective treatments, and where effective drugs are still available they are substantially more expensive.

In many respects, however, the uses of the AGPs and therapeutic antibiotics are inextricably linked. The free availability of AGPs has been a key factor in the super-intensification of farm animal production, because in addition to promoting growth and increasing feed conversion they also provide a prophylactic effect against several significant diseases of intensive livestock production. As such it was the introduction of cheap and freely available antibiotic feed additives, ostensibly only for growth promotion, which effectively made it possible to keep pigs, poultry and, to some extent, calves in such close confinement. Since intensive conditions provide the ideal environment for the rapid development and spread of other livestock diseases, it can be argued that this type of antibiotic use is indirectly linked to the high demand for therapeutic antibiotics as well.

In Sweden and Denmark considerable strides have been made in changing to production systems which rely far less on antibiotics, and significant changes have also been made in the way in which veterinary medicines are made available. In the UK the industry has recently, and for the first time, accepted that the use of antibiotics needs to be reduced in the long term (RUMA 1999), but it is nevertheless largely waiting and hoping that new technological solutions will arrive before more fundamental changes are needed. As a result, while the use of some antibiotics has now been reduced or eliminated, demand for others is increasing.

The scientific evidence linking the use of therapeutic antibiotics in agriculture to resistance in human therapy is, in fact, considerably more extensive than the evidence against the AGPs. Imposing restrictions on the therapeutic use of antibiotics, though, raises moral and practical issues, and presents dilemmas for governments, regulators, veterinary surgeons and farmers. This aspect was largely ducked by the Swann Committee thirty years ago and has still not been addressed in any systematic way.

The situation cannot continue to be ignored however, and this report suggests ways in which improvements might be made.

While it is easy to blame farmers, veterinary surgeons, the pharmaceutical industry and the successive administrations which have allowed these problems to arise, we must all, perhaps, accept some responsibiity for the antibiotic resistance problem we now face and question whether our desire for large quantities of cheap livestock products is not a fundamental part of the problem too.

What is ultimately needed is a complete reappraisal of the ways in which most farm animals are kept and cared for and the circumstances under which they are medicated. But before that can happen we need:

- wider recognition of the threat to human health from the routine use of antibiotics in livestock production
- wider public debate on whether we still want cheap food at any price.

It is our hope that this report will help to provoke such a debate and that it will go some way towards providing the information on which it must be based.

1 ANTIBIOTIC RESISTANCE

1.1 Background

Concerns about antibiotic resistance are not new; they date from soon after the introduction of penicillin in the early 1940s. However, a number of recent trends have converged to make the long-term public health threat posed by the development of antibiotic resistance potentially the single most serious issue facing health experts as we approach the new millennium:

- the global use of antibiotics in human medicine, animal husbandry, crop protection and food preservation is almost certainly at an all-time high
- resistance has now arisen in all classes of antibiotics currently developed
- multiple drug resistance is becoming increasingly common
- no new class of antibiotic is expected to be developed within the next decade

At the heart of the problem is a paradox that is not easily resolved. The cost of bringing a new antibiotic to the market has been estimated at between $100 million and $350 million in the United States (Gold and Moellering 1996). Any drug company which makes this sort of investment looks to achieve maximum return by selling as much as possible. However, that is precisely what we as society need them not to do. We need the investment to be made, but then the drug to be used in the most sparing way possible to maintain its effectiveness. In a market economy, that is likely to be very difficult to achieve.

While most of the obvious naturally-occurring antibiotic substances have already been investigated or developed for medical purposes, there are still possibilities for finding new classes of antibiotics, with the sea being a current area of interest (Costing the Earth 1999). However, it is clear that we may face serious resistance problems before any new class of antibiotics can be developed and that as time goes on the process will inevitably become harder and more expensive. Any new drug that is developed is also likely to fall prey to resistance unless used very differently from those which have been available in the past.

There is no question that the use of antibiotics in human medicine is a major cause of resistance in many bacterial diseases, and that addressing this problem is of major importance. This report, however, considers the evidence for the impact of antibiotic resistance passing from farm animals to humans. To do this it is helpful to give an account of the key mechanisms and events in the development of the resistance problem, and since these span both human and veterinary medicine it is necessary to draw examples from both.

1.2 Bacteria

Bacteria are normal and essential inhabitants of the intestines of humans and farm animals. They are also present on the skin, in the mouth and in the respiratory and genito-urinary tracts. On the whole, they are not just beneficial, but essential to life. A very small proportion of strains, however, cause disease and it is with these that we are concerned.

Antibiotic-resistant bacteria have existed since long before the development of antibiotics. They have developed over millions of years through the process of mutation along with the evolution of bacteria and are simply one of the multitude of variables that give rise to the diversity of life. The mechanisms of resistance are complex and intriguing and sometimes resistance to a single antibiotic can arise in more than one way. Where antibiotic resistance genes already exist in nature, the use of antibiotics is a powerful factor in their selection and spread. Where they do not already exist, some delay can be expected before they begin to emerge.

Tetracycline-resistant *E.coli* strains, for example, become predominant in the gut within 36 hours of the beginning of tetracycline therapy (Richmond 1981) whereas *Streptococcus pneumoniae* remained sensitive to penicillin for 34 years until 1977 (Gold and Moellering 1996).

Since resistance is an inevitable consequence of antibiotic use, resistant strains are more common where antibiotics are used more widely - in children more than in adults, in hospitals more than in the community, in intensive care wards more than in general hospital wards and on intensive livestock farms more than on organic farms. Interestingly, the incidence of resistant strains of *S. pneumoniae* in the US is higher in children from wealthy families than in poor families because the wealthier parents have been able to afford higher levels of antibiotic use to treat ear infections (Lieberman and Wootan 1998).

E.coli are the rabbits of the bacterial world and can double in numbers every 20 minutes. A pocket calculator will show that one single bacterium could in theory produce over two billion billion clones within 24 hours. Since a mutation occurs roughly once per billion cell divisions, a single bacterium has the potential to produce up to one billion mutants in 24 hours.

Most of these mutations will bring no advantage to the bacterium and may make it weaker. In the presence of an antibiotic, however, a single resistant mutant can quickly multiply to become the predominant strain.

Where antibiotics are appropriately selected to combat sensitive bacteria and used at full therapeutic doses for short periods of time in individual people or animals, any resistant strains that develop are generally short-lived and replaced by sensitive bacteria within a relatively short time. Where two people in the same household are taking antibiotics at the same time, resistance can persist for longer than when just one person is taking them. However, in intensive livestock houses and hospitals where antibiotics are used continually and where there is less contact with new sensitive strains to compete with the resistant ones, resistance can eventually become firmly established.

1.3 The early emergence of antibiotic resistance in the UK

Antibiotic-resistant strains of *(E. coli)* were observed during the development of penicillin. They started to show up in hospitals within a year of the first widespread use of penicillin in 1943 (Todd et al 1945). Initially this took the form of reduced sensitivity; dosages of penicillin which had initially killed off harmful bacteria had to be increased and then increased again. Soon, totally resistant strains began to appear. At the Hammersmith Hospital in London in 1947, 38 out of 100 cases of *Staphylococcus pyogenes* were found to be resistant to penicillin with a degree of resistance described as 'gross' (Veterinary Record 1948) and *Staph. aureus* was shown to be able to increase its resistance 3000-fold. (Todd et al 1945).

Staph. aureus is a common bacteria found, for example, on the skin of people and animals, and in the intestines and in the udders of dairy cows. Some strains can cause serious infection of wounds and, after operations, in other parts of the body. In the 1940s approximately 95% of *Staph. aureus* strains were sensitive to penicillin; today approximately 95% are resistant to it (Livermore 1999). By 1948, the British Medical Journal was beginning to address itself to 'the magnitude of this unwelcome change' (which had been found with streptomycin as well as penicillin), and an editorial in the *Veterinary Record* was asking: 'what are the causes of this waning power of penicillin?' It concluded:

The present enormous consumption of the drug can be accounted for only by a good deal of indiscriminate use and it is generally considered that widespread use

particularly of inadequate doses, is a potent factor in breeding resistant strains of bacteria

(Veterinary Record 1948).

By 1951, the problem of antibiotic resistance had been widely acknowledged in the medical, veterinary and pharmaceutical press. Comments by Dr Stanley Banks, who described the development of drug resistance as 'sinister' and stated that 'a continuous succession of new therapeutic drugs may be required if control of acute infections is to be maintained', originally published in *Practitioner* in April 1951 were reprinted in both the *Pharmaceutical Journal* (21 April 1951) and the *Veterinary Record* (28 April 1951). Throughout the 1950s, resistance to penicillin continued to increase. By 1961, 70% of all staphylococci in mastitis infections were resistant to penicillin.

It should be noted, however, that although resistance has developed in many types of bacteria, this is not universally the case. Concerns expressed in the *Veterinary Record*

Seeds of a problem sown early

While most people remember Alexander Fleming as the man who gave the world penicillin, the major credit should in fact go to Howard Florey and Ernst Chain. Fleming's famous discovery in 1929 was important, but while he noted the antibacterial activity of penicillin, he only considered the substance as a microbiological diagnostic tool and an antiseptic.

Florey and Chain, who had seen an account of his research, applied to the Medical Research Council in 1939 to investigate penicillin as a possible antibiotic drug. They were granted just £25. As a result Florey turned to the Rockefeller Foundation in America which made a grant of £9,000 over three years and allowed him to establish a research team in Oxford.

Despite striking results on mice in 1940 and then on six human patients in 1941, only the Wellcome laboratories took an interest in penicillin and they did not have time to work through the technical problems its production involved, being under pressure already to increase their output of existing drugs for the war effort.

To get increased supplies for further human trials, Florey had to turn back to the Rockefeller Foundation, through whom he eventually managed to interest several American companies including Pfizer. In Britain Florey and Chain had been refused permission to patent their work on the basis that medical discoveries were for the good of mankind. However, within six months the Americans applied for international patents and when British companies did begin to manufacture penicillin in 1943 they had to pay royalties.

More significantly still, Florey had passed his team's research methods and findings to the Americans and effectively seeded the US antibiotics business which still predominates today. Income from penicillin sales and royalties funded a massive search for new antibiotic substances and the development of dozens of new antibiotics and other drugs. Antibiotic production became a major commercial business, where maximum sales were always the prime goal. In this context, it is perhaps just possible to understand how the world's first and arguably still its most important safe antibiotic came to be being fed to pigs and poultry to make them grow faster just a few years after its development.

The myth which grew up about Fleming's involvement in the development of penicillin led to substantial donations to the London hospital where he was based, but the Oxford researchers were unable even to attract funding for new work and one of the most successful scientific collaborations ever had to split up. Chain went to Italy where in 1954 he began work which led to the development of a wide range of second generation penicillins such as methicillin, ampicillin and amoxycillin.

(Sources: Fleming 1929, Macfarlane 1980, Brander 1981, Horizon 1991)

(James 1953), for example, that the use of penicillin for growth promotion might lead to resistant strains of erysipelas, a fatal infection of pigs which can also affect humans and poultry, have proved unfounded, since penicillin is still the treatment of choice today (Black's Veterinary Dictionary 1995, Clark 1998). *Corynebacterium pyogenes*, which causes summer mastitis in cattle, has also remained sensitive to penicillin so far, despite the massive use of penicillin to control mastitis.

1.3.1 Transferable drug resistance

In 1959, it was discovered that in addition to arising by mutation, antibiotic resistance could also be passed from one (even unrelated) bacteria to another (Watanabe 1963), and Smith (1970) demonstrated that resistance could pass between *E. coli* and salmonella bacteria in a calf 's stomach.

1.3.2 Tetracyline resistance

While the situation is still unclear over penicillin there is substantial evidence that resistance to the tetracyclines in food poisoning bacteria derives almost entirely from the farm use of the antibiotics. It is interesting, however, that while chlortetracyline and oxytetracycline were licensed for growth promotion along with penicillin and additionally used therapeutically in UK agriculture during the 1950s, the incidence of tetracyline resistance in the six dominant strains of salmonellae in 1961 and 1962 was only 2.9%. Once established, however, it appears to have spread rapidly. By 1964 it stood at 21% and by 1965 it had reached 61% (Anderson 1968).

1.3.3 Multiple drug resistance

Between 1964 and 1966 there was an epidemic outbreak of tetracycline-resistant salmonella infection in intensively-reared calves. Vets tried almost every antibiotic at their disposal in a desperate but vain attempt to control the infection. Unfortunately, however, they thereby accidentally developed one of the first, if not the very first, strain of multidrug-resistant salmonella. By late 1963 it had also acquired resistance to streptomycin and the sulphonamides, and by 1964 this had spread to include eight further antibiotics (Anderson 1968). The strain, *Salmonella typhimurium* type 29 caused food poisoning infections in a large number of humans who could not then be treated successfully with antibiotics and a number of people died as a result (Swann et al 1969).

Since that time, resistance has continued to increase in many salmonella strains and multiple drug resistance in a new strain, *S. typhimurium* DT104 - now the main cause of salmonella infection in cattle and the second most important strain to affect humans - has become chromosonally encoded (Wray 1998). Multidrug resistance has also transferred to or developed in many other infectious bacteria and is widely seen as one of the most serious aspects of the antibiotic resistance problem.

1.3.4 Chloramphenicol and the persistence of resistance

Chloramphenicol, the first broad-spectrum antibiotic, was developed in Britain in 1947 by the American company Parke-Davis. Unfortunately, it caused bone marrow damage, blood disorders and even blindness in some people and as a result came to be more widely used in veterinary than human medicine. Despite this, it was the only really effective drug for treating typhoid fever, one strain of meningitis and a few other serious infections. However, it was also one of the antibiotics used against the outbreak of *S. typhimurium* type 29 in the mid-1960s and resistance had developed to it also. Since typhoid fever is itself caused by a strain of salmonella there were fears that chloramphenicol-resistant strains of typhoid would develop. As a result, chloramphenicol use in farm animals was initially restricted in 1971 and later phased out altogether. The wisdom of this became obvious the following year when an outbreak of chloramphenicol-

resistant typhoid in Mexico led to significant loss of life and two British holidaymakers returned home carrying the infection.

The example of chloramphenicol has broader significance and should, perhaps, influence our approach to other similar antibiotic resistance problems today. Despite the phasing out of chloramphenicol use in farm animals, its inclusion in a multiple drug-resistant complex has caused its continuing selection for nearly 30 years. Parke-Davis ceased production of the drug 18 months ago, though there is still limited production by another company.

1.3.5 Trimethoprim resistance

New multidrug-resistant strains of salmonella in calves appeared in 1977, where in addition to the now persistent chloramphenicol resistance and resistance to six other important antibiotics, resistance to trimethoprim was also found, again the result of its widespread use by vets. By 1979, nearly 300 cases of these multidrug-resistant strains of salmonella food poisoning had affected people in the UK (Threlfall et al 1980).

1.4 Early attempts to regulate the farm use of antibiotics

1.4.1 Early legislation

The Penicillin Act of 1947 restricted the use of penicillin and streptomycin to that prescribed by a medical doctor, a veterinary surgeon or a dentist. The Therapeutic Substances Acts of 1953 and 1954 extended this to new antibiotics such as chloramphenicol, chlortetracyline and erythromycin, but in one of the most significant events in the sorry saga of antibiotic resistance, penicillin and chlortetracyline (marketed as Aureomycin) were separately made available to farmers and feed compounders to be added to pig and poultry rations in small amounts to make the animals grow faster (Harvey and Mason 1998). Similar legislation in 1956 took on board further new antibiotics but significantly failed to include tylosin which was already in use for growth promotion in pig production. As a result, tylosin remained an unscheduled antibiotic until 1971.

1.4.2 Advisory committees

In 1960, the Agricultural and Medical Research Councils established a joint committee (the Netherthorpe Committee) to examine the consequences of feeding antibiotics to animals, but gave it only limited terms of reference - it is usually remembered only for its conclusions that the practice was quite safe and its recommendation (not implemented until 1971) that the use of growth promoting antibiotics could be extended to include calves up to three months of age.

As a result of widespread concern arising from the outbreaks of multiple drug-resistant salmonella food poisoning in the mid-1960s, the government eventually established an independent advisory committee in 1968, specifically to examine the issue of transferable antibiotic resistance and the possible consequences for human and animal health arising from the use of antibiotics for growth promotion and in veterinary medicine. The Swann committee reported in 1969, with the principal recommendation that:

permission to supply and use drugs without prescription in animal feed should be restricted to antibiotics which

(a) are of economic value in livestock production under UK farming conditions

(b) have little or no application as therapeutic agents in man or animals and

c) will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms

(Swann et al 1969).

Agricultural Antibiotics - The Development of a Problem

1941	First use of penicillin in human therapy.
1942	First use of penicillin in farm animals.
1943	Penicillin resistance first noted.
1944	First use of streptomycin in humans.
1947	Penicillin Act restricts use of antibiotics to therapy on prescription of a doctor, veterinary surgeon or dentist.
1949	Growth promoting effects of chlortetracycline established (US).
1953	Therapeutic Substances (Prevention of Misuse) Act allows penicillin and chlortetracycline to be used for growth promotion.
1956	Therapeutic Substances Act fails to regulate tylosin, already in use for growth promotion.
1958	Vancomycin developed (no major use in hospitals for 20 years).
1959	Discovery of transferable drug resistance.
1960-4	Netherthorpe Committee gives green light to growth promoters and recommends extension of use to calves.
1963-6	Epidemic of salmonella in UK calves leads to first multidrug-resistant food poisoning outbreak.
1969	Swann Committee Report. Recommends that antibiotics currently used in human therapy should not be used for growth promotion but fails to address routine use of prescribed therapeutics.
1970	Industry anti-Swann campaign gets into full swing.
1971	Penicillin, tetracycline and tylosin banned in UK for growth promotion. Tylosin relicensed after Department of Health lobbied by drug companies. Penicillin and tetracycline use declines slightly.
1972	Avoparcin licensed for use as growth promoter in poultry, pigs and calves.
1973	Britain and Ireland given a five- year EEC derogation on growth promoting use of tylosin. Joint Committee on Antimicrobial Substances (JCAMS) established to advise VPC, instead of more powerful committee recommended by Swann.
1976	Use of avoparcin becoming widespread in poultry production. Avoparcin allowed for adult cattle against Swann recommendations.
1978	Tylosin added to Annex 1 of EEC Directive 70/524 allowing use for growth promotion throughout the Community. Vancomycin starting to be used in hospitals.
1981	JCAMS abolished by Peter Walker and Patrick Jenkin after committee falls out with VPC which prevents it from reviewing safety of growth promoting antibiotics.
1984	Sweden bans use of avoparcin.
1986	Commercialisation of VMD begins. Government cuts back on 'near market' research. Sweden bans the use of all antibiotics for growth promotion. VRE first found in France and UK.

