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SESSION I

Emergence of Antibiotic Resistance in Hospitals, 1935–1975

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A limited review of the changes in susceptibility of common bacterial pathogens to available antibacterial agents is presented. Significant developments in recent years include the following: (1) the emergence of *Streptococcus pneumoniae* with decreased resistance to penicillin and of some strains resistant to several antibiotics; (2) a decline in prevalence of multi-drug-resistant *Staphylococcus aureus* after 1960 following their increasing prevalence in the preceding years (these changes were associated with changes in phage types of the staphylococci); (3) the emergence of methicillin-resistant (and multi-drug-resistant) *S. aureus* and the marked differences in their prevalence in different areas (these changes also were related to appearance of new phages in those organisms); (4) an increasing resistance to multiple drugs among enterococci but not among viridans streptococci or among nonenterococcal group D streptococci; (5) the emergence of β -lactamase-producing *Neisseria gonorrhoeae*; (6) the emergence and spread of sulfonamide-resistant *Neisseria meningitidis*; (7) the occurrence of β -lactamase-producing strains of *Haemophilus influenzae* and occasional strains resistant to chloramphenicol; (8) the focal occurrence of chloramphenicol-resistant *Salmonella typhi* in Vietnam and in epidemic form in Mexico; (9) the demonstration of marked differences in prevalence of resistance to multiple drugs in common pathogens to the most widely used antibiotics in different geographic areas. The dominant factor in the emergence and spread of antibiotic-resistant bacterial pathogens, whether in hospital wards or in the community, is clearly the intensive use of the antibiotic agents to which resistance emerges and then spreads.

The literature on the emergence of antibiotic-resistant bacteria was extensively reviewed in 1955 [1], and the effects of chronic intake of antibiotics, particularly in animals fed low levels of the agents to increase their rate of growth and improve feed efficiency, were also reviewed at that time [2]. I do not propose to present a similarly thorough review of the vast literature that has accumulated since that time. Instead, I wish here to review some of the important changes in the patterns of resistance observed mostly in hospitals, particularly at the Boston City Hospital and in the last two decades, although some of this material was presented in 1972 [3]. Great advances have been made in recent years in elucidating the mechanisms of resistance to anti-

microbial agents, but these developments will be covered by other participants at this symposium.

Methods

Data demonstrating changes in susceptibility of bacteria are usually presented as the results of tests of groups of strains of relevant species collected over a specified period and compared with results of similar tests of comparable strains collected at other periods, or in other places at the same or different times. The results are presented in tables giving the number or percentage of strains inhibited (or killed) by increasing concentrations of the antibacterial agents expressed as the minimal inhibitory concentration (MIC) or minimal bactericidal concentration (MBC). If standardized disk susceptibility tests are used, the diameters of zones of inhibition, instead of the MIC, are measured.

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Changes in susceptibility are more readily appreciated if the quantitative data (MICs or MBCs in serial dilution tests or zone diameters in disk diffusion tests) are presented graphically by charting the number or percentage of strains on the ordinate against the MIC, MBC, or zone diameter on the abscissa. When several such plots are superimposed, the resulting distributions may be difficult or even impossible to compare. This difficulty is largely obviated by the use of the cumulative percentage of distribution as the ordinate, which usually permits comparisons of several curves at a glance. The difference was clearly demonstrated in our earliest presentation of data accumulated before 1950 on the susceptibility of various coliform bacteria to all of the antibiotics that were available at that time [4]. The use of an inocula-replicating apparatus, such as that of Steers et al. [5], permitted the more efficient performance of quantitative dilution tests of large numbers of strains on suitable solid media.

Such graphic representation of results of tests for susceptibility also permits comparisons of various other factors such as changes in media; size of inoculum; and variations among strains of the same or different subspecies, strains from different sources, and particularly strains of the same species collected and tested under comparable conditions at different times with the same antibiotic. In addition, the activity of any antibiotic against strains of different species may be compared, thus providing a sort of "antibacterial spectrum" of that antibiotic. This last use produced such a spectrum of spectinomycin, which showed it to be more active against *Neisseria gonorrhoeae* than against all other common pathogens, and this antibiotic has, in fact, been used as an alternative treatment for uncomplicated gonorrhea [6].

The simple and most widely used statistical methods that are available to evaluate the significance of differences between sets of data are readily applicable to data derived from susceptibility tests when the distribution of the data is normal, or nearly so, or at least when the data extend over a narrow or moderate range. However, with bimodal, trimodal, or very wide ranges of distribution, or with different proportions that are very highly resistant, these simple statistical

methods are not applicable. Under these conditions the graphic representations using cumulative percentage of distribution are most helpful and generally adequate for clinical and epidemiological purposes; the method has therefore been generally accepted and used.

Limitations of space do not permit inclusion of the detailed data or of the large number of text figures shown during the verbal presentation, but reference to the sources of the data will be provided for the interested reader. As in many of the earlier reviews, most of the changes in the patterns of susceptibility will be presented for each of the most common and most important bacterial species observed over the years at Boston City Hospital.

Early Patterns of Resistance

Pneumococcus

Inspection of the curves representing the distribution of MICs for the pre-1950 strains of *Escherichia coli*, and also those for *Enterobacter (Aerobacter)*, showed that individual isolates were inhibited over wide ranges of concentrations of four of the antibiotics tested, although they were uniformly susceptible within a narrow range of concentrations of two polymyxins and resistant to high concentrations of bacitracin [4]. By contrast, all of the strains of pneumococci (*Streptococcus pneumoniae*) isolated before June 1949 were inhibited over a narrow range of concentrations of each of the same seven antibiotics [7]. A similar distribution over narrow ranges of concentrations of each of 11 antibiotics (including six of those employed in the earlier study) was demonstrated for inhibition of strains of pneumococci isolated in 1953–1955 [8]. The MICs of each antibiotic against isolates in the two periods were the same except with bacitracin, for which a larger proportion of isolates required concentrations that were higher (but within the same range) in the later period.

More recently, subtle changes in susceptibility patterns were noted at Boston City Hospital when pneumococci isolated in 1972 and 1973 were tested with a larger number of antibiotics, including several analogues of penicillins, cephalosporins, tetracyclines, aminoglycosides, and

others [9]. With the inoculum usually used (namely, a 10^{-3} dilution of culture or about 10^3 cfu/ml), clear-cut bimodal distributions were noted in the MICs of all of the penicillinase-resistant penicillins except nafcillin. This pattern was seen more strikingly with undiluted culture ($\sim 10^6$ cfu/ml), and with the larger inoculum the MICs of nafcillin and penicillin G each showed a striking bimodal distribution. Only neomycin among the aminoglycosides showed a wide range of MICs (0.4–100 $\mu\text{g/ml}$) with the 10^{-3} inoculum, and all strains were highly resistant (≥ 100 $\mu\text{g/ml}$) when the undiluted cultures were used.

