Report / Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine.

Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine

REPORT

Presented to Parliament by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food and the Secretary of State for Wales
by Command of Her Majesty
November 1969

LONDON
HER MAJESTY'S STATIONERY OFFICE
8s. 6d. [42½p] net
Cmnd. 4190

Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine

REPORT

Presented to Parliament by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food and the Secretary of State for Wales
by Command of Her Majesty
November 1969

LONDON
HER MAJESTY'S STATIONERY OFFICE
8s. 6d. [42½p] net

Cmnd. 4190

Note: The estimated cost of preparing and publishing the Report is £13,261 of which £916 represents the estimated cost of printing and publication.

JOINT COMMITTEE ON THE USE OF ANTIBIOTICS IN ANIMAL HUSBANDRY AND VETERINARY MEDICINE

MINUTE OF APPOINTMENT

We hereby appoint

Professor M. M. Swann, M.A., Ph.D., F.R.S., F.R.S.E.

Dr. K. L. Blaxter, Ph.D., D.Sc., F.R.S., F.R.S.E.

Mr. H. I. Field, M.Sc., M.R.C.V.S., F.C.Path., F.R.S.A.

Dr. J. W. Howie, M.D.(Aberd.), F.R.C.P.(Lond. & Glasg.), P.C.Path.

Professor I. A. M. Lucas, M.Sc., B.Sc.

Dr. E. L. M. Millar, M.Sc., M.D.(Sheff.), M.B., Ch.B., D.P.H.(Lond.)

Professor J. C. Murdoch, B.Sc., Ph.D.

Mr. J. H. Parsons, M.R.C.V.S.

Professor E. G. White, D.Sc., Ph.D., B.Sc.(Vet. Sci.), B.Sc.(Physiol.), F.R.C.V.S.

to be a Joint Committee to obtain information about the present and prospective uses of antibiotics in animal husbandry and veterinary medicine, with particular reference to the phenomenon of infective drug resistance, to consider the implications for animal husbandry and also for human and animal health, and to make recommendations.

We further appoint Professor M. M. Swann to be Chairman of the Committee, Dr. J. M. Ross, C.B.E., M.B., D.P.H. to be Medical Assessor, Mr. D. C. Todd to be Secretary, and Dr. N. J. B. Evans, M.A., M.B., B.Chir., M.R.C.P., D.P.H., and Mr. C. J. Randall, M.A., Vet.M.B., M.R.C.V.S. to be Technical Secretaries.

(Signed) WILLIAM ROSS
Secretary of State for Scotland

(Signed) CLEDWYN HUGHES
Minister of Agriculture, Fisheries and Food

(Signed) KENNETH ROBINSON
Minister of Health

(Signed) J. D. CHICHESTER-CLARK
Minister of Agriculture for Northern Ireland

July, 1968.

1. The Rt. Hon. WILLIAM ROSS, M.B.E., M.P.
   Secretary of State for Scotland
2. The Rt. Hon. CLEDWYN HUGHES, M.P.
   Minister of Agriculture, Fisheries and Food
3. The Rt. Hon. RICHARD CROSSMAN, O.B.E., M.P.
   Secretary of State for Social Services
4. The Rt. Hon. P. R. H. O'NEILL, D.L.
   Minister of Agriculture for Northern Ireland
5. The Rt. Hon. GEORGE THOMAS, M.P.
   Secretary of State for Wales

My colleagues and I have now completed our inquiry into the use of antibiotics in animal husbandry and veterinary medicine and I have pleasure in forwarding our report. I am glad to say that we are unanimous in our conclusions and recommendations.

We have received a considerable quantity of evidence and we think that all the interested parties have had opportunity to present facts or opinions for our consideration. We have tried to deal thoroughly with the subject of our inquiry and to set out the position fully in our report. We think that this, in itself, may be valuable in that it will bring together the arguments both for and against the use of antibiotics in this field and place them before a wider public.

We have been aware of both real and potential dangers implicit in the present uses of antibiotics and we hope that the implementation of our recommendations will enable them to be prevented or forestalled.

On behalf of the Committee I should like to record our grateful appreciation for the assistance which has been given to us by those who submitted evidence, by officials of various Departments and, in particular, by Mr. Todd, Dr. Evans and Mr. Randall of our Secretariat and by Dr. Ross of the Department of Health and Social Security.

MICHAEL SWANN

September, 1969.

CONTENTS

CHAPTER I

REPORT OF THE JOINT COMMITTEE ON THE USE OF ANTIBIOTICS IN ANIMAL HUSBANDRY AND VETERINARY MEDICINE

INTRODUCTION

1.1. One of the important issues of our time is the growing influence which man exerts on all aspects of his environment. Increases in population, particularly increases in urban population density, lead to greater sophistication of the goods and services which individuals need. These needs can be met only by greater industrialisation of production, in farm or factory, and these processes not infrequently give rise to biological problems. Such problems must be solved, whether they concern the disposal of industrial and biological wastes, the use of pesticides and toxic chemicals in the production of food and other materials, or the epidemiology and treatment of infection in communities intrinsically much larger than any we have previously known. Their solution is essential if future generations are to reap the benefits of present progress. One such problem is posed by the widespread use of antibiotics in man and animals which can give rise to populations of micro-organisms which are resistant to certain of the agents used. Concern about this has been expressed by members of the medical and veterinary professions who have to deal with the resultant difficulties, and their concern is also shared by many other scientists and by members of the general public.

1.2. Solutions to such problems come not from dwelling on the ethical dilemma but by scientific dissection of the basic problems. We have sought solutions in this way to the problems posed by resistance to antibiotics of micro-organisms which cause disease in animals and man. We have attempted to explain in simple and straightforward terms how the use of antibiotics in animals may affect both humans and animals. This has involved setting out both the benefits and the dangers to health and welfare which may arise from using antibiotics.

History of the Problems

1.3. The search for substances to cure disease is as old as history. Early in this century Ehrlich and his co-workers found that arsenical compounds were effective against parasitic organisms and they introduced salvarsan for the treatment of syphilis. In 1934 the sulphonamides, which inhibit the growth of some organisms by preventing their reproduction, were applied for medical and veterinary purposes. The discovery of chemotherapeutically useful antibiotics stemmed from observations that certain fungi and moulds produced

substances which had similar antibacterial effects without being poisonous to the cells of man and animals. Of these substances, the first to be therapeutically useful for treatment of systemic infections was penicillin. Penicillin and its early successors were used originally in human medicine to control bacterial infection. Their use was later extended to animals. These antibiotics were found to have a certain spectrum of activity, being effective against some genera of bacteria but not against others. Hence there was a need to continue the search for new antibiotics so that a range would be available from which to select the most effective for the treatment of a given infection.

1.4. The discovery of penicillin was followed by that of other antibiotics which extended the range of bacterial infections which could be effectively treated by them. Despite continued effort, the rate of discovery of new antibiotics slowed down; and although synthetic substances with similar activity have been developed the range of available antibiotics is unlikely to be substantially widened in the foreseeable future. Experience showed that if an antibiotic came into common use, a given bacterium could develop resistance to it; but there seemed little cause for alarm as the bacterium could be controlled by using another antibiotic. Further experience however showed that resistance to one antibiotic frequently extended to related antibiotics. It also became apparent that the use of antibiotics tended to act by exerting selection pressure favouring resistant strains of organisms which consequently multiplied more than did sensitive strains. Concern therefore arose lest the development of resistant strains of organisms should outrun the development of new therapeutic antibiotics.

1.5. Parallel to the development of the use of antibiotics to control disease in man, veterinary use extended to provide a similar control in both farm animals and domestic pets. This usage proved very effective and has contributed greatly to animal welfare as well as to the very marked increase in the production of livestock and livestock products which has taken place in the past 20 years. The veterinary use of antibiotics has greatly reduced the burden of animal disease and reduced the overall incidence of diseases which are common to both man and his domestic animals.

1.6. In the 1940's there was considerable interest, especially in the United States of America, about "unidentified growth factors" which caused more rapid growth and better feed utilisation in animals. By 1950, research had shown that the addition of small amounts of antibiotics to the feed of animals increased their rate of growth and the efficiency with which they converted feed into meat or other products. The mechanism by which this happens is still not fully understood. We discuss this in greater detail later (paragraph 2.36). Although these feed additives were observed to produce some increase in the production of resistant organisms isolated from the faeces of animals, there seemed at that time no cause for concern about the implications for the health of man because of the continuing supply of new antibiotics and of the fact that few pathogenic species of organisms from the digestive tracts of animals colonise the human intestine. The use of specific antibiotics in restricted amounts to promote growth in certain classes of livestock was therefore permitted and such use has been common practice in the United States of America since 1949 and in Britain since 1953.

1.7. In Britain, concern about possible dangers resulting from the reported increase in the incidence of strains of bacteria resistant to antibiotics arose

in both the medical and veterinary professions. This concern was recognised by the Agricultural and Medical Research Councils who judged that an assessment of the situation was called for. A joint ARC/MRC Committee was therefore set up in 1960 under the Chairmanship of Lord Netherthorpe "to examine the possible consequences of the feeding of antibiotics to farm animals and to consider whether this use constitutes any danger to human or animal health". This Committee reported in January 1962 that it saw no reason to discontinue the permitted usage of feed additives and indeed recommended that the use of feed additives could be extended to young calves. This latter recommendation was never implemented. The Committee, however, also recommended that the usage of antibiotics should continue to be watched and that if a new antibiotic were to be developed with comparable efficacy in growth promotion to those permitted for use as feed additives in Britain, (i.e. penicillin, chlortetracycline and oxytetracycline) but with little or no therapeutic application, the continued use of the permitted antibiotics should be reconsidered. It was agreed that the Committee should remain in existence for consultation on any general questions which might arise.

1.8. After 1960 a new factor appeared. Observations were made of a hitherto unrecognised phenomenon which is now called infectious or transferable drug resistance (the terms infective or transmissible drug resistance are sometimes also used). In certain circumstances a micro-organism which is resistant to one or more antibiotics can transfer its ability to resist to other micro-organisms although these may not have been exposed to the antibiotics concerned. There was a mechanism in existence, therefore, whereby resistance might be transferred more widely and rapidly than was originally thought possible. This new finding caused the Secretaries of the two Research Councils, with the agreement of Lord Netherthorpe, to refer to the Scientific Sub-Committee of the Netherthorpe Committee the consideration of questions arising from reports of:

(*a*) the growing incidence of antibiotic resistance among strains of Salmonella, especially those associated with calf disorders;

(*b*) the emergence in these strains of a new pattern of multiple resistance against several antibiotics;

(*c*) the discovery that these resistance patterns could be transferred to hitherto sensitive strains not only of Salmonella but also of Shigella and *Escherichia coli*.

1.9. The Netherthorpe Sub-Committee in its report in 1966 agreed that there were some grounds for concern in these new discoveries but did not find evidence to suggest that the use of the three specified antibiotics permitted in pig and poultry feeding had played a part in bringing about the situation. Since the Committee's terms of reference dealt only with the feeding of antibiotics to animals and not with other uses of antibiotics in veterinary medicine or animal husbandry it recommended that an appropriate body with wider terms of reference should consider the evidence about these uses of antibiotics. This recommendation was accepted by Ministers with the result that the present Joint Committee was set up in 1968.

1.10. We have sought evidence from published work, from public and private organisations, professional bodies, trade associations, research workers,

and others known to have interest in the use of antibiotics, animal husbandry, or veterinary medicine; press notices were also issued inviting evidence. We received communications from numerous organisations and individuals of whom some 90 submitted evidence for our consideration. We invited a number of those submitting evidence to discuss various points with us where we thought that such discussion could contribute to our deliberations. A list of those who submitted evidence is given at Appendix D.

CHAPTER II

USE AND VALUE OF ANTIBIOTICS IN ANIMALS

A. USE OF ANTIBIOTICS IN ANIMALS

Definitions

2.1. An antibiotic is generally defined as a chemical substance produced wholly or partially by a micro-organism (usually a fungus or bacterium) which has the capacity in dilute solution to inhibit the growth of, or to destroy, bacteria and other micro-organisms. Well over a thousand antibiotics have been discovered, but very few of these have proved suitable for medical and veterinary use. Most antibiotics which are of use in man have found a parallel use in animals, although there are examples of some which have application in one field only.

2.2. The greatest number of substances in common use in veterinary medicine and agriculture which we considered were true antibiotics as defined above. Although the sulphonamides and nitrofurans are synthetic in origin and so are not strictly antibiotics, no consideration of bacterial resistance—which is central to our report—would be complete without an evaluation of these compounds. We have therefore interpreted the term antibiotic, as it relates to our terms of reference, to constitute:

(*a*) the true antibiotics, and

(*b*) the synthetic sulphonamides and nitrofurans.

Although the term antibiotic fails accurately and collectively to describe categories (*a*) and (*b*), we have, for simplicity, retained its use throughout our report. Where sulphonamides and nitrofurans are named, their synthetic origin is indicated.

Description of Use

2.3. Antibiotics may be used in a variety of ways. Some which are employed for treating disease may also be capable of promoting growth in one or more species of animal; others are only of value either as chemotherapeutic agents or for growth promotion. The tetracyclines and penicillin have a well defined therapeutic role and are also capable of promoting growth, whereas antibiotics such as neomycin and ampicillin are used for therapy alone. Antibiotics which have only a limited use outside growth promotion are exemplified by bacitracin and virginiamycin (paragraph 2.26). Nitrovin (a nitrofuran derivative) promotes growth and is claimed to have no therapeutic action. Apart from these two main functions, limited use is made of antibiotics for preserving fish caught at sea, as well as some dairy products, and bananas.

2.4. In veterinary medicine antibiotics are used to treat bacterial infections and some are also active against the larger viruses, mycoplasmas, fungi, protozoa, and nematode worms. For instance, griseofulvin, nystatin, and

amphotericin B possess antifungal properties; hygromycin B may be used to suppress intestinal worm infestations in some animal species; and both furazolidone (a synthetic nitrofuran) and chlortetracycline may be employed against some pathogenic protozoa. Certain antibiotics may be used to treat several types of infection, whereas others are much more specific in their action. Compatible and synergistic antibiotics (*e.g.* penicillin and streptomycin) may be combined in a preparation which will permit their simultaneous administration to man and animals, so giving a wider spectrum of activity. It is to the antibacterial properties of antibiotics that we have given most attention, although we realise that the mode of action of antibiotics in growth promotion is not yet fully understood.

2.5. The route by which an antibiotic is given depends on its properties, the species of animal involved, and the site and nature of infection. Generalised bacterial infections are usually treated by parenteral (injectable) administration. Oral administration is used only if the antibiotics are quickly absorbed from the gastro-intestinal tract or if the infection is localised to the gut. Localised infections may respond to topical treatment but if these are severe or not fully accessible it may also prove necessary to administer doses of the same antibiotic parenterally. The fact that some antibiotics (*e.g.* streptomycin and neomycin) are very poorly absorbed from the digestive system may make these suitable for treating certain gut infections.

2.6. If individual medication is impossible or impracticable, the inclusion of medicines in feed or in drinking water is one way of ensuring that animals are dosed. Such situations often arise in large flocks of poultry: consequently both sick and healthy birds are treated alike.

2.7. Antibiotics are effective in growth promotion only if given by mouth: a similar growth promotional effect is not produced if they are injected into animals.

Quantities of Antibiotics Used

2.8. Statistical evidence on antibiotic usage from 1963 to 1967 was received through the Association of the British Pharmaceutical Industry (representing 90–95 per cent of this section of the industry). In 1967 medical uses were estimated to account for 239,882 kilograms (240 tons) of pure antibiotic sold, while the veterinary and agricultural markets absorbed 168,011 kilograms (168 tons). This latter figure when split down further seems to show that usage is divided about equally between veterinary and agricultural uses. The overall usage of antibiotics (*i.e.* the true antibiotics, sulphonamides and nitrofurans) in man and animals was therefore in the ratio of 6:4. If penicillins and tetracyclines only are considered the ratio would be 8:2 (see Appendix A).

2.9. We received in evidence no data to show the amounts of antibiotic given to different species. By inference from the figures tabulated in Appendix A the growth promotional use of penicillin and the tetracyclines would indicate that more of these drugs are used in pigs and poultry since these antibiotics are not used for growth promotion in other species. Because dosage of antibiotics for therapy is calculated on body weight, large animals receive larger individual doses than do small animals. This does not mean however that greater quantities are used to treat cattle than, for instance, poultry,

since this does not take into account the total numbers of animals being treated. If the livestock population continues to increase, a rise in the amount of antibiotics used may be expected.

2.10. The amount of antibiotic that an animal receives for therapeutic purposes and for growth promotion purposes respectively, differs considerably. For example a pig weighing 100 lb might consume about 36 mgm of an antibiotic such as oxytetracycline daily for growth promotion (at a rate of 20 grams per ton of feed). If the pig were given therapeutic treatment with the same antibiotic by a veterinary surgeon it might be given doses of about 1 gram orally or 200 mgm by injection. Thus the therapeutic dose would be approximately from 5 to 28 times the amount used for growth promotion. The higher the level of inclusion of an antibiotic in the ration for growth promotion, the less is the disparity between these figures. If for instance, an antibiotic were given to animals that were described as "stressed" it would be common practice to administer a dosage below the recommended therapeutic dose but above an accepted growth promotional level.

2.11. Data were available to us showing the amounts of antibiotic used in human medicine and in animals. Statistical information is also available about the numbers of people and animals in the United Kingdom, and so a very crude *per capita* rate of antibiotic administration can be obtained. It is doubtful whether this rate is meaningful, but at least it indicates very roughly the relative intensity of use in animals and in man. Numbers are obviously a poor denominator to use to determine such a crude rate because a cow weighs 8 times as much as a man, and a man 70 times as much as a chicken. The total body weight of the animals and humans which could receive antibiotic seems therefore a more rational denominator to use.

2.12. The number of people in the U.K. who could receive antibiotics in a year is simply the total population, and the mean weight of an individual can be taken to be 60 kg, a figure which roughly equates for age and sex differences in weight. With animals, particularly with poultry, the number which could receive antibiotics in a year is not given by the total population at a point of time, since within a year several crops of animals are killed. Accordingly, one must consider separately breeding stocks and slaughtered animals, and the total population which could receive antibiotics is considerably greater than the population at a particular point in time. The calculations in the Table below show that current overall use of antibiotics in human medicine is 4 times that in animal husbandry and veterinary medicine per unit of body weight.

Calculation of total mass of people and farm animals 1968*

	Species	*Population (millions)*	*Mean weight (kg)*	*Total live weight (million metric tons)*
A.	Man	55·1	60	3·31
B.	CATTLE			
	Breeding	5·3	500	2·65
	Slaughtered/year	4·2	400	1·68
				4·33
	SHEEP			
	Breeding	15·7	60	0·94
	Slaughtered/year	13·2	50	0·66
				1·60
	PIGS			
	Breeding	1·6	130	0·21
	Slaughtered/year	12·4	90	1·12
				1·33
	POULTRY			
	Breeding & Laying	82·4	2	0·16
	Slaughtered/year	200		0·53
				0·69
			Total animal mass	7·95

Relative Figures	*Antibiotic† consumption (relative percentage)* (a)	*Mass (relative percentage)* (b)	*"Dose"* (a/b)
Man	60	29	2·1
Animals	40	71	0·56

People who use antibiotics in animals

2.13. A farmer is currently permitted to include, without veterinary prescription, three scheduled‡ antibiotics—penicillin, chlortetracycline, and

* Based on Annual Abstract of Statistics (1969) HMSO: Agriculture's Import Saving Role (1969) HMSO: and information about dressing percentages of carcasses. The poultry figure is based on amounts of poultry meat entering human consumption rather than from the estimate of the annual number of poultry slaughtered. Figures for breeding stock include replacement animals, *i.e.* animals destined for breeding rather than slaughter.

† As defined in paragraph 2.2.

‡ Scheduled under the Therapeutic Substances Act, 1956. (See Appendix C). Scheduled antibiotics cannot be bought freely and with the above exceptions are available on veterinary prescription only.

oxytetracycline—in the rations of growing pigs and poultry up to a maximum concentration in the diet of 100 parts per million (100 gm/ton). Such rations must not be fed to adult breeding stock, laying poultry, or ruminants. If more than 100 p.p.m. of any one of these antibiotics are required in the feed, a veterinary prescription is necessary, just as it would be if any other animal were being treated with a scheduled antibiotic.

2.14. Although farmers may buy penicillin and the tetracyclines in a particular ration by asking their feed compounders to include one or the other, this is not usually how it is done. More often the compounder decides which antibiotic to include for growth promotion and formulates ready-mixed feeds for sale to farmers. For home mixing a concentrated supplement (containing not more than one part of penicillin or the tetracyclines to 90 parts of supplement) may be purchased by farmers; and advice about the restrictions on its use is given on the label on the container.

2.15. The unscheduled antibiotic tylosin* and the nitrofurans may be bought by farmers for treating their own stock at any dosage and farmers may also include them in rations which already contain the permitted scheduled antibiotics. These unscheduled antibiotics are also used by veterinary surgeons for treating animals. The sulphonamides come in a special category with regard to purchase. They are scheduled under the Pharmacy and Poisons Act, 1933 but farmers may buy them for administration to their own livestock without veterinary prescription.

2.16. A veterinary surgeon may order and prescribe any scheduled or unscheduled antibiotic; these substances are mainly used by him at therapeutic dosage although they may also be used at lower dosages. In general, veterinary surgeons in practice do not deal with antibiotics for the purposes of growth promotion except when virginiamycin and bacitracin are used and require prescription. It is of value to the veterinary surgeon to know which antibiotics pigs and poultry are receiving for growth promotion if antibiotic treatment should become necessary.

Antibiotic Use in Veterinary Therapy

2.17. As in human medicine, veterinary surgeons have taken advantage of the discovery of new antibiotics and other antimicrobial drugs in combatting disease and the patterns of prescription have changed with the years. In particular, the growth of intensive methods of animal production has led to more mass medication. We have no clear evidence, however, of marked change in amounts prescribed in the last few years.

2.18. In deciding which antibiotic to prescribe, the veterinary surgeon is in much the same position as the medical practitioner. For ideal control of therapy, the sensitivity of the causal organism should always be ascertained before therapy is started. In practice, this may often not be feasible. If an animal's life is at risk, or if there are signs of rapid spread of the disease among contacts, treatment must be started on the basis of clinical diagnosis. Even so the sensitivity of the causal organism should, where possible, be

---

* A preparation of the antibiotic tylosin which may be used to promote growth in pigs together with oral and injectable forms employed in treating poultry diseases are on free sale to farmers. Although tylosin is unscheduled, formulations of this antibiotic used for treating pigs and other mammals are intended for sale on veterinary prescription only.

determined so that if treatment fails, it can be changed in the light of the test results. The evidence we have received suggests that good use is made of the laboratory facilities available for the testing of specimens taken by veterinary surgeons to confirm diagnosis and determine therapy.

Antibiotic Use in Disease Prevention

2.19. When applied to an antibiotic, this description is open to misinterpretation. A distinction must be made between:

(*a*) a group of animals containing some with overt signs of disease and

(*b*) a group of animals in which there is no such evidence.