1986-8	Ban on use of hormones in beef production leads to increased use of avoparcin in beef cattle.
1993	Fluoroquinolone antibiotics licensed for use in farm animals.
1993	First evidence that VRE coming from avoparcin rather than hospital use of vancomycin.
1995	Sweden negotiating for accession to EU - given until end 1998 to justify its 1986 ban on medical grounds or come into line with rest of EU.
1996	VPC considers use of avoparcin and advises ministers it is safe to continue unrestricted use for growth promotion.
1997	VPC considers Finnish evidence of link between tylosin use in farm animals and erythromycin resistance in humans, but decides to take no action. UK Public Health Laboratory Service reports that resistance to fluoroquinolones in *Salmonella typhimurium* DT104 has increased exponentially. Avoparcin banned EU-wide. Britain votes against the ban, Belgium abstains.
1998	Danish scientists demonstrate that the growth promoter avilamycin is totally cross-resistant with new therapeutic antibiotic everninomycin. Less than 10% of UK broiler chickens receiving avilamycin. Danish food animal industries adopt a voluntary ban on avilamycin and other growth promoters. December - EU votes to ban six of ten antibiotic growth promoters, but does not include avilamycin because everninomycin still under development.
1999	Schering Plough begin trials with everninomycin against drug-resistant pneumonia, meningitis and VRE in UK hospitals.
July 1	EU ban on virginiamycin, tylosin phosphate, zinc bacitracin and spiramycin comes into force.
July	Virtually all intensively-farmed broiler chickens in the UK receiving 10mg/tonne of avilamycin in feed
September 1	EU ban on carbadox and olaquindox comes into force. Four AGPs still remain licensed. Treatment failure with fluoroquinolones reported.

Swann specifically mentioned penicillin, the tetracyclines and tylosin as antibiotics which did not satisfy these criteria, and which should therefore be banned for sale without prescription, i.e., for growth promotion. He also recommended the establishment of a single permanent committee to oversee both the medical and veterinary use of antibiotics which was to be responsible, among other things, for monitoring trends in antibiotic use and resistance and for periodically reviewing older antibiotics. It seems clear from the report that the Swann Committee would have liked to go further in its recommendations, but it was made fully aware of the commercial pressure to retain the use of antibiotics for growth promotion and was conscious that many of its concerns could not be fully supported by the evidence then available.

1.4.3 The industry campaign against the Swann Report

The Swann report met with howls of protest from the farming and pharmaceutical industries. The Graham Cherry Organisation, a public relations company, collated 107 press and journal cuttings between December 1969 and March 1970 for its client, the pharmaceutical company Cyanamid, the overwhelming majority of which were antagonistic and focused on likely increased costs to the industry and estimates that the price of bacon might go up by 3d per lb (Graham Cherry Organisation 1970). Bower (1970), however, showed that the hostile press coverage was principally due to a range of public relations initiatives staged by the pharmaceutical industry to undermine the integrity of the Swann Committee. She showed

that the adverse publicity mostly emanated from two tame academic sources, whose output was carefully orchestrated by the public relations company. The same company also helped to stage an influential symposium on the issue, where the invitations appeared to have come from the Council of the Royal Society of Medicine, when in fact they came from Cyanamid, which simply rented the conference facilities for the day.

1.4.4 Failure to implement Swann in full

The overall effect of the anti-Swann campaign is unquantifiable, but it seems likely that it helped create the political atmosphere in which it became possible for the incoming administration in 1970 to ignore or water down several key aspects of the Swann report.

While successive governments have claimed to be guided by the Swann principles, it should be noted that they have significantly failed to implement many of the report's actual recommendations. The initial ban on tylosin as a growth promoter, for example, was overturned when Department of Health officials caved in to industry pressure (Mackinnon 1981); the crucial recommendation for an over-arching committee was downgraded to a joint sub-committee without any of the powers or responsibilities which Swann envisaged (Howie 1981) and many of the recommendations on monitoring, education, research and regulation have never been taken up in any systematic way.

What is more, in 1976 the use of growth promoting antibiotics was allowed in cattle over three months old (Browning 1997), including dairy cows (VMD 1996) - against Swann's specific recommendation that they should not be used in breeding animals.

One other consequence of the industry campaign against Swann was that veterinary surgeons and farmers were given the distinct impression that Swann had got it wrong and that the ban on the use of penicillin and the tetracyclines for growth promotion was over-cautious. Such use continued in the USA, which rejected this aspect of the Swann report, and it was from here, of course that much of the commercial pressure to maintain sales of antibiotics in the UK came. In his preface to this report Professor Linton has pointed out that veterinary surgeons continued to prescribe both penicillin and tetracyclines for growth promotion and it seems likely that the anti-Swann campaign may have helped them to feel morally justified in doing this.

1.4.5 Joint Sub-Committee on Antimicrobial Substances (JCAMS)

Rather than establish an over-arching committee as Swann recommended, with 'responsibility for the whole field of use of antibiotics and related substances, whether in man, animals, food preservation, or for other purposes', the government instead in 1973 established a Joint Sub-Committee on Antimicrobial Substances (JCAMS) which was given few powers and rather clumsily made responsible to both the Veterinary Products Committee (VPC) and the Committee on Safety of Medicines. The committee, under the chairmanship of Sir James Howie, a former director of the Public Health Laboratory Service, was made up of microbiologists and kept busy advising the VPC on new veterinary medicines licensing applications. As time went on, however, members began to feel they could not do their job properly without some of the crucial powers which Swann had recommended. One of these, 'that it should review periodically existing antibiotics and their uses to ascertain whether changing circumstances justify either greater relaxation or more restrictive control' had become important in the late 1970s at a time when a range of antibiotics variously allowed in different EEC countries were being considered for scheduling as non-prescription feed additives for growth promotion under EEC Directive 70/524. Among these were avoparcin,

spiramycin, virginiamycin and tylosin, some of the growth promoting antibiotics which have only recentlly been banned. It seems the VPC would not allow the sub-committee to carry out such a review, or indeed to obtain data on the usage of any antibiotics or to monitor resistance. The committee discussed the problems in detail and eventually Sir James Howie wrote to Peter Walker, the Minister of Agriculture, Fisheries and Food, and Patrick Jenkin, the Minister of Health, explaining their concerns and asking for increased powers. The ministers refused even to discuss the issue and immediately disbanded the sub-committee (Howie 1981, BMJ 1981, Walton 1981) and from then until now the VPC has been without a sub-committee to advise it on antibiotic resistance.

Two microbiologists were, however, appointed to the VPC after the abolition of JCAMS. For a time during the mid-1980s they were Professor Alan Linton, who has kindly written the preface to this report, and Professor Richard Lacey. Linton's research was with farm animals. He published a large number of studies highlighting potential antibiotic resistance issues and was vocal in his views that not enough was being done to prevent serious problems arising. Lacey, on the other hand, had experience in hospital pathology, but during the late 1970s and 1980s was studying whether the use of antibiotics in agriculture (particularly, but not exclusively, the growth promoters) posed a threat to human health (Lacey 1981, 1984). While he qualified his conclusions carefully, his opinion was that they did not pose a problem. Linton and Lacey equally shared concerns about the development of resistance but on the issue of the growth promoters they effectively cancelled each other out on the VPC.

We asked Professor Lacey to comment on this period and he told us rather modestly, 'I think I was probably the wrong person for the job [...] my expertise was elsewhere [...] as with my diet and other things in my life I have changed my opinion over the years'.

1.4.6 Swann's greatest failing

The Swann Committee was also aware of the threat to human health from routine prophylaxis and inappropriate therapy with antibiotics, but it concluded that, 'it would in any case be difficult to frame or enforce legislation to allow the prescription of antibiotics for some purposes but not for others. We recommend therefore that no change should be made to the law which allows the supply of antibiotics on veterinary prescription.' In view of what has happened since, it is easy to look back and say that this was Swann's greatest failing. In view of the prevailing views and commercial pressure at the time, however, it would almost certainly have been politically impossible for the committee to go much further.

1.4.7 Historical conclusion

It is important to make clear that there are very few absolutes in the science on these issues. Microbiologists are constantly re-evaluating and re-assessing the situation in the light of new research, but always have to make assumptions. Dr Norman Simmons summed up the situation concisely with an analogy he made in evidence to the House of Lords sub-committee which considered the issue of resistance last year: 'It reminds me of the man who threw himself out of the Empire State Building and as he passed each window he said "So far so good, so far so good": I know that we are out of the window, I just do not know how far we are above the ground!' (House of Lords 1998a).

2 THE SCIENCE OF RESISTANCE

2.1 How resistance works

Bacteria are the smallest, unicellular, free-living organisms known. Like many single-celled organisms, bacteria multiply by cell division, whereby a bacterial cell divides into two cells which will each normally contain the same genetic information in their single chromosome as the mother cell. Bacteria multiply very quickly - on average a bacterial population will double in size in about 30 minutes.

Antibiotics are substances originally fermented from natural microorganisms, but now often produced synthetically. If antibiotics work, they either kill or cause the dissolution of bacteria (this is how penicillin works, for example), or they merely inhibit the growth and multiplication of bacteria (as with, for example, chloramphenicol). If bacteria are resistant to the antibiotic used against them, the infection is not cured and they survive to infect other patients or animals.

Bacteria become resistant to antibiotics as a result of one or several of the following mechanisms:

- **Competitive selection:** in the presence of an antibiotic, a bacteria which possesses the corresponding resistance has a greater chance of survival. As bacteria multiply very fast, a resistant strain can quickly become the predominant bacterial population. One single resistant *E. coli*, for example, can produce several billion resistant bacteria overnight.

- **Mutation(s):** these are random genetic changes in existing genes, which occur naturally during bacterial multiplication. The resistance trait is initially confined to the mutant clone, but resistance may be quickly transmitted to new hosts as the bacteria multiplies (vertical transmission).

- **Gene transfer:** this enables resistance to spread from one bacterial clone to another, and from one bacterial species to another (horizontal transmission) by the transfer of a resistance gene from one bacteria to another. This usually occurs by *conjugation*, a form of mating between bacteria where genetic material passes via a tube inserted by one bacteria into another or by *transformation*, when dead bacteria pass DNA to living ones. These processes involve the movement of one of two entities, a plasmid or a transposon. Plasmids are small loops of DNA, made up of 5-10 genes, which are separate from the bacteria's single chromosome, and which are not necessary for the bacteria to survive. In some cases several resistance genes may become linked within the plasmid, and when transferred lead to co-resistance (also called cross-resistance). Transposons, known as a 'jumping genes', are small mobile pieces of DNA carrying one or several genes. They can move from chromosome to plasmid and from plasmid to plasmid, which allows genes to evolve and disseminate and for resistance to be transferred very easily. Resistance genes can also, less commonly, be transferred by *transduction* when a virus carrying bacterial DNA enters a bacterial cell.

Horizontal transmission has now been recognised as a major cause of increasing antibiotic resistance. It is worth therefore noting that this process, pushed well beyond its natural limits, is used by scientists to create genetically modified (GM) plants and animals. As antibiotic

resistance genes are also widely used in genetic engineering, some scientists are concerned this could be contributing to the resistance problem (see appendix III).

Resistant bacteria counter the action of antibiotics in many different ways. For example:

- the target organism can disable the antibiotic (bacteria resistant to penicillins and cephalosporins have the enzyme beta-lactamase, which breaks up the antibiotic's structure)
- they can change to avoid the action of the antibiotic (resistance to antibiotics such as streptomycin can take the form of small genetic changes which interfere with protein synthesis)
- they can reject the antibiotic (resistance can be expressed in the synthesis of a bacterial protein which pumps antibiotic out of the cell - this is called cell-wall impermeability)

2.2 How resistance can pass from livestock to man

The majority of antibiotics used in livestock production are the same as, or related to, antibiotics prescribed for humans (see appendix II). Large mammals have an estimated 20 trillion bacteria in their alimentary systems, so farmed animals receiving antibiotics can therefore provide a substantial reservoir of resistant bacteria which may infect humans. These may directly contaminate humans or may transfer their resistance to other bacteria in the human microflora. In the case where this resistance is transferred to a pathogen and disease then occurs, that disease will be untreatable by one or more antibiotics. Even non-pathogenic bacteria can still become resistant to antibiotics, and act as a reservoir of antibiotic resistance potentially transferable to pathogenic strains of the same or different species of bacteria in the human gut, or in other nutrient-rich environments. There are several possible routes by which such resistant bacteria can then transfer to the human population:

- **by direct contact with infected animals:** this can happen in the case of farmers or abattoir workers. The resistance may then be transferred from them to other members of the human population
- **by eating contaminated meat:** during slaughter, resistant bacteria may spread from excrement and the gut contents to the rest of the animal, or to other carcasses in the abattoir. High throughputs in slaughter houses, and the use of mechanical evisceration and scald tanks in poultry plants, greatly enhance the spread of bacteria in this way. A further spread of resistant bacteria may then occur during the preparation of food. While thorough cooking will kill all types of bacteria, the continuing high levels of food poisoning demonstrate how easily bacteria can pass from food animals to humans
- **by eating contaminated eggs or milk:** eggs are a common source of resistant bacteria, and may transfer them to humans if inadequately cooked or consumed raw. Unpasteurised or improperly pasteurised milk may also transmit resistant bacteria to humans and pasteurised milk may be recontaminated during processing
- **by eating food containing antibiotic residues:** residues of antibiotics in some animal food products may allow the selection of antibiotic-resistant bacteria in the consumer of the food
- **by eating contaminated fruit and vegetables:** plants may also carry

resistant bacteria and transfer them to people. Where this happens in the UK they are likely to have become contaminated by animal bacteria through the application of fresh manure. However in some EU member states and other countries, such as the USA, spraying of some specific crops with antibiotics against bacterial diseases is permitted and may lead to the development of resistance. Produce imported from these countries can therefore also be infected (see appendix IV)

- **by eating food containing antibiotics used as food preservatives.**

Although most foods are heat-treated before consumption, infectious doses of bacteria are still relatively common. It has been suggested that in the normal human population, for example, most resistant enterobacteria (e.g. E. coli , salmonella and campylobacter) come from contaminated food (Corpet 1988 cited in Report 1997, p. 107). Some bacteria, such as *Enterococcus faecium*, may also have increased their heat tolerance over time (Report 1997, p. 107).

3 EVIDENCE OF RESISTANCE

3.1 Introduction

It is generally accepted that resistance arising in animals can cause problems in human therapy in relation to four groups of bacteria:

- enterococci - resistance is caused by antibiotic growth promoters (AGPs)

- salmonellae
- *E. coli*
- campylobacter

} resistance is caused by therapeutic and prophylactic antibiotics

In addition, there is limited evidence of the transfer of resistance from animals to man in a number of other infections, but it is not possible at the present time to assess how significant this has been.

Even where the animal reservoir of antibiotic resistance has not yet contributed significantly to the development of resistance in human pathogens, there is no guarantee that this will not happen in the future. As a recent report from the Ministry of Agriculture, Fisheries and Food concluded, 'in principle there is no reason why most pathogenic species transmitted in food or resident in the human gut should not be recipients of antimicrobial resistance genes' (MAFF 1998).

Bacteria are classified as either gram-positive or gram-negative according to whether they take up a particular stain. The difference is not just superficial, but relates to fundamental features of the bacteria such as the thickness of its cell wall. To kill or inhibit a gram-positive bacteria, such as a staphylococcus, you need a gram-positive antibiotic, such as penicillin. Conversely, a gram-negative antibiotic, such as streptomycin, is needed to treat diseases like tuberculosis, caused by gram-negative bacteria. Some antibiotics have 'broad spectrum' activity against both types of bacteria.

There are also serious concerns that resistance in the hospital superbugs known as VRE (vancomycin resistant enterococci), which generally only affect people in high-dependency hospital areas may transfer to a second superbug, MRSA (methicillin-resistant *Staphylococcus aureus*). MRSA is already the cause of major problems on wards, and has even been contracted by some outpatients.

3.2 Gram-positive bacteria and the growth promoting antibiotics

The growth promoting antibiotics are predominantly active against gram-positive bacteria. Three important groups of gram-positive bacteria are the staphylococci, the streptococci and the enterococci. These groups are large and each includes many perfectly harmless strains and some which cause infection.

It has been known for a long time that the AGPs cause resistance in these strains in farm animals, but the question is: can these bacteria survive in the human gut or transfer their resistance to bacteria already living there? The general scientific consensus until recently was that this would not happen to any significant extent. In 1993, however, research emerged which challenged this view for the enterococci, and over the last six years the evidence to support this has gradually strengthened with the publication of a number of new studies.

Each of the three groups: enterococci, staphylococci, and streptococci include one or more strains which have become known as 'superbugs' because they have become resistant to most and occasionally all antibiotics. The principal link with the growth promoting antibiotics relates to the enterococci, but there is an ever-present threat that this resistance could pass on to other staphylococci in particular and make an already serious problem a very great deal worse.

3.2.1 Enterococci - superbug VRE

Enterococci are inhabitants of the large bowel and an important part of the normal

human gut flora in that they help to fight invading organisms (Zarb 1999). They can, however, cause life-threatening infections in other parts of the body, especially in those with increased susceptibility to them. They are a particular threat to hospital patients undergoing renal dialysis and bone marrow transplants. *E. faecalis* and *E. faecium*, the two most significant strains of enterococci, can cause infections of wounds and the urinary tract, septicaemia, and endocarditis.

A particular problem with the enterococci is that they are naturally resistant to some antibiotics and have the ability to develop resistance more quickly than most other bacteria - this is particularly true in the case of *E. faecium*. For many years two glycopeptides (vancomycin and teicoplanin) have been the only antibiotics which could be assumed with any degree of confidence to work against them. It was originally assumed by some microbiologists that resistance to these would not develop (Livermore 1999). However, vancomycin-resistant enterococci (VRE) were first found in France in 1986 (Wegener et al 1999). They appeared in the UK in the same year, and spread to many hospitals.