From other hospitals and communities in the United States, and particularly in Australia, New Guinea, and the United Kingdom, there have been a number of reports of pneumococci isolated from both cases and carriers with increased resistance to one or more antibiotics, including penicillin, tetracycline, erythromycin, lincomycin, and chloramphenicol; many of those strains were resistant to multiple drugs [10–17]. The resistant pneumococci were of diverse capsular types, although individual types predominated in some communities. Some of the patients infected with such antibiotic-resistant strains showed poor responses or failures to respond to therapy with those antibiotics. As was to be expected, strains resistant to one tetracycline were also resistant to other tetracycline analogues. To my knowledge, production of penicillinase by these resistant pneumococci has not been reported to date.

β -Hemolytic Group A Streptococci

The life-saving therapeutic effect of sulfanilamide, the chemotherapeutic agent that ushered in the modern antibacterial era, was first demonstrated against serious infections due to hemolytic streptococci. Subsequently, the extensive and continuous use of the greatly improved sulfanilamide derivative, sulfadiazine, in the prophylaxis of streptococcal infection and recurrences of rheumatic fever resulted in the emergence and rapid spread of strains that were highly resistant to sulfonamides. These strains, in turn, gave rise to extensive epidemics of severe streptococcal respiratory infections, particularly in military installations, and were responsible for a high mortality; these epidemics were terminated

only by the timely introduction of penicillin. The sulfonamide-resistant streptococci were limited to types 17 and 19, and only small proportions of sulfadiazine-resistant streptococci were reported from nonmilitary institutions; they were also restricted to group A, types 17 and 19 [1].

All strains of group A hemolytic streptococci isolated at Boston City Hospital before 1950 and tested for susceptibility to the seven antibiotics then available were susceptible within a narrow range of concentrations of each of these antibiotics [18]. Subsequently, strains isolated in 1953–1955 and tested with 11 antibiotics, including six of the seven previously used, showed similar patterns of susceptibility to all of these antibiotics except bacitracin, which showed a distinct bimodal distribution. A similar bimodal distribution was shown for the strains of group B streptococci tested at that time [19].

Tests of group A hemolytic streptococci isolated in 1963 demonstrated strains resistant to tetracyclines for the first time [20]. At that time only a small proportion of strains from patients at Boston City Hospital, but a larger proportion of those isolated at the same time in Syracuse, N.Y., were resistant to each of five tetracycline analogues with which they were tested. Additional strains of group A streptococci isolated in 1972 and tested with 65 antibiotics did show bimodal distributions of MICs of some penicillins and cephalosporins, but marked resistance to tetracyclines was not observed in these strains [21]. However, McCormack et al. did report tetracycline-resistant strains about 10 years earlier [22].

Group A streptococci resistant to tetracyclines have also been reported in the United Kingdom [23]. Here, too, cross-resistance among tetracycline analogues was noted. Of interest in this report was that the proportion of tetracycline-resistant β -hemolytic streptococci declined from 35% in 1965 to 9% in 1972.

From July 1962 through June 1963, increasing numbers of cases of group B streptococcal infections were seen at Boston City Hospital. The strains isolated from these cases showed striking bimodal distributions of MICs of all seven tetracycline antibiotics with which they were tested. Bacitracin, erythromycin, and lincomycin, but not penicillins or any of the other antibiotics tested, showed bimodal distributions of MICs with these group B streptococci [24].

Viridans Streptococci

This group of organisms (aerobic streptococci that are not β -hemolytic and not serogroup D) is the most common component of the normal oral flora and includes the organisms that most frequently cause subacute bacterial endocarditis but that seldom cause other focal infections. At least 12 separate biochemically (physiologically) defined species are recognized, all of which are generally found to be susceptible to penicillin [25].

Our first tests for susceptibility of strains of this group isolated at Boston City Hospital before 1950 showed bimodal distribution and broader ranges of MICs of penicillin, bacitracin, and streptomycin as compared with those exhibited by the group A β -hemolytic streptococci [18]. Biochemical differentiation of the viridans group was not carried out routinely at that time or since, and further studies of collections of these strains were not done except for occasional strains from clinical cases in relation to therapy [26]. However, there is considerable evidence that resistant strains of organisms of this group have not emerged either in cases of endocarditis [27, 28] or in the oral flora as a result of long-term use of penicillin for therapy [29] or prophylaxis [30, 31]. However, Sprunt et al. [31a] reported obtaining isolates of α -streptococci with an MIC of 5.0 $\mu\text{g}/\text{ml}$ from pharyngeal cultures from 55 (76%) of 72 patients after 13 days of oral penicillin prophylaxis. Strains of decreased susceptibility were also found, but significantly less frequently, after prophylaxis with im penicillin.

Enterococci (Group D Streptococci)

The first group of strains of enterococci that we tested—those isolated at Boston City Hospital before 1950—were classified largely on the basis of resistance to heat (60 C for 30 min). The MICs of penicillin, streptomycin, and bacitracin for these strains each showed a bimodal distribution [18]. In subsequent studies the enterococci were more fully differentiated by their biochemical reactions and were generally identified to be of serogroup D.

Enterococci isolated at Boston City Hospital from November 1953 through December 1954 were tested with 11 antibiotics, including six of

the seven used in the previous study [32]. Bimodal distributions were noted for penicillin (slight) and, more strikingly, for erythromycin, streptomycin, and the three tetracyclines that were then available. Each of the three species of enterococci that were differentiated exhibited the bimodal distribution for each of these antibiotics, but they differed in the proportions of sensitive and resistant strains, except with erythromycin, which showed a broad range of MICs that was quite similar for each of the three species [32].

When strains isolated from August 1968 through May 1969 were compared with those of 1953–1954 [33, 34], the only qualitative changes noted were that some of the recent strains of one species, *Streptococcus liquefaciens*, were highly resistant to penicillin, and that the MICs of erythromycin now assumed clearly bimodal distributions for each of the three subspecies, with the largest proportion of resistant strains among those of *S. liquefaciens*. Also, in the tests with chloramphenicol, whereas the strains of the three subspecies isolated in 1953–1954 were shown to be susceptible within the same narrow range of concentrations, the strains isolated in 1968–1969 showed a clearly bimodal distribution with widely different proportions of sensitive and resistant strains for each of the three subspecies. With tetracycline and each of three analogues, the MICs for the same three subspecies as well as for those of *Streptococcus faecium*, which were also included, all showed marked bimodal distributions with much smaller proportions of sensitive strains than among the 1953–1954 isolates. The 1968–1969 strains were nearly all resistant to streptomycin, whereas those isolated in 1953–1954 showed clearly different proportions of sensitive and resistant strains among each of the three subspecies [33, 34].

