Section of Epidemiology and Preventive Medicine

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SYMPOSIUM ON EPIDEMIOLOGICAL RISKS OF ANTIBIOTICS

Dr. E. J. L. Lowbury (Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital): *Hospital Infection*

The rise of antibiotic-resistant bacteria, especially in hospitals, has led to some apprehension about the future of chemotherapy. A glance at the Registrar-General's Statistical Review of England and Wales since 1925 (Fig. 1) is reassuring, for it shows that the death-rate from infective diseases—and from their chief representative, tuberculosis—has continued to fall, and with less fluctuation than before. But it is obvious that many factors have contributed to this fall, and there is nothing in the collective record which clearly indicates the contribution—or exhaustion—of the antibiotics[1]; the downward trend was, in fact, present before

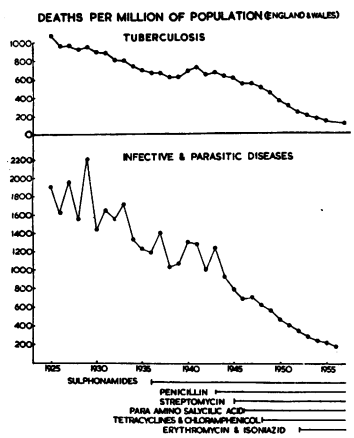

FIG. 1.

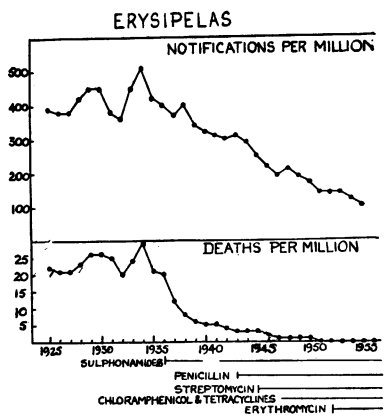

FIG. 2.

the arrival of the sulphonamides. If, however, we plot the deaths and notifications in respect of erysipelas over the same period (Fig. 2), this disease is shown to have become less lethal and also less common since the arrival of the sulphonamides. A number of other relevant diseases (e.g. puerperal pyrexia, meningococcal infection, osteomyelitis) show in the same period a striking fall in death-rate which for various reasons is not always accompanied by a fall in notifications. For some infections (e.g. the pneumonias, which are not classified with infective diseases) the death-rate has not fallen dramatically, and deaths from bronchopneumonia have, if anything, become a little more common since 1946. But the Registrar-

[1]I use the word "antibiotic" to include all antibacterial drugs which can be administered by systemic routes.

General's Review tells us little or nothing about those infections against which the antibiotics have suffered their biggest reverse; I mean hospital infections with *Staphylococcus aureus* and Gram-negative bacilli in which the emergence and spread of resistant strains have been of special importance.

Drug resistance was described as long ago as 1887, and Ehrlich recognized its dangers. Soon after the arrival of the sulphonamides, resistance became a familiar problem in the treatment of streptococcal, gonococcal and other infections; the emphasis (as later with streptomycin) was on strain variation and on the emergence of resistance under treatment. With the increasing use of penicillin a new phenomenon was revealed in the mid-1940s by North and Christie (1945) and by Mary Barber and her colleagues (1948), and amplified by many workers in the years that followed. Briefly, staphylococci carried by patients and staff in hospitals were shown to reflect the use there of antibiotics—of penicillin, streptomycin, tetracycline and, more recently, erythromycin; the hospital flora differed from the nasal staphylococci of the general population also in showing a preponderance of strains belonging to phage group III. It was shown that cross-infection plays a major role in producing this state of affairs.

These ecological adjustments of the staphylococci have had important clinical consequences. Howe (1954) and Blowers and his colleagues (1955) have quoted increases in the incidence of post-operative sepsis during recent years, the infections being due usually to antibiotic-resistant staphylococci and associated with the increase in their numbers. There have been many outbreaks of staphylococcal sepsis in maternity wards. Advances (e.g. in chest surgery) which were made possible by antibiotics have been jeopardized by the break-through of organisms resistant to all available drugs. Some of the blame may, as McDermott (1956) points out, be attributed to inadequate resistance in patients kept alive by other forms of treatment; but there is also evidence to show that some staphylococci selected by antibiotic therapy (especially those of phage type 80) have enhanced virulence and communicability (Rountree and Freeman, 1955). Such facts have made it necessary to reconsider the indications for antibiotic therapy, especially in hospital, and also to discover ways of preventing the emergence of resistant variants and expelling those which have appeared.

