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INFERTILITY

Edited by

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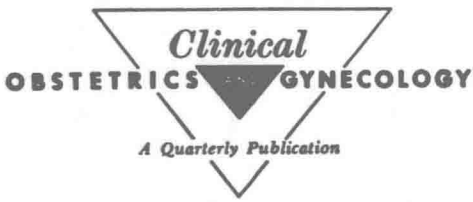

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OBSTETRIC INFECTIONS

Edited by
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FOREWORD

INFECTION, TRADITIONALLY ONE of the principal hazards of reproduction, has faded from the obstetric limelight. Concern has given way to complacency as the death rate from infection has continued to fall. Within the five year period of 1952 to 1957, in Bronx County, New York, for example, the mortality from obstetric infections declined 80 per cent, almost all of the most recent deaths resulting from illegal abortion.

This reduction in mortality from infection is attributable in large measure to the widespread use of the rapidly growing battery of antibiotics. Indeed, Selman Waksman, codiscoverer of streptomycin, has wistfully suggested that the present era might be called the age of antibiotics instead of the atomic age. The incalculable boon of these drugs has been accompanied, however, by two undesirable by-products: a tendency toward the relaxation of aseptic technique, and the emergence of antibiotic-resistant bacteria.

The staphylococcus, standing foremost among the organisms of increasing prevalence and resistance to therapy, has been responsible for serious epidemics in many hospitals, especially in the surgical wards and newborn baby nurseries. In a recent seven month period one hospital in New York reported a rash of staphylococcus infections involving 120 newborn infants. Staphylococcic pneumonia caused most of the deaths in the Asian influenza epidemic of 1957–58; and nearly one half of all the fatalities among women of childbearing age in New York City occurred among the pregnant.

Up to 80 per cent of the prevalent strains of staphylococcus are now resistant to penicillin. It is estimated that over 50 per cent of the population carry one or more of these drug-resistant strains on the skin or in the nasopharynx, and these organisms abound in hospitals. Dr. Carl W. Walter of Harvard University's Department of Surgery recently reported on a patient with a staphylococcus infection who was hospitalized overnight in a sterilized room. By morning, bacteriologic culture showed the bedding, walls, floor, and air to be teeming with the same strain of staphylococcus. Partly because of the hazard of hospital infection, Thaddeus Montgomery has suggested that both mother and baby might be better off if discharged within 24 to 36 hours after delivery.

Staphylococcus infections, characterized as a problem of "national significance and growing magnitude" by U.S. Surgeon General L. B. Burney, came under the critical scrutiny of delegates from 59 professional organizations at a recent 3 day conference sponsored by the U.S. Public Health Service and the National Research Council. Among the

measures for coping with this menace the conference recommended the following:

1. Establishment of criteria for the discriminate use of antibiotics in medicine and surgery, with routine prophylactic use discouraged.

2. Newborn baby nursery precautions: elimination of overcrowding, maintenance of rigid sanitary standards, antiseptic baths immediately after birth, and sample surveys of families, after babies have been discharged, to permit early detection of nursery-acquired infection.

In the meantime the frenzied quest for new, more effective antibiotics continues. At the Sixth Annual Symposium on Antibiotics, held in Washington, D. C., October 1958, 181 papers were presented. During this symposium vancomycin emerged as the most promising new weapon against the staphylococcus.

In gratifying contrast to the resurgent problem of pyogenic infection, the continuing conquest of tuberculosis may be noted. The death rate from this disease in the United States, having declined four times more rapidly during the past 10 years than during any other decade of this century, now stands at only 4 per cent of the mortality rate from tuberculosis in 1900. Of greatest obstetric interest is the fact that therapeutic abortion need rarely be carried out now for tuberculosis.

