

had no previous history of antibacterial therapy and had not been in hospital.

It is generally accepted that therapy with a particular drug selects bacteria resistant to the drug, which may result in a predominantly resistant bacterial flora. It was surprising therefore to find that only 7 (39%) of the 18 infants who had received either penicillin or ampicillin had a predominantly ampicillin-resistant bacterial flora. There was some evidence, however, to suggest that penicillin or ampicillin therapy did have a selective effect, because a higher proportion of treated than of untreated infants had confluent growth up to the ampicillin disc. There was no evidence from our small number of tetracycline-treated infants that the drug had acted as a selective agent; the proportion of infants showing a predominantly tetracycline-resistant enterobacterial flora was higher in the untreated than in the treated group.

Sensitive strains only were isolated from 19 infants; four of these had received antibacterial therapy. If these drugs had exerted any selective pressure, we might have expected to isolate resistant bacteria from the faeces with our direct selection method.

It is impossible to determine the source of any of these 81 resistant enterobacterial strains. The 16 infants who were less than 3 months old and born in a hospital might have acquired their resistant strains from members of the hospital staff or other mothers in the wards. Apart from this possibility in

16 cases, the infants must have acquired their resistant strains from others in their homes. Three infants had contacts who had been in hospital. These three contacts might have acquired resistant enterobacteria while in hospital (Moorhouse and McKay, 1968) and subsequently infected the infants. Eight other contacts who had received antibiotics were possible sources of resistant enterobacteria. Twenty-five of the 81 infants were only children. We must assume that they were infected with resistant strains from a parent or other adult in the home.

The results of the survey confirmed our opinion that resistant enteric bacteria, most of them carrying transmissible R factors, are widely disseminated in the infant population of this city.

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## Drug Resistance and R Factors in the Bowel Bacteria of London Patients before and after Admission to Hospital

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**S**ummary: The content of drug-resistant coliform bacteria in faecal specimens collected before admission from patients awaiting non-urgent surgery were compared with specimens collected in hospital. Resistant strains of *Escherichia coli* were isolated from 52% of pre-admission specimens and were present in large numbers in 28%. Tetracycline, sulphonamide, and streptomycin resistance were commonest: 60% of resistant strains carried transmissible R factors and multiple resistance was commoner than single. No characteristically resistant intestinal bacteria of any genera were found in hospital specimens as compared with those from outside.

### Introduction

Over the last decade there has been clear evidence of a rapidly increasing incidence of antibiotic resistance in salmonella, shigella, and enteropathogenic types of *Escherichia coli* all over the world. At the present time something like 50% of isolates of these pathogens are resistant to one or more antibacterial drugs (Manten, Guinée, and Kampelmacher, 1966; H. W. Smith, 1966; Watanabe, 1966; Lebek, 1967; Anderson, 1968b; Davies, Farrant, and Tomlinson, 1968a). The resist-

ance is for the most part determined by R factors. The observed increase in the proportion of enteric pathogens resistant to drugs dates from about 1959, when R factors were discovered, but is nevertheless a true increase and not merely a reflection of greater awareness of the problem.

The occurrence of antibiotic resistance in enteric pathogens is of obvious clinical importance and is well documented. Resistance in this group might be supposed to have become common as a result of the treatment of diarrhoeal disease with antibiotics, with consequent selection of resistant strains.

There is less information available on the incidence of resistance and of R factors in the normal bowel bacteria of healthy people. R factors in these bacteria present two possible dangers. Firstly, they may be transferred to enteric pathogens within the bowel of infected patients. There was epidemiological evidence for such transfer in Japan at the time of discovery of R factors (see Watanabe, 1963), and since then in other parts of the world—for example, Davies *et al.* (1968b). Secondly, and perhaps more important, resistant bacteria which are harmless in the bowel may infect the urinary tract or cause other parenteral infections.

*E. coli*, like salmonellae and shigellae, is normally drug-sensitive. R factors, relatively easily detected in these species, are transmissible to many other bacterial genera, including those, such as *Klebsiella*, *Proteus*, and *Pseudomonas*, which are inherently resistant to certain antibacterial drugs. Acquisition

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of R factors extends the range of their resistance. A hospital population of coliform bacteria with accumulated resistance genes might be expected by analogy with hospital staphylococci.