The difficulty of preventing cross-infection in a burns unit is notorious. In the Birmingham Accident Hospital burned patients occupy two wards of an old-style hospital. Some control of cross-infection has been achieved by the use of a plenum-ventilated dressing station and other prophylactic measures especially against *Streptococcus pyogenes* (Colebrook, 1950). In recent years the need to accommodate a larger number of patients has made it difficult to maintain all the barriers against cross-infection at full efficiency; and since tetracycline and erythromycin, rather than penicillin, have had to be used for the therapy of streptococcal infection (Lowbury and Cason, 1954), there has been an abundance of staphylococci resistant to these antibiotics in the burns; *Strep. pyogenes* has also been found resistant to tetracycline and, occasionally, to erythromycin (but never to both).

In Fig. 3 I have tried to show what association exists between the use of these two antibiotics (shaded areas) and the proportion of resistant strains in the burns wards during 1955, 1956 and 1957. It represents only a sampling—20 strains of *Staph. aureus* from consecutive patients swabbed at the beginning of each month plotted on the same scale as the average number of patients per day treated with the antibiotics in the last week of the previous month. In the middle of 1956 we found an increasing incidence of tetracycline-resistant streptococci, and therefore replaced tetracycline by erythromycin as our routine antibiotic for streptococcal infections. After that time tetracycline-resistant staphylococci became less common, but erythromycin-resistant staphylococci increased in numbers. In spite of the restricted sampling, there was a considerable association between the rise and fall of resistant staphylococci and the

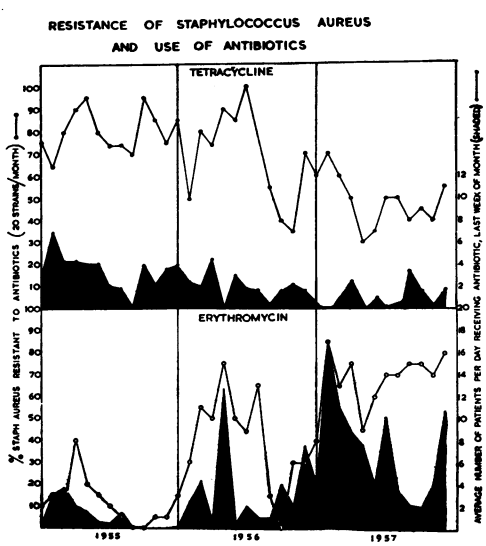

FIG. 3.

varying use of erythromycin, in particular, from month to month. It is tempting to infer from this that resistant organisms can be expelled from a ward readily enough merely by withholding the antibiotic in question; but our experience with novobiocin suggests that it is unsafe to generalize on these lines. A trial of novobiocin therapy in 1956 led to the emergence of a large proportion of novobiocin-resistant staphylococci. Fig. 4 shows the position as it stood at the end of the trial (in January 1957) and for the remainder of that year; weekly resistance rates for *all* strains of *Staph. aureus* are plotted here. During the five months after the trial there was a fall to zero, followed by a prompt return of resistant staphylococci on resumption of novobiocin therapy for a few patients in July. After this, however, there was no decline in the small incidence of novobiocin-resistant staphylococci, in spite of the fact that the antibiotic was not being used: this may have been due to the prolonged stay in the Burns Unit of certain carriers of novobiocin-resistant staphylococci.

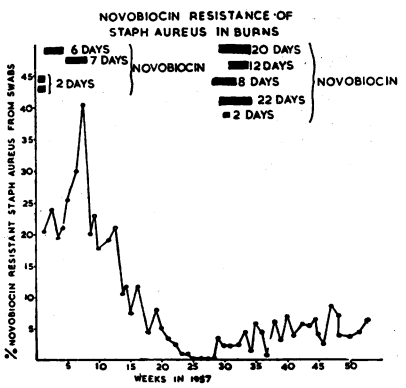

FIG. 4.