The 1968–1969 strains were tested with a number of more recently introduced antibiotics. Susceptibilities to ampicillin and penicillin were qualitatively similar, but all of the strains were clearly more susceptible to ampicillin, and strains of *S. faecium* showed the clearest bimodal distribution to both. Susceptibility to bacitracin appeared to decline steadily in the three studies [32–34]. The tests with penicillinase-resistant penicillins, cephalosporins, and aminoglycosides showed bimodal distributions of the 1968–1969

strains with only small proportions of sensitive strains [33, 34].

Enterococci isolated in 1971 and 1972 were also tested with each of a number of analogues of aminoglycosides, polymyxins, tetracycline, penicillins (including penicillinase-resistant ones), cephalosporins, lincomycins, and several other antibiotics [35, 36]. All of the tetracyclines, aminoglycosides, penicillins, cephalosporins, and lincomycins showed bimodal distributions with various proportions of strains sensitive and resistant to each of them. Only about 15% of these strains were resistant to chloramphenicol.

It is of interest that among more than 100,000 distinct clinical strains of the six more common species isolated at Massachusetts General Hospital during the six years 1971–1976, only the enterococci showed a distinct decline in the percentage of strains susceptible to cephalothin—from about 30% in 1971 to 9% in 1976 [37].

Nonenterococcal Group D Streptococci

During the past few years, various numbers of strains of group D streptococci from human infections have been identified and classified as nonenterococci [38]. Strains of these species, *Streptococcus bovis* and *Streptococcus mutans*, are of special interest because they are the cause of appreciable proportions of cases of group D streptococcal endocarditis [39, 40]. Moreover, their patterns of susceptibility to antibiotics are similar to those of viridans streptococci rather than to those of enterococci [39–41]. However, strains of *S. bovis* from two patients with infective endocarditis, although susceptible to penicillin G, oxacillin, and cephalothin in disk diffusion tests, were found to be resistant to the lethal effects of penicillin G, cefazolin, and vancomycin [42].

Staphylococcus

Strains of *Staphylococcus aureus* isolated from patients with infections at Boston City Hospital at various intervals through 1974 were tested for susceptibility to increasing numbers of antibiotics as those antibiotics became available. The strains isolated before 1950 and tested with seven

antibiotics already showed wide ranges of MICs of Aureomycin® (chlortetracycline) and streptomycin with bimodal distribution. Among these strains, 85% of those isolated before 1946 were highly sensitive to penicillin G within a narrow range; the rest required increasing concentrations ($\leq 25 \mu\text{g/ml}$). By contrast, of strains isolated in 1946–1949, only a small proportion were highly sensitive to penicillin G, and the others were inhibited by increasing concentrations over the entire range tested (up to $\geq 250 \mu\text{g/ml}$) [43]. Over the next three years, more clearly defined bimodal distributions of MICs of penicillin became evident with various proportions of highly resistant strains, depending on the source of the strains [44].

Clearly defined bimodal patterns were demonstrable in 1952 for penicillin, chlortetracycline, Terramycin® (oxytetracycline), and streptomycin, the penicillin resistance of *S. aureus* being clearly related to penicillinase production [45]. However, all 500 strains tested at that time were inhibited by low concentrations of erythromycin, which had not been used in therapy. In Chicago, Lepper et al. [46] also found that all strains of *S. aureus* isolated at that time from patients and personnel were highly susceptible to erythromycin, but most of them were markedly resistant to penicillin and chlortetracycline. They then withdrew the last two drugs from use and employed erythromycin for treatment of all susceptible infections. Over the next six months, strains with increasing resistance to erythromycin emerged and spread among patients and personnel until >70% of isolated strains were highly resistant to that antibiotic, and the proportion of penicillin- and chlortetracycline-resistant strains declined. Erythromycin was then completely withdrawn from use, whereupon the proportion of erythromycin-resistant *S. aureus* promptly declined, and resistance to penicillin and chlortetracycline increased with the resumption of their use.

Elsewhere, strains resistant to chloramphenicol were shown to spread rapidly among patients in a “burns ward” when that antibiotic was used to treat all wounds infected with penicillin-resistant *S. aureus* because most of those strains were resistant to chlortetracycline, which had been used in such cases. When chloramphenicol

col was withdrawn, the proportion of strains resistant to it declined sharply, but resistance to chlortetracycline again increased [47]. These findings were clear-cut demonstrations of the effect of intensive use of an antibiotic on the prevalence of resistance to that antibiotic. Dowling et al. [48] and Lepper et al. [49] had also shown that penicillin- and chlortetracycline-resistant strains of *S. aureus* acquired by patients within the hospital were spread to their family contacts after the patients were discharged.

Strains of *S. aureus* isolated at Boston City Hospital in 1955 showed a clearly bimodal distribution of MICs of erythromycin and also of the related macrolide, oleandomycin, although the latter had not been used in the treatment of patients in that hospital. The proportions of strains resistant to penicillin, streptomycin, and tetracycline had also increased over those observed in earlier studies. On the other hand, the 1955 strains were uniformly susceptible to 10 antibiotics that were new, that were not closely related chemically to antibiotics previously in common use, or that had been available but used only rarely. Chloramphenicol was the only widely used antibiotic to which few of the strains were resistant [50].

For the most widely used antibiotics (namely, penicillin, streptomycin, tetracycline, and erythromycin), a considerably greater proportion of resistant strains of *S. aureus* were isolated during or after treatment with (any) antibiotics as compared with those isolated from patients before they had received such treatment. A relationship between bacteriophage types and resistance was also noted among the 1955 strains. Thus, staphylococci of phage pattern 52/42B/81 were almost all resistant to penicillin, streptomycin, and tetracycline but sensitive to erythromycin, whereas of those lysed by other phages or not phage-typable, a considerable proportion were sensitive to the first three while many were resistant to erythromycin [50].

Further tests were done with staphylococci isolated from patients at Boston City Hospital in the fall of 1958; these isolates included strains obtained from outpatients. A smaller proportion of the latter strains were resistant to the antibiotics most commonly used within the hospital,

and the proportion of strains resistant to each of those antibiotics increased with increasing length of stay of the hospitalized patient before the sample was obtained for culture. Clear correlations of phage patterns and proportions of strains resistant to various antibiotics were again demonstrated [51].

A more extensive study involving 1,550 strains of *S. aureus*, most of them isolated in previous years but 40% of them isolated in 1959–1960, was carried out by Wallmark and Finland [52]. In this study the results of tests for susceptibility were correlated with the years the strains were isolated, their phage type, isolation from outpatients or hospitalized patients, duration of hospitalization before the culture was made, and prior treatment of the patient with antibiotics. A definite relationship was shown between the proportion of antibiotic-resistant strains and the length of previous hospitalization of the patients from whom the strains were obtained; the proportion increased with length of hospital stay and was highest in strains isolated at autopsy. The differences in proportions of resistant strains were shown to be related to the frequency, duration, and intensity of treatment with antibiotics, although the resistance of individual strains was not specifically related to the particular antibiotic(s) used to treat the patients from whom the strains were obtained. Changes in proportions of resistant strains were also related to changes in the prevalence of strains of various phage patterns from both outpatients and hospitalized patients.