Resistance to vancomycin can lead to a higher probability of mortality from enterococcal infection. In one study examining cases of bacteraemia caused by *E. faecium*, it was found that if the strain was vancomycin-sensitive there was a 35% chance of mortality, but that this increased to 57% if the strain was vancomycin-resistant (Linden et al 1996). Numerous scientific studies have implicated the use of the drug avoparcin in agriculture, (Aarestrup 1995, Aarestrup et al 1998, Das 1997, Klare et al 1995, van den Bogaard et al 1997a, b), but other growth promoters also have an effect on the enterococci.

3.2.2 Avoparcin

Precise figures are not available, but from the mid-1970s until it was banned throughout the EU on 1 April 1997, avoparcin was probably the most widely-used growth promoting antibiotic in Europe. This was because it brought about higher rates of growth in pigs, poultry and cattle than rival products. It was also used to increase milk production in dairy cows in the UK. While its use in some countries may still continue as old stock is used up, it is no longer manufactured anywhere in the world (Mudd 1999) and Thailand, from which the UK imports approximately 7,000 tonnes of chicken annually, gave an undertaking last year to stop importing it (VMD 1998).

AVOPARCIN

Marketed as Avotan by Roche Products Ltd. Use in EU suspended in 1997. Was allowed from 1972 for growth promotion in broiler chickens, turkey, pigs, growing-finishing cattle and lambs. as well as for improving milk production in dairy cows. At growth promoting levels, it has a prophylactic effect on necrotic enteritis in chickens. It was also strongly suspected of increasing the prevalence of salmonella-infected poultry flocks (Smith and Tucker, 1978).

Member of the glycopeptide group of antibiotics - related to vancomycin.

Avoparcin is an analogue of vancomycin, and it has been demonstrated that vancomycin-resistant enterococci (VRE) develop in the intestinal tract of animals fed with avoparcin. In countries in which pigs and poultry are fed avoparcin, the animals are commonly colonised with VRE, but in countries where avoparcin has not been used no VRE are found in farm animals (van den Bogaard 1996). A Danish study has compared poultry flocks raised with and without AGPs. No VRE was found in birds raised without AGPs, whereas VRE was found in five out of eight of the flocks raised conventionally (Aarestrup 1995).

Until the early 1990s, it had been believed that VRE infections in hospitals had only

acquired their resistance from the hospital use of antibiotics and not from food or farm animals. But an outbreak of multidrug-resistant infection in the renal unit of an Oxford hospital in 1993 left doctors suspecting that the source of the resistance was outside the hospital. Their subsequent research (Bates et al 1994) found the same type of resistant bacteria in both meat and the sewage outflow from a local pig farm. Similar work in Germany isolated vancomycin-resistant *E. faecium* strains from a pig and poultry farm where avoparcin was used, but failed to find any in isolates from a farm producing eggs where avoparcin was not used (Klare et al 1995). This study also isolated resistant *E. faecium* in 12 out of 100 non-hospitalised humans in a rural area where glycopeptides are exceptionally rarely used in the two local hospitals.

Since 1993, evidence suggesting that in Europe, these bacteria (or at least their resistance genes) may have spread to humans from animals via the food chain has continued to grow (House of Lords 1998a, p. 44).

- A study by Dutch scientists, conducted when avoparcin was still licensed, showed that a high percentage (14%) of the human population living in the province of Limburg where farming is very intensive were carriers of VRE (van den Bogaard et al 1997b).

- In 1996 an infection occured in a driver at a chicken packing factory, who was admitted to hospital in Birmingham with a broken arm. The wound became infected and antibiotic treatment was ineffective. A wound swab found VRE, and samples were then taken from chicken carcasses (originating from a number of EU countries) at the factory. Nine of 22 samples contained VRE. The scientists involved said that the case showed 'that the animal use of glycopeptides may represent a risk to patients' (Das et al 1997).

- a study which found the same strain of VRE in a turkey and a turkey farmer (van den Bogaard et al 1997a), demonstrating that transfer of resistance from animals to humans can occur naturally.

Possibly the strongest evidence yet of that avoparcin may be the principal cause of VRE in humans has come from the use of a technique called DNA sequencing. Scientists at the Danish Veterinary Laboratory Service examined the genetic makeup of VRE in pigs, poultry and humans, enabling them to classify the VRE isolates into 'G variants' and 'T variants'. They found that nearly all isolates (97%) from pigs were T variants and all of the isolates from poultry were G variants. In humans however there was a mixture of G variants (65%) and T variants (35%). This supports the hypothesis that VRE has passed from animals to humans and not *vice versa*. In the same study the scientists found that all human isolates from a Muslim country were G variants, the same variant infecting poultry. They concluded that:

The absence of pork variant types in a Muslim country suggests that food of animal origin is a major reservoir for VRE in humans

(Wegener et al, 1999).

3.2.3 Virginiamycin

Virginiamycin is not used in human medicine, but a combination of two closely-related drugs, quinupristin and dalfopristin (provisionally named Synercid) is being developed as a treatment for MRSA and VRE. Another closely related antibiotic, pristinamycin, is already used in human medicine in some countries.

In the USA, resistance to quinupristin/ dalfopristin has been found in animals by researchers who evaluated the antimicrobial resistance of enterococci from three separate turkey flocks on two farms owned by a large

VIRGINIAMYCIN

Marketed as Stafac by Pfizer. Banned as a growth promoter in the EU from 1 July 1999. Used in cattle, pigs and poultry. Until recently also used prophylactically and therapeutically elsewhere in the EU. It has a prophylactic effect at growth promoting levels on necrotic enteritis in poultry and swine dysentery in pigs.

Member of the streptogramin group of antibiotics - related to quinupristin/dalfopristin and pristinamycin.

poultry production company. Each flock comprised about 30,000 birds in a barn, and all were given antibiotic growth promoters, including virginiamycin. In samples of *E. faecium* grouped by the age of the birds, resistance to quinupristin/dalfopristin occurred in up to 35% of animals. As the turkeys aged, there was a higher percentage of quinupristin/dalfopristin-resistant *E. faecium* isolates, with 100% of isolates of this bacteria from the flock at slaughter age being resistant. The authors warned that:

The significance of the findings of this study is that we found quinupristin/dalfopristin-resistant strains in animals before the drug combination has been used in humans. Since antibiotic-resistant bacteria that can cause human infection may be transferred via food from animals to humans, great caution should be exercised in the use of streptogramins in animals

(Welton et al 1998).

A study in the Dutch province of Limburg (where farming is particularly intensive) at a time when virginiamycin was still used as a growth promoter, isolated pristinamycin-resistant enterococci which were also quinupristin/dalfopristin-resistant from 35% of faecal samples taken from humans and from 75% of samples from pigs.

The researchers summarised their conclusions in the *Journal of Antimicrobial Chemotherapy*:

[The results] clearly demonstrate cross-resistance between the antibiotics used as growth promoters and those in the same class that are used for therapeutic purposes. The resistant enterococci isolated from a high proportion of the humans making up our study population may have originated from animals which were part of the food chain

(van den Bogaard et al 1997b).

In September 1997, the UK's Public Health Laboratory Service (PHLS) alerted microbiologists to quinupristin/dalfopristin resistance in four isolates of vancomycin-resistant *E. faecium* from two centres in the UK. Three of the resistant isolates were from raw chicken, yet again raising 'the contentious issue of a possible threat posed to public health by the non-clinical use of antibiotics'. The scientists concluded:

Our observation indicates that, even before quinupristin/dalfopristin enters into wide clinical use, there is resistance to this agent in E. faecium

(Woodford et al 1997).

Further evidence to suggest that the use of virginiamycin as a growth promoter has led to the emergence of resistant bacteria in humans has come from Germany and Denmark. Although streptogramins have not been used in human therapy in either country, resistance to them has appeared both in animals and humans in Germany, and in food animals in Denmark, probably driven by the use of the related antibiotic virginiamycin in animal feed for the past 20 years (Witte 1998, Aarestrup et al 1998, Hammerum et al 1998). Resistance of *E. faecium* to streptogramins has also been reported in samples from humans in the USA, despite the fact that these antibiotics have yet to be used there in humans (Eliopoulos et al 1998).

3.2.4 Avilamycin

Avilamycin is not used in human therapy, but is structurally almost identical to an important new antibiotic currently in the latter stages of development as a treatment for highly resistant MRSA, meningitis, pneumonia and enterococcal infections.

A 1998 survey conducted by MAFF states that 'data exist in the private domain to confirm that resistance to avilamycin can develop in enteric bacteria, principally enterococci. [...] No reference to this was found in the literature.' Indeed, it appears that the only published statistics on the issue come from the Danish official monitoring programme, which in 1997 found that 69% of *E. faecium* isolates from broilers were resistant to avilamycin. Of that year's consumption of avilamycin in feed in Denmark, 84% went into poultry rations. In pigs, where the use of avilamycin was far lower, only 2% of isolates were resistant (Bager et al 1998).

Although it has been possible to find reference to unpublished studies on resistanct to avilamycin conducted by a pharmaceutical company and presented as evidence to the European Standing Committee on Animal Nutrition in 1997, it is notable that these studies omitted any mention of the the crucial issue of resistance in the enterococci.

Because neither avilamycin nor related antibiotics are currently used in human medicine, its associated resistance problems have received scant attention, and as a result it escaped last December's EU ban. However, a closely related drug, everninomycin (Sch 27899), is under development by Schering Plough for the treatment of multidrug-resistant gram-positive infections. Provisionally called Ziracin, this antibiotic is already on trial in a number of hospitals around the world including two in the UK. In one UK trial it is being used against drug-resistant strains of *Streptococcus pneumoniae*, which causes meningitis, pneumonia and serious ear infections, and in the other it is being tested on vancomycin-resistant strains of the enterococci .

In a study published last year, Danish microbiologist Frank Aarestrup investigated whether the high level of resistance to avilamycin in *E. faecium* from broilers found in Denmark might be linked with resistance to everninomycin (Sch 27899). He found 'complete agreement between decreased susceptibility to avilamycin and everninomicin'. He concluded that:

The resistance that has already been created by the use of avilamycin as a growth promoter will most likely reduce and shorten the life span of everninomicin as a therapeutic in humans

(Aarestrup 1998).

As Aarestrup points out in his paper, avilamycin was first licensed at a time when the oligosaccharides had not been considered as human antibiotics. However, due to the bans on its major rival growth promoting products its use is now increasing dramatically in the UK and some other EU member states. It has been pointed out that information is still deplorably lacking - no studies are available on the way in which resistance to avilamycin develops, or on genes conveying resistance, transfer of resistance or bacterial hosts for resistance genes (Report 1997).

A further concern with avilamycin is that its use may also help perpetuate the serious problem with VRE in poultry which arose from the use of avoparcin in poultry until 1997.

AVILAMYCIN

Marketed as Maxus G200 by Elanco Animal Health. Allowed for growth promotion in pigs and poultry for the foreseeable future. At growth promoting dosages has a prophylactic effect on necrotic enteritis in poultry

A mixture of the oligosaccharide and the orthosomycin groups of antibiotics - related to an antibiotic under development, everninomycin.

3.2.5 Bambermycin

Bambermycin (also known as flavophospholipol), is still licensed for growth promotion. It is not related to any antibiotic currently used in animal or human medicine. However, it has qualities (low toxicity, prolonged activity in blood) which make it an attractive candidate for therapy in the future. The authors of the 1997 Swedish commission report comment that 'in the present situation [...] these substances [flavomycin and its relatives] would appear to be a welcome addition to the therapeutic arsenal'.

There is little relevant information regarding resistance to this antibiotic. Point prevalance studies carried out in Denmark and Belgium indicate there is resistance to bambermycin among the enterococci (although *E. faecium* seems to have natural resistance) (Devriese and Haesebrouck 1996, Bager et al 1998). However, there is a great lack of research into the effect of feeding the antibiotic at growth promoting doses over a period on the resistance status of the bacteria in the animal.

Research in the 1970s found a 5.8% rise in the level of resistant *E. coli* when bambermycin was fed to calves at growth promoting levels (Dealy and Moeller 1977). In the light of the fact that bambermycin is active mainly against gram positive bacteria rather than the gram negatives which include *E. coli*, similar research concerning gram positive bacteria would seem to be strongly indicated.

BAMBERMYCIN

Marketed as Flavomycin by Hoechst Roussel Vet Ltd. Licensed for growth promotion. Used in cattle, pigs and poultry.

Also known as flavophospholipol. Member of the glycolipid group of antibiotics. Not used therapeutically in human or animal medicine, but glycolipids are one of the few remaining antibiotic classes considered suitable for development as medicinal drugs.

Research into resistance to bambermycin (and avilamycin) is important because resistance would normally only be detected when antibiotics are used for therapy and not for growth promotion.

A further concern over the use of bambermycin as an AGP is its effect on necrotic enteritis in poultry, a disease which is now endemic in some poultry producing systems. Because the bacteria causing the condition are resistant to bambermycin, feeding the antibiotic to chickens could increase its incidence. No research into this possible effect at growth promoting levels has been done (Report 1997).

3.2.6 Zinc Bacitracin

Zinc Bacitracin cannot be given by injection because it causes kidney damage. For many years its principal use in humans has been in combination with neomycin for the topical treatment of some skin conditions. One study (Wright et al 1978) showed it was effective in reducing post-operative pelvic infection after vaginal hysterectomy. There are occasional references to its use for sterilising the gut prior to abdominal surgery (eg Hammond and Lambert 1978), though it appears this is not practised in the UK at present.

More recently (O' Donovan et al 1994) demonstrated that bacitracin was effective in eradicating vancomycin-resistant *E. faecium* from the alimentary tract and it was also successfully used for the same purpose in connection with an outbreak of VRE in California (Chia et al 1995). The Californian researchers also suggested its possible prophylactic use in long-term care facilities which refuse to accept patients infected with VRE. It has been pointed out, however, that *E. faecium* (the strain which most readily develops resistance to bacitracin) accounts for only 12%

ZINC BACITRACIN

Marketed as Albac by Alpharma. Used in calves, piglets, lambs and poultry for growth promotion, and to improve the egg production of chickens. Used therapeutically in some EU countries, but not the UK. Banned for growth promotion in the EU since 1 July 1999, but will remain licensed for therapeutic use in member states where used.

At growth promoting levels has a prophylactic effect on necrotic enteritis in poultry. Adult cattle can suffer adverse reaction, including sudden drops in milk production, if their feed is contaminated with bacitracin.

A mixture of polypeptide antibiotics, it is of potential use in controlling VRE and MRSA.

of VRE cases and that attempts to eradicate VRE by oral antibiotic use 'seem to have only a transient effect' (Linden and Millar 1999), an analysis not entirely confirmed by Chia et al who encountered a relapse in only one of eight patients or by O'Donovan et al in whose tests 25% relapsed. Zinc bacitracin is also under development for the treatment of patients with MRSA (Health Council of the Netherlands 1998).

While there is no evidence that bacitracin resistance is naturally transferable between bacterial species, the use of bacitracin as an AGP does increase resistance in strains of *E. faecium* and *E. faecalis* (EU 1998), and there is additionally evidence that the use of bacitracin encourages an increase in *E. faecium* at the expense of *E. gallinarum* (Klaukas et al 1988).

3.2.7 Staphylococcus aureus ***- superbug MRSA***

Staphylococcus aureus is commonly found on the skin without causing infections. However, some strains are pathogenic and it is one of the commonest causes of hospital- and community-acquired infections worldwide. It can infect wounds, causing trivial or deep-seated disease, and cause bacteraemia, endocarditis or pneumonia. Infections are highly contagious and can be life-threatening.

By the early 1960's most *Staph. aureus* infections had become untreatable with penicillin. However strains resistant to second generation penicillin-type antibiotics, erythromycin, streptomycin and many other antibiotics emerged in the late 1970's and spread rapidly. These are known collectively as methicillin-resistant *Staph. aureus* (MRSA). Nowadays the only drugs consistently effective against serious MRSA infections are the glycopeptides vancomycin and teicoplanin. In recent years there has been a very large increase in the incidence of MRSA in England and Wales: during 1989-91 only 1.5% of *Staph. aureus* isolates were methicillin-resistant, whereas by 1997 31.7% were resistant (SMAC 1998, p. 34) making the reliance on vancomycin and teicoplanin ever greater. MRSA infections in the nose and on the skin are also becoming resistant to mupirocin, an antibiotic specifically reserved for this use (Working Party Report 1998).

Many types of resistance are common to MRSA and the enterococci (House of Lords, 1998a, p. 44) and there is considerable concern that the now-common vancomycin resistance in the enterococci could transfer to MRSA. In 1996, the first documented case of infection caused by *Staph. aureus* with intermediate levels of resistance to vancomycin (vancomycin-intermediate *Staph. aureus* or VISA) was reported from Japan and there have since been two cases of VISA in the USA. In 1998 the first incidence of VISA in Europe was reported from a French hospital (Ploy et al 1998) and this year the first British cases were reported from the Glasgow Royal Infirmary (Daily Mail 1999). However, there are many different resistance mechanisms which make vancomycin resistance possible and the cases of VISA so far observed have not acquired their resistance from the enterococci (Woodford 1999, Paulsen et al 1997). As such, this unwelcome development is

likely to be due to human rather than animal use of antibiotics. Nevertheless, it has already been shown in the laboratory that vancomycin-resistance can transfer from enterococci to MRSA both *in vitro and in vivo* (Noble et al 1992).

The prospect of vancomycin-resistant MRSA developing in the UK is alarming, and PHLS scientists have warned that the public health and economic consequences of its emergence would be catastrophic (House of Lords 1998a, p. 44). Scientists from the Advisory Committee on the Microbiological Safety of Food (ACMSF) have also warned that if vancomycin-resistant *Staph. aureus* comes to United Kingdom hospitals, 'we are going to face a problem that could take a substantial part of the health budget to control' (House of Lords 1998a, p. 375). So far there is no evidence to implicate the agricultural use of antibiotics in this problem, but the continuing selection of VRE by other antibiotics used in livestock production and the increasingly high level of vancomycin resistance in enterococci make such a development an ever-present threat. Reviewing the situation, Paulsen et al (1997) concluded, 'it seems likely that the emergence of staphylococcal strains resistant to high levels of vancomycin is only a matter of time'.

3.2.8 Streptococci - superbug penicillin-resistant
Streptococcus pneumoniae

Streptococcus pneumoniae causes pneumonia, meningitis and otitis media, a serious ear infection. Resistance to a wide range of antibiotics has developed in recent years and it is now seen as a worrying and growing problem which is caused by the overuse of antibiotics in human medicine. (see appendix VII)

3.3 Food poisoning bacteria and the therapeutic antibiotics

The use of therapeutic antibiotics in livestock production is clearly essential to save lives and cure debilitating infections. Diseases and infection can appear without warning and for little apparent reason.

