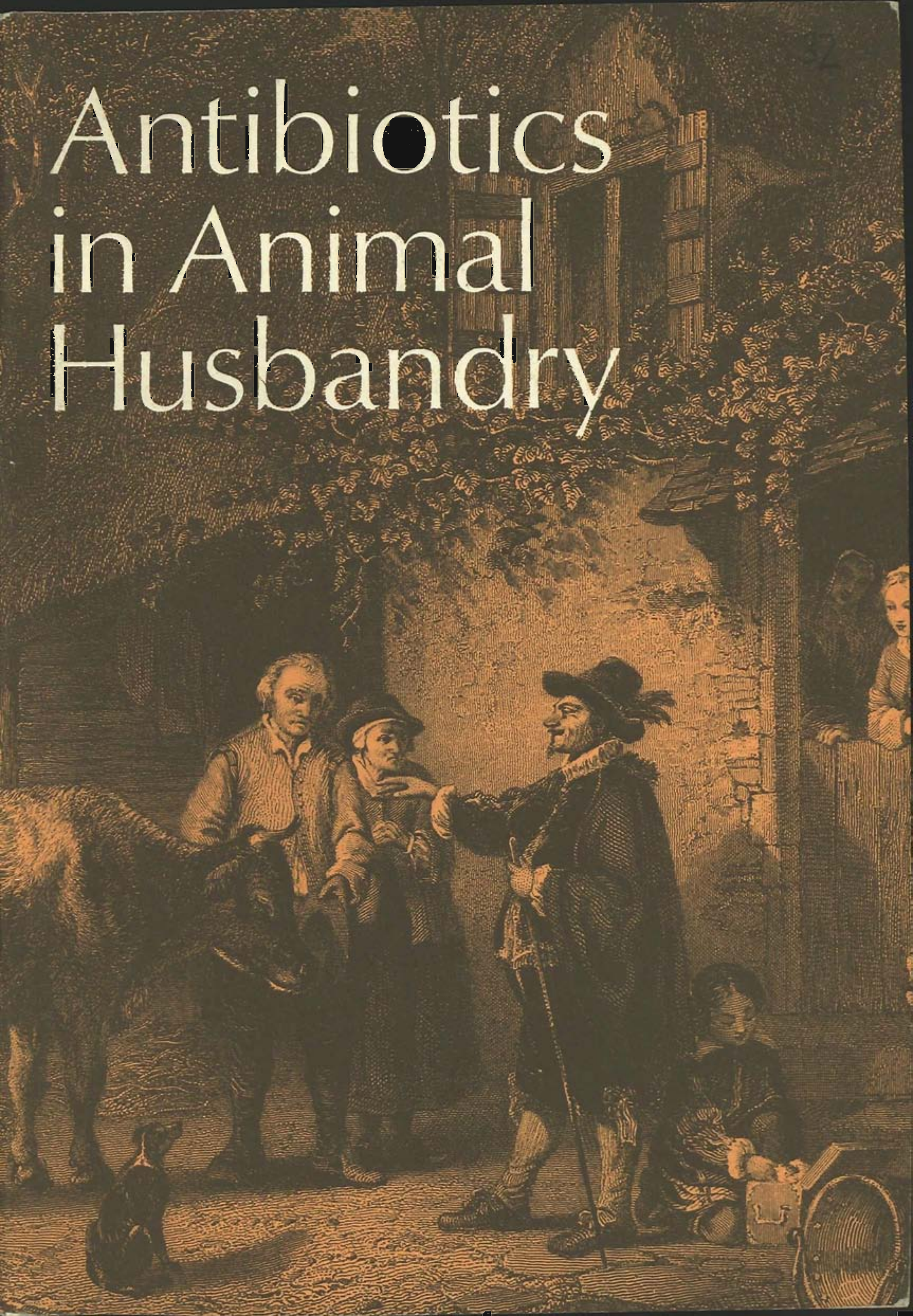
Antibiotics in Animal Husbandry



Antibiotics in Animal Husbandry

Office of Health Economics
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No. 32 in a series of papers on current health problems published by the Office of Health Economics. Copies are available at 3s. 0d. postage free. For previous papers see inside back cover.

Office of Health Economics

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Foreword

It has generally been the policy of OHE, in this series of occasional papers, to avoid controversial topics directly involving the pharmaceutical manufacturers, who still provide much of the finance for our Office. We are departing from the tradition on this occasion partly by accident and partly by intent.

We first started to look at the "non-medical" use of antibiotics in animal husbandry some time ago, when there appeared to be a straightforward case for assessing what economic benefits these yielded. Almost at once, however, the work of Dr E. S. Anderson and others focussed attention on the potential hazards of antibiotic resistance spreading from animals to man. The resulting publicity and widespread concern prompted the Association of the British Pharmaceutical Industry to call on the Minister of Agriculture to hasten the setting up of an official Enquiry into the question, and (while OHE was still studying the subject) the government's Committee under the Chairmanship of Professor Michael Swann was established. That Committee may indeed have reported before this booklet is published.

The extent of public discussion, which has continued since the Swann Committee started work, indicates that the subject is still one of very general interest. We, therefore, felt it would be wrong for OHE to abandon its work, which has now reached the stage of publication. Our study still deals largely with the economic benefits from the use of antibiotics in animal husbandry. In doing this, we hope that we may have provided a broader economic background to the conclusions of the Swann Committee. It also necessarily discusses the much publicised potential hazards. These, we hope, are put into perspective by identifying some of the different aspects of the problem which have sometimes been confused in previous public discussion. For instance, the possible transfer of resistant pathogens from calves to man (following therapeutic or high level "prophylactic" doses of antibiotics) must be distinguished from the question of resistance induced in non-pathogens in other types of animal by low doses of antibiotics for growth promotion. Recent evidence tends to suggest that the latter may remain little more than a theoretical hazard. As with so many of our publications, however, this booklet concludes that many questions remain unanswered. It also asks – as in all health matters – that the potential hazards should be fairly balanced against the benefits.

Antibiotics in Animal Husbandry

THE objective of animal husbandry is to produce the largest quantity of good quality meat or animal produce as economically as possible. One major contribution to this over the past 120 years has come from selective breeding to rear animals which grow more quickly and yield large quantities of desirable food. Another has come from improvements in feeding stuffs and there have also been important contributions from advances in veterinary medicine. A further recent approach has been through the use of antibiotics and other feed supplements. A combination of these factors has made very substantial improvements in the yields of poultry, lamb, veal and beef farming, particularly over the past two decades.

Table A shows the estimated animal population of Britain between 1946 and 1967. A steady increase has occurred in most species, but has been most notable in pigs and chickens. Table B shows the corresponding trends in consumption. For bacon, imports have risen substantially along with home production. For other products the rise in home production has been associated with a reduction of imports.

Figure 1 shows the fatstock prices paid to farmers (including the government subsidy) for the years 1959/60 to 1967/68. For comparison the Figure also shows wholesale and retail price indices for goods and manufactures. The gross fatstock prices paid for pigs and sheep have risen relatively little over the period and the fatstock price of cattle has just kept pace with wholesale prices generally. Prices for poultry have fallen sharply. This is a reflection of the efficiency and productivity of animal husbandry over the period. As an example, whereas in 1950 it needed 3·5 pounds of feed per pound of live-weight to produce a 3 pound broiler in nine or ten weeks in 1966 it needed only 2·5 pounds of feed per pound of live-weight to produce a 3·5 pound broiler in eight to nine weeks.

Over this period, antibacterials have been extensively used in animal medicine and husbandry.[1] In 1963 some 40 per cent by weight of all antibacterials used in Britain were given to animals. By 1967 the total usage had increased although the proportion given to animals had fallen to about 35 per cent. Thus over this five year period animal health preparations accounted for between two-fifths and one-third of the total usage of antibacterials in Britain.

[1]The term antibacterial is used to include both antibiotics and synthetic substances with an antibacterial action, such as the sulphonamides.

