Characteristics of Antimicrobial Resistance of *Escherichia coli* from Animals: Relationship to Veterinary and Management Uses of Antimicrobial Agents

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Five-hundred fifty-five (555) isolates of *Escherichia coli* were obtained from fecal specimens of a representative number of animals from five farms in the United States. Antibiotic exposure of the selected herds was determined by an epidemiological survey of these farms. The incidence of multiple resistance in the *E. coli* isolates was higher in herds exposed to continuous feeding of antimicrobial agents (84.8%) than in a herd not receiving antimicrobials (15.7%). The most common resistance configuration observed was the triple pattern of dihydrostreptomycin (DS), sulfonamide (SU), and tetracycline (TE). The second most frequent pattern consisted of four resistances: ampicillin (AM), DS, SU, and TE. The frequency of transfer factors was much higher in multiply resistant organisms from the herds exposed to antimicrobial medicaments. The *E. coli* isolates were relatively efficient in fostering and transferring heterologous resistance factors. AM resistance factors occurred more frequently in herds which were exposed to feed levels of penicillin (27.9%) than in those that were not (6.4%).

The phenomenon of the transfer of multiple antibiotic resistance by conjugation was first reported in Japan (13) in 1959 to 1960 and in Great Britain in 1962. Between 1962 and 1965, English investigators (1–3, 5) published several papers on the subject and showed that *Salmonella typhimurium* strains from human and animal sources which had resistance to several important antimicrobials [tetracycline (TE), streptomycin (SM), ampicillin (AM), and sulfonamide] could transfer all of these resistances to sensitive *E. coli* strains. Likewise, resistant *E. coli* could transfer its resistance to sensitive *E. coli*. More recently, other investigators (9–11) obtained evidence that infectious drug resistance was prevalent among nonpathogenic *Escherichia coli* from humans, calves, pigs, and fowl. It is possible, therefore, that these bacteria, which formed the bulk of the aerobic enterobacterial flora of the alimentary tract, were a reservoir of infectious resistance from which animal pathogens could become resistant and also potential donors upon ingestion of R factors to human intestinal flora.

The overall use of antibacterial drugs in livestock rations for various purposes supplies a continuing pressure to maintain the process of resistance transfer. A survey was deemed necessary to determine how widespread these infectious resistant bacteria were in animal populations in the U.S. It was also important to determine the relationship between the use of antimicrobial agents in feed and the occurrence of multiply resistant organisms which contained transfer factors.

A traceback system was used to select each farm for the study. A continuous supply of *Salmonella* isolates was obtained from the Diagnostic Services, Animal Health Division, National Animal Disease Laboratory at Ames, Iowa. Antibiograms were determined for each isolate received. Alternate farms of origin of multiply resistant and completely sensitive *Salmonella*, and the willingness of the farm owner to cooperate, were used as criteria for selection of premises. A cooperative agreement was established between the Food and Drug Administra-

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tion, Center for Disease Control, and U.S. Department of Agriculture, which provided a mechanism for obtaining samples from the farms of origin of the traceback cultures. This arrangement provided for the epidemiological support necessary to the study.

MATERIALS AND METHODS

Selective media were utilized to determine whether any Salmonella isolates could be obtained from each fecal sample collected. No Salmonella isolates were detected from any of the animals examined on any of the farms.

To isolate E. coli, rectal swabs were inoculated onto MacConkey agar plates which were then streaked on the premises and incubated overnight prior to return to the laboratory. Three typical lactose-fermenting colonies were picked to Triple Sugar-Iron-Agar slants and incubated at 37 C overnight. Strains giving typical E. coli reaction were further screened on Simmons citrate agar and adonitol and were checked for motility and for production of ornithine de-carboxylase and oxidase.

The antimicrobial susceptibilities of confirmed E. coli were tested by the technique of Bauer et al. (4), except that dihydrostreptomycin (DS) was substituted for SM; studies in our laboratory demonstrated equivalent zone sizes against E. coli. The following antimicrobials were used in the testing system: AM, DS, cephalothin (CEPH), sulfamethoxypyridazine (SU), colistin (CL), chloramphenicol (CHLOR), furazolidone (FU), neomycin (NEO), TE, and nalidixic acid (NA).