But a substantial proportion of the therapeutic antibiotics used in agriculture are to prevent or 'control' disease, rather than to treat it. Even where infection is present intensive housing often means that large numbers of animals are given antibiotics even though only a few are ill. In many cases this is simply a management tool to make life easier for the stockman or an insurance policy to guard against a remote risk, but one which could threaten profit margins.

Most of the problems against which prophylactic medication is used arise as a result of the intensive and unnatural way in which many farm animals are kept and attempts to push them to and sometimes beyond their metabolic limits. In view of this, changing the systems under which they are reared offers the best method of reducing antibiotic usage. A good example would be the early weaning of baby pigs at 21 days. This is now common practice in the UK, but the problems it causes to the immature piglet invariably provoke ill health immediately and start it on a succession of antibiotic treatments for the rest of its short life. Piglets weaned at seven to eight weeks and kept in free-range conditions rarely require antibiotics at all.

Prophylactic medication can be included in feed or water for a month or longer in some situations. The doses are low, but the routine use of small amounts of therapeutic antibiotics is, in fact, far more likely to encourage resistant bacteria than their high level use for short periods.

Since virtually all of the antibiotics used in veterinary medicine are either the same as, or closely related to, those used in human

medicine (see appendix II) there is an ever-present risk that resistance will transfer from one to the other.

While some prophylactic use of antibiotics may be preferable to treatment later, especially where this is to counter a specific threat in individual animals, perhaps after surgery or assisted parturition, there is no legal distinction between these two clearly different uses of therapeutic drugs.

The routine use of therapeutic antibiotics as a substitute for good animal husbandry increases the pool of antibiotic resistance and risks compromising some of man's most powerful medicines for dubious and short-term gains. This is particularly the case if the bacteria transferring from animals to man are directly pathogenic. The principal examples of this relate to food poisoning bacteria which transfer from animals to humans on food.

The food-poisoning bacteria include salmonella, campylobacter, *E. Coli* and listeria. According to the Public Health Laboratory Service, most infections caused by these enteric bacteria (or enterobacteria) are acquired from animal sources, either through the food chain, or by direct contact with the animals (House of Lords 1998a, p. 55). Although drug resistance in enterobacteria usually arises in the farm animals before transmission to humans, some farm animals do not show signs of disease and simply act as carriers.

3.3.1 Salmonella

Salmonella food poisoning will typically cause enteritis with symptoms of diarrhoea, vomiting and nausea. The infection can be severe, even resulting in death in vulnerable patients. Some salmonellae can be carried by apparently healthy animals, but still cause disease in humans. *S. typhimurium* DT104, for example, affects about 3,000 people each year. In 1-2% of cases the infection is invasive. As such antibiotics are essential to save life. *S. typhi* on the other hand, which causes typhoid fever, invariably requires antibiotics. In 1997 it affected 151 Britains returning from holiday mostly on the Indian sub-continent (Threlfall et al 1999).

The drug of choice in salmonella infections is the fluoroquinolone ciprofloxacin.

An outbreak of resistant *S. typhimurium* DT29 in the mid-1960s led to the development of the first multiresistant strains. Since 1975 there has been another big upsurge in the incidence of multiresistant salmonellae among farm animals and a concurrent increase in multiresistant samples from humans. Table 3.1 shows how multiresistance is still increasing.

Scientists have noted the epidemic spread of *S. typhimurium* DT104 since 1990, to the point where it is now the second most common salmonella in man in England and Wales (House of Lords 1998a, p. 220). Many of the samples tested show *in vitro* resistance to ampicillin, chloramphenicol, streptomycin,

Table 3.1 Multiresistance in England and Wales of zoonotic salmonellae.

	1990	1994	1996	1991	1994	1996	1990	1994	1996	1981	1994	1996
S. enteritidis	4	5	5	0.1	0.4	0.8	1	<1	<1	0.5	0.4	0.5
S. typhimurium	17	59	80	0.3	1.4	12	21	18	32	5.5	62	81
S. virchow	9	11	26	2.5	5.1	10	12	27	26	0.2	9	19
S. hadar	-	31	59	2	39.6	60	-	7	8	0	13	56

Source: PHLS

Notes: 1. The figures for 1996 are provisional. 2. Multiresistance means resistance to four or more antibiotics

Table 3.2 - *S. typhimurium* DT104 from humans in England and Wales, 1990-96: resistance to individual antimicrobials.

	1990	1991	1992	1993	1994	1995	1996
Ampicillin	37	50	72	85	88	90	95
Ciprofloxacin	0	0	0.2	0	1	7	14
Streptomycin	38	52	75	85	92	97	97
Tetracyclines	36	50	74	83	88	90	97
Trimethoprim	0.4	3	3	2	13	30	24

Source: PHLS

Table 3.3 Resistance (%) of *E. coli* bacteria to antibacterial agents in gram-negative bacteria from blood and CSF: England and Wales.

	1990	1991	1992	1993	1994	1995	1996	1997
Ampicillin	55	54	53	54	55	56	57	59
Ciprofloxacin	0.8	0.7	0.9	1.2	1.7	2	2.6	
Trimethoprim	19	19	22	24	24	28	27	29

Source: PHLS

sulphonamides, tetracycline, apramycin and ciprofloxacin (see table 3.2). It is significant that all of these antibiotics are used for routine prophylaxis in animal husbandry in the UK.

3.3.2 Campylobacter

Campylobacter infections range from mild stomachache to severe illness. For immuno-compromised patients who have invasive campylobacter infections, treatment failure can be fatal (Wegener 1999). Infections in humans may be treated with fluoroquinolone antibiotics or with the macrolide erythromycin.

Campylobacter species already carry resistance to zinc bacitracin, novobiocin, rifampicin, streptogramin B, trimethoprim, vancomycin and cephalothin. The introduction of the fluoroquinolones for veterinary use, and the use of the macrolides for growth promotion (a practice now banned) and for routine prophylaxis have been contributing to the emergence of further resistances, which may have serious consequences for human health.

3.3.3 E. coli

E. coli bacteria are usually a harmless part of the human gut microflora, though some strains are pathogenic. They are, for example, the most common cause of urinary-tract infection. *E. coli* 0157 causes abdominal pains, bleeding, and kidney failure. Kidney damage can be permanent, and in children and the elderly there is a significant risk of mortality. *E. coli* 0157 is the most important food poisoning strain in the UK.

A study 30 years ago established that antibiotic resistance could be transferred from animal strains of *E.coli* to *E. coli* in the human gut (Smith 1969). It has subsequently been shown that such a transfer does indeed occur in practice, primarily via the food chain (Linton 1986).

Resistance in all *E. coli* is important for two reasons. Firstly because some strains are significant causes of human disease and when the infection is invasive antibiotic treatment is important (an exception is the case of *E. coli* 0157).

Secondly, it is important because these bacteria have a tendency to transfer their resistance genes to other bacteria which may be pathogenic and necessitate antibiotic therapy. Thus resistance in *E. coli* 0157 is still of concern, despite the fact that it is itself rarely targeted with antibiotics. Multiple drug resistance in *E. coli* 0157 is not yet a major problem in the UK: in isolates taken from humans in 1996 in England and Wales, 18% were drug-resistant and only 1% possessed multiple drug resistance. However there are concerns over the increasing levels of resistance of *E. coli* to a number of antibiotics widely used in agriculture (see table 3.3).

3.3.4 Apramycin

Apramycin is closely related to gentamicin, neomycin and streptomycin, all drugs used in human therapy to treat serious infections caused by gram-negative bacteria.

3.3.4.1 Apramycin resistance in salmonella

Resistance to apramycin in salmonella was first detected in 1982, two years after its introduction into veterinary medicine in the UK (MAFF 1998 p. 37). Resistance in *S. typhimurium* DT104 had risen from 0% to 16% by 1990 (Low et al 1997). Resistance to gentamicin, an important drug closely related to apramycin which is used to treat severe systemic salmonella infections in humans, also arose in the same bacteria as a result of the use of apramycin (MAFF 1992, para. 4.27). In 1997, vets at the Scottish Agricultural College found evidence that apramycin resistance had emerged in *S. typhimurium* DT104. Screening of faecal samples from farm animals identified widespread apramycin resistance in *E. coli* and farm records showed that apramycin had been used extensively to treat enteric infections. Transmission of resistant strains between animals is known to take place and transfer of apramycin resistance has been described between *E. coli* and *S. typhimurium*. The Scottish vets therefore concluded that it was possible that transfer of apramycin resistance occurred between different species of bacteria on farms involved in the study:

The occurrence of resistance is consistent with usage of apramycin and since the majority of field isolates of typhimurium *DT104 are almost invariably resistant to multiple antimicrobials it is probable that further strains with apramycin resistance will arise through the use of this antimicrobial. [The findings] must be of major concern to both veterinary and human clinicians*

(Low et al 1997).

The evidence that apramycin resistance and gentamicin resistance are linked is very compelling. Apramycin resistance mediated by the enzyme AAC(3)IV has been identified in isolates of *S.* DT 204c from both humans and animals. Resistance mediated by this enzyme is unique to apramycin, but apramycin is not used in humans (MAFF 1998). Therefore it would seem certain that the resistant human isolates must be due to agricultural use. This case also provides evidence for the possible spread of

APRAMYCIN

First used in animals in 1980. Used in feed and water to treat pigs, poultry, calves and lambs, for up to 28 days at a time, especially against *E. coli*, and salmonella consequent on early weaning and other intensive practices. Routinely given by mouth to day-old lambs and pigs.

An aminoglycoside antibiotic related to gentamicin, neomycin and streptomycin which are all used in humans. Streptomycin resistance in S. typhimurium grew from 62% in 1994 to 81% in 1996 (House of Lords 1998a).

resistance genes within the gut: the same enzyme has been found in other enterobacteria from man (Wray 1997, MAFF 1998).

3.3.4.2 Apramycin resistance in E. coli

It seems that apramycin resistance in *E. coli* was negligible before the antibiotic came into veterinary use in 1980. Subsequently, resistance to apramycin in isolates of *E. coli* from farm animals was monitored by Wray et al (1986), and between 1982 and 1984 it increased from 0.6% to 2.6%. In 1992, a MAFF expert group published the Lamming Report, in which they expressed concern over the effect that this might be having on human health because of cross-resistance between apramycin and gentamicin: 7 out of 26 (27%) gentamicin-resistant clinical isolates of *E. coli* submitted for examination to the PHLS were also resistant to apramycin.

A later study underlined this danger: Hunter et al (1994) found apramycin-resistant *E. coli* in a stockman which had the same resistance plasmid as *E. coli* isolated from pigs on the farm.

3.3.5 The Fluoroquinolones

The fluoroquinolones are an extremely important class of drugs in human therapy, used to treat infections caused by organisms such as MRSA, salmonella, campylobacter and *E. coli*. It had been thought in the late 1980s that resistance to fluoroquinolones would not develop (House of Lords 1998a, p. 445), but evidence to the contrary rapidly emerged after enrofloxacin began to be used in poultry in the Netherlands. Despite this, the VPC approved their introduction into veterinary use in the UK in 1993 (SMAC 1998).

3.3.5.1 Fluoroquinolone resistance in salmonella

The fluoroquinolone ciprofloxacin is the therapeutic agent of choice for invasive salmonella infections in humans (Frost et al 1995), so the development of resistance to it is of grave concern as it may lead to treatment failure, especially when the salmonella is resistant to a range of other antibiotics. Ciprofloxacin resistance has increased in *S. hadar* from 2% in 1991 to 60% in 1996, in *S. virchow* from 5% in 1994 to 10% in 1996 and in *S. typhimurium* from 1% in 1994 to 12% in 1996 (PHLS data). These three types of salmonella are all commonly isolated from poultry, in which fluoroquinolones are widely used. Scientists from the Central Public Health Laboratory have warned of the risk to human health that this represents (Frost et al 1996).

Of particular concern has been the appearance of fluoroquinolone resistance in already highly resistant *S. typhimurium* DT104: in 1996 and 1997, 12% of isolates which were resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines had also acquired resistance to ciprofloxacin (Threlfall et al 1999), making the choice of antibiotic for treating cases of invasive disease very limited. In a recent outbreak of quinolone-resistant DT104 associated with pork in

THE FLUOROQUINOLONES

Enrofloxacin, marketed as Baytril by Bayer, is the principal fluoroquinolone used in animals. First licensed for poultry in 1993, it has been used prophylactically against salmonella (Humbert et al 1997, Barrow 1998), though this is no longer recommended. It is cross-resistant with ciprofloxacin, an extremely important medical drug for the treatment of resistant organisms such as some salmonella blood poisoning and MRSA (see 3.2.7). Many new fluoroquinolones have recently been introduced into human medicine but all are cross-resistant with enrofloxacin.

Danofloxacin, first licensed in 1996, is used for the treatment of respiratory and enteric disease in farm animals. Sarafloxacin is licensed for prophylactic and therapeutic purposes in farmed Atlantic salmon.

Denmark, six people were treated with fluorquinolones and one died (Anon 1998).

In the USA on the other hand, where the fluoroquinolones have to date had limited veterinary use (the first licence was granted for use in poultry in late 1995), none of the human or veterinary isolates of *S. typhimurium* DT104 identified by 1998 were resistant to the fluoroquinolones (Threlfall et al 1998).

3.3.5.2 Fluoroquinolone resistance in campylobacter

Campylobacter exist as a variety of strains in their animal hosts making it impossible to link a specific antibiotic-resistant campylobacter strain with a particular use of fluoroquinolones. However, prior to the introduction of the fluoroquinolones into the poultry industry in 1993, only 1% of chicken bred in the UK carried fluoroquinolone-resistant bacteria (Endtz et al 1991), and no such bacteria were known in humans with no prior exposure to the drugs (Witte 1998).

By contrast, 14% of chicken carcasses imported from the Netherlands in 1993 contained resistant bacteria (Health council of the Netherlands 1998, p. 52) - fluoroquinolones had been introduced in poultry farming there in 1987. And by 1997, fluoroquinolone resistance in *C. jejuni* in chicken bred in the UK had risen to an average of 11% (SMAC 1998).

These increases in resistance in isolates from poultry have been paralleled by increased resistance in bacteria infecting man. In the Netherlands, for example, the proportion of enrofloxacin-resistant campylobacter taken from man rose from 0% to 11% between 1982 and 1989 (House of Lords 1998a, p. 61).

In the UK, quinolone-resistant campylobacter were first reported in 1991. Since then, microbiologists at Oxford's Public Health Laboratory have collected information from human stool samples submitted to the laboratory. Campylobacter have been, and continue to be, the commonest pathogen found in samples and there has been a steady rise in quinolone resistance with nearly 7% of camplyobacters showing resistance according to the most recent figures. The Oxford microbiologists have stated that, in their experience, quinolones are rarely prescribed by doctors to treat gastrointestinal disease in the Oxford area. This has led them to conclude that 'it is unlikely therefore that this increase is due to failure of therapy due to prior exposure to the drugs in the patients. A more likely explanation is the widespread use of quinolones in the poultry industry' (Bowler et al 1996). Such widespread use is 'likely to lead to the potentially more serious problem of quinolone resistance in salmonella species', cases of which had already been reported. The microbiologists added that they regretted that enrofloxacin had been licensed for use in the UK poultry industry.

Scientists from the Laboratory of Enteric Pathogens, which is the national reference centre for campylobacter species from humans, have reported that of 5,800 isolates referred to the laboratory in 1996 and 1997, 12% were resistant to ciprofloxacin and a further 4% had a lower level of resistance. They warn of the 'possible clinical consequences of the continuing use of fluoroquinolone antibiotics in food animals' (Threlfall et al 1999).

All 4,953 *C. jejuni* isolates from humans received by the Minnesota Department of Health between 1992 and 1998 were tested for resistance to quinolones. The proportion of resistant isolates rose from 1.3% in 1992 to 10.2% in 1998 (Smith et al 1999), a rise which seems clearly associated with the introduction of enrofloxacin for poultry in the US in 1995. Some of these infections were travel-related and others were domestically-acquired. The researchers also found that 14% of *C. jejuni* isolated from domestically produced chickens in 1997 were ciprofloxacin-resistant, and documented DNA fingerprints from resistant *C. jejuni* in domestically produced chickens which were identical to those in the domestically acquired resistant *C. jejuni* in humans.

3.3.5.3 Fluoroquinolone resistance in E. coli

Resistance in *E. coli* is also causing concern. Resistance to ciprofloxacin in *E. coli* in England and Wales increased from 0.5% to 2.6% between 1989 and 1996 (PHLS data). Furthermore, PHLS scientists have found the level of resistance of each resistant *E. coli* bacteria to be much higher than it is for resistant salmonella bacteria (Threlfall et al 1997). The scientists warn:

The emergence of high level resistance to ciprofloxacin in E. coli *from cases of invasive disease is of serious concern, particularly as in the majority of cases, isolates were already resistant to a wide range of alternative antibiotics. Physicians should be aware that with the emergence of* E. coli *with high-level resistance to ciprofloxacin, there is now the possibility of treatment failure when this antibiotic is used for patients with invasive disease*

(Threlfall et al 1997).

A study of fluoroquinolone resistance in *E. coli* has found that in order to achieve high-level resistance, bacteria must possess at least three genetic mutations. The authors suggest that the conditions of low selective pressure that occur with the use of fluoroquinolones in agriculture could foster an environment where such multiple mutations can occur (Everett et al 1996).

In India up to 60% of *E. coli* are already resistant to ciprofloxacin (SMAC 1998, p. 39), so it is clear that with continued excessive use of these drugs resistance may yet develop into a much more serious problem.

3.3.6 The macrolides

Both tylosin and spiramycin were licensed until recently for growth promotion, and tylosin is still licensed for therapeutic/prophylactic use. Another macrolide, erythromycin, is an important human agent for treating infections caused by organisms such as staphylococci, streptococci and campylobacters, and is closely related to tylosin and spiramycin. Lacey (1984) claimed that the fact that the types of resistance to macrolides and other related antibiotics found in animal strains of staphylococci are different to those found in human strains 'argues against the importance of an "animal reservoir" of resistance genes capable of infecting human cultures'. This point is still broadly accepted today (MAFF 1998, p. 60).