Table A

Crop Acreages and Livestock Numbers at June in the United Kingdom[1]

	1946	1953	1960	1961	1962	1963	1964	1965	1966	1967
Crop Acreages ('000 acres)										
Wheat ..	2,062	2,217	2,102	1,827	2,256	1,928	2,206	2,535	2,238	2,305
Rye ..	55	68	19	19	18	21	21	18	10	15
Barley ..	2,211	2,226	3,372	3,828	3,987	4,713	5,032	5,395	6,130	6,027
Oats ..	3,567	2,840	1,974	1,733	1,519	1,295	1,125	1,014	907	1,012
Mixed corn	458	804	203	147	125	99	80	73	73	88
Potatoes ..	1,423	985	829	703	737	768	778	741	668	708
Sugar Beet	436	415	436	427	424	423	443	455	446	457
Total tillage	13,300	12,304	11,182	10,871	11,077	11,199	11,496	11,950	12,204	12,354
Temporary grass (²)	5,679	5,803	6,869	7,084	7,022	7,012	6,886	6,573	6,280	5,971
Total arable (²)	18,980	18,107	18,051	17,955	18,099	18,212	18,382	18,523	18,484	18,325
Livestock Numbers ('000 head)										
Dairy cows	3,538	3,682	3,165	3,245	3,290	3,247	3,144	3,186	3,162	3,214
Beef cows ..			848	908	978	1,013	982	1,118	1,106	1,141
Heifers in calf	885	828	823	827	802	742	798	760	750	816
Total cattle and calves	9,629	10,444	11,771	11,936	11,859	11,716	11,627	11,943	12,206	12,342
Sows for breeding	221	699	725	773	857	876	903	945	822	824
Total pigs	1,955	5,165	5,724	6,042	6,722	6,859	7,379	7,979	7,333	7,107
Ewes ..	8,294	8,717	11,232	11,505	11,829	11,832	11,918	11,946	12,019	11,760
Shearlings	2,132	2,153	2,560	2,472	2,534	2,490	2,461	2,596	2,566	2,463
Total sheep and lambs..	20,358	22,455	27,871	28,967	29,498	29,344	29,657	29,911	29,957	28,885
Total poultry	67,117	92,119	103,005	114,289	109,030	112,175	118,377	118,141	118,940	125,624

(¹) The Table relates to agricultural holdings exceeding one acre in extent in Great Britain and, from 1954, of one acre or more in Northern Ireland. Until 1954, figures for Northern Ireland included holdings of one quarter acre or more. Numbers of livestock in Northern Ireland are collected from all owners irrespective of the size of the holding, and also from landless stock-holders, and these numbers are included in the Table.

(²) Owing to changes in the definition of "Temporary grass" in the Agricultural Census, figures from 1959 onwards for these items are not directly comparable with those for the preceding years. Temporary grass includes lucerne.

Source: Ministry of Agriculture, Fisheries and Food - Annual Review and Determination of Guarantees 1968. Cmnd. 3558

Table B

U.K. Meat and Egg Supplies

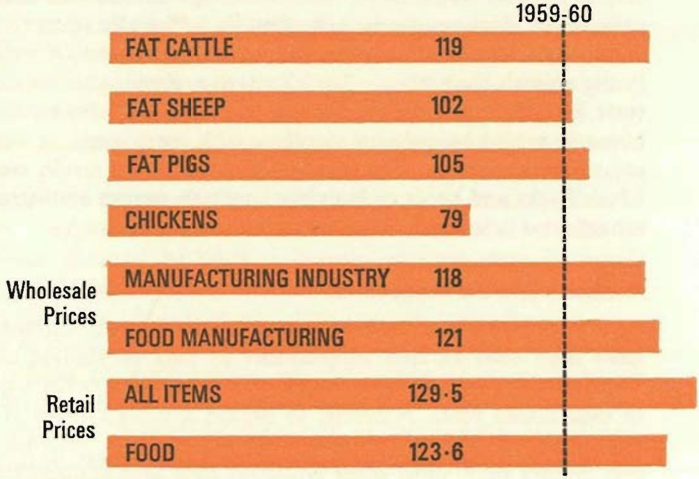
	Beef and veal '000 tons	Mutton and lamb '000 tons	Pork '000 tons	Bacon and ham '000 tons	Poultry meat '000 tons	Total '000 tons	Eggs and egg products million dozen
1946/47							
Home-fed	550	135	15	87	70	857	451
Imported	398	427	29	156	27	1037	436
1953/54							
Home-fed	645	172	280	223	101	1421	764
Imported	336	314	37	296	17	1000	188
1960/61							
Home-fed	758	237	434	189	307	1925	1043
Imported	401	381	22	391	6	1201	85
1961/62							
Home-fed	865	251	471	208	346	2141	1093
Imported	342	334	20	406	4	1106	69
1962/63							
Home-fed	896	249	517	224	340	2226	1092
Imported	394	362	13	392	5	1166	68
1963/64							
Home-fed	903	252	536	216	356	2263	1146
Imported	329	337	12	377	5	1060	46
1964/65							
Home-fed	793	248	582	225	373	2221	1219
Imported	345	371	13	400	13	1142	47
1965/66							
Home-fed	803	249	628	229	401	2310	1165
Imported	310	310	19	401	9	1049	44
1966/67							
Home-fed	852	263	572	198	424	2309	1203
Imported	316	338	7	399	9	1069	55
1967/68 (forecast)							
Home-fed	906	246	564	205	455	2376	1228
Imported	205	347	11	406	11	960	48

Source: Ministry of Agriculture, Fisheries and Food - Annual Review and Determination of Guarantees 1968. Cmnd. 3558

The contribution of antibacterials and other medicines must be measured in different ways in man and in other animals. The purpose in human medicine is to maintain fitness, to alleviate suffering and to prevent premature mortality. The success of prevention and treatment is, therefore, measured in terms of the

Figure 1

Comparative Price Index



quality and length of life of the individual. Of all modern medical discoveries, the antibacterials have probably contributed as much as any to progress in these terms. Certainly they have made one of the greatest contributions to the prevention of premature mortality. (OHE 1962, 1966.)

In animal husbandry, on the other hand, the primary objective is to bring animals in the peak of condition to market weight as quickly and as economically as possible. In addition, of course, antibacterials play an important part in the prevention of suffering from disease; but whereas the success of medicine in humans is judged primarily in humanitarian terms, its success in animal husbandry is judged primarily in economic terms.

Not only does their purpose differ, but antibacterials are also used differently in man and in other animals. For some animals, of course, individual diagnosis and treatment is possible and economic, as it is in human medicine. In other cases, however, individual treatment of animals is not possible; it therefore becomes necessary to dose whole flocks or herds. Although this may not theoretically be an ideal approach, it is effective sufficiently often to yield worthwhile economic benefits and of course to reduce suffering in the animals themselves. The alternative of trying to isolate and treat individual animals (in the way that one can always do with humans) would be quite uneconomic with many types of veterinary medical problems. The economic savings which result, whether whole flocks and herds or individual animals receive antibacterials, are reflected in lower costs for Britain's food.

Antibacterial Feed Supplements

As well as their use in the treatment of animal disease, antibacterials have been used as feed supplements as part of routine animal husbandry in every major livestock producing country for a period of over fifteen years. Although in Britain a limited range of antibiotics and antibacterials have been permitted in growing pigs and poultry only, most other countries have also allowed the use of antibiotics in other species and classes of livestock.

The growth promoting activity of antibiotics, when incorporated in animal diets at very low concentrations, was discovered fortuitously in 1948 by Stockstad *et al.* (1949). Other workers had earlier described experiments in which sulphonamides, organic arsenicals, and streptomycin produced increases in the growth rate of rats and chicks. High doses of the chemicals were used in these earlier studies and it was concluded that the growth promoting effects observed were due to the elimination of specific infections.

Stockstad *et al.* showed that a growth promoting effect was produced in chicks when crude preparations of *Streptomyces aureofaciens* cultures, from which most chlortetracycline had been extracted, were added to the diet. They had designed their experiments to assay the vitamin B. 12 content of *S. aureofaciens* culture residues, but found that these residues produced more rapid growth than could be obtained from adding either crystalline vitamin B. 12 or liver extract to the diet. Stockstad *et al.* first attributed the growth promoting properties of *S. aureofaciens* cultures to 'new' unidentified growth factors, which they tentatively designated vitamin B. 12_B. However, subsequently they demonstrated that the response was due to the presence of traces of chlortetracycline in the extracted fermentation materials.

Early in 1949 samples of fermentation materials were made available to other investigators who confirmed Stockstad's observations and showed that a response was also obtained in turkeys and pigs.

These preliminary observations excited interest amongst animal scientists and nutritionists and it was soon shown that the growth promoting properties of chlortetracycline were shared by certain other antibiotics, notably oxytetracycline and penicillin and that a response was obtained in most of the species of animal investigated, including man. The effect on growth occurred in apparently healthy animals on diets adequate in all known nutrients, as well as in animals on deficient diets. It was also found, not unexpectedly perhaps, that the growth promoting effect was even more marked in the presence of certain intestinal infections. The amounts of antibiotic required to elicit a growth response were so small, 5 to 10 parts per million of diet, that it was economically feasible to incorporate them in commercial diets for farm animals.

The evidence in support of the growth response to be obtained from adding chlortetracycline, oxytetracycline or penicillin to the diet of farm animals, with the resultant economic benefits, led most countries throughout the world to approve the use of antibiotic feed supplements as part of routine animal husbandry. In the United Kingdom amendments were made to the Therapeutic Substances Act (Statutory Instruments 1953/1174: 1954/1647) permitting the unprescribed sale to farmers of antibiotic feed supplements containing not more than 1 part of chlortetracycline, oxytetracycline or penicillin in 90 parts of supplement (5 g/lb), and antibiotic supplemented animal feeds containing not more than 1 in 10,000 parts of the same antibiotics (100 g/ton).