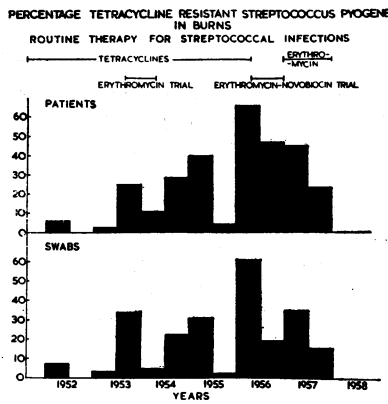

FIG. 5.

Strep. pyogenes is still the most important pathogen commonly found on burns in hospital, as it is much more liable than other bacteria to cause the failure of skin grafts. It is more vulnerable than *Staph. aureus* to the antibiotics; indeed, true penicillin resistance is unknown. But we have found an increasing incidence of tetracycline-resistant streptococci, and recently erythromycin-resistant strains have appeared. Fig. 5 shows the proportion of tetracycline-resistant streptococci isolated in six-month periods since 1952 (before which all strains were sensitive). It shows a mounting incidence and suggests the establishment of a "hospital streptococcus". Serological studies have shown that a number of different types are represented among these tetracycline resisters; e.g. the predominant strain in 1955 was of type 9, and in 1957 it was of type 5/11 and related patterns (which have been the commonest to show resistance). Erythromycin resistance appeared in streptococci of two types (3 and 14). It would appear that resistant mutants of *Strep. pyogenes* have emerged on a number of occasions. This view is supported by the multiplicity of types, and by the appearance, after treatment, of streptococci of the same types as those of sensitive strains isolated before treatment—a phenomenon we have also observed repeatedly in the case of *Staph. aureus*. But since there is no appreciable increase in the frequency of streptococcal infections between 1952 and 1957, it appears likely that resistant strains have to some extent become endemic and one may with reason speak of a "hospital streptococcus".

There are two approaches by which we can attempt to combat these evils: (1) by aiming to prevent the emergence of resistant variants, and (2) by using methods to prevent their spread. Of the former, combined therapy with two or more agents has had most attention and has been successful against tuberculosis. Our experience during a trial in which novobiocin was used only in combination with erythromycin was somewhat disappointing; in spite of the therapeutic effectiveness of this mixture, about 20% of doubly resistant staphylococci appeared after three months of the trial (Lowbury, 1957). The use of antibiotics in rotation—and with economy—may perhaps be more effective. Our best hopes probably lie in the development of agents which, like bacitracin, neomycin, chlorhexidine and vancomycin against *Staph. aureus* and polymyxin against *Ps. pyocyanea*, never, or hardly ever, select variants which are resistant and capable of causing infection. But until (and perhaps even after) we are supplied with the ideal therapeutic compounds of this kind, the most profitable line of attack is, undoubtedly, to improve aseptic discipline and to block the lines of bacterial communication.

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Tubercle Bacilli in the Community

Between June 1955 and March 1956 the Medical Research Council's Tuberculosis and Statistical Research Units and the Group for Research on Drug Sensitivity in Tuberculosis carried out in Great Britain a national survey of the incidence of drug-resistant strains of tubercle bacilli in newly diagnosed cases of pulmonary tuberculosis (Fox *et al.*, 1957; Mitchison and Selkon, 1957). In order that the findings should permit an unbiased estimate of the prevalence of drug-resistant infections in the whole of Britain, 80 clinics were randomly selected. These clinics supplied sputum specimens from 1,404 patients, which comprised a third of the total number of previously untreated patients diagnosed during that time.

Patients eligible for this study were defined as those with newly diagnosed and previously untreated pulmonary tuberculosis, aged 15 years and over, producing sputum and normally resident in the clinic area. An early morning specimen of sputum was sent to the central laboratory (M.R.C. Group for Research on Drug Sensitivity in Tuberculosis) and to the local laboratory, before treatment was started.

Of the 1,404 patients included in the survey, 60 were later diagnosed as not suffering from tuberculosis, leaving 1,344 newly diagnosed patients. Bacteriological confirmation was obtained on 974 at the central laboratory, and on a further 172 at the local laboratories. In the remaining 198 patients the diagnosis was made on clinical grounds alone. Of 1,344 patients 63·7% were males and 36·3% females. Whereas 68·1% of the male patients were 35 years or older, 63·9% of the female patients were under 35 years of age.