All strains resistant to two or more antimicrobials, including resistance to either tetracycline or ampicillin, or both, were examined for transferable resistance. The R-factor transfer procedure and media used were those of Schroeder et al. (8) with slight modifications. Four media were used: I, MacConkey agar; II, MacConkey agar plus 25 μg of NA per ml; III, MacConkey agar plus 25 μg of NA and 4 μg of TE per ml; and IV, MacConkey agar plus 25 μg of NA, 10 μg of AM, and 10 μg of dioxacillin per ml. To test for R factors, equal volumes (0.5 ml) of overnight cultures in Mueller Hinton broth (MHB) of the donor E. coli and recipient non-lactose-fermenting E. coli (NA-resistant strain of K-12F−, courtesy of H. Williams Smith) were mixed and incubated at 37 C for 2 hr. At the same time, MHB tubes were inoculated with recipient alone and with a multiply resistant Salmonella control alone and were incubated for the same time interval. After 2 hr, all cultures were streaked onto plates of media I and II, and 0.1-ml portions were spread onto plates of media III and IV. For results to be valid, the Salmonella control strain was required to grow on all four plates and recipient control strain only on plates I and II. In conjugated mixtures, both recipient and donor must have been present on plate I and only recipient on plate II. Typical colonies of the recipient strain appearing on plates III or IV, or both, were picked and tested for antimicrobial susceptibility.

RESULTS

Table 1 outlines the major species of animals tested on each farm. Farms 1, 3, and 4 utilized a continuous program of medication with antibiotics. Farm 2 was primarily a cattle operation utilizing a management system which included the administration of antimicrobials during periods of "stress" to the animals. Farm 5 utilized three separate locations for the production of swine, calves, and dairy cattle. The swine were receiving continuous low levels of oxytetracycline in the feed. The calf operation utilized nitrofurazone at therapeutic levels (e.g., administered as one dose at the time of birth). The dairy cows were receiving no continuous medications, but two cows had been treated for mastitis the previous 2 weeks before the test. These two cows were the source of 40% of the multiply resistant strains isolated from this herd.

Animals exposed to continuous levels of antimicrobials (farms 1, 3, 4) had a much higher percentage of resistant organisms and had a frequency of occurrence of multiple resistance substantially greater than animals on the other farms (Table 2). Of the E. coli isolates from the swine populations of farms 1, 3, 4, and 5, 67 to 95.9% were multiply resistant.

The cattle population on farm 2, receiving intermittent antimicrobial pressure, yielded 38.4% multiply resistant E. coli. In contrast, the calves and dairy cattle on farm 5, receiving no continuous antimicrobial pressure, had substantially lower frequencies of multiple resistance, 19.0 and 15.7%, respectively (Table 2). Correspondingly, the incidence of sensitive organisms was higher in the animals which were not being exposed to continuous levels of antimicrobial agents.

Table 3 clearly illustrates that as the antimicrobial pressure was reduced there was a corresponding drop in multiply resistant strains. In Table 4 can be seen the ratio of homologous resistances (resistant factors in fecal flora which are the same as the antimicrobial being used in the feed) to the heterologous resistances (resistant factors not related to the antimicrobial used in the feed).

When an antimicrobial was used in the feed, the percentage of isolates resistant to it was substantially higher than when the antimicrobial did not appear in the feed. Multiple resistance was also correspondingly high in these herds and showed a definite correlation to the content of the antimicrobial in the feed. A striking exception to this general tendency was the high incidence (65.0%) of DS-resistant organisms (Table 5). There was no evidence that this drug had been used on any of the farms for the previous 6
months prior to the study. It was also noted (Table 4) that AM resistance occurred more frequently when penicillin was used in the feed (27.9%) than when it was not used in the feed (6.4%). This finding appears to be in contrast to an earlier report (6) which indicated that penicillin in feed may have little influence on the buildup of AM-resistant, gram-negative organisms.