Many attempts have been made to discover how antibiotics, when incorporated in feed at levels of a few parts per million, bring about an improvement in the growth of animals. The available evidence is in favour of theories which postulate that antibiotics facilitate growth through their antibacterial activity and their action on the intestinal flora. The two cornerstones which support this contention are; first, that a number of antibiotics with dissimilar chemical properties all produce a growth promoting effect; second, that 'germ-free' animals bred in a sterile environment show no antibiotic growth response, but their growth parallels that of normal animals treated with antibiotics. It is possible that the mode of action depends on the inhibition of specific bacteria in the intestinal tract which produce growth retarding toxins; or the inhibition of bacteria which by themselves or in association with others can cause sub-clinical diseases; or the inhibition of bacteria which compete with the host for essential nutrients; or on the indirect stimulation, by inhibition of competitive flora, of intestinal bacteria which synthesise vitamins and other nutritional factors essential to the growth of the host animal. These various possibilities are not mutually exclusive and each of the suggested modes of action may contribute to the overall effect.

Changes in the thickness of the gut wall, increased absorption and utilisation of nutrients, increase in the weight of certain endocrine glands and changes in liver physiology, all of which have been observed in antibiotic fed animals, are probably secondary to the action of antibiotics on the intestinal flora. Indeed many of these changes have also been observed in 'germ-free' animals.

Economic Benefits from Feed Supplements

The benefits from the use of antibiotics as animal feed additives were reported in many publications in the 1950s and early 1960s. For example, the chapter on Non-medical Uses of Antibiotics in *Advances in Applied Microbiology* (Goldberg, 1964) states that "excellent reviews on the use of antibiotics in animal nutrition are available by Jukes (1955), Fernando and Jacquet (1958), and Luckey (1959). These reviews emphasise the fact that antibiotics stimulate appetite, increase food efficiency, reduce requirements for vitamins, increase survival, and most significant of all, increase the growth rate". Many other review articles have described the benefits of antibiotics in animal feed supplements. (e.g., Taylor 1957, Preston 1962, Robinson 1962 and Coates 1962).

In recent years, however, doubts have been expressed as to whether these benefits have continued. Two factors, apart from the effectiveness of feed supplements, will affect the picture. The first is the improvement in the strains of animal, which themselves will tend to increase growth rates and feed conversion factors over time. The second is the conditions under which the animals are reared. Both these factors may have clouded the issue in some cases. Nevertheless, there are studies which indicate that both pigs and poultry can continue to show worthwhile improvements in performance as a result of antibiotic feed supplements over periods of at least ten years.

One such study was on the use of chlortetracycline in pigs between 1949 and 1959. (Drain and Kwoek 1959). Tables C and D show the growth rates and feed conversion efficiencies for both treated and untreated pigs in half yearly experiments carried out at various U.S. State and government experimental stations. Over the ten year period chlortetracycline (Aureomycin) in quantities ranging from 9 to 100 grams per ton was used continuously at the experimental stations.

Table C

Experiment Station Data on Average Daily Gains of Growing-finishing Swine

STATION (No. Pigs)	*TREATMENT*	*CHRONOLOGICAL EXPERIMENT NUMBER – (HALF-YEAR INTERVALS)*																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Florida	Control	1·40*	1·28		1·53				1·64											
(182)	Aureomycin	1·47	1·34		1·60				1·93											
Georgia	Control	1·34	1·27	1·62	1·60					·67										
(222)	Aureomycin	1·56	1·45	1·83	1·70					1·75										
Indiana	Control	1·61				1·47	1·72	1·31		1·35	1·45			1·52		1·48				
(501)	Aureomycin	1·89				1·70	1·82	1·50		1·35	1·68			1·66		1·58				
Iowa**	Control	0·93		1·19	1·12	1·35	1·14	1·53			1·60				1·40					
(884)	Aureomycin	1·23		1·32	1·24	1·42	1·37	1·52			1·44				1·52					
Kansas	Control	1·38	1·54	1·72	1·61															
(36)	Aureomycin	1·60	1·85	1·87	1·68															
Kentucky	Control	1·30	1·59		1·18							1·36	1·48							
(220)	Aureomycin	1·56	1·81		1·48							1·47	1·58							
Minnesota	Control	1·40		1·45		1·74	1·59		1·54		1·49						1·50			
(91)	Aureomycin	1·63		1·63		1·79	1·73		1·68		1·66						1·58			
Missouri	Control	1·70	1·48	1·23		1·10			1·49			1·33				1·73	1·59			
(304)	Aureomycin	2·00	1·64	1·53		1·32			1·56			1·40				1·68	1·68			
Nebraska	Control	1·55			1·42	1·30		1·45												
(208)	Aureomycin	1·64			1·56	1·78		1·53												
New Jersey	Control	1·50	1·65	1·70	1·91	1·64	1·60	1·73	1·87	1·96	1·63		1·96	1·65	1·74					
(164)	Aureomycin	1·57	1·77	1·55	1·86	1·63	1·85	1·87	1·99	1·95	1·78		1·96	1·69	1·90					
New York	Control	1·26	1·30	0·97			1·51	1·34	1·46	1·30	1·43									
(427)	Aureomycin	1·36	1·45	1·23			1·67	1·50	1·66	1·34	1·55									
Ohio	Control	1·21		1·68		1·58	1·60			1·70	1·72						1·60	1·57	1·64	1·52
(346)	Aureomycin	1·70		1·83		1·62	1·60			1·76	1·82						1·71	1·64	1·84	1·64
S. Dakota	Control	1·61				1·38	1·65				1·57	1·48	1·58	1·60	1·65		1·57			
(362)	Aureomycin	1·84				1·47	1·75				1·81	1·75	1·58	1·78	1·79		1·73			
U.S.D.A.	Control	1·39	1·56	1·33		1·38	1·46	1·53												
(208)	Aureomycin	1·50	1·71	1·44		1·38	1·51	1·62												

*Average daily gain expressed in pounds.

**Data for Iowa pertains to growing phase (weaning to 100 lb.) – not included in final summary.

Source: Drain & Kwoek (1959)

Table D

Experiment Station Data on Feed Efficiencies of Growing-finishing Swine

STATION (No. Pigs)	TREATMENT	CHRONOLOGICAL EXPERIMENT NUMBER – (HALF-YEAR INTERVALS)																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Florida (182)	Control	3·47*	3·42		3·09				3·26											
	Aureomycin	3·36	3·35		3·05				3·19											
Georgia (222)	Control	4·48	3·92	3·72	3·66					3·52										
	Aureomycin	3·84	3·56	3·63	3·55					3·37										
Indiana (510)	Control	3·50				3·43	3·37	3·63		3·49	3·77			3·09		3·40				
	Aureomycin	3·36				3·35	3·40	3·43		3·28	3·44			3·11		3·30				
Iowa** (884)	Control	2·34		3·37	3·35	3·16	3·05	2·74			2·67				2·49					
	Aureomycin	1·98		3·21	3·07	3·05	2·73	2·65			2·32				2·43					
Kansas (36)	Control	3·83	3·41	3·89	3·20															
	Aureomycin	3·64	3·31	3·62	3·48															
Kentucky (220)	Control	3·58	3·61		4·20							3·72	3·99							
	Aureomycin	3·61	3·03		3·94							3·62	3·59							
Minnesota (91)	Control								3·78		3·76						3·36			
	Aureomycin								3·74		3·71						3·25			
Missouri (304)	Control	3·99	3·91	3·68		3·98			3·64			3·64				3·04	3·84			
	Aureomycin	3·41	3·64	3·46		3·63			3·52			3·50				3·09	3·47			
Nebraska (208)	Control	3·30			3·19	3·10		3·42												
	Aureomycin	3·27			3·36	3·18		3·42												
New Jersey (164)	Control	3·75	3·59	3·47	3·76	3·29	3·47	3·55	3·57	3·40	3·50		3·44	3·34	3·46					
	Aureomycin	3·74	3·58	3·18	3·90	3·40	3·68	3·61	3·60	3·48	3·47		3·62	3·16	3·17					
New York (427)	Control	3·92	3·90	3·99			3·60	3·55	3·56	4·00	3·68									
	Aureomycin	3·89	3·84	3·95			3·58	3·50	3·52	3·78	3·64									
Ohio (346)	Control	3·83		3·55		3·60	3·49			3·58	3·56						3·53	3·69	3·29	3·49
	Aureomycin	3·51		3·43		3·51	3·40			3·48	3·44						3·46	3·58	3·24	3·39
S. Dakota (362)	Control	3·70				3·65	3·42				3·31	3·33	3·98	3·35	3·55		3·39			
	Aureomycin	3·48				3·56	3·44				3·26	3·31	3·91	3·29	3·32		3·26			
U.S.D.A. (208)	Control	3·82	3·62	3·34		3·69	4·09	3·44												
	Aureomycin	3·72	3·43	3·40		3·68	3·76	3·58												

*Pounds of feed required per pound of gain.