In the first category both sick and healthy animals receive treatment with *therapeutic* levels of an antibiotic, because, unless this procedure is followed, healthy animals are likely to contract the disease because of its infectious nature. Examples of such a use are quoted in the following paragraphs.

2.20. Diarrhoea (scours) in pigs, is often associated with the presence of *Escherichia coli* infections in different age groups, but not all the pigs in any one group are liable to be scouring at the same time. It is probable that the veterinary surgeon will treat every pig in the group rather than only those which are visibly affected.

2.21. A number of viruses are capable of invading the respiratory tracts of calves, and pneumonia may result if secondary infections from common residential bacteria and mycoplasmas are superimposed. An antibiotic or a combination of antibiotics given to both healthy and unhealthy calves within a group may effectively cut down the incidence of clinical pneumonia by reducing secondary infection and in some cases by acting on the larger viruses.

2.22. Early work showed the value of penicillin in the prevention of summer mastitis in cattle. An organism commonly associated with this type of infection is *Corynebacterium pyogenes*, and although not high in overall incidence, cases of summer mastitis may be of great severity and may cause death or loss of affected quarters. Some controlled experiments have shown that the infusion of penicillin into the udders of cattle at the end of their lactations in summer months before turning them out to pasture gives a high protection against this infection. This practice is well established and is of considerable value in areas where the disease is common.

2.23. A similar example of preventive use is that of antibiotics in non-lactating cows to control mastitis infection in subsequent lactations. In recent work antibiotics were infused into the udders of cows at the end of their lactation after mastitis pathogens (streptococci and staphylococci) had been demonstrated in their milk. Further samples of the next lactation taken one month after calving showed that the number of these pathogens was reduced by up to 50 per cent, the precise reduction depending on the antibiotic used. It was considered that this practice—called "dry cow therapy"—would reduce chronic infections of the udder and cut down the spread of mastitis within the herd.

2.24. The other preventive use of antibiotics (referred to in paragraph 2.19(*b*)) is that in which, despite no clear evidence of overt disease in a group of animals, antibiotics are administered to prevent its possible occurrence. The amounts of antibiotic given are usually *below the recommended thera-*

peutic dose. The commonest example of this practice is encountered when young animals have been subjected to "stress". This term has been loosely interpreted to mean an adverse reaction of an animal to an environmental change. Thus when young birds are being handled, moved, or vaccinated, when pigs are weaned, or when 7–10 day old calves are brought from market to a home farm, they are all described as having been "stressed". Such adverse change may also result when members of different groups of animals are mixed and indeed there are numerous ways in which a "stress" situation is thought to be produced. The bodily mechanisms brought into play during "stress" are extremely complicated but it has been postulated that such environmental changes may interfere temporarily with the defence mechanisms of the body, possibly allowing any acquired or naturally resident pathogenic micro-organisms to multiply and cause disease. It is common practice in the poultry industry for both scheduled and unscheduled antibiotics to be given in short courses during these "stress" periods and for farmers to administer antibiotics to young pigs in similar situations. If these antibiotics are incorporated into feeding stuffs, they are frequently referred to as "anti-stress" rations but it would appear that their use in this way is empirical and not applied on a clear scientific basis. Indeed we have been informed that "stresss" is best defined as that state in which the giving of antibiotics in dietary concentrations below therapeutic dose levels leads to an economic response in terms of growth, reduced morbidity, and reduced mortality (see paragraphs 2:31 2.34). Antibiotics (mainly the tetracyclines) below therapeutic levels may be included in the creep feeds of suckling piglets but here it would seem that the object is not so much growth promotion as disease suppression or prevention. The fact is that healthy pigs and poultry receive preventive doses of either penicillin or the tetracyclines within the permitted feed maximum of 100 p.p.m. Since it is impossible to determine the level at which these antibiotics have only a purely growth promotional effect and the level at which they take on a preventive role as well, the definition of such use depends on what is in the mind of the user.

Antibiotics Use in Growth Promotion

2.25. Growth promotion may be regarded as the stimulation of an animal's growth during early life by the addition to its diet of small quantities of substances which may or may not be antibiotics.

2.26. In the United Kingdom relaxing regulations were made in 1953 and 1954 under the Therapeutic Substances (Prevention of Misuse) Act, to allow the sale of penicillin, chlortetracycline, and oxytetracycline for growth promotion purposes. This Act was repealed under the Therapeutic Substances Act, 1956 but the regulations made thereunder still remain in force. Since the original introduction of these three antibiotics for growth promotion, other substances have also been marketed for application in this field. For example copper salts are commonly used in pig rations instead of (or as well as) antibiotics and, in both pigs and poultry, arsenical compounds are employed to some extent. The antibiotic tylosin has also been used in pig feeds; and nitrovin (a nitrofuran derivative) has been employed to promote growth in broilers. Tylosin may be used therapeutically in animals but nitrovin has no known therapeutic use and has no reported antimicrobial activity. Tylosin*, copper

* See footnote to paragraph 2.15.

salts, arsenicals, and nitrovin do not need a veterinary prescription for their use. Two antibiotics requiring prescription which are sold for growth promotion are virginiamycin and bacitracin. These two substances are not used in veterinary therapeutics in Great Britain; but virginiamycin, although it is not sold in the U.K. for this purpose, has a possible restricted application to human medicine. Bacitracin has a limited, but possibly important application in human surgery.

B. VALUE OF ANTIBIOTIC USAGE IN ANIMALS

Therapy

2.27. Antibiotics are used by veterinary surgeons to treat many types of infection in a wide variety of animal species, and it is not possible to envisage modern veterinary practice without their use. Apart from the direct benefit to the animal population, effective antibiotic treatment also serves to reduce the spread of bacterial disease that may be passed directly or indirectly from animals to man (*e.g.* salmonellosis, leptospirosis, listeriosis, and erysipelothrix infections).

2.28. As in medical practice, the prime concern of the veterinary surgeon is to restore his patient to health. The veterinary surgeon in farming practice must carefully weigh up whether any treatment he institutes will be of economic value to the farmer; in some cases a decision will be made to slaughter a sick animal since this action may represent the smallest financial loss. The fact that most antibiotics with a veterinary application are introduced to this field after their successful medical use is due to their high initial cost. Antibiotics are expensive and they would not be used by veterinary surgeons if they did not achieve good results; by enabling successful and economic treatment to be carried out, antibiotics contribute to every type of animal production and this is reflected in more efficient food production. Considerations of the monetary worth of an animal do not usually apply to the same extent to household pets since the involvement of the pet in family life and the regard in which it is often held frequently outweigh economic considerations of treatment.

2.29. Disease is one of the principal causes of suffering in animals and in all types of animals the use of antibiotics to control infection reduces suffering and makes an important contribution to animal welfare. It has been estimated that losses due to disease in animals amount to £150 million annually and the use of antibiotics is an important weapon helping to reduce this total.

Disease prevention

2.30. Examples have been quoted in paragraphs 2.20–2.23 to illustrate the use of preventive antibiotic treatment. If the presence of an infectious pathogen is known within a group, the administration of therapeutic doses of antibiotic to both healthy and sick animals may cure the clinically affected individuals and reduce the spread of disease (or prevent symptoms appearing) in the remainder. This use is based on an economic advantage gained by the farmer and will also mean that the veterinarian has to make fewer visits.

"Stress"

2.31. The administration of antibiotics below the recommended therapeutic dose to young animals when "stressed", is widely accepted by farmers and agricultural advisers. The antibiotics commonly used for this purpose in pigs and poultry are obtainable without prescription and may thus be used without reference to veterinary advice.

2.32. Part of the difficulty in estimating the financial worth (if any) of this type of antibiotic usage lies in defining "stress" and in finding a means by which it may be conveniently measured. Our attention was drawn to a substantial number of references to literature on this subject but these were of limited use in clarifying the matter. It is possible to define "stress" in either physiological or pathological terms but the present concept of "stress" in agriculture is by no means clear (see paragraph 2.24); indeed it has been suggested to us that antibiotic usage in this manner may have acquired the status of an "industrial myth." The practice is believed to bring financial gain but it is difficult to separate such reported benefits from the known value of growth promotion.

2.33. Reference has been made (paragraph 2.24) to the complexity of bodily response which may be brought into play when an adverse environmental change is experienced. It might then be postulated that an animal experiencing this change would be placed at a disadvantage when exposed to potential pathogens and that a link could therefore be established between a "stress" situation and the administration of antibiotics. No scientific evidence was received which either supported or detracted from this hypothesis. We consider that it is first necessary to establish physiological evidence that interference with the response to infection either does or does not take place in the common situations on farms where animals are described as "stressed" before any such link can be substantiated.

2.34. If there is a sound physiological basis for doing so, the administration of antibiotics to "stressed" animals should then be made at full therapeutic dosage. We find the present practice of giving antibiotics below therapeutic levels to "stressed" animals indefensible from a bacteriological standpoint. We are convinced that such practice will encourage the emergence of resistant bacterial populations and that both human and animal life may be exposed to unnecessary hazard as a result.

Growth Promotion

2.35. The historical record of the discovery of the growth promoting properties of antibiotics is of interest. In 1946 American workers showed that streptomycin and sulphasuxidine increased the weight gain of chicks but the significance of these observations went unnoticed for several years. It was later found that waste products from the commercial production of streptomycin and chlortetracycline, which were being investigated for their vitamin B_{12} content, produced growth responses in chicks beyond the potential of the pure vitamin. This led to the discovery that residues of these antibiotics remaining in the waste products were responsible for the increased performance, as a result of which numerous workers investigated a variety of antibiotics for this property. An interesting fact to emerge from this early work was that combinations of antibiotics did not produce a more favourable

response than when they were employed singly. It was also found that not all antibiotics produced the same effect in different species of animal; penicillin, for instance, is capable of promoting the growth of pigs and poultry but not of calves, whereas the tetracyclines may increase growth rates in all three species of animal. By 1952 it was known that penicillin, chlortetracycline, and oxytetracycline were potent agents in promoting growth. There has subsequently been a world-wide acceptance of the idea and practice of growth promotion.

2.36. The way in which antibiotics bring about growth promotion is by no means fully understood and several theories have been put forward. One is that antibiotics may influence metabolic processes taking place in the intestines of the recipient animal. The possibility of a nutrient-sparing action has also been raised. This could be brought about either by suppressing the growth of micro-organisms which compete with the host for these substances or even by increasing intestinal absorption due to a thinning of the gut wall. It is generally believed, however, that most antibiotics suppress elements of the bacterial population which might otherwise produce harmful effects; it is known, for instance, that chickens reared under germ-free conditions will grow faster than their experimental fellows receiving antibiotics in conditions resembling those in a more usual commercial environment. One view put to us is that this action is likely to be qualitative (*i.e.* on a few unidentified components of the microflora) rather than quantitative.

2.37. There are many variable factors which make it difficult to express the growth promoting effect of any one antibiotic quantitatively; the type of food and the level at which the antibiotic is included, together with age, health and environmental conditions, may all markedly alter the growth promotion effect. There is usually a period during the early part of life when the effect is greatest. Thus, in chickens there is little response to antibiotics fed after 30 days of age, and the maximum effect is secured in pigs between weaning and approximately 100 lb body weight. There are numerous reports in the literature that feed-conversion efficiency is also improved by antibiotics.

2.38. There is widespread use of growth promoting substances throughout the broiler, turkey, and pig rearing industries in this country. Those substances need not be antibiotics alone since, as referred to in paragraph 2.26, copper salts and arsenical preparations may be incorporated into diets instead of (or in addition to) antibiotics. Examples of improvement in performance that have been received in evidence are:—

Pigs 6–10 per cent improvement in growth rate
5–7 per cent improvement in feed conversion.

Broilers 2½–6 per cent improvement in growth rate
1½–3½ per cent improvement in feed conversion.

2.39. Overall, such figures tally well with the large volume of published evidence although, just as in experimental work, the figures we received in evidence indicate a considerable spread and variation in improvement dependent on the particular farm and species of animal concerned. The cause of this variation is as little understood as are the factors influencing the growth promotional response itself (see paragraph 2.36). What may be said is that economic benefit results from this practice, which may be very important to the individual farmer and could possibly mean a difference between profit

and loss. In contrast on other farms there is, for no apparent reason, much less dependence on antibiotics for good performance of growing pigs and poultry. From the known usage of antibiotics in this manner, a conservative estimate has been computed of the annual profits attributable to the use of antibiotics for growth promotion in the broiler, turkey, and pig industries. This recently published estimate of benefit from present usage amounted to about £1,000,000; if growth promoting agents were used to the full, the potential benefit was estimated to be over £3,000,000 annually.

CHAPTER III

POSSIBLE DANGERS OF ANTIBIOTICS

3.1. Antibiotics are used by veterinary and medical practitioners for the treatment of patients infected by harmful micro-organisms. It may be useful to summarise here the possible undesirable effects of such treatment, and then to list the known and potential dangers to the well-being of animals and of man which are posed by the use of antibiotics in animal husbandry and veterinary medicine. In subsequent sections we examine the evidence to see how far these dangers are borne out in reality.

Side Effects of Antibiotic Treatment of Man

3.2. An antibiotic, like any other drug, may have a direct toxic action on the recipient if given in sufficiently large dosage. Exceptionally, an unusually susceptible or allergic individual may have a severe or even fatal reaction to a dose of antibiotic which would normally be without adverse effect. Some allergic patients develop rashes when in contact with quite minute amounts of antibiotic. In most cases the susceptible or allergic patient can be shown to have encountered the same antibiotic on some previous occasion. The earlier sensitising exposure may be to full therapeutic doses or to mere traces of the antibiotic such as are encountered occupationally by nurses and medical practitioners.

3.3. Some antibiotics when given by mouth in therapeutic dosage are so effective in killing the bacteria ordinarily present in the bowel that they may almost sterilise it. The bowel, which is thus denuded of its normal flora, is particularly liable to be invaded by a variety of bacteria, yeasts, or fungi resistant to the antibiotic; the presence of these unusual micro-organisms may be associated with soreness of the tongue or with irritation around the anus. Very exceptionally the bowel may be invaded by highly virulent organisms causing an overwhelming diarrhoea which may be rapidly fatal.

3.4. The use of an antibiotic may lead to the appearance of bacteria resistant to its action. The resistant bacteria may come to predominate, so that an antibiotic previously effective becomes useless in the treatment of continuing infection, or subsequent episodes of infection, by the same strain of micro-organism. If the resistant strain spreads to other patients, the antibiotic in question remains useless for the treatment of the new victims.

Possible Dangers to Man from the Administration of Antibiotics to Animals

3.5. The unwanted effects described in paragraphs 3.2–3.4 may hinder veterinary as well as medical practice and the risks to the animal population are similar in kind though not necessarily in importance to those attending the use of antibiotics in human medicine. However, because men tend animals, and eat their flesh and products, the administration of antibiotics to animals

is accompanied by some potential risk to the human as well as to the animal population. The possible dangers to man may be grouped into those resulting from antibiotic residues and those arising from the appearance of antibiotic resistance among the bacterial populations which may be transferred from animals to man.

3.6. If animals or their products (*e.g.* milk, eggs) contain traces of an antibiotic when eaten by man, the effect of these antibiotic residues on the consumer is presumably that of the equivalent doses of antibiotic given directly. The consumption by man of antibiotic residues could produce harmful effects from direct toxicity or from allergic reactions in persons who have been previously sensitised. Theoretically antibiotic residues could also provoke sensitisation and so expose the consumer to the future risk of an allergic reaction to the antibiotic. In theory also, antibiotic residues in food could lead to the emergence of resistant strains of organisms in man.

3.7. The appearance in animals of antibiotic-resistant strains of bacteria which are harmful to man is clearly potentially hazardous if the micro-organisms can pass from animals to man and cause disease. The treatment of such a disease in a sick patient may then be complicated, or rendered unavailing, by the resistance. The discovery of infectious drug resistance has suggested other less direct routes by which the development of antibiotic-resistant organisms in animals could threaten man, because some antibiotic-resistant organisms, whether they are harmful or not, which may pass from animals to man are known to be capable, in the laboratory, of transferring their resistance to other organisms. It is known that this transfer of resistance happens in living animals or man as well as in the test-tube, and that antibiotic-resistant organisms may transfer their resistance to organisms which inhabit the human bowel. The recipient organisms which become antibiotic-resistant in this way may themselves be harmful or may be the normal bacteria of the bowel; if the latter they may eventually transfer the resistance to pathogens (harmful organisms). It is feared particularly that *Salmonella typhi*, the typhoid organism, and other invasive salmonellas, might in this way acquire resistance to chloramphenicol, which is at present considered the most effective antibiotic for the treatment of such infections. The evidence for the passage of organisms from animals to man is considered in Chapter IV; antibiotic-resistance is discussed in Chapter V.

3.8. The possible dangers outlined above are those which might affect the general public from the use of antibiotics in animal husbandry and veterinary medicine. Persons whose occupation brings them into contact with these uses of antibiotics may be at greater risk than the general public. For example, those in contact with animals have more opportunities of contracting infection (including infection with antibiotic-resistant bacteria) from the animals, while feed-compounders and others exposed to the dust of antibiotic-containing feed face the same potential hazards from the dust as are outlined in paragraph 3.6.

CHAPTER IV

THE TRANSFER OF ORGANISMS FROM ANIMALS TO MAN

4.1. We suggest in paragraph 3.7 that antibiotic resistance affecting micro-organisms in animals could be transmitted to man. The likelihood of such transmission depends in part on the frequency with which organisms pass from animal hosts to man. It has of course been known for many years that a number of infectious diseases may be passed from animals to man. In Britain two types of infection which have achieved a good deal of notice in this context are tuberculosis and brucellosis, but there are many others. Recently, increasing attention has been directed to the bowel organisms which are found in animals and man and which may pass from the former to the latter in food. Most of the evidence on this point has come from study of the illnesses caused by bacteria of the Salmonella genus and perhaps for this reason these organisms have attracted most notice in connection with the use of antibiotics in agriculture and veterinary medicine.

Salmonellae

4.2. Salmonella organisms are intestinal pathogens of both man and animals. The genus is divisible into more than a thousand named species or serotypes (such as *Salmonella typhimurium*, *Salmonella montevideo*, and *Salmonella virchow*) some of which may be further sub-divided into phage-types. Some serotypes are pathogenic only for specific hosts (*e.g. Salmonella typhi*, the typhoid organism, infects only man while *Salmonella pullorum* infections are largely confined to poultry) but others may infect various hosts. Even so, most salmonella serotypes show a distinct "preference" for certain hosts in that the bacteria appear to flourish more readily in these preferred hosts than in others; *Salmonella typhimurium* is unusual in this respect as it readily infects most kinds of animals. Salmonella infections do not necessarily produce overt disease, and the host may pass organisms in its excreta for months or years without giving any clinical indication that this is the case; man carries only a few species for long periods, notably the host-specific organisms of typhoid and paratyphoid.

4.3. In man, salmonella infections other than typhoid or paratyphoid are usually confined to the bowel and produce fever, abdominal pain, and diarrhoea. Most patients recover after a few days though they may continue to carry (and hence to excrete) the organism for a few weeks or even months. Antibiotic treatment is usually not necessary; if given it is not very effective and may prolong the period during which carriers continue to excrete the organism. Most patients who are otherwise healthy are likely to recover, but infants and old people may succumb to the acute illness. Sometimes the

salmonella infection is systemic, *i.e.* it spreads from the bowel and involves the body generally. Systemic infections are usual in typhoid and paratyphoid but are also sometimes seen with other serotypes, *e.g. Salmonella typhimurium* and *Salmonella choleraesuis*. They are, in general, more severe than the infections which are confined to the bowel and they are associated with potentially serious complications, thus threatening life. Systemic salmonella infections, especially typhoid and paratyphoid fevers, are likely to need effective antibiotic treatment. Chloramphenicol is a particularly valuable antibiotic for the treatment of human systemic salmonellosis if the organism is sensitive to the drug. In typhoid the range of effective alternative antibiotics is small and chloramphenicol stands out as the treatment of choice.

4.4. Leaving aside the special cases of typhoid and paratyphoid, most salmonella infections in man in England and Wales are cases of "food-poisoning" contracted by eating infected food. Infection does not spread readily from person to person and direct transmission is seen mainly within hospitals and other institutions or within the family. Evidence gathered by investigating food poisoning incidents and by searching the environment for salmonella organisms suggests that in most cases the infection derives directly or indirectly from farm livestock or poultry.

4.5. Salmonella infections are the major cause of food poisoning, though not of gastroenteritis as a whole since many gastro-intestinal upsets are not caused by food poisoning. In 1967*, 3,259 of the 4,256 reported incidents of food poisoning (5,527 of the 11,095 cases) were shown to be due to salmonellas and since in many incidents the causal agent was not discovered these organisms accounted for 97 per cent of all incidents (66 per cent of all cases) of which the cause was ascertained. Moreover of the 27 deaths from food poisoning the same year, 23 were associated with salmonella organisms. Of the 25 patients who died and whose age was stated, all but 4 were over 60 or under 3 years. The commonest vehicles (the food by which the organism was conveyed to the patient) were meat and animal products.

4.6. Precise identification of the causative organism by serotyping and, where appropriate, by phage typing, helps to establish the sources from which these organisms come. Relatively few of the thousand-odd salmonella serotypes are isolated in any one year from man. The commonest by far (though apparently declining in absolute and relative importance) is *Salmonella typhimurium* which itself accounts for over half the incidents; the ten most frequent reported serotypes (including *Salmonella typhimurium*) cause together about 80 per cent of the incidents. Most of the same common serotypes are also isolated each year from food-producing animals, and more refined investigation of the phage-type distribution of *Salmonella typhimurium* in man and in livestock in several successive years confirms that the organisms found in man and farm animals are similar. The relative importance of the various serotypes as causes of disease is different in man and animals because of the host-preferences shown by the bacteria, but when allowance is made for these host-preferences, it appears that the common salmonella types found in

* These figures, which relate only to England and Wales as no comparable figures are available for Scotland, refer to illness which is believed to have been caused by food but exclude diseases separately notifiable such as typhoid and paratyphoid. Apart from salmonellosis there are a number of other recognised bacterial and chemical causes of food poisoning.

man also occur in our domestic animals. This similarity in pattern does not apply to any other potential source of organisms; thus although salmonellas are often isolated from animal feedingstuffs, bonemeal, and imported meat, many of the serotypes or phage-types are not those most commonly found in man.

4.7. On a local scale it has been shown that the exact type of organism commonly infecting man in an area may often be isolated from the drain of the local abattoir, and on occasion a human outbreak has been predicted in this way. Several investigators have tracked back from particular patients to the farms from which the infection came, and a number of routes have been identified by which organisms can be transmitted. For example, organisms have been shown to be carried from farm to man through butcher's meat, poultry, milk and knacker's meat sold for pets. A small random survey suggested that 1·5 per cent of butcher's meat is infected with salmonellas, and 11 per cent of knacker meat. Batches of infected animals may carry a much higher proportion of infection into the butcher's shop; thus 8 of 84 calf palates followed to a butcher's shop were found to carry *Salmonella typhimurium* of the phage-type under investigation. The association of human salmonella infections with salmonellas of livestock is restricted to cattle, pigs, and poultry in Britain; sheep have not, so far, been incriminated.