Of the 491 isolates from animals exposed to antimicrobials in feed, 394 (80%) were resistant strains and fell into 39 different antimicrobial patterns. In contrast, of the 64 isolates obtained from animals not exposed to antimicrobials in feed, 14 (15.6%) were resistant strains falling into 10 different antimicrobial resistance patterns. Table 6 illustrates the distribution patterns of singly and multiply resistant isolates. The most commonly occurring resistance patterns were those organisms resistant to three and four antimicrobials. The least common were organisms resistant to five and six antimicrobials. The occurrence of one and two resistance factors was equally prevalent. Nearly 70% of all isolates contained three or four resistance factors. Following in sequence of occurrence were two resistances (12%), five resistances (11%), single resistances (6%), and six resistances (1%).

| Farm no. | Location       | Animal species | No. of animals sampled | History and levels of antimicrobial exposure | Continuous/feed | Therapeutic/preventative |
|----------|----------------|----------------|------------------------|---------------------------------------------|----------------|--------------------------|
| 1        | Collum, Ill.   | Swine          | 50                     | Chlortetracycline, 100 g/ton Penicillin, 50 g/ton Sulfamethazine, 100 g/ton Tylosin (level undetermined) | Erythromycin   |                          |
| 2        | Cedar Falls,   | Cattle         | 50                     | None                                         | Chlortetracycline, 350 mg per head per day Sulfamethazine, 350 mg per head per day (given for 2-week intervals during periods of stress) | Nitrofurazone  |
|          | Iowa           |                |                        |                                              |                |                          |
| 3        | Stanford, Ill. | Swine          | 50                     | Chlortetracycline, 100 g/ton Penicillin, 50 g/ton Sulfamethazine, 100 g/ton Nitrofurazone, 0.05% |                |                          |
| 4        | Cunningham,    | Swine          | 29                     | None                                         | Chlortetracycline, 100 g/ton Penicillin, 50 g/ton Sulfamethazine, 100 g/ton (given regularly to prevent disease) | Nitrofurazone  |
|          | Ky.            |                |                        |                                              | None           |                          |
| 5        | Hanska, Minn.  | Swine          | 10                     | Oxytetracycline, 50 g/ton                    |                |                          |
|          |                | Calves         | 9                      |                                              |                |                          |
|          |                | Dairy cows     | 31                     |                                              |                |                          |

| Table 2. Relationship between exposure to antimicrobials and frequency of resistances of Esherichia coli |
| Exposed | Nature of exposure | Total strains | Percentage of strains |
|---------|---------------------|---------------|-----------------------|
|         |                     |               | Multiply sensitive | Singly resistant | Multiply resistant |
| Farm 1  | Continuous          | 99            | 0.0                   | 4.1             | 95.9               |
| Farm 2  | Intermittent        | 138           | 44.9                  | 16.2            | 38.4               |
| Farm 3  | Continuous          | 131           | 10.7                  | 22.2            | 67.2               |
| Farm 4  | Continuous          | 77            | 4.9                   | 0.0             | 95.1               |
| Farm 5  | Continuous          | 25            | 8.0                   | 16.0            | 76.0               |
| Swine Calf | Intermittent | 21            | 76.2                  | 4.8             | 19.0               |
| Sub-total| Not exposed        | 491           | 24.1                  | 10.6            | 65.3               |
| Farm 5  | Not exposed         | 64            | 78.1                  | 6.2             | 15.7               |
| Dairy cows | Not exposed        | 555           | 31.8                  | 9.9             | 58.2               |

These data suggest that the majority of E. coli of animal origin isolated from farms utilizing antimicrobials in feed will be multiply resistant. Not all animals yielding multiply resistant isolates of E. coli harbored strains with transfer factors (R factors). The frequency was as follows: farm 1, 19 of 43 (44%); farm 2, 5 of 47 (11%); farm 3,
27 of 47 (57%); farm 4, 15 of 30 (50%); and farm 5, 14 of 50 (28%). These data indicate that, on farms 1, 3, and 4 where there was a continuous antimicrobial pressure, a higher percentage (50%) of the resistant organisms contained R factors that were capable of transferring than on farms 2 and 5 receiving less constant antimicrobial pressure (50% compared to 20%).