This study was made as an attempt to assess the present state of bowel bacteria in relation to antibiotic resistance, and, in particular, the incidence of R factors in an adult urban population, and to find out whether people in hospital acquire a more resistant bowel flora. The bacteria studied were aerobic Gram-negative faecal bacilli and are referred to for brevity as "coliforms."

### Materials and Methods

Nutrient agar was Oxoid blood agar base No. 2, with or without 4% saponin-lysed horse blood. MacConkey agar was Oxoid code No. CM7. Minimal salts medium, with or without added proline and methionine, was that of Tatum and Lederberg (1947). Nutrient broth was Oxoid tryptone soya broth, code No. CM129. Media for identification of bacteria were those in current use in this department (Darrell, 1967).

*Antibacterial drugs* (abbreviations in parenthesis) incorporated in solid media were ampicillin (A) 25 µg./ml., streptomycin (S) 15 µg./ml., tetracycline (T) 10 µg./ml., chloramphenicol (C) 25 µg./ml., kanamycin (K) 25 µg./ml., sulphathiazole (Su) 100 µg./ml., polymyxin B (P) 25 µg./ml., nitrofurantoin (F) 25 µg./ml., and nalidixic acid (Nal) 25 µg./ml. Oxoid Multodisk, code No. 30-44K, together with Mast Laboratories sensitivity disc containing 30 µg. of nalidixic acid, covered the same range of drugs.

*Stock culture of E. coli* K12 J5-3, which is F- and requires proline and methionine, was used as control in sensitivity tests. Mutants of this strain, resistant to 50 µg. of nalidixic acid per ml. or to 1,000 µg. of streptomycin per ml., were selected in the laboratory and used as recipients in resistance transfer.

### Collection of Specimens

Patients on the waiting-list for non-urgent surgery at Hammersmith Hospital were sent a letter asking them to help in a research project by bringing a fresh faecal specimen with them on admission; instructions for collecting and delivering it were given. With the letter went a cotton-wool swab mounted in the lid of a plastic universal container. When the patient arrived in the ward the specimen was delivered immediately to the laboratory. Requests went to patients likely to stay a week or more in hospital; they came for a wide variety of surgical procedures, the commonest being repair of hernia or prolapse, or hysterectomy. Patients having gastrointestinal surgery other than hernia repair were not included. There were more women (68%) than men; ages ranged from 17 to 74, and a majority (65%) were between 30 and 50. Most patients (70%) came from near the hospital, postal district W.12, and adjoining areas. The other 30 came from other parts of London and the nearer suburbs.

Requests were sent during the first half of 1968 and were stopped when the 100th satisfactory admission specimen was received.

All patients were in large, open wards partially subdivided into groups of six beds. Each patient was visited by a laboratory worker who gave a brief explanation of the investigation and inquired whether the patient had been in hospital or had had any antibacterial drugs (pills, capsules, or medicine) in the previous six months; where there was any doubt about whether a patient had had antibacterial therapy or about what drug he had had, inquiry was made of his general practitioner. The patient was given another specimen container and asked to collect a further faecal specimen after operation and before leaving hospital. Despite willing collaboration of patients and staff, second specimens were obtained from less than half the

patients. Some were discharged before they could be interviewed and others went home without having defaecated since their operation.

Because most of the patients in the series were in hospital for less than two weeks, a further 20 faecal specimens were collected from other patients who had been more than three weeks in hospital, and who were not currently receiving any antibacterial drug.

### Isolation and Identification of Resistant Bacteria

The cotton-wool swab, which had been thoroughly soiled with faeces by the patient, was rubbed all over the surface of one MacConkey agar plate and spread in the conventional way on another. The latter was to show whether the specimen was satisfactory in containing about normal numbers of coliform bacteria. A Multodisk was placed on the surface of the first plate, and, in addition, a nalidixic acid disc was placed near its edge; the inoculum was about 1-5 mg. of faeces. Both plates were incubated at 37° C. overnight. Next day a record was made of the appearance of the plates, in particular of growth resistant to any of the drugs incorporated in the filter paper discs, by comparison with a "control" plate of drug-sensitive *E. coli* K12. Resistant growth sometimes appeared as isolated colonies within a zone of inhibition; sometimes no inhibition of growth could be detected round one or more of the discs. Quantity of growth between these extremes was recorded by an arbitrary scoring method, to give an estimate of the proportion of the total growth resistant to each drug. Scoring was based on control cultures inoculated with known proportions of sensitive and resistant organisms and its accuracy checked by sensitivity-testing colonies isolated from the drug-free faecal cultures. The flora was remarkably homogeneous. Swabs taken from different areas of large faecal specimens collected in hospital always gave the same score.