These data were compatible with the concept that the increased prevalence of antibiotic-resistant staphylococci resulted in the reduction or elimination of sensitive staphylococci by antibiotic therapy, permitting resistant ones to persist and multiply. Increases in resistance of originally sensitive strains directed specifically to the antibiotic(s) that the patient was receiving could be demonstrated only infrequently.

Serious staphylococcal infections with bacteremia, both community-acquired and hospital-acquired, had increased markedly in incidence at Boston City Hospital during the 1950s [53]. This trend was reversed during the 1960s, as was the increasing resistance of *S. aureus* to the antibiot-

ic that had been in common use; these reversals were associated with the introduction and increasing use of methicillin and other semisynthetic, penicillinase-resistant penicillins and later the cephalosporins [54]. At Boston City Hospital [54], in the University Hospital in Seattle, Wash. [55], and in hospitals in England [56], although the proportion of strains resistant to penicillin G continued to be high, the proportion of strains also resistant to other antibiotics declined markedly among isolates from infections in hospitalized patients, whereas the prevalence of resistance in strains from community-acquired infections, which previously had been much less than the prevalence of resistance in hospital strains, increased [54, 55]. These changes in resistance of the staphylococci were associated with shifts in the prevalence of strains with various phage patterns [54, 56].

At the Boston City Hospital, resistance to methicillin was first noted by Kjellander et al. [57] among strains of *Staphylococcus epidermidis*; about 10% of 175 strains isolated from clinical specimens (mostly blood cultures) between September 1962 and February 1963 were methicillin-resistant (M-R). On the other hand, no M-R strains of *S. aureus* were demonstrable at that hospital at that time or among >1,000 additional strains tested before 1967. Subsequently, M-R strains of *S. aureus* were recognized and increased to 1.4% by 1968, although the proportion of M-R strains of *S. epidermidis* stayed between 9% and 10% [58]. The M-R strains of *S. aureus* in 1968 were also resistant to other penicillinase-resistant penicillins and cephalosporins, whereas most M-R *S. epidermidis* remained moderately susceptible to these agents. M-R strains of both *S. aureus* and *S. epidermidis* produced β -lactamase and grew in the presence of high concentrations of methicillin and cloxacillin. M-R strains of both were predominantly resistant to other commonly used antibiotics but susceptible to vancomycin. Only small proportions of the cells in the cultures of M-R strains, 2.0%–0.002% of *S. aureus* and 0.002%–0.0001% of *S. epidermidis*, were highly resistant to these penicillinase-resistant penicillins [58].

The M-R strains of *S. aureus* were isolated predominantly from hospital-acquired infections.

Evidence of patient-to-patient spread of infection was found during a ward outbreak of clinical cases, and a nurse was shown to be a nasopharyngeal carrier [59]. Elsewhere, M-R *S. aureus* assumed epidemic proportions: in Denmark 45% of bacteremic strains were reported to be M-R by 1971 [60], and in Zurich such strains accounted for $\cong 20\%$ of *S. aureus* isolated between 1966 and 1971 [61]. In Zurich [61] the M-R strains of *S. aureus* were isolated predominantly from patients with infections acquired within large hospitals but not from outpatients who had not recently been in such hospitals or from patients in several smaller hospitals. At Boston City Hospital, the M-R *S. aureus* were phage-nontypable, whereas in Europe the increased incidence of M-R and multiple antibiotic-resistant strains was associated with the demonstration of new phage types in those strains [56, 60, 61]; these types were not available to us for testing our strains.

Two additional recent developments regarding the antibiotic resistance of *S. aureus* should be noted. One is the demonstration of the frequent occurrence of what is called a new type of penicillin resistance manifested by failure of high concentrations of penicillins to kill strains that are inhibited by normal (low) concentrations. These organisms are deficient in the activity of enzyme required for autolysis, a deficiency that results from a large excess of an inhibitor of that autolysin. They have been called "penicillin-tolerant," and most such strains show cross-tolerance to the killing action of cephalosporins and vancomycin to which they are otherwise sensitive (inhibited). They are killed at normal rates by gentamicin, cycloserine, and rifampin. Only a small proportion ($\leq 7\%$) of cells within each culture show this tolerance. However, 44% of strains of *S. aureus* from bacteremic patients exhibited penicillin tolerance [62]. On the other hand, it was encouraging to note the report of Moellering [37], who found essentially no evidence of resistance of *S. aureus* to cephalothin at Massachusetts General Hospital over the six years 1971–1976.

The last groups of strains of *S. aureus* and *S. epidermidis* were isolated in 1973–1974 and tested with a 10^{-3} dilution of culture and with 65 antibiotics. The strains of both species appeared

to be more susceptible to the penicillins than in previous studies, and only a small proportion of *S. epidermidis* were resistant to some of the cephalosporins. All of the *S. aureus* were sensitive to all aminoglycosides (except for some that were resistant to streptomycin), whereas a small proportion of the *S. epidermidis* were resistant to all of the aminoglycosides except sisomicin and verdamicin. Only about 10% of *S. aureus* but 40% of *S. epidermidis* were resistant to all of the tetracyclines. All strains of both species were sensitive to chloramphenicol. Only a small proportion of *S. epidermidis* but none of *S. aureus* were resistant to erythromycin and lincomycin [63].

Neisseria gonorrhoeae

Resistance of gonococci to sulfonamides developed and spread after those agents became widely used [64, 65]. At Boston City Hospital, evidence of reversal to predominant sensitivity to sulfadiazine was obtained from strains of gonococci isolated in 1953–1954, after penicillin had gained universal use for therapy of gonorrhea [66], and all but a small proportion of strains isolated and tested there in 1973 were found to be susceptible to sulfamethoxazole [67].

After the late 1950s, however, increases in the range and mode of MICs of penicillin for clinical strains of *N. gonorrhoeae* isolated from penicillin treatment failures were generally encountered [68]. Decreases in susceptibility to tetracycline and streptomycin as well as to chloramphenicol and erythromycin were also noted [69]. Spectinomycin then became the drug of choice for treatment of penicillin-resistant gonorrhea [22], but strains resistant to spectinomycin have already been encountered [69].

Most important, however, has been the recent emergence of penicillin-resistant, β -lactamase-producing *N. gonorrhoeae*, first among United States servicemen returning from the Far East and among cases in Liverpool, England, and subsequently from many widely reported localities throughout the world. Fortunately, most of these strains appear to be susceptible to tetracycline, spectinomycin, and trimethoprim-sulfamethoxa-

zole, antibiotics that can be used as alternative therapy for cases due to such organisms [70].

