been accompanied by a significantly reduced rate of total rejection in our patients. We cannot, of course, be certain that the introduction of the initial higher dose of azathioprine and of the two early boluses of methylprednisolone did not also contribute to the improved results. Nevertheless, the improvement was in keeping with our previous finding of benefit from transfusion and HLA-B matching.

The object of a kidney-sharing scheme must be to ensure that the recipients of the organs receive the maximum benefit and that rejection rates are kept as low as possible by suitable tissue matching. Furthermore, the shortage of donor organs and the cost of matching, sharing, and transporting kidneys demands that the best use should be made of available resources.

In our patients matching for B locus antigens was more important than that for A locus antigens and (in a small sample) one DR locus antigen. The accuracy and completeness of the data are likely to be greater in a single-centre analysis than in multicentre national or international studies. We invite other centres to examine their data to see if they agree or disagree with this conclusion. If there are no conflicting results we urge the UK Transplant Service to change over to B locus matching as its main criterion for distributing kidneys pending further information on the value of full DR matching.

We are grateful to Mrs R Grieveson, who is responsible for our unit records, for this service and for secretarial help.

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# Trimethoprim resistance in hospitals

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## Abstract

**During November 1980 to April 1981, 1561 urinary tract pathogens were collected from Turku City Hospital, Turku University Central Hospital, and Kuopio University Central Hospital. Resistance of the strains was tested by agar-plate dilution against trimethoprim, sulphamethoxazole-trimethoprim, sulphamethoxazole, ampicillin, and nitrofurantoin. Resistance to trimethoprim (⩾8 mg/l) occurred in 8·6-12·2% of strains from the university hospitals (Pseudomonas excluded) and 38·3% of strains from Turku City Hospital. Resistance of Escherichia coli occurred in 4·1-6·2% of strains from the university hospitals and 21% of strains from Turku City Hospital. Proteus mirabilis was the most resistant of the clinically important bacterial species with resistance to trimethoprim in 29-78%.**

**Attention is called for in defining the type of hospital used for a particular study: bacterial resistance in different hospitals cannot be compared direct and one hospital is not necessarily representative for a whole country. After seven years' use of plain trimethoprim the prevalence of resistance in the two university hospitals in Finland was similar to that in a London hospital just before plain trimethoprim was registered for use in Britain.**



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## Introduction

Trimethoprim is now registered in several countries for prophylaxis and treatment of urinary tract infections: in Finland this happened as early as 1973.[1] In 1980 we found that 31·6% of bacterial strains isolated from hospital patients (*Pseudomonas* excluded) were resistant to trimethoprim.[2] The specimens were received from Turku City Hospital and the health centre wards in Turku. We have now compared the prevalence of resistance in Turku City Hospital with that in two university hospitals. We also studied bacterial resistance to sulphamethoxazole-trimethoprim, sulphamethoxazole, ampicillin, and nitrofurantoin.

## Materials and methods

Consecutive urinary samples were collected during November 1980 to April 1981, from Turku City Hospital for six months and from Turku University Central Hospital and Kuopio University Central Hospital for two months in the beginning of the period. Only one specimen from each patient was accepted.

Strains were isolated by the dipslide technique (Uricult; CLED and MacConkey agars) and bacterial isolates identified by routine methods including the API 20E procedure.[3 4] Resistance of all bacteria to five antimicrobial drugs was tested by agar-plate dilution using PDM-ASM agar (Ab Biodisk, Solna, Sweden).[5] *Escherichia coli* K 12 and *Staphylococcus aureus* K 209 were inoculated as control strains on each plate. Minimum inhibitory concentrations (MIC) generally used in Scandinavia to determine the resistance breakpoints were applied (trimethoprim ⩾8 mg/l; sulphamethoxazole-trimethoprim (20:1)

$\geqslant$64 mg/l; sulphamethoxazole $\geqslant$512 mg/l; ampicillin $\geqslant$32 mg/l; nitrofurantoin $\geqslant$64 mg/l).[6 7] The strains were inoculated by multipoint inoculator (Denley) and the results read after 18 hours' incubation at 37°C.

The two university hospitals are similar, with all medical disciplines represented and with a relatively short duration of hospital stay (table I). Patients with chronic diseases are removed to the wards of health centres. Turku City Hospital, which includes the wards of the health centre of Turku, has four departments: infectious diseases, surgery, psychiatry, and geriatrics. Most of the samples from Turku City Hospital came from the psychiatric and geriatric departments, representing patients receiving long-term care.

TABLE I—*Numbers of beds and durations of stay in three hospitals*

| | Turku City | Turku University | Kuopio University |
|---|---|---|---|
| No of beds | 1171 | 1071 | 786 |
| Mean duration of hospital stay (days) | 36·9 | 7·0 | 6·4 |

## Results

Table II shows the distribution of species and number of strains collected from each hospital. *E coli* and coagulase-negative staphylococci were more common in the university hospitals than in Turku City Hospital ($p<0.005$ and $p<0.001$; binomic $t$ test), whereas *Proteus mirabilis* and *Providencia* were more common in the city hospital ($p<0.001$).

