NEW ANTIBACTERIAL TREATMENT OF NOSOCOMIAL INFECTIONS*

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IN considering the topic assigned me, I was rather confused by the title "New Antibacterial Treatment of Nosocomial Infections." It sounds as if nosocomial infections were somehow different from all other kinds and required some special approaches to chemotherapy to which I might address myself. We are all aware that this is not the case; there is virtually no aspect of the treatment of nosocomial infections that will not be covered by other speakers in this symposium. Therefore, I intend to broaden my comments somewhat in order to take up the only other thing we can do about nosocomial infections, that is, to prevent them.

The past two decades have produced so much literature on the subject that we all should be well aware of the general problem of nosocomial infection. For the record, however, let us establish a baseline of information from which to proceed. A nosocomial infection is simply an institutional or hospital-associated infection. Whether or not the hospital or its staff was in any way responsible for the development of the infection, or whether the infection was exogenous or endogenous, is not the issue. The mere fact that an infection occurred in a patient during hospitalization establishes that infection as nosocomial in origin.

An appreciation of the magnitude of the over-all problem can be gained from Table I, which summarizes the prevalence and incidence of hospital infections as reported in selected studies during the past eight years.[1-7] The prevalence of hospital infections at the Boston City Hospital in each of three separate surveys has been 12% or more.[1-3] Lest anyone think that such problems are confined to municipal hos-

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TABLE I. PREVALENCE AND INCIDENCE OF HOSPITAL INFECTION, 1964-1971

Source	*Prevalence** (%)	*Incidence†* (%)
Boston City Hospital, 1964(1)	13.5	
Boston City Hospital, 1967(2)	15.5	
Boston City Hospital, 1970(3)	12.0	
University of Kentucky, 1965(4)		6.1
Johns Hopkins Hospital, 1965-1967(5)	4.7	4.0
Six community hospitals, CDC, 1965-1966(6)		3.5
68 survey hospitals, CDC, 1970(7)		5.0

*Proportion of hospitalized patients with hospital-associated infection at any given time.

†Rate of hospital infection among patients, usually expressed per 100 admissions or discharges.

CDC=Center for Disease Control, HEW, Atlanta, Ga.

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pitals or to university teaching centers, it should be noted that the six community hospitals studied by the Center for Disease Control had an incidence rate of 3.5%. In a more recent report 68 hospitals (of which 40 were community hospitals) participating in the National Nosocomial Infections Study reported an incidence rate of 5%.[7] It is important to appreciate the difference between prevalence and incidence, as shown in the table, and to appreciate the fact that these two kinds of figures cannot be compared directly, inasmuch as they are based on wholly different means of data collection.

Evidence available to date indicates that approximately 5% of all patients admitted to hospitals develop an infection during the course of their hospitalization. It may be estimated conservatively that there are 30 million admissions to general hospitals in the United States per year. Therefore, it follows that approximately 1.5 million hospital infections occur annually in this country.

Table II shows the distribution of hospital infections according to major site of infection, as summarized from several recently reported studies.[3, 5, 6] When data from a municipal hospital, a university hospital, and six community hospitals are compared, a remarkable similarity in the distribution of kinds of infection is apparent. Note particularly that infections of the urinary tract regularly account for more than one third of all nosocomial infections.

TABLE II. CLINICAL DISTRIBUTION OF HOSPITAL INFECTIONS

Site of infection	*Boston City Hospital 1970*(3) (%)	*Johns Hopkins Hospital 1965-1967*(5) (%)	*Community hospitals 1965-1966*(6) (%)
Respiratory tract	20	14.5	15.4
Urinary tract	41	40.5	36.4
Surgical wounds	19	30.1	25.3
Skin and subcutaneous	15	0	7.0
Other	6	14.9	16.0