In Table 7 are presented the frequency and rank in which six of the antimicrobials were commonly included in resistance patterns and which occurred with additional resistances. NEO was found to be the most dependent on other resistance factors. It never occurred as a single resistance and thus was most likely to appear in a multiply resistant pattern. On the other hand, DS apparently has less dependency on other R-factors. It occurred more often as a single resistance than did any of the other antibiotics.

The nine most common and frequently occurring resistance patterns found in the study are presented in Table 8. DS, SU, TE was the most frequently occurring pattern, followed by the pattern AM, DS, SU, TE. However, the pattern which was most consistently transferred was DS, SU, NEO, TE.

**DISCUSSION**

Antimicrobials have received widespread popularity as constituents of animal feeds in the United States. They are used at low levels for growth promotion purposes, at median levels for disease prevention, and at therapeutic levels for the treatment and control of disease. One of the five farms surveyed in this study (farm 5) utilized a growth promotion level (50 g/ton) of oxytetracycline in the swine ration. Three other farms (1, 3, 4) were utilizing a combination of drugs (penicillin, chlortetracycline, and sulfamethazine) at a combined level of 250 g/ton. This level of drugs is commonly used for disease prevention. In comparing the percentage of multiply resistant isolates from these farms (86% for farms 1, 3, and 4 versus 76% for farm 5) there apparently was little difference in the levels of resistant organisms stimulated by the use of either of these dosage levels.

The cattle on farm 2 were receiving a dosage level of chlortetracycline (350 mg per head per day) and sulfamethazine (350 mg per head per day) which might be considered disease prevention levels. These drugs were used on an intermittent basis, and the level of multiply resistant organisms was much lower in this group of animals (38.4%). The calves on farm 5 received a single therapeutic dose of nitrofurazone at birth. The incidence of multiply resistant organisms

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**Table 3. Frequency (%) of multiple resistance among herds with different exposure intensities**

| Nature of antimicrobial exposure | Total strains | Avg. range per cent |
|----------------------------------|---------------|---------------------|
| Continuous                       | 332           | 83.6 (67.2-95.9)     |
| Intermittent                     | 159           | 28.7 (19.0-38.4)     |
| None                             | 64            | 15.7                |

**Table 4. Relationship between antimicrobial exposure and per cent of occurrence of homologous- and heterologous-resistant isolates: correlation of multiple resistance to feed-use antimicrobials**

| Farm | Antimicrobials used in feed<sup>a</sup> (resistant isolates/total isolates) | Per cent multiple resistance with +1 resistances to feed-use drugs | Antimicrobials not used in feed<sup>a</sup> (resistant isolates/total isolates) |
|------|--------------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------|
|      | AM  | TE  | SU  | FU  | Total per cent resistance | AM  | TE  | SU  | FU  | |
| 1    | 36/99 | 67/99 | 92/99 | —   | 99 | 96.0 | 100.0 | —   | —   | —   | 0/99 |
| 2    | 53/138 | 77/131 | 73/131 | 3/131 | 208 | 77.7 | 99.3 | —   | —   | —   | —   |
| 3    | 27/131 | 77/131 | 70/131 | 0/131 | 208 | 77.7 | 99.3 | —   | —   | —   | —   |
| 4    | 23/77 | 66/77 | 73/77 | 3/77 | 208 | 77.7 | 99.3 | —   | —   | —   | —   |
| 5    | 19/25 | —   | —   | —   | 25 | 76.0 | 89.5 | —   | —   | —   | —   |
| a    | 18/25 | —   | —   | —   | 21 | 76.0 | 89.5 | —   | —   | —   | —   |
| c    | 20/21 | —   | —   | —   | 64 | 15.6 | 25.0 | —   | —   | —   | —   |
| Totals | 86/307 | 283/470 | 290/445 | 3/229 | 382 | 76.0 | 89.5 | 18/110 | 10/85 | 18/110 | 3/326 |
| Per cent ratio | 27.9 | 60.0 | 65.1 | 1.7 | —   | —   | —   | 16/248 | 10/85 | 18/110 | 3/326 |

<sup>a</sup> Abbreviations: AM, ampicillin; TE, tetracyclines; SU, sulfamethazine; FU, nitrofurazone.