In total resistance (all strains isolated except *Pseudomonas*) against trimethoprim a clear difference between Turku City Hospital and the university hospitals was observed ($p<0.001$) (table III). A total of 38·3% of strains from Turku City Hospital were resistant to trimethoprim $\geqslant$8 mg/l compared with 12·2% and 8·6% of strains from the university hospitals (difference between the two university hospitals not significant). Strains of *E coli* from Turku City Hospital included 21% that were resistant to trimethoprim, strains from Turku University Central Hospital 4·1%, and strains from Kuopio University Central Hospital 6·2% (table IV). *Pr mirabilis* was the most resistant species with 78%, 73%, and 29% of strains resistant, respectively. In Turku City Hospital 82% of *Providencia* strains were resistant, but only 11 strains were isolated. High resistance to trimethoprim (MIC >1000 mg/l) occurred in 22·9% of strains from Turku City Hospital and 2·7% and 3·6% of strains from the university hospitals (table III). The prevalence of Gram-negative rods highly resistant to trimethoprim was 60% of all strains resistant to trimethoprim (MIC $\geqslant$8 mg/l) in Turku City Hospital and 38% of all strains in both university hospitals.

The prevalence of strains resistant to sulphamethoxazole-trimethoprim, sulphamethoxazole alone, and nitrofurantoin was higher in Turku City Hospital than in the university hospitals ($p<0.001$), whereas no differences were observed in the resistance to ampicillin ($p>0.10$) (table III).

During the year before the study consumption of trimethoprim in the city hospital was four times more than in Turku University Central Hospital and 6·6 times more than in Kuopio University Central Hospital (table V). Similarly, consumption of nitrofurantoin in Turku City Hospital was twice as much as in Turku University Central Hospital and 6·9 times more than in the Kuopio hospital. Ampicillin was used very little in the city hospital and consumption of sulphonamide-trimethoprim combinations and of sulphonamides alone was similar in the three hospitals. In Kuopio the most common combination of trimethoprim and sulphonamide was sulphadiazine-trimethoprim and in the Turku area sulphamethoxazole-trimethoprim.

TABLE II—*Distribution of species in three hospitals*

| | Turku City | | Turku University | | Kuopio University | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| *Escherichia coli* | 358 | 51·5 | 268 | 61·5 | 243 | 56·5 |
| *Proteus mirabilis* | 88 | 12·7 | 11 | 2·5 | 17 | 4·0 |
| *Klebsiella* | 67 | 9·6 | 28 | 6·4 | 33 | 7·7 |
| *Pseudomonas* | 52 | 7·5 | 25 | 5·7 | 21 | 4·9 |
| *Streptococcus faecalis* | 49 | 7·1 | 41 | 9·4 | 37 | 8·6 |
| *Staphylococcus* (coagulase-negative) | 25 | 3·6 | 35 | 8·0 | 45 | 10·5 |
| *Enterobacter* | 18 | 2·6 | 7 | 1·6 | 5 | 1·2 |
| *Citrobacter* | 14 | 2·0 | 6 | 1·4 | 7 | 1·6 |
| *Providencia* | 11 | 1·6 | | | | |
| Others | 13 | 1·9 | 15 | 3·4 | 22 | 5·1 |
| Total | 695 | 100·1 | 436 | 99·9 | 430 | 100·1 |

TABLE III—*Percentages of strains resistant to antimicrobial agents in three hospitals (Pseudomonas excluded)*

| | Turku City | Turku University | Kuopio University |
|---|---|---|---|
| Trimethoprim $\geqslant$8 mg/l | 38·3 | 12·2 | 8·6 |
| Trimethoprim >1000 mg/l | 22·9 | 3·6 | 2·7 |
| Sulphamethoxazole-trimethoprim ($\geqslant$64 mg/l) | 28·1 | 7·8 | 5·1 |
| Sulphamethoxazole ($\geqslant$512 mg/l) | 39·8 | 23·1 | 24·4 |
| Ampicillin ($\geqslant$32 mg/l) | 22·2 | 22·1 | 18·1 |
| Nitrofurantoin ($\geqslant$64 mg/l) | 12·3 | 4·6 | 3·7 |

TABLE IV—*Percentage of strains resistant to trimethoprim (MIC $\geqslant$8 mg/l) in three hospitals according to species, Pseudomonas excluded*

| | Turku City | Turku University | Kuopio University |
|---|---|---|---|
| *Escherichia coli* | 21 | 4·1 | 6·2 |
| *Proteus mirabilis* | 78 | 73 | 29 |
| *Klebsiella* | 46 | 18 | 15 |
| *Streptococcus faecalis* | 55 | 7·3 | 0 |
| *Staphylococcus* (coagulase-negative) | 72 | 43 | 20 |
| *Enterobacter* | 28 | 29 | 20 |
| *Citrobacter* | 50 | 17 | 0 |
| *Providencia* | 82 | | |
| Others | 31 | 33 | 0 |
| Total | 38·3 | 12·2 | 8·6 |