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TABLE III. DISTRIBUTION OF PATHOGENS IN HOSPITAL INFECTIONS

Pathogen	*Boston City Hospital 1970*(3) (%)	*68 hospitals CDC 1969-1970*(7) (%)
Staphylococcus aureuses	14.3	16.1
Staphylococcus epidermidis	0.	3.6
Pneumococci	2.7	3.1
Streptococci*	4.1	3.8
Enterococci	7.5	5.3
E. coli	10.9	20.2
Klebsiella and *Enterobacter*	23.1	11.0
Proteus	11.6	10.9
Serratia	3.4	0.9
Pseudomonas	15.0	8.9
Others	7.5	15.1

*Other than enterococci.
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Table III, showing the distribution of bacterial pathogens in hospital infections, compares two recently reported studies.[3, 7] In each of these studies the pathogens listed were isolated frequently in mixed culture; it does not necessarily follow that each isolate of each pathogen represents a clinical infection caused by that organism. The data thus can be interpreted only as indicating the broad pattern of pathogens associated with nosocomial infection. A remarkable similarity is shown in the data reported from widely diverse sources; staphylo-

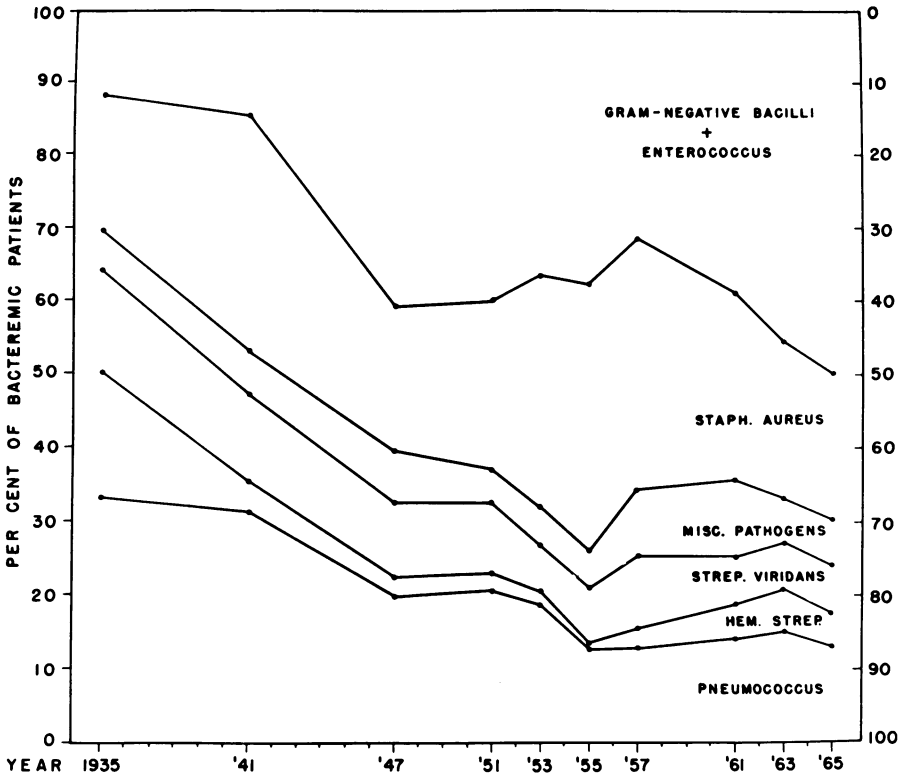

Fig. 1. Distribution of bacteremic patients according to etiologic agents for each of the 10 selected years. The divergence or convergence of each pair of adjacent lines connecting the dots for the indicated years depicts the changes in the proportions of cases attributed to each of the organisms during the intervening years. The vertical scale reads cumulatively up on the left and down on the right to emphasize the striking changes over the years. Reproduced by permission from Finland, M.: Changing ecology of bacterial infections as related to antibacterial therapy. *J. Infect Dis. 122*:419, 1970.

cocci, very prevalent in the 1950s and early 1960s, now account for less than 20% of nosocomial infections. Well over half of nosocomial infections are now regularly accounted for by Gram-negative enteric bacilli, including *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Pseudomonas*, and *Serratia*.

The changing character of nosocomial infections is well illustrated in Figure 1, which gives a synopsis of decades of work by Maxwell Finland and his colleagues at the Boston City Hospital.[8] Note the relative decline in the frequency of bacteremic infection caused by *Staphylococcus aureus* beginning in the late 1950s, accompanied by a

dramatic increase in bacteremic infection caused by Gram-negative bacilli plus enterococci.

