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SYMPOSIUM ON 'FOOD ADDITIVES AND CONTAMINANTS'

The use of antibiotics as feed additives for farm animals

By I. A. M. LUCAS, *University College of North Wales, Bangor*

Antibiotics are added at low concentrations to feeds as growth stimulants and at therapeutic levels to cure known diseases. As their action in both instances is to modify bacterial, protozoal or fungal populations, the division between the two categories is indistinct; this is especially so when intermediate levels are considered. The present outline of use includes other feed additives which stimulate growth if they act or might act in a similar way to antibiotics, but hormones, enzymes and other chemicals (Shillam, 1971), which have a different mode of action, are excluded.

The scientific literature on growth stimulants is very extensive and many reviews and symposia have been published. There is a wealth of evidence and detail on antibiotics which, although proven to be effective in improving the performance of poultry, especially broilers, pigs, calves, beef cattle and, sometimes, lambs, are no longer allowed to be used in the United Kingdom without veterinary prescription. The object of the present review is to consider those additives which may now be used.

The Swann Report

In 1968 a committee under the chairmanship of Professor M. M. Swann was appointed to study the implications of antibiotic usage in animal production, and in human and animal health. The Committee reported in 1969 (Swann, 1969).

It was recognized that antibiotics – defined to include the sulphonamides and nitrofurans – have greatly reduced the incidence of diseases of animals and diseases common to man and animals, and also that they are of considerable economic benefit as growth stimulants. The Committee concluded, however, that administration of antibiotics to animals, through the proliferation of resistant organisms, has caused difficulties in veterinary practice. Furthermore, there is a flow of bacteria from animals to man and if these are resistant to antibiotics that are used therapeutically they represent a hazard to health either if they can cause human disease or if they can transmit their resistance to other bacteria which can cause disease. Those Salmonellae that cause food poisoning are in the first group and they are a particular hazard if infections become systematic, especially in the old and very young; *Escherischia coli* is in the second group. The emergence of *Salmonella typhi* that is resistant to chloramphenicol would be a particular danger. The evidence of transfer

of resistance in normal animals and man is scanty; nevertheless, to reduce these possible hazards the Committee recommended that 'permission to supply and use an antibiotic without prescription for adding to animal feeds should be restricted to (feed) antibiotics which: (1) are of economic value to livestock production under United Kingdom farming conditions, (2) have little or no application as therapeutic agents in man and animals, and (3) will not impair the efficacy of a prescribed therapeutic antibiotic through the development of resistant strains of organisms.'

Many other recommendations and suggestions were made, including research into stress and improved methods of animal husbandry, but it is particularly relevant to the present outline that the Committee believed that economic benefits through growth promotion may be secured with the 'feed antibiotics', which would be similar to those that were achieved with the antibiotics that were in use in 1969.

Use of antibiotics as feed additives in the UK, 1971

In 1969, UK farmers were allowed to include without veterinary prescription penicillin, chlortetracycline and oxytetracycline up to 100 mg/kg feed for growing pigs and poultry. Tylosin, nitrofurans, sulphonamides, copper and arsenicals could be used at any level.

The Swann Report (Swann, 1969) has not been without critics (Mennie, 1970) and there is much technical information upon which to base arguments 'for and against'. Nevertheless, permission for the unprescribed use, by farmers, of penicillin, the tetracyclines, tylosin, most sulphonamides and four nitrofurans has been withdrawn, and only zinc bacitracin, flavomycin, virginiamycin, sulphaquinoxaline and sulphanitran are officially recognized as 'feed antibiotics', although other materials are available as growth stimulants.

Unfortunately, comparisons of quantitative responses to these stimulants with those used previously can be misleading unless many experiments involving large numbers of animals have been reported. In most instances such information is not yet available.

