Growth-promoting substances

By R. BRAUDE, *National Institute for Research in Dairying, University of Reading, Shinfield, Reading RG2 9AT*

The organisers of the Symposium on Growth quite rightly included in the programme a paper on growth-promoting substances. However, as there is very little new to report on the subject, I intend to restrict my comments to a few relevant aspects rather than attempt a detailed review on individual products.

In animal production one aims at maximum growth within the constraints of available feed resources and economics. When dealing with feed additives purporting to promote growth, one should appreciate the fact that in many circumstances their scope is rather limited. In Table 1 a rather simplified summation is presented of the basic components contributing to maximum growth (represented by the squares) and of factors affecting growth. All are continuously interacting. In extreme situations each of the factors affecting growth is finite, e.g. if one starves the animal, it cannot live, a virus can terminate life, germ-free animals cannot suffer from infectious disease, etc. Also, if all basic requirements for life are satisfied and the interactions are at the optimum, the chance of obtaining a response from growth-promoting substances is nil. However, as these extreme conditions seldom, if ever, operate in real life, and the arising intermediate situations leave room for innumerable interactions, one can see how an application of the right feed additive at the right time may prove to be effective and economically worthwhile. It is virtually impossible to generalize about the way the growth promoters exert their effects, and I am oversimplifying the issue by attributing to them a role of regulators of the interactions. The evidence that in certain circumstances a similar response can be obtained by several unrelated substances could be taken to suggest the idea that an equilibrium of components controlling growth may be attained by different routes. Also, the facts that animals respond differently to different substances and to different doses of the same substance, point to some 'computer system' regulating the interacting factors. In some cases the role of the feed additives is clear, e.g. if they correct a hormonal imbalance, or affect the intestinal flora, but more often than not, their mode of action is obscure. One thing, however, can be taken for granted, namely, that there must be a physiological ceiling to improvement of growth rate. I have no doubt that at present even with best performing animals, there is still some room for advancement, but it must be clear that as the performance of the animals continues to improve, the scope for growth promoters narrows.

Table 1. *Maximum growth (an over-simplified scheme)*

Life functions Cell synthesis Tissue formation	10–20% Internal environment 80–90% External environment	Growth rate Feed intake Efficiency of feed utilization Carcass quality
Genetic potential Physiological processes Biochemical processes, etc. *interacting*	Endogenous secretions: enzymes, hormones, etc. *Intestinal flora* Nutrition Disease Climate Management, etc. *interacting*	*interacting*

Our lack of understanding of the mode of action of some of the growth-promoting substances often leads to hypothetical explanations which may confuse the issue. Two examples associated with current controversies will illustrate my point; lack of growth-promoting response to antibiotics in germ-free animals is taken by some as evidence that antibiotics promote growth through their effect on the flora of the digestive tract; if the germ-free animals grow at a maximum rate, lack of growth response should not be taken as conclusive evidence to explain responses under other circumstances. Similarly, the fact that an additive 'is not absorbed' from the intestines need not be a valid argument that the recorded effect must be due to an action within the digestive tract. Absorption of even 1%, which often can escape scrutiny, may be sufficient to elicit a systemic effect.

There are two other general points on which I wish to comment. As with many biological variables, response to a growth-promoting additive in a population usually follows a normal distribution. Once this distribution has been established, a further single record, however well established, can do no more than provide one point on the distribution curve. This should be only too obvious, but frequently claims are based on a single experiment, even if it contradicts a well established response. Often the culpable author shelters behind the statement that the results of his experiment were 'statistically significant'. With growth-promoting substances, the response to which is often affected by many interacting and sometimes antagonistic factors, one should not be allowed to challenge the established distribution without a very substantial replication. I will illustrate this point with evidence concerning copper sulphate as a growth-promoting additive for diets of growing pigs. Recently, I have reviewed this subject (Braude, 1976). The results for improvement of growth by addition of 250 mg Cu/kg diet when compared with performance of the control animals is diagrammatically presented in Fig. 1. The mean response of 9·1% was statistically highly significant and the two extreme values are also given. One can clearly see than an additional single point, or even several points added to the diagram would not substantially alter the conclusion that addition of 250 mg Cu/kg diet has a beneficial effect on growth.