TABLE I.—PREVALENCE OF PRIMARY DRUG RESISTANCE IN DIFFERENT AREAS

Area	Total strains isolated	Resistant strains No.	Resistant strains %
London and South East*	187	9	4·8
Birmingham†	159	4	2·5
Manchester†	106	8	7·5
Liverpool†	73	6	8·2
Rest of England	218	8	3·7
Wales	62	1	1·6
Scotland	169	14	8·3
Great Britain	974	50	5·1

*The 4 Metropolitan Regional Hospital Board areas.
†The Birmingham, Manchester and Liverpool Regional Hospital Board areas.

The data on drug resistance is based on the 974 positive cultures obtained at the central laboratory. Of these 974 positive cultures, 924 (94·9%) were sensitive to streptomycin, PAS and isoniazid and 50 (5·1%) were resistant to one or more of these three antituberculous drugs. Of the 50 resistant strains, 44 were strains of *Myco. tuberculosis* var. *hominis* or *bovis*, the remaining 6 being other mycobacteria, one an avian strain. Of the 44 strains of *Myco. tuberculosis* 22, i.e. 2·3% of the positive cultures, were resistant to streptomycin, 21, i.e. 2·2%, were resistant to PAS, and 7, i.e. 0·7%, were resistant to isoniazid. 5 strains (0·5%) were resistant to more than one drug, 1 being resistant to all three. This accounts for the total of 50 instances of resistance amongst 44 strains. It is possible from these figures to say that at the time of the survey the prevalence of primary streptomycin resistance is unlikely to have been less than 1·5% or greater than 3·3%. The corresponding limits for PAS resistance are 1·5% and 3·1% and for isoniazid resistance 0·3% to 1·4%.

The geographical distribution of the 974 patients with positive cultures, and of those with resistant strains, is shown in Table I. The prevalence of resistant strains was above the national average of 5·1% for the Manchester (7·5%) and Liverpool (8·2%) areas and for Scotland (8·3%). Wales showed a very low prevalence of drug-resistant strains (1·6%). The number of resistant strains, however, is small, and these differences may therefore be no more than chance fluctuations.

Table II gives the age and sex distribution of the 974 patients whose sputum yielded a positive culture at the central laboratory and of the 50 of these who were infected with drug-resistant organisms. The prevalence of resistant strains was 3·8% among male patients and 7·7% among females. This contrast in prevalence was particularly marked under the age of 35, where 3·0% of males as compared to 9·3% of females had resistant strains. Each of these differences is statistically significant at the 5% level. This higher incidence of infections with drug-resistant organisms in females under the age of 35 is of particular interest. Their proportion of tuberculous contacts was similar to that for the men and older women and so was their proportion of home contacts. One cannot therefore explain this difference as due to more frequent or closer contact with patients excreting drug-resistant organisms. A possible explanation which would link this up with the difference in incidence of clinical pulmonary tuberculosis between the sexes in this age group is that the clinical manifestation of pulmonary tuberculosis in young women is more frequently due to recent exogenous infection than is the case in men or in older women. In men or in older women, clinically manifest disease may more frequently be due to previous latent infection. The prevalence of infection with drug-resistant organisms may therefore be much higher than our figure of 5·1% for clinically manifest disease. If this explanation is correct, it can therefore be expected that the prevalence of drug-resistant organisms in future manifest disease in men and in older women will approximate, or even be higher than, that found for young females in this survey.

TABLE II.—RESISTANCE BY AGE AND SEX

	Males			Females		
	Total	Resistant		Total	Resistant	
Age	strains	No.	%	strains	No.	%
15–34	199	6	3·0	216	20	9·3
35+	436	18	4·1	123	6	4·9
Total	635	24	3·8	339	26	7·7

In order to obtain information on the possible sources of infection with these drug-resistant strains, intensive contact histories were taken from the patients infected with these strains and from control patients infected with sensitive strains, chosen and individually matched according to age, sex and area of residence. Table III summarizes the contact histories of the resistant and the sensitive control patients. Of the 22 patients infected with streptomycin-resistant strains, 13 were known to have been in contact with patients who had received streptomycin. In comparison only 6 of the 22 matched control patients knew of a similar

TABLE III.—PATIENTS INFECTED WITH RESISTANT STRAINS, AND THEIR MATCHED CONTROLS WITH SENSITIVE STRAINS, SUBDIVIDED ACCORDING TO THE POSSIBLE SOURCE OF TUBERCULOUS INFECTIONS THROUGH CONTACT

	Sensitivity status of patients in survey					
	Streptomycin		PAS		Isoniazid	
Status of source of infection	Resistant patients	Sensitive controls	Resistant patients	Sensitive controls	Resistant patients	Sensitive controls
No known chemotherapy with relevant drug ..	9*	16	9	18	4	7
Chemotherapy with relevant drug; sensitivity not known	10	6	7†	3	1	0
Resistant to relevant drug	3	0	5	0	2	0
Total patients or controls	22	22	21	21	7	7

*One patient lived in a common lodging house frequented by a number of treated tuberculous patients.