**Data for Iowa pertains to growing phase (weaning to 100 lb.) – not included in final summary.

Source: Drain & Kwoek (1959)

The results in Tables C and D were then analysed in the way described in Appendix I. The results, given in Figure C of the Appendix, show that the feed conversion rate improved steadily in both treated and control groups over the ten years, and were still significantly different at the end. On the other hand, the growth rate of the treated group remained constant, while that of the control group rose. Nevertheless, it remains of considerable economic significance that the feed requirements per pound of growth were still 0·11 lb lower in the treated group at the end of ten years.

Another study examined the response of chickens to penicillin and the tetracyclines which were used continuously over a ten year period although controlled experiments were not carried out in all years, (Heth & Bird, 1962). The results are shown in Table E which compares the weight of the untreated (basal) groups with those of treated groups at the age of three weeks. Although the results were somewhat more variable in the later years, there was little difference in the average response in the years before and after 1954. For penicillin, the treated groups averaged 108·5 per cent of the basal weight in the early years and 108·8 per cent in the later years. The comparable figures were 112·3 and 110·2 for the corresponding periods with the tetracyclines. Other work shows that the improved weight gain is maintained up to the age of eight or nine weeks when broiler chickens are ready for the market and suggests that weight at that age, after feeding with chlortetracycline, for example, is 2·5 per cent greater while total feedstuff consumption is about 2·5 per cent less. (Smith 1966.)

It is undoubtedly possible to use antibiotics as feed supplements in dosages and in circumstances in which they contribute nothing to the growth or feed conversion rates. However, the studies quoted have demonstrated that even after prolonged use the supplements can cut down food requirements by some three per cent and can increase growth rates by as much as ten per cent. This evidence that they can still yield substantial benefits in animal husbandry after prolonged administration was supported in two papers at a Symposium held in 1967 under the auspices of the National Academy of Sciences – National Research Council. The first by Hays (1969) pointed out that "antibiotic feed supplements have now been used routinely and successfully in livestock production for more than 15 years. As the demand for animal protein increases with expanding world population, the use of antibiotics will become increasingly important for maintaining an efficient and competitive livestock industry". The second, by Bird (1969) concluded that "the beneficial effects of low levels of antibiotics on growth rate, feed efficiency and viability of chickens and turkeys are clearly established. This use of antibiotics is a factor of major importance

Table E

Effect of procaine penicillin and tetracyclines on the growth of chicks fed an adequate diet

Date experiment started	3rd week average weight			Weight – % of basal	
	Basal gm.	Penicillin gm.	Tetracycline gm.	Penicillin	Tetracycline
9–50*	173	226 (10)		131	
9–50*	173	226 (20)		131	
9–50*	173	219 (30)		127	
10–50	214	230 (5)		107	
10–50	214	204 (10)		95	
10–50	214	222 (20)		104	
11–50	181	196 (10)		108	
11–50	181	215 (10)		119	
5–51*	251		287 (25–c)		114
5–51*	240		269 (25–c)		112
5–51*	264		273 (25–c)		103
5–51*	255		278 (25–c)		109
6–51*	185		233 (25–c)		126
6–51*	221		245 (25–c)		111
6–51*	181		212 (25–c)		117
11–51*	153	168 (15)	201 (15–c)	110	131
11–51*	132	160 (15)	172 (15–c)	121	130
11–51*	139	178 (15)	165 (15–c)	128	119
11–51*	196	198 (15)	224 (15–c)	101	114
11–51*	173	219 (15)	190 (15–c)	127	110
11–51*	217	228 (15)	229 (15–c)	105	106
12–51*	232	264 (15)	271 (15–c)	114	117
12–51*	230	252 (15)	257 (15–c)	110	112
12–51*	228	249 (15)	252 (15–c)	109	111
12–51*	222	226 (15)	228 (15–c)	102	103
12–51*	208	236 (15)	234 (15–c)	113	112
2–52*	219	226 (15)	258 (15–c)	103	118
2–52*	228	205 (15)	217 (15–c)	90	95
2–52*	187	192 (15)	200 (15–c)	103	107
2–52*	184	218 (15)	198 (15–c)	118	108
2–52*	170	210 (15)	221 (15–c)	124	130
3–52*	164	190 (10)		116	
3–52*	212	251 (15)		118	
3–52*	206	216 (15)		105	
3–52*	222	240 (15)		108	
3–52	251	270 (15)		108	
3–52	204		217 (15–c)		106
3–52	198		237 (15–c)		120
3–52	214		239 (15–c)		112
3–52*	241		250 (15–c)		104
4–52*	225	237 (15)	224 (15–c)	105	100
4–52*	136	164 (15)	164 (15–c)	121	121
4–52*	266	283 (15)	270 (15–c)	106	101
4–52*	201	214 (10)		106	
5–52*	174	122 (15)	152 (15–c)	83	103
(2 wk trial)					
6–52*	202	208 (10)		103	
9–52*	285	277 (15)		97	
9–52*	248	245 (15)		99	
9–52*	269	264 (15)		98	
9–52*	215	225 (15)		105	

Date experiment started	Basal gm.	3rd week average weight Penicillin gm.	Tetracycline gm.	Weight – % of basal Penicillin	Tetracycline
9–52*	196	210 (1)		107	
9–52*	196	198 (4)		101	
12–52*	204	208 (4)		102	
1–53*	189	189 (4)		100	
5–53*	198	197 (4)		99	
5–53*	206	223 (15)		108	
7–53*	196	190 (15)		97	
11–55	273	284 (15)	286 (35–c)	104	105
3–56	125	154 (30)		123	
4–56	144	166 (30)		115	
7–56	163	188 (30)		115	
8–56	212	221 (30)		104	
11–56	160	154 (30)		96	
11–56	128	150 (5)	157 (35–c)	117	123
11–56	128		181 (10–c)		141
1–57	141	123 (5)	156 (10–c)	87	111
1–57	141		167 (35–c)		118
2–57	134		152 (35–c)		113
10–57	182	227 (35)	232 (35–c)	125	127
11–57	177	160 (35)	169 (35–c)	90	95
2–58	262	250 (10)	257 (35–c)	95	98
3–58	233	262 (10)		112	
10–58	172	226 (4)	236 (10–c)	131	127
11–58	215	225 (4)	224 (10–c)	105	104
12–58	177	200 (4)	199 (10–o)	113	112
1–59 (floor pen)	235		237 (10–o)		101
1–59	230		256 (10–o)		111
2–59	210		229 (10–o)		109
2–59	208		209 (10–o)		101
4–59	196		188 (10–o)		96
5–59	192		222 (10–o)		116
6–59	185		207 (10–o)		112
12–59 (2 wk trial floor pen)	149		141 (10–o)		95
2–60	257		284 (10–c)		110
2–60	257		313 (20–c)		122
2–60	257		246 (10–o)		96
5–60	272		302 (10–c)		111
5–60	272		288 (20–c)		106
5–60	272		283 (10–o)		104
12–60 (floor pen)	302		316 (10–c)		105
12–60 (floor pen)	302		322 (20–c)		107
12–60 (floor pen)	302		331 (10–o)		110

Numbers in parentheses refer to milligrams per kilogram of antibiotic used. Letter following tetracycline level denotes kind tetracycline fed – c chlortetracycline, o oxytetracycline.
*Date previously reported by Waibel *et al.*

(Extracted from *Poultry Science* 41.755 – Heth, D. A. and Bird, P. R.)

Table F

National Economics of Use of Chlortetracycline for Chickens in United Kingdom

	Chickens (0–8 to 9 wks of age)
National crop (approximate no)	220 million
Live weight produced approx. (tons)	0·40 million
% extra live weight from chlortetracycline	2·5%
∴ extra live weight from chlortetracycline (tons)	10,000
Value of chickens meat/tons live weight	£168
∴ Value of extra meat from chlortetracycline	£1,680,000
Total live weight provided (tons)	0·41 million
Total food required (F.C.E.=2·4) (tons)	0·984 million
Saving in food from chlortetracycline	2·5%
∴ Feed saved from chlortetracycline	24,600
Value of feed saved at £40/ton	£984,000

The use of chlortetracycline as recommended, on a national basis for broiler chickens would result in the production of an extra 10,000 tons of chickens and a saving of 24,600 tons of feed. In terms of economics this represents extra liveweight worth £1·68 million and savings in feed wroth £0·984 million, a total value of £2·664 million.

in our modern efficient production of poultry meat. It is as important now as it was in the early 1950s."

The substantial economic benefits from the use of these antibiotics can be measured in financial terms. On the basis of the savings estimated above, the use of chlortetracycline for all the 220 million broiler chickens reared in Britain each year would yield savings of £2·7 million (Table F). Similar estimates relating to Britain's crop of approximately 10 million pigs annually suggest that the total savings, from increased weight gain and reduced food consumption, would be about £8·6 million (Table G). Clearly these figures will vary according to the exact circumstances, and another estimate given by Braude (1968) suggests that the combined potential economic saving for both species was about £5 million a year. On either basis, the savings are substantial, and price competition will ensure that the majority of this benefit is passed on to the eventual consumer.