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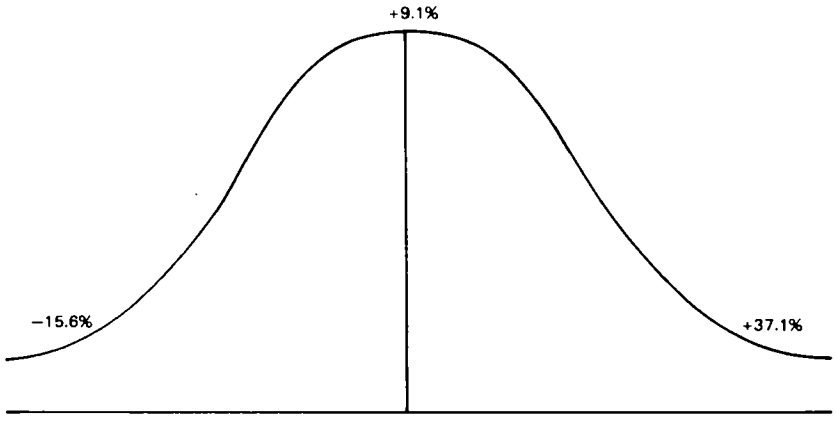

Fig. 1. The improvement of growth in pigs by addition of 250 mg copper/kg diet.

The second general point I wish to illustrate with results relating to a recently completed experiment in Shinfield (Barber, Braude & Mitchell, unpublished results). In this experiment we attempted to test the value of virginiamycin as growth promoter, and particularly whether it has an additional value when added to diets containing 250 mg Cu/kg. Experiments of this kind we run in a four treatment design, and control strictly some of the basic variables such as litter origin, sex and initial live weight. Our normal current procedure is to run two replicates with twelve individually fed pigs per treatment in each replicate, i.e. twenty-four pigs per treatment and a total of ninety-six pigs. In this particular experiment a third replicate was run involving twelve pigs per treatment. In Table 2 results for feed to gain ratio are presented. It is interesting to study the results for each replicate separately and for the combined results. Two comments I wish to add to the otherwise clear conclusions: perhaps in studies of this kind one should refrain from attaching too much significance to chances 1 in 20 ($P>0{\cdot}05$). I would respectfully suggest that chances 1 in 100 ($P>0{\cdot}01$) are more appropriate. It is perhaps indicative of my personal beliefs that, based on long experience, in our own experiments of this kind involving individual feeding we have increased the number of animals per treatment from 6, through 8, 12 to 24, and the example quoted above points out that even 24 may not be sufficient to give a clear result. One should also bear in mind that results, however well established in one centre, must be subjected to scrutiny at other centres.

Table 2. *FCE of growing pigs on a standard diet with or without copper (Cu) or Virginiamycin (V)*

Expt	*n*	C	Cu	V	Cu+V	SEM	Cu	V	CuxV
1	12	3·32	3·15	3·22	3·11	0·047	××		
2	12	3·20	3·08	3·12	3·11	0·032	×		
3	12	3·10	3·11	3·11	3·00	0·032			
1–3	36	3·20	3·10	3·15	3·07	0·022	×××	×	

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Twenty years ago, I reviewed the subject of feed additives as growth promoters in pigs (Braude, 1957) and suggested that four questions must be adequately answered when considering their usage in the field. These are just as relevant today, and apply to all species of livestock: 1. Does the additive fulfil any useful purpose? (Does it improve growth, efficiency of feed utilization, egg production, wool production, etc?); 2. How does it affect the animal? 3. How does it affect the consumer of animal products? and 4. What are the economics involved? To answer these questions a very considerable amount of research and testing is required and eventually requirements laid down by law and regulations have to be met before a product can be marketed. These differ in various countries and have been made more stringent and severe with the progress of time. In fact, in my view, they exceed sometimes the intention of the legislators, whose main interest was to safeguard man and beast from products which carry risk to their well-being, and on occasions were misled by over-anxious politicians and bureaucrats using unproven and often highly speculative evidence to produce rather irritating restrictions. In the UK, the Fertilisers and Feedingstuffs Act 1926, augmented in 1968, governs the sale of feedingstuffs and in some circumstances require a declaration of the amount of additives included (e.g. natural or synthetic hormones, copper). The Therapeutic Substances Act 1956 introduced controls on the use of antibiotics in feedstuffs augmented in 1971, following the adoption by the government of the recommendations of the Swann Report. The Medicines Act 1968 led to the establishment of the Veterinary Products Committee which now scrutinizes all matters concerning feed additives.