Resistant growth was purified by plating first on medium containing the relevant drug and then on drug-free medium. MacConkey agar was used except with the sulphonamide, which was incorporated in lysed blood agar. Pure cultures were identified by tests in current use in the department (Darrell, 1967) and their resistance patterns determined by the Multodisk. All resistant strains were tested for resistance transfer.

### Transfer of Resistance

Each resistant culture was grown overnight in broth; one drop (about 0.05 ml.) was added to a fresh 5-ml. broth already inoculated with 0.5 ml. of an overnight broth culture of *E. coli* K12, nalidixic acid resistant (Nal<sup>r</sup>). If the culture to be tested for resistance transfer was resistant to nalidixic acid, K12 resistant to 1,000 µg. of streptomycin (S<sup>r</sup>) per ml. was used instead.

The mixed cultures were incubated at 37° C. overnight, and a loopful was streaked on a series of plates containing nalidixic acid, 50 µg./ml. (or streptomycin, 1,000 µg./ml.), as well as each separate drug to which the test (donor) culture was resistant. The medium used was MacConkey agar except with sulphonamide, when it was lysed blood agar. Heavy growth (defined for this purpose as >100 colonies) on any of the drug-containing plates was taken as evidence that resistance to that drug had been transferred to the recipient K12. Where there was only a small growth, colonies were purified, identified by their nutritional requirements as *E. coli* K12, and their drug sensitivity was tested by Multodisk. They sometimes proved not to be K12, but mutant clones of the test culture, resistant to the drug (nalidixic acid or streptomycin) used to select K12, but there were never more than a few such colonies on control plates inoculated with pure cultures.

The mixed cultures were diluted 1:10 in fresh broth and reincubated overnight; where no transfer of resistance was demonstrated from the first plating, the mixtures were centrifuged and the deposit (about 10<sup>9</sup> bacteria) was spread on drug-containing selection plates. Small numbers of recipient bacteria resistant to S, T, C, or K were detectable from this heavy inoculum, but ampicillin and sulphonamides could not be used to select resistant bacteria in the presence of a large excess of sensitive ones (J. T. Smith, 1969), and on these drugs the 48-hour mixed cultures were streaked out.

**Results**

**Drug-resistant Bacteria from Outside Hospital**

Of 100 preadmission specimens 70 yielded resistant coliform bacilli of some kind and 52 yielded resistant *E. coli* (Table I). Resistant bacteria were present in large numbers (25–100% of the total growth) in 36 specimens, in most of which (28) it was resistant *E. coli* which predominated. Frequently there was more than one species of resistant bacteria. Table I shows the incidence of isolation of resistant coliform bacteria of any kind, of resistant *E. coli*, and of resistant strains of other genera in each group of specimens—preadmission, postadmission from the same patients, and specimens from other patients who had been over three weeks in hospital. It also shows whether resistant bacteria were present as over 25% of the total flora cultured.

The excretion of resistant bacteria was not usually correlated with previous antibacterial therapy. Information about therapy was complete for 88 patients, of whom only 13 (15%) had received any relevant drug during the previous six months. Of these, nine were excreting bacteria resistant to the drugs which they had taken (penicillins, tetracyclines, or sulphonamides), which is a proportion no higher than for the group as a whole, and in only two of these cases did the resistant bacteria represent a large proportion of the faecal flora. Only two patients had taken antibiotics within one month of admission; one of them was excreting large numbers of bacteria resistant to the relevant drug, the other was not.

*Resistant E. coli.*—Altogether there were 81 different resistant *E. coli* strains, since many people excreted strains with more than one pattern of resistance. The resistance most commonly encountered in *E. coli* were to the sulphonamides and tetracyclines, and multiple resistance was commoner than resistance to a single drug (Tables II and III). Strains with multiple resistance were as likely as others to be present in large numbers in the faeces. There were no *E. coli* resistant to polymyxin or nalidixic acid. Strains from four people showed some resistance to nitrofurantoin, in no case related to a history of treatment with this or related drugs.