Obstetricians have almost forgotten about syphilis, their present concern with the disease being virtually limited to the routine antenatal drawing of a blood sample for serologic test. The infant mortality from syphilis has plunged more than 99 per cent since 1910. In 1955 not a single death from syphilis in infancy was reported by 29 states. Recent observations, however, show a rising incidence of syphilitic infection. During the first half of 1958, for example, in accordance with a trend that began in 1956, 68 per cent more cases of primary and secondary infection were reported in New York City than in the corresponding period of the preceding year, and a similar increase is being noted in other parts of the United States. The obstetrician's principal role in the continuing battle against this disease lies in his unremitting effort at case detection.

The pages that follow reflect the views of a group of authorities invited to participate in this symposium because of their special interest and experience in the selected topics. On the prophylactic use of antibiotics, practices differ and no effort has been made herein to reconcile them, but this therapy finds progressively fewer advocates as its limitations and dangers achieve wider recognition. To all who have contributed to this symposium the editor expresses his sincere thanks.

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ANTIBACTERIAL CHEMOTHERAPY

Indications and Selection

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THE NUMEROUS ANTIBACTERIAL chemotherapeutic agents available today, while still constituting extremely powerful weapons for combating infection, are being recognized as a growing source of danger because of their widespread and indiscriminate administration. This danger stems in considerable part from the physician's failure to recognize the therapeutic limitations of these drugs, and from his overwillingness to ascribe to them curative or preventive powers that they do not possess. The resultant misuse is most strikingly exemplified in the prescription of antibiotics for the "treatment" of many common diseases of viral etiology, particularly those of the respiratory tract.[8] The effect of aggressive advertising campaigns, often grossly biased in favor of a particular product, have virtually put the burden of proof on physicians who refuse to use these agents in an uncritical manner. The magnitude which this aspect of the problem has reached has been ably delineated in the lay press, indicating that the public is also becoming advised of the danger.[12, 13] With these considerations in mind, the management of antibacterial therapy in pregnancy should rest on well recognized principles common to all clinical situations in which bacterial infection, proven or suspected, may be a major factor in the patient's welfare. In this discussion, an attempt will be made to outline some of these principles In addition, a few specific problems will be considered which in some respects are peculiar to pregnancy.

BACTERIOLOGIC DIAGNOSIS

It is obvious that accurate bacteriologic diagnosis is the cornerstone of effective therapy. When sought with vigor and competence, such diagnostic information can become available soon enough to be of real value to the physician in deciding which drugs to use. More and more aids to diagnostic bacteriology are coming within reach of the office practitioner, to whom hospital bacteriologic laboratory facilities are not al-

ways accessible. Such aids include many packaged sterile media which can be used by the physician at the bedside or in the office, standard discs for antibiotic sensitivity testing, and a variety of inexpensive basic equipment to carry out the simple but fundamental procedures of initial bacteriologic diagnosis. Even if causative bacteria are not revealed until 24 to 36 hours after infection has been suspected and specimens have been taken for culture, therapy, based on clinical judgment alone, may often be instituted when the patient is first seen, and then changed if necessary when the specific diagnosis is established. It follows that clinical diagnostic criteria, although beyond the purview of this summary, bear significantly on the evaluation of laboratory data, most especially those resulting from bacteriologic investigation.

It is remarkable that the susceptibility of microorganisms to the action of penicillin is closely correlated with their reaction to the Gram stain, which itself remains an altogether empirical basis of classification. Thus, with a few notable exceptions cited below, only gram-positive microorganisms are susceptible in vitro to penicillin and cause infections which can be effectively treated with this drug, or with certain of the newer agents, such as erythromycin or novobiocin, which resemble penicillin in range of antibacterial action. Streptomycin, on the other hand, is primarily characterized by its effect, both in vitro and in vivo, on gram-negative species which almost without exception are uninfluenced by penicillin. Streptomycin, however, is also effective against certain gram-positive bacteria, and therefore may be considered a broad spectrum antibiotic, along with others that inhibit both gram-positive and gram-negative microorganisms. As indicated in Table 1, the pathogenic species of bacteria that are uniformly susceptible to penicillin and to the broad spectrum antibiotics are the commonly encountered gram-positive organisms, including pneumococci, group A beta hemolytic streptococci and clostridia, the Neisseria, particularly meningococci and gonococci, and the spirochetes. Occasional strains of enterococci (*Str. fecalis*) are relatively resistant to penicillin, but the majority are readily inhibited, as is true also of the ordinary viridans streptococci and micrococci. Many strains of *Staph. aureus*, even some acquired in hospital, are still sensitive enough to warrant therapeutic trial with penicillin. Certain newer drugs (ristocetin, vancomycin and kanamycin) are limited at present to use in resistant staphylococcal infection. All of the gram-negative bacilli, while uniformly insusceptible to penicillin, are sensitive to streptomycin and, with some exceptions to be noted, to the broad spectrum antibiotics. These species include, besides *Shigella* and *Salmonella, E. coli* and a fair proportion of the *Klebsiella-Aerobacter* group. It may be noted that for practical purposes *A. aerogenes* and *K.*