4.8. At one end of these chains of transmission is an infected animal; at the other end the infected food reaches man. Even if the food itself is sufficiently cooked to kill salmonella organisms, there are many ways in which infected food may contaminate hands, cutlery, and kitchen surfaces and the infection may then reach the consumer through the contamination of uncooked or previously cooked dishes.

Other Organisms

4.9. The evidence indicates that salmonella organisms, which are relatively occasional denizens of the animal bowel, are often conveyed to man and are then capable of infecting him. It is presumed that other organisms from the animal's gut may be carried along the same routes to man. Organisms such as *Escherichia coli* and others which together form the usual flora of the animal and human guts are most likely to be transmitted in this way and to be eaten by man. Unlike salmonellas however, these organisms are not likely to cause symptoms in man. Indeed there is evidence that the *Escherichia coli* strains found in animals and man are distinct and that strains originating in animals are unlikely to become established in the human bowel. It seems likely therefore that large numbers of living *Escherichia coli* from animal sources are eaten by man but do not survive long in the human gut.

4.10. Even though it is often difficult to demonstrate that any one particular strain of organism—for example a strain showing resistance to antibiotics—has come from animals, it is clear that the number of organisms passed to man must be quite large. Each year in England and Wales, some 4,000 or more persons are known to contract salmonella food-poisoning, mainly from meat and meat products, and there are probably many more cases which are not notified. The minimal infecting dose is probably many million organisms (depending on the serotype), so the number of salmonella organisms transmitted must be correspondingly great. To these must be added a conjectural

number of *Escherichia coli* and similar harmless organisms. If antibiotic resistance is widespread among animals, this flow of organisms from the animal environment is available to carry the resistance to man.

Direct and Indirect Transmission

4.11. The indirect transmission of micro-organisms in food is believed to be quantitatively the most important route in Britain for the transmission of animal infection to man, but infections may also be passed directly from animals to man and vice-versa. It is well recognised that persons in contact with animals may share some of their infectious diseases, so that it is not at all uncommon for example, to find a farmer or his family taken ill with the same type of salmonella infection as his cattle. Domestic pets, too, may be affected in a family outbreak of salmonellosis. The fact that both animals and man are infected in an incident of this kind does not in itself suggest that animals have infected man, for the reverse may apply, or animals and man alike may be infected from an extraneous source such as contaminated knacker meat sold for pets.

CHAPTER V

NATURE OF RESISTANCE TO ANTIBIOTICS

5.1. It very soon became apparent that some types of bacteria had an innate or natural resistance to particular antibiotics. Penicillin, for example, killed streptococci or staphylococci but was virtually without effect on salmonellas, escherichias or *Mycobacterium tuberculosis* (the causative organism of tuberculosis). The range of organisms over which the drug was effective came to be known as its spectrum of activity; antibiotics like tetracycline and erythromycin were termed "broad spectrum" since they were active against a wider range of organisms than a narrow spectrum antibiotic such as penicillin. Experience quickly showed that a bacterial population which was initially sensitive to an antibiotic could be replaced by one resistant to its action, so that an infection due to the resistant organisms could no longer be treated effectively with the drug.

5.2. The development of antibiotic drug resistance is believed to be due to natural selection. Among large numbers of bacteria, although most organisms are sensitive, one or two mutants may happen to have some resistance to an antibiotic; in the presence of the antibiotic, these bacteria and their descendants will have an evolutionary advantage. In the rapid succession of bacterial generations (and in some organisms a bacterial cell divides every twenty minutes) the selective advantage is soon shown by the appearance of a population of organisms most of which are resistant to the drug; the strain has thus developed antibiotic resistance. In a few instances the nature of the mutational change is known. Thus when staphylococci become resistant to penicillin they do so because they possess an enzyme, penicillinase, which destroys penicillin.

5.3. The resistance thus established is proof against the concentration of the antibiotic to which the organism was exposed. The strain may still be sensitive to higher doses of the same antibiotic, though of course the evolutionary mechanism will continue with the possible emergence of a strain resistant to a greater concentration of the drug (with a "higher" resistance). Hence every mention of antibiotic resistance should properly be in quantitative terms, such as "resistant to antibiotic x at concentration y"; in practice, however, the clinician is interested only in the therapeutic concentrations of the drug which may be attained in his patients and it is sufficient for most purposes to define "sensitive" and "resistant" by these concentrations.

5.4. A strain of an organism which has developed resistance to one antibiotic may prove also to have developed resistance to a second antibiotic to which it has not been exposed. This phenomenon is called "cross-resistance" and is common; it is often predictable, especially between antibiotics which are chemically similar or which act in similar ways. For example, organisms with resistance to streptomycin will often show cross-resistance to kanamycin,

and those resistant to tetracycline will be cross-resistant to chlortetracycline and oxytetracycline. In addition, and quite distinct from cross-resistance, a strain of organisms which has developed resistance to one antibiotic may, if exposed to a second antibiotic, develop resistance to this too. Strains may thus develop with double or multiple resistance. Once developed, antibiotic resistance is fairly stable and may persist for long periods even in the absence of the antibiotic. Strains with a low degree of resistance may, however, revert to their original sensitivity after a number of serial transfers in antibiotic-free media or in animals. In the presence of the antibiotic the resistance continues indefinitely.

5.5. Antibiotic drug resistance of this type develops more readily with some bacteria (*e.g.* staphylococci) and with some antibiotics (*e.g.* streptomycin). The development of resistance is encouraged by the use of low (subtherapeutic) concentrations of antibiotic and by prolonged exposure. In practical terms this means that the development of resistance is minimised by the use of full dosage of antibiotic for short periods.

Transferable Drug Resistance

5.6. The development of antibiotic drug resistance by mutation described above was thought until recently to account for every instance in which organisms acquire resistance. It is now known, however, that in a few types of bacteria another mechanism may also operate by which an organism may acquire resistance to one or more antibiotics simply from contact with other resistant organisms.

5.7. Infectious or transferable drug resistance as this process is known, was first described in Japan in 1959–1960 and has since been intensively studied both for the light it throws on bacterial genetics and for the potential implications it has for the public health. Unlike the evolutionary development of antibiotic resistance described in paragraph 5.2, transferable drug resistance is apparently confined to certain tribes of bacteria, notably the *Enterobacteriaceae*. Included in the enterobacteria, whose normal habitat is the animal and human intestine, are the salmonellas and *Escherichia coli* organisms mentioned in Chapter IV and the shigellas or dysentery organisms. Within this class of organisms, transferable drug resistance is now thought to be the most common method of acquiring resistance. Antibiotic resistance may spread rapidly among different strains of one genus (*e.g.* of salmonellas) or between different genera (*e.g.* from a *Salmonella* to an *Escherichia coli*) much as infections spread through an animal population. Transferable drug resistance has been sought unsuccessfully in some other families of bacteria. In staphylococci, for example, antibiotic resistance is known to be controlled by a cytoplasmic genetic factor but has not been shown to be transmissible.

5.8. Resistance is passed from one organism to another by the transfer of a fragment of genetic material (DNA) in a manner akin to bacterial sexuality. This process is described in Appendix B. The resistance so transferred may be to one or several antibiotics *en bloc*. Resistance to most of the common antibiotics affecting these organisms (*i.e.* to which these organisms do not have an innate resistance) has been shown to be transferable. Under suitable conditions, resistance to ampicillin, chloramphenicol, kanamycin, neomycin, streptomycin, sulphonamides, tylosin, and the tetracyclines is readily transferable; resistance to furazolidone (a synthetic nitrofuran) has been transferred

but transfer does not occur readily. As the donor and recipient enterobacteria possess an innate resistance to some antibiotics, such as bacitracin and penicillin, transferable resistance to these drugs in any ordinary practical sense has not been demonstrated. Transferable ampicillin resistance, however, is associated with a penicillin-destroying enzyme and experiments using high concentrations of penicillin have shown that a heightened degree of resistance to this latter antibiotic can be transferred.

5.9. Transfer of drug resistance may take place in the absence of any antibiotic and the recipient organism need never have been exposed to the drug. In the presence of an antibiotic, however, organisms to which the appropriate resistance is transferred are at an advantage, and selection ensures that the strain emerging will be resistant. Since multiple antibiotic resistances can be transferred *en bloc*, the presence of any one of the antibiotics suffices to give a selection advantage to organisms carrying multiple drug resistance. Hence among the *Enterobacteriaceae* the prolonged use of one antibiotic, *e.g.* tetracycline, may favour the prevalence of multiple-resistant strains. Antibiotic resistance may be transferred even in the presence of a high (therapeutic) level of an antibiotic to which the recipient organism is sensitive; the donor strain need not itself become established though there is some evidence that transfer is more readily achieved between strains which are multiplying rapidly.

5.10. The knowledge of transferable drug resistance summarised in the four preceding paragraphs has been obtained from experimentation *in vitro* (outside the living body, in cultures); the organisms used are growing outside their natural environment and the strain may have been cultivated *in vitro* for many generations. In assessing the relevance of transferable drug resistance, it is essential to confirm that resistance is transferable among ordinary wild organisms, and indeed it is necessary to estimate how far, if at all, the transfer of resistance occurs in the living animal or man (*in vivo*).

Transferable Drug Resistance *in vivo* **and** *in vitro*

5.11. In laboratories it is convenient to use familiar or easily identifiable strains of organisms as the recipients in transfer experiments. Among *Enterobacteriaceae*, mutant strains and those grown *in vitro* for many generations usually differ from naturally encountered wild strains in being "rough". (The adjective describes the appearance of colonies of the organism growing on a culture plate.) Roughness is associated among the *Enterobacteriaceae* with a decline in virulence because rough strains of bacteria are more susceptible to the natural defence mechanisms of the body. There is evidence to suggest that rough strains are more avid recipients of transferable antibiotic resistance than are normal, wild, smooth strains and this observation is of interest to bacterial geneticists concerned with the mechanism of transfer. It is certainly easier to design experiments and to detect the transfer of resistance when a suitable mutant (rough) strain is used as recipient. However, there is no doubt that wild-type smooth strains of *Escherichia coli* and of various *Salmonella* species are perfectly competent donors and recipients of infectious drug resistance.

5.12. A strain of bacteria which has acquired antibiotic resistance is not necessarily thereby made more or less virulent than before it became resistant. Strains which have become resistant by mutation often grow more slowly

than sensitive strains *in vitro*, but virulence—the ability to cause disease in animals or man—is not usually measurably affected. Organisms which have acquired resistance by transfer appear to grow normally *in vitro*, and epidemiological evidence in shigella and salmonella outbreaks suggests that the virulence of such organisms is neither enhanced nor impaired. There is in addition abundant evidence that many strains of harmful enterobacteria which have acquired transferable antibiotic resistance have retained at least their normal virulence. Nevertheless it is possible that bacteria which have acquired transferable resistance are at a selective disadvantage in the absence of any antibiotic to which they are resistant. There is some evidence, for example, that outbreaks of dysentery due to multiple-resistant strains of *Shigella sonnei* spread less than outbreaks due to sensitive strains. On balance it seems from the evidence so far available that in the absence of an antibiotic, the virulence of a particular strain of organism is not greatly altered by the receipt of transferable resistance. On the other hand in the presence of an antibiotic the ability of a sensitive strain to cause disease is greatly reduced but the danger to a host of a strain resistant to the antibiotic is unchanged or may even be considerably increased because of the reduction in the normal bacterial flora.

5.13. Several workers have demonstrated that the transfer of antibiotic resistance may take place between strains of bacteria in the bowel of a living animal when the bacterial population of the bowel is low. Experiments with animals leave no doubt that under these conditions transferable drug resistance is seen *in vivo*. One report estimates that the frequency of transfer *in vivo* is similar to that seen *in vitro*. Despite the considerable technical difficulties, there is suggestive experimental evidence of in-vivo transfer of resistance to salmonella organisms in pigs. In man, experiments with human volunteers are reported to have proved that multiple drug resistance can be transferred from multiple drug resistant *Escherichia coli* to shigellas in the intestinal tract. We were told too that in-vivo transfer in man has been observed occasionally from *Escherichia coli* of animal origin to *Escherichia coli* of human type. The experimental evidence for or against the transfer of resistance in normal animals or man is scanty, but what little there is indicates that transfer is seen *in vivo*, that it takes place more readily to certain strains of bacteria (such as *Salmonella typhimurium* phage type 29) and that its effect is considerably accentuated by the presence of an antibiotic.

5.14. It would be helpful to have more substantial experimental confirmation of transferable drug resistance between wild-type smooth organisms in the intact normal animal, and we hope that ways will be found to circumvent the considerable technical problems. It must not be forgotten, however, that the strongest evidence that antibiotic resistance is often transferred *in vivo* is not experimental but epidemiological. The phenomenon of transferable drug resistance was not discovered by chance. During epidemiological studies of multiple antibiotic resistant shigellas it was realised that the mechanisms then known by which bacteria acquired antibiotic resistance could not adequately explain all the observed facts. It was necessary to postulate another, hitherto unknown, mechanism by which resistance could be passed from one strain of organisms to another; once such a mechanism was suspected experiments were devised and transferable drug resistance was demonstrated.

5.15. The previously inexplicable findings which were thereby explained had come to notice during investigation of repeated outbreaks of bacillary dysentery in Japan. From 1955 onwards, more and more of the Shigella strains isolated showed multiple antibiotic resistance. Several workers found that organisms with multiple resistance could be isolated from some patients while others, infected in the same epidemic with the same serological type of shigella, excreted sensitive organisms. Some patients excreted both sensitive and multiple-resistant organisms of the same type at the same time. Patients initially excreting sensitive organisms sometimes excreted organisms with multiple-resistance after treatment with a single antibiotic. The observations summarised above could not, and cannot, be attributed to mutations. Together with one other finding (that patients excreting multiple resistant shigellas often also excrete *Escherichia coli* resistant to all the same antibiotics) they pointed to the infectious transfer of resistance; in-vitro experiments subsequently confirmed the in-vivo studies. Similar observations have been made in other human outbreaks: for example, in a large hospital epidemic of *Salmonella typhimurium* infection in London the investigation of the few inexplicable multiple-resistant strains isolated led to the first demonstration of transferable drug resistance in this genus of bacteria, and the first example of this type of resistance in any organism outside Japan.

Prevalence of Multiple Antibiotic Resistance

5.16. The choice of antibiotics now available is such that if a harmful strain of bacteria develops resistance to a single antibiotic it is probable that there will still be other antibiotics which may be used successfully in treatment. This does not mean, of course, that resistance to a single drug is of no consequence, for the drug of first choice may have a number of advantages over alternative treatment. Resistance to several antibiotics is a more serious matter, for there may be no other antibiotic to which the organism has an innate sensitivity, or the drugs which remain effective against the bacteria may be unsuitable for other reasons such as toxicity or allergy. There are strong indications, in the *Enterobacteriaceae* at least, that the prevalence of multiple antibiotic resistant strains has increased considerably over the last decade or so, and that most of this resistance is transferable.

5.17. Most of the information on which this conclusion is based has been derived from the examination of strains of bacteria isolated in this and other countries from specimens sent in by practitioners seeking laboratory help with treatment. The figures from such series do not necessarily measure the true frequencies with which strains are present in the community, but there are surprisingly few other data and it is clear, that with the outstanding exceptions of Dr. H. Williams Smith and his colleagues, the quantitative epidemiological survey has had little attention. Yet the fear that bacterial resistance will result from the unwise use of antibiotics is the main reason for controlling the supply and use of antibiotics, and the best way of measuring the adequacy of the controls must be to monitor the frequency and therapeutic significance of the antibiotic resistance amongst the animal and human populations. We are glad to know that a reference centre has recently been set up, but we should like to see facilities provided for the establishment of routine sampling so co-ordinated as to provide comprehensive serial information on the bacteria of animals and man. **We recommend that Ministers should provide**

adequate facilities to establish the regular and much wider surveillance of the bacteria of animals, animal products, and man, including their antibiotic resistance.

5.18. Our report would be incomplete without a direct reference to the important work of Dr. E. S. Anderson on the prevalence of multiple antibiotic resistance in strains of *Salmonella typhimurium*. It is unnecessary to set out the findings here as the author has published a full account elsewhere (*Anderson E. S.* 1968 *Brit. Med. J.*, 3, 333–339, "Drug resistance in *Salmonella typhimurium* and its implications"). We agree that the outbreaks of infection due to *Salmonella typhimurium* phage type 29, described by Dr. Anderson, include instances in which human disease and death resulted from multiple-resistant organisms which acquired their resistance through the use of antibiotics in animals.

CHAPTER VI

ANTIBIOTIC RESISTANCE OF BACTERIA ISOLATED FROM ANIMALS

6.1. Descriptions of the ways in which bacteria develop resistance to antibiotics are recorded in previous paragraphs. If observations are restricted to acquired rather than innate resistance it would appear that relatively few bacterial types are involved; the fact remains, however, that these types represent organisms that are responsible for much of the bacterial disease which veterinary surgeons have to contend with today in the food producing animals.

6.2. The *Enterobacteriaceae*, specifically the genera Escherichia and Salmonella, stand out as one of the principal causes of loss in young livestock and also as the bacterial family in which the emergence of antibiotic resistance has assumed the greatest importance due to the phenomenon of transferable drug resistance. Staphylococci responsible for much bovine mastitis and arthritis in fowls have been shown to develop non-transferable resistance in the presence of some antibiotics as have some species of clostridia and mycoplasmas.

6.3. It is equally important to record that antibiotic resistance has not been seen to develop in a number of significant pathogenic bacteria of animals, these include the pasteurellas, *Corynebacterium pyogenes*, *Erysipelothrix rhusiopathiae*, and most species of streptococci. It has been argued—and we believe rightly so—that resistant strains of these bacteria would already have emerged if they were going to do so. *Streptococcus agalactiae*, which at one time played such an extensive part in bovine mastitis, is now much less of a problem in the dairy herd since the use of intramammary penicillin, to which it did not develop resistance, and its role has been supplanted by strains of staphylococci which are capable of developing resistance to this antibiotic.

6.4. Before the discovery of transferable drug resistance, surveys conducted in this country had shown that the use of anibiotics for growth promotion had brought about detectable changes in the enteric flora of farm livestock. It was demonstrated in 1957 that a high proportion of *Escherichia coli* isolated from the faeces of pigs and fowls receiving a tetracycline for growth promotion were resistant to that drug; the high proportion with resistance persisted for several months after withdrawal of the antibiotic. In the next decade a number of workers related increases in antibiotic resistance among members of the *Enterobacteriaceae* to the practice of feeding antibiotics for growth promotion and also to their preventive and therapeutic use. Changes in resistance to a particular drug in *Escherichia coli* isolated from poultry coincided with the popularity of the drug for growth promotion. Most research has been concerned with the non-pathogenic and pathogenic strains

of *Escherichia coli* but in recent years considerable emphasis has been given to the salmonellas isolated from man and animals. This work is well recognised and documented, and attention may be drawn to reviews which discuss the subject as it affects both man and animals in detail (*e.g. Anderson E. S.* 1968, *Brit. Med. J.* 3, 333–339, *Smith H. W.* 1967, *N. Z. Vet. J.* 15, 153–166).

6.5. In the early 1960's it was apparent that bacteria were being isolated from man and animals which showed multiple patterns of resistance to a variety of antibiotics. More antibiotics were being marketed and this situation was being reflected in the isolates examined. Possibly the most spectacular incident was that between 1963 and 1965 when *Salmonella typhimurium* phage type 29 exhibited a great increase in multiple resistance. A high proportion of salmonellas and *Escherichia coli* isolates from diseased and healthy animals was found to be capable, under experimental conditions, of transferring all or part of their resistance pattern to suitable recipients. In these experiments resistance was donated to pathogenic and non-pathogenic bacteria alike.

6.6. In-vitro tests performed on bacteria isolated from enteric conditions in farm animals at laboratories indicate that large numbers are resistant to antibiotics. Multiple resistant strains are common and in recent times it has become more difficult for veterinary surgeons to select a suitable drug for treating enteric bacterial disease of farm animals.

CHAPTER VII

SOME GENERAL PRINCIPLES OF ANTIBIOTIC USE

7.1. Early in our discussions it became clear that the most contentious problems were to be found when antibiotics were used not for straightforward therapy alone but in situations in which the prevention or prophylaxis of disease was included amongst the aims of the prescriber. We think it may be helpful to consider here the theory and practice of antibiotic therapy in a number of situations, together with the evidence for supposing that the practices are or are not soundly based; and in the paragraphs which follow we have attempted to analyse the possible ways in which antibiotics are used. Unless otherwise stated we have assumed that full (therapeutically effective) doses of antibiotic are given, as it is accepted that lower dosage is almost always ineffective and indeed is very likely to favour the development of resistance. The rare exception to this rule (such as the use of low dosage of penicillin in some streptococcal infections) should not distract attention from the more usual need to use full dosage to minimise development of resistance.

Treatment

7.2. In the most obvious case, the antibiotic is given to a sick individual to treat the disease actually present—disease which is therefore known or believed to be due to an organism susceptible to the medicine chosen. The situation is commonplace to the veterinary surgeon and medical practitioner, and neither has any doubts about the propriety of prescribing an antibiotic if the condition of the patient warrants treatment. In these circumstances an antibiotic offers a direct prospect of advantage. The main disadvantages (toxicity and possible induction of antibiotic resistance) may be minimised by suitable choices of antibiotic, dosage, route of administration, and duration of the course of treatment, and in making his choice the prescriber is able to rely on a considerable amount of accumulated knowledge about the efficacy of specific antibiotics for the treatment of particular infections. Since individual observation and unquantified experience are fallible, it is generally agreed by both professions that the best guides to the likely usefulness of an antibiotic for treatment of man and animals are provided by clinical trials in which the response to treatment with the antibiotic is compared with the response to treatment with a different antibiotic, or to no treatment. In general the use of antibiotics for the direct treatment of disease is firmly based on the results of such clinical trials.

Attempted Prevention of Complications

7.3. An antibiotic may also be given to a sick individual to prevent bacterial complications arising during the course of some other illness; in such a case the disease actually present is not due to an organism susceptible to the

antibiotic but it is known that the organisms usually concerned in complications are susceptible. Most of the discussion of the prophylactic use of antibiotics in human medicine has been concerned with this type of prevention. For example, in measles the virus disease itself does not respond to antibiotics but the ear infection which is a fairly common complication usually responds quite well to an antibiotic such as penicillin. It is obviously tempting to suppose that the routine administration of one of these antibiotics to each case of measles would prevent most, if not all, of the ear infections and no doubt many doctors have acted on this supposition. A careful analysis of the results showed, however, that these expectations were not borne out, and it was concluded that the disadvantages of routine antibiotics in these circumstances outweighed the advantages.

7.4. Another similar instance, in which the prophylactic use of antibiotics was once much debated in medical circles but has now largely been abandoned, is the use of antibiotics to try to prevent complications or post-operative infection, particularly after major abdominal or thoracic surgery. It is now generally agreed that the "antibiotic umbrella" does not prevent post-operative complications and that the infections which arise are more likely to be caused by resistant organisms, the treatment of which may present major difficulties. The main exception to this general statement is in surgery of the large gut (in man), in which tissues may easily become soiled with heavily infected bowel content. It has been shown that pre-operative "sterilisation" of the bowel by an antibiotic is moderately effective in preventing bacterial infection of the tissues. Treatment with a poorly absorbed antibiotic like neomycin is started by mouth not more than two days before the operation; prolonged administration is avoided as it is ineffective in reducing the total flora and promotes the spread of resistant strains.