Neisseria meningitidis

The marked susceptibility of meningococci to sulfonamides and the widespread use of these drugs resulted in a marked reduction in mortality from meningococcal meningitis and meningococcemias. When used for prophylaxis, these antibiotics were also highly successful in terminating and preventing epidemic spread of these infections.

Resistance to sulfonamides first came into prominence in 1964 among United States military personnel and their families residing in Germany; the infections there were with group B strains, whereas the predominant strains in previous epidemics were of serogroup A. In our last study of susceptibility of contemporary isolates of *N. meningitidis* to most of the antibiotics available at the time, strains from patients at Boston City Hospital (all group B, except one group C) were susceptible to each antibiotic within a narrow range of concentrations; they were also sensitive to sulfadiazine, whereas 10 strains obtained from cases in the military were all confirmed to be highly resistant to sulfadiazine [71]. A few strains isolated and tested in 1972 with sulfamethoxazole included some that were highly resistant, but most of them were sensitive to the drug [67].

Subsequent observations at the Center for Disease Control (Atlanta, Ga.) documented shifts in the prevalence of serotypes to a predominance of sulfadiazine-resistant group C strains and the appearance of substantial numbers of group Y strains, many of which were also sulfonamide-resistant. From 1972 to 1974 the proportion of sulfonamide-resistant strains of all types declined considerably; the proportion of resistant serogroup C strains declined from 82% to 69% [72]. There is still reluctance to recommend use of sulfonamide for prophylaxis for close contacts of patients with serious meningococcal infections [73]. More recently, a sulfonamide was successfully used for community-wide prophylaxis during an outbreak of serogroup B meningococcal disease [74].

During the last few years, however, work on prophylaxis has been directed toward the development of effective polysaccharide vaccines against the common serotypes of meningococci [75]. Vaccines directed against groups A and C have been successful; those directed against group Y seem promising [76], but against group B they have not been effective.

Haemophilus influenzae

Results of tests of susceptibility of groups of strains of *H. influenzae* isolated at Boston City Hospital in different years from the late 1940s [7] to 1972 [9] with use of increasing numbers of contemporary antibiotics have been reported. These tests were generally carried out on suitable chocolate agar under increased pCO₂ (candle jar) with use of undiluted culture ($\pm 10^6$ cfu/ml); results were read after incubation for 48 hr. On each of these occasions, all strains tested were inhibited within a relatively narrow range of concentrations by each of the antibiotics. Most of the strains tested in 1972, however, were resistant to sulfamethoxazole but highly sensitive to trimethoprim alone and even more sensitive (synergistically) when trimethoprim was combined with sulfamethoxazole [67].

As previously noted with respect to gonococci, the disturbing recent development has been the emergence of β -lactamase-producing strains of *H. influenzae* that are highly resistant to ampicillin, which had become the drug of choice for therapy of *H. influenzae* type b meningitis and bacteremic infections in children and also in the treatment of recurrent respiratory tract infection in adults [77]. By August 1977, about 8% of strains of *H. influenzae* isolated from children with otitis media in the Washington, D.C., area were resistant to ampicillin [78], and a similar proportion of resistant strains are currently being demonstrated in similar cases at Boston City Hospital (J. O. Klein, personal communication). Combinations of erythromycin and sulfisoxazole [78] or trimethoprim and sulfamethoxazole [79] were recommended for treatment of infections with ampicillin-resistant strains. Equally or even more disturbing have been the sporadic reports of strains of *H. influenzae* with R factor-

associated resistance to ampicillin, tetracycline, chloramphenicol, and kanamycin, singly or in combination [80].

Somewhat more encouraging have been the development of an *H. influenzae* type b polysaccharide vaccine [81] and the recent demonstration of the effectiveness of such a vaccine in producing specific antibodies and in preventing bacteremic disease in children older than 18 months during field trials in Finland [82].

Changing Ecology of Serious Bacterial Infections

Among the most significant and striking events associated with the availability and extensive use of the succession of highly active antibacterial agents were the changes in the relative frequency of occurrence of some of the common pathogenic bacteria as causes of serious disease. In the study of bacteremic infections carried out at Boston City Hospital during 12 selected years between 1935 and 1972 [53], the following changes were noted. (1) The proportion of all bacteremic infections that were due to pneumococci dropped from 32.5% in 1935 to 12.5% in 1955 and subsequently ranged between 13% and 15%. (2) Hemolytic streptococcal bacteremia other than that due to group D organisms accounted for 17.2% of all cases of bacteremia in 1935; the proportion dropped sharply after the sulfonamides came into use and then further when penicillin became available—to 0.7% by 1955. However, the proportion of these infections rose in later years to between 4% and 7%. (3) *S. aureus* accounted for 21% of bacteremic infections in 1935. This proportion increased to 36% by 1957 and then declined steadily to a low of 12% in 1972. (4) Most striking were the emergence and increasing occurrence of cases of bacteremia due to "enterobacteria," including enterococci, which increased from zero to 4%–7% after 1947, and of those due to gram-negative rods, the four most common groups of which (*E. coli*, *Proteus* species, *Klebsiella-Enterobacter*, and *Pseudomonas aeruginosa*) increased progressively from 12% (mostly *E. coli*) in 1935 to about 40% in 1969. Cases of bacteremia due to *Klebsiella-Enterobacter* and *Pseudomonas* were much more frequent among cases of hospital-acquired bacter-

emia than among those that were community-acquired. (5) Other "opportunistic pathogens" occurred in considerable numbers in the 1960s. For example, there were 58 cases of bacteremia due to *Herellea vaginicola* with 15 deaths in 1965, 27 cases due to *Mima polymorpha* with six deaths in the same year, 20 cases (five of them fatal) due to *Serratia marcescens* in 1972, and 30 cases of candidemia with 17 deaths, also in 1972. (6) Most of the changes in proportions of the common pathogens noted in all cases of bacteremic infections were found to be similar qualitatively but not always quantitatively to those in cases of acute bacterial meningitis [83] and acute purulent empyema [84] at Boston City Hospital during the same 12 selected years.

Similar changes in prevalence of various pathogens were reported for sepsis of the newborn at Yale-New Haven Hospital (New Haven, Conn.) over about the same years [85].

These changes in occurrence of the various pathogens were also associated with emergence and increased occurrence of multiple antibiotic-resistant strains of the newly emerging organisms.

Escherichia coli

As noted previously, the first report of tests of susceptibility of clinical isolates of *E. coli* at Boston City Hospital showed wide ranges of MICs and bimodal distributions for penicillin, streptomycin, chlortetracycline, and chloramphenicol and a narrow range for the polymyxins; only to bacitracin were all of the strains highly resistant [4].