Table 1. Activity Spectrum of Antibacterial Drugs

Penicillin	*Broad spectrum antibiotics*	
Spirochetes (P)	*Neisseria:* gonococci (P),	Gram-negative bacteria
Clostridia (P)	meningococci (Sulfa; P)	*E. coli* (T, C, S; Sulfa in urinary tract infections)
Corynebacteria (P)		*Klebsiella* (S, T, C)
	Gram-positive bacteria	*Proteus* (C, No, Ne)
	Streptococci (P; P+S in SBE)	*Salmonella* (C)
	Pneumococci, Micrococci (P; any BSA)	*Shigella* (T)
	Staph. aureus (hemolytic, coagulase+) (P, S, T, E, C, No, Ne, B-topical. Also ristocetin, vancomycin, kanamycin)	*Hemophilus* (C, S)
		Brucella (S+T)
		Pseudomonas (C, PB, Ne)
		Myco. tuberculosis (S+ INH and/or PASA)

Key: P = Penicillin
S = Streptomycin
BSA = Broad spectrum antibiotics
C = Chloramphenicol
T = Tetracyclines
E = Erythromycin
No = Novobiocin
Ne = Neomycin
B = Bacitracin
PB = Polymyxin B
Sulfa = Sulfonamide
INH = Isonicotinic acid hydrazide (Isoniazid)
PASA = Para-aminosalicylic acid
SBE = Subacute bacterial endocarditis

pneumoniae (Friedländer's bacillus) are virtually identical. Although considerable trouble is often taken to distinguish them, they should be classed together as *Klebsiella.*[4] Streptomycin, in combination with isoniazid (INH) and/or para-aminosalicylic acid (PASA), has its greatest value in treating infections caused by *Myco. tuberculosis.* The combination of streptomycin and tetracycline for brucellosis has been established as superior to either drug alone. Likewise, streptomycin and penicillin appear to act synergistically in subacute bacterial endocarditis, especially in those cases caused by enterococci, which are often relatively unresponsive to penicillin alone. Two polypeptide antibiotics, bacitracin and polymyxin B, lie at opposite ends of the spectrum, having limited power

against penicillin-resistant staphylococci and *Pseudomonas* species, respectively. The so-called broad spectrum antibiotics range to both extremes of the scale. Chloramphenicol, the first to be discovered, is still one of the most valuable of these agents. Novobiocin, while exhibiting a spectrum of activity more nearly resembling that of penicillin, is also effective against some strains of *Proteus*.

Table 1 also gives for each microorganism the antibacterial drug found to be most suitable for treating each specific infection. Other than the staphylococcus, the gram-positive organisms present relatively little difficulty as to choice of drug, since the important species are all readily treated with penicillin. If penicillin cannot be used, a broad spectrum antibiotic may be given almost as effectively. The story is somewhat different, however, with certain commonly encountered gram-negative bacilli, particularly *Proteus, Pseudomonas,* and the coliforms. Problems of antibiotic resistance, either initial or consequent upon therapy, frequently are encountered with these organisms. *Proteus* infections of the urinary tract are among the most difficult to treat with any antibiotic, although novobiocin and neomycin, and occasionally even chloramphenicol and the tetracyclines show some in vitro activity. Similarly, *Ps. aeruginosa* (*B. pyocyaneus*) infections may respond only to polymyxin B, an antibiotic which must be used sparingly because of its renal toxicity.