7.5. It is convenient and appropriate to mention here the only two other prophylactic uses of antibiotics in man which still command general approval. The first is the administration of an antibiotic before dental extractions in patients with certain types of heart disease. Organisms disturbed from the mouth may lodge on an abnormal heart valve and set up a serious infection there, but can often be prevented from doing so by a suitable antibiotic. The penalty of using an inadequate dose of antibiotic in these circumstances may be disastrous, for resistance is readily induced and may prove to be one of the most difficult therapeutic problems in medicine. The remaining accepted prophylactic use is for the prevention of second or subsequent attacks of rheumatic fever. This disease is due to an abnormal sensitivity to a streptococcal organism which fortunately does not acquire resistance to penicillin. Quite low daily doses of this antibiotic have been shown to be effective in reducing the frequency of relapses.

7.6. In each of these three situations the individual treated is known to be particularly at risk to a potentially serious complication and the treatment is known to be at least partially effective in preventing the complication. Epidemiologically, the cases treated in this way form an insignificant proportion of the human population. Apart from these three restricted situations, medical opinion does not now favour the attempted prevention of complications by antibiotics.

7.7. The prophylactic use of antibiotics to combat an infection of the liver which is common in calves fattened on barley affords a fully investigated

example of the use of antibiotics to deal with a bacterial complication. When weaned calves are fed diets consisting largely of barley, they may gain weight quickly but the characteristic fermentation of the diet is associated with unusually acid conditions in the rumen. The acidity produces changes in the rumen wall which render it abnormally susceptible to injury. The minute wounds caused by the plant fragments may then become infected so that the walls of the rumen become dotted with small abscesses; from these, infection is carried in the blood to the liver where similar abscesses form, with or without secondary infection by other micro-organisms. Some series have shown over a quarter of the animals to have liver abscesses.

7.8. The addition of an absorbable antibiotic to the animal's diet, in doses of 5 to 20 parts per million, reduced the incidence of liver abscesses but did nothing to eliminate the underlying abnormality of the rumen wall. In contrast, when the mechanism of the pathological processes was elucidated it was found possible to reduce the hyper-acidity in the rumen simply by adding some sodium bicarbonate to the diet with the gratifying result that the rumen walls of calves so fed remained normal. Exactly the same effect can be produced by the addition of a little roughage to the diet. Thus a simple dietary manipulation may be more effective than the addition of an antibiotic in reducing the economic losses from liver abscesses. It may also be noted in passing that although in these investigations the addition of an antibiotic to the calves' diet sometimes produced an increase in the rate of weight gain and in the efficiency of feed conversion, these responses were confined to the farms on which the overall performance of the untreated animals was poor, and on which low standards of management and hygiene were noted.

Medication of Contacts in the Presence of Infection

7.9. In face of an outbreak of infectious disease, appropriate antibiotic treatment may be given to apparently healthy individuals who are in contact with cases of the disease as well as to the sick, with the intention of preventing cases of illness among the healthy individuals or of forestalling the infection if contacts have already contracted it.

7.10. Circumstances in which this course of action is followed arise much more often in veterinary than medical practice. When infection breaks out in a large flock, for example, it may be almost impossible to ascertain which birds are sick, let alone to isolate them or give them individual treatment. The opportunities for cross-infection are in many cases so great that it is almost inevitable that every member of the population will have been exposed to infection and will probably become infected. Whether or not all infected individuals become ill depends partly on the nature of the infecting organism, for some infections are characterised by a low clinical attack rate despite wide spread of infection, but the infections of greatest consequence in the veterinary field are those in which most infected animals sicken. Moreover, the animals comprising the population may sometimes be very similar in genetic constitution, age, sex, and environmental history; such homogeneity makes it more likely that all individuals will react similarly to a similar bacterial challenge. Consequently it may often be predicted with fair accuracy that during an outbreak (say of scours in a group of calves) all the animals will be infected within a fairly short time, and, other things being equal, that all will require treatment when they fall sick.

7.11. It by no means follows that it is helpful to give an antibiotic in advance of clinical necessity in each individual case. Indeed, when the causative organism is already resistant to the antibiotic used, the effects of the infection can be increased and the ravages of the outbreak multiplied. Such at least is the conclusion to which bacteriological theory points; it would be helpful to know from comparative studies how far this is a real danger to set against the practical conveniences of prescribing for and treating all the animals at once. In the absence of such epidemiological guidance we accept that practical considerations may make it virtually impossible to separate sick animals from their contacts and that when antibiotic treatment is really needed (a proviso to which we return later) it may have to be given to both groups. It is important, of course, to minimise the chances of development of antibiotic resistance by using full therapeutic doses.

7.12. In ordinary medical practice antibiotics are not given to the contacts of patients with an infectious disease unless they themselves are ill. The exceptions to this general statement are of considerable interest as they are found in circumstances which resemble those often seen in veterinary practice. For example, outbreaks of infectious disease in institutions such as boarding schools are hard to control for in them man is brought closest (in epidemiological terms) to the conditions prevailing on an intensive farm. The mass medication of contacts has been tried; the results show that where the causative organism is sensitive *and does not readily become resistant to the drug used* such treatment can cut short an outbreak. For example, an epidemic of meningococcal meningitis in a school may be terminated by giving a sulphonamide drug to each of the boys. In contrast, outbreaks of disease in which the causative organisms quickly acquire resistance cannot be successfully treated in this way; this means in particular that medical experience suggests it is fruitless to try to control an outbreak of intestinal infection (*e.g.* one due to salmonella or shigella organisms) by the administration of antibiotics.

7.13. The successive attempts which have been made to prevent epidemics of infection with certain strains of streptococci show how carefully chemoprophylaxis has to be studied and supervised in order to leave a favourable balance of advantage. Extensive trials using sulphonamides to prevent scarlet fever and other streptococcal infections in army barracks, though initially promising, later showed failure of prevention due to the spread of resistant strains and the final outcome was less satisfactory in those treated than in those left untreated. Subsequent trials using penicillin (to which the streptococci concerned do not develop resistance) have been more successful and it is accepted that, in closed communities at least, mass chemoprophylaxis with penicillin can be effective as an emergency measure provided that its use is controlled and monitored bacteriologically by competent personnel. Even so it is important to consider with what degree of confidence an epidemic situation can be predicted, to define carefully the particular group at risk, and to be aware of the route by which the infection is spreading if mass penicillin prophylaxis is to be used widely.

Medication of Healthy Individuals in the Absence of Infection

7.14. It is sometimes advocated that an antibiotic should be given to apparently healthy animals (not known to be in contact with infection) with

the intention of preventing cases of a specific illness or illnesses which previous experience has suggested may be expected. It is hard to find any excuse in logic or theory for this practice, and even harder to find any practical evidence that it does any good at all. The expected disadvantages—the development of antibiotic resistance, the selection of multiple-resistant strains, and the subsequent tragic ineffectiveness of antibiotic therapy—were all well shown in the sequence of *Salmonella typhimurium* outbreaks in calves.

7.15. It may be argued (and, if anything, we are disposed to favour this argument) that the administration of an antibiotic to healthy individuals at times of "stress" is merely an extreme form of the practice criticised above and a form which calls for even greater condemnation. The intention is to prevent cases of non-specific illness so mild as to be clinically undetectable and shown only as a reduction of the rate of weight-gain. Such an argument would presumably not be supported by proponents of the antibiotics-for-stress theory, but the very fact that it is a perfectly tenable argument shows how great is the need for reliable and independent comparative studies.

Treatment of Carriers

7.16. The spread of some infectious diseases is facilitated by "carriers", *i.e.* by individuals who harbour the infection in an inapparent way and can pass it on to others. It is obviously good practice to break this chain of transmission by removal of the carrier or, where possible, by eliminating the infection from the carrier; equally it is regrettable if ineffective antibiotic treatment renders resistant the infection that is carried. "Dry-cow therapy" for mastitis in dairy cattle may be regarded as an example of the attempted chemotherapeutic eradication of carriers which is accepted as good practice.

7.17. Medical experience is very variable, depending on the site at which the infection is carried and the readiness with which the organism becomes resistant. Throat carriers of diphtheria or streptococcal organisms can be more often successfully treated than nasal carriers of staphylococci. Convalescent carriers of *Salmonella typhimurium* continue to excrete the organism longer if antibiotics are given than if they are withheld. Most troublesome, and potentially most serious, is the continued excretion of organisms by a typhoid carrier; it has sometimes proved impossible to stop excretion of typhoid organisms from a carrier despite surgical treatment and chemotherapy.

Relevance of Medical Experience to Veterinary Practice

7.18. When considering various ways in which antibiotics might be used in veterinary practice we found it useful to look for medical comparisons at each stage, and we have set out some of them in the foregoing paragraphs. In doing so we do not wish to suggest that veterinary practice is always paralleled by medical experience, nor to imply that all the conclusions reached by one profession must be adopted by the other. Indeed, we think that all along there have been too many unsubstantiated assumptions about animal epidemiology and therapeutics and would certainly not wish to introduce any such generalisation. Nevertheless it seems foolish to disregard medical experience if only because the major use (quantitatively) of antibiotics is medical and because most antibiotics from the sulphonamides onwards have been introduced first into human medicine; doctors first savoured the triumphs

of antibiotic therapy, doctors first encountered antibiotic resistance, doctors were the first to use antibiotics unwisely—and perhaps doctors have been the first to learn something from their mistakes.

CHAPTER VIII

REAL AND POTENTIAL DANGERS TO MAN

8.1. The possible dangers which may arise from the use of antibiotics in animal husbandry and veterinary medicine were outlined in Chapter III, and in Chapters IV–VII we have set out some of the practical and theoretical issues which have to be taken into account when trying to estimate where the dangers are merely hypothetical and where they are real. We have grouped the possible dangers into those resulting from antibiotic residues and those arising from the appearance of antibiotic resistance, and it is convenient to list our conclusions in similar form.

A. RESIDUES ARISING IN FOOD AS A RESULT OF ADMINISTRATION OF ANTIBIOTICS TO ANIMALS

Milk

8.2. Unless withdrawal times are rigidly observed the infusion of antibiotics into the udders of cows for the treatment of mastitis may result in residues of these medicines in milk sold for human consumption. Parenteral administration of antibiotics to milking cows can also result in the same phenomenon. Some of the more common antibiotics (*e.g.* penicillin) that are infused into udders are partially stable to the heat treatments to which milk may be subjected. As a consequence, bulked milk may contain detectable amounts of antibiotic, and cases have been described in this country and abroad of patients whose skin rashes were definitely provoked by penicillin in bulked milk. Even so, although milk is almost certainly the commonest food in which antibiotics are likely to be encountered, this fact must be placed in perspective against the small number of proven cases in which harmful effects have actually arisen from such consumption. We do not wish to decry the importance of these effects to the sensitive individual but must note that only a handful of such cases has been recorded in this country, and indeed few are known throughout the world. This may, however, arise from difficulty of proof.

8.3. We have, in evidence, data from the Milk Marketing Boards which show the marked reduction that has taken place in detectable antibiotic residues in milk recorded over the last three to four years. This reduction has primarily stemmed from recommendations made in 1963 by the Milk Hygiene Sub-Committee of the Milk and Milk Products Technical Advisory Committee, following an extensive survey carried out on antibiotic residues in milk in England, Scotland and Wales (1961–1962). The introduction of financial penalties by the Boards which were written into their contracts with milk producers, the testing and surveillance of milk from each producer at dairies and by the Food and Drug Authorities, and the clarification of withdrawal

times for both short and long acting antibiotic mastitis preparations, have all contributed to this much improved situation. Despite this, the present scheme and the sensitivity level of the test (0·05 i.u. penicillin/ml) are unlikely to effect any further improvement.

8.4. It is recognised that the test carried out to detect antibiotic residues in milk is particularly sensitive to penicillin and to a lesser and varying extent to other antibiotics. Prescription patterns alter and there is now a diversity of antibiotics available to the veterinary surgeon for treating mastitis. It is possible to envisage situations in the future in which antibiotics other than penicillin would come to be used just as widely and on the basis of the existing test their presence would go undetected. For this reason **we reiterate as a matter of some urgency one of the Milk Hygiene Sub-Committee's own recommendations, that "the search for a suitable marker—not necessarily a dye—capable of quick and easy detection should be continued".**

Other Animal Products

8.5. There are no known instances in which harmful effects in man have resulted from antibiotic residues in food other than milk. Nevertheless, that antibiotic residues can exist in some instances in the tissues of animals to which they have been administered, is unquestionable and the significance of such residues has been the subject of comment and anxiety in this country and elsewhere. Pharmaceutical manufacturers provided us with evidence on the antibiotic residues which either did or did not result after administration of their products to animals, and in recent years similar data have been examined on a voluntary basis under the Veterinary Products Safety Precautions Scheme; where necessary withdrawal times have been agreed in the light of the residue levels known to persist after the administration of recommended doses.

8.6. There is little evidence to suggest that the growth promotional use of antibiotics either in the past or the present has given rise to tissue residues; indeed it is claimed for several of the newer products used for growth promotion that no detectable residues are formed. In general, antibiotic residues are not detectable in animal tissues unless the dose has approached or even exceeded a therapeutic level, but whether or not this takes place is dependent on a number of variable factors. These include, for example, the properties of the antibiotic, the species of animal to which it is being given, the route of administration, the duration and level of dosage, the distributional pattern of the antibiotic throughout the tissues together with the rate and extent of its degradation and excretion from the body. When the antibiotic residues are known to exist, they are often found at higher concentrations and for longer periods of time in the kidneys and liver of most species of animals. If residues are present, this still does not necessarily mean that they will be consumed by man, because the survival of the antibiotic in the tissues after slaughter and the effects of cooking are additional variables influencing the situation.

Residues Arising from the Use of Antibiotics for the Preservation of Food

8.7. Antibiotics, and in particular the tetracyclines, are widely employed throughout the world as food preservatives. In Great Britain oxytetracycline and chlortetracycline may be incorporated in ice used for preserving fish caught at sea, providing that no more than 5 p.p.m. of the antibiotic is

contained in the final product. It is known that normal cooking tends to destroy these residues. Nystatin, an antibiotic with a spectrum of activity against fungal organisms, may be used on the skin of bananas but not in the flesh. The antibiotic nisin which occurs naturally in some dairy products may also be employed in the preservation of cheese, clotted cream, and canned foods.

Conclusion—Residues

8.8. The recommendations of the manufacturers and the Veterinary Products Safety Precautions Scheme, and the statutory controls, have been framed partly to minimise antibiotic residues in food. When the recommendations of dose and withdrawal time are complied with, we see no reason to suppose that residues present any danger. However, as we have shown above, milk may occasionally contain antibiotics and it is believed that most of these instances are due to failure to observe the recommended withdrawal periods between treatment of the cow and the resumption of marketing of her milk. It is possible that similar human errors occur in the observance of other recommendations, and that antibiotic residues are present in other animal products. Although no harm has been attributed to any such residues it seems sensible to form some estimate of the magnitude of this problem. We suggest therefore that the Minister of Agriculture, Fisheries and Food should request appropriate bodies (perhaps the Committee for Analytical Methods for Residues of Pesticides and Veterinary Products in Foodstuffs, and the Panel for the Collection of Residues Data) to consider the need for a survey to determine the presence or absence of antibiotic residues, including degradation products, in animal products (other than milk) on sale or destined for sale in Britain.

B. ANTIBIOTIC RESISTANCE

8.9. There is ample proof that the giving of antibiotics to animals encourages the emergence of resistant strains of micro-organisms. Equally there is no doubt that many micro-organisms, whether resistant to antibiotics or not, whether potentially harmful to man or not, can be transmitted from animals to man in a variety of ways. Hence, where man and animal share a common microbial pathogen, there can in many cases be no doubt that the giving of antibiotics to animals encourages the prevalence of resistant pathogenic micro-organisms in man. In Britain this seems most likely to happen in the case of salmonella organisms. In salmonella infections in man which are confined to the bowel and which do not need antibiotic treatment it is of no immediate significance whether or not the particular salmonella strain causing the infection is resistant to an antibiotic or antibiotics. In systemic infections, however, antibiotic therapy may be life-saving and the treatment may be made more difficult or the patient's life even imperilled because of antibiotic resistance. We accept that this has already happened and we have no doubt that it could do so again. The number of persons likely to be affected is hard to determine but should not be exaggerated, for systemic salmonellosis is not common though there is growing awareness of its dangers. Typhoid and the paratyphoid fevers are types of systemic salmonellosis to which special considerations apply (see paragraphs 10.20–10.23) and as the causative organisms are not normally animal pathogens they cannot acquire resistance from animals by this direct route.

8.10. The transmission of resistant pathogens from animals to man can and does take place whether or not the resistance is transferable. Transferable resistance provides a mechanism whereby the pathogenic micro-organisms can very rapidly acquire resistance, even in circumstances where no antibiotic is currently being given to the animal, but "conventional" chromosomal resistance can equally well be passed directly.

8.11. In contrast to this direct pathway, it is harder to estimate the significance of the other routes by which antibiotic resistance can be carried from animal to man. That resistance factors are very commonly carried to man by *Escherichia coli* of animal origin cannot be doubted, but these organisms rarely colonise the human bowel and such evidence as is available suggests that usually there is little transfer to human types of *Escherichia coli*. We do not know how great a contribution the antibiotic resistance from this source makes to the total pool of transferable antibiotic resistance in man. It may be that this mechanism is of little significance and that most of the transferable resistance factors to be found in the organisms in the human bowel are there because of the use of antibiotics in man and in man alone. We think it quite possible, however, that the resistance factors resulting from the use of antibiotics in animals and those arising from their use in man both contribute to maintain a pool which, otherwise, would tend to diminish, because in the absence of antibiotics, organisms carrying transferable resistance are at a disadvantage, and there is a tendency for resistance factors to be lost. Perhaps if either source were reduced the size of the pool would fall.

8.12. We are concerned at the high proportion of the population which carries transferable antibiotic-resistance factors in the *Escherichia coli* of their bowel flora. The resistance factors attached to harmless organisms in the human intestine do no harm of themselves. They pose a threat only when and if they are transferred to a pathogenic organism causing an infection which requires antibiotic treatment. Because transferable resistance is almost confined to the *Enterobacteriacea* it seems that *Escherichia coli* carrying resistance factors could cause harm to man only if they set up infection elsewhere in the body (such as the urinary tract) or if they transfer their antibiotic resistance to salmonella organisms causing systemic infections. The part played by transferable resistance in *Escherichia coli* urinary infections has not yet, however, been elucidated. The transfer of resistance from *Escherichia coli* of the bowel flora to salmonella and other human pathogens is known to occur, but we do not yet know how often such transfer gives rise to real difficulties in antibiotic therapy. In the absence of unassailable evidence we are bound to say that the indirect pathway, whereby antibiotic resistance originating in the *Escherichia coli* of animals is transferred to human pathogens *via* an intermediate pool of antibiotic-resistant *Escherichia coli* in the human bowel, seems to pose only a potential threat to man. Nevertheless it is a potential threat, for even if the pathway may prove to be of very little significance most of the time, it should be noted that an occasional exceptional strain of organisms (*e.g.* an exceptionally good donor or recipient strain) might be able to exploit this mechanism for the very rapid multiplication and transfer of resistance.

8.13. Some strains of *Escherichia coli* are themselves intestinal pathogens of infants. We have studied the evidence (including the reports of the Regional Hospital Boards concerned) about the outbreaks of infantile gastroenteritis

in Tees-side (November-December 1967) and in Manchester (December 1968–April 1969). We consider it is unlikely that the strain of *Escherichia coli* causing either outbreak had originated in animals, and we see no convincing reason for supposing that part or all of the multiple antibiotic resistance shown by either strain was derived directly or indirectly from animals. In various sections of this report we have discussed possible indirect ways in which the administration of antibiotics to animals might influence human disease, but there is no positive evidence to suggest that they were operative in these cases. Hence we believe that the origin and course of these outbreaks were probably not affected by the uses of antibiotics with which we are concerned.

Conclusions—Antibiotic Resistance

8.14. We conclude that the administration of antibiotics to animals in ways at present permitted has already caused some difficulties in veterinary practice and has caused harm to human health. Furthermore, if antibiotics are used unwisely, the mechanisms we have described can facilitate the massive and rapid propagation of antibiotic resistant organisms, for bacterial populations change and new strains arise, some of which may be able to exploit any opportunities they are offered much more effectively than the organisms we are used to. In effect this is what happened when the new strain of *Salmonella typhimurium* phage type 29 emerged; a combination of circumstances allowed the new strain (which was a particularly good recipient of transferred resistance) to prosper and the results show something of the potential for harm.

8.15. We do not accept the statement that twenty years of experience goes to show that there are no serious ill-effects from giving antibiotics to animals. Apart from the rather obvious direct harm which we believe to have resulted, we are only now becoming aware of the more subtle kinds of harm which may be due to present policies.

8.16. It will be apparent that the evidence available is not yet sufficient to allow a precise quantitative assessment of all the different aspects of the argument, and we recommend elsewhere an intensification of quantitative epidemiological and bacteriological study, to enable a continuing and precise assessment of the dangers to be made. Yet, despite the gaps in our knowledge, we believe that a general assessment—albeit lacking in quantitative definition—can be made on the basis of the evidence presented to us and that this assessment is a sufficiently sound basis for action on the lines we have recommended. Further research is certainly desirable, but we hold strongly that the cry for more research should not be allowed to hold up implementation of our recommendations.

8.17. We believe that it is sensible to reduce as far as possible the actual and potential dangers to man which may result from the giving of antibiotics to animals, and we believe that the effect of the changes we recommend in subsequent chapters will in fact reduce the dangers considerably. Moreover, we believe that this reduction in danger can be achieved without adverse effect on animal husbandry or on veterinary medicine.

CHAPTER IX

DISCUSSION AND PROPOSALS I

9.1. Many of those who have submitted evidence to us have emphasised the dangers to the health of animals and man which can follow if antibiotics are used improperly. Other evidence has stressed the economic and humanitarian advantages which would attend their free use. It was urged upon us on the one hand that the sale and use of antibiotics should be unrestricted, and on the other hand that antibiotics should be entirely withdrawn from animal use. We are satisfied that neither of these extremes is desirable.

9.2. Throughout the evidence has run the thread of man's inextricable involvement with his microbiological environment, so much of which he shares with his pets and livestock. Any use of antibiotics modifies this environment, and the use of over four hundred tons of antibiotics each year can change it profoundly. The advantages and disadvantages of some uses of antibiotics are known from experience or are predictable, but not all the mechanisms of antibiotic action or of microbial behaviour are known, nor can all the effects be foreseen. Consequently, we are convinced that the sale and use of antibiotics should be controlled strictly and the results of that control monitored with care.

9.3. We have referred briefly in Chapters I and II to the present statutory control of antibiotics and a detailed account of these controls is given in Appendix C. The practical effect of the law is to allocate most antibiotics into one or other of two groups; those in one group may be bought and used freely without prescription, whereas for those in the other group, the therapeutic substances, a professional prescription is invariably required. Special provision is made by exempting (relaxing) regulations to allow a very few antibiotics to straddle both categories, so that although normally available only on prescription they may also be obtained freely in low concentration for incorporation in animal feeds and other specified uses. In reviewing the use of antibiotics in animal husbandry and veterinary medicine it is appropriate to start by looking at the justification for these exempting regulations, not least because the feeding of antibiotics to animals for growth promotion has been the subject of such lively controversy.