†One patient was a laboratory technician examining the sputa of tuberculous patients receiving chemotherapy.

contact. For 3 of the 13 patients, the source case was known to have had streptomycin-resistant organisms, compared with none in the control group. For PAS resistance, 12 of the 21 patients had been in known contact with patients previously treated with PAS compared with 3 in the sensitive control group. 5 of the PAS-resistant group had been in contact with patients known to have had PAS-resistant organisms, but none of the controls. The figures for isoniazid resistance, though smaller, similarly suggest that those in contact with patients who had received isoniazid, or who were excreting resistant organisms, were more likely to be infected with resistant organisms than patients not similarly exposed.

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Dr. H. Williams Smith (The Animal Health Trust, Stock, Essex):

Drug-resistant Bacteria in Domestic Animals

There is little doubt that the diseases of human beings in which antibiotic-resistant strains of bacteria are the most troublesome are those caused by *Staphylococcus aureus* and *Mycobacterium tuberculosis*.

The position in veterinary medicine is quite different. Tuberculosis is, of course, a very serious disease of cattle but it is controlled in Britain by the tuberculin testing of herds with the elimination of all cattle giving a positive reaction. Progress has been so satisfactory that it is hoped that within a few years all our cattle population will be virtually tubercle-free. *Staph. aureus* does cause an appreciable amount of bovine mastitis but this form of mastitis does not respond well to the intramammary injection of antibiotics—the only really satisfactory method of treating most cases of mastitis. Consequently, an increase in the proportion of resistant strains of *Staph. aureus* associated with this disease would not be so serious as it might appear at first sight. Nevertheless the proportion of penicillin-resistant strains has definitely increased. Tee (1957) found that the proportion of pencillin-resistant *Staph. aureus* cultures isolated from herd samples of milk had increased from 11% in 1954 to 47% in 1956. It would be incorrect to assume that this increase has resulted directly from the use of penicillin in treating staphylococcal mastitis. It is largely an indirect result of its widespread use in the treatment of *Streptococcus agalactiæ* mastitis. Antibiotics have been used more in the treatment of this very common condition than in the treatment of all other diseases of animals put together. Some authorities are of the opinion that about 1½ million million units of penicillin are used every year in Britain for treating mastitis. Whatever the actual amount is, it is so great that the extent to which it is present in bulk milk is such as to give concern to those interested in public health and the manufacture of dairy products. Other drugs such as streptomycin, the tetracyclines, chloramphenicol and the sulphonamides, are employed to a much lesser extent. Except in severe acute cases, drugs are given by the intramammary route only. Usually, clinical cases only are treated but, sometimes, all the cows in a herd may be treated in the hope of eradicating infection from the herd. Despite this exhibition of drugs on the grand scale, no resistant strains of *Strep. agalactiæ* have ever been reported and it appears unlikely now that any ever will be.

The bacterial species that presents the greatest veterinary problem from the point of view of drug resistance is probably *Bacterium coli*. This bacterium is usually only associated with disease in the very young and, since young farm animals receive less care and attention than young human beings, it is not surprising that *B. coli* is much more important from the veterinary than from the human point of view. This organism has an important association with a diarrhœa in young calves that is commonly called white scours, a disease that kills 5%–10% of all the calves born in Britain. A somewhat similar disease causes serious losses in piglets. Certain strains of *B. coli* are also associated with a disease of pigs called bowel œdema. The more modern chemotherapeutic agents are commonly employed in the treatment of these diseases and it is not surprising, therefore, that the emergence of drug-resistant strains of *B. coli* would be a matter of some concern to veterinary surgeons.