3.3.6.1 Macrolide resistance in campylobacter

Macrolides have been very widely used for growth promotion and prophylaxis in the pig sector, and a number of studies have looked at resistance in the serotype *C. coli* which is associated primarily with swine. Burridge et al (1986) found that 55% of pigs which had not been treated with tylosin yielded *C. coli* resistant to tylosin, but 70% of those which had received tylosin did yield resistant *C. coli*.

Macrolide resistance in poultry and cattle is at a much lower level, however: a study in Denmark found that 55% of pig samples, 5% of

TYLOSIN PHOSPHATE AND SPIRAMYCIN (Macrolides)

Marketed as Tylamix and Tylan by Elanco Animal Health. Tylosin phosphate was widely used as a growth promoter in pigs until the EU ban of 1 July this year. Spiramycin was also licensed as an AGP in cattle, sheep, pigs and poultry, but was rarely used. Both will remain licensed for therapy: tylosin is used therapeutically in cattle and for routine prophylaxis to control swine dysentery for up to 30 days at a time, spiramycin and tylosin are both used to treat mastitis.

Another macrolide, erythromycin, is important in treating human diseases caused by campylobacters, staphylococci and streptococci.

Macrolides are part of a broader group of drugs including lincosamides and streptogramins, known as MLS antibiotics, which all exhibit similar resistance mechanisms.

cattle samples and 10% of poultry samples were resistant to macrolides (there was co-resistance of the macrolides erythromycin, tylosin and spiramycin) (Aarestrup and Nielsen 1997). Subsequently another Danish study found that 73% of isolates of *C. coli* from pigs were resistant to tylosin, 74% to erythromycin and 72% to spiramycin, whereas 18% of poultry isolates of *C. coli* were resistant to tylosin, erythromycin and spiramycin, and 14% of human isolates of *C. coli* were resistant to tylosin, erythromycin and spiramycin.

There are also significant differences between levels of macrolide resistance in *C. coli* isolates taken from man and *C. jejuni* isolates taken from man (*C. jejuni* are primarily associated with poultry): in England and Wales, in 1997, 13% of *C. coli* isolates were resistant to erythromycin, whereas only 1% of *C. jejuni* isolates were resistant to the same drug.

Taylor (1998) has acknowledged that 'the exact origin of the erythromycin resistance found in campylobacters of food animal origin has not been proven, but it appears to be selected by the use of MLSB in them, either in therapy or as antimicrobial growth promoters.'

3.3.7 Trimethoprim

Trimethoprim is used in human medicine mainly to treat urinary-tract infections which are mostly caused by *E. coli*, but also to treat cases of invasive salmonella.

3.3.7.1 Trimethoprim resistance in salmonella

In recent years there has been a significant increase in resistance to trimethoprim in both *S. typhimurium* and *S. virchow* in isolates from humans (see table 3.1). This is of concern because trimethoprim is used to treat invasive salmonella infections in humans.

The case of *S. typhimurium* DT104 is again attracting particular attention: resistance has increased from 0.4% in 1990 to 24% in 1996 (see table 3.2), and 21% of isolates which are resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines were also resistant to trimethoprim in 1996 (Threlfall et al 1998). Although it is suspected that this reduced susceptibility can be put down to the use of the drug to treat salmonella infections in cattle (Threlfall et al 1996), there is clearly a danger that the use of trimethoprim for routine prophylaxis in pigs and poultry will lead to further increases in resistance, as *S. typhimurium* DT104 has now spread from cattle to other food animals.

TRIMETHOPRIM

Marketed by C-Vet Livestock Products, Vetoquinol UK Ltd and Cheminex Laboratories Ltd. Used therapeutically and prophylactically in conjunction with sulphonamides as a broad-spectrum treatment for a wide variety of infections in poultry, pigs and farmed fish, including *E. coli*, salmonella and pasteurella. In pigs, used to preempt infections around farrowing time and streptococcal meningitis (to which early-weaned pigs are vulnerable).

Also used in humans to treat *E. coli* and salmonella.

Trimethoprim is widely used in agriculture, both for therapy and for routine prophylaxis. According to the PHLS, the use of 'trimethoprim in food animals has contributed to the development of resistance [...] in zoonotic salmonellae' (House of Lords 1998a, p. 60).

3.3.7.2 Trimethoprim resistance in E. coli

Resistance in *E. coli* isolates taken from humans increased from 19% to 29% between 1990 and 1997 (see table 3.3). Such an increase is of concern as this is a drug used in human therapy to treat *E. coli* infections.

Significant levels of trimethoprim resistance have been found in all animals fed or treated with trimethoprim: a survey conducted by the

Central Veterinary Laboratory between 1986 and 1991 examined isolates from farm animals in England and Wales, and found resistance in 19% of isolates from pigs, in 15% of isolates from poultry, in 26% of isolates from cattle and in 20% of isolates from sheep (Wray et al 1993).

3.4 Other in-feed antibiotics which overlap with human medicine

These antibiotics are all used for mass medication of farm animals for disease prevention and control. They are all either used themselves or are related to drugs used for the treatment of humans.

3.4.1 The penicillins/beta lactams

procaine penicillin - used prophylactically in combination with chlortetracycline against respiratory infection in pigs. Courses of medicated feed can be up to six weeks long. Can affect those allergic to penicillin, sometimes seriously. A long-acting drug, both it and the short acting version, benzylpenicillin are used very widely in humans.

amoxycillin - used in farmed fish, pigs (for prophylactic control of post-weaning disease), chickens and turkeys. The EU has now imposed a seven-day withdrawal period for laying hens, because of concern that resistance could transfer to humans. The same drug is used in humans, and it is closely related to ampicillin.

ampicillin - used in dry cow therapy, and in human medicine. Resistance to ampicillin in human *E. coli* has been gradually increasing for many years, resistance in salmonellae has increased dramatically.

cloxacillin - used in dry cow therapy. It is a penicillin effective against certain bacteria such as staphylococci which do not respond to penicillin itself.

3.4.2 The tetracyclines

Being very broad-spectrum antibiotics, tetracyclines are commonly used in humans as well as animals. Their use in human medicine is declining because so many organisms have now acquired resistance (SMAC 1998). In 1984, 18 people in the USA were infected with chlortetracycline-resistant *Salmonella newport* which was traced to a beef herd which had received chlortetracyline for growth promotion (Holmberg et al 1984). It is still used for this purpose in the USA (SMAC 1998), from which the UK imported 'hormone-free' beef until a suspension on this trade in the EU earlier this year.

oxytetracycline - used prophylactically in farmed and ornamental fish, and in cattle and pigs against respiratory infections. The manufacturers note that use of the product in the long term can give rise to resistance in all of these species.

chlortetracycline - used prophylactically in pigs against a number of organisms, including those which cause respiratory disease and streptococcal meningitis. Also used prophylactically in chickens to combat chronic respiratory disease, salmonella and pasteurella. Used in calves to treat respiratory infection, and also in turkeys to treat *E. coli* infections.

tetracycline hydrochloride - in this form, tetracycline is administered to chickens for the treatment of necrotic enteritis.

3.4.3 The macrolides and lincosamides

lincomycin - used prophylactically and therapeutically in pigs (in combination with spectinomycin) against swine dysentery and mycoplasmal pneumonia. Lincomycin is an important therapeutic veterinary drug with good absorption but cross-resistant with clindamycin which is used in humans. In the US and other countries lincomycin is still used for growth promotion, though this was banned in the UK 20 years ago due to concerns about

resistance. However, Lincospectin, a mixture of lincomycin and spectinomycin, can be used prophylactically in the UK for up to 30 days. The manufacturers Pharmacia and Upjohn are currently looking for 'more UK trial sites to prove the cost effectiveness of the antibiotic' (Lodge 1999).

spectinomycin - an aminocyclitol used in combination with lincomycin in pigs against *E. coli* and salmonella infections. Used prophylactically to preempt infections of the uterus and teats around farrowing. Guidelines about how long it should be administered for are vague - for farrowing sows courses lasting for longer than a month are envisaged, for 'control of enteric conditions' (that is, where there are no clinical signs in the animal), spectinomycin is to be fed 'daily throughout the period of risk'. Also used in human medicine; prescribed for patients who are allergic to penicillin.

3.4.4 neomycin

A broad-spectrum aminoglycoside antibiotic used prophylactically against *E. coli* in pigs and broiler chickens. Neomycin can be used topically in humans; the use of other aminoglycosides, including streptomycin and the important gentamicin, is more widespread.

3.4.6 tiamulin

Used to prevent and treat swine dysentery and pneumonia in pigs. Campylobacter, staphylococci and streptococci are also sensitive to tiamulin. No human medical equivalent as yet, although a new agent, pleuromutilin is in line for registration (MAFF 1998).

3.5 Has penicillin resistance in farm animal bacteria passed to strains affecting humans?

It is still not clear today to what extent the use of penicillin in agriculture also contributed to the rapid development of resistance in diseases affecting people. Lacey (1984) set out the still largely accepted view that penicillin resistance in staphylococci and streptococci does not transfer easily between animal and human strains and that because the use of penicillin in human medicine has been so large, any additional contibution from farm use has probably been quite small. He did however, concede that 'once the appropriate genes have become established in a new host, further transfer within that host - whether animal or human - occurs at higher frequencies'. The Swann Committee reviewed evidence that penicillin use may have contributed to the development of transferable ampicillin resistance (Swann et al 1969). A recent report (MAFF 1998) has also drawn attention to research in 1993 which demonstrated that antibiotic resistance in staphylococci can transfer to human bacteria via milk.

4 CAN WE DEAL WITH RESISTANCE ONCE IT HAS DEVELOPED?

The emergence of antibiotic resistance is always progressive. Initial low-level resistance requires a higher dose of the drug to treat the infection. With time widespread high-level resistance usually follows. Once resistance has developed, there are two courses of action:

4.1 The development of new antibiotics

NOAH, which represents animal drug manufacturers in Britain, reassuringly tells us that 'new antibiotics are being developed all the time; dozens of new therapeutic options are currently in development worldwide to relieve the over-reliance on existing products for man' (NOAH, 1996). This view is clearly not shared by Harvard microbiologists, who have bluntly summarised the seriousness of the current situation by saying:

The prevalence of antimicrobial-resistant human pathogens is rapidly increasing, but the discovery and development of new antimicrobial drugs that are active against multidrug-resistant organisms have slowed dramatically

(Gold and Moellering, 1996).

In fact, no major new class of antibiotics has been discovered for over 20 years (House of Lords 1998a, p. 179), and the 'new' drugs to which NOAH refer are nearly always closely-related to existing antibiotics to which they are often cross-resistant.

4.2 Suspending or reducing the use of existing antibiotics

At first it may seem that restricting antibiotics once resistance has developed can resolve the problem. It proved possible to renew antibiotic sensitivity in a British hospital through the restriction of antibiotics throughout the building (Barber et al 1960). There have also been successes in reducing resistance on farms. Large reductions in resistance of *S. typhimurium* to tetracycline in pigs and humans occurred in the Netherlands after the drug was banned for use as a growth promoter in 1974 (van Leeuwen et al 1979), and in Sweden resistance to several antibiotics declined after all antibiotics were banned there for growth promotion in 1986 (see table 3.1).

Table 4.1 Resistance in S. typhimurium in Sweden

	Resistance to streptomycin (%)	Resistance to tetracycline (%)
1978-1986	78	14
1988-1991	32	6
1992-1994	17	0

Source: Tronstad 1997

But there have also been many cases when resistance to an antibiotic has persisted long after the the use of the drug has been suspended. Chloramphenicol resistance in Britain is still widespread although the antibiotic was banned for prophylactic use on farms in the early 1970s (Riley et al 1993), (see 1.3.4) and the prevalence of streptomycin resistance in the United States and many other countries has not decreased despite restrictions on use in clinical medicine and animal husbandry (Sundin and Bender 1996).

There are, however, microbiological explanations for this. For the removal of the antibiotic to reduce resistance, sensitive strains of bacteria must be more likely to survive than resistant strains in an antibiotic-free environment. Lenski (1997) has shown that although this happens with bacteria which have recently acquired resistance genes, resistant bacteria can, given time, mutate and significantly improve their capacity to survive in the absence of antibiotics. Experiments with resistant bacteria *in vitro* corroborate this hypothesis: if resistant bacteria are mixed with sensitive bacteria in an antibiotic-free environment soon after they have acquired their resistance, they are gradually replaced.

On the other hand, if resistant bacteria are grown for hundreds of generations in the presence of an antibiotic, they can mutate to become as strong as, or sometimes stronger than sensitive strains when mixed with them in the absence of antibiotics (Lenski 1997).

So with sustained long-term antibiotic use, as in farm animals fed antibiotics for growth promotion or routine prophylaxis, bacteria can 'prepare' for the eventual withdrawal of the antibiotic. Earlier research also confirmed that in animals fed antibiotics continuously at sub-therapeutic levels, resistance persisted for far longer than when antibiotics were administered at therapeutic levels for short periods (Linton et al 1975).

These findings are often overlooked in the debate over the relative contributions of human medicine and agriculture to the resistance problem. The overall tonnage used in each is certainly important, but in general antibiotics used at low doses for long periods (such as those used prophylactically in livestock production) contribute proportionally more persistently resistant bacteria to the environment than antibiotics used at higher doses for shorter periods (as is generally the case in human medicine). The exception to this would appear to be sometimes where the same antibiotics are used therapeutically in a succession of individual animals or people in the same environment (intensive care unit or intensive livestock building). A recent study in Denmark, for example (Bager et al 1999a) has shown that glycopeptide resistance has declined more rapidly in broiler production (over 20 generations) where systems are 'all in, all out' with thorough disinfection and no contact between batches, than in pig production where the production systems are continuous.

4.3 Co-selection (multiple-drug resistance)

Another phenomenon which may impede the renewal of antibiotic sensitivity is co-selection. Two or more resistance genes relating to different antibiotics can become linked, so that if a bacteria has one of the genes it will also have the others. Resistant bacteria can then be selected by either antibiotic. This phenomenon has recently been suggested as an additional explanation for the persistence of glycopeptide-resistant enterococci (GRE) in Danish pigs, despite a ban on the use of the growth promoter avoparcin in Denmark in 1995. Therapeutic antibiotics such as penicillin, tetracycline and tylosin, which are still widely used in pig production, appear to be selecting for GRE (Bager et al 1999a).

The same study also shows how replacing avoparcin with the growth promoter avilamycin may maintain selection for GRE. As the researchers state:

For broilers it is apparent that for the antimicrobials shown [10 different antibiotics] there is no preferential selection of GRE, except by the growth promoter avilamycin

(Bager et al 1999a).

Samples taken from broilers showed that in 1996, 71% of GSE (glycopeptide-sensitive enterococci) but 86% of GRE were also resistant to avilamycin. In 1997 the figures were 59% and 89% respectively. This suggests an urgent need for further research.

5 REGULATION OF ANTIBIOTIC USE ON FARMS

Young (House of Lords 1998a pp. 500-1) noted that at least ten different government departments, executive agencies and other organisations have a statutory role in regulating the use of antibiotics on UK farms, and argued that there is inadequate coordination of their work, particularly in relation to antibiotic resistance. While there are regulatory issues of concern relating to each of these areas, this section principally considers the role of government (and parliament) and that of the veterinary profession.

5.1 Government and Parliament

Ultimately, responsibility for the regulation of antibiotics in the UK rests with parliament. There is nevertheless an increasingly European dimension, with responsibility for antibiotic growth promoters recently passing to the EU Commission (but with the VPC and VMD still responsible for advising ministers on the UK position in negotiations) and the harmonisation of community veterinary medicines legislation proceeding fitfully. The process of 'recasting' community veterinary legislation, however, which had reached a fairly advanced stage (EC 1996) was abandoned in 1997 (MAVIS 1997) - it would appear because differences of approach between member states were too great to resolve.

Parliament was clearly guilty of a serious error of judgement when it first allowed the use of antibiotics for growth promotion in 1953, but MPs may well have felt they had acted to correct this when they incorporated the broad principles drawn up by Swann into the 1971 Medicines Act. The industry campaign against the Swann report, however (see 1.4.3), created a widespread impression among farmers - well represented among MPs at the time (Dalyell 1970) - and others, that Swann had been unnecessarily cautious. This inevitably helped make it possible for governments to ignore some of the committee's more far-reaching recommendations, such as the need:

- for a single committee to oversee all antibiotic use,
- for legislation requiring returns on antibiotic usage
- for routine monitoring for antibiotic resistance
- to prevent the advertising of prescription only medicines direct to farmers

It may also have helped create the political climate in which a number of subtle backtrackings from initially agreed Swann recommendations also became possible. Among these:

- the relicensing of tylosin for growth promotion (Mackinnon 1981)
- the licensing of avoparcin as a growth promoter for adult beef and dairy cattle (Mounsey 1995, Browning 1997)
- the licensing of virginiamycin as a growth promoter in adult beef cattle and heifers destined for breeding (Mounsey 1995), which seems likely to have contributed to the resistance problems faced today

A great deal has changed however over the last thirty years. With the exceptions of a debate in the House of Lords to consider the Select Committee's report (Hansard 1998) and a recent ten minute rule bill (Hansard 1999) we have found no evidence that Parliament has discussed the agricultural use of antibiotics in any significant way over the last three decades.

5.1.1 Regulation during the 1980s

Changes made during the 1980s have also had a major impact on the development of the resistance problem. Some idea of the situation prevailing in the early 1980s can be gauged from comments made by Sir James Howie:

There are advisers who advocate a free-for-all in the use of antimicrobials; and the popularity of such a reckless policy can easily be understood, although not accepted

(Howie 1981).

While there was in fact no open policy of free-for-all, it is clear that deregulation and free market economics were popular concepts and that government did not take action to restrict the escalating use of antibiotics for growth promotion or the increasingly routine prophylactic use of important therapeutic antibiotics. This was despite warnings from a number of independent microbiologists (such as Professor Linton) and a further serious outbreak of multi-resistant salmonella food poisoning which resulted in loss of life. Free access to antibiotics helped to make possible the continuing intensification of livestock production in line with government and Common Agricultural Policy at the time. As such, it is arguable that the sacking of the Joint Committee on Antimicrobial Substances (see 1.4.5) was necessary within this context since an analysis of the available evidence (Howie 1981, Walton 1981 a, b, British Medical Journal 1981) would suggest that had the members of that committee been given a chance to review the safety of the growth promoting antibiotics they would have given them a hard time. It has even been suggested (Erlichman 1998) that Professor Richard Lacey's appointment to the VPC was politically motivated and accounted for by his known support for the growth promoters at that time, though it has to be said that this was 'balanced' by Professor Alan Linton, who was known to be far more cautious (see 1.4.5).