Antibiotics for Growth Promotion

9.4. There is considerable evidence that the growth rates of young pigs and fowls can be increased when their feed contains a low concentration of antibiotic. The animals achieve marketable weight sooner and in some cases they eat less food in reaching this weight than they otherwise would. The commercial advantages from this increased productivity usually outweigh the cost of the antibiotic.

9.5. The growth rates of germ-free animals without antibiotics are at least equal to those attained in normally kept animals given antibiotics in their feed, and these high rates of growth are not further improved by adding antibiotics. These observations suggest that animals kept under commercial conditions are held back from their potential growth rates by micro-organisms in the environment, and that antibiotics somehow reduce this restraint. We considered the allegation that is sometimes made—that antibiotics are effective for growth promotion only in so far as they compensate for deficiencies in the method of husbandry—and we are unable to accept it as a generalisation. We were told, for example, that antibiotics given under conditions of really poor hygiene are less effective than if given under average conditions and that on balance the growth of poultry raised under even the best commercial methods of husbandry could be expected to benefit from antibiotic supplements though there might be marked differences in response from farm to farm. In one research establishment poultry which were the first to occupy new pens showed very little response to antibiotics given for growth promotion; after a time, when the pens were no longer new, similar birds placed in the building required antibiotic supplements to achieve the same growth rates as the first group. Cleansing and disinfection of the pens to a level of cleanliness higher than would be expected in ordinary commercial practice did not abolish the response to antibiotics. In commercial establishments the response to antibiotics may be erratic and a number of large producers do not use antibiotics for growth promotion but prefer to give other non-antibiotic feed additives for this purpose.

9.6. We accept the view that at present it is commercially profitable to allow low concentrations of specific antibiotics to be added to animal feeding-stuffs for the purpose of growth promotion but we know that the growth-promotional effect is very variable. We were told, also, that the growth-enhancement to be expected from an antibiotic may decline over the years and some quantitative information available confirms this view. Even if it is now financially beneficial to use antibiotics in this way it does not follow that it will always remain so. In the long term we believe it will be more rewarding to study and to improve the methods of animal husbandry than to feed diets containing antibiotics. It is implicit in the evidence we have studied that alterations in the microbial environment may enhance the growth of farm animals and can increase the economic returns for the farmer; the feeding of antibiotics is one way of altering the microbial environment but it is not necessarily the most effective or economical way in the long run. We consider that more attention should be paid to other possible ways of modifying the environmental microflora of animals and we suggest that there is a need for research into the consequences (including the economic consequences) of influencing the bacterial environment by higher standards of hygiene and other means. Such research could be pursued conveniently in conjunction with a department of veterinary epidemiology.

9.7. In this country, antibiotics are added to animal feed for growth promotion at levels of the order of 5 to 100 parts of the antibiotic (by weight) in 1 million parts of feed. Even at these relatively low concentrations the antibiotic exerts an effect on the populations of micro-organisms living on or in the animals—indeed this is believed to be why the antibiotic has the desired effect on growth rates. It has been shown repeatedly that the normal

intestinal flora of a flock or herd which is receiving an antibiotic at these levels in the feed may become resistant to the antibiotic used if the bacteria concerned are initially sensitive. It has also been shown that resistance acquired in this way may be transferred to other organisms by the infective process described in Appendix B and Chapter V. The resistant organisms so produced are resistant not only to the drug concerned but also to those drugs showing cross-resistance and even when the use of antibiotics is stopped, resistant organisms may continue to predominate in the intestinal flora for many months, perhaps because all the sensitive organisms have been eliminated. The feeding of penicillin to fowls leads to penicillin-resistance in the organisms (staphylococci) of the skin and nose of the fowls and of the skin and nose of their human attendants; the effects of penicillin on intestinal bacterial populations is more doubtful as many intestinal organisms have an innate resistance to the drug. It has been suggested however that certain strains of *Salmonella typhimurium* resistant to ampicillin which were isolated from pigs had acquired their resistance to ampicillin (a semi-synthetic penicillin) from the use of penicillin (benzyl penicillin) in their feed. (See also paragraph 5.8).

9.8. Thus it is certain that the use of an antibiotic in animal feed produces large numbers of resistant organisms, including organisms with transferable resistance, and that these resistant organisms may be transmitted to man. The potential dangers of the wide spread of resistance to therapeutic antibiotics have been sufficiently set out earlier in this report. We were told that the use of an antibiotic in animal feed often means that the antibiotic will be ineffective (because of the development of resistance) for the treatment of clinical disease of the animals, but apart from this we were urged that no definite ill-effect has been shown from this use, as distinct from the other uses, of antibiotics. That this may be so does not mean, however, that there has been no ill-effect, still less that there will never be any ill-effect if therapeutic antibiotics continue to be added to animal feeds. We judge that there are grave potential disadvantages for animal and human health in adding in this way to the pool of organisms which are resistant to the antibiotics of most value for the treatment of disease. We consider therefore that if antibiotics are added to animal feed to promote growth (and we have accepted in paragraph 9.6 that there is a case for doing this) the antibiotics should be chosen and used so as to minimise the development and selection of micro-organisms resistant to important therapeutic drugs. This can be done if antibiotics are separated into "feed" and "therapeutic" classes.

9.9. The classification of antibiotics into those to be permitted for animal feeding only and those to be reserved for strictly therapeutic use was considered in 1962 by the Scientific Sub-Committee of the Joint ARC/MRC Committee on Antibiotics in Animal Feeding. At that time, it was thought to be impracticable so to classify the antibiotics then available, but in looking to the future the Sub-Committee reported that it would recommend amendments of the regulations to permit the use of a further specified "feed" antibiotic "only if substantial scientific evidence was brought to show (*a*) that the proposed 'feed' antibiotic would have little or no application as a therapeutic agent, (*b*) that the efficacy of other prescribed therapeutics would not be impaired through the development of strains of pathogens resistant to the proposed 'feed' antibiotic, and (*c*) that the proposed 'feed' antibiotic

would be of economic value in livestock production under U.K. farming conditions." We agree that with slight modification these criteria effectively define a class of "feed" antibiotics which could be usefully employed in animal husbandry without detriment to the therapeutic armoury and that antibiotics in this class could conveniently and safely be supplied without professional prescription.

9.10. In 1962 no antibiotic commercially available in the United Kingdom satisfied these three conditions and so the Joint Committee was unable to recommend that the principles they had put forward should be applied at once to all antibiotics used for animal feeding, since to do so would then have deprived farmers of the economic advantages of feeding antibiotics. Since then, however, the commercial development of antibiotics has been influenced by the recommendations of the Joint Committee so that there is now on the market at least one drug, zinc bacitracin, which comes near to satisfying the desired criteria and other antibiotics are under assessment. Moreover the recognition that non-antibiotic substances (such as some compounds of copper or arsenic) may be used to promote growth has reduced the economic dependence on antibiotics. Consequently we have decided after careful consideration that principles of the type set out in 1962 by the Scientific Sub-Committee for the selection of *additional* "feed" antibiotics may now be extended and applied to *all* antibiotics used for this purpose. We are convinced that it is necessary to do this and are satisfied that it may now be done without substantial economic detriment to the farming industry. We are encouraged in this view by the great majority of the evidence we have received.

9.11. Accordingly, **we recommend that permission to supply and use an antibiotic without prescription for adding to animal feed should be restricted to the antibiotics which:**

(i) are of economic value in livestock production under United Kingdom farming conditions,

(ii) have little or no application as therapeutic agents in man or animals (paragraph 9.12) and

(iii) will not impair the efficacy of a prescribed therapeutic antibiotic or antibiotics through the development of resistant strains of organisms (paragraph 9.13).

9.12. In recommending above that a "feed" antibiotic shall have little or no application as a therapeutic agent we include an antibiotic that is withheld from use in treatment although it has some potential uses in the therapeutic field. It was argued in evidence that it must necessarily be against the public interest ever to withhold such an antibiotic from therapeutic use; doubtless this will usually be so, but we think it is possible that on occasion the balance of interest between use as a "feed" antibiotic and use in therapy might favour the former. For example, this position could arise if an antibiotic which on all other grounds was clearly suitable for use as a "feed" antibiotic were also used therapeutically in situations where some other medicine could equally well be used. As we think it is highly desirable that a permitted "feed" antibiotic should be withheld from therapeutic use we believe that in such cases recognition as a "feed" antibiotic should be conditional on the withdrawal of the antibiotic from use in therapy.

9.13. The wording of our recommendation 9.11 (iii) differs from that used by the Scientific Sub-Committee because of the recognition of transferable drug resistance. The development of resistant strains of organism is probably inevitable when a "feed" antibiotic is used but will be harmful only if the efficacy of a therapeutic antibiotic or antibiotics is thereby threatened. The development of organisms (which need not be pathogens) resistant to a "feed" antibiotic might impair the efficacy of a therapeutic antibiotic if:

(*a*) the "feed" antibiotic were itself to be used in therapy, or

(*b*) the "feed" antibiotic were to have cross-resistance with the therapeutic antibiotic, or

(*c*) resistance to the "feed" antibiotic were to be part of a multiple resistance pattern transferable *en bloc* such that selection pressure imposed by the use of the "feed" antibiotic would favour the prevalence of multiple-resistant organisms.

The use of a "feed" antibiotic would also threaten the efficacy of a therapeutic antibiotic if in any other way it led to the development of organisms resistant to the latter (as penicillin may have promoted the emergence of ampicillin-resistant organisms—see paragraph 9.7).

9.14. Chlortetracycline and oxytetracycline do not conform to the last two criteria which we have recommended in paragraph 9.11 above since both are important therapeutic drugs and both show cross-resistance to other prescribed therapeutics. There is considerable evidence to show that their use as feed antibiotics has led to the emergence of bacterial strains with widespread resistance to them and this resistance includes transferable resistance. We have already indicated that the unnecessary proliferation of resistance to therapeutic antibiotics is to be deplored; the advent of newer antibiotics which are effective as feed additives and which are therapeutically irrelevant has made it unnecessary to continue to use these valuable therapeutic drugs as "feed" antibiotics. Thus we agree with the recommendation made in 1962 by the Joint ARC/MRC Committee on Antibiotics in Animal Feeding, that . . . "if an antibiotic were to be developed which has little or no therapeutic application, but is comparable in its efficacy as a feedingstuff additive to the antibiotics now permitted, the continued use of existing permitted antibiotics would need to be reconsidered", and we believe that this time has now arrived. **We therefore recommend that the legislation permitting the supply and use without prescription of chlortetracycline and oxytetracycline should be revoked.**

9.15. Similar considerations apply to penicillin, though we recognise that the balance of evidence against the use of this drug as a "feed" antibiotic is not quite as formidable as in the case of chlortetracycline and oxytetracycline. Whereas the other drugs seem to have lost some of their economic advantages and effectiveness as feed antibiotics for poultry, the loss for penicillin has been less marked. Moreover the common intestinal organisms, both pathogens and non-pathogens, have innate resistance to penicillin so that there are no therapeutic problems from the development of penicillin resistance by these bacteria. However, we think that the undoubted development of resistance by staphylococci, the doubts about the transferability of penicillin resistance, and particularly the possibility that the use of penicillin as a feed antibiotic encourages the emergence of ampicillin resistance (see paragraphs 5.8 and 9.7)

make up an effective case against the continued use of penicillin as a "feed" antibiotic. **We recommend that the legislation permitting the supply and use without prescription of penicillin should be revoked.**

9.16. Some preparations of the antibiotic tylosin have been available without prescription (because unscheduled) and the drug has been widely used both for veterinary therapy and as a feed additive. It is chemically related to other macrolide antibiotics, at least one of which—erythromycin—is an important therapeutic drug. As a result of cross-resistance, micro-organisms resistant to tylosin may also be resistant to the other macrolides. Tylosin itself is a valuable antibiotic in veterinary practice, and it would be regrettable if indiscriminate use on the farm, or use as a feed additive, should impair the therapeutic usefulness of this or other macrolide antibiotics. In conformity with the recommendation in paragraph 9.11 above **we therefore recommend that tylosin should not be available without prescription for use as a "feed" antibiotic.** Furthermore, we consider it is unfortunate that tylosin was not scheduled under the Therapeutic Substances Act, 1956, and **we recommend that tysolin should be available only on the same terms as a scheduled antibiotic,** *i.e.* **only on prescription.**

9.17. We have also considered the sulphonamide group of antimicrobial drugs. Sulphonamides are not commonly used as feed additives for growth promotion but they are widely used for therapy in veterinary and medical practice, though their usefulness in recent years has been increasingly limited by drug resistance. In the *Enterobacteriaceae*, resistance to sulphonamides is easily induced and readily transferable. Sulphonamides have usually been included in the list of antibiotics to which multiple-resistant organisms are resistant; as explained elsewhere this means that exposure to sulphonamides may serve preferentially to select such a multiple-resistant strain. Legal control of sulphonamides, which antedated the development of true antibiotics, was exerted through the Pharmacy and Poisons Act, 1933, and it is possible to secure these drugs for agricultural purposes without a prescription. We consider that this is no longer desirable and **we recommend that sulphonamides should be available only on the same terms as a scheduled antibiotic,** *i.e.* **only on prescription.**

9.18. The position of the nitrofuran group of drugs is somewhat similar. Though little used in medicine, large quantities of these unscheduled antibacterial substances are used on farms, with or without veterinary prescription. Bacterial resistance to these drugs is known and is transmissible, and in theory the use of a nitrofuran could probably provide the selection pressure for development of a multiple-resistant organism. It is true that resistance to nitrofurans seems not to transfer easily and is fairly easily lost, and that resistance to this group of drugs does not cause cross-resistance with any other type of therapeutically useful antibiotic. Nevertheless on balance we think that these drugs, being therapeutically useful antimicrobial compounds to which resistance is known, should be used only by persons with professional knowledge; hence **we recommend that the nitrofuran drugs should be available only on prescription.** This restriction need not, in our view, apply to any nitrofuran derivative which is shown to be devoid of antimicrobial activity and shown not to cause drug-resistance to its own action nor to cause cross-resistance to any therapeutically useful antibiotic (including, of course, the other nitrofurans).

9.19. We considered the levels of "feed" antibiotic which should be permitted, and received evidence favouring both raising and lowering the permitted levels. It was suggested that if we were to recommend the virtual separation of "feed" and "therapeutic" antibiotics (as we have done in paragraph 9.11) it would be possible to allow unrestricted use of the newly-permitted "feed" antibiotics. However, these antibiotics are to be permitted without prescription to increase growth rates, and they are known to be effective for this purpose in low dosage; it is unnecessary for higher levels to be used and it is undesirable to allow greater use than is required for this purpose. To allow *ad libitum* use would be to tempt farmers to misapply these drugs for therapeutic purposes. In some countries the levels of antibiotic permitted for growth promotion are considerably lower than in Britain (*e.g.* 20 parts per million instead of 100) but in those countries the regulations usually allow higher doses (as high as or higher than the doses permitted here) to be used for special purposes such as in milk-substitutes. **We recommend that the maximum permitted level of a "feed" antibiotic conforming to paragraph 9.11 should remain unchanged** and we would remind users that lower levels will in most circumstances yield equal economic returns for a lower expenditure on antibiotics.

9.20. We have indicated in paragraph 8.6 the lack of evidence showing the existence of antibiotic residues in the tissues of animals receiving antibiotics in animal feeds at the levels now permitted for growth promotion. There is no evidence that such residues have ever caused harm to man. If the recommendations we have made in paragraph 9.11 are put into effect we think it even more unlikely that any harm could result to man from the residues of "feed" antibiotics. To ensure that this remains so, **we recommend that when a particular antibiotic is under consideration as a "feed" antibiotic, account should continue to be taken of the possible dangers to human health which might result from consumption of the residues of the antibiotic in the tissues of the animals fed.**

9.21. Current legislation permits the feeding of antibiotics (without prescription) only to pigs and poultry. The ARC/MRC Joint Committee recommended in its first report, in 1962, that permission be extended to allow their use for young calves. No action was taken on this recommendation, and in the Joint Committee's second report in 1966 it was recommended that action should be further deferred. We agree that it would be unwise to permit the feeding of the currently permitted antibiotics (penicillin, oxytetracycline, and chlortetracycline) to calves, and indeed we have recommended above that their use should be confined to the therapeutic field. However, the objections to currently permitted antibiotics do not apply in the case of "feed" antibiotics as defined in paragraph 9.11 and provided the recommendations we have made there are applied we see no objection to the extension of "feed" antibiotics to calves if it is commercially desirable to do so. **We therefore recommend that "feed" antibiotics conforming to paragraph 9.11 should be available without prescription for calves up to 3 months of age as well as for pigs and poultry.** We see no reason why this availability should not be extended to other ruminants should such use be shown to be beneficial.

9.22. The beneficial effect, if any, which an antibiotic may exert on the growth rates of pigs and poultry is seen only during the animals' early grow-

ing phase. Partly for this reason, and partly to minimise the transmission of resistant organisms to successive generations of animals, the antibiotics whose use as feed additives is at present controlled may not be fed to adult breeding stock or laying poultry (except on veterinary advice). For the same reasons **we recommend that "feed" antibiotics conforming to paragraph 9.11 should similarly be withheld from laying poultry and from adult breeding stock of all species.**

9.23. At present penicillin, chlortetracycline, and oxytetracycline may be supplied to farmers without prescription, either already incorporated into pig or poultry food or as concentrated preparations of which the maximum strength is specified in the regulations. We were told that easy access to these concentrates might on occasion lead farmers to misapply the antibiotics for therapeutic purposes. If our recommendations in paragraph 9.11 are put into effect such misuse should become less frequent and would give less cause for anxiety. **We recommend that concentrates of "feed" antibiotics (paragraph 9.11) should continue to be permitted for use by farmers who prefer to mix their own feeds rather than to buy ready-compounded feeds.**

9.24. When an animal feed is sold ready-compounded with a "feed" antibiotic we believe that it should at all times be brought to the notice of the purchaser and user that the feed contains an antibiotic. **We recommend therefore that any advertisement, order form and label for such feed should be required to display clearly the amount and official name of the constituent "feed" antibiotic(s).** With this proviso we see no reason why a "feed" antibiotic, or ready-compounded feed containing a "feed" antibiotic, should not be advertised and promoted without restriction.

9.25. In this chapter of our report we have considered the use of antibiotics at low levels for the purpose of enhancing growth rates. We have recommended that the use of certain antibiotics which conform to the criteria set out in paragraph 9.11 should be permitted without prescription. We consider that antibiotics which do not conform to these criteria should be reserved for therapeutic use and should not be used at low levels, whether for growth promotion or other purposes, particularly for prolonged periods. In a subsequent chapter we consider a practitioner's rights to prescribe antibiotics freely, but we will anticipate here by saying that we believe veterinary practitioners should not prescribe any antibiotic, which is not a permitted "feed" antibiotic conforming to paragraph 9.11, for continuous administration other than for specific therapeutic purposes. It is highly desirable that only antibiotics which satisfy the criteria we have recommended are used for growth promotional and allied purposes.

9.26. The allocation of particular antibiotics between the categories of "feed" antibiotic and "therapeutic" antibiotic cannot necessarily be permanent. For example, the continued use of a permitted "feed" antibiotic might become undesirable if a related drug, with cross-resistance, came into use as a "therapeutic" antibiotic. Hence any recognition as a permitted "feed" antibiotic must be regarded as temporary only and subject to review; this might perhaps be achieved by a system of renewable licences.

CHAPTER X

DISCUSSION AND PROPOSALS II

Antibiotics in Veterinary Practice

10.1. In the previous chapter we have defined a class of "feed" antibiotics and made recommendations on their use. Those antibiotics—in the wide sense in which we have used this term—which do not fall in this class have been called "therapeutic" antibiotics. **We recommend that a "therapeutic" antibiotic, *i.e.* an antibiotic which is not a "feed" antibiotic within the criteria set out in paragraph 9.11, should be available for use in animals only if prescribed by a member of the veterinary profession who has the animals under his care.**

10.2. The class of "therapeutic" antibiotics includes virtually all the antibiotics which are or will be used for the treatment of animals and of man. At present the veterinary surgeon and practitioner is free to prescribe any antibiotic. We have had to consider whether the interests of animal or human health demand any limitation in the number or type of antibiotics which can be given to animals or the ways in which they may be used. We were well aware that the veterinary surgeon and practitioner, like his medical counterpart, treasures the freedom enjoyed by members of his profession to prescribe as he thinks best in the interest of his patient. We would not lightly wish to detract from this privilege and responsibility. Nevertheless, just as the medical practitioner's freedom to prescribe heroin has recently been curtailed in the public interest, it is obvious that the veterinary surgeon and practitioner's freedom to prescribe as he wishes is not sacrosanct. The ability to prescribe is a privilege reserved to the professions by law for the protection of the public, but continuation of the privilege is in the last resort conditional on the responsible exercise of the power it confers.

10.3. Contrary to one suggestion made to us, we are in no doubt that some antibiotics must continue to be used for the treatment of animals. To deny completely to the veterinary profession the use of effective antimicrobial drugs would needlessly increase animal suffering and disease, reduce the supply of human food of animal origin and have adverse effects on human health, human nutrition, and farming economics. We are sure that the advantages which might be expected to accrue from a complete ban on the veterinary use of antibiotics would not compensate for the harmful effects of such a ban. Moreover we are satisfied that the advantages can be achieved without the adoption of so extreme a measure.

10.4. Another suggestion made to us was that the antibiotics used in the treatment of animals should be quite different from those used in man. At the very least such a distinction would make it easier to quantify the extent to which antibiotic resistance in man's bacterial flora derives from the use of antibiotics in animals. We therefore considered whether it was possible to subdivide the class of therapeutic antibiotics into a section reserved for

veterinary use and another section kept for use in the treatment of man. We found that no such division could be made, since (with minor differences due to species variation or to the costs of drugs) the most effective and useful drugs for human therapy are also the most effective and useful drugs in veterinary medicine and *vice versa*. This is to be expected because of the physiological similarity of man and animals and the similarities of many of their microbial pathogens. These same factors make it probable that this situation, in which no biologically-based division of antimicrobial drugs is practicable, will continue indefinitely. The number of distinct types of antibiotic (*i.e.* not showing cross-resistance) is of course still quite small. It is possible that at some time in the future so many unrelated antibiotics will be known that it will be possible on some arbitrary basis to allocate them for use in animals or man without detriment to the treatment available for either category. This is unlikely to occur in the foreseeable future.

10.5. For the time being then the antibiotics used in veterinary medicine must continue to overlap extensively with those used in human medicine. With the exception of chloramphenicol, which is considered separately in paragraphs 10.20–10.23, we have received no representation that any particular antibiotic or class of antibiotic should be withdrawn from use in animals. Although some of the evidence we received was critical of instances of antibiotic use both in man and in animals these were not of the type which could be remedied by forbidding the use of particular antibiotics; rather they were instances of ill-informed prescription. We see no purpose therefore in seeking to limit the number or type of antibiotics which veterinary surgeons or practitioners may prescribe.