Following the entry of the UK into the EEC, we will have to comply with the provisions of the Directive No. 70/524 (Nov. 1970) concerning additives in animal feeds. Their current regulations require proof that the feed additive is harmless to the intended animal, leaves insignificant residues in edible tissues and is effective for the purpose claimed.

When generalizing on growth promoting substances one must distinguish them from other feed additives which usually have no direct effect on growth such as anthelmintics, antifungal and antiprotozoal compounds, tranquillisers, antioxidants, pigments, emulsifiers, preservatives, appetisers, etc. In the literature more than 500 feed additives have been mentioned, but in Table 3 I have brought together most of the growth promoters currently used in the UK and USA. Some of these are advocated for several species of livestock, while others are limited to one species only (as indicated in the Table 3). I have listed them in alphabetical order so as to eliminate any subjective judgment of their efficacy. One must be careful with names, because the same product occasionally appears under different names, and confusion often arises because of usage of proprietary names (e.g. Bambermycin = flavomycin; Nitrovin = Payzone; Halquinol = Roxolin = Quixalud). In other countries several different growth-promoting additives are also recommended, and I selected a few only which are widely used in the country of their origin: Spiramycin (France), Delvomycin (Holland), Glapondin (Hungary), Thiopeptin (Japan). In addition to these, perhaps one should mention the rapidly

becoming fashionable term of 'probiotics' which covers a group of substances which enhance the activity of the microbial flora of the digestive tract (e.g. acidifying or neutralising agents, various cultures, etc.). The Russians are particularly keen on 'biologically active substances', and some similar compounds are hawked in this country, but I know of no adequate evidence to support claims made on their behalf. In fact, some have been tested and found to be of no benefit.

Table 3. *Feed additives used in the UK and USA for growth promotion*

		Pigs	Cattle	Poultry	Sheep	Other
Apramycin	○	+				
Arsanilic acid	●	+		+		
Bacitracin	●	+	+	+		
Bambermycin				+		
Carbadox		+				
Copper	●	+				
Chlortetracycline	●†	+	+	+	+	horses, mink
Dichlorvos		+				
Dimetridazole	●	+		+		
Ethylenediamine		+	+	+	+	
Flavomycin	●	+		+		
Furazolidone	●	+		+		
Halquinol	○	+				
Ipronidazole		+		+		
Lincomycin				+		
Maxymin	●†	+				
Melengestrol			+			
Nitrovin	●	+	+	+		
Oleandomycin		+		+		
Oxytetracycline	●†	+	+	+	+	rabbits, mink
Penicillin	●†	+	+	+		
Ronidazole	●	+		+		
Roxarsone		+		+		
Stilboestrol			+			
Thyroprotein		+	+	+	+	
Tylosin	●†	+	+	+		
Virginiamycin	●	+				

●Used in UK.
○On test at present.
†In UK on veterinary prescription only.

Finally, I would like to mention efforts to affect growth of the young animal by supplementation of the diet of its mother. It is suggested that by feeding some progestogens to the sow, her milk yield can be increased, thus benefiting her litter. Only a few recent references are given here to stimulate interest in the subject which, as far as I am concerned, remains as uncharted territory (Megestrol acetate, Arbeiter, Onderscheka, Choi, Weber & Jöhle, 1974; Chlormadinone acetate, Jöhle, Smidt, Holz & Spangenberg, 1975).

REFERENCES

Arbeiter, K., Onderscheka, K., Choi, H. S., Weber, E. & Jöhle, W. (1974). *Theriogenology* **2** (4), 77.

Braude, R. (1957). *Vet. Rec.* **69**, 178.
Braude, R. (1976). *Proc. Symp. Copper in Farming, 1975*, p. 79 Copper Development Association.
Jöhle, W., Smidt, D., Holtz, W. & Spangenberg, B. (1975). *Theriogenology* **3** (4), 130.

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