5.1.2 Near market research

Another change during the 1980s also had, and continues to have, a profound effect. The move to so called 'near market' research, whereby industry was deemed responsible for all research relating to its products, brought savings for the Treasury. However, it led to a significant scaling down in epidemiological research in the UK, something which Swann had wanted to see increased. Academics and researchers found that traditional government funding for key areas of research ran dry and work could only be sustained if industry was prepared to pick up the bill. Dr Paul Barrow, head of the salmonella group at the Institute for Animal Health at Compton says, for example, that research examining whether the use of antibiotics for growth promotion led to increased levels of salmonella infection in poultry effectively came to a halt in the UK in the mid-1980s because it was deemed 'near market' (Barrow 1998) and the drug companies were hardly likely to fund work which might eventually undermine sales of their products.

5.1.3 Independence of advisory committees

Many universities and research institutes have come to rely heavily on industry funding. Quite how much this has influenced the choice and design of studies remains unclear, but it is apparent that a very high proportion of those with expert knowledge in these areas, and therefore those most suited to serve on government advisory committees are, in one way or another, now dependent for either their own research or that of their faculties or institutes, on the largesse of the very companies they are supposed to be regulating and whose products some of them have to assess.

5.1.4 Veterinary Medicines Directorate (VMD)

The VMD was established from an earlier MAFF department as an executive agency responsible for its own funding in 1990, but had been moving in that direction since at least 1986. William Waldegrave, the then Minister of Agriculture, stressed its considerable progress in demonstrating 'significant efficiency gains' (Waldegrave 1990). What was sacrificed to make those savings, however, is only now becoming apparent. Government pays the VMD for work it commissions, such as statutory antibiotic

residue monitoring and advice, but for everything else the VMD must recover its full costs from the charges it levies. Much of that income is derived from the licensing of veterinary medicines and as such the pharmaceutical companies, which apply to the VMD for authorisations, are effectively now its principal paymasters. Increasing European competition for the 'business' of licensing veterinary medicines means that the very survival of the VMD, at least in its present form, is dependent on it maintaining a good relationship with the drug industry. Companies now have the option of getting products licensed in other EU member states and then approved throughout the EU under simplified procedures. This point was used by the government to justify its decision not to accept Professor Phillip James's recommendation in the green paper on the Food Standards Agency, that responsibility for evaluating the safety of veterinary medicines should pass from MAFF to the Food Standards Agency. In the words of the White Paper:

It was suggested that those wanting access to UK markets would take alternative routes, either seeking authorisation from VMD's competitors overseas and applying for authorisation here under "mutual recognition" arrangements, or seeking authorisation from the European Agency for the Evaluation of Medicinal products for a licence valid in all Member States

(A Force for Change 1998).

With such tight budgetary constraints it is perhaps not surprising that the VMD has only concentrated on those areas for which either government or industry are paying it. The long-debated issue of antibiotic resistance, for example, has not been looked into because it was not funded and there was always concern that interest in it might put off customers.

Most VMD staff (fortunately not all) appear to have come to view things from the industry's perspective. During the many telephone calls we have made to the VMD during the preparation of this report it was striking that on a few occasions, when staff mistakenly assumed we were from within the pharmaceutical industry, that they either 'gave away' or feigned a total empathy with the industry's opposition to the ban on the antibiotic growth promoters. It should be stressed however that we do not see this as a criticism of VMD staff, rather an unfortunate facet of the situation in which they have been placed, when two of their primary responsibilities are to 'enhance confidence in licensed veterinary medicines and *encourage their use* by increasing public knowledge and understanding' (VMD 1990) [our emphasis] and 'assess customer satisfaction and identify customer needs through surveys' (VMD 1996).

5.1.5 Veterinary Products Committee (VPC)

The desire to play down the significance of antibiotic resistance is also reflected in the Veterinary Products Committee (VPC), an independent committee which provides advice to ministers and for which the VMD provides the secretariat. The shortened minutes of VPC meetings which are made public clearly show that the VPC took no action when presented with scientific evidence from Finland that tylosin was implicated in the development of erythromycin-resistant infections in people (Ministry of Agriculture and Forestry Finland 1997, VPC News Releases 15 May 1997 and 18 December 1997). British representatives on an EU committee in late 1996 also strongly opposed the introduction of the avoparcin ban on the advice of the VPC (VPC 1996 and three other sources). And three years after the publication of widely publicised British research implicating avoparcin in the development of vancomycin-resistant enterococci in hospitals, Professor Aitken, chairman of the VPC, in evidence to the House of Commons Agriculture Committee, amazingly told that committee in October 1997,

There is no scientific evidence on whether the

development of resistance to antibiotics in animals is important to man

(Aitken 1997).

More recently Professor Aitken also claimed that antibiotic resistance posed no greater threat than antibiotic residues (Aitken 1999).

The VPC also licensed the use of the fluoroquinolone antibiotic enrofloxacin in 1993, despite strong evidence from the Netherlands that such use led rapidly to resistance in enrofloxacin used in human medicine. Taken together these examples appear to support the concerns of Sir James Howie and others about the disbanding of the VPC's advisory committee on antibiotic resistance (the JCAMS) in 1981. It is also of note that MAFF, somewhat embarrassingly, had to organise a 'beginners' guide to antibiotic resistance, seminar at the Royal Pharmaceutical Society of Great Britain for the benefit of some members of the VPC on 18 June 1998.

5.1.6 The government's position today

The British government has now acknowledged that 'antimicrobial resistance is a major public health threat' and also stated that it is 'determined to play a leading part in tackling the problem' (Government Response to the House of Lords, 1998). The reality, however, is that in relation to resistance arising in farm animals, far from playing a 'leading role' within the EU, Britain is at least two years behind countries such as Denmark and more than a decade behind Sweden and is doing nothing centrally to help producers find and adopt production methods with lower antibiotic requirements.

In an important move, the British government has now decided to establish a Multi-disciplinary Expert Group on antimicrobial resistance, thirty years after it was first called for by the Swann Committee, and has already set up an interdepartmental Steering Group to 'develop, co-ordinate and monitor the Government's strategy on antimicrobial resistance' (Government Response to the House of Lords, 1998). In practical terms, however, there is little sign of urgency and ministers and civil servants appear to be proceeding as slowly as possible and doing as little as they can get away with in addressing the root causes of the agricultural aspect of the problem. The British government also appears to be struggling to develop a clear and forward-looking approach and we would suggest this is because in the UK we have few, if any, research establishments which have studied less intensive livestock production methods or researched drug-free preventative medicine. We have also lost the Agricultural Development and Advisory Service (ADAS) which could have provided practical advice to producers on how to manage without routine antibiotics, just as it previously helped them to intensify.

5.1.7 Monitoring

Accurate up-to-date information on antibiotic usage and resistance in farm animal pathogens is essential if we are to prevent the problem of antibiotic resistance getting worse. This was a key recommendation of the Swann Committee which was never implemented. In Denmark such information has been established and collated in a comprehensive way since 1995 and is published each year (e.g. DANMAP 1997, 1998). In the UK, the VMD first wrote on 30 June this year to distributors of antimicrobial products asking them if they would 'kindly compile 1998 sales figures' (Gray 1999). There is no statutory requirement for such information to be disclosed and therefore no threat of prosecution for incomplete or inaccurate returns.

While salmonella resistance in farm animals is monitored in the UK, no similar data have yet been collected on enterococci.

5.1.8 World Trade

We import significant quantities of poultry

(e.g. about 7-14,000 tonnes from Thailand and 17,000 tonnes from South America) each year. In addition, US 'hormone-free' beef, only recently suspended after residues of synthetic hormones were discovered, can still be produced with growth promoters such as virginiamycin. As a result we have not yet prevented public health consequences arising from the use of now banned AGPs.

5.2 The Veterinary Profession

A detailed consideration of the veterinary profession's role in relation to the antibiotic resistance problem is outside the scope of this report. Nevertheless, in view of the pivotal role played by veterinary surgeons it is necessary to make some points and suggestions as to where solutions may lie.

In his report on antibiotic resistance (Joint Committee 1969) Professor Swann placed his trust in the veterinary profession saying 'We are confident that the veterinary profession, will rise to these responsibilities.' Swann was referring to the veterinary surgeon's right to prescribe therapeutic antibiotics and the responsibilities that go with this. While his committee's report pointed out that vets had made mistakes and significantly contributed to the problem of antibiotic resistance in the past, he felt it was impractical and unnecessary to place restrictions on the circumstances under which they could prescribe antibiotics. Prescribing antibiotics has often been described as both
a science and an art and it is of note that a wide range of factors must be taken into consideration before a vet applies the science and prescribes for individual animals or groups.

Linton (1977) claimed that, while antibiotic use fell immediately post-Swann it soon started to rise again. As this report details, much of this resulted from the prescription of antibiotics for growth promotion and their excessive routine prophylactic use on a herd or flock basis. In the light of this, it has to be concluded that the profession as a whole has not lived up to the high expectations placed on it by Swann.

Evidence presented in sections 1& 3 of this report makes it clear that the antibiotic resistance problem owes a good deal to the way in which veterinary medicines have been prescribed and used over several decades. Blame, however, does not rest solely with the profession, since it has merely been one part of an alliance which has also involved MAFF, with its promotion of specialisation and intensive livestock production, agribusinessmen bent on building empires on the exploitation of farm animals and drug companies anxious to sell as much of their products as possible.

There is a compelling need today to reduce the overall use of antibiotics used on farms, perhaps by as much as 50%, but this needs to be done in a way which will not prevent vets exercising their professional judgement, even where, on occasions, that leads to an unusual choice of drugs. There are, however, a number of factors which must to be considered:

- the practicalities of prescribing for farm animals mean that it is not always possible to identify disease precisely before antibiotics are administered and therefore broad-spectrum drugs are chosen more often than is desirable, and the inappropriate selection of antibiotics occurs from time to time
- vets derive about 70% of their income from dispensing antibiotics which they themselves prescribe. Vets rarely charge farmers for advice, but if antibiotics are not prescribed at the end of a telephone consultation or visit the vets derives little or no income
- farmers are under no requirement to seek or accept preventative medicine advice from a vet, but vets have a responsibility to prescribe appropriate

medication for ill animals

- vets faced with ill animals want to do their best for them. As such there is a strong temptation to prescribe antibiotics in order to ensure there is some improvement, even when it is known that good stockmanship or careful nursing could bring full recovery. Where a possibility of treatment failure with older drugs exists, vets can be tempted to use modern drugs like the fluoroquinolones just to be on the safe side

While almost all vets take their responsibilities very seriously, two situations probably contribute to overuse more than any others:

- a very small number of vets, some of whom may be highly commercial in their approach, in financial difficulties or perhaps employed or influenced by the industry, have the ability and may be tempted to prescribe and dispense a larger quantity of antibiotics than is strictly necessary

- a proportion of vets may behave in a responsible manner, yet nevertheless prescribe antibiotics inappropriately or unnecessarily, either because they are not fully aware of the potential resistance problems they may create, or because they have developed poor prescribing practice over the years and have not attended the BVA's refresher courses

5.2.1 Preventative Medicine

From 1971 until 1975 Professor Swann also chaired a committee which inquired into the veterinary profession. Principal among the committee's 62 recommendations was that

Active steps should be taken by the Agricultural Departments in the UK to promote the further development of preventative medicine on the farm.

(Veterinary Record ed. 1975).

At the time the British Veterinary Association (BVA) already ran a successful joint 'Exercise' with ADAS which provided top quality management, husbandry and preventative medicine advice on a fee-paying basis to a small number of progressive farmers. Swann calculated that the benefits to the industry of extending this scheme more widely would run into 'tens of millions of pounds annually'. He also, no doubt, had in mind that such action would lead to an overall reduction in the use of antibiotics, something he clearly felt to be necessary.

The problem was that the farmers most in need of such advice were the ones least likely to be prepared to pay for it. He therefore recommended a state-financed scheme starting modestly, but rising to an annual cost of about £8m by 1990 (not allowing for inflation). Somerset vet Roger Eddy, however, was among those who knocked this idea on the head. 'The BVA', he wrote, 'must not try to persuade the Government to initiate a free preventative medicine scheme. Farmers are more inclined to implement advice they pay for than that which they receive free' (Eddy 1975).

6 ANALYSIS AND RECOMMENDATIONS

6.1 Antibiotic Growth Promoters (AGPs)

Despite action already taken by the European Commission in banning avoparcin in 1997 and six other AGPs this year, the use of antibiotic growth promoters remains a serious concern because:

- the use of those still licensed is increasing in the UK
- the suspension on the banned AGPs will be reviewed next year and the pharmaceutical companies will fight hard to get their products reinstated, because they do not want the EU ban to lead to a worldwide ban
- large amounts of poultry and some pork are still imported from countries where banned AGPS are still used
- the prophylactic use of tylosin may be responsible for the development of erythromycin-resistant campylobacter (Taylor 1999) and the prophylactic use of lincomycin, which has known growth promoting properties, appears to be increasing (Lodge 1999)

At the heart of the problem is the fact that in addition to increasing growth rates and the efficiency of feed conversion, the use of the antibiotics licensed purely for growth promotion is a cheap and reasonably effective means of controlling some of the major diseases of livestock intensification. They fulfil this function because they are just as much antibiotics as those used in therapy and not the totally benign substances which their recent European reclassification as 'zootechnical feed additives' might suggest.

The AGPs are cheap because they are not regulated by the 1968 Medicines Act and have therefore undergone a less rigorous and cheaper assessment process than therapeutic antibiotics. They are not prescribed by veterinary surgeons and therefore avoid the normal one-third mark up on veterinary drugs. In addition most of them have been available for many years and their manufacturers, having long since recovered their development costs, can now afford to retail them at relatively low prices. It can cost, for example, as little as a third of penny to keep a broiler chicken on zinc bacitracin throughout its 42-day life.

The use of growth promoting antibiotics for disease control in this way is illegal, as the EU Scientific Steering Committee recently made clear (EU 1999). However, it is effectively unpoliceable, while we have no independent scrutiny of farm use analysed against purchases and production methods.

The routine use of antibiotics in this way is also part of the vicious circle begun in 1953 when growth promoting use first started (Harvey and Mason 1998). This makes intensive livestock production possible, but also increases the demand for other antibiotics at the same time. It can usually avoid the welfare problems associated with widespread mortality from infectious diseases, but keeps most animals alive only to endure an unsatisfying, short, often painful and unnatural life.

Just as the AGPs can have a prophylactic effect in controlling disease, so several widely prescribed therapeutic antibiotics conversely also have a growth promoting effect if used at lower doses than those prescribed for disease treatment or control. This provides a major loophole to allow their continuing use for growth promotion, since medicated feed simply needs to be mixed with non-medicated feed to achieve growth promoting concentrations. While industry sources to whom we have spoken have all played down the significance of this, a number of them have admitted off the record that pressure for this would inevitably increase after the 1 July bans.

The prophylactic use of the tetracyclines (which have a significant growth promoting effect) is no longer recommended in the UK, however, globally an estimated 71% of the annual tetracycline production (2.73 million Kg) is used at low levels to promote growth (Johnson and Adams 1992). Pfizer, the company which produces and markets oxytetracyline in the UK, also promotes and markets it for growth promotion elsewhere in the world. Since tetracycline use in livestock production has increased by 1600% in the last 30 years in the UK (Harvey and Mason 1998) while livestock numbers have increased by less than half that, there must be strong suspicions, that despite changes in recommendations and a tightening of prescribing legislation last year, much of the 350 tonnes of tetracycline prescribed by vets in the UK each year is still effectively used for growth promotion in pig and poultry production.

6.2 Recommendations

6.2.1 Avoparcin, virginiamycin, tylosin phosphate and spiramycin

Recommendation - the ban on the use of avorparcin, virginiamycin, tylosin phosphate and spiramycin as AGPs should not be revoked and ways must be found to prevent the importation of livestock products from countries where any of these antibiotics continue to be used.

6.2.2 Avilamycin

Until December last year avilamycin was little used in the UK. For many years it had not been a popular product with pig or poultry producers because it was more expensive and less effective both in promoting growth and controlling disease than its main competitors avoparcin, virginiamycin, zinc bacitracin and tylosin phosphate. After the ban on avoparcin in 1997, Elanco Animal Health (part of Eli Lilly) the manufacturers of Maxus G200, the AGP which contains avilamycin, spotted a marketing opportunity for their product and its use appears to have started to rise from the beginning of 1998.

A letter published in *Veterinary Practice* in February this year (Grace 1999) and written in fact on 17 December 1998, just two days after EU Agriculture ministers agreed to ban four rival AGPs, makes it clear that the company intended to exploit the situation and promote the product aggressively. As the letter says,

Elanco offer Maxus (avilamycin) to both pig and poultry producers and will be embarking on a targeted promotional campaign. It is already established as product of choice in broiler and turkey production – and in young pig diets . . . They [Elanco] will be actively communicating this data to farmers, vets, the feed industry, meat producers and retailers over the coming months.

In March an advertisement for Maxus appeared in the widely read *Farmers Guardian* promoting its benefits, but making no mention that it contains an antibiotic. Reliable sources have indicated that avilamycin is now included in the feed of many pigs and practically every single broiler chicken reared conventionally in the UK.

The case for and against avilamycin

Both Denmark and Holland, in addition to Sweden and Finland, have already banned the use of avilamycin. In the UK the Soil Association issued press releases on 28 November, 2 December, and 10 December calling for avilamycin to be included in the ban with other AGPs and has subsequently repeated this call in a letter to the Minister of Health, Frank Dobson (Young 1999) and on other occasions. In reply, Elanco Animal Health has stated that the Soil Association's claims are 'alarmist' and that 'avilamycin has been reviewed by the EU Commission as recently as December 1998 and was allowed to remain on the market'. A recent report from the EU's Scientific Steering Committee (EU 1999) fudged the issue on avilamycin, and while

recommending in general that 'regarding the use of antimicrobials as growth promoting agents, the use of agents from classes which are or may be used in human or veterinary medicines . . . should be phased out and ultimately abolished' (EU 1999), failed to suggest any timescale for its withdrawal. This is believed to have reflected a difference of opinion between Swedish, Danish and Dutch representatives who called for an immediate ban and others, including the British representative, who would prefer that its use should continue until such time as everninomycin, the medical drug under development to which avilamycin is cross-resistant, is actually approved for human use (Johnston 1999, Van den Bogaard 1999).