10.6. Criticism of the use of antibiotics in veterinary medicine appears to centre not on the identity of the drugs prescribed by veterinary surgeons but on the reasons for which the drugs are sometimes given. In particular there has been criticism of the ways in which some veterinary surgeons have thought it right to manage outbreaks of infection, or expected outbreaks, amongst a herd or flock of animals. To some extent it became apparent that medical and veterinary practitioners differed in their approaches to some of the problems encountered in their practices; we found it necessary to look in some detail at the ways in which antibiotics have been used and we attempted to set these out in Chapter VII. Present medical attitudes to the use of antibiotics (in so far as there are any generally held views) have evolved gradually. Though fortified with bacteriological and epidemiological theory, medical opinion is based, at least in part, on the critical evaluation of experience. In ordinary clinical therapeutics the importance of comparative trials is now well established in human and veterinary medicine. In human medicine such trials have also been carried out in the wider aspects of attempted prevention and disease control and have led to the rather pessimistic conclusions outlined in Chapter VII. We realise that these conclusions may not be applicable in every respect to veterinary work, but we think that until comparable work has been carried out in animals, under the conditions of husbandry encountered in ordinary practice, it would be wise to expect that the limitations of antibiotic treatment are much the same in man and in animals.

Limitations of Antibiotics

10.7. In human medicine, where the survival and welfare of each single individual might be thought to be the dominant consideration and where

(in the National Health Service) the cost of antibiotics need not deter their use when clinically indicated, the medical profession has set its face against mass medication with antibiotics and with few exceptions confines their use to the treatment of individual sick patients. It is accepted that antibiotics are of little or no value in controlling the spread of infectious disease through a population. It is recognised that diseases caused by organisms which readily acquire resistance cannot be prevented by antibiotics, and that antibiotic medication of healthy individuals is more likely to create trouble than to prevent it.

10.8. These conclusions seem to us to be inevitable except in those relatively unusual circumstances where an organism does not appear capable of acquiring resistance to the action of a particular antibiotic. Although we consider it is important to define in veterinary practice the exact boundaries of the beneficial and the undesirable uses of antibiotics, and have commented earlier that medical experience is not necessarily relevant to veterinary practice, we expect these general conclusions to be as true in veterinary practice as they have been shown to be in medicine. If antibiotics could be developed to which resistance did not develop, entirely different circumstances would prevail and it is possible to imagine antibiotics then having wider uses in the control and prevention of disease; the remaining disadvantages of toxicity and sensitisation might well prove acceptable for the protection of individuals against certain microbial risks, just as chemoprophylaxis is practised with fair success against malaria and the coccidial parasites of poultry. Until then, however, we believe that the ability of micro-organisms to acquire resistance greatly restricts the scope of antibiotic therapy. We believe it is imperative that both medical and veterinary practitioners should be aware of these limitations and take them into account in their prescribing, for failure to do so can have serious consequences.

10.9. The limitations of antibiotic therapy are shown particularly clearly in diseases due to *Enterobacteriaceae* (including salmonella and *Escherichia coli* infections), presumably because strains of these organisms acquire resistance particularly rapidly by transfer. As noted above, human experience suggests that antibiotics have no place in attempts to control the spread of intestinal infections, and we expect that suitable studies would show this to be equally true in animals. We note with approval the indications that both medical and veterinary practitioners have begun to question whether the use of antibiotics for such infections is not self-defeating. Because the behaviour of many salmonella and coliform infections in animals and animal populations is different from that in man, we think it important that studies directed to the answering of this question should be carried out in animals as well as in man.

10.10. Whatever the value of drug therapy for sick individuals it is certain that antibiotics did not prevent repeated outbreaks of calf salmonellosis. Thereafter they were often ineffective for treatment of generalised infections and it is probable that the use of antibiotics compounded disaster by producing and selecting a multiple-resistant strain of *Salmonella typhimurium*. Infection with this organism spread widely in calf-rearing units, causing severe losses, and was subsequently transmitted to the human population. With the benefit of hindsight we suggest that the attempts made to check the spread of this infection with antibiotics were misguided, and that it would have been

much more rewarding to pay attention to the ways in which the disease spread through the farm population. It now seems certain that the increase in calf salmonellosis was related to the change in the system of calf husbandry which took place at the time, a change which afforded greater opportunities for the dissemination of infection. Taken from many herds, calves were brought together at dealers' premises in order later to be sold in batches to calf-rearing units. The mixing of immature animals after they had travelled from distant farms is ideally calculated to promote the rapid spread of infection through the group, and the subsequent distribution of sick animals ensures that they carry the infection with them. (When the calves fell ill they usually did so at the recipient units, and the animals already at the unit then developed the disease.)

10.11. To describe the way in which calf salmonellosis is spread—even in such simple terms as those above—is in itself to suggest ways of controlling the spread. When the epidemiology is known it is easy to suggest ways of control. Thus the resistance of individual animals could be increased by keeping them on their home farms until they are more mature, or by vaccinating them. Opportunities for cross-infection could be curtailed by reducing the number of farms from which calves are bought and by avoiding the intermediate mixing at dealers' premises or markets. The merits of any particular suggestion can then be tested by observation and experiment, in the hope and expectation that a pattern of husbandry can be evolved which retains the economic advantages of specialised calf-rearing but which minimises the dangers and losses associated with the spread of infection. Application of some of these commonsense principles seems more likely to prevent calf disease than does the administration of antibiotics, and happily the farming industry is now well aware of the dangers to their livelihood implicit in the trade in young calves.

10.12. In singling out these outbreaks of calf salmonellosis as instances in which inadvised attempts were made to control animal disease by chemotherapy, we do not wish to castigate the practitioners who were faced with these problems at the time. Our critiscims are made with the knowledge that these attempts failed, and are made possible by the leisurely contemplation of the evidence which has since accrued from a number of sources. It may be that each individual practitioner who was called on to advise on the management of such an outbreak was too close to the detail of that isolated outbreak and could not appreciate the overall pattern. The wider picture was suspected when the routine collation of information in a reference laboratory suggested that many different outbreaks of calf disease were in some way linked. Officers of the Veterinary Investigation Service, after a careful survey, were then able to describe the epidemiological significance of the type of calf trade outlined above. Although the results of this survey are of great value, special surveys of this type are most useful when they complement an established system of data collection and evaluation because no special investigation can be started until a problem is recognised and defined.

10.13. We think it possible that recognition, elucidation, and solution of similar problems might be achieved more quickly and more easily if the development of veterinary epidemiology (to which we refer again later) were to include the further evolution of a veterinary equivalent of the Medical Officer of Health. In some respects the veterinary staff of the Ministry of Agriculture.

Fisheries and Food already function in this role but their responsibilities and powers are limited and do not enable them, for example, to investigate outbreaks of salmonellosis if the farmer is unwilling for them to do so. The Medical Officer of Health, for his part, has certain powers over animal products but except in the case of milk these do not extend to living animals—nor indeed does his training prepare him for any such extension. Consequently there are outbreaks of infectious disease of animals, some of which appear to threaten the public health by the ill-advised use of antibiotics or otherwise, in which no investigation can be made and no official action taken. **We recommend that the Agriculture Ministers should give an appropriate veterinary officer responsibility for all infectious disease of animals in the area, or at least of all such disease as appears to threaten the public health, and should grant him adequate powers to minimise the spread of disease;** rights of entry and investigation would be needed. It is important to ensure that on those occasions in which an animal source is suspected of causing human infection, there should be a concerted medical-veterinary attack on the situation; we believe that an extension of the veterinary officer's powers on these lines would help to bring this about. It may seem strange that we should be discussing the need to establish a veterinary officer of health at the very time when others are beginning to recast the role and responsibilities of the Medical Officer of Health, but there is no conflict here since the problems which confront the veterinary surgeon on the farm today are, in outline, those faced in human society a century or more ago.

10.14. This is a period of rapid change in farming methods, and as recent experience has shown, changes in the system of husbandry can bring unexpected difficulties because of consequential changes in the pattern of disease. The development of intensive husbandry has introduced many new problems, partly because the density of animal populations in intensive units is higher than that encountered in older methods of husbandry. But though it brings new problems, intensive husbandry also brings new opportunities to tailor the environment and the farming methods to the needs of the animals. It is our impression that so far farmers have shown a better appreciation of the physiological needs of the animals than they have of the other factors which influence the spread of infectious disease. It is readily accepted that nutrition, warmth, and lighting affect the growth and health of animals and so are worth careful attention but there is relative neglect of the simple proposition that infectious diseases are passed from animal to animal in ways which can be ascertained and interrupted. The common intestinal infections, for example, are contracted by mouth, by eating contaminated food, or by bringing the mouth into contact with the excreta of an infected animal, so that premises and farming methods designed to reduce or eliminate this kind of cross-infection should cut the losses caused by these diseases. In general we believe that the deliberate modification of methods of husbandry to take account of these and similar epidemiological facts is likely in the long term to be more effective and safer than any attempts to control disease with antibiotics. We should like to see more use made of the veterinary surgeon as adviser when the introduction of an intensive enterprise is contemplated by a farmer so that disease may in some measure be prevented.

Veterinary Epidemiology

10.15. For some diseases most of the details on which a preventive policy

could be based are already known, but in others it will be necessary to carry out further research. **We recommend that further studies be set up of the economically important infectious diseases of animals to determine how the disease is introduced into herds or flocks and how it is maintained there once established, what the reservoirs are, by what routes the disease is transmitted, and what factors favour its spread.** Concurrent with this, **we recommend that experimental research be initiated into the effectiveness, feasibility, and economic consequences of deliberate changes in animal husbandry introduced in the light of epidemiological knowledge.** It is clear that the organisational and academic framework in which such studies are carried out will need strengthening if research effort is to be expanded in the directions we have suggested.

10.16. We consider that it would be valuable to build up the epidemiological component of the governmental veterinary services. The work already done by Ministry officers has been of a high order, but the resources available for this part of the work do not match the importance of the subject or its potential advantages. **We recommend that the Agriculture Ministers should take steps to increase the resources devoted to epidemiology by their departments. We recommend too that the Agricultural Research Council should be asked to consider how best it could promote epidemiological studies of infectious disease and of the prevalence of antibiotic resistance. We further recommend that the Agricultural Research Council and the Medical Research Council should be asked to consider jointly how best they may promote epidemiological studies of the infectious diseases which are common to farm animals and to man, particularly salmonellosis, and of antibiotic resistance in these diseases.**

10.17. Similarly we consider that epidemiology should now be further recognised in the universities and developed as an important part of veterinary medicine which is of considerable potential value to the agricultural industry and **we therefore recommend the establishment of university departments of veterinary epidemiology.** We accept that epidemiology can properly claim the status of a distinct discipline, but quite apart from the academic merits of the subject we are confident that the formation of such departments would help to harness the talents and energies of workers from a number of other disciplines to the practical problems of animal husbandry. To make the contribution of new departments most effective we think their activities should be directed towards the evolution of purposive, enlightened, and profitable changes in the methods of animal husbandry; this might perhaps be facilitated if departments were developed close to a department of agriculture or of public health.

Educational Influences

10.18. In addition to the advantages we have already mentioned, the establishment of academic and other units interested in the spread of animal diseases will serve to increase the amount of independent information available to the veterinary profession. We were often conscious of the relative paucity of independent sources of advice, particularly of advice based on critical observation, on the proper use of antibiotics and the dangers of misusing them. The availability of such independent advice, and of vigorous professional discussion and continuing postgraduate education, can do nothing but good and is an important factor in the maintenance of responsible professional attitudes. Perhaps we may also comment parenthetically (for the

use of antibiotics by doctors lies outside our terms of reference) that there is a continuing need to make independent advice available to the medical profession too, so that the standards of antibiotic prescribing of all practitioners approximate to those of the best-informed.

10.19. The development and maintenance of a sensible antibiotic policy is made more difficult for veterinary surgeons who are subjected to pressures from laymen, who may be clients or employers. The selection of the best antibiotic, if any, to be used on a particular occasion requires professional skill and judgement which in the nature of things the lay client does not possess; we regard attempts by pharmaceutical companies to influence the choice of the lay client towards a particular antibiotic as unjustified and improper, and **we recommend that the advertisement and promotion of therapeutic antibiotics to laymen should be forbidden.**

Chloramphenicol

10.20. Although it will be evident from the foregoing discussion that we are not seeking to limit the powers that veterinary surgeons enjoy to prescribe the great majority of antibiotics, we must single out one antibiotic, chloramphenicol, for special consideration. Chloramphenicol is a powerful antibiotic which is not used very widely in human medicine because of the potentially fatal blood disease which sometimes complicates its use. So seriously is this toxic complication regarded that chloramphenicol is likely to be used in medicine only in cases of grave disease when it alone is likely to be effective or where it has unquestionable advantages over other antibiotics. Typhoid fever is such a disease, as are the other enteric fevers and systemic salmonella infections. In Britain the causative organisms of these diseases are at present only rarely resistant to chloramphenicol, probably because this antibiotic has been relatively little used here; but there is no doubt that they can acquire chloramphenicol resistance. We were told, and we accept, that it is very important to retain the effectiveness of chloramphenicol for the treatment of these diseases, especially typhoid fever, and that human lives would be lost if these organisms became resistant to this antibiotic.

10.21. It was strongly argued, and we accept, that the incautious use of chloramphenicol in animal husbandry and veterinary medicine will very likely lead to the frequent development of chloramphenicol resistance (including transferable resistance) in the intestinal bacteria of animals and, less often, of man. We agree too that if a man whose intestinal bacteria carried transferable chloramphenicol resistance were already a typhoid carrier, or subsequently became infected with typhoid, the resistance could be transferred in the patient's intestine to typhoid organisms. For this to happen, two rather infrequent events would have to coincide: firstly typhoid is relatively rare in Britain and secondly it seems unlikely that the carriage of chloramphenicol resistance by the bowel flora of man would be common unless the use of chloramphenicol were to be increased. Nevertheless we recognise that this combination of events is possible, and if such a patient were then treated (for typhoid) with chloramphenicol, the stage would be set for the selection of a chloramphenicol resistant strain of typhoid. We have to agree that if chloramphenicol is used routinely in agriculture this will sooner or later happen. The consequences would be serious.

10.22. Chloramphenicol resistant typhoid has been reported overseas, and since about half of the typhoid cases in England and Wales contract their

infection abroad it is possible that a resistant strain of typhoid organisms could be imported and become established. There is no specific way of guarding against this possibility, but we consider that this does not make it any less important to try to prevent chloramphenicol resistance arising in Britain. We are alarmed at the increasing use of chloramphenicol in veterinary medicine and we do not accept the contention that because the increase is largely confined to injectable and topical (surface) preparations it is appreciably less undesirable. Far from condoning the present use of chloramphenicol for animals, we have given very serious consideration to the suggestion received in evidence that, because of the risks to the public health, the use of chloramphenicol should be forbidden in animal husbandry and veterinary medicine.

10.23. A complete ban on the use of chloramphenicol in animal husbandry and veterinary medicine could be achieved by withdrawing the veterinary profession's right to prescribe this particular antibiotic. Such a ban would cause little or no hardship to some veterinary practitioners, or their clients, but we were told that there are some situations in veterinary practice (with both large and small animals) when chloramphenicol is likely to be the only effective drug. To deny chloramphenicol to the veterinary practitioner would, exceptionally, deprive him of his only weapon. We have tried to estimate the relative probabilities, and to weigh the relative advantages to human health if use of the antibiotic were banned and to animal health if its use were still permitted, and we confess that this is one of the most taxing decisions we have been asked to make. We have concluded that chloramphenicol should be reserved by veterinary surgeons, as it is by doctors, for use in very special situations when it is specifically indicated for individual animals, and that if it is used in this responsible way it should not be necessary to withdraw it from animal use. **We recommend therefore that, to preserve the effectiveness of chloramphenicol, veterinary practitioners should retain the use of this antibiotic as an exceptional measure reserved for special situations. We recommend that consideration should be given to the incorporation of a warning or advisory label in these or similar terms on each retail pack of chloramphenicol supplied for veterinary use and on each advertisement relating to the use of chloramphenicol in animals.** Finally, we recognise that our decision may prove to have been mistaken, and we consider it would be prudent to monitor the amounts of chloramphenicol used in human and veterinary medicine, and the prevalence of chloramphenicol resistance in organisms isolated from farm animals and from the intestinal flora of healthy humans, so that prompt action can be taken on reliable evidence if either increases significantly. **We recommend that the Minister of Agriculture, Fisheries and Food and the Secretary of State for Social Services should take steps accordingly.**

Conclusion

10.24. We began this review of the use of antibiotics in veterinary medicine by asking whether the freedom at present enjoyed by the veterinary profession (to prescribe antibiotics of all kinds for all purposes in all quantities) should be continued. Our examination showed that there were certainly instances in which antibiotics had been used in the past in ways which can now be regarded as unwise. These instances were related to certain limitations in the philosophy of drug use then current rather than to any kind of malpractice or incompetence at that time. We think that it would be wise for

practitioners to temper credulity with a more critical analysis of the advantages and disadvantages of the antibiotics they prescribe. In so doing they will be exercising their professional judgement and deciding between alternative courses of action on the basis of criteria which are essentially veterinary rather than legal. We believe too that implementation of the recommendations we have made earlier in this chapter will do more to achieve wise use of antibiotics than would legal restrictions. It would in any case be difficult to frame or enforce legislation to allow the prescription of an antibiotic for some purposes but not for others. **We recommend therefore that no change should be made in the law which allows the supply of antibiotics on veterinary prescription.** We are confident that the veterinary profession will rise to these responsibilities.

CHAPTER XI

CONTROL OF ANTIBIOTICS

11.1. The legislation under which antibiotics and similar substances are at present controlled stems largely from the Therapeutic Substances Act, 1956. The mechanisms of control are complex and are set out in some detail in Appendix C which is concerned with the true antibiotics only.

11.2. In the future, control will be effected under the Medicines Act, 1968. This Act makes general provision for the overall control of drugs but until such time as detailed regulations are promulgated, the present control mechanisms will continue to operate. The changeover to new regulations must necessarily take some time to put into effect.

11.3. Under the Medicines Act, responsibility for control will lie with Ministers advised by the Medicines Commission and by advisory committees. **We recommend that one such committee should have overall responsibility for the whole field of use of antibiotics and related substances whether in man, animals, food preservation, or for other purposes.** Although such a committee will have to operate through sub-committees we are convinced that one body must be able to look at all uses and their possible inter-relationships. The committee, in addition to all its routine work in connection with new antibiotics or new uses of existing antibiotics, should review periodically existing antibiotics and their uses to ascertain whether changing circumstances justify either greater relaxation or more restrictive control. We note that it will be possible within the new control mechanisms to retain the processes of consultation which presently exist whereby the pharmaceutical industry, the veterinary profession, and other interested parties are consulted when changes in legislation are being considered.

11.4. Under the present legislation there are no satisfactory statutory controls over an antibiotic unless it has been scheduled under the Therapeutic Substances Act. Individuals have also been able to import antibiotics for use, other than for resale, although we have not received evidence that this has happened on any significant scale. We anticipate that the Medicines Act will close such potential loopholes and we welcome this.

11.5. We gratefully acknowledge the assistance which we have received from the Association of the British Pharmaceutical Industry, its members and numerous others in providing information to aid our deliberations. For reasons of commercial confidentiality, detailed statistics are not published and the information given in Appendix A is a summation of individual confidential returns. Although we appreciate the commercial reasons why suppliers wish to keep their sales figures from competitors, we are convinced that the public interest demands that the committee to which we refer in paragraph 11.3 should be fully informed of the current usage of antibiotics

in all fields and so be able to review changes in the volume or patterns of usage of different drugs. **We therefore recommend that the committee should be empowered to demand, on a basis of confidentiality, such returns as it considers to be necessary.**

CHAPTER XII

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

12.1. From our consideration of the written and oral evidence presented to us, we have concluded that the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health. We are satisfied that these hazards can largely be avoided and should not therefore be allowed to continue.

12.2. It is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit this resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock.

12.3. There is ample and incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin. This usually occurs through consumption of food of animal origin, such as meat and meat products, but those in close contact with animals can acquire these bacteria more directly.

12.4. Some enteric organisms, particularly of the salmonella group, are able to cause disease in man and also in some species of farm livestock. A notable example is *Salmonella typhimurium*. It is disturbing to note that the tendency for this organism to give rise to generalised infection in man has increased, for such cases require antibiotic treatment. If, however, the strain of *Salmonella typhimurium* of animal origin shows multiple resistance to antibiotics, treatment by this means may not be possible and in the absence of other suitable treatment the life of the patient may be endangered.

12.5. Man is exposed to other risks through the ingestion of resistant enteric bacteria of animal origin, for although such organisms as *Escherichia coli* may be incapable of causing disease in adult humans, they may nevertheless be resistant to antibiotics. In the human intestine this resistance may be transferred to strains of bacteria which are normal inhabitants of the human bowel and could conceivably be transferred either directly or indirectly to such highly dangerous organisms as the typhoid bacillus (*Salmonella typhi*). Such a chance meeting between resistant organisms and highly dangerous (pathogenic) ones could give rise to a potentially explosive situation. We recognise that the chances described are theoretical possibilities and that there is little recorded evidence of such situations having arisen.

12.6. It is clearly undesirable that situations should be allowed to arise in which the treatment of human illness would be limited because of antibiotic resistance in the causal organism or that highly pathogenic organisms, such as *Salmonella typhi*, should acquire resistance to antibiotics.

12.7. The limited evidence available to us does not suggest that antibiotic residues in food of animal origin pose any significant hazards to the consumer, either from direct toxicity or by inducing a state of allergy, but we are satisfied that a survey of animal products is desirable in the public interest.

12.8. Under the relaxing regulations three antibiotics are at present permitted for use to promote growth in pigs and poultry, *i.e.* penicillin and two tetracyclines. All three are extensively used for the treatment of human and animal infections. The use of these antibiotics, in particular the tetracyclines, for growth promotion has been of major importance in the development of antibiotic resistance in the enteric bacteria of the animals in which they have been used for this purpose and for the resulting hazards to the human population.

12.9. We are conscious of the economic benefits which have accrued to the livestock industry from the use of antibiotics for growth promotion, but it is now evident that similar effects may be secured with antibiotics which have little or no therapeutic application in man and animals and which are unrelated to antibiotics used for this purpose. Clearly, the development of resistance by bacteria to such antibiotics is of no public or animal health consequence. Given that the same economic advantage follows their use for growth promotion, the use of antibiotics that have therapeutic uses is no longer necessary and, because of the problems that have arisen from their use, is clearly undesirable.