ANTIBIOTIC SENSITIVITY TESTING

Many studies have been made to assess the susceptibility of pathogenic microorganisms to various antibiotic and chemotherapeutic agents, studies based on the assumption that drugs which inhibit bacterial growth under artificial laboratory conditions will also effectively combat infection in the human or animal host. In general this assumption is valid, since there is a high degree of correlation between in vitro sensitivity and successful eradication of specific infection. The vast amount of such correlative data that have now accumulated for most of the antibiotic agents in clinical use permit the selection of an antibiotic having maximum possibility of therapeutic effectiveness against almost any of the known pathogenic bacteria. Contrary to widely held beliefs, therefore, institution of correct antibiotic therapy need not always await the completion of "antibiotic sensitivity" tests by the laboratory. Once the precise bacteriologic diagnosis is established, proper therapy may be selected on this basis alone. Antibiotic sensitivity tests, as performed in the routine diagnostic laboratory, are helpful only if doubt exists whether a given species of bacterium may be sensitive or resistant to

antibiotics. This is occasionally the case with *Staph. aureus* and certain of the coliform organisms; in such instances in vitro sensitivity tests may furnish valuable information. It is well known that all coliform bacteria are capable of rapidly acquiring resistance to streptomycin and the broad spectrum antibiotics not only in vitro, but also during the treatment of infections, particularly of the urinary tract. A sensitivity test performed on a strain isolated during the course of treatment therefore may reflect only one brief stage in a rapidly changing pattern. Knowledge of antecedent therapy is thus extremely important in appraising the results of in vitro sensitivity tests in cases of infection due to these gram-negative species.

The most widely employed method for testing sensitivity to antibiotics is the qualitative disc-plate method, which, it is well to bear in mind, has inherent limitations imposed by a variety of purely technical considerations. Factors such as the size of inoculum, moisture of the medium, duration of incubation, concentration and rate of diffusion of antibiotic agents into the medium from the discs, all have a bearing on the outcome of the test. If these factors are not standardized as far as possible, successive tests may give widely varying and often misleading results. Fortunately, a degree of standardization is attainable so that even these qualitative tests may be meaningful. In Fig. 1 are shown the results of such tests performed in the laboratory. A heavy inoculum from a fresh broth suspension was spread evenly over the dry agar plate containing a standard enriched nutrient agar (Case Laboratories test medium C) and all visible moisture was then allowed to soak in. The paper wheel (Difco Unidisc) containing the several antibiotics was then pressed into place, one or more single discs being added to the center, and the plate inverted and incubated for 16 to 18 hours. The amounts of antibiotic used in each disc are chosen so that differences in their effects, resulting from variation in stability and rate of diffusion, are minimized. Thus a relatively low concentration of penicillin (10 units or 6 μg.), stable and readily diffusible, is employed, as compared with 30 μg. of tetracycline, chloramphenicol, and others (some of which are much less stable than penicillin), and 100 μg. of streptomycin (which diffuses less readily than penicillin). Such adjusted concentrations of antibiotics are nevertheless each high enough to give clear-cut inhibition with organisms of intermediate sensitivity, and to single out those of maximal in vitro resistance. The actual amounts of each antibiotic used in the test are given in Table 2. Within broad limits, it is thus possible to predict that an organism inhibited in vitro will usually be susceptible in vivo, provided other unrelated factors that might diminish the effectiveness of chemotherapy are minimally operative. No quanti-

