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Antibiotics and other growth-promoting substances

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It has become accepted practice to include in the diet of poultry and other animals a range of additives which have no apparent direct nutritional value, but which, nevertheless, help to maintain or increase the level of animal production. Such supplements are usually incorporated in the feed at a very low level and are given on a continuous or semi-continuous basis. The feed serves merely as a convenient vehicle, and sometimes subcutaneous implantation or addition to the drinking water is a possible alternative.

Non-nutritional feed additives may be classified into two groups:

(a) Those substances that prevent or reduce the incidence or severity of infectious disease. In this context the term 'disease' includes not only obvious clinical disease, but any detrimental modification of the microbial flora of the host animal which is reflected in reduced productivity. Such compounds produce no growth response in birds reared in a sterile environment and they normally remove a growth-depressing effect rather than produce a direct growth stimulation. This group includes anti-bacterial and antiprotozoal agents as exemplified by the antibiotics, the sulphonamides, the nitrofurans and a range of specific coccidiostats and histomonostats. Organic arsenical compounds may also fall largely within this group.

(b) Those substances that bring about changes in the metabolism of the animal, producing an increase in rate of growth or productivity. Such compounds show little or no antimicrobial activity and would be likely to produce a consistent growth stimulation in either a sterile or conventional environment. This group consists mainly of substances having hormonal activity; they are of considerably less practical importance at present than the antimicrobial agents.

Thus it is apparent that most of the so-called growth-promoting substances in use are, in effect, controlling clinical or subclinical disease, and in this way are reducing the growth depression normally associated with intensive animal production.

Antibiotics

It has been shown by many workers that the continuous dietary administration of very small quantities of certain antibiotics, particularly during the first few weeks of life, increases growth rate and improves food conversion efficiency in chicks (e.g. by Moore, Evenson, Luckey, McCoy, Elvehjem & Hart, 1946; Stokstad & Jukes, 1950; Coates, Harrison, Kon, Mann & Rose, 1951; Heuser & Norris, 1952; Cuthbertson & Glasser, 1954). In particular, the administration of chlortetracycline, oxytetracycline, penicillin and bacitracin at levels of between 5 and 50 p.p.m. has frequently produced a growth response in the young chick of about 10%, and an improvement in food conversion efficiency of about 5–10%. These benefits are frequently associated with a reduced morbidity and mortality rate, particularly during the first few weeks of life. Practical experience, particularly in the U.S. broiler industry, has shown the value of administering appreciably higher levels of the tetracycline antibiotics under conditions of intensive production and severe exposure to disease (White-Stevens, 1957).

In the U.K. the continuous administration of 25 p.p.m. of chlortetracycline to laying birds produced a statistically and economically significant increase in egg production, except in those flocks having a level of egg production above average (Smith, Taylor & Quenouille, 1961). The magnitude of the antibiotic response has borne an inverse relation to the level of production of each particular flock. As with broilers, the use of higher levels (100 p.p.m.) of chlortetracycline has proved economically justifiable in the control of disease conditions associated with chlortetracycline-sensitive organisms.

The response obtained from the administration of an antibiotic varies considerably both between and within farms, and it is therefore important to understand the probable modes of action. This subject has been extensively investigated and reviewed by many workers (e.g. Stokstad, 1954; Coates, Davies, Harrison, Kon & Porter, 1955; Taylor, 1957) but there is still no single explanation which can account for all the observed effects.

In view of the exceptionally low levels of antibiotics which produce a growth response, it was at first assumed that these agents must produce a direct or indirect nutritional or metabolic effect. It has been shown on many occasions that in a marginally deficient diet the utilization of most dietary constituents has been increased by antibiotic treatment. This effect has been attributed either to a favourable modification of the intestinal microflora or to a reduction in the thickness of the wall of the small intestine, which is a constant feature of animals receiving antibiotic supplements. This 'sparing' effect has been noted particularly with the vitamin B complex, but the importance of these observations is limited by the fact that birds receiving a diet considered to be nutritionally adequate still show a significant growth response to antibiotics. Extensive studies of the changes of the intestinal microflora have, in

general, failed to show any consistent changes in the proportion of viable organisms (Jukes, 1955), but there is evidence to suggest that in penicillin-fed chicks there may be a change in the metabolism of the bacterial cell, leading, in *Clostridium welchii*, to a reduction of lecithinase (α -toxin) production (Lev, Briggs & Coates, 1956). There is also evidence to show that the continual administration of chlortetracycline to the calf may influence the metabolism of the microflora of the gut in such a way as to make the bacterial cell more susceptible to the normal process of phagocytosis (Radisson, Bartley, Lord & Swenson, 1956). Modification of the intestinal flora may either permit increased synthesis or availability of nutrients, depress bacterial toxin production or control organisms which in limited numbers may depress growth and in excess may bring about severe clinical disease.