Since this is a symposium on antibiotic therapy, it is appropriate to address the question of what role the use and abuse of antibiotics in the past 25 years has played in shaping today's problem of nosocomial infection. Antibiotics, after all, account for more than one third of the total cost of drugs in hospital pharmacies. In Colorado General Hospital, we found that the cephalosporins alone account for 15% of the total expenditure of the pharmacy.[9] In this respect our own data confirm those reported by Dr. Calvin Kunin from the University of Wisconsin.[10]

Antibiotic therapy has generally not been considered to have a major direct effect on the defense mechanisms of the host, save in instances of adverse drug reactions precipitating severe dermatitis, bone-marrow depression, renal failure, or the like. Antibiotic therapy does, however, exert a profound effect on the microflora of the host and thus appears to act primarily by determining the character of hospital infection. Virtually all antibiotics in therapeutic doses will produce marked changes in the microflora of the skin, the upper respiratory tract, and the gastrointestinal tract. Antibiotic-resistant organisms, if present, are selected out and multiply freely, replacing the susceptible organisms inhibited by antibiotic therapy. The medical literature is replete with examples of the emergence of staphylococci which are resistant to one or more drugs—under the selective influence of a drug widely used in that hospital. More recently, numerous examples of the emergence of gentamicin-resistant *Pseudomonas aeruginosa* have been documented in hospital situations in which gentamicin was used broadly in the hospital environment, for example, in the form of gentamicin-containing cream in the management of sepsis following burns.[11] There is no evidence that multiple-drug-resistant staphylococci or Gram-negative enteric bacilli are more virulent than their drug-susceptible relatives, but there is good evidence that these resistant hospital pathogens have a distinct survival advantage in hospitalized patients exposed to the selective pressures of antibiotic therapy.

One of the most dramatic examples suggesting a major contribution of antibiotic therapy to the problem of nosocomial infections in a hospital was reported in 1970 from a British neurosurgical unit by Price

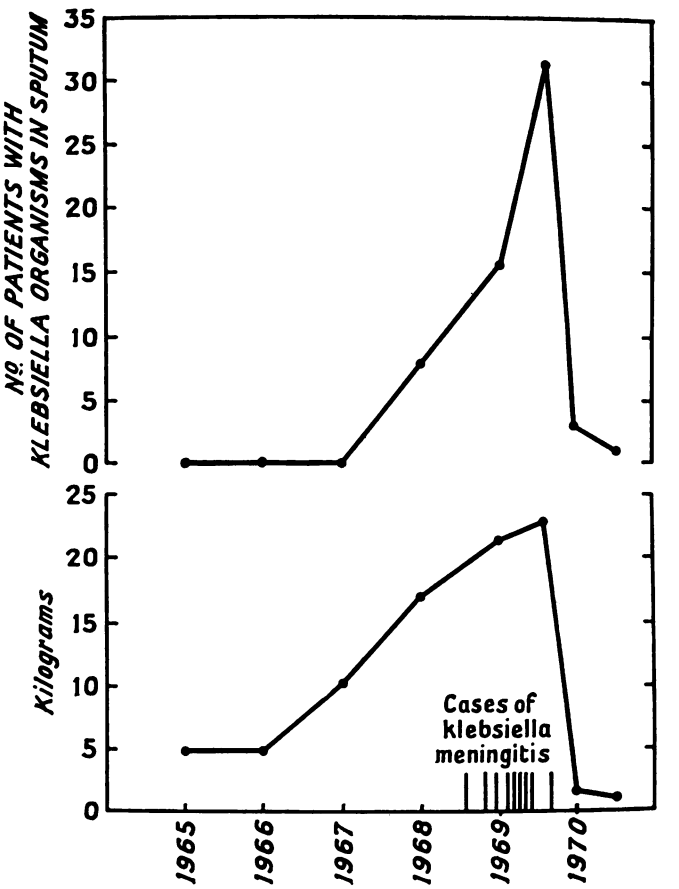

Fig. 2. Isolation of *Klebsiella* from sputum specimens (first 100 patients admitted to intensive-care ward each year) and annual consumption of ampicillin and cloxacillin. Reproduced by permission from Price, D. J. E. and Sleigh, J. D.: Control of infection due to *Klebsiella aerogenes* in a neurosurgical unit by withdrawal of all antibiotics. *Lancet 2*:1213, 1970.