*Other Resistant Species.*—From the 43 people who, before admission, excreted resistant coliform bacilli other than *E. coli* there were isolated 30 strains of resistant *Klebsiella* species, 11 *Proteus* species, 4 *Enterobacter*, 7 *Citrobacter*, and 5 *Pseudomonas aeruginosa*. These bacteria were less frequently present

TABLE I.—Isolation of Drug-resistant Bacteria from Faeces

Specimens from:	No. of Specimens	All Coliform Genera		<i>E. coli</i>		Other Coliform Genera	
		Total Incidence	Over 25% of Yield	Total Incidence	Over 25% of Yield	Total Incidence	Over 25% of Yield
Patients before admission .. ..	100	70	33	52	28	43	15
Same patients after admission ..	47	33 (67%)	20 (42%)	27 (55%)	18 (38%)	24 (50%)	7 (15%)
Other patients over 3 weeks in hospital	20	16 (80%)	10 (50%)	13 (65%)	9 (45%)	10 (50%)	4 (20%)

TABLE II.—Resistance Determinants of *E. coli*

Faecal Specimens from Patients	Total No.	Sensitive Strains Only	No.* of Patients Excreting Strains Resistant to:					
			A	S	T	C	K	Su
Before admission .. ..	100	48	17	27	34	8	1	38
After admission .. ..	47	20 (42)	4 (8.5)	9 (19)	17 (36)	2 (4.2)	1 (2.4)	19 (40)
Other patients over 3 weeks in hospital	20	7 (35)	7 (35)	9 (45)	10 (50)	5 (25)	2 (10)	9 (45)

\*Percentages in parentheses.

TABLE III.—Patterns of Resistance

Strains of:	Resistance Pattern	No. of Isolations from:				Transferred Resistance to K12
		Pre-admission Specimens (100)	Post-admission Specimens (47)	Specimens from Patients over 3 Weeks in Hospital (20)	Total Specimens (167)	
<i>E. coli</i>	T	16	10	4	30	18
	Su	10	10	2	22	6
	S Su	10	3	1	14	8 (1)*
	S T Su	6	4	3	13	9
	T Su	8	2	0	10	6 (5)
	S T	4	1	0	7	6 (3)
	A S T C Su	3	2	2	7	7 (1)
	A	4	2	1	6	1
	A S Su	4	0	0	4	0
	A S T Su	3	1	1	4	4
	S T C Su	3	0	0	4	4
	A T	2	1	1	3	2
	A Su	2	1	0	3	2
	Other patterns	4	1	7	12	11 (1)
		Total	81	36	22	139
<i>Klebsiella and Enterobacter</i>	A	18	10	3	21	0
	A Su	4	6	1	11	0
	A with various combinations of S, T, C, K, Su, Nal	12	12	3	27	4
	Total	34	28	7	59	4
<i>Citrobacter</i> <i>Proteus</i> <i>Ps. aeruginosa</i>	Various patterns	7	1	0	8	0
		11	6	4	21	1
		5	2	1	8	0

\* Number of strains which transferred only part of their resistance pattern is given in parentheses.

in large numbers (Table I) and their commonest patterns of resistance were different from the *E. coli* strains (Table III).

### Drug-resistant Bacteria Isolated after Admission

No very great change was found in the drug resistance of the bowel bacteria after a short stay in hospital (Tables I and II).

*Resistant E. coli.*—The numbers of strains isolated from post-admission specimens and their patterns of resistance were similar to those for preadmission specimens, but resistant *E. coli* were present in large numbers (25–100% of the total flora) in more of the post-admission specimens (Tables I and II).

*Other Resistant Species.*—No important increase in the carriage of resistant *Klebsiella*, *Enterobacter*, *Proteus*, or *Pseudomonas* species was found in warded patients; strains of these genera isolated after admission were similar in their range of resistance to those in preadmission specimens.