It should not be assumed, however, that the action of antibiotics which are absorbed from the digestive tract is only a local one upon the microflora of the gut. It has been clearly shown, for example, that levels of chlortetracycline as low as 10 p.p.m. in the feed may produce a detectable level in the blood in the very young chick (Table 1). Levels of 25 p.p.m. will reduce deaths due to certain systemic

Table 1. *Blood serum levels (mg/ml) of chlortetracycline in relation to drug level in diet and age of chick*

(From White-Stevens, 1957)

Age and days on drug	Chlortetracycline in diet		
	10 p.p.m.	55 p.p.m.	110 p.p.m.
1	0.025	0.145	0.355
7	0.050	0.085	0.190
14	Negative*	0.055	0.095
11 weeks	Negative*	0.015-0.050	0.020-0.060

*Test sensitive to 0.005 μ g/ml.

infections (e.g. pullet disease and certain bacterial respiratory infections), and levels of 50-100 p.p.m. will effectively reduce losses due to other systemic infections such as chronic respiratory disease and infectious synovitis. Under standard conditions, the degree of control depends upon the severity of infection and the level of antibiotic administered. The effect is essentially a graded one wherein the level of antibiotic administered exerts a quantitative effect on the level in the blood, on disease control and growth response. Although within these limits the magnitude of response may vary widely, there appears to be no qualitative variation. There is thus little justification for the arbitrary use of the terms 'nutritional level' for low-level feeding, or 'prophylactic level' only for high-level feeding, for it is becoming increasingly apparent that in this context no realistic division can be made between nutrition and infectious disease, the latter term being used in its broadest sense. It is probably incorrect to assume that, at any level of administration, antibiotics produce primarily a nutritional effect or exclusively a therapeutic effect. The weight of experimental evidence, however, suggests that the predominant effect is the control of subclinical disease of microbial aetiology. This theory is supported by the following facts:

(1) Chicks reared in a sterile environment generally show no growth response to antibiotics. (2) The morphological changes observed in antibiotic-fed birds closely resemble those changes seen in chicks reared in a sterile environment, and may be due to a reduction in lymphatic tissue. (3) In a new or thoroughly disinfected chicken-house, little or no antibiotic response is observed and the rate of growth is abnormally high. The introduction of birds or their faeces from an old house will bring about a growth depression which can largely be overcome by antibiotic supplementation. (4) The introduction of heat-sterilized faeces from normal 'infected' birds will not depress the growth rate of clean 'uninfected' birds. (5) Detectable serum concentrations of antibiotics are frequently found in animals receiving an antibiotic supplement, especially during the early stages of life when the greatest response to antibiotics occurs. (6) Under practical conditions the greatest benefits from antibiotic supplements have been seen under conditions of depressed growth, stress, intensive production and high exposure to disease.

If one accepts the theory of subclinical (and, to a lesser extent, clinical) disease control, it is possible to present criteria for the use of antibiotic feed supplements. They are: (1) A growth-depressing effect of microbial origin must be present. (2) The antibiotic selected must be effective in controlling this 'infection'. (3) The level of administration in the feed must be sufficient to supply an adequate level of antibiotic per unit body-weight, irrespective of a changed feed intake per unit body-weight in the growing chick. (4) If there is reason to suppose that an antibiotic may be required at sites other than the digestive tract, the antibiotic should be one which is well absorbed and should be administered in such a way as to ensure maximum absorption and retarded excretion.

Recent developments in this field have been concerned with increasing systemic concentration of the tetracyclines both by enhancing absorption and retarding urinary excretion. It has been shown that a reduction in dietary intake of calcium by the chick from a conventional 1-1.4% to 0.6-0.8% will at least double blood levels of the tetracyclines (Cover, Benton, Greene & D'Armi, 1959) owing to increased absorption of the antibiotic from the digestive tract. Similarly, the use of a number of potentiating agents, notably terephthalic acid and its salts, has been shown to increase significantly blood levels of the tetracyclines owing to retardation of urinary excretion (Price & Zolli, 1959). The value of enhancing the levels of the tetracyclines in the blood has been clearly shown in the presence of clinical or subclinical systemic disease such as chronic respiratory disease and infectious synovitis. If, however, one assumes that under many circumstances the response to the antibiotic is associated with a beneficial modification of the intestinal microflora, then enhancement of systemic concentration may not be indicated.