Feed antibiotics

Zinc bacitracin. Zinc bacitracin may be added to feeds for growing pigs and poultry, and calves and lambs up to 6 months old at 5150 i.u. bacitracin (122 mg zinc bacitracin)/kg. Husaas (1969) has summarized much of the evidence of responses; other references are given below. Recommended rates of inclusion for growth stimulation are, per kg feed, 5–10 mg for broilers, 20–30 mg for turkeys, 10–20 mg for pigs and 50–100 mg for calves. At these levels satisfactory responses occur with broilers (Coates & Harrison, 1969; Šatava, Karlová, Dřevjaný & Slavík, 1970; Pivnjak & Konjahin, 1970; Wallace, 1970) and turkeys (Balloun, Miller, Arends & Speers, 1969; Chang & Waibel, 1970). Growth in early-weaned pigs was improved with 100 mg/kg feed (Costain & Lloyd, 1962; Livingstone & Livingstone, 1968; Clawson & Alsmeyer, 1971) and by the recommended level in pigs from weaning to slaughter, although the response with zinc bacitracin might be slightly less and more variable than with the tetracyclines. There is probably no additive

effect with copper sulphate (Homb, 1959; Holme & Robinson, 1963; Barber, Braude & Mitchell, 1965). Calves also respond (Preston, 1962) but no results are available for lambs.

At 200 mg/kg feed the stressing effect of vaccination in chickens was counteracted as effectively as with chlortetracycline (Kočiová, Peter, Mikulaj & Húšt'avová, 1969).

Flavomycin. Flavomycin is allowed at up to 25 mg/kg feed for poultry and 63 mg/kg for pigs. Little published information is available on this antibiotic. In broilers, growth responses occurred with as little as 0·6 mg flavomycin/kg feed (Turek, Lettner & Steinacker, 1967). At 1 or 2 mg/kg, weight gain and feed conversion efficiency to 8 weeks were improved by 5–7% and 3–4% respectively (Vogt, 1969*a*; Vogt & Gürocak, 1970). In other experiments, responses were greater in a deep-litter house but less in cages (Krüger & Vollrath, 1969) and a combination with chlortetracycline was better than flavomycin alone (Dřevjaný, Hejzlar & Šatava, 1970).

In laying hens, mortality was reduced and egg production increased with 1·25–5·0 mg flavomycin/kg feed, but in one report the 5 mg level was detrimental (Krüger & Vollrath, 1969; Tüller, 1969).

The recommended level for pigs is 8 mg/kg feed (Rosen, 1971). At lower levels, of 4 mg, decreasing to 2 mg for pigs of over 60 kg, there was no effect on performance (Krüger, Dzapo & Jesswein, 1969).

Flavomycin, when given daily at 10 mg/kg feed to calves weighing up to 100 kg, improved weight gains by 5–9% and when given at 20 mg/kg feed to those weighing from 100 to 120 kg, improved gains by 2–4% (Kobow, 1969).

Virginiamycin. Virginiamycin is allowed at up to 7 mg/kg feed for broilers. Experimentally, it has given growth responses with broilers equivalent to and sometimes better than those with other antibiotics when added, per kg feed, at 5 mg (Payne & Lewis, 1967) 4·5 or 5 mg and 10 mg (Yates & Schaible, 1962; Reyntens & Keppens, 1966), 10 mg (Vanschoubroek, 1964; Vanschoubroek & Vermeersch, 1966), 10, 20 or 50 mg (Eyssen, 1962; Eyssen, De Prins & De Somer, 1962) and 4·4–17·6 mg (Combs & Bassard, 1963). The greatest responses were at the higher levels (Eyssen *et al.* 1962; Combs & Bassard, 1963). It was suggested that stimulation is by antibacterial action against Gram-positive micro-organisms which interfere with the absorption of nutrients (Eyssen & De Somer, 1963).

With weanling pigs, growth was improved with up to 44 mg virginiamycin/kg (Jones & Pond, 1963). Elsewhere, a level of 20 mg/kg was effective and there was no further response at 40 mg/kg (Hennaux, Vandenbyvang & Bodart, 1965). More recently, Miller (1969) reported that a level of 22 mg/kg improved rate of gain by 15% and feed conversion efficiency by 10% and that the antibiotic was also beneficial to the growth of early weaned pigs.

Sulphaquinoxaline and sulphanitran. Sulphaquinoxaline and sulphanitran, used as coccidiostats for poultry, are allowed at up to 156 and 375 mg/kg feed respectively. The Swann Report (Swann, 1969) recommended that sulphonamides should be available only on veterinary prescription. But coccidiostats are most effective during the first 4 d of the 8-d life-cycle of coccidia, before the symptoms of diarrhoea with

blood and shivering appear, consequently they are best given prophylactically (Reid, 1969). As no diagnostic ability is then required, veterinary control is not necessary.