and Sleigh.[12] As shown in Figure 2, the total cessation of all antibiotic therapy in that unit was associated with termination of an outbreak of pneumonia and meningitis caused by multiple-drug-resistant *Klebsiella*.

Data do not exist from which valid conclusions can be drawn defining the exact role of antibiotics in determining either the magnitude or the frequency of hospital infection.[13] One is left with sharp differences of opinion. Professor R. E. O. Williams has stated[14] that "The statistical information to answer this question properly does not exist, but

there are indications that the rise in numbers of cases of Gram-negative bacteremia is very largely due to changes in the population and in our ability to recognize the condition, rather than to the back-wash of antibiotic therapy."[14]

In contrast, in the same year Dr. Maxwell Finland wrote: "The major factor presumed to be responsible for the changing ecology of the serious bacterial infections, and for the marked increase in their occurrence, at least at Boston City Hospital, is the selective pressure of the antibiotics so widely and intensively used in therapy, and especially for prophylaxis."[8]

Thus, there is strong indication that because of cost, adverse effects, and data such as those published by Price and Sleigh, already mentioned, the medical profession in the very near future may have to re-think its entire orientation toward the use of antibiotics. One approach was recently described by McGowan and Finland, who reviewed the amounts of certain antibiotics used at Boston City Hospital during recent years, and correlated such usage with the institution of a requirement to justify a choice of those antibiotics.[15] This mild restraint on the prescribing of antibiotics for hospitalized patients substantially limited the use of certain potentially toxic or expensive drugs; removal of the restriction was promptly followed by an increase in their use. Thus, relatively simple requirements may promote more effective and economical use of antibiotics in hospitalized patients.

Time does not permit extensive discussion of the epidemiology of nosocomial infections or of the many approaches to their control. However, I should like to highlight two special problem areas about which a great deal could be done.

Virtually every survey of hospital-associated infections has demonstrated that infections of the urinary tract regularly account for a third or more of all nosocomial infections. The association of infection of the urinary tract with prior instrumentation or catheterization is similarly well documented. Kunin and McCormack[16] have demonstrated clearly that careful use of sterile, closed catheter drainage systems can effect a substantial reduction in urinary tract infection and subsequent Gram-negative sepsis. One need only look about the wards of most hospitals in the United States for a short while to appreciate the mistakes in the usage of catheters that occur daily. These include not only the inappropriate use of indwelling Foley catheters for the convenience

of medical and nursing personnel, but also the lack of careful aseptic technique during insertion of catheters, frequent breaking of the closed system by disconnecting the catheter and the drainage bag for irrigation or for the obtaining of urine specimens, as well as the frequent finding of drainage bags placed above bladder level which, even for a short while, insures a backflow of potentially contaminated urine. As Edward Kass points out, "It surely must be apparent that the sacred voluntary approach has serious drawbacks if this type of inadequacy can be so frequently documented."[17]

A second area to be underscored is the use of intravenous catheters. Phlebitis and septicemia resulting from indwelling intravenous catheters are known to be increasingly important nosocomial infections. The necessity of using surgically aseptic technique while inserting intravenous catheters must be emphasized, and the area of contact between the catheter and the skin should be treated with the care given a surgical wound. A critical factor in determining whether an infection will occur is the length of time the catheter is left in place. Forty-eight hours is often stated to be the maximum permissible length of time, but this standard is arbitrary and may be impractical in some clinical situations. Nevertheless, we were somewhat surprised to observe that in Colorado General Hospital, where we surveyed the use of intravenous catheters, more than 25% are left in place longer than 48 hours.[18] Further, surveillance data indicated that, on the average, four catheter-associated episodes of septicemia occur per month in this 400-bed hospital. Thus, if a decision is made to leave an intravenous catheter in place for longer than 48 hours, the physician should be cognizant of the additional risks of infection being incurred and should record in the chart the justification for his decision. Mere convenience for the patient or hospital personnel is not sufficient reason to incur such risks.