TABLE V—*Use of antimicrobial agents during 1980 (g/bed) in the three hospitals*

| | Turku City | Turku University | Kuopio University |
|---|---|---|---|
| Trimethoprim | 2·56 | 0·65 | 0·39 |
| Sulphonamide and trimethoprim | 14·07 | 19·59 | 11·29 |
| Sulphonamide | 2·81 | 3·92 | 3·40 |
| Ampicillin | 9·09 | 9·48 | 13·16 |
| Nitrofurantoin | 1·06 | 14·78 | 29·28 |

## Discussion

Our findings show how different bacterial resistance against antimicrobial agents may be in different hospitals, even within one city. That 31·6% of strains were resistant to trimethoprim in 1980[2] cannot therefore be taken as representative for Finland as a whole. The findings show that resistance in the two university hospitals had remained low, even after seven years' use of plain trimethoprim.

The level of resistance to trimethoprim observed by us was similar to that described by Hamilton-Miller *et al*, who reported 11·5% of strains resistant to trimethoprim in the Royal Free Hospital, London, at the end of 1979,[8] before trimethoprim was used in Britain. As early as 1975 Amyes *et al* had found resistance to trimethoprim in 8·1% of strains collected in hospital, and in 1977 this figure had risen to 11·6%.[9] During 1971-7 Grüneberg found sensitivity to trimethoprim at a level of 75-80%, and in 1974 the figure was 71·5%.[10] In 1977-8 we observed resistance to trimethoprim in 31-49% strains in different long-stay wards in Turku[11] and found the same prevalence in Turku City Hospital in this study. It will be interesting to see whether a plateau has been reached in this particular hospital, which mostly treats patients referred by other hospitals for long-term care and has a high consumption of trimethoprim and nitrofurantoin. Differences in bacterial resistance are apparently not due solely to differences in the drug consumption but also to factors such as the nature of the patient and of the hospital. For instance, two hospitals with the same consumption of trimethoprim in our other study showed very different patterns of resistance, the

resistance being strikingly lower in an oncology hospital than in a geriatric unit.[11]

Among strains of *E coli*, Busk and Korner reported a resistance of 2·5% in Denmark in 1976-7 before trimethoprim was in clinical use,[12] and Hamilton-Miller *et al* reported 7·1% resistance in Britain in 1978-9.[8] Our present figure in the university hospitals is 4·1-6·2%.

To facilitate comparison of the results obtained in different countries, MIC breakpoint values should be uniform. A value of 8 mg/l is best for trimethoprim, based on concentrations achieved in the urine and kidney after therapeutic doses. Using a breakpoint of 2 mg/l (as used by some workers[8]), we found a total resistance (*Pseudomonas* excluded) of 42·9% in Turku City Hospital, 15·3% in Turku University Central Hospital, and 12·2% in the Kuopio University Central Hospital. An MIC of 1000 mg/l is used only to define highly resistant strains, which usually show plasmid-mediated resistance.

Resistance to trimethoprim was transferable in about half of our highly resistant *E coli* strains (unpublished observations). Most of the strains with transferable resistance were collected from Turku City Hospital. Hamilton-Miller *et al* reported transferability in 25% of strains highly resistant to trimethoprim[8]; however, the type of wards was not explained.

Our findings call for attention in defining the type of hospital used for a particular study and show that bacterial resistance in different hospitals cannot be compared direct and that one hospital is not representative of a whole country. Secondly, our study shows that the total prevalence of strains resistant to trimethoprim $\geqslant 8$ mg/l in two large university hospitals in different parts of Finland is around 8·6-12·2%.

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# Variations in cancer mortality among local authority areas in England and Wales: relations with environmental factors and search for causes

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## Abstract

**Geographical variations in specific causes of mortality among the 1366 local authority areas of England and Wales as defined at 1971 were studied by examining extracts from death certificates held on computer tape. Five items of information on each death—year of death, age at death, sex, local authority area of residence, and the underlying cause of death, during the 11 years 1968-78—permitted a more detailed investigation than had been possible before.**

**Analysis of some early results of the study—including maps of mortality for pleural mesothelioma, nasal cancer, and bladder cancer—suggested that, despite the known limitations of death certification, systematic study of the mortality of small areas may give clues to aetiological factors in the environment. Analyses relating mortality to the distribution of environmental factors and examining disease profiles of each area may also provide clues. These will be followed up by other methods of study, such as case-control techniques.**



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## Introduction

There have been substantial variations in mortality from one part of Britain to another for at least 80 years.[1 2] With exceptions for certain causes, death rates are higher in the north and west than in the south and east. In the latest report on area mortality from the Office of Population Censuses and Surveys, covering the years 1969-73, overall mortality was shown to be about 20% higher in the North-western region than in the East Anglian.[3] Past studies of geographical variations in mortality have generally used large areas (such as regions or counties) or county and London boroughs and included deaths from only a limited number of years.[3 4] This has led to restricted investigation of the less common causes of death, particularly in small areas, so that there may be unsuspected geographical clues to causes of disease buried in the data. We have explored how known industrial carcinogens might have been detected in this way.