12.10. It is on the basis of these considerations and conclusions that we have put forward in the text of our report the following recommendations and proposals. The term "antibiotic" when used in these recommendations and proposals includes both the true antibiotics and the synthetic sulphonamides and nitrofurans. (2.2)

(a) General Aspects of Control

12.11. The principles set out by the Scientific Sub-Committee for the Netherthorpe Committee for the selection of additional "feed" antibiotics can now be extended to all "feed" antibiotics. (9.10)

12.12. We **recommend** that permission to supply and use drugs without prescription in animal feed should be restricted to antibiotics which (a) are of economic value in livestock production under UK farming conditions, (b) have little or no application as therapeutic agents in man or animals and (c) will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms. (9.11)

12.13. We **recommend** that when a particular antibiotic is under consideration as a "feed" antibiotic, account should continue to be taken of the possible dangers to human health which might result from consumption of the residues of the antibiotic in the tissues of the animals fed. (9.20)

12.14. Allocation of a particular antibiotic to the classes of "feed" antibiotic and "therapeutic" antibiotic should not be regarded as permanent. (9.26)

12.15. We **recommend** that a "therapeutic" antibiotic, *i.e.* an antibiotic which is not a "feed" antibiotic within the criteria set out in paragraph 9.11, should be available for use in animals only if prescribed by a member of the veterinary profession who has the animals under his care. (10.1)

12.16. We **recommend** that one committee should have overall responsibility for the whole field of use of antibiotics and related substances whether in man, animals, food preservation or for other purposes. (11.3)

12.17. We **recommend** that this committee should be empowered to demand, on a basis of confidentiality, such returns as it considers to be necessary. (11.5)

(*b*) *Details of Control of "Feed" Antibiotics*

12.18. We **recommend** that the maximum permitted level of a "feed" antibiotic in animal feed should continue to be 100 ppm although in most cases lower levels will be more economically beneficial. (9.19)

12.19. We **recommend** that "feed" antibiotics which meet the criteria established in paragraph 9.11 should be available for use in calves up to 3 months of age as well as in growing pigs and poultry. (9.21)

12.20. We **recommend** that "feed" antibiotics conforming to paragraph 9.11 should be withheld from laying poultry and from adult breeding stock of all species. (9.22)

12.21. We **recommend** that concentrates of "feed" antibiotics (paragraph 9.11) should continue to be permitted for use by farmers who prefer to mix their own feeds rather than to buy ready-compounded feeds. (9.23)

12.22. We **recommend** that any advertisement, order form and label for feed containing antibiotic should be required to display clearly the amount and official name of the constituent "feed" antibiotics. With this proviso we see no reason why a "feed" antibiotic, or ready-compounded feed containing a "feed" antibiotic, should not be advertised and promoted without restriction. (9.24)

(*c*) *Control of Specific Antibiotics*

12.23. Chlortetracycline and oxytetracycline do not satisfy the criteria established in paragraph 9.11 and we **recommend** that the legislation permitting their supply and use without prescription should be revoked. (9.14)

12.24. Penicillin does not satisfy the criteria and we **recommend** that the legislation permitting its supply and use without prescription should be revoked. (9.15)

12.25. We **recommend** that tylosin should not be available without prescription for use as a "feed" antibiotic and should be available only on the same terms as a scheduled antibiotic, *i.e.* only on prescription. (9.16)

12.26. We **recommend** that sulphonamides should be available only on the same terms as a scheduled antibiotic, *i.e.* only on prescription. (9.17)

12.27. We **recommend** that the nitrofuran drugs should be available only on prescription. This restriction need not, in our view, apply to any nitrofuran derivative which is shown to be devoid of antimicrobial activity and shown not to cause drug resistance to its own action nor to cause cross-resistance to any therapeutically useful antibiotic (including, of course, the other nitrofurans). (9.18)

12.28. We **recommend** that the veterinary profession should retain the use of chloramphenicol for special situations but distinctive labelling should be considered. The use of this drug and the prevalence of resistance to it should be monitored in human and veterinary medicine and prompt action taken if either increases significantly. (10.23)

(d) Control of Veterinary Therapeutic Use

12.29. We see no purpose in seeking to limit the number or type of antibiotics which the veterinary profession may prescribe. (10.5)

12.30. We **recommend** that no changes should be made in the law which allows the supply of antibiotics on veterinary prescription. (10.24)

12.31. We **recommend** that the advertisement and promotion of "therapeutic" antibiotics to laymen should be forbidden. (10.19)

(e) Research and Investigation on Antibiotics and Allied Problems

12.32. It is undesirable to use antibiotics for the treatment of "stress" unless the basis for their administration can be established. (2.33)

12.33. We **recommend** that the search should be continued for a marker which could be added to antibiotic preparations for intramammary use and which could be detected quickly and easily in milk. (8.4)

12.34. Consideration should be given to the need for a survey to determine the presence or absence of antibiotic residues, including degradation products in animal products other than milk. (8.8)

12.35. We consider that more attention should be paid to other possible ways of modifying the environmental microflora of animals and we suggest that there is a need for research into the consequences (including the economic consequences) of influencing the bacterial environment by higher standards of hygiene and other means. (9.6)

(f) Veterinary Epidemiology

12.36. We **recommend** that Ministers should provide adequate facilities to establish the regular and much wider surveillance of the bacteria of animals, animal products, and man, including their antibiotic resistance. (5.17)

12.37. We **recommend** that further studies be set up of the economically important infectious diseases of animals to determine how the disease is introduced into herds or flocks and how it is maintained there once established, what the reservoirs are, by what routes the disease is transmitted, and what factors favour its spread. Concurrent with this, we **recommend** that experimental research be initiated into the effectiveness, feasibility, and economic consequences of deliberate changes in animal husbandry introduced in the light of epidemiological knowledge. It is clear that the organisational and academic framework in which such studies are carried out will need strengthening if research effort is to be expanded in the directions we have suggested. (10.15)

12.38. We **recommend** that the Agriculture Ministers should take steps to increase the resources devoted to epidemiology by their departments. We **recommend** too that the Agricultural Research Council should be asked to consider how best it could promote epidemiological studies of infectious disease and of the prevalence of antibiotic resistance. We further **recommend** that the Agricultural Research Council and the Medical Research Council should be asked to consider jointly how best they may promote epidemiological studies of the infectious diseases which are common to farm animals and to man, particularly salmonellosis, and of antibiotic resistance in these diseases. (10.16)

12.39. Veterinary epidemiology has the status of a distinct discipline and we **recommend** that departments should be established in Universities. (10.17)

12.40. We believe that greater attention to epidemiology should result in an increase in the amount of independent information available to the veterinary profession. (10.18)

12.41. We should like to see more use made of the veterinary surgeon as adviser when the introduction of an intensive enterprise is contemplated by a farmer so that disease may in some measure be prevented. (10.14)

12.42. We **recommend** that the Agriculture Ministers should give an appropriate veterinary officer responsibility for all infectious disease of animals in the area, or at least of all such disease as appears to threaten the public health, and should grant him adequate powers to minimise the spread of disease; rights of entry and investigation would be needed. (10.13).

MICHAEL SWANN	E. L. M. MILLAR
K. L. BLAXTER	J. C. MURDOCH
H. I. FIELD	J. H. PARSONS
J. W. HOWIE	E. G. WHITE
I. A. M. LUCAS	

September 1969

APPENDIX A
(See Paragraph 2.8)

USAGE OF ANTIBIOTICS (AS DEFINED IN PARAGRAPH 2.2) IN THE UNITED KINGDOM

The figures given below are compiled from returns of sales from members of the Association of the British Pharmaceutical Industry and other firms. They are thought to represent 90–95 per cent of the trade. In each case the figures are in kilograms of active ingredient.

The antibiotics are shown in six groups which are:—

Group I Penicillins and penicillin-like antibiotics
Group II Polysaccharide-type antibiotics
Group III Polypeptide-type antibiotics
Group IV Tetracyclines
Group V Sulphonamides
Group VI Antibiotics of miscellaneous structure (including the nitrofurans and chloramphenicol)

For use in human medicine	*1963*	*1964*	*1965*	*1966*	*1967*
Group I (Penicillins)	50,953	56,502	69,618	76,409	91,186
Group II (Polysaccharides)	13,413	15,462	18,443	18,199	18,291
Group III (Polypeptides)	124	121	109	165	207
Group IV (Tetracyclines)	36,522	44,350	52,277	73,037	70,197
Group V (Sulphonamides)	66,544	60,797	62,509	59,072	53,416
Group VI (Miscellaneous)	7,470	7,027	6,933	7,526	6,585
TOTALS	175,026	184,259	209,889	234,408	239,882

For use in animals (whether on prescription or not)

	1963	*1964*	*1965*	*1966*	*1967*
Group I	15,078	13,098	13,386	16,825	19,711
Group II	6,337	10,738	16,362	20,421	24,849
Group III	—	—	—	—	316
Group IV	25,905	24,090	21,819	19,635	21,969
Group V	54,502	53,169	64,872	59,422	57,791
Group VI	33,235	31,228	34,648	35,051	43,375
TOTALS	135,057	132,323	151,087	151,354	168,011

These figures indicate that the percentages of the total trade in antibiotics used in human medicine were:—

1963	*1964*	*1965*	*1966*	*1967*
56%	58%	58%	61%	59%

If only the groups including those antibiotics which are the subject of relaxing regulations under the Therapeutic Substances Act, 1956, (*i.e.* Groups I and IV) are considered, medical usage represents a considerably higher percentage:—

1963	*1964*	*1965*	*1966*	*1967*
68%	73%	78%	81%	79%

Only for 1967 are detailed figures available to us to divide the quantities of antibiotics used in animals between different types of preparation. The separation can be made into two groups, (*a*) feed additives and (*b*) other preparations for injection, intramammary use and oral dosage, which may or may not require veterinary prescription. The breakdown yields the following table:—

	(*a*) *Feed additives*	(*b*) *Other products*
Group I	12,591	7,120
Group II	7,792	17,057
Group III	316	—
Group IV	19,483	2,486
Group V	2,140	55,651
Group VI	41,691	1,684
TOTALS	84,013	83,998

From this it would appear that in 1967 approximately half the amount of antibiotics used in animals was in the form of feed additives.

APPENDIX B
(See Paragraph 5.8)

MEMORANDUM ON SOME BACTERIOLOGICAL AND GENETIC ASPECTS OF TRANSMISSIBLE DRUG RESISTANCE

Note by Professor M. R. Pollock and
Professor W. Hayes, University of Edinburgh

1. Transmissible drug resistance is mediated by small genetic (DNA) structures called sex (or transfer) factors which are cytoplasmic, replicate independently of the bacterial chromosome, and enable the bacteria which carry them (termed "males") to conjugate with other bacteria which lack them ("females"). Following conjugation, the sex factor (or a replica of it) is transferred to the female, in whose cytoplasm it multiplies rapidly and, in turn, determines the male state. Thus a conjugation event initiates a chain reaction which results in the rapid and efficient infective spread of the sex factor throughout the bacterial population.

2. There are several simple ways in which the presence of sex factors can be looked for in strains of bacteria which are not drug-resistant, *i.e.* under conditions where there are no obvious environmental factors leading to their selection. The incidence of strains of Gram-negative intestinal bacteria carrying sex factors, unassociated with drug-resistance, turns out to be unexpectedly high so that they may be assumed to be ubiquitous in the intestines of animals and man. Thus in recent surveys, 63 per cent of 90 sensitive *Salmonella typhimurium* strains, and about 25 per cent of 26 independently isolated sensitive *Escherichia coli* strains, were found to carry sex factors.

3. The vast majority of strains of sex factor are naturally "repressed", *i.e.* a sex factor gene determines synthesis of a cytoplasmic repressor which switches off its conjugal functions. However, this repression occasionally suffers physiological breakdown in individual cells, so that there is always a small proportion of the male population which can conjugate and transfer the sex factor. Since the cytoplasm of female cells contains no repressor, the transferred sex factors are initially fully active, so that their infective spread is very efficiently promoted by newly-infected bacteria. Later, the transferred sex factors begin to produce repressor again, so that the potentiality of the infected population to transfer the sex factor drops again to a low level. Thus the fact that transfer factors are usually repressed should not be construed to imply that they are inefficiently transmissible.

4. Although it is not known for certain how sex factors incorporate into their structure, or otherwise mobilise, resistance determinants, three methods whereby they mediate the infective transfer of other bacterial genes are now clearly understood. It is very likely that resistance transfer occurs in one or another or, more probably, in all of these ways. There is now considerable direct evidence to support this view.

(*a*) The sex factor undergoes genetic interactions (recombination) with the bacterial chromosome, with the result that a region of the chromosome, which may be quite long, is incorporated into the sex factor. Thereafter, the incorporated piece of chromosome is replicated and transferred as part of the sex factor. These events are very rare by normal standards; however, the large size of bacterial populations, and the fact that the hybrid factors spread infectively if female bacteria are present, ensures that they can readily be isolated from small volumes of broth culture, provided selective methods are available. Thus in the animal body, and in the presence of an antibiotic to which mutational resistance can develop, the frequent emergence of resistance transfer factors (by the kind of mechanism described in paragraph 6) would be expected.

(*b*) Certain bacterial characters, such as production of some colicins in coliform bacteria, and resistance to penicillin and erythromycin in *Staphylococcus pyogenes*, are determined by genes located not on the chromosome, but on small, self-reproducing, cytoplasmic genetic elements called plasmids. In the case of coliform bacilli, if bacteria carrying such plasmids are infected with a sex factor, the plasmids become highly transmissible, independently of the sex factor—*i.e.* transfer is not due to physical association between plasmid and sex factor.

(*c*) When a plasmid and a sex factor, or two sex factors inhabit the same cell, recombination can occur between them, welding them into a single transferrable structure which is usually unstable and may dissociate again following transfer.

5. The infectivity of sex factors is not restricted to *Escherichia coli*, *Shigella* and *Salmonella*, but extends to a wide range of different genera, and even orders, of bacteria such as *Pasteurella*, *Proteus*, *Pseudomonas*, *Vibrio* et cet., to which the factors can be transferred by conjugation. Although initial inter-species transfer is usually a rare event, the sex factors, once transferred, may be propagated by these other species and determine conjugation and their own transfer among them at the frequency characteristic of intra-species transmission. It is known that resistance transfer factors, introduced into the human or animal intestine by infection with pathogenic bacteria, can spread in this way and become established in the normal intestinal flora. However, sex factors may show variable degrees of instability in their hosts, so that it is only in an environment favouring their selection that they come to dominate the intestinal flora. In addition, other circumstances exist, such as host restriction, which tend to limit their normal spread.

6. There is no doubt that the first step in the evolution of transferable resistance is the use of antibiotics, which select resistant bacterial mutants among the intestinal flora. The determinants of resistance may be located on the bacterial chromosome or on a plasmid. Subsequent association of the resistance determinant with a sex factor (paragraph 4), which is a likely event (paragraph 2), will lead to spread of the determinant and the sex factor through the bacterial flora. Thus, use of the antibiotic ensures that the bacterial populations carrying the sex factor will tend to dominate the intestinal flora. The factor is now well placed to incorporate or mobilise the determinants of resistance to other antibiotics as these in turn are selected by mutation, in response to the subsequent employment of these drugs in the environment, so that factors associated with multiple-resistance arise. Alternatively, some factors carrying multiple-drug resistance may arise by recombination between independent factors, carrying different resistance patterns, which infect the same cell (paragraph 4(c)). This has been demonstrated experimentally.

7. The efficiency of the development and spread of resistance transfer factors, predictable from experimental studies of sex factors and plasmids (paragraph 4(*a*)), is more than borne out by epidemiological and ecological studies of transmissible drug resistance. For example, in Japan, the first multiple-resistant *Shigella* strain was isolated in 1955. In 1956 the number of resistant isolates was negligible. By 1959, 10 per cent of all strains of *Shigella* isolated were resistant to four drugs; by 1964 this figure had risen to 50 per cent. Similarly, in Britain, between 1962, when the first resistance transfer factor was identified here, and 1964–65, the incidence of resistant strains of *Salmonella typhimurium* rose from about 3 to 61 per cent. Resistance transfer factors are now widespread throughout the world. Again, as new antibiotics come into use, the appearance of bacterial strains resistant to them, and of sex factors which carry the determinants of resistance, follows quickly.

CONTROL OF ANTIBIOTICS

Note by Department of Health and Social Security

1. Introduction

1.1. Statutory control of antibiotics is effected by the Therapeutic Substances Act, 1956, which applies to the United Kingdom, and is described in detail in paragraph 2 below.

1.2. New preparations of antibiotics or of medicines containing antibiotics and intended for use in human medicine, like all other drugs for this purpose, are subject to consideration by the Committee on Safety of Drugs, which may give or withhold clearance for use in clinical trials or for marketing. The Committee has no statutory powers and submissions to it are made on a voluntary basis, but since its appointment in 1964 it has enjoyed the confidence of the pharmaceutical industry and the closest co-operation has existed between the Committee and the industry. Only very rarely have preparations been marketed without clearance by the Committee and on these occasions the facts have been reported to the Health Ministers who are able to inform the profession of the facts. Clearance by the Committee does not, of course, absolve manufacturers or distributors from the licensing obligations imposed by the Therapeutic Substances Act.

1.3. The use of new antibiotics or new uses of existing antibiotics in veterinary products on direct sale to farmers or for use in trials are considered under the voluntary Veterinary Products Safety Precautions Scheme which applies to Great Britain. The aim of the Scheme is to ensure that potential dangers to users, to livestock, to wildlife and to consumers of animal products arising from the use of such veterinary products are scientifically considered. Clearance may be given or withheld and recommendations for safe use may be made. No statutory sanctions are available but if a product were made available without having been submitted for consideration or without observing any safeguards recommended following submission, the matter would normally be brought to the attention of the offending company and potential users. Clearance under the Scheme does not necessarily mean that the requirements of the Therapeutic Substances Act have been, or need not be, complied with but notifying firms are advised to contact the Department of Health and Social Security to ascertain the position under the Therapeutic Substances Act, 1956. The way in which the scheme operates is considered in more detail in paragraph 3 below.

1.4. The Medicines Act, 1968, makes new and more detailed provision for the control of manufacture, importation and marketing of medicinal products, including antibiotics, primarily by means of a licensing system. It will replace the Therapeutic Substances Act and Regulations. The existing systems of voluntary submission of drugs for consideration by the Committee on Safety of Drugs and under the Veterinary Products Safety Precautions Scheme will in due course be replaced by a statutory obligation to hold manufacturing or product licences. The Act is considered in greater detail in paragraph 5 below.

2. The Therapeutic Substances Act, 1956

2.1. "Therapeutic Substance" is not defined in the Act but is generally interpreted to mean a substance which has an ascertained therapeutic use in human or veterinary medicine. The Act consists of two quite distinct parts which are dealt with separately below.

2.2. **Part I of the Act** deals with **substances, the purity or potency of which cannot be adequately tested by chemical means,** and provides for quality control and safety by licensing and inspection of manufacture for sale or importation of substances specified in the First Schedule to the Act, or added to it by regulation from time to time. Vaccines, sera and human blood products are controlled under this Part as are most antibiotics in current use, together with their derivatives and preparations, when intended for parenteral injection. (A detailed list of antibiotics controlled under Part I is at Annexe 1).

2.3. Part I of the Act does not apply to therapeutic substances intended solely for veterinary purposes provided they are labelled "to be used for animal treatment only". The corresponding control of veterinary therapeutic substances is under Part II and Schedule 3 of the Diseases of Animals Act 1950.

2.4. The licensing authorities for the purposes of Part I of the Act are, for England, the Secretary of State for Social Services; for Wales, the Secretary of State for Wales; for Scotland, the Secretary of State for Scotland; and for Northern Ireland, the Minister of Health and Social Services. The four Ministers form a Joint Committee for the purpose of making regulations under Part I of the Act and for securing uniformity of standards, and are assisted in the framing of regulations by an Advisory Committee (see paragraph 4.1 below).

2.5. **Part II of the Act** is concerned with the control of sale, supply, dispensing and administration of penicillin and such other therapeutic substances as are prescribed by regulations, being substances which appear to be **capable of causing danger to the health of the community if used without proper safeguards.** (A list of the substances subject to control is at Annexe 2).

2.6. Broadly, the sale, supply, dispensing and administration of these substances are permissible only under the direction or by prescription of duly qualified medical, dental or veterinary surgeons or practitioners. Provision is made in Section 9(3), however, for regulations to relax the restrictions on sale or supply in prescribed circumstances and subject to such conditions as may be specified.

2.7. Regulations to specify substances to be subjected to control (or to relax control in the case of a specified substance) under Part II of the Act are made jointly by the Secretary of State for Social Services, the Secretary of State for Wales, the Secretary of State for Scotland and the Minister of Health and Social Services for Northern Ireland. Before making control regulations the Ministers are required to consult the Medical Research Council; before making regulations relaxing control they must consult the Medical Research Council and, if the regulations concern agricultural matters, the Agricultural Research Council.

2.8. *Control Regulations.* The process of making control regulations is normally initiated by advice, usually from the Antibiotics Panel (see paragraph 4.2) or the Department's Pharmaceutical Section, to the Department of Health and Social Security that it would be appropriate to subject the particular substance to control under Part II of the Act. The Medical Research Council is consulted as in 2.7 above. Draft regulations are prepared and circulated to interested Government Departments and other organisations for comment. The draft is revised as necessary in the light of comments received, and after approval by the Ministers, the regulations are made.

2.9. *Relaxing Regulations.* Control of antibiotics scheduled under Part II of the Act has so far been relaxed only for preparations for uses other than in human medicines. (A list of relaxing regulations is at Annexe 3). Consideration of the possibility of relaxation is initiated by applications to the Veterinary or Scientific Sub-Committee of the Advisory Committee on Pesticides and Other Toxic Chemicals by manufacturers for clearance to market particular substances for purposes other than use in human medicines. If the application relates to a substance already controlled under Part II of the Act, consideration is given to the question whether

the restrictions imposed thereby should be relaxed for the particular use to which the application refers; if the application relates to an antibiotic which has not been scheduled under Part II of the Act, consideration will be given to the questions of whether it should be so scheduled and whether or how far the controls should be relaxed in the case of the specific proposed usage.

2.10. Manufacturers wishing to market antibiotic preparations for use as a veterinary product or in agriculture (including home gardening) or food storage notify their products under the Veterinary Products or Pesticides Safety Precautions Schemes. These are considered respectively by the Veterinary Sub-Committee and as appropriate by the Scientific Sub-Committee of the Advisory Committee on Pesticides and Other Toxic Chemicals. The relevant data is forwarded by the Sub-Committee to the Antibiotics Panel which considers public health aspects of the application.

2.11. The recommendation of the Sub-Committee and the observations of the Antibiotics Panel are considered by the Advisory Committee on Pesticides and Other Toxic Chemicals which then tenders advice to the Ministry of Agriculture, Fisheries and Food, which in turn informs the Department of Health and Social Security. If control is advised, the procedure outlined in paragraph 2.8 is followed, and if relaxation is also recommended, the Department consults the Medical Research Council and, when appropriate, the Agricultural Research Council.

2.12. Draft relaxing regulations are prepared and circulated to interested Government Departments and other organisations for comment. A revised draft is prepared in the light of comments received, submitted for Ministerial approval, and, if approved, the regulations are made.

3. Veterinary Products Safety Precautions Scheme

3.1. The Ministry of Agriculture, Fisheries and Food operates this scheme as the co-ordinating department on behalf of the Department of Health and Social Security, the Department of Agriculture and Fisheries for Scotland and the Scottish Home and Health Department, as advised by the Advisory Committee on Pesticides and Other Toxic Chemicals and its Veterinary Sub-Committee. Applications for clearance under the Scheme are required to be accompanied by data sheets and by such information as may reasonably be required to enable departments to advise on any precautionary measure which should be employed when these products are used. The applicant is advised to consult the Department of Health and Social Security about the position under Part II of the Therapeutic Substances Act, 1956, and the Sub-Committee considers the data on specification, toxicity and residues. The views of the Antibiotics Panel are also sought, particularly on:—

(*i*) the chemical structure of the antibiotic and its relationships with other antibiotics,

(*ii*) cross-resistance in organisms pathogenic in man or animals,

(*iii*) cross-sensitization reactions in man.