<sup>b</sup> Dashes indicate antimicrobial was not used in feed.

<sup>c</sup> Dashes indicate antimicrobial was used in feed.
found in these animals was also comparatively low (19.0%) and comparable to that found in the herd of dairy cows receiving no antimicrobials in feed (15.7%). Forty per cent of the multiply resistant isolates from these animals could be traced to two cows which had recently been treated for mastitis. These findings indicate that the level of drug may not be the major factor in determining the amount of resistance that will develop. The continuous antimicrobial pressure seems to have a greater influence. This was true for both the level of resistance and the percentage of transfer factors that was observed.

This work also confirms the earlier work of Walton (12), who found a definite association between the types of drugs supplied to the animals and the isolation from their feces of strains of E. coli resistant to these drugs and capable of transferring this resistance.

The high incidence of DS resistance, even though this drug was not being used on the premises investigated, cannot be explained with the information available from these farms. One can only speculate about the origin of such a high

### TABLE 5. Frequency of all resistances among the 555 tested strains

| Drug                      | No. of strains resistant | Per cent frequency |
|---------------------------|--------------------------|--------------------|
| Dihydrostreptomycin       | 352                      | 65.0               |
| Sulfamethoxypyridazine    | 308                      | 55.4               |
| Tetracycline              | 293                      | 52.8               |
| Ampicillin                | 102                      | 18.4               |
| Neomycin                  | 45                       | 8.2                |
| Cephalothin               | 38                       | 6.8                |
| FURazolidone              | 6                        | 1.1                |
| Nalidixic acid            | 6                        | 1.1                |
| Colistin                  | 6                        | 1.1                |
| Chloramphenicol           | 5                        | 0.9                |

incidence of resistance. It is well recognized that DS is commonly utilized as a therapeutic agent for many diseases of domestic animals. The drug may have been used therapeutically on these farms. Specific inquiries regarding such exposures were included in the questionnaire but could have failed to verify this fact. Another possibility would be the dependence of DS on the transfer factors of other antibiotics for its continual influence on resistance. This does not seem likely, since it was shown (Table 7) to be the least dependent upon the cross-transfer of R factors. However, recent work by Datta et al. (7) may provide some insight into this observation. They found that TE exerted strong selection, not only for TE resistance but also for multiple resistance, significantly increasing the frequency of resistance to AM, SM, CHLOR, and sulfonamide.

A higher incidence of ampicillin resistant organisms was observed in herds which were receiving feed additive penicillin. The combination of three drugs (penicillin, chlortetracycline, and sulfamethazine) was substantially more effective in producing AM resistance of the E. coli isolates from swine than was oxytetracycline alone (86 of 307 strains versus 6 of 110 strains). This occurrence could be explained, and in fact might be expected, since both AM and penicillin are susceptible to the action of penicillinasin, and penicillin would induce this enzyme among gram-negative enteric flora. However, since the use of both sulfonamides and TE may be associated with the emergence of heterologous resistance to AM, the role of penicillin per se can not be confidently ascertained.