Sulphaquinoxaline is used prophylactically at 125 mg/kg feed, or therapeutically at higher concentrations in the mash or drinking-water. Sulphanitran is used in combination with other anticoccidial drugs (Reid, 1969; Conney & Hitchings, 1969).

Growth stimulants not classed as 'feed antibiotics'

Copper and arsenicals. Copper, usually from pulverized copper sulphate, at the rate of 250 mg/kg feed improves both the growth rate and feed conversion efficiency of pigs from weaning to slaughter by 5–8%, but there are variations in response, as with antibiotic (Braude, 1967). Growth response is least in the heavier pigs and may average as high as 22% in pigs weaned at 10–28 d (Wallace, 1970). Improvements are smaller and less consistent with 125 mg Cu/kg (Lucas, Livingstone & McDonald, 1961), but 170 mg/Cu kg might be fully effective (Braude, Mitchell, Newport & Pittman, 1970).

Cu toxicity has occurred with 500 mg Cu/kg and occasionally with 250 mg/kg (Lucas, 1964; Hanrahan & O'Grady, 1968; Miller, Ullrey, Ellis, Schoepke & Hoefer, 1969). But protection against toxicity is afforded by also including adequate levels of iron and zinc (Suttle & Mills, 1966; Hanrahan & O'Grady, 1968).

Arsanilic acid and 3-nitro-4 hydroxyphenylarsenic acid, added at 30–100 mg/kg to diets for growing chickens and pigs, and sometimes at up to 300 mg/kg for short periods, are the arsenicals most frequently used to promote growth. Responses have been similar to those with antibiotics or Cu, but there appears to have been little recent experimentation. However, Barber, Braude & Mitchell (1971) found that 100 mg arsanilic acid/kg feed improved growth rate and feed conversion ratio (feed:gain ratio) of pigs between 20 and 90 kg by 6 and 2% respectively. Performance was not improved further with a diet already containing 250 mg Cu/kg, but liver Cu values were reduced. There is no evidence that arsenicals give unacceptably high tissue concentrations of arsenic after slaughter. The mode of action of Cu and arsenicals in stimulating growth is not known.

Nitrovin (*Payzone*). Nitrovin is a guanidine derivative which has no known utility in the prevention or treatment of disease in animals or man. When included at 10 mg/kg mash in commercial trials on broilers it has given consistent improvements at 9 weeks of 6% in weight and of 5% in feed conversion efficiency. It has a wide margin of safety and tissue residues have not been detected (Pensack, 1968; Shor, 1968; Smith & Banks, 1968). Improvements ranging from 3–10% in growth rate and feed conversion efficiency have occurred in other European trials. As with antibiotics, there is probably decreased response with increasing age (Keppens, 1969; Vogt, 1969*b*; Brüggemann & Gropp, 1969; Zohari, 1969; Lettner, 1970*a*).

With pigs, 20 or 23 mg nitrovin/kg feed has improved both growth rate and feed conversion efficiency of apparently healthy animals in two experiments by 11 or 5–6% (between about 16 and 45 kg live weight) (Batterham & Fagan, 1970). In the

UK, response to 20 mg nitrovin/kg was similar to that from 250 mg Cu/kg feed for pigs growing probably from about 20 to 90 kg. Performance with both supplements was better than with either given alone (Braude, Mitchell & Pittman, 1971). It may also be noted that the effects of nitrovin and chlortetracycline on broiler growth rate have been reported to be additive (Pensack, 1968).

Grofas. Grofas is the trade name of quindoxin, quinoxaline 1:4 di-*N*-oxide. Recommended levels of inclusion for growth stimulation are 20 mg/kg feed for broilers, capons and turkeys and 20–50 mg/kg for pigs between weaning and slaughter. Safety margins are wide, since levels of up to 250 mg/kg are not harmful to broilers and tissue residues are low.