In addition, the Panel considers whether exemption from control under the Therapeutic Substances Act should be recommended.

3.2. If the Panel's views and the Sub-Committee's recommendations are accepted the applicant is asked to accept conditions (*e.g.* recommendations for safe use) under which clearance for marketing will be given. It is also made clear that clearance should not take effect, and supply to farmers should not begin, until the antibiotic has been scheduled under the Therapeutic Substances Act (if it is not already so scheduled) and until relaxation of control has been provided for. The responsibility for relaxation of control rests with the Health Ministers but they have a statutory obligation to consult the Medical Research Council and if appropriate the Agricultural Research Council.

4. Advisory Bodies

4.1. *Therapeutic Substances Advisory Committee.* This Committee is established by Section 4(2) of the Therapeutic Substances Act, 1956. Its function is to assist the Joint Committee of Ministers in framing regulations under Part I of the Act and it has no function in relation to Part II. It consists of a Chairman appointed by the Secretary of State for Social Services—usually a Deputy Chief Medical Officer of the Department of Health and Social Security—and members appointed by the Secretary of State for Scotland, the Secretary of State for Wales, the Minister of Health and Social Services for Northern Ireland, the Medical Research Council, the General Medical Council, the British Medical Association, the Pharmaceutical Society and the Council of the Royal Institute of Chemistry.

4.2. *The Antibiotics Panel.* The Panel was established in 1956 by the Ministry of Health and was reconstituted in 1966 as an advisory panel of the Committee on Medical Aspects of Food Policy. It advises on the extent of hazards to human health involved in proposals to use antibiotics for the preservation of food, in agriculture, horticulture (including home garden use), food storage practice and animal husbandry which are referred to it by various committees or by Departments. Its terms of reference are set out in Annexe 5.

4.3. *The Advisory Committee on Pesticides and Other Toxic Chemicals* is primarily responsible to the Department of Education and Science although it is serviced by a Ministry of Agriculture, Fisheries and Food secretariat. Its terms of reference are:—

"To keep under review all risks that may arise from the use of:—

(*i*) pesticides:

(*ii*) potentially toxic chemicals on sale to farmers for veterinary use and veterinary medicines prescribed for use by veterinary surgeons: and

(*iii*) any other potentially toxic chemical specifically referred to the Committee by Ministers;

and to make recommendations to the Ministers concerned".

4.4. *Veterinary Sub-Committee.* This is a sub-committee of the Advisory Committee on Pesticides and Other Toxic Chemicals and was established following the recommendations of a Working Group appointed in 1962. Its terms of reference are set out in Annexe 4.

4.5. *Scientific Sub-Committee.* This is also a sub-committee of the Advisory Committee on Pesticides and Other Toxic Chemicals. It advises, if necessary, on notifications submitted to it under the Pesticides Safety Precautions Scheme. The Scientific Sub-Committee's terms of reference are not specific, but the parent committee, *i.e.* Advisory Committee, looks to it for scientific assessment of matters it is considering under its own terms of reference.

4.6. *The Medical Research Council* must be consulted by the Ministers before prescribing substances which are to be controlled under Part II of the Therapeutic Substances Act, and also before making regulations to relax control. So far as Part I of the Act is concerned, the Council nominates one member of the Advisory Committee established under Section 4(2) and, in addition, provides certain services to the Department in connection with the testing and comparison of therapeutic substances and advising on requirements to be included in regulations.

4.7. *The Agricultural Research Council* must be consulted by the Ministers before making relaxing regulations which concern agricultural matters.

5. The Medicines Act, 1968

5.1. The Medicines Act, 1968, applies to the United Kingdom and provides for a comprehensive system of control of the manufacture, importation, distribution,

sale, supply and description of medicinal products for human or veterinary use. Most of its provisions will become effective only on "appointed days" to be specified in regulations or orders made by the appropriate Ministers. Thus the Therapeutic Substances Act, 1956, and Part II and Schedule 3 of the Diseases of Animals Act, 1950, will not be repealed until some future date to be specified by those Ministers and following the introduction of new controls under the Medicines Act superseding the present controls.

5.2. The limited licensing arrangements under Part I of the Therapeutic Substances Act and Part II of the Diseases of Animals Act will be replaced under Part II of the Medicines Act by a comprehensive but flexible licensing system under which the Health and Agriculture Ministers will have powers designed to ensure eventually that all medicinal products offered for sale or supply in the United Kingdom are adequately tested for safety, quality and efficacy in the light of current medical and scientific knowledge and that any safeguards that need to be observed by the licence holders are made conditions of the licence.

5.3. The restrictions on the sale of proprietary medicines in the Pharmacy and Medicines Act, 1941, the provisions of current Poisons legislation relating to the sale and supply of medicines and the restrictions imposed by Part II of the Therapeutic Substances Act, in so far as they relate to products which fall within the definition of "medicinal products" under the Medicines Act, will all be replaced by the provisions of Part III of the latter Act. This Part deals with the sale and supply of medicinal products mainly at the retail stage. Its basic provision restricts to registered pharmacies the retail sale or supply of medicinal products which are not on a general sales list specified in a statutory order. Other provisions enable the appropriate Ministers by statutory order or regulations to prohibit the retail sale or supply of medicinal products except on the prescription of a doctor, dentist or veterinarian; also in exceptional circumstances to restrict sale and supply to sale and supply by, or on the prescription of, practitioners authorised by virtue of special knowledge; also to prohibit altogether the sale, supply or importation of specified medicinal products or medicated animal feeding stuffs. Exceptions and exemptions can be provided for in such statutory instruments, either absolute or subject to specified conditions and limitations.

5.4. "Medicinal product" is defined in Section 130 of the Act; other relevant definitions appear there and in Section 132, *e.g.* "administration", "composition", "disease", "treatment". The characteristics of a "medicinal product" are that it is:—

(*i*) a substance (defined generally in Section 132(1) as any natural or artificial substance, whether solid, liquid, gas or vapour) or article (*e.g.* a capsule, tablet etc.);

(*ii*) but not an instrument, apparatus or appliance (which would otherwise be included in the term "article");

(*iii*) manufactured, sold, supplied or imported;

(*iv*) for use **wholly or mainly** in either or both of the following ways:—

(*a*) by administration to a human or an animal for one of the medicinal purposes set out in Section 130(2)

or

(*b*) as an ingredient to be used in a pharmacy or hospital or by a doctor, dentist or veterinarian in making up medicine.

The definition thus includes antibiotics prepared for administration in human or veterinary medicine whether by incorporation in feeding stuffs or not. Although medicated feeding stuffs themselves are not "medicinal products" they are subject to control under the Act. Antibiotic preparations for non-medicinal uses, *e.g.* in food preserving or horticulture, are not "medicinal products" either but the Act contains provision whereby in certain circumstances they could be controlled.

5.5. *Animal Feeding Stuffs.* Section 130(7) makes it clear that the incorporation of a medicinal product in animal feeding stuffs does not make the latter medicinal products, but special provisions are made in the Act relating to animal feeding stuffs which incorporate a medicinal product or *any* substance incorporated for a medicinal purpose. Broadly, Section 40 prohibits (a) the sale or supply, or (b) the procurement of either of these things or the manufacture for sale or (c) the importation, in the course of business of any animal feeding stuff which includes a medicinal product unless (i) some person holds a valid product licence or animal test certificate for the medicinal product concerned which contains provisions governing the incorporation of the product into feeding stuffs—and these provisions have been observed, or (ii) it is incorporated in accordance with a prescription by a veterinary surgeon or practitioner. Section 42 provides that, for the purpose of Section 40(3) (which prohibits the making up of medicated animal feeding stuffs unless one of the alternative conditions noted above is satisfied), *any* substance is to be treated as a medicinal product if it is incorporated in the feeding stuff for a medicinal purpose.

5.6. *Prohibition Orders.* In addition, "in the interests of safety" the Health and Agriculture Ministers can make orders under Section 62 prohibiting the sale or supply or importation of specified medicinal products, of classes of products or of animal feeding stuffs in which specified medicinal products or classes of products have been incorporated. Prohibition may be subject to exceptions, either absolute or subject to conditions or limitations. Except for temporary prohibitions in cases of urgency orders can only be made after consultation with the appropriate Section 4 advisory committee, or in the absence of such a committee, the Medicines Commission (see paragraph 5.9), and with organisations representative of interests likely to be affected by the order. There is provision for representations from such organisations to be referred to the Medicines Commission.

5.7. *Antibiotics which are not medicinal products* can be controlled by the use of powers contained in Section 105 of the Act which provides for the application of appropriate provisions of the Act to substances which are not themselves medicinal products but which (a) are used as ingredients in the manufacture of medicinal products or (b) are substances which are capable of causing danger, if used without proper safeguards, to the health of the community or of animals or species of animals in general, *i.e.* not individual persons or animals to which they were administered. These powers at (a) are likely to be used to secure adequate control of certain products currently controlled under Part I of the Therapeutic Substances Act, (*i.e.* substances whose purity and potency cannot be adequately tested by chemical means); those at (b) could be used in relation to some non-medicinal use of antibiotics, for example in food preservation or for horticultural purposes. One way of exercising control under (b) would be by specifying that Section 58 (sale or supply on prescription only) should apply to specified substances or classes of substances; this control could be relaxed under Section 58(4) to allow sales other than on prescription, subject to conditions and limitations which are provided for in Section 58(5), thus achieving the result now obtained by the making of control and relaxation regulations under Part II of the Therapeutic Substances Act. A more direct method would be to apply Section 62 and then make orders to prohibit sale or supply except in accordance with specified conditions and limitations.

5.8. *Labelling.* Part V of the Act provides powers to regulate labelling, leaflets and containers and the identification of products; Part VI provides powers to regulate advertising and the promotion of products, whether to the public or to practitioners; and Part VIII contains miscellaneous and supplementary provisions, of which Section 104 and Section 105 (referred to in 5.7 above) are of most interest to the Committee. Section 104 enables appropriate provisions of the Act to be applied by order to medical and veterinary devices, or to products which are either not administered to the patient or animal (*e.g.* antiseptic and sterilising agents) or not marketed primarily as medicinal products.

5.9. *The Medicines Commission and expert advisory committee.* The Act provides for the appointment of a Medicines Commission with wide advisory functions and some appellate functions where representations are made against adverse decisions by an expert committee under the licensing scheme and in certain other instances. The Commission will consist of persons of eminence in their respective spheres of activity, medicine, pharmacy, veterinary medicine, chemistry and the pharmaceutical industry. One of its most important immediate tasks will be to advise on the pattern of and suitable membership for the expert committees referred to in Section 4 needed to advise the licensing authorities and the Ministers on various matters connected with the Act. These committees will be appointed by the Ministers, after considering recommendations from the Medicines Commission and after consultations with approved organisations. Committees may be established for any purpose connected with the execution of the Act; the pattern adopted will depend largely on the recommendations of the Medicines Commission but it seems probable that there will be at least six and perhaps more.

5.10. The first step in implementing the Act is to set up the Medicines Commission. Establishment of expert committees will follow; and most of the remaining provisions will become effective in stages on a series of "appointed days" specified by orders or regulations. Section 129(6), however, requires consultation with organisations representing the interests likely to be substantially affected by any proposed regulations or orders before they are made, and it will therefore be some time before the provisions superseding the existing legislation governing antibiotics becomes effective.

INJECTABLE ANTIBIOTICS CONTROLLED UNDER PART I OF THERAPEUTIC SUBSTANCES ACT, 1956

(*i.e.* quality control of substances whose purity and potency cannot be adequately tested by chemical means)

Amphotericin B.	
Bacitracin	
Capreomycin	
Chlortetracycline	
Colistin	
Erythromycin	
Gentamycin	
Kanamycin	
Lincomycins	
Neomycin	
Oxytetracycline	
Penicillin	(includes all penicillins for injection)
Polymyxin B.	
Rifamycins	
Streptomycin	(includes Dihydrostreptomycin)
Tetracycline	
Vancomycin	
Viomycin	

Note:—
No antibiotics are controlled under the Diseases of Animals Act 1950

LIST OF SUBSTANCES WHOSE SALE AND SUPPLY IS LIMITED TO PRESCRIPTION UNDER PART II OF THE THERAPEUTIC SUBSTANCES ACT, 1956

Preparation	Year	S.I. No.	Preparation	Year	S.I. No.
Amphomycin	1967	1851	Nalidixic acid	1967	1851
Amphotericins	1961	1066	Neomycin	1954	1646
Bacitracin	1956	346	Novobiocin	1957	798
Capreomycin	1967	1851	Nystatin	1967	1851
Cephaloridine	1967	1851	Oleandomycin	1957	798
Chloramphenicol	1951	919		1959	732
Chlortetracycline, listed under			Oxytetracycline	1954	1646
			Paromomycin	1967	1851
aureomycin	1951	919	Penicillin	Act. Defined by Part I regulations in force (1966, No. 505)	
Corticotrophin	1954	1646			
Cortisone	1954	1646			
	1959	732			
Cycloserine	1959	732	*Polymyxins	1954	1646
Demethylchlortetra-			Prednisolone	1957	798
cycline	1961	1066		1959	732
Erythromycin	1954	1646	Prednisone	1957	798
	1961	1066		1959	732
Framycetin	1961	1066	Rifamycins	1967	1851
Fusidic acid	1967	1851	Ristocetins	1961	1066
Gentamycin	1967	1851	Spiramycin	1957	798
Griseofulvin	1967	1851	**Streptomycin	1948	1735
Hydrocortisone	1954	1646	Tetracycline	1956	346
	1959	732	Tetracyclines	1967	1851
Isoniazid	1953	1173	Vancomycin	1961	1066
Kanamycin	1961	1066	Viomycin	1956	346
Lincomycins	1967	1851	Virginiamycin	1967	1851

* Colistin is deemed to be covered by the Polymyxins definition.

** Includes dihydrostreptomycin.

S.I. = Statutory Instrument.

LIST OF RELAXING REGULATIONS MADE UNDER PART II OF THE THERAPEUTIC SUBSTANCES ACT, 1956

The Therapeutic Substances (*Supply of Antibiotics for Agricultural Purposes*) *Regulations, 1953* (*S.I. 1953 No. 1174*) permit the sale of chlortetracycline (under the name aureomycin) and penicillin in defined dilutions for supplementing the feed of pigs and poultry.

The Therapeutic Substances (*Supply of Oxytetracycline for Agricultural Purposes*) *Regulations, 1954* (*S.I. 1954 No. 1647*) permit the sale of oxytetracycline for the same purpose.

The Therapeutic Substances (*Supply of Streptomycin and Oxytetracycline for Horticultural Purposes*) *Regulations, 1958* (*S.I. 1958 No. 614*) permit the sale of streptomycin, and oxytetracycline, subject to defined conditions, for horticultural purposes.

The Therapeutic Substances (*Preservation of Raw Fish*) *Regulations, 1964* (*S.I. 1964 No. 883*), permit the sale of chlortetracycline and oxytetracycline in approved diluents, for adding to ice and "dipping solutions" used in the preservation of raw fish.

The Therapeutic Substances (*Supply of Substances for Analysis*) *Regulations, 1958* (*S.I. 1958 No. 214*) *and the Therapeutic Substances* (*Substances for Analysis*) *Amendment Regulations, 1965* (*S.I. 1965 No. 1673*) permit the supply for the purpose of analysis to public analysts, agricultural analysts, or their deputies, sampling officers appointed under the Food and Drugs Act, Pharmaceutical Society Inspectors, persons concerned with the testing scheme in connection with the National Health Service, and persons concerned with the testing in the course of manufacture of the controlled substances.

ADVISORY COMMITTEE ON PESTICIDES AND OTHER TOXIC CHEMICALS.

VETERINARY SUB-COMMITTEE

Terms of Reference

1. To examine evidence both written and oral relating to veterinary products which are referred to it for consideration in accordance with the terms of the Veterinary Products Safety Precautions Scheme.

2. To assess the dangers likely to arise from the use of such products:

(*a*) to persons using them;

(*b*) to consumers from residues in food from treated animals;

(*c*) to other human or animal populations and wildlife.

3. If the use of a product is agreed, other than in cases of quick clearance, to recommend to the Advisory Committee or in cases of delegated authority to departments whether and under what conditions the use of a given product is acceptable.

4. To consider any information which may be referred to the Veterinary Sub-Committee of any hazards from veterinary products whether notified or not and report accordingly.

5. To review from time to time the working of the Veterinary Products Safety Precautions Scheme and to recommend to the Advisory Committee any changes which the Sub-Committee thinks may be advisable.

COMMITTEE ON MEDICAL ASPECTS OF FOOD POLICY

The terms of reference of the Antibiotics Panel are as under:

Terms of Reference:

To advise on the extent of the hazard to human health involved in the use of such antibiotics and other antimicrobial substances with similar activity proposed for the preservation of food and other treatment and for the use in agriculture, horticulture (including home garden use), food storage practice and animal husbandry, as are referred to the Panel by—

the Advisory Committee on Pesticides and other Toxic Chemicals
the Food Additives and Contaminants Committee
the Milk and Milk Products Technical Advisory Committee
the Committee on Medical Aspects of Food Policy
or by their Sub-Committees, or by Departments.

APPENDIX D
(See Paragraph 1.10)

JOINT COMMITTEE ON THE USE OF ANTIBIOTICS IN ANIMAL HUSBANDRY AND VETERINARY MEDICINE

List of Individuals who submitted Evidence

*E. S. Anderson, Esq., M.D., F.R.S.
C. J. Baxter, Esq., M.R.C.V.S.
N. J. Berridge, Esq., Ph.D., D.Sc.
W. Bolton, Esq., D.Sc., F.R.I.C., F.R.S.E.
*R. Braude, Esq., Ph.D., D.Sc., Dip. Agr., Dip.An.Husb.
T. C. Carter, Esq., O.B.E., M.A., D.Sc., F.R.S.E.
Miss H. R. Chapman, N.D.D.
*Miss M. E. Coates, F.P.S., Ph.D.
H. A. Cole, Esq., C.M.G., D.Sc., F.I.Biol.
J. E. Cooper, Esq., B.V.Sc., M.R.C.V.S., D.T.V.M.
P. Copestake, Esq., B.V.Sc.
Mrs. N. Datta, M.D., M.B., B. S., Dip.Bact., M.C.Path.
F. H. Dodd, Esq., B.Sc., Ph.D.
G. A. Embleton, Esq., B.Vet.Med.
R. F. Gordon, Esq., D.Sc., M.R.C.V.S.
Professor W. Hayes, M.B., Sc.D., D.P.H., F.R.C.P.I., F.R.S.
Dr. W. N. Hewson
G. Hobbs, Esq.
M. Ingram, Esq., M.A., Ph.D.
E. B. Jones, Esq., B.V.Sc., M.R.C.V.S.
Dr. A. H. Linton
C. E. Lucas, Esq., C.M.G., D.Sc., F.I.Biol., F.R.S.E., F.R.S.
L. A. Mabbitt, Esq., B.Sc., Ph.D.
F. K. Neave, Esq., B.S.A.
D. J. H. Payne, Esq., M.B., B.S., F.C.Path.
Professor M. R. Pollock, M.A., M.B., B.Ch., F.R.S., F.R.S.E.
Professor J. R. Raeburn, M.S., B.Sc.(Agr.), Ph.D., M.A., F.R.S.E.
K. C. Sellers, Esq., Ph.D., B.Sc., M.R.C.V.S., D.V.S.M.
F. Seymour, Esq., M.B., Ch. B., D.P.H.
*H. Williams Smith, Esq., D.Sc., Ph.D., F.R.C.V.S., Dip.Bact., M.C.Path.
W. J. Sojka, Esq., M.R.C.V.S.
Mrs. J. Taylor, B.Sc., M.B., B.S., M.R.C.S., L.R.C.P., D.P.H., F.C.Path.
J. R. Walton, Esq., Ph.D., B.V.M.S., M.R.C.V.S., Dip.Bact.
F. White, Esq., Ph.D., B.Sc., M.R.C.V.S., B.Sc.Vet. Sc.
J. E. Wilson, Esq., D.V.M.&S., B.Sc., M.R.C.V.S., F.R.S.E.

* Also gave oral evidence.

List of Organisations which submitted Evidence

Abbott Laboratories Ltd.
Aberdeen and District Milk Marketing Board
Allied Farm Foods Ltd.
A/S Apothekernes Laboratorium
*Association of the British Pharmaceutical Industry
Association of River Authorities
Astra-Hewlett Ltd.
Babcock Farms Ltd.
Baywood Chemicals Ltd.
Beecham Pharmaceutical Division
British Medical Association
British Society of Animal Production
British Trout Farmers' Association
British United Turkeys Ltd.
British Veterinary Association
Ciba Agrochemicals Ltd.
The Compound Animal Feeding Stuffs Manufacturers National Association Ltd.
Consumer Council
Crown Chemical Company Ltd.
H. M. Customs and Excise
Cyanamid of Great Britain Ltd.
Day and Sons (Crewe) Ltd.
Elanco Products Ltd.
Farm Animals Welfare Advisory Committee
Federation of British Poultry Industries
Glaxo Laboratories Ltd.
Imperial Chemical Industries Ltd.—Pharmaceutical Division
Lennig Chemicals Ltd.
Medical Research Council
Milk Marketing Board
Milk Marketing Board for Northern Ireland
Ministry of Agriculture, Fisheries and Food
  Fisheries Division I
  Salmon and Freshwater Fisheries Laboratory
  National Agricultural Advisory Service
  Veterinary Investigation Service
National Association of Corn and Agricultural Merchants Ltd.
National Council of Concentrate Manufacturers
National Farmers' Union
North of Scotland Milk Marketing Board
Northern Ireland Veterinary Association
Osmond and Sons Ltd.
Parke, Davis and Co.
Pfizer Ltd.
The Pharmaceutical Society of Great Britain
Ross Poultry Laboratory
The Royal College of Veterinary Surgeons
Salsbury Laboratories
The Scottish Milk Marketing Board
Silcock and Lever Feeds Ltd.

Smith, Kline and French Laboratories Ltd.
The Society of Medical Officers of Health
Sphere Laboratories (London) Ltd.
E. R. Squibb and Sons Ltd.
F. & G. Sykes Ltd.
Upjohn Ltd.
Veterinarians' Union
T. Wall and Sons (Meat and Handy Foods) Ltd.
Warren-Studler Breeding Farm Ltd.

* Also gave oral evidence.

Printed in England for Her Majesty's Stationery Office
by J. W. Arrowsmith Ltd.

Dd. 148223 K 60 11/69

HER MAJESTY'S STATIONERY OFFICE

Government Bookshops
49 High Holborn, London W.C.1
13A Castle Street, Edinburgh 2
109 St. Mary Street, Cardiff CF1 1JW
Brazennose Street, Manchester M60 8AS
50 Fairfax Street, Bristol BS1 3DE
258 Broad Street, Birmingham 1
7 Linenhall Street, Belfast BT2 8AY

Government publications are also available through any bookseller

SBN 10 141900 7