Table G

National Economics of Use of Chlortetracycline as Recommended for Growing-fattening Pigs

	Bacon Pigs	*Pork Pigs*	*Total Effect*
National crop (approx. no)	5 million	5 million	
Live-Wt produced approx. (tons)	450,000	300,000	
% extra live weight from chlortetracycline	2·6%	5·5%	
Extra live weight from chlortetracycline (tons)	11,700	16,500	28,200
Value of pig meat/ton live weight (approximately)	£200	£200	
Value of extra meat produced by chlortetracycline	£2,340,000	£3,300,000	£5,640,000=3·7%
Total tonnage live weight produced	461,700	316,500	
Total food required (F.C.E. of 3·5) million tons	1·62	1·11	
Saving in feed from chlortetracycline %	2·6	5·5	
Feed saved from chlortetracycline (tons)	42,170	61,050	103,220
Value of feed saved at £30/ton by chlortetracycline	£1,263,600	£1,831,500	£3,095,100=3·7%

The use of chlortetracycline as recommended on a national basis for growing and fattening pigs would result in the production of an extra 28,200 tons of pig and a saving of 103,220 tons of feed. In terms of economics this represents extra liveweight worth £5·5 million and saving in feed worth £3·1 million, a total value of £8·6 million.

Development of Resistance in Bacteria

SINCE the first development and use of antibiotics, it has been known that bacteria could develop resistance to them so that the antibiotics ceased to be effective. Originally, it was assumed that resistance to antibiotics arose by a natural process of selection. If a small proportion of any population of bacteria were naturally less susceptible than the rest to a particular antibiotic, the process of natural selective breeding would favour this small proportion if the population were exposed to that antibiotic. Thus over a period of time, in the presence of the antibiotic, the whole bacterial population would be of the resistant type. This type of resistance could emerge only gradually in a population of bacteria exposed to antibiotics for a prolonged period. High doses of antibiotic usually destroy the bacteria before such resistance emerges. Once the antibiotic is withdrawn a reverse natural selective breeding pressure comes into play, because the sensitive bacteria, in the absence of antibiotics, are usually hardier than the resistant organisms. Thus, the bacteria tend once again to lose their resistance to the antibiotic.

In 1959, however, it was demonstrated that in some cases antibiotic resistance could be transferred to other bacteria of related species by an "infective" or "sexual" process. By this process, whole populations of bacteria could acquire resistance very quickly without waiting for natural selective breeding to produce its effect. Furthermore, the resistance could continue to spread even when the bacteria were no longer exposed to the antibiotic which might have produced resistance in the first place. "Infectiously resistant" bacteria (not necessarily themselves pathogenic) passing from one person or animal to another could induce antibiotic resistance in similar bacteria in their new host. This phenomenon is also known as "transferable" resistance.

It was first studied in Japan, almost exclusively in dysentery bacilli which are purely human pathogens. It was not, therefore, originally associated with the use of antibiotics in animals, although it has since been discussed very largely in that context. So far, the problem of infectious drug resistance appears to be confined to the enterobacteriaceae and a few other genera of Gram-negative bacilli (e.g., *Shigellae, Salmonellae* and *E. coli*), and hence to antibiotics used in the treatment of diseases caused by these organisms. These, therefore, present a special situation.

As far as the enterobaceriaceae are concerned, the prolonged use of antibiotics in animal husbandry can lead to an increase in strains of bacteria which have multiple infectious resistance. Similarly, the prophylactic and therapeutic use of antibiotics, for example in calves, can also be shown to lead to the recovery of resistant strains of bacteria. The potential hazards to human health arising from this situation have received extensive publicity. The problem falls into two parts, which should be considered separately. First, infectiously resistant organisms could be a source of antibiotic resistance in humans, even though the organisms themselves were non-pathogenic. Second, pathogenic organisms from animals, also resistant to antibiotics, can actually cause infections in man.

The safety in use of antibiotics as veterinary products is the responsibility of the veterinary profession, while the safety in use of antibiotics as animals feed supplements is the responsibility of Government acting on the advice of various committees. One of these, the Joint Committee on Antibiotics in Animal Feeding (The Netherthorpe Committee), examined the problem and concluded in their Report in 1962 that the then current practices and legislation in relation to the use of antibiotics in animal husbandry were satisfactory, in that the economic benefits outweighed any theoretical hazards. In particular, it recommended that the use of antibiotics for growth promotion, at present restricted to poultry and pigs, should be extended to calves. Although this recommendation was not implemented, the general conclusions of the Netherthorpe Committee were not questioned in the light of the knowledge then available. Largely because of the question of transferable resistance, however, it has now been suggested that changes are in fact necessary in the law. A further Committee under the Chairmanship of Professor Swann is, therefore, meantime re-examining the subject.

Antibacterials on 'Free Sale'

Any transfer of infectiously resistant organisms from animals to man could arise from two sources. The first would be the use of antibacterials on sale without veterinary prescription as feed additives. In addition to the freedom granted for penicillins and some tetracyclines, a new antibiotic, tylosin, used exclusively for animals, has also since been exempted from the Therapeutic Substances Act. The sulphonamides and nitrofurans are other antibacterial substances available without prescription as food additives.

In Britain, penicillin and tetracycline may be used at low dosage levels for long periods without veterinary supervision in growing fowls and pigs but not in calves; yet it is in the latter that resistance appears to be the greatest problem. Williams Smith has shown that bacterial resistance to the tetracyclines, for example, occurred more often in calves than in pigs or fowls (1968). Furthermore, he showed that the proportion of resistant *E. coli* collected from humans was much the same as the proportion among *E. coli* collected from pigs, and very much higher than the figure for fowls. This calls into question whether the availability of "free sale" and the prolonged use at low dosage in pigs and poultry represent specific hazards in relation to the development of resistance.[1]

Britain appears to have considerably stricter controls on the use of antibacterials for growth promotion than most other countries. Table H is taken from *Advances in Applied Microbiology* (Goldberg, 1964) and shows that at that time the range both of products permitted and the animals to whom they could be administered were generally wider than in Britain.

Appendix 2 is taken from the draft EEC regulations, showing the proposals for permitted feedstuffs additives. Again, these cover a wider range of substances and species of animal than at present applies in Britain.

The greatest significance of this is that, in so far as these antibacterials stimulate growth, their use could make overseas farming more economic than Britain's. Furthermore, it means that British experience in antibiotic resistance cannot be regarded in isolation. If British regulations are thought to have been responsible for the present extent of antibiotic resistance in Britain, the more liberal regulations in other countries should be associated with more widespread antibiotic resistance in those countries. Evidence on this point appears to be lacking, but it is not generally argued that antibiotic resistance in Britain has been less of a problem than overseas (as would be expected from the argument that limited "free sale" in Britain had been a significant causal factor in respect of the problem in this country).

Veterinary Use

The second problem concerns the circumstances where the administration of antibacterials should be under veterinary supervision. The principal cause for concern in this respect appears to be the administration of antibiotics to calves particularly as there is

[1]A possible explanation for this situation is contained in the work of Bandaranayake (1959) who has shown, both *in vitro* and *in vivo*, that in *E. coli* the level of persistence of induced resistance to chlortetracycline and streptomycin and the rapidity with which resistance develops is dependent on the level of antibiotic to which the organism is exposed. The administration of antibiotic in drinking water to mice at levels corresponding to those used in feed for growth promotion (10 to 100 gm per ton) caused a gradual increase in the resistance of an implanted strain of *E. coli* on repeated oral passage. With chlortetracycline the degree of resistance achieved was such that the organism would still be susceptible to therapeutic doses of the antibiotic. When antibiotics were administered in drinking water at levels corresponding to those used in therapy (200 to 400 g per ton) *E. coli* rapidly developed a higher degree of resistance. On repeated passage in non-medicated mice, *E. coli* which had developed a low degree of resistance reverted to their original sensitivity whilst some of those with a high degree of resistance remained resistant.

Table H

National Regulations for Antibiotic Feed Supplements

Country[1]	*Antibiotics*	*Animals*	*Maximum level (p.p.m.)*
Austria	OTC–CTC–penicillin	Pigs–poultry	60
Belgium	OTC–CTC–penicillin–bacitracin	Calves–pigs–poultry	50
Denmark	OTC–CTS–penicillin	Young growing animals	25
Finland	OTC–CTC	Pigs–poultry–fur bearers	50
France	OTC–CTC–penicillin–bacitracin[2]	Pigs–poultry	200
Germany	OTC–CTC–penicillin	Pigs–poultry–calves	200
Great Britain	OTC–CTC–penicillin	Growing pigs–poultry	100
Holland	Not specified	Pigs–poultry–calves	100
Norway	OTC–CTC–penicillin	Pigs–poultry–calves	50
Sweden	OTC–CTC–penicillin	Pigs–poultry–calves–mink	20
Switzerland	OTC–CTC–penicillin–bacitracin	All except dairy cattle	50
United States	OTC–CTC–penicillin–bacitracin[2]	Pigs–poultry–calves	2000

[1]Ireland, Greece, Israel, Italy, and Portugal have no restrictions.