Many more problems are associated with nosocomial infection, but these are two areas in which the risk is clearly documented, and for which relatively little in the way of aggressive control can be found in hospitals nowadays.

Thus, there is neither new treatment nor new prevention of nosocomial infection. The conscientious application of what is already known would significantly reduce this major hazard of hospitalization.

REFERENCES

1. Kislak, J. W., Eickhoff, T. C., and Finland, M.: Hospital-acquired infections and antibiotic usage in the Boston City Hospital, January, 1964. *New Eng. J. Med. 271:*834, 1964.
2. Barrett, F. F., Casey, J. I., and Finland, M.: Infections and antibiotic use among patients at Boston City Hospital, February, 1967. *New Eng. J. Med. 278:*5, 1968.
3. Adler, J. L., Burke, J. P., and Finland, M.: Infection and antibiotic usage at Boston City Hospital, January, 1970. *Arch. Intern. Med. 127:*460, 1971.
4. McNamara, M. J., Hill, M. C., Balows, A., and Tucker, E. B.: A study of the bacteriologic patterns of hospital infections. *Ann. Intern. Med. 66:*480, 1967.
5. Thoburn, R., Fekety, F. R., Jr., Cluff, L. E., and Melvin, V. B.: Infections acquired by hospitalized patients. *Arch. Intern. Med. 121:*1, 1968.
6. Eickhoff, T. C., Brachman, P. S., Bennett, J. V., and Brown, J. F.: Surveillance of nosocomial infections in community hospitals. I. Surveillance methods, effectiveness, and initial results. *J. Infect. Dis. 120:*305, 1969.
7. Bennett, J. V., Scheckler, W. E., Maki, D. G., and Brachman, P. S.: Current national patterns—United States. In: *Proc. Int. Conf. Nosocomial Infections.* Chicago, Amer. Hosp. Ass., 1971, p. 42.
8. Finland, M.: Changing ecology of bacterial infections as related to antibacterial therapy. *J. Infect. Dis. 122:*419, 1970.
9. Tenney, J. H., Guenette, S. A., and Eickhoff, T. C.: Unpublished data.
10. Kunin, C. M., Tupasi, T., and Craig, W. A.: Use of antibiotics: A brief exposition of the problem and some tentative solutions. *Ann. Intern. Med. 79:*555, 1973.
11. Shulman, J. A., Terry, P. M., and Hough, C. E.: Colonization with gentamicin-resistant *Pseudomonas aeruginosa,* Pyocine type 5, in a burn unit. *J. Infect. Dis.* (Suppl.) *124:*5-18, 1971.
12. Price, D. J. E. and Sleigh, J. D.: Control of infection due to *Klebsiella aerogenes* in a neuro-surgical unit by withdrawal of all antibiotics. *Lancet 2:*1213, 1970.
13. Wolff, S. M. and Bennett, J. V.: Gram-negative rod bacteremia. *New Eng. J. Med. 291:*733, 1974.
14. Williams, R. E. O.: Changing Perspectives in Hospital Infection. In: *Proc. Int. Conf. Nosocomial Infections.* Chicago, Amer. Hosp. Ass., 1971, p. 1.
15. McGowen, J. E., Jr., and Finland, M.: Usage of antibiotics in a general hospital. *J. Infect. Dis. 130:*165, 1974.
16. Kunin, C. M. and McCormack, R. C.: Prevention of catheter-induced urinary tract infections by sterile closed drainage. *New Eng. J. Med. 274:*1156, 1966.
17. Kass, E. H.: Surveillance as a Control System: Statement of Panelist. In: *Proc. Int. Conf. Nosocomial Infections.* Chicago, Amer. Hosp. Ass., 1971, p. 292.
18. Guenette, S. A. and Eickhoff, T. C.: Unpublished data.