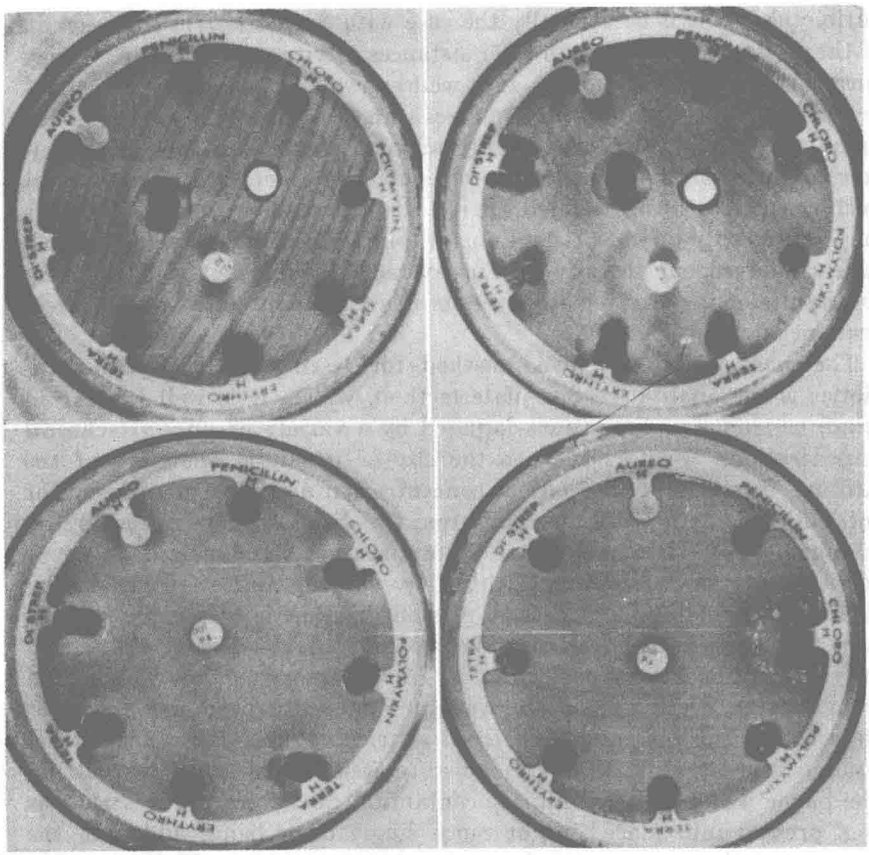

Fig. 1. Qualitative antibiotic sensitivity tests. Top left, Staph. aureus. **Resistant to all except erythromycin, novobiocin *(AL in center)*, bacitracin *(dark disc in center)*, and ristocetin *(white unmarked disc, narrow zone of inhibition, in center). Top right, Staph. aureus.* Sensitive to all drugs except polymyxin B. *Bottom left, Klebsiella* from urinary tract infection. Sensitive to all except erythromycin, penicillin, and nitrofurantoin *(center). Bottom right, Klebsiella* from urinary tract infection. Resistant to all except chloramphenicol.**

tative significance is to be ascribed to the width of the inhibition zone—any appreciable zone indicating that the strain is "sensitive," little or no inhibition that it is "resistant." This type of antibiotic sensitivity testing has its widest application in the management of urinary tract infections.

Table 2. Sensitivity to Antibacterial Drugs of Four Common Gram-Negative Urinary Tract Pathogens

Per cent of strains[a] (July 1956–July 1957)[b] sensitive in vitro to:

Antibacterial drug	*Streptomycin*	*Chloram-phenicol*	*Tetracycline*	*Nitro-furantoin*	*Neomycin*	*Polymyxin B*	*Novobiocin*
Micrograms per disc[c]	*100 (100)*	*30 (60)*	*30 (60)*	*150*	*30*	*30 (30)*	*30*
Bacterial species[d]							
Escherichia coli	86 *(46,47)*	97 *(91,95)*	73 *(52,49)*	93	89	81 *(68,81)*	—
Klebsiella (Klebsiella pneumoniae or *Aerobacter aerogenes)*	37 *(27,30)*	87 *(87,86)*	38 *(47,38)*	74	91	57 *(61,74)*	—
Proteus sp.	55 *(53,49)*	85 *(80,75)*	12 *(16,7)*	69	75	2 *(4,3)*	77[e]
Pseudomonas sp. *(B. pyocyaneus)*	21 *(6,28)*	13 *(20,44)*	6 *(11,13)*	4	52	56 *(94,93)*	—

[a]Values in parenthesis taken from Horton and Knight,[7] each pair representing per cent of organisms found sensitive in the years 1953 and 1954, respectively.