[2]Also several other antibiotics.

Extracted from *Advances in Applied Microbiology* (Goldberg 1964).

evidence that resistant pathogens can be transferred from this source to man. (Anderson E.S. 1968.) The first possibility is that the spirit of the law is not being observed and that antibiotics are, in fact, being used at high levels by breeders without supervision. This could occur either because they were bought without prescription (possibly from abroad), although a prescription should have been required, or because antibiotics bought legally for one purpose were used improperly for another. If this is the case, the solution lies in adequate and properly enforced sanctions for misuse and certainly in better education of farmers about the importance of complying both with the law and with manufacturers' instructions. There are obviously good economic reasons why farmers should not use antibacterial feed additives in cases where they will yield no benefit.

To cut down the risk of misuse of antibacterials on free sale to farmers, the Association of the British Pharmaceutical Industry has recently advocated to the Swann Committee that feed compounders (including farmers who mix their own feeds) should have to be licensed. Antibacterial feed supplements should then be supplied without prescription only to these licenced feed manufacturers.

The second possibility of misuse recognises the veterinary profession's difficulty in supervising the use of antibacterials which they have prescribed. The problem is comparable to that in human medicine, where the doctor cannot be certain that the tablets he prescribes are used as directed; only on the farm it becomes an immeasurably greater problem. The effects of this could, in turn, be accentuated by some unsatisfactory current practices in animal husbandry, and by inadequate hygiene control in food handling. In particular, farmers should be aware that persistent outbreaks of infection caused by resistant organisms can only effectively be controlled by a complete withdrawal of the antibacterials in question.

It is, however, worth pointing out that the undoubted spread of drug resistance in recent years does not appear to have been associated with any increase in the number of cases of *Salmonella typhimurium* infections in humans. Infections from this organism have been responsible for the greatest public health concern in respect of the use of antibiotics in animal husbandry because of the severity of the infections which they cause. Figure 2 shows that the reported incidents of food poisoning due to *S. typhimurium* infection fell from 3329 in 1958 to 1721 in 1965 (Vernon 1966). Walton (1968) has stated that this trend, associated with a rise of *S. typhimurium* infection in calves, suggested that "the calf is not the main reservoir of *S. typhimurium* in man". It must also be remembered that there are very substantial benefits from antibacterials as prophylactics against infection, when they are used to supplement and not as a substitute for good husbandry.

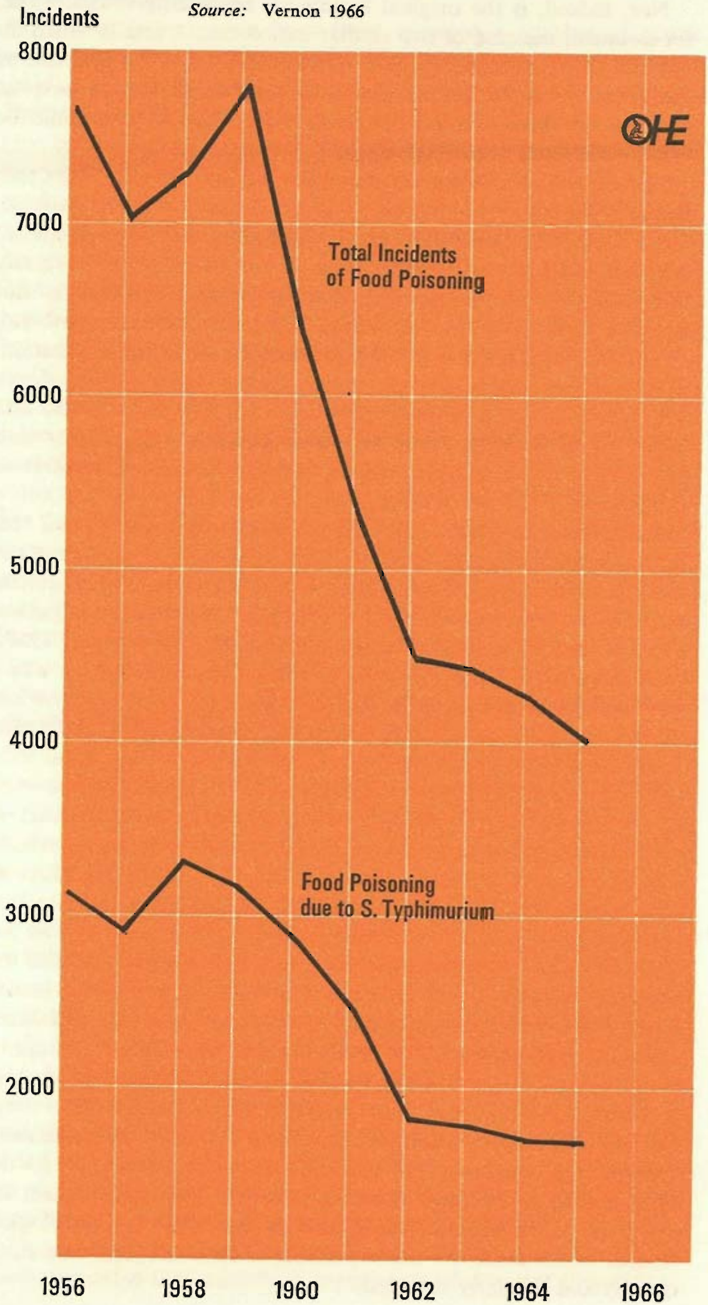
Antibacterials in Human and Animal Medicine

It is often said that the ideal situation would be for antibacterials used in human medical practice not be to used for animals, and vice versa. Clearly, when products are of specific value for particular purposes they should be used only for those purposes and should not also be used in other ways where they would be inappropriate. It appears increasingly likely that new products will be discovered which are of value in such specific circumstances so that they will not be marketed for a wide range of different purposes. At present, however, the control and treatment of infections in veterinary practice presents a less easily soluble problem. The logical consequences of restricting some antibacterials to animal medicine and some to human medicine would be either that valuable antibacterials were withheld from medical practice or that the veterinary surgeons were left only with an armamentarium of less efficient products. It seems likely that the former situation would be unacceptable to the medical profession, and the latter unacceptable to the veterinary profession.

Figure 2

Incidents of Food Poisoning; England and Wales; 1956-65.

Source: Vernon 1966



Nor, indeed, is the original hypothesis necessarily sound. Take, for example, the case of two similar antibiotics, A and B which do not induce cross-resistance. It is quite possible that the problem of resistance would be greater if A were used exclusively in hospital and B used exclusively on the farm, rather than if both could be used alternatively in each situation.

In fact, the overriding consideration in the use of all antibacterials is the very considerable range of alternatives now available. Some forty different antibacterials (excluding the sulphonamides) are now available for prescription. It has become an extremely rare situation to find an infection or organism which is not sensitive to a number of alternatives. The much-publicised outbreak of enteritis on Tees-side in 1968 represented an extreme situation. The causative organism was tested against eight out of eleven antibiotics to which it might have been expected to respond and found to be resistant to all of them. There is a possibility that even in this extreme case, however, it might have been sensitive to at least one of the other three.

Valman and Wilmers (1969) reported an outbreak of *E. coli* infection in an acute gastroenteritis ward in London where the otherwise resistant organisms were sensitive and responded to gentamicin. In the Manchester outbreak in the same year, the causative organism was sensitive to colistin sulphate and gentamicin. (*Lancet*, 1969.) As a contrast to these incidents where antibiotic resistance was a very serious problem, in a widespread *Salmonella typhimurium* epidemic in Glasgow in 1968, which was associated with the occurence of the organism in pigs, it was sensitive to all the usual antibiotic and chemotherapeutic agents. (Miller *et al*, 1969.) A position somewhere between these extremes is probably more typical; in such cases although faced with the problem of resistance a clinician will be left with a choice of several effective antibiotics. Just as pharmaceutical and medical research is gradually solving the problem of strains of organisms which have always proved intractable (such as the Pseudomonas), so it is tending to diminish the potential significance of acquired resistance. There is no justification for complacency in regard to antibiotic resistance in human medicine, but, on the other hand, there is no evidence to suggest that the total range of effective antibacterials available to doctors is becoming diminished over time. What is needed is a more efficient information system to ensure that the resistance patterns of troublesome organisms are established and made known to the clinicians at the earliest possible moment. This could mean an extension of the bacteriological services and better epidemiological studies which could be made possible if serious cases were more quickly and regularly reported.