Very soon after streptomycin became available for clinical trial, my colleagues and I demonstrated the rapid emergence of highly resistant variants (mutants) of *E. coli* and other gram-negative rods, not only in vitro, but also during treatment of urinary tract infections caused by these organisms in spite of the iv or im administration of large doses (4 or 6 g daily). The cultures of specimens before treatment showed large numbers (10^7 – 10^9 cfu/ml) of bacteria, and the MICs for organisms from urine cultures during therapy were generally about 2,000 times those obtained before therapy [86]. We were then able to demonstrate that alkalinization of the urine before and during treatment with streptomycin

generally prevented the emergence of the resistant variants [87].

Devetski et al. [88] reported that oral administration of chloramphenicol to 30 of 100 inmates of a state school for two weeks was accompanied by a marked increase in chloramphenicol-resistant strains of *E. coli* recovered from rectal cultures to nearly 90% in the treated patients and ~20% in the untreated patients; in both groups levels returned to the low levels found before treatment over the next four weeks. Parallel increases in chloramphenicol-resistant strains of *S. aureus* from nasal cultures were also demonstrated in the treated (from zero to 68%) and untreated inmates (from zero to 40%); these increases also were temporary [88].

Strains of *E. coli* isolated from the blood of infected patients at Boston City Hospital between November 1965 and August 1966 [89] showed bimodal distributions of MICs of all penicillins and cephalosporins, with generally small proportions of highly resistant strains. About 30%–40% were highly resistant to each of the tetracyclines, and about 10%–35% were resistant to the aminoglycosides when 10^6 organisms (undiluted cultures) were used for inoculum, but smaller proportions were resistant when the inoculum was 10^{-3} organisms. However, none of the strains were resistant to gentamicin even when tested with the undiluted cultures. Interestingly, about one-fourth of the strains were resistant to chloramphenicol even when tested with the smaller inoculum, but all were sensitive to polymyxin [89].

When strains of *E. coli* isolated from blood cultures during 1972 were similarly tested with most of the available antibiotics, the results were similar, but a smaller proportion of these strains were resistant to the tetracycline antibiotics, and again, none were resistant to gentamicin. In this study the proportion of resistant strains was greater among those isolated from hospital-acquired infections than among those from community-acquired infections [90].

Studies of other strains of *E. coli* isolated at about that time and tested with 65 antibiotics with use of the smaller inoculum gave essentially similar results [35, 36]. The strains were all highly susceptible to trimethoprim alone and even more so to trimethoprim in combination with

sulfamethoxazole, but a small proportion was highly resistant to the latter alone [67].

Klebsiella-Enterobacter

Like *E. coli*, the strains of *Klebsiella pneumoniae* and *Enterobacter (Aerobacter)* collected before 1950 showed broad ranges of MICs of penicillin, streptomycin, chlortetracycline, and chloramphenicol, and all were resistant to bacitracin; the strains of *Enterobacter* were uniformly sensitive to the polymyxins. The MICs of some *Klebsiella* varied over a wide range [4]. Also, as with *E. coli*, streptomycin resistance was shown to develop rapidly in *Klebsiella* and *Enterobacter* by exposures to the antibiotic in vitro or during treatment of both pulmonary [91] and urinary tract [86] infections. Resistance of these organisms was prevented by alkalinization of urine during therapy [87].

A study of the susceptibility of strains of *Klebsiella* and *Enterobacter* isolated at Boston City Hospital in 1964 [92] showed the following results. (1) Similar proportions of strains of *Enterobacter* and of *Klebsiella* were resistant to the aminoglycosides, the tetracyclines, and chloramphenicol, and nearly all strains of both species were resistant to the penicillins and cephalosporins. Neomycin, kanamycin, and paromomycin showed complete cross-resistance, but not to streptomycin, to which most strains were resistant, or to gentamicin, to which all but a small proportion were highly sensitive. About one-fifth of the strains of *Klebsiella* and one-third of the *Enterobacter* were resistant to the polymyxins. (2) Strains of *K. pneumoniae* type 24, which was the most prevalent type, were nearly all resistant to tetracycline, chloramphenicol, and streptomycin but not to kanamycin. Smaller proportions of strains of other types were resistant to the same antibiotics. (3) Larger proportions of strains of *Klebsiella* isolated from urinary tract infections were resistant as compared with those isolated from the respiratory tract. (4) A larger proportion of strains isolated from hospital-acquired infections were resistant to the commonly used antibiotics as compared with strains from community-acquired infections. (5) The proportion of strains resistant to the most commonly

used antibiotics was greatest for patients who had been treated with the same drug, somewhat smaller if they received any other antibiotic, and least if no antibiotic had been received by the patient before the strain was isolated.

Essentially, all of these findings were confirmed in a study of strains of *Klebsiella* and *Enterobacter* isolated in 1967 [93], particularly the relation of the proportion of resistant strains to prior therapy and the resistance of nearly all strains of *Klebsiella* type 24, which was still the most prevalent type. Type 2 strains of *Klebsiella* were nearly as prevalent in that year, but a smaller proportion was resistant. The type 24 strains were predominantly from hospital-acquired infections on surgical wards, whereas the type 2 strains were from more widely scattered sources. Both types were associated with instrumentation, mostly with urinary catheters. Nearly all strains were highly sensitive to gentamicin, but the proportion of strains resistant to polymyxin remained unchanged [93].

The tests of strains isolated from blood cultures in 1965–1966 [89] showed the marked effect of increasing the inoculum from a 10^{-3} dilution (1,000 cfu/ml) to the undiluted culture (10^6 cfu/ml) on resistance to antibiotics, including the aminoglycosides, polymyxins, and chloramphenicol, among others. With the large inoculum the strains were all, or nearly all, resistant to the penicillins and cephalosporins. Subsequent tests of strains of *Klebsiella* from blood cultures isolated in 1972 [90] were done with the smaller inoculum; these tests brought out some differences among the penicillins (there was more resistance to nafcillin and cyclacillin than to the others) and the cephalosporins (a large percentage of strains were more resistant to cephalothin than to six others). Larger proportions of strains of *Klebsiella* from hospital-acquired than from community-acquired infections were resistant to almost all antibiotics tested [90]. About one-third of the strains were resistant to sulfamethoxazole alone, but all were highly sensitive to trimethoprim and even more so to the combination of trimethoprim with sulfamethoxazole (ratio, 1:16) [67]. In other respects the results were similar to those found among the 1964–1965 strains that were tested with the same agents.

A more detailed study of susceptibility of *Enterobacter* to 19 antibacterial agents was carried out with 199 strains isolated from June 1969 through February 1970 [94]. Two-thirds of the strains were from sputum, and one-sixth from urine; 60% were *Enterobacter cloacae*, and the others were *Enterobacter aerogenes*. All strains of both species were highly susceptible to gentamicin; those of *E. cloacae* were all sensitive to neomycin, but about 10% of *Klebsiella* were resistant. Quantitatively, the strains of the two species varied only slightly in susceptibility to the other individual agents. The use of undiluted culture for inoculum showed only slight or moderate increases in MIC for most antibiotics when compared with use of a 10^{-4} dilution; however, the MICs of carbenicillin, polymyxin B, and colistimethate increased from 32- to 64-fold. Most strains of both species were resistant to the tetracyclines and chloramphenicol, and there was marked cross-resistance among kanamycin, neomycin, and streptomycin. There were numerous patterns of multiple antibiotic resistance involving two to six antibiotics.