*Changes in Bowel Flora after Admission.*—Patients from whom two specimens were cultured can be classified into four groups according to whether resistant or only sensitive bacteria were recovered from their faeces (Table IV). Evidently patients in group 2 had acquired resistant bacteria in hospital, those in group 4 had lost them, while those in group 1 showed no change in this respect. Patients in group 3, who constituted the majority, excreted resistant bacteria in both specimens; acquisition of resistant coliforms by this group was shown if the second specimen yielded a higher proportion of resistant bacteria than the first or of bacteria resistant to a wider range of drugs. Of the 47 patients from whom pre- and post-admission specimens were cultured a total of 20 (43%) had acquired a more resistant faecal flora, 18 (38%) showed no change, and 9 (19%) had a less resistant flora after their stay in hospital. Comparable figures for *E. coli* alone are: more resistant 17 (36%), no change 24 (53%), less resistant 6 (13%). The average time in hospital between specimens for the whole group was 8.6 days. Those patients who had acquired a more resistant flora had generally been in hospital rather longer (average 9.8 days) than those who had not (average 7.7 days). Thus there was a tendency to acquire resistant bacteria in hospital (Table V).

TABLE IV.—Patients Classified by Acquisition or Loss of Resistant Coliform Bacteria

Group	Resistant Bacteria Isolated from Specimen:		No. of Patients/Group	
	1	2	For All Coliforms	For <i>E. coli</i>
1	—	—	9	17
2	—	+	6	10
3	+	+	28	18
4	+	—	4	2

TABLE V.—Changes in Enteric Flora After Admission to Hospital

	All Coliforms	<i>E. coli</i>
More resistant .. ..	20 (43%)	17 (36%)
No change .. ..	18 (38%)	24 (53%)
Less resistant .. ..	9 (19%)	6 (13%)

Acquisition of resistant bacteria was not related to antibacterial therapy. Twelve patients were given antibiotics between the first and second specimens, by mouth in all but one case. The bowel flora of four showed increased resistance, of five less resistance, and in three there was no change. With these small numbers possible different effects of different drugs could not be detected.

### Resistant Bacteria from Long-term Patients

Resistant strains of *E. coli* were isolated from a higher proportion and in larger numbers from this group of patients, but there was no marked difference in their carriage of resistant strains of other coliform genera (Table I). Eight of these 20 patients had been treated with antibiotics (six by mouth) but the carriage of resistant bacteria was not related to treatment; treated and untreated patients excreted resistant bacteria in similar proportions. Nor did the length of time in hospital beyond three weeks alter the picture; half of these patients had been in hospital between three and five weeks and the others between 5 and 12 weeks, but no more resistant bacteria were isolated from the latter.

### Resistance Transfer

*E. coli.*—A majority (61%) of the 139 resistant strains of *E. coli* transferred resistance in mixed culture to K12 (Table III). The greater the multiplicity of resistance, the greater was the likelihood that some or all of the resistance determinants would be transmissible. All *E. coli* strains resistant to four or more drugs transferred resistance to K12. The proportion transferring resistance was the same for each group of patients. In most cases (78 out of 85) transfer was demonstrated after overnight mixed growth of donor and recipient; only seven more positive results were obtained by incubating the mixtures for 48 hours and plating a heavier inoculum (see Methods section).

*Other Genera.*—Transfer of resistance to K12 was demonstrated from only a small proportion of strains of *Klebsiella*, *Enterobacter*, and *Proteus* and none of *Citrobacter* or *Pseudomonas*. Among these genera even strains resistant to four or more drugs did not usually transfer resistance.

### Discussion

We found the strikingly high rate of carriage of drug-resistant *E. coli* of 52% by people in their own homes, mostly without any recent exposure to antibacterial drugs and with no more experience of a hospital environment than a visit to the out-patient department. A high proportion (28%) of these were excreting large numbers of resistant *E. coli*. Resistance was determined by transmissible R factors in 60% of strains, and extrachromosomal genes probably accounted for a higher proportion, since transmissibility is not always an integral function of resistance plasmids (Anderson, 1965, 1968b). Resistance to tetracycline and the sulphonamides was commonly present, either alone or both together, and in either case was often accompanied by resistance to streptomycin.

The carriage of resistant bacteria other than *E. coli* in 43% of patients before admission to hospital is not surprising. Genera such as *Klebsiella*, *Enterobacter*, *Proteus*, and *Pseudomonas* are characteristically resistant to certain antibacterial drugs and are recognized intestinal commensals of man. They were not usually found in large numbers, and their resistance was seldom transmissible to *E. coli*. Their patterns of resistance show, however, that many intestinal bacteria have acquired drug-resistant genes in addition to those characteristic of their genus.