Recent Developments

Since the Netherthorpe Committee reported a number of newer antibacterial preparations have been introduced and in some cases, these appear to show advantages over the older preparations. Tylosin, virginiamycin, nitrovin, spectinomycin, nalidixic acid and zinc bacitracin are six products which have come into use in animal husbandry since then, although the last three are not yet on the market for this purpose in Britain. Tylosin and virginiamycin are used exclusively for animals in Britain (the latter exclusively for growth promotion in poultry). The former is excluded from TSA regulations and available on free sale to farmers; the latter is restricted to prescription by a veterinary surgeon. Both products have been shown to produce significant improvements in growth and feed conversion.

There is a possibility of cross-resistance developing between tylosin and other related antibiotics (macrolides) used in human medicine. Virginiamycin can show cross-resistance with such closely related antibiotics as streptogramin and pristinamycin and has "one-way" cross-resistance with erythromycin. Neither cause cross-resistance with other widely used antibiotics. Most important of all, in neither case does the resistance affect the enterobacteriaciae (the organisms commonly subject to infectious resistance) because these antibacterials have no activity against these organisms. Hence there appears to be no obvious risk of infectious drug resistance from the use of either of these products. The case for allowing these antibacterials on free sale as feed supplements appears even stronger than the case which was accepted by the Netherthorpe Committee in respect of the older products. Nitrovin (a nitrofuran) has been introduced for use in poultry, and it also appears to give better growth rates and feed conversion for this purpose than the older antibiotics.

Zinc bacitracin and nalidixic acid, although permitted as feed additives in many other countries, are not yet on the market as such in Britain. Permission has, however, been sought to introduce the former for this purpose, and it is understood that the Department of Health and Social Security proposes to permit its use in feedingstuffs for broilers, growing chickens, turkeys and pigs.

A further recent development has been the use of antibacterial feed supplements in low doses for the treatment of animals in periods of 'stress'. Farmers and veterinary surgeons have frequently found that at times when animals are moved or weaned or handled for vaccination, for example, their performance is upset. Their growth may temporarily stop and they may become prone to disease. Although the precise mechanism for the upset is not known, it is understandable that disturbing experiences of this sort should have an adverse effect. In the economic environment of modern intensive farming it is important to avoid this sort of set-back if possible. It was discovered empirically that low doses of antibiotics given for short periods could achieve this, although once again there is no scientific explanation for this effect. The doses of antibacterials used in this connection are rather higher than for growth promotion, but are still below the limits permitted by the T.S.A. relaxing regulations and well below the levels used in veterinary medicine. The benefits cannot be measured so precisely as those from prolonged use in growth promotion. However the principles on which the risks and benefits should be balanced are similar.

The Future

THERE have been very substantial human and economic benefits from the use of antibiotics and similar products in both man and animals. These benefits are being maintained or increased as the range of available antibacterial substances is extended, largely as a result of research in the pharmaceutical industry laboratories.

As far as animal feed supplements are concerned, the Netherthorpe Committee in 1962 took the view that the benefits outweighed the potential hazards of the use of penicillin and tetracycline for growth promotion in pigs and poultry, and recommended that their use should be permitted for the same purpose in calves. Since then, the existence of infectious drug resistance has been publicised and doubts have been expressed about the benefits now derived from this use of antibiotics.

Evidence is fast accumulating that infectious drug resistance is common in human intestinal bacteria, whether pathogenic or not. It has also been found in similar bacteria causing infections of the urinary tract. In all recent studies of drug resistance in bacteria from these sources, it has been found to be transferable in 60 per cent or more of the cultures examined. In other words, this is the usual form that drug resistance takes in bacteria of this kind, although the fact has only recently been recognised. How common it is may be judged from the recent studies of Datta (1969), who found that a large proportion of patients had such organisms in their gut on admission to hospital, and of Moorhouse (1969), who found such bacteria in a large proportion of healthy infants in an urban community. Each of these authors has also produced evidence that such resistant bacteria can be acquired during a stay in hospital, evidently by transfer from other patients. It seems that there must be a fairly free exchange of intestinal bacteria by various means between different individuals, and much of the common drug resistance which is now seen may well have arisen in this way. Whether this is so or not, the resistance is already widespread, and it is difficult to contest the view expressed in the British Medical Journal (1969) that however this resistance has arisen, "it is doubtful whether further contributions from any extraneous sources are likely to make much difference to it".

The likelihood of transference from animals to man may depend on the species transmitted. When it is capable of causing human disease, it will multiply freely in the human gut. But if it is only a normal animal bowel inhabitant, with which meat and other foods may sometimes be contaminated, can this establish itself in the human bowel and transfer resistance to the local species? There is apparently no evidence that it can, and some interesting recent evidence that it usually will not. Williams Smith (1969) fed large numbers of drug-resistant *E. coli* from pigs, oxen and fowls to a human subject and examined the faeces, both for their organisms and for native *E. coli* to which the resistance had been transferred. Fourteen different cultures were used, and none of these was recoverable for more than a few days: in many experiments they could never be found at all. In contrast some human cultures administered appeared and persisted for up to 35 days. Transfer of resistance to native *E. coli* was even more difficult to achieve, and on the few occasions when it occurred, the number of affected bacteria was small and they soon disappeared. These findings strongly suggest that the small numbers of animal *E. coli* which food may contain have little chance of establishing themselves in an environment foreign to them, and are very unlikely to transfer any resistance they possess to native bacteria.

By way of contrast, there is genuine cause for concern in respect of the possible transfer of pathogens from other animals to man, for example from calves. Treatment of the resulting human infection will be hampered if the pathogen is antibiotic resistant. Although human infections from the most virulent organism, *Salmonella typhimurium,* have been less frequent in recent years, there is evidence that in at least one outbreak the source was from calves. It is important that antibiotics are not misused in this connection, and that standards of husbandry and of hygiene are raised. However, this problem should not be confused with the more theoretical risk that non-pathogens, developing resistance due to antibiotics used in low dosage for growth promotion, could then commonly transfer their resistance to human pathogens.

At present the further government Committee under Professor Swann is investigating the present and prospective uses of antibacterials in animal husbandry and veterinary medicine, with particular reference to the phenomenon of infectious drug resistance and the implications for animal husbandry and human and animal health. Like the Netherthorpe Committee before it, it is likely to acknowledge the overall economic benefit arising from the use of antibacterials. Problems occur partly because the situation is changing rapidly at present with the introduction of several new products and, above all, because many of the gaps in scientific knowledge which have been revealed in this field in recent years are only now beginning to be filled by studies such as those conducted by Williams Smith.

On the one hand, it is tempting to say that new developments have made it less necessary to rely on traditional antibiotics and penicillin in animal husbandry. Indeed, their use is already declining as they are superseded by newer products. There appears to be a strong case for permitting the newer products the same freedom of use by farmers as is enjoyed by the older ones. On the other hand, it is not always wise to abandon completely well-tried procedures, even if they have known risks, in favour of newer methods whose possible disadvantages may not yet have become apparent.

It is also important to recognise the practicalities of the situation. Unduly stringent regulations on the use of growth promoting feed additives in animal husbandry would only invite farmers and others to evade them. The problem of enforcement would be exaggerated if the regulations were based on contentious scientific premises.

Thus, the first priority – as in so many other fields – must be to carry out more research. Do the great theoretical dangers from infectious drug resistance represent substantial hazards in practice? Could it be prevented as other "infectious" conditions can be prevented? What are the comparative economic benefits to farmers of the use of different growth promoting substances in Britain now? As far as the prophylactic and therapeutic use of antibacterials is concerned, to what extent does the effective control of animal disease reduce public health dangers? Uncontrolled infection must be set against the risk of antibiotic resistance. In this last connection, there has recently been much publicity for the dangers of salmonellae infection from broiler chickens and in some cases it has been shown that the causative organisms have been sensitive to a number of common antibacterials. (Semple, Turner and Lowry 1968.) Could the proper use of antibiotics have suppressed these infections and hence eliminated a human health hazard?

The pharmaceutical manufacturers in particular would welcome the results of studies on these matters, and would willingly co-operate with them. Nothing is more frustrating than being permitted under existing regulations to do something and then being criticised by sincere scientists as being irresponsible for doing it. Once one has established a strict framework of regulations, as has been done for the use of antibacterials, one cannot then expect manufacturers to behave as if the regulations have been wrongly constructed, and to impose further voluntary restraints themselves. Manufacturers put on trust will act responsibly on their own judgement as happened under the Voluntary Safety arrangements for human medicines. However, once the law has been invoked to lay down what may or may not be done, companies are entitled to assume that they are behaving responsibly if they comply with the law.

In practice, in any field of science, the regulations laid down under the law can only operate in the best public interest if they are based on sound principles derived from established facts. It is these facts which are to some extent lacking on the use of antibacterials in animal husbandry. Even more, perhaps, there has been a lack of balanced scientific appraisal of those facts which have been established. This situation can and should be corrected over a period of time, within a framework of flexible regulations intelligently applied.