Finally, tests done with 65 antibiotics and organisms isolated at Boston City Hospital in 1972 [35, 36] showed the following results. (1) Nearly all strains of both *Klebsiella* and *Enterobacter* were sensitive to gentamicin, tobramycin, amikacin, and sisomicin. (2) More than one-third of the strains of *Klebsiella* but only 10%–15% of *Enterobacter* were resistant to neomycin, kanamycin, and streptomycin. (3) Resistance to polymyxin B and colistin was much more frequent (~40%) among *Enterobacter* than among *Klebsiella* (~10%). (4) One-third or more of the *Klebsiella* but $\leq 15\%$ of strains of *Enterobacter* were resistant to the tetracyclines. (5) All strains of *Enterobacter* were susceptible to chloramphenicol, whereas about one-fourth of those of *Klebsiella* were highly resistant. (6) A bimodal distribution of MICs for *Klebsiella* was shown for all penicillins and cephalosporins; although only about one-half of the strains were highly resistant and the rest moderately resistant to all penicillins, the strains were all susceptible to the cephalosporins. (7) Strains of *Enterobacter* were more susceptible than those of *Klebsiella* to the penicillins, especially to the carbenicillin-

like penicillins, but less sensitive to the cephalosporins; larger proportions of *Enterobacter* were resistant to most of the cephalosporins.

Serratia marcescens

Serious infections due to *Serratia*, many with bacteremia, were observed in considerable numbers of patients at Boston City Hospital and in other hospitals after 1962 [53, 95, 96]. A study of 111 strains isolated at Boston City Hospital from September 1967 through January 1968 showed bimodal distribution of MICs for seven antibiotics (gentamicin, kanamycin, erythromycin, ampicillin, chloramphenicol, tetracycline, and cephaloridine), with different proportions of strains that were highly resistant. All of the strains tested were resistant to polymyxin B and cephalothin, cephalixin, and cephaloglycin, and from three to seven of them were resistant to rifampin and carbenicillin.

A comparison of these results with those obtained with 17 "type" strains from the Center for Disease Control that had been isolated and tested in 1957–1958 showed that all of the earlier strains were highly sensitive to gentamicin, kanamycin, and nalidixic acid; a much smaller proportion of the earlier strains were resistant to streptomycin.

Strains isolated at Boston City Hospital in 1971–1972 were tested with 65 antibiotics [35, 36]. From 40% to 80% of these strains were highly resistant to 10 aminoglycosides, including gentamicin, tobramycin, and sisomicin, but all were susceptible to amikacin. All were moderately or totally resistant to each of the seven tetracycline analogues, to polymyxin and colistin, as well as to chloramphenicol, spectinomycin, and sulfamethoxazole. However, all of the strains were highly susceptible to trimethoprim alone or combined in a 1:16 ratio with sulfamethoxazole [67]. Cefamandole and cefoxitin inhibited nearly all strains in concentrations of $\leq 25 \mu\text{g/ml}$, but these strains were all moderately or highly resistant to nine other cephalosporins and to 11 penicillins other than penicillinase-resistant ones, which were not used in these tests. Rifampin inhibited nearly all strains with 25–50 $\mu\text{g/ml}$, and erythromycin was about one-fourth as

active against the same strains. The strains were even more resistant to the lincomycins [36].

Selected Epidemiological Reports of Emergence and Spread of Resistance

Only a few reports from hospitals other than Boston City will be cited. In Israel, Sompolinsky et al. [97] studied the fecal flora of hospitalized and nonhospitalized volunteers who had not received any antibiotic therapy for at least six months. They determined the emergence and persistence of resistant aerobic bacteria before, during, and up to two months after administration of a tetracycline or chloramphenicol for five days. Before treatment, about 26% of fecal strains from hospitalized subjects and 11% from nonhospitalized subjects were resistant to tetracycline, and about 3% were resistant to chloramphenicol.

During treatment of hospitalized subjects with a tetracycline, sensitive strains rapidly disappeared from the feces, and tetracycline-resistant strains persisted in up to 80% of organisms for as long as two months after therapy was stopped. In the tetracycline-treated subjects, chloramphenicol resistance increased to about 70%, promptly declined after therapy was stopped, and persisted in lower proportion for two months. A similar increase in tetracycline resistance occurred during administration of a tetracycline to nonhospitalized subjects, but in these subjects resistance virtually disappeared within the following eight weeks.

Treatment of hospitalized patients with chloramphenicol resulted in similar increases in chloramphenicol resistance in the fecal flora during treatment; the resistance to chloramphenicol persisted in a smaller proportion of subjects over the next two months. Resistance to tetracycline in the chloramphenicol-treated hospitalized subjects also rose to nearly 70% during therapy but disappeared promptly after therapy was discontinued. Tetracycline resistance did not emerge in the aerobic fecal flora of the nonhospitalized chloramphenicol-treated subjects, but chloramphenicol resistance emerged and persisted in a large proportion of the nonhospitalized subjects treated with chloramphenicol.

In the hospitalized subjects the emergent fecal

flora during therapy was usually resistant to multiple drugs and infected with a large number of R factors. In the nonhospitalized subjects, although emergent resistance was just as frequent, it was limited largely to the drug administered, disappeared rapidly, and was not transferable. In general, resistance emerged more completely with tetracycline than with chloramphenicol treatment.

From Denver, Colo., Seldin et al. [98] reported on a prospective study of the role of intestinal colonization of patients admitted to the hospital during a time when nosocomial infections with multiple antibiotic-resistant *Klebsiella* were endemic. Among patients admitted to four wards from October 1968 through February 1969, 14 of 31 patients who became intestinal carriers of *Klebsiella* subsequently became infected with *Klebsiella* of the same serotype, whereas only 11 of 101 patients who did not become intestinal carriers developed infections with that organism. Antibiotic therapy was shown to predispose the patient to intestinal carriage and to exert a selective pressure in favor of multiply resistant *Klebsiella*. Thus, gastrointestinal acquisition and carriage of *Klebsiella* by the patients appeared to be an important step in the development of nosocomial infections with *Klebsiella* and served to perpetuate a significant reservoir of organisms in the hospital.

At Johns Hopkins Hospital (Baltimore, Md.), Pollack et al. [99] studied the factors influencing colonization and antibiotic resistance patterns of gram-negative bacteria in hospitalized patients. Serial cultures showed almost a fourfold increase in the percentage of hand cultures and more than a twofold increase in the percentage of throat cultures positive for *Klebsiella* after two weeks of hospitalization. These increases occurred almost entirely in patients receiving antibiotics. One-fourth of the strains of *Klebsiella* were resistant to multiple drugs, and more than half contained R factors. The frequency of R factors was greatest among *Klebsiella* and least in *E. coli*. Here again the role of the use of antibiotics in the acquisition of resistant gram-negative organisms was confirmed.