The site of action of penicillin has, so far, been mainly restricted to the digestive tract owing to the relative instability and poor absorption of this antibiotic after oral administration. The development of new penicillins which are stable in gastric juice (phenoxymethylpenicillin and 1-phenoxyethylpenicillin) and others which can withstand the presence of penicillinase (dimethoxyphenylpenicillin) may, however, ultimately change the role of penicillin as a feed supplement.

Arsenicals

Several organic arsenical compounds have been widely used as supplements to poultry rations, the most common being 3-nitro-4-hydroxyphenylarsonic acid, *p*-aminophenylarsonic acid (arsanilic acid), 4-nitrophenylarsonic acid and arsenosobenzene. Such compounds may be used either for the control of specific disease conditions such as coccidiosis and histomoniasis or, more frequently, to produce an increase in growth rate and feed conversion efficiency in the apparently healthy bird. The mechanism of this effect is not clear and may be due to the general pharmacological properties of arsenic or to the inherent antimicrobial activity of these compounds. It has been shown by Coates, Davies & Kon (1955) that the administration of arsanilic acid to chicks at a level of 20 p.p.m. in the diet produces a significant reduction in gut weight similar to that produced by a penicillin supplement, but that chloramphenicol, which does not normally promote a growth response in chicks, exerts no such consistent effect. Similarly, as with antibiotics, 3-nitro-4-hydroxyphenylarsonic acid has been shown to produce a significant growth response in an 'old' environment, but not in a 'new' environment (Morrison, Hunsaker & Aitken, 1954).

The effect of arsanilic acid on the gut flora of the chick has been somewhat variable, but in many ways is similar to that observed with antibiotics under the same conditions (Elam, Jacobs, Tidwell, Gee & Couch, 1953). In most conditions, however, the response obtained from arsanilic acid and antibiotics has been additive (Combs, Romoser & Bishop, 1954) especially with low levels of antibiotics (West, 1956). The comparative antimicrobial activity of antibiotics and arsanilic acid is shown in Table 2. Antibiotics normally produce a 'sparing' effect on the chick's

Table 2. *Bacteriostatic activity of antibiotics and arsonic acids*

(From Frost & Spruth, 1956)

Compound	Minimal inhibitory concentration ($\mu\text{g/ml}$)	
	<i>Escherichia coli</i> *	<i>Clostridium perfringens</i>
Sodium arsanilate	10 000	1000
3-nitro-4-hydroxyphenylarsonic acid	7 000	100
Chlortetracycline	3-100	0.01-0.02
Procaine penicillin		0.08

*These bacteriostatic levels are also representative for *Streptococcus faecalis*, *Proteus vulgaris*, and *Salmonella enteritidis*.

requirements for many nutrients. The administration of arsanilic acid, however, has not usually produced a 'sparing' effect, but has increased dietary requirements for vitamin K, thiamine, riboflavin and certain unidentified growth factors present in fish products and dried whey (Combs *et al.* 1954).

Studies with 3-nitro-4-hydroxyphenylarsonic acid and *p*-aminophenylarsonic acid have shown that the inclusion of 50-100 p.p.m. in the diet of growing chicks or turkeys will frequently produce a significant increase in rate of growth and may be associated with improved feed conversion efficiency and carcass quality (Abbott, Bird & Cravens, 1954; Milligan, Wilcke, Marr & Bethke, 1955; Pepper & Slinger,

1955; West, 1956). Levels as high as 500 p.p.m. have been used without depressing rate of growth (Abbott *et al.* 1954). Administration to laying birds has, on some occasions, resulted in improved egg production and feed conversion efficiency (Price, Stelzner, Reid & Couch, 1956; Thornton & Moreng, 1958).

Hormones

Oestrogens. The deposition of body fat in the chicken occurs mainly after the initial stage of rapid growth and before the onset of sexual maturity. In the male, the onset of sexual maturity depresses fat deposition during the later stages of the growing period. In the female bird, however, oestrogen produced in the active ovaries enhances blood lipid levels and encourages body fat deposition. Thus the administration of synthetic oestrogen to male poultry (a) depresses undesirable secondary sexual characteristics, and (b) modifies lipid metabolism, increasing fat deposition. These effects differ from those seen in the ruminant in which oestrogen supplementation at a low level causes increased growth rate and reduced fat deposition.

The subcutaneous implantation of pellets of diethylstilboestrol (or hexoestrol) has been shown to reduce markedly the weight of gonads and comb (Breneman, 1942) and has produced a desirable increase in body fat deposition and tenderness of muscle tissue (Lorenz, 1943, 1945). These changes have been observed in birds of widely varying ages and appear to be to some extent reversible after removal of the implant.