While the development of a genuinely new class of antibiotics is still expected to be more than a decade away, everninomycin is not the only new drug under development for the treatment of otherwise resistant enterococcal, staphylococcal and streptococcal infections. Synercid which is similar to virginiamycin is just about to be licensed and will therefore become available to hospital doctors before Ziracin. However, Synercid is only effective against one of the two main resistant strains of enterococci. Other products include gram positive fluoroquinolones such as clinafloxacin, ketolides and linezolid (Jones et al 1999). Linezolid is already in use to treat resistant meningitis and is likely to be used against other superbugs as well. Eli Lilly, the parent company of Elanco Animal Health also has a product in the early stages of development (Elanco 1999C) which is believed to be able to 'trick' vancomycin resistant enterococci into becoming sensitive again (Westwell 1999).

However, everninomycin is considered to be perhaps the most promising of all these, because it is active against a wide range of these hospital superbugs, has very good absorption and low toxicity. Professor Richard Wise of the Birmingham City Hospital told us, 'Avilamycin is far to good an antibiotic to be fed to chickens'.

However, Elanco points out that Schering-Plough carried out an extensive study of 'thousands of recent isolates from around the world and reported no evidence of preexisting resistance'. A major EU-wide study into resistance into enterococci has also been started and the industry wants to see the results of this before accepting there is a potential problem with avilamycin (Johnston 1999).

Poultry producers argue that they, in particular, need avilamycin to control necrotic enteritis and as a growth promoter to help them remain competitive with poultry imports from non-EU countries still using AGPs no longer available in the EU.

However, recent evidence from Denmark (see section 4) shows that avilamycin may be co-selecting for glycopeptide resistance and therefore maintaining the flow of VRE from animals to humans.

Conclusion

While there is so far insufficient evidence to be certain that the continuing use of avilamycin as an AGP will compromise the efficacy of everninomycin, all the available evidence suggests that this is highly likely. The fact that preexisting resistance in human enterococci has not yet been detected should therefore be seen as a golden opportunity to introduce a highly effective antibiotic into one of the most worrying areas of human medicine, and not as an excuse to continue using avilamycin until such resistance shows up. Experience with other antibiotics would suggest that if we wait until then it is likely to be too late, and that once avilamycin resistance has become established in animals and people it may persist for years or even decades after its use is stopped. For this reason it appears to us to be most gravely irresponsible of the EU Commission and the British government to have allowed the situation to arise in Britain at least where

avilamycin use has increased dramatically in recent months, just at the time when its analogue is being prepared for use in life-threatening conditions.

Recommendation - avilamycin should be banned immediately in Britain. We believe this would trigger a similar ban in all other EU countries still using avilamycin. In view of the extreme potential seriousness of the situation we believe that member states should consider compensating farmers, feed compounders and others for the destruction of existing stocks and that these should not, as is the usual process, be allowed to be used up by the industry during a period of grace.

6.2.3 Zinc Bacitracin

The ban on zinc bacitracin as an AGP has been justified by the EU Commission on the basis that some use of it has been made for controlling VRE, because chickens receiving bacitracin carry a higher proportion of resistant enterococci and because 'these resistances could be transferred from animals to humans and reduce the effectiveness of zinc bacitracin used as a human medicinal product' (EU 1998).

The ban was agreed by MAFF and the Department of Health on the recommendation of the Veterinary Products Committee, but not the Advisory Committee on the Microbial Safety of Food. (Government response to House of Lords 1998).

Alpharma (the giant US/Norwegian Corporation which makes bacitracin) has been fighting to get it reinstated within Europe, though in a press release clearly aimed at its shareholders it was at pains to point out that sales of bacitracin within Europe accounted for only a tiny fraction of the company's annual turnover (Alpharma 1998).

The company has also made it known that if the EU ban were to lead to a world wide ban on bacitracin, production would cease, since the use in human medicine is so tiny (Renney 1999).

The recent medical use of zinc bacitracin has been to eradicate VRE as a source of infection (O'Donovan et al 1994); it cannot be used systemically to treat blood poisoning caused by VRE. However, bacitracin may be the most effective antibiotic suitable for oral use (compare Linden and Millar 1999 with Chia 1995) and as such reducing the prevalence of bacitracin-resistant enterococci could prove important. Its wider prophylactic use in long-term care facilities as also mentioned by Chia (1995), would appear to be a highly dubious practice since studies showed that up to 25% of patients relapsed within three weeks, and eradicating enterococci is likely to reduce natural immunity and leave a temporary ecological niche for recolonisation with other organisms. Bacitracin may have a role in eradicating VRE prior to intestinal surgery or *in extremis* be applied directly by surgeons to bones and joints infected with otherwise resistant strains of *Staph. aureus*, but no recent references to this could be found in the literature.

Recommendation - the ban on zinc bacitracin is justified by the scientific evidence, however its use presents a smaller and less immediate threat than the continuing use of avilamycin. In order to facilitate an immediate cessation in the use of avilamycin, the British government should consider applying to the EU Commission for a limited (12 months) exemption for the use of zinc bacitracin in poultry production to be reallowed for the control of necrotic enteritis on farms where the disease cannot be controlled immediately by management means. Bacitracin should not, however, be relicensed as a therapeutic antibiotic for veterinary use since its routine use poses a potential threat to human health and its only proven application in agriculture is routine low-level inclusion in feed for prolonged periods.

6.2.4 Bambermycin

Bambermycin is not related to any antibiotics currently in medical usage. However, it has potential to be developed as a therapeutic agent since it is effective against a range of gram-positive bacteria and has low toxicity. Professor Mackenzie Johnston, from the Royal College of Veterinary Surgeons and a member of the EU Working Party on Antibiotic Resistance told us that it is essential to retain bambermycin as an AGP in order for British producers to remain competitive.

Recommendation - In view of its relatively low past usage, the lack of genuinely new classes of antibiotics, its low toxicity and potential as a therapeutic agent, broader considerations must apply and it should be banned as an AGP and phased out over the next 12 months.

6.2.5 Olaquindox and carbadox

These antibiotics are being banned for reasons of toxicity rather than resistance and are therefore not the subject of this report.

6.2.6 Monensin sodium and salinomycin sodium

There is evidence to suggest that the use of these antibacterial drugs presents a threat to human health. However, this does not relate to the issue of antibiotic resistance and is therefore not the subject of this report.

6.2.7 Therapeutic antibiotics

Therapeutic antibiotics are essential for the treatment of disease in farm animals, but it is clear that we must find ways to reduce their overall use in agriculture. We believe that several elements are needed to achieve this:

6.2.8 Further bans or restrictions

Recommendation - Antibiotics cross-resistant with any drug normally reserved for hospital use in saving life should be banned from mass medication and only permitted in individual animals if no other drug is likely to be effective.

Recommendation - Fluoroquinolones should no longer be permitted in water (or feed) for mass medication. Individual animals of all species could still be treated in certain situations. Vets should record their reasons for selecting them in the farm medicines book. It is also important that fluoroquinolones and also third generation cephalosporins - used by doctors when fluoroquinolone resistance arises (Threlfall et al 1999) - should not be permitted against enteric infections in animals, because the development of food poisoning bacteria resistant to third. generation cephalosporins would compromise the last currently effective group of antibiotics.

Agricultural policy and management change

Assistance and encouragement to intensive producers to adopt management changes is urgently needed and we should look to Denmark and learn from its experience in recent years. British pig and poultry producers were very much encouraged to adopt intensive systems of production by UK government and the CAP. The adoption of better-designed, less intensive systems is now critical to reduce antibiotic use, and both practical and advisory help must be given.

We recommend that government should adopt an active policy of researching, developing and promoting less intensive methods of livestock production and with other member states should further reform the Common Agricultural Policy to make such methods more attractive.

School of Preventative Medicine

This process could be further assisted by finding ways to provide better advice to farmers (both conventional and organic), veterinary surgeons and others on drug-free preventative

medicine. In the current climate we see little point in advocating the nationally-funded scheme suggested by Professor Swann in 1975, however, we believe that the establishment of an independently run School of Drug-free Preventative Medicine attached to an established veterinary or agricultural college which would research, collate and disseminate accurate information and reliable advice could make a major contribution to reducing over-dependence on antibiotics. We suggest that such a school could attract matching funding from private or charitable sources and that it should make information available free of charge via the internet, and at cost price by other means. We would also suggest that it build a team of skilled advisers prepared to undertake consultancy work on a paid basis. Our expectation is that such a team would be largely made up of veterinary surgeons. We therefore recommend that government should make a grant for the establishment of a School of Drug-free Preventative Medicine.

6.3 Veterinary Surgeons

In some EU member states, such as Germany, veterinary surgeons have for many years only been permitted to prescribe antibiotics and not to dispense them. In Denmark in 1995, legislation was introduced which took away the veterinary surgeon's right to dispense veterinary medicines, and it would appear that this has already brought about a fall in real terms in the the use of therapeutic antibiotics during a period when the growth promoting antibiotics have already been banned (DANMAP 97, 98).

Such an option should be considered for the UK. However, while removing a veterinary surgeon's right to dispense antibiotics (except small amounts at minimal mark up as is still allowed in Denmark) would remove the commercial imperative for over-prescribing it would not resolve the problem of poor prescribing by some vets. Further, if such a change were introduced rapidly it would inevitably put many small practices out of business and farmers would lose the vitally important 24-hour cover which these provide for ill animals.

While we would like to see veterinary surgeons finding ways to charge more for advice (such as telephone consultations by premium rate telephone calls) and a corresponding reduction in the proportion of their income which comes from drug sales, we believe that a better solution might be the introduction of independent scrutiny of prescribing practice.

6.3.1 Independent scrutiny

Farmers and vets would clearly find it difficult to deal with further regulation and paperwork, but we believe there may be a way in which this could be achieved with the minimum of inconvenience to both. Farmers are already required by law to complete records for every animal treated with veterinary medicines. These records may be examined by veterinary surgeons, state veterinary officers and trading standards officers. However, such examination does no more than establish that the records have been completed. There is no cross-checking against purchases of drug and no consideration of whether drugs are regularly being prescribed for conditions which could be controlled by management means. The use of medicated feed is policed seperately, by the Royal Pharmaceutical Society of Great Britain.

We believe that meaningful inspections could be established at reasonable costs if one 'agency' was given responsibility for all farm use of antibiotics. Inspections should cross-check use against purchases and also assess this in the light of the production system. Inspection reports should be analysed by trained staff. Irregularities or higher than expected use should trigger an advisory visit, with a requirement that basic advice be followed. There would be no additional paperwork for vets or farmers. The veterinary surgeon should

be identified in the record book for each prescription and this would allow unintrusive monitoring of prescribing practice. This should make vets think just a little harder before prescribing and could resolve many problems quickly. We estimate that inspectors could visit up to three farms daily (depending on size) and that the overall annual cost would be in the range £100-£500 per farm. This could be partly funded by the axing of the existing overlapping inspection systems.

6.4 World Trade

Evidence to support the ban on antibiotic growth promoters is stronger than that for hormones. Britain should therefore push for the introduction of an immediate unilateral ban on any livestock products produced with drugs banned in the EU. This would be of immediate benefit to hard-pressed UK pig and poultry producers.

6.5 Advertising

There can be no justification for advertising prescription only medicines (POM) direct to farmers. This is designed to persuade farmers to put inappropriate pressure on vets to select drugs against their professional judgement. We would, however, like to see more technical information about individual antibiotics made available to farmers by veterinary surgeons. We therefore **recommend** that advertising of any POM veterinary medicines, except in the veterinary press, should be illegal.

6.6 VMD

We believe that the licensing and monitoring of veterinary medicines should be carried out soberly in the interests of the public good and not be seen as a commercial operation. We do not believe the VMD should be trying to 'win' custom. We therefore **recommend** that the requirement for 'full cost recovery' be removed from the VMD and that it should be encouraged to view issues as much from the consumers' view point as from industry's.

6.7 Salmonella

Outbreaks of serious enteric salmonella in cattle are usually treated with antibiotics in the UK. We believe this to be misguided since it is well known that while this deals with the symptoms of disease, many animals become carriers and continue to spread infection. We **recommend,** therefore, that *S. typhimurium* DT104 in cattle should become a notifiable disease and that unless there are exceptional circumstances a slaughter and compensation policy should be introduced. This would be more cost-effective and safer in the long run than treating infected animals with antibiotics. Consideration should also be given to extending this to other strains and other species of animal.

6.8 Cost implications

It has been impossible to obtain detailed information on the costs associated with antibiotic resistance for this report. However, even minor resistance problems require more expensive drugs. Methicillin, for example, can be ten times more expensive than penicillin and vancomycin ten times more expensive still. The cost in terms of suffering cannot be quantified and the financial cost to the health service of additional isolation facilities and disruption are clearly substantial. Scientists from the ACMSF's Working Group on Antimicrobial Resistance told the House of Lords' select committee on Science and Technology that if vancomycin resistance develops in MRSA that it could take a substantial part of the National Health budget to control. While the vancomycin resistance which has so far appeared in MRSA is not related to the agricultural use of antibiotics it cannot be wise to be including an antibiotic (avilamycin) in the feed of all broiler chickens when research suggests it is also selecting for vancomycin resistance in the enterococci.

APPENDIX I - SUMMARY AND RECOMMENDATIONS FROM THE FIRST REPORT IN THIS SERIES, CURRENT USAGE

This report is part of the Soil Association's continuing campaign against the excessive use of antibiotics in agriculture. It aims to provide an overview of the scale and nature of antibiotic usage on UK farms in order to inform the debate on the extent to which this may be contributing to the problem of drug-resistant disease in the human population. It exposes a number of failures in the regulatory system and through the publication of the first detailed statistics for thirty years on the tonnages of antibiotics used on farms, highlights the extent to which antibiotics use in intensive livestock production has continued to rise despite all previous attempts to curtail it.

Key findings of the report are:

- tetracycline use has increased by 1500% in 30 years, when it was supposed to fall
- penicillin type drug use has increased by 600% over the same period
- comparing industry estimates with published figures from the DOH suggest that about 1225 tonnes of antibiotics are used annually in the UK in the following proportions: Farm animals 37%, Pets and horses 25%, medical use 38%
- inclusion of the ionophores, a major class of in-feed antibiotics, which the industry leaves out of its tables on a technicality, would give a considerably higher percentage figure for farm use
- the Ministry of Agriculture, Fisheries and Food does not collect data on antibiotic use on farms, despite this being a recommendation of several independent committees
- as many as 10,000 farmers in the UK may be illegally top dressing livestock feed with antibiotics
- there is a major disagreement between the British Veterinary Association and the pharmaceutical industry over the advertising of Prescription Only Medicines direct to farmers
- virtually all growing pigs and broiler chickens receive antibiotics in their feed throughout their lives up to and including the day of slaughter
- most intensively-reared cattle are fed antibiotics routinely throughout their lives, both in replacement milk powders, compounded feed and feed blocks
- banning individual antibiotics will not stop the problem continuing to get worse. A complete change in the way in which animals are reared is required

The Soil Association's Recommendations

The Soil Association is calling for:

- a ban on all non-medical use of antibiotics in agriculture
- the prophylactic use of therapeutic antibiotics to be restricted to cases of genuine need and only made available as part of a planned disease reduction programme involving changes in housing, feeding and management practice
- coordination of all government departments, agencies and other bodies with a statutory involvement in the regulation of antibiotic use on farms to be undertaken by the proposed Food Standards Agency
- responsibility for the safety evaluation of veterinary medicines to pass to the proposed Food Standards Agency, as suggested in the Green Paper
- the establishment by government of a surveillance system for antimicrobial resistance, comparable with that for antimicrobial residues
- the central, annual collection of data on the use of antimicrobial agents on farms, in order to monitor trends in usage
- livestock products imported into the European Union to be subject to routine surveillance for bacteria carrying antibiotic resistance and subject to the same controls in relation to permitted antibiotics as those produced within the EU.
- a ban on the advertising of antibiotics directly to farmers.

The Soil Association further recommends that:

- veterinary surgeons should charge directly for advice and recoup a smaller proportion of their income from the sale of drugs.
- veterinary and agricultural colleges should place greater emphasis on the teaching of drug-free preventative medicine

Copies of this report can be obtained by email from report1@kitesnest.demon.co.uk, and will be published shortly on the Soil Association website: http:www.soilassociaton.org.

APPENDIX II - ANTIBACTERIALS AND ANTIBIOTICS LICENSED FOR USE IN FARM ANIMALS AND FISH IN THE UK

Active Ingredient	Cattle	Sheep	Pigs	Poultry	Fish	Individual therapeutic (i)/group therapeutic or prophylactic (f)/ growth promotion (g)	Used in human medicine	cross resistant with medical drugs
Amoxycillin	x	x	x	x	x	i,f	yes	-
Ampicillin	x	x	x			i,f	yes	-
Apramycin	x	x	x	x	x	i,f	no	yes
Avilamycin			x	x		g	no	yes
Bambermycin	x		x	x		g	no	no
Bacitracin Zinc*	x	x	x	x		g	yes	-
Cefoperazone	x					i	no	?
Cefquinome	x					i	no	?
Ceftiofur	x		x	x		i	no	?
Cefuroxime	x					i	no	?
Cephacetrile sodium	x					i	no	?
Cephalexin	x	x	x			i	yes	-
Cephalonim	x					i	no	?
Chlortetracycline	x		x	x		i,f	yes	-
Cloxacillin	x	x				i	yes	-
Danofloxacin mesylate	x			x		i	no	yes
Enrofloxacin	x		x	x		i,f	no	yes
Erythromycin	x			x		f	yes	-
Florfenicol	x					i	no	?
Framycetin Sulphate	x		x			i	yes	-
Lincomycin	x		x	x	x	i,f	yes	-
Marbofloxacin	x		x			f	no	yes
Monensin Sodium	x			x		g	no	no
Neomycin Sulphate	x	x	x	x		i,f	yes	-
Olaquindox*			x			g	no	?
Oxolinic acid					x	f	no	?
Oxytetracycline	x	x	x		x	f	yes	-
Phenoxymethylpenicillin			x			f	yes	-
Procaine Penicillin	x	x	x			i	yes	-
Salinomycin Sodium			x	x		g	no	no
Spectinomycin	x	x	x	x	x	i,f	yes	-
Spiramycin*	x	x	x	x		i,g	no	yes
Streptomycin Sulphate	x	x	x			i	yes	-
Sulphadimidine	x	x	x			i,f	yes	-
Sulphamethoxypyridazine	x	x				i	no	?