[b]Sensitivity tests performed by Louis Goode, Department of Microbiology, Columbia University, College of Physicians and Surgeons, New York.

[c]Figures in parenthesis are "high" concentrations used by Horton and Knight.[7]

[d]100 strains of each species except as noted.

[e]47 out of 61 strains tested.

INFECTIONS OF THE URINARY TRACT

Because infection of the urinary tract is a frequent complication of pregnancy, it would be well to re-emphasize certain aspects that have otherwise been amply and repeatedly reviewed.[1, 10] Firstly, it cannot be said too often that the accuracy of bacteriologic diagnosis is directly proportional to the care with which the sample of urine is obtained for culture. An increasing number of authorities in the field warn that catheterization, performed solely for the purpose of obtaining cultures, is to be avoided because of the real danger of introducing infection. "Clean" mid-stream specimens, which can easily be obtained from a cooperative patient, are to be preferred. The necessity for prompt planting of such specimens on appropriate media is obvious, since the normal vaginal and fecal flora, which unavoidably contaminate even catheterized specimens,[2, 6, 17] will multiply in a few hours in a urine sample left standing at room temperature. Although true mixed infections do occur, especially in chronic pyelonephritis, the recovery of more than one bacterial species on culture casts doubt on the significance of any individual organism as the true pathogen, and suggests that contamination and overgrowth may have occurred. As repeatedly stated by others,[9, 15, 19] the presence of bacteria in sufficient numbers to be visible in a Gram stain of unconcentrated urine probably indicates infection, and therapy may be instituted on the basis of this single examination, supplemented by subsequent results of culture. Furthermore, significant acute infection of the urinary tract is rare in the absence of pyuria, also detectable on direct smear.

The majority of acute urinary tract infections are caused by gram-negative organisms constituting normal intestinal and vaginal flora. The most important are *E. coli* and related paracolon species, *Klebsiella, Proteus* sp., and *Pseudomonas* sp. (*B. pyocyaneus*). Enterococci (including *Str. fecalis* and group D streptococci), as well as staphylococci, are less frequently encountered. As pointed out earlier, antibiotic sensitivity testing is not necessary, in most cases, for determining optimal therapy, even with the gram-negative organisms mentioned. It should be emphasized, however, that while good correlation generally exists between in vitro and in vivo efficacy against gram-negative organisms, such correlation is best when the bacteria are highly susceptible and least when they are more resistant. This is equivalent to stating that a given strain can often be eradicated from the urinary tract with an antibiotic to which it shows evidence of resistance in the usual in vitro sensitivity test. Thus for *E. coli* and *Klebsiella* infections, drugs of the tetracycline group or chloramphenicol may be used with considerable success, despite the in vitro resistance demonstrable with occasional strains, particularly

Klebsiella. Nitrofurantoin (Furadantin) has found wide application and is successful against the coliforms as well as against *Proteus* strains. The latter are notoriously difficult to eradicate from the urinary tract, even with multiple antibiotics. The newer antibiotics, notably novobiocin and kanamycin, show some promise of usefulness in these infections. Most strains of *Pseudomonas* are resistant to all antibiotics except polymyxin B.