Oral administration of a variety of synthetic oestrogens has provided a wide range of activity in the chick as judged by oviduct weight (Table 3). Diethylstilboestrol has

Table 3. *Summary of results of assays of the activity in chickens of oestrogens given orally*

(From Jaap, 1945)

	Amount (mg/lb feed)	Relative potency*
No oestrogen	0	0
Diethylstilboestrol	23	2.1
Hexoestrol	30	3.4
Dienoestrol	30	11.5
Dianisylhexene	20	45.0
	50	41.9
Dianisylhexane	20	32.3
	30	37.8

*Increase in oviduct weight per 100 g body-weight per mg oestrogen in each lb feed.

shown little activity, whereas its dimethyl ether (dianisylhexene) has shown considerable activity (Jaap, 1945). These results have been reflected by variations in body fat deposition in which diethylstilboestrol has been almost inactive at the levels used (Lorenz, 1945; Thayer, Jaap & Penquite, 1944), whereas the administration of

40–50 mg dianisylhexene/lb feed during the fattening period has produced a consistent increase in fat deposition and market quality. This effect has been reported in chickens and turkeys of both sexes, and in broilers as well as in older birds (Thayer, Jaap & Penquite, 1945; Thayer & Davis, 1948). Synthetic oestrogens have, however, generally produced no improvement in growth rate or in feed conversion efficiency.

Thyroid-active agents. Many attempts have been made to increase the rate of growth of young birds by inducing hyperthyroidism, and to increase fat deposition by producing hypothyroidism in older birds. Iodinated casein has been prepared containing approximately 3% thyroxine with a biological activity considerably greater than that of dried thyroid gland. Oral administration of approximately 10 g/100 lb feed has consistently produced earlier feathering in chicks and has frequently been associated with small improvements in growth rate and feed conversion (Wheeler, Hoffmann & Graham, 1948; Quisenberry & Krueger, 1948). The administration of thiouracil has generally depressed the rate of growth, especially in younger birds. It can, however, be used to induce a state of mild hypothyroidism immediately before slaughter, and, in this way may increase fat deposition and carcass quality (Kempster & Turner, 1945; Andrews & Schnetzler, 1946).

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Wild birds as human food

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'And these are they which ye shall have in abomination among the fowls; they shall not be eaten, they are an abomination: the eagle, and the ossifrage, and the ospray, and the vulture, and the kite after his kind; every raven after his kind; and the owl, and the night hawk, and the cuckow, and the hawk after his kind, and the little owl, and the cormorant, and the great owl, and the swan, and the pelican, and the gier eagle, and the stork, the heron after her kind, and the lapwing, and the bat.' (Leviticus, XI, 13-19). This 'Mosaic' prohibition, it will be noticed, is a list of birds which few of us would venture to eat even if it were not forbidden us, 'lapwing' being, of course, a mistranslation for 'hoopoe'. Few people, for example, can have eaten or thought of eating a hawk, with the exception of the fictional Federigo degli Alberighi in the *Decameron*, who served up his falcon (his last and most precious possession) to his lady at dinner, as a token of his love: Boccaccio, however, does not tell us if the meal was, gastronomically, a success. On the other hand more than one species of owl, although carnivorous, is edible; the little owl (*Athene noctua*) is eaten in Sardinia and the eagle owl (*Bubo bubo*) is said by the Persians to be a delicacy. Nevertheless the main principle in the above passage from the Old Testament still remains—that for a bird to be chosen as food for man it should be palatable.

We have three principles that govern the choice of birds as food: (1) ease of capture, (2) size, (3) palatability.

Ease of capture. It is obvious that birds which nest in colonies or consort in flocks will be easier to exploit, although many of these, being seabirds, are not necessarily very palatable. In our 'advanced' society there is only one surviving instance in Britain of the exploitation of a seabird colony for food and that is the annual raid by the men of Ness on Sula Sgeir, when young gannets (*Sula bassana*) are killed, cured and, under the name of 'gugas', are sent to Lewis men all over the world; but, within the memory of a young man (personal communication by Police Constable Calum Nicolson) the Shiant Isles were regularly visited by the people of Limervay in Lewis to kill the young puffins (*Fratercula arctica*) and the economy of St Kilda depended largely on seabirds, chiefly the fulmar (*Fulmarus glacialis*). On Tristan da Cunha a frequent Sunday dinner was another seabird, the great shearwater (*Procellaria gravis*), which could simply be extracted from its burrow, and on