Our first impression that the numbers of drug-resistant *B. coli* associated with animal disease were, in fact, increasing, was gained by comparing the results of testing the drug sensitivities of strains of *B. coli* found to be associated with cases of white scours in calves in 1951–53 with those obtained in a similar survey carried out in 1955 (Smith and Crabb, 1956*a*); a greater proportion of resistant strains were found in the second survey than in the

first. Studies on the dynamics of the emergence of resistant *B. coli* in animals under treatment were then performed employing phage typing for classifying strains of *B. coli* (Smith and Crabb, 1956*b*) and a plate method for sensitivity testing (Smith and Crabb, 1956*a*; Smith, 1958). The plate method consisted simply of rubbing a rectal swab over a plate of MacConkey agar, applying paper discs containing different drugs and then incubating at 37°C. The plates could be read in six to eight hours.

The results with calves suggested that when a dominant drug-resistant *B. coli* intestinal flora emerged, it usually did so as a consequence of the depression of the multiplication of the sensitive strains accompanied by their replacement by resistant strains previously present in very small numbers only. However, in a small number of cases treated with either streptomycin or chloramphenicol, the available evidence suggested that the resistant *B. coli* arose from mutation of sensitive strains (Smith, 1958).

In vitro it was possible to make strains of *B. coli* of white scours origin permanently resistant to streptomycin, chloramphenicol and sulphadimidine both singly and multiply. Despite continuous efforts for six months it was not possible to make strains of *B. coli* resistant to either the tetracyclines or Furamazone.

Very few resistant strains of *B. coli* were found in the fæces of calves from self-contained herds in which drugs had never been used. The position in herds in which they had been used frequently was quite different. A close relationship existed between the drugs used in these herds and the resistance of the predominant *B. coli* intestinal flora in the calves in them. For example, in a herd where streptomycin had been used frequently, the predominant *B. coli* in the fæces of the scouring calves in this herd that had not responded to this form of treatment were streptomycin-resistant; these resistant strains had also spread to untreated calves in these herds. In many of the herds, as a result of sensitivity tests, it was possible to suggest replacing an ineffective drug with an effective one. However, unless other measures were taken to reduce the incidence of scours and hence the number of calves requiring treatment, a position was soon reached when the new drug also became ineffective. Multiple resistance was a serious position in such herds. In some of them the predominant *B. coli* fæcal flora were resistant to streptomycin, the tetracyclines, chloramphenicol and the sulphonamides.

Apart from the therapeutic use of drugs, the continuous feeding of animals on diets containing low levels of some of these agents has also had a profound effect on the emergence of resistant strains of *B. coli*. The tetracyclines in levels of 10–100 grams per ton of food are the agents most commonly used, the purpose of which, of course, is to stimulate the growth of the animals to which they are fed. I should estimate that about 50% of all the pigs in Britain are so fed and that nearly all unweaned piglets have access to food containing tetracyclines. Most of the broiler chickens, but very few of the other classes of poultry, are fed diets containing either tetracyclines, penicillin or both.

Examination of pigs and poultry kept on many different farms showed that the *B. coli* in the fæces of tetracycline-fed animals were predominantly tetracycline-resistant, while those in the fæces of animals on farms where tetracycline feeding was not practised were predominantly tetracycline-sensitive (Smith and Crabb, 1957). In some herds in which tetracycline feeding was just being introduced it was possible to trace the change of the *B. coli* fæcal flora from tetracycline-sensitive to tetracycline-resistant. In other herds tetracycline feeding was discontinued after being practised continuously for two to three years. Tetracycline-resistant *B. coli* still formed the mass of the *B. coli* fæcal flora of animals in these herds for several months afterwards. A survey of pigs entering a bacon factory revealed that the *B. coli* in the fæces of 36% of them were all tetracycline-resistant; this is probably a fairly reliable indication of the effect of tetracycline feeding on the pig population in general.

The piglets of tetracycline-fed sows quickly acquired from their mothers a *B. coli* intestinal fæcal flora that was predominantly tetracycline-resistant. Needless to say, any diarrhœa associated with *B. coli* that occurred in these piglets was not amenable to treatment with tetracyclines. Other drugs that were much more expensive, more difficult to administer and/or to which *B. coli* quickly became resistant, had to be employed instead.

The emergence of resistant strains belonging to bacterial species that are usually drug-sensitive during antibiotic feeding is not confined to *B. coli*. Under certain conditions we have found a somewhat similar state of affairs to apply, for example, in the case of *Clostridium welchii*.

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