Table 2 shows the results of qualitative antibiotic sensitivity tests performed on 100 strains each of *E. coli, Klebsiella, Proteus,* and *Pseudomonas,* recovered from urine cultures during the one year period July 1956 to July 1957. These strains were tested in pure culture with uniform technique by one person. As anticipated, the majority of strains of *E. coli* were found sensitive to the broad spectrum antibiotics and to nitrofurantoin, but somewhat less regularly sensitive to streptomycin (73 per cent). In contrast, less than half of the strains of *Klebsiella* were sensitive to tetracycline and streptomycin but most were inhibited by chloramphenicol and nitrofurantoin. Tetracycline, however, is useful in *Klebsiella* infections more often than these figures would suggest. Only 12 per cent of the *Proteus* strains were susceptible to tetracycline and about half (55 per cent) to streptomycin. Chloramphenicol, nitrofurantoin, and novobiocin were about equally effective. The most uniformly resistant organism was *Pseudomonas* (*B. pyocyaneus*), against which polymyxin B was the only drug giving inhibition with any frequency. Analogous values taken from another and more extensive study[7] are also given in Table 2, being based on essentially similar techniques and criteria. The findings are generally in good agreement, and are presented only to illustrate a now well established pattern in this group of organisms. It should be emphasized that the foregoing considerations mainly apply to acute uncomplicated infections of the urinary tract, from which it is possible to eliminate sensitive bacteria, in more than 90 per cent of cases, with the correct drug, i.e. one to which in vitro sensitivity is accurately predictable on the basis of past experience, or is demonstrated by actual testing. It is important to give adequate therapy over a relatively short period of time, because after five to six days of treatment the chances of replacing the original sensitive strain with a resistant one of the same species will increase greatly. This, as already pointed out, is due to the ability of the common gram-negative urinary pathogens to acquire resistance rapidly to streptomycin and somewhat more slowly to the other antibiotics. The outlook for permanent cure in chronic pyelonephritis is much less good, even though antibiotic therapy may cause a temporary disappearance of bacteriuria. The value of sulfonamides, particularly the newer, more soluble compounds, such as sul-

fisoxazole (Gantrisin), should not be overlooked, especially in acute *E. coli* infections.

THE STAPHYLOCOCCUS AND THE PROBLEM OF MIXED INFECTIONS

While much has been written in recent months about staphylococcal infections, particularly those due to hospital-acquired antibiotic resistant strains, too much emphasis has often been placed on the importance of the in vitro sensitivity as it may relate to therapy. Although most so-called "hospital strains" appear to be penicillin resistant when tested by the usual qualitative methods, penicillin can nonetheless be given in sufficient dosage to achieve blood levels that are often effective against such relatively resistant organisms. This antibiotic should therefore always be the first to be used, supplemented by chloramphenicol, erythromycin, or novobiocin, in the treatment of staphylococcal disease, regardless of the results of antibiotic sensitivity tests. It might be added that "treatment failures" are less often due to apparent in vitro resistance of a given strain to the antibiotic being used, than to the nature and distribution of the staphylococcal infection in the patient, which render the organisms unassailable by even the most potent antimicrobial agents.

All of the foregoing is predicated on the assumption that accurate and reliable bacteriologic diagnosis is possible in each individual case. It is here, however, that the argument appears to lose force, since even with the best judgment and techniques specific bacteriologic diagnosis is not always established with certainty. One common problem is that of anaerobic endometritis, a complication to which prolonged labor, with ruptured membranes or retention of a dead fetus, necrotic tissue or blood, predispose. These conditions favor invasion of the normal body flora into tissues usually free of bacteria. A mixed culture is almost always recovered, even if samples are taken of exudate at the os cervicis. Gram-negative organisms, anaerobic streptococci, and other anaerobic organisms such as bacteroides are found. Assigning the role of primary pathogen is admittedly difficult unless an organism is also recovered from the blood stream. The latter circumstance, however, is more the exception than the rule. The effect of antibiotic therapy on such mixed infections is almost impossible to assess in retrospect, and therefore also difficult to outline exactly in advance. Sensitivity tests on mixed cultures are useless as a guide, since it is impossible to establish under these circumstances a correlation between in vitro sensitivity and therapeutic effect. Penicillin and streptomycin would appear to take care of many of the major etiologic possibilities, when supplemented by any of the