Changes in the bowel flora in respect of drug resistance after admission to hospital were not dramatic in our patients, but a tendency to acquire resistant bowel bacteria in hospital was evident, and in particular resistant *E. coli* were isolated in large numbers from a higher proportion of patients after admission to hospital. Our methods did not show whether this was the result of acquisition of resistance in initially sensitive bacteria or replacement of the original strains. Acquisition of resistant strains of *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, or

*Pseudomonas* occurred in some cases, but carriage rates for these genera were no higher after admission to hospital.

No characteristically resistant population of coliform bacteria was found in faecal specimens collected in hospital as compared with those from outside. Cultures were not made from patients currently being treated with antibacterial drugs. No evidence of emergence of resistant bacteria after completed therapeutic courses was found, but this survey was not suitable for the study of the effects of drugs on the faecal flora, since most of the patients received none. Antibiotics are used in acute infections which are a contraindication for non-urgent surgery and so would not have been expected in our patients, who were chosen to represent, as nearly as possible, the normal healthy population.

The high incidence of drug resistance determined by R factors in non-pathogenic faecal *E. coli* of townspeople outside hospital confirms some other recent reports (Salzman and Klemm, 1966; Lewis, 1968; Moorhouse and McKay, 1968; Moorhouse, 1969), but from bushmen living in areas remote from civilization, Maré (1968) isolated no *E. coli* with multiple or transmissible resistance, though he did find strains with non-transmissible ampicillin resistance.

Is it possible to say whether the incidence of resistance in normal bowel bacteria rose steeply in parallel with resistance in enteropathogenic bacteria? Few records are available and no large collections of normal flora are preserved. D. H. Smith (1967) demonstrated a transmissible R factor in one out of 30 strains of enteric bacteria lyophilized before 1950. This seems to indicate that R factors were not rare before the use of antibiotics in medicine, but one strain provides inadequate evidence, and published data over the years show that the incidence of resistance in normal *E. coli* strains has risen like that in shigella and salmonella types, but the baseline and the time scale of the rise are uncertain.

Resistance, determined by R factors, to sulphonamides, tetracyclines, and streptomycin is now common in the normal flora, resistance to ampicillin fairly common, and resistance to chloramphenicol and kanamycin less so. The frequency of resistance to particular drugs probably reflects their use over the years, but it cannot be assumed that the intestinal bacteria of townspeople in the preantibiotic era resembled that of present-day African bushmen. If normal bowel bacteria have acquired R factors on a large scale in the past 10 years, then urinary infections would be expected to be increasingly caused by resistant strains. There is evidence for this in hospitals and perhaps also in domiciliary practice (Robertson, 1968).

The incidence of resistance in strains of *E. coli* causing hospital infections appears to have risen to reach a plateau in the 1960s. Whether the same is true of intestinal *E. coli* in normal people remains to be seen.

It is not possible to determine the origin of the resistance. The faecal bacteria of pigs and fowl fed antibacterial drugs are more uniformly drug-resistant (R+) than human intestinal bacteria, and R factors carried in bacteria may have spread from farm animals to man by means of raw meat and meat products introduced into the kitchen (Smith and Halls, 1966; Walton, 1966; Anderson, 1968a, 1968b; H. W. Smith, 1968). Whether this has constituted an important or only a minor source of resistant bacteria in the human population cannot now be determined, since the same drugs are used in animals

and man, the same resistances encountered, and identification of non-pathogenic *E. coli* or of R factors is not accurate enough to allow epidemiological tracing of their passage.

The clinical importance of drug resistance, and of R factors, in coliform bacilli obviously depends on the importance of these bacteria in causing infective disease and on the part played by the relevant drugs in the treatment of such disease. In hospital medicine there is no doubt of the importance of coliform infections of the urinary tract, of surgical wounds, and of the blood stream (Finland, Jones, and Barnes, 1959), and outside hospital *E. coli* in the urinary tract is one of the commonest causes of infective illness. The prevalence of resistance makes it more than ever necessary to determine the sensitivity of bacteria causing infections of all kinds. R factors are important because they limit the choice of therapy. Drugs to which coliform bacilli are still usually sensitive, such as kanamycin or gentamicin, must be brought into use, which will in turn have the effect of favouring resistant bacteria and may result in the dissemination of R factors conferring resistance to increasing numbers of drugs. Resistance, usually determined by R factors, may still be on the increase. Any measures which may be introduced to control or eliminate the spread of R factors will be assessable only if their incidence is followed over a period of years in normal intestinal bacteria as well as in enteric pathogens.

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