The observation of a substantially higher frequency of transmissible resistance among multiply resistant strains that come from animals exposed to antimicrobials invites further speculation. Presumably, a selective advantage is conferred to

### Table 6. Frequency with which each antimicrobial resistance appeared alone or in combination

| Resistance patterns in which occurred | Resistance to antimicrobial* | Total instances | Per cent |
|---------------------------------------|------------------------------|-----------------|----------|
| One                                   | AM  | DS  | CEPH | SU  | CL  | CHLOR | FU  | NEO | TE  | NA  |       |
| Two                                   | 1   | 31  | 1    | 4   | 1   | 0     | 0   | 0   | 23  | 2   | 63    |
| Three                                 | 3   | 53  | 2    | 40  | 2   | 0     | 2   | 1   | 36  | 3   | 142   |
| Four                                  | 16  | 159 | 3    | 158 | 0   | 1     | 2   | 8   | 139 | 0   | 486   |
| Five                                  | 62  | 80  | 15   | 77  | 3   | 4     | 0   | 13  | 67  | 1   | 322   |
| Six                                    | 17  | 26  | 16   | 26  | 0   | 0     | 0   | 20  | 25  | 0   | 130   |
| No. of strains                        | 102 | 352 | 38   | 308 | 6   | 5     | 6   | 45  | 293 | 6   | 1161  |

* AM, ampicillin; DS, dihydrostreptomycin; CEPH, cephalothin; SU, sulfamethoxypyridazine; CL, colistin; CHLOR, chloramphenicol; FU, furazolidone; NEO, neomycin; TE, tetracycline; NA, nalidixic acid.
TABLE 7. Frequency of single antimicrobial resistances appearing as part of a multiply resistant pattern

| Rank | Drug                  | Per cent frequency |
|------|-----------------------|--------------------|
| 1    | Neomycin              | 100.0              |
| 2    | Sulfamethopyridazine  | 98.5               |
| 3    | Cephalothin           | 97.3               |
| 4    | Ampicillin            | 97.0               |
| 5    | Tetracycline          | 92.0               |
| 6    | Dihydrostreptomycin   | 91.0               |

TABLE 8. Nine most frequently occurring resistance patterns and percentage of transfer

| Pattern* | No. of instances | No. of transfers | Per cent |
|----------|------------------|------------------|----------|
| DS, SU, TE | 136              | 56               | 41.2     |
| AM, DS, SU, TE | 49              | 11               | 22.4     |
| DS, SU       | 29               | 0                | 0        |
| DS, TE       | 22               | 13               | 59.0     |
| AM, DS, SU   | 13               | 1                | 7.7      |
| SU, TE       | 11               | 0                | 0        |
| AM, DS, SU, NEO, TE | 10         | 5                | 50.0     |
| DS, SU, NEO, TE | 9              | 8                | 88.8     |
| DS, CEPH, SU, NEO, TE | 9         | 5                | 55.6     |

* DS, dihydrostreptomycin; SU, sulfamethopyridazine; TE, tetracycline; AM, ampicillin; NEO, neomycin; CEPH, cephalothin.

such strains in the presence of pressures from antimicrobial agents.

It is probable that humans and animals ingest small and continuing doses of enteric organisms carrying resistance determinants; in the absence of antimicrobial selective pressures, such strains may conjugate with indigenous flora but no selective advantage accrues to their offspring. However, if a population of strains resistant to drugs being administered is present, and these strains carry transfer factor at a much higher frequency, as the data show, then the likelihood of transfer of resistance determinants to “outsiders” is increased; such transfers would confer a survival advantage to a recipient and its progeny which now carry the combined resistances of initial donor and recipient. This postulated mechanism may account for the appearance of heterologous resistance in animals exposed to agents such as sulfonamides and TE.

Another area for concern was the inordinately high incidence of resistance observed in the swine herds. One herd yielded 100% resistant isolates, and the other herds ranged from 89% to 95% resistant isolates. A logical question would be whether these levels of resistance could be tolerated in high-density production procedures, especially if an infectious disease outbreak occurred. This is a particularly interesting question when one considers that the majority of the isolates were multiply resistant and contained viable transfer factors and that one of the major causes of early swine mortality and morbidity is colibacillosis. The selection of an effective therapeutic agent under these circumstances could become very difficult.

The results of this survey suggest that a high incidence of resistant organisms does exist in animals being exposed to continuous levels of antimicrobial drugs. R factors were common in these organisms, and multiple resistance to three or more antimicrobials was usually prevalent. Serious consideration must be given to the desirability and future acceptability of producing livestock in an environment comprised primarily of highly resistant microorganisms.

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