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CLINICAL USES OF CURRENTLY AVAILABLE ANTIBIOTICS*

BY

MAXWELL FINLAND, M.D.†

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts)

In approaching this subject I have taken the liberty of giving it a rather liberal interpretation. I have not considered it my task to present a thoroughly documented review of the clinical results that have been reported in the vast and rapidly growing literature on the medical uses of the currently available antibiotics. It has seemed to me more suitable to give some general views and interpretations concerning current clinical uses of available antibiotics, first from the point of view of the individual agents and then with respect to their application to special diseases or in special situations. There is still left too wide a range of topics, so that, of necessity, only a few can be touched upon, and these only briefly. For more complete reviews of recent literature with adequate documentation and interpretation the reader is referred to Dr. Welch's book, in its forthcoming revision, and to the papers in the *Annual Reviews of Microbiology* for the years 1951, 1952, and 1953 by Herrell, Kirby, and Heilman, respectively.

In recent years it has become abundantly clear that new antimicrobial agents with activity which clearly overlaps or even closely parallels that of previously available agents can achieve wide acceptance and use in a rather brief time. Moreover, new agents and some which had previously been unpopular, or generally thought to be inferior or even discarded, can gain acceptance and, in some instances, even supersede others which have been regarded as of proved efficacy or superiority. This phenomenon is of considerable significance in relation to the understanding of current usages and is open to diverse interpretations.

First and foremost, one is confronted with the fact that by far the greatest proportion of the antibiotics that are used to-day are prescribed for conditions which have no clear relation to the efficacy of those agents. Indeed, in most instances the relative efficacy of the various agents for the particular uses to which they are put has not been clearly assessed, and in fact is usually difficult or impossible to evaluate. In the choice of agents for most prophylactic purposes or for the treatment of mild and relatively unimportant infections, or for the combined use of multiple agents, preference is likely to be shown to those which are considered relatively harmless rather than to be superior. When any

one agent is used freely over long periods and without proper indications, there almost inevitably comes an awareness of the sensitizing and other potential toxic effects of the agent so used and also of its inadequate therapeutic effectiveness. Under such circumstances it seems easier to shift to a new one rather than to become more selective with respect to the patients to be treated and agents to be used.

Investigators who conduct the initial clinical trials of new antibiotics in their anxiety to discover and reveal as much as possible about the potential usefulness of these agents often publish their results prematurely. Although they may present these results accurately and interpret the findings with the greatest caution, their findings and the conclusions are often grossly exaggerated and misinterpreted or given new meanings, both by readers who wish to justify some particular applications and by manufacturers who wish to exploit their products. Such preliminary trials can generally be expected to uncover only the broad outlines of the field of usefulness of a new agent. More definitive evaluations, concerning both the absolute and the relative efficacy and toxicity, require prolonged and controlled clinical trials, and such trials have only rarely been made before the use of a new and promising agent has already been widely adopted.

Real or apparent increases in clinical resistance have been encountered in infections caused by staphylococci, *Pseudomonas*, *Proteus*, and some coliform organisms (and possibly also enterococci and non-haemolytic streptococci); these have obviously offered a legitimate field for new antimicrobials or for changing the emphasis in the use of the available ones. Such changes, however, have frequently, and sometimes unavoidably, been carried beyond the proper and proved indications.

The desire of the physician to do everything possible and "not to miss a trick" has also led to the persistent use of agents in infections or conditions in which they are known to lack efficacy, such as viral, fungal, or parasitic diseases, and in fevers of undetermined aetiology, when an infectious agent cannot be readily determined or excluded. The fact that most of these patients recover in the course of such therapy seems to be accepted as adequate justification for continuing this practice.

Then there is the growing use of multiple agents. This has its legitimate origin and sanction from *in vitro* experiments with certain specific organisms and combinations of antibiotics, and also has been demonstrated in a very limited number of specific infections, likewise with well-defined combinations of antibiotics. It has, however, been broadened in general practice to include

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almost all serious infections, or merely febrile illnesses that seem to resist treatment with individual agents. This use of combined therapy has reached the point where it is uncommon, in certain areas, to encounter a patient who has had fever for several days and has not already been given many agents, either in succession or, more often, simultaneously, so that he is receiving as many as four or even six antimicrobials at one and the same time. While most physicians are apt to be apologetic about such usage, others not only condone it but actually recommend it as the preferred practice.

Finally, there is the ever-present and overwhelming mass of commercial literature and persuasive advertising and "detailing" by manufacturers and their representatives, emphasizing the virtues of their own respective product and of course the glaring faults in the products of others, while ignoring or minimizing the limitations and undesirable features of their own products. This is an almost inevitable but also a very highly valuable feature of our free economy; but its advantages to the patient can be fully realized only if there is a properly critical attitude on the part of the physician at whom all this is directed.

Penicillin

It seems almost commonplace to mention that penicillin is still the most effective and least toxic agent available for the treatment of most infections due to organisms which are moderately or highly sensitive to it *in vitro*. Some of its usefulness, however, has been reduced by excessive and unnecessarily widespread usage over the past few years, which has resulted in the sensitization of large numbers of individuals and, in the case of the staphylococcus, by the gradual elimination of sensitive strains. The general recognition of the increase in resistance of pathogenic staphylococci to penicillin in all hospitals and communities where this agent is used very extensively has also raised the obvious question of whether penicillin might be losing some of its effectiveness in other infections for which it is generally employed. The tendency to prescribe dosages which appear inordinately high and ever increasing in relation to the previously known sensitivity of the strains of organisms in the diseases for which it is being used has inevitably given the impression of diminished efficacy; it is more likely, however, that this has little or no relation to any established factors other than fashion and usage.

Thus far, there appears to be no evidence of any decreased activity *in vitro* among recently isolated strains of organisms, at least of the more sensitive species—namely, gonococcus, pneumococcus, and group A streptococcus. Likewise, there seems to be no change in the clinical efficacy of penicillin against infections caused by these organisms. There also has been no significant change in the effectiveness of penicillin in the treatment of syphilis since the use of purified crystalline penicillin G was standardized. In subacute bacterial endocarditis, on the other hand, it is possible that some decrease in efficacy of penicillin is responsible for the present need for large doses. This, too, may have its origin in the widespread use of penicillin, which may have resulted in a general, though not so marked, reduction in the sensitivity of strains of the viridans group of streptococci, which are so universally present as part of the normal flora of the mouth and which are also the major cause of this disease.

Little can be said about the relative effectiveness of the various new forms of penicillin. L-Ephenamine penicillin G ("compenamine") and penicillin O (allylmercaptyl penicillin G), with its repository form chlorprocaine penicillin O, are presumed to be equivalent in their therapeutic effectiveness to penicillin G and to procaine penicillin; although this has not been conclusively proved, there is no evidence to the contrary. In the case of penethamate (the hydriodide of diethylaminoethyl ester of penicillin G,

"neo-penil") conclusive proof is still lacking for any superiority in its therapeutic effectiveness over penicillin G or procaine penicillin in conditions in which a specific localization might be considered advantageous. These agents are of particular interest with respect to hypersensitivity reactions.

Perhaps the most important problem concerning penicillin relates to the choice of the dosage form for its systemic use. Oral penicillin in the buffered tablets of the sodium or potassium salts is well absorbed; even so, it is only about 10 to 30% efficient, so that from three to ten times the intramuscular dose is necessary to achieve the same therapeutic effect. Oral penicillin should