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Appendix 1

For purposes of statistically analysing the data obtained, all yearly observations within each station were grouped into two six-month categories based on the initiation date of experiments in either the first or last half of each year reported. All average daily gains and feed efficiencies were weighted according to the number of animals used. The earliest data reported were from the autumn of 1949 and the latest were from the autumn of 1958. Conceivably, if each state reported at least one experiment during each half-year of the 9½ year period, a total of 19 sets of observations would be available for each state. A suitable measure of the length of time Aureomycin had been fed was achieved by assigning the first reported half-year data within each state a value of one. Succeeding half-year data were assigned successively increasing values and values for missing data were omitted. As an example, data submitted for autumn-1952, spring-1953, autumn-1954 and autumn-1956 would be assigned values designed in time as one, two, four and eight.

For each station, regression of Y on X was computed; Y being the dependent variable (average daily gain or feed efficiency) and X being the independent variable (chronological experiment number by 6-month periods). Regressions were also computed using the differences between control and treated means. An analysis of variance was then computed to determine whether or not regressions from the 13 stations could be pooled together and to test the significance of the pooled regression.

Results and Discussion

The results of the analysis are graphically presented in figures A, B and C. The results are further summarized below.

Y Value	*Change in Production Per Half-year (lb).*	*Standard Error (lb).*
Average Daily Gain		
Aureomycin	Constant with time	
Control	+0·0075*	±0·0036
Difference	−0·0067*	±0·0022
Feed/Pound of Gain		
Aureomycin	+0·0126†	±0·0039
Control	+0·0161†	±0·0054
Difference	Constant with time	

†Significant at the 1% level. *Significant at the 5% level.

For the groups fed Aureomycin the regression of average daily gain on the chronological experiment number was not significant (Figure C). There is thus no evidence that the gains of pigs fed

Figure A

Regressions of Feed Efficiency or average daily gain on time for all control and treated groups.

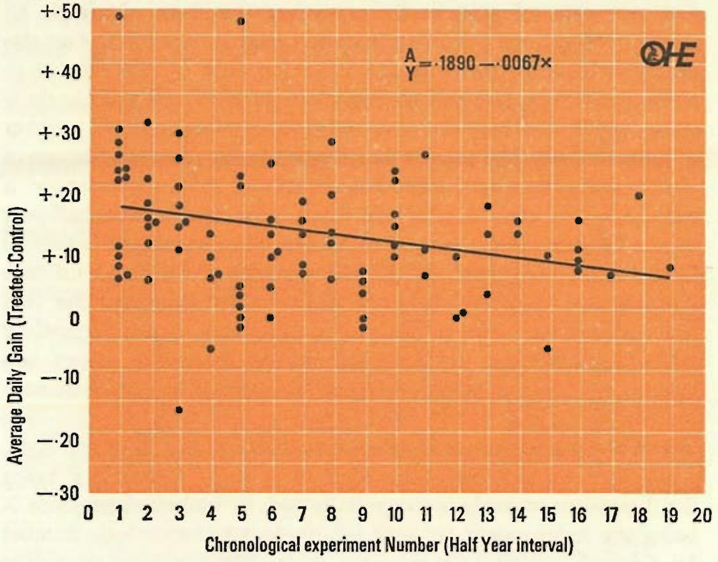


Figure B

Difference between treated and control average daily gain plotted against time.

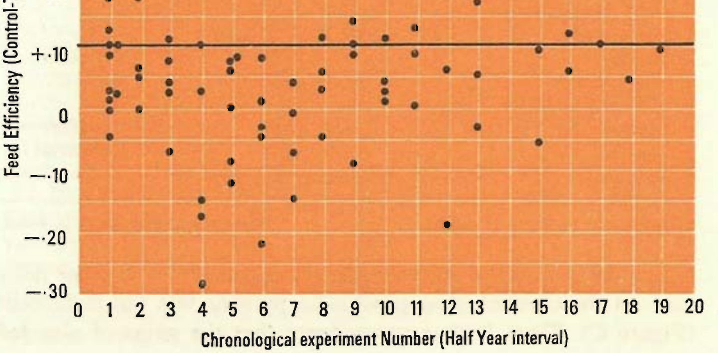
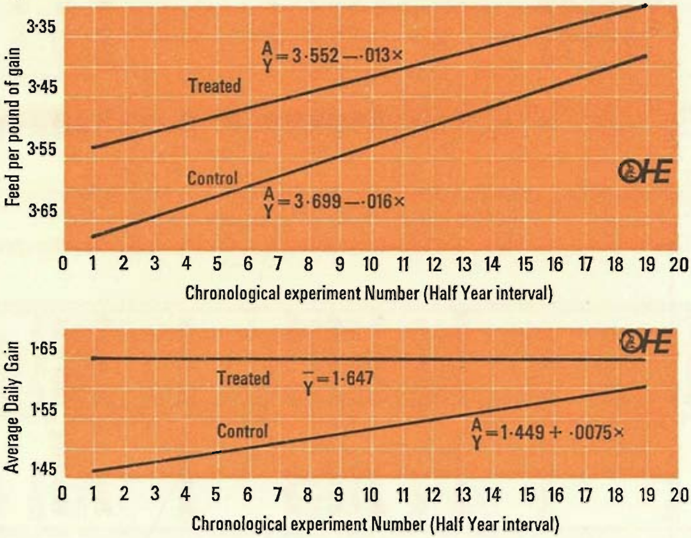


Figure C

Difference between control and treated feed efficiencies plotted against time.



Aureomycin are changing with time. It follows that the best estimate of the average daily gains of the treated groups is given by the mean, 1·647 ± 0·012 pound. Figure C also depicts a significant regression for average daily gain of the control of pigs (P 0·05). During the 9½-year period the gains of control pigs have increased from 1·46 to 1·59 pounds per day, a total of 0·13 pound. Figure A shows that the differences in average daily gains between treated and control groups diminished at a highly significant rate with time (P 0·01). This result substantiates the results for the separate regressions and strongly indicates that the differences in gains are decreasing primarily as a result of changes in the control group.

The regression of feed efficiencies on time for both the control and treated groups was significant at the 1 per cent level of probability (Figure C). For the respective control and treated groups the improvements in feed requirements per pound of gain have been 0·29 pound and 0·23 pound for the 9-year period. It appears that although there tends to be a decrease in differences with time, the values for control and treated groups are not converging, as evidenced by a lack of significance when the feed efficiency differences between treated and control groups were analysed (Figure B). Rather, the feed requirements per pound of gain have averaged a relatively constant 0·11 pound apart throughout the 9½-year period.

Appendix 2

(*Extracted from a draft E.E.C. Council Directive*) *June* 1967

E.E.C. No.	*Usual Description*	*Chemical Formula or Description*	*Animal Species*	*Age*		*Minimum Quantity*	*Maximum Quantity*	*Other Conditions*
				From	*To (inclusive)*	*(ppm of complete feed)*		
E 650	*A. Amino acids and derivatives* 1. All amino acids 2. Derivatives Methionine hydroxyana-logue	$C_{10}H_{18}O_6S_2Ca$						Impurities are admitted in the proportion in which they are technically inevitable.
E 700	*B. Antibiotics* Bacitracin	$C_{66}H_{103}O_{16}N_{17}S$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	5	20	
			Calves	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	
E 701	Tetracyclin	$C_{22}H_{24}O_8N_2$	Poultry (with the exception of ducks, geese, laying hens,	Hatching	10th week	5	20	
			Pigs	Birth	6th month	5	20	Milk replacers
E 702	Chlortetracyclin	$C_{22}H_{23}O_8N_2Cl$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	5	20	

			Calves	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	
E 703	Oxytetracyclin	$C_{22}H_{24}CoN_2$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	5	20	
			Calves	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	
E 704	Oleandomycin	$C_{35}H_{61}C_{12}N$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	2	10	
			Pigs	Birth	6th month	2	10	
E 705	Penicillin	$C_{16}H_{18}N_2O_4S.R$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	5	20	
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers

continued overleaf

E.E.C. No.	Usual Description	Chemical Formula or Description	Animal Species	Age From	Age To (inclusive)	Minimum Quantity (ppm of complete feed)	Maximum Quantity (ppm of complete feed)	Other Conditions
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	
E 706	Salts of Penicillin	$C_{16}H_{18}N_2C_4S.R.$	Poultry (with the exception of ducks, geese, laying hens)	Hatching	10th week	5	20	
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	
E 707	Spiramycin	a. $C_{45}H_{78}O_{15}N_2$ b. $C_{47}H_{30}O_{16}N_2$ c. $C_{48}H_{82}O_{16}N_2$	Poultry (with the exception of ducks, geese laying hens)	Hatching	10th week	5	20	
			Calves	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Lambs–Kids	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Pigs	Birth	6th month	5	20	
					—	5	80	Milk replacers
			Fur bearing animals		—	5	20	

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Printed by White Crescent Press Ltd., Luton August 1969