Active Ingredient	Cattle	Sheep	Pigs	Poultry	Fish	Individual therapeutic (i)/group therapeutic or prophylactic (f)/ growth promotion (g)	Used in human medicine	cross resis-tant with medical drugs
Tylosin	x		x	x		i,f	no	yes
Tylosin Phosphate*			x			g	no	yes
Viginiamycin*	x		x	x		g	no	yes
Ampicillin/Cloxacillin	x					i	yes	-
Amoxycillin/clavulanic acid	x					i	yes	-
Baquiloprim/sulphadimidine	x		x			i,f	related	-
Benzathine Penicillin/procaine penicillin	x	x	x			i	related	-
Benzyl Penicillin/ dihydrost reptomycin/nafcillin	x					i	related	-
Benzyl Penicillin/neomycin/ procaine penicillin	x					?	related	-
Chlortetracycline/ dihydrostrepto-mycin/neomycin sulphate	x					i	related	-
Chlortetracycline HCl/ dihydro-streptomycin	x					?	?	?
Chlortetracycline/ procaine penicillin/sulphadimidine			x			f	related	-
Dihydrostreptomycin/ nafcillin/ procaine penicillin	x					?	related	-
Dihydrostreptomycin/ neomycin/ novobiocin/ procaine penicillin	x					i	related	-
Dihydrostreptomycin/ procaine penicillin	x	x	x			i	related	-
Dihydrostreptomycin/ streptomycin	x	x	x			i	related	-
Framycetin/ dihydrostreptomycin	x					i	related	-
Framycetin/procaine penicillin	x					?	?	?
Procaine Penicillin/neomycin	x					i	related	-
Procaine Penicillin/sodium nafcillin	x					i	related	-
Procaine Penicillin/streptomycin	x		x	x		f	related	-
Trimethoprim/sulphachlorpyridazine	x	x	x	x	x	i,f	yes	-
Trimethoprim/sulphadiazine	x		x			i	related	-
Trimethoprim/sulfadoxine				x		f	related	-
Trimethoprim/sulphaquinoxaline	x	x	x			i	related	-
Trimethoprim/Sufatroxazole			x			f	related	-
Tylosin/Sulphadimidine			x			f	related	-

* Bacitracin Zinc, Spiramycin, Virginiamycin and Tylosin Phosphate were banned from use as growth promoters in the EU from 1 July 1999, and Olanquindox will be banned from use in the EU from 31 August 1999.

Note:
In the column 'used in human medicine', 'related' means that at least one of the antibiotics in the drug combination is so used. Antibiotics which are in the same family as an antibiotic used in human medicine (e.g. apramycin is in the same family as gentamicin) have not been described as 'related'. Thus, although this table shows that 24 antibiotics are not used in human medicine, many of these are in fact also closely related to antibiotics used in human medicine.

Amended from: (House of Lords 1998a, pp. 216-234)

APPENDIX III - ANTIBIOTIC-RESISTANCE AND GENETIC ENGINEERING

There is growing concern about the possible effects that some genetically modified (GM) organisms, crops and food may have on the problem of antibiotic resistance. In order to ensure that the transfer of a gene to a microorganism or a crop has occurred, a gene for antibiotic resistance is often inserted as a marker. The genes involved can carry resistance to antibiotics such as ampicillin, kanamycin, streptomycin or gentamicin. The worry is that the widespread use of these genes may result in them being transferred to bacteria pathogenic to man.

Scientists who support the growing of GM plants have claimed that:

- The resistance genes have no direct impact on the plant
- We do not know any process whereby genes could escape from plants back to bacteria
- The resistance genes are already widespread in bacteria
- Processing destroys the resistance genes

(Estruch et al 1997 cited in SMAC 1997).

Critics of genetic technology, however, claim that there is already enough evidence to suggest there is an urgent need for greater restrictions on this technology:

- Genes, including marker genes, have been found to have transferred from GM plants to soil fungi (Hoffman et al 1994) and soil bacteria (Schluter et al 1995). It is worth noting that although Schluter et al found a high frequency of transfer in the laboratory, they 'calculated' that in 'natural conditions' it would have been 3 million billion times less
- Early studies had supported the assumption that DNA is broken down into small pieces in the stomach, but using more sensitive methods, large pieces have been found in the faeces and bloodstream of mice (Schubbert et al, 1994). Recent research has shown that DNA remains intact for several minutes in the large intestine, confirming that genetically modified bacteria can transfer their antibiotic resistance genes to bacteria in the gut (MacKenzie 1999)
- Legally permitted releases of genetically modified micoorganisms can vastly exceed the minimum infective dose of some pathogens: in Denmark the legal limit is 10,000 colony forming units/ml in air or water versus a minimum infective dose of 50 bacteria for *E. coli* 0157:H7
- In September 1997, the US Environmental Protection Agency authorised a biotech company to sell 500,000 lb of genetically engineered *Rhizobium melitoti* for coating alfalfa seeds. These *Rhizobium* contain a gene conferring resistance to the antibiotics streptomycin and spectinomycin which are used to treat tuberculosis
- Microorganisms, such as *E. coli*, which are used in the process of genetic engineering are biologically 'crippled' for safety. But a number of studies have shown that these bacteria may nonetheless survive in the environment: Cremers and Groot (1991)

Genetic engineering, both for medicinal purposes and for the purpose of producing GM food, relies on the transfer of genes from one cell to another through the environment rather than by reproduction. This is called horizontal gene transfer and can in fact occur naturally between fairly closely-related bacteria.

The mobile pieces of DNA which carry genes from one cell to another are called vectors. Natural vectors include plasmids, transposons and viruses. Genetic engineers have constructed artificial vectors by joining together parts of the natural vectors, in order to be able to transfer genes between two completely unrelated species. Natural vectors would not be able to do this since they tend to be species-specific, and because even when DNA does transfer to a cell, foreign DNA is usually broken down in the cell and prevented from integrating into the genome. Artificial vectors enable man to circumvent these natural barriers so that the gene is maintained and replicated in the cell.

E. coli bacteria are also very often used in genetic engineering, for cloning genes. The genes are inserted into the *E. coli*, where they multiply, and are then transferred by the artificial vectors to the plant or animal for genetic modification (Ho et al 1998).

found strains of *E. coli* K12 on lab coats after 20 days

- Chemical inactivation of modified microorganisms may not be completely effective. This could be of concern as one company, Novo Nordisk, recycles inactivated modified microorganisms as fertilizers for crops under the trade name NovoGro

(Ho et al, 1998).

Horizontal gene transfer has now been recognised as one of the main causes of the spread of antbiotic-resistance genes. It is also known that virulence genes can spread by horizontal transfer, transforming usually benign bacteria such as *E. coli* into pathogens. The very nature of genetic engineering is to exploit horizontal gene transfer, and the vital question is: has the introduction of genetic engineering in the last 15 years caused an increase in horizontal gene transfer in the environment?

The spread of artificial vectors in the environment would be a matter for major concern since they are the constructions which facilitate horizontal gene transfer (see section 2.1). We do not yet have sufficient data to know the exact frequency of transfer of these vectors from plants to bacteria in the soil, nor do we know the full extent of releases of microorganisms, live or supposedly inactivated, which have been transformed by these highly infectious vectors. However, Ho et al (1998) have pointed to some circumstantial evidence that suggests that horizontal gene transfer is now a more common event than it was prior to the introduction of genetic engineering:

- When antibiotics were first introduced, resistance took decades before it became a serious problem, whereas now resistance to a newly-introduced antibiotic can become widespread in just a few years
- At least 30 new infectious diseases have emerged over the last twenty years (WHO Report 1996 and Lederberg 1997), suggesting that the spread of virulence genes through horizontal gene transfer has also been increasing
- Many unrelated bacterial pathogens causing diseases ranging from bubonic plague to tree blight have been found to share an entire set of genes for invading host cells; these have almost certainly spread by horizontal gene transfer

While Ho et al point out that contributory factors to the resurgence of infectious diseases and resistant bacteria include the overuse of antibiotics in medicine and agriculture, population growth and rapid urbanization, increasing travel, social changes, and a number of other factors, they nonetheless believe that there is now sufficient evidence to warrant a full public enquiry into genetic engineering and the causes of infectious diseases.

APPENDIX IV - ANTIBIOTICS USED AS CROP SPRAYS

Since the 1950s, antimicrobials have been used by some farmers as crop sprays to prevent diseases in plants. This practice is very common in the USA, particularly in fruit farming. It is also permitted in the EU and used to varying degrees, and with varying restrictions, in different member states. In the UK, antimicrobials are used on ornamental plants. Those involved include important antibiotics used in human medicine (e.g. streptomycin and oxytetracycline) and drugs that are related to those used in human medicine (e.g. kasugamycin). Other antibiotics which have in the past been licensed for crop spraying include the highly toxic chloramphenicol (EU 1999).

Although evidence that this is having any impact on human health has, until recent years, been sparse, this has primarily been due to a lack of research on the problem. What seems clear is that spraying crops with antibimicrobials increases resistance in plant pathogens. Resistance in plant pathogens to kasugamycin and streptomycin has been noted since the 1950s (Tabei and Mukoo 1955 cited in EU 1999), and more recently resistance to streptomycin and oxytetracycline has been found in orchards in the US (Chiou and Jones 1993, EU 1999). There seems to have been little research into resistance resulting from the widespread use of antibiotics in the production of ornamental plants, and Falkiner (1998) has suggested that research could be done into pot plants (commonly taken into hospitals as gifts) as a source of antibiotic resistant pathogens.

Resistance in plant pathogens is unlikely to cause a direct increase of resistance in human pathogens since these organisms have never been known to cause disease in humans. There are, however, a number of other ways by which this use of antimicrobials could still be causing resistance in bacteria infecting humans.

Firstly, there is a risk of horizontal gene transfer (see 2.1): the gene encoding resistance in the plant pathogen may be transferred either directly to human pathogens or indirectly via bacteria indigenous to animals. Gene transfer may also occur from bacteria contained in water or soil which is then ingested (EU 1999). The exchange of genes between bacteria indigenous to humans, animals and plants has been suggested as an explanation for the persistence of streptomycin resistance in clinical bacteria, despite the usage of the drug having diminished in clinical medicine and animal husbandry (Sundin and Bender 1996).

Secondly, bacteria of animal origin pathogenic to humans are often present on crops, particularly if they have been fertilised with animal manure. These pathogens may develop resistance to the antimicrobials used in crop spraying (EU 1999) and may then infect humans.

Finally, those who undertake the spraying could become colonised with resistant bacteria which might then spread to the rest of the population.

In the US, the annual use of antimicrobials, mainly streptomycin and oxytetracycline, on fruit trees is 22,000 kg. Streptomycin is also used on vegetables, tobacco and ornamentals but there is no accurate record of the amounts involved (EU 1999). In the EU there is unfortunately very little information available on total amounts used. A recent enquiry by the European Commission has shown that the total use of kasugamycin in Spain in 1997 was 1,994 kg, The same enquiry showed that usage of streptomycin in Austria in 1998 was 12kg, in Belgium in 1997 it was 755 kg and in the Netherlands in the same year it was 170 kg (EU 1999).

Due to the increasing incidence of streptomycin resistance in some bacterial crop pests US farmers are now campaigning to be allowed to use gentamycin (APUA 1999).

APPENDIX V - WIDER IMPLICATIONS FOR HUMAN HEALTH

For most consumers and most farmers until fairly recently, mention of the words antibiotics and food together would invariably bring to mind the issue of residues. When attention began to focus on antibiotic resistance in 1996/7 industry spokesmen frequently replied to questions about resistance by quoting statistics about residues. This was misleading, but it also indicated the low level of understanding of the resistance problem at that time.

Resistance and residues, however, are just two of a number of areas where the use of antibiotics has an impact on human health. A more complete list is given below:

Disadvantages

- Resistance - the development of bacteria carrying antibiotic resistance which can transfer through food or directly between animals and people
- Residues - their presence in food could potentially cause resistance
- Adverse reactions - allergic and other reactions due to residues in food or through direct contact
- Food poisoning - the encouragement of food poisoning bacteria in animal through suppression of other competitive species and strains
- Disease patterns - changes in disease patterns and transfer to other species, through selective antibiotic pressure
- New pathogenic strains - the little studied issue of the role that may have been played by farm antibiotics in the development of new livestock infections such as *E.coli* 0157 and *S. typhimurium* DT104
- Changes to the biosphere - the largely unstudied impact of antibiotics on soil and other environmental bacteria
- Cheap meat has led to increased consumption compared with fruit and vegetables and red meat has been linked to both cancer and heart disease

Benefits

- The ability to cure zoonotic diseases before they pass to people is potentially the principal benefit - however, there are very few examples where antibiotics are significant; with salmonella they may have made the problem worse

- The ability to cure disease in domesticated animals is important to those who care for them
- Better nutrition for those on low incomes, especially in the immediate post-war period
- Safer and quicker for vets and stockmen to treat animals with antibiotics for some conditions

APPENDIX VI - THE SOIL ASSOCIATION ORGANIC STANDARDS ON ANTIBIOTICS AND EARLY VIEWS OF THE ORGANIC MOVEMENT

5.7 Animal Health and Veterinary Treatments

5.701 The prevention of disease is central to the approach of organic livestock husbandry. Health in farm animals is not simply the absence of disease, but also the ability to resist infection, parasitic attack and metabolic disorders, as well as the ability to overcome injury by rapid healing.

5.702 An objective of organic agriculture is to sustain animals in good health by the adoption of effective management practices, including high standards for animal welfare, appropriate diets and good stockmanship.

5.703 The practices employed in the management of livestock must therefore be directed towards preventing conditions where the use of remedial treatments, particularly chemotherapy (the use of chemical agents in the treatment or control of disease) become necessary.

5.704 If illness does occur, the aim must be to complement the animal's natural powers of recovery and to correct the imbalance which created the disorder, rather than simply to deal with the symptoms of the illness alone.

5.705 Medication must never be withheld where this will result in unnecessary suffering, even if in extreme circumstances, the use of such medication will cause the animal to lose its organic status permanently. Should treatment be withheld in these circumstances, the Certification Committee reserves the right to withdraw the Registration from that enterprise.

5.706 When any veterinary medicine is used, the withdrawal periods specified in paragraphs 5.745 and 5.746 must be observed and the treatments recorded as required in paragraph 2.314.

5.707 Recommended

1) Isolation or hospitalisation facilities for quarantined or sick animals conforming to the MAFF Code of Recommendations for Animal Welfare.

5.708 Restricted

Preventative chemotherapy may only be used to deal with specifically identified diseases or as part of an agreed conversion or disease reduction plan. Such a plan should be agreed between the farmer and a nominated veterinary surgeon working as a partnership during and after conversion to develop and operate an organic livestock system which conforms to these Standards for Livestock Husbandry (see paragraph 3.207).

5.709 Prohibited

1) Prophylactic use of veterinary medicinal products where no known farm problem exists.

Antibiotics

5.710 The use of antibiotics and some other conventional products may reduce natural immunity and, although providing rapid initial recovery, can leave an animal more prone to re-infection. They should only be used under the advice of the nominated veterinary surgeon where effective alternative treatments are not available and where they are considered the best method of reducing suffering, saving life or restoring an animal to health.

5.711 Permitted

1) The use of antibiotics in clinical cases where no other remedy would be effective or after major trauma as a consequence of surgery or accident.

5.712 Prohibited

1) The prophylactic use of antibiotics on a herd or flock basis.

2) The prophylactic use of Dry Cow Therapy on a herd or flock basis.

Source: Soil Association Standards for Organic Food and Farming, Revision 12, March 1999. Bristol, Soil Association.

EARLY COMMENT ON ANTIBIOTICS FROM THE ORGANIC MOVEMENT

For several decades, the organic farming movement has published its concerns about antibiotics. Lady Eve Balfour in the 1976 edition of The Living Soil (although interestingly not as far as we could see in the 1943 original edition) briefly mentions her scepticism on the bacterial theory for explaining scouring in calves. Frank Newman-Turner was also sceptical about the germ theory. While such views must now appear outdated, what lay behind them is still relevant today; the belief that good diets and good stockmanship can do a great deal both to prevent and cure disease. Milton (1957) provides an early and more comprehensive view of the problems associated with antibiotics.

The following references are not exhaustive, but give a selection of some of the principal points that have been made. (Balfour 1976, Boehncke 1985, Easterbrook, 1958, Mother Earth Editorials 1953a, b, 1958, 1959, 1960, 1963, 1969, Milton 1957, Newman-Turner 1949 and 1953, Turner 1954, Woodward 1980).

Detailed standards on antibiotics were first published in 1987 by the Soil Association. After much criticism in the veterinary press by vets who assumed organic farmers could not use antibiotics at all, a joint liaison committee was established by the Soil Association and the British Veterinary Association (Young 1991) which helped to improve mutual understanding and led to minor changes in the standards.

One Soil Association certified farmer has recently been prosecuted by the RSPCA and fined £500 with £1,500 costs for not calling in a veterinary surgeon to advise on a bullock who was lame in one leg. The farmer, possibly mistakenly, believed it was already recovering.

APPENDIX VII- STREPTOCOCCUS PNEUMONIAE

The streptococci are a vast family of bacteria and it is difficult to make generalisations (Lacey 1984). Penicillin resistance has, however, generally developed more slowly in this species than in the staphylococci. One of the most worrying resistance trends in recent years has been the development of strains of *Streptococcus pneumoniae* which are muliply resistant to penicillin and a wide range of other antibiotics.

Streptococcus pneumoniae causes pneumonia, meningitis and otitis media, a serious ear infection, but it remained fully sensitive to penicillin until the 1960s when intermediate resistance was first observed. Fully resistant strains appeared in Africa in the mid-1970s and today this has become a global health problem accounting for 40% of cases in the US (Gold and Moellering 1996, Lieberman and Wootan 1998).

It seems probable that this resistance has developed entirely as a result of the use of antibiotics in human medicine. However, antibiotics are commonly used to treat and prevent streptococcal navel and joint infections in calves and lambs, to treat mastitis in dairy cows and against streptococcal menigitis in pigs and some of this use could be prevented by changes in managment practices.

It might therefore be sensible to maintain an open mind about whether the farm use of antibiotics played any part in the development of this multi-resistant strain and might cause resistance in other streptococcal infections in the future.

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