At the City Hospital in Edinburgh, Scotland, Shaw and others [100] studied the effects of oral antibiotic therapy and of hospitalization on the

patterns of antibiotic resistance of the fecal flora. In nearly two-thirds of patients who were not receiving antibiotics, the fecal flora was sensitive to all of the drugs with which it was tested. Administration of either tetracycline or ampicillin, whether in the hospital or at home, significantly increased the percentage of bowel coliforms more resistant to tetracycline than to ampicillin. Administration of amoxicillin, however, did not significantly increase the percentage of patients with resistant fecal flora.

Other similar observations were reported among hospitalized patients and in medical practice in England [101, 102].

A sequential hospital outbreak of resistant *Serratia* and *Klebsiella* was reported from the Nashville Veterans Administration Hospital (Nashville, Tenn.) [103]. Nosocomial infections with *S. marcescens* began to occur in late 1973 and increased in number for six months; then as they began to decline, multiple drug-resistant *K. pneumoniae* infections appeared and increased, while the multiple drug-resistant *Serratia* continued to occur through 1975. Approximately 400 patients had substantial infections with these organisms over the two and one-half years. The outbreak occurred after gentamicin had been used at the hospital for more than three years before the first cases were recognized. The patterns of drug resistance were similar in isolates of both species, and the outbreaks were considered to be related to transferable R plasmids.

Olarte and Galindo [104] reported an extensive epidemic of typhoid fever in Mexico; the outbreak began in February 1972 and involved more than 10,000 cases in a few months. The great majority of isolates of *Salmonella typhi* from this outbreak that were tested were resistant to chloramphenicol, tetracycline, streptomycin, and sulfonamide; were of a single phage type, and were considered to be associated with a single R factor. Strains isolated later in the outbreak were also resistant to kanamycin and ampicillin and were considered to be associated with two R factors.

At about the same time, Butler and others [105] identified four isolates of *S. typhi* from patients with typhoid fever in Vietnam that were also resistant to chloramphenicol, tetracycline, streptomycin, and sulfadiazine, and the patients

failed to respond to treatment with chloramphenicol. Here there were three distinct Vi-phage types, but the R factor-mediated drug resistance was considered to be similar to that experienced in Mexico, and the strains were susceptible to ampicillin and to trimethoprim-sulfamethoxazole. The latter was used successfully, and either of the two was recommended as an alternative drug of choice for therapy in such cases, although chloramphenicol was recommended for infections with susceptible strains [106].

Workers at the Center for Disease Control [107] compiled reports of 80 cases in the United States between February 1972 and August 1973 of infections with strains of *S. typhi* that were related to the outbreak in Mexico. The cases in the United States occurred in association with travel in Mexico before, during, and after the epidemic there.

Geographic Differences in Resistance

The marked differences in the prevalence of methicillin-resistant *S. aureus* in different countries were already mentioned. Recently, O'Brien and several collaborators [108] compared the prevalence of resistance to the most commonly used antibiotics of the most frequently encountered pathogenic species of bacteria among clinical isolates from a general hospital in Paris and one in Boston. The average percentage of isolates resistant to individual antibiotics was three times greater and the percentage of isolates resistant to six or more antibiotics was 14 times greater among isolates in the Parisian hospital than among those in the Boston hospital. The differences were nearly as great among strains isolated from patients during the first three days in the two hospitals, a finding that suggests differences in the bacterial flora in the communities. The authors noted that the percentage resistant to any of the antibiotics was reported to be remarkably similar among other hospitals in the United States. Different patterns of antibiotic usage in the two areas may underlie these differences in resistance.

Thus, the dominant feature in the emergence and spread of resistant enterobacteria, as was shown for *S. aureus*, appears to be the widespread use of antibiotics, particularly in the in-

dividuals from whom the antibiotic-resistant bacteria are isolated.

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Discussion

DR. HUBERT PELTIER. Dr. Finland, I believe that Harry Dowling and Mark Lepper later used methicillin in the same manner in which they had earlier used penicillin G and erythromycin. Methicillin was administered to every patient (on certain hospital wards) with infections due to gram-positive cocci. I believe that the results, in terms of emergence of resistance to methicillin, were quite different from those obtained with penicillin G and erythromycin. Furthermore, Leon Sabath et al. studied the prevalence of methicillin-resistant *Staphylococcus aureus* at the Boston City Hospital and found that even after 10 years of use of methicillin, only 1.4% of strains were resistant. Do you think that this rate is unusually low compared with what has been seen elsewhere?

DR. MAXWELL FINLAND. Methicillin resistance is not much different in Sabath's data from what has been observed in most hospitals in the United States, except when there is a period of epidemic spread of a single methicillin-resistant strain. The increase in resistance that occurred in Britain did not materialize in the United States. The studies in Denmark and Switzerland, in which high rates of methicillin resistance were observed, were associated with newly introduced bacteriophage types of staphylococci, and this high rate of resistance to methicillin seems to have declined. Furthermore, Robert Moellering and his associates have shown no increase in resistance to the cephalosporins for most common species of microorganisms, including staphylococci, but excepting enterococci.

DR. FRANK YOUNG. Has anyone compared the relative frequency of resistance in obligative anaerobic organisms such as *Bacteroides fragilis* with

resistance in facultative anaerobic and aerobic organisms in hospitals?

DR. SYDNEY FINEGOLD. The major change in resistance of anaerobes is the development of significant resistance to tetracyclines by virtually all groups of anaerobes. Aside from this there has not been a great deal of change in resistance. There has been some change in the pattern of susceptibility to clindamycin, particularly in the genus *Peptococcus* in which about 10% of strains have become resistant to clindamycin. Occasional strains of *B. fragilis* are now resistant to clindamycin, and some strains of *Bacteroides melaninogenicus* have appeared that are resistant to penicillin G. In the latter case, these have been strains that have an MIC as high as 32 units/ml.

DR. HAROLD NEU. In the past year or two, we and others around the country have seen increases in the prevalence of methicillin-resistant *Staphylococcus epidermidis* in large hospitals, particularly in neurosurgical and orthopedic units in which a great deal of semisynthetic penicillin is used.

DR. FINLAND. I am glad to hear of these observations. We have not continued studies with *S. epidermidis*. Our data were obtained before penicillinase-resistant penicillin and cephalosporins were used as intensively as they are being used now. Parenthetically, one reason that we stopped working with *S. epidermidis* was that we felt it was necessary to attempt to differentiate strains either by phage typing or by serologic methods, and this distinction has been difficult to achieve. Without such differentiation, there may be some problem in interpreting the data from different institutions.