The manufacturers (Imperial Chemical Industries Limited, 1971; Broome & Hoskin, 1971) quote results from otherwise unpublished experiments, which show that the gains in performance of broilers and pigs are about the same as with other recognized growth stimulants and that there is a response with pigs given diets already containing about 200 mg Cu/kg.

Carbadox. Carbadox is another quinoxaline derivative which has been used experimentally but is not marketed in the UK. At 80 mg/kg feed, or at 50 mg/kg for 2 weeks followed by 25 mg/kg, it has improved the performance of calves (Ferrando & Raynaud, 1969*b*; Lettner, 1970*b*). It has also improved performance in pigs when given at levels ranging from 55 mg/kg feed for animals of 9 kg to 20 mg/kg feed for older animals. Responses were greatest in the youngest animals and were sometimes particularly associated with increased feed intake (Shively, Thrasher, Askelson, Babcock & Charlquest, 1969; Ferrando & Raynaud, 1969*a*; Bekaert, Eeckhout & Buysee, 1970; Thrasher, Shively, Askelson, Babcock & Charlquest, 1969, 1970; Caballero Hidalgo, Sierra Plana & del Aguila Alascio, 1970).

Dimetridazole and ronidazole. These drugs are used for the treatment of histomoniasis in turkeys. Dimetridazole is marketed in the UK as Emtryl. It is active against spirochaetes, species of *Vibrio* and *Fusiformis*, and protozoa, and it is effective in controlling enteric diseases of pigs, the complexities of which were reviewed recently by Cavill (1971). The recommendation is to give 200 mg/kg feed for 4 weeks after weaning.

Dimetridazole stimulates the growth of turkeys and chickens and has improved the growth rate and feed conversion efficiency of pigs growing from 10 to 27 kg and from 27 to 86 kg, although not all of the differences were statistically significant (Moeller, 1967).

Ronidazole at 60 or 120 mg/kg feed led to 9–12% better rates of gain and 3–5% better feed conversion efficiencies in pigs growing from 5 or 8 weeks to 14 or 20 weeks of age (Cox, Ott & Cobb, 1970). In these experiments there was little or no sign of clinical disease.

Conclusion on growth stimulants. Several chemicals are available to farmers as growth stimulants for growing chickens, pigs and calves. Their effects on lambs have not been investigated. Although there is less experimental evidence available on them than for those antibiotics which have been used as growth stimulants since

1953, with the exception of Cu for pigs, it is probable that equally satisfactory improvements in performance are achieved.

Several stimulants, however, are not absorbed from the gut and consequently they might have less effect than the tetracyclines given at high concentration when systemic infections, perhaps subclinical, are limiting growth. Further large-scale field trials will no doubt show whether or not this is so.

Therapeutic levels of drugs in feeds

The Swann Committee (Swann, 1969) drew attention to some therapeutic uses of antibiotics which can be regarded as unwise, especially attempts to control by mass medication the spread of intestinal diseases caused by the Enterobacteriaceae which rapidly become resistant, and it called for more studies of epidemiology, which might lead to better long-term methods of control through husbandry practices. Nevertheless it recognized that when individual medication is impossible or impracticable, medicines might have to be given in the feed or drinking-water. As this practice is now under veterinary control, a joint committee of the veterinary, pharmaceutical and feed manufacturing professions has drawn up both a recommended form to be used by the farmer and veterinarian in ordering medicated feeds, and a schedule setting out recommended levels of antibiotics to be added to feeds (Anonymous, 1971*a*). This schedule lists thirteen antibiotics, nitrofurans and sulphonamides, and it gives the recommended levels for poultry and calves, the minimum duration of treatment and some special notes on usage. Guidance has also been given (Anonymous, 1971*b*) about the principles by which a veterinarian should decide whether he should leave antibiotics to be administered by the farmer. A clear instance where the administration may be left to the farmer is the use of antibiotic infusions into the udders of cows at the end of lactation to control mastitis. Equally clear is that the administration of chloramphenicol preparations should not be left to the farmer.

In recommending that no restrictions be put on veterinarians to prescribe antibiotics as they wish, the hope was expressed (Swann, 1969) that they would take a responsible attitude in avoiding indiscriminate antibiotic use. There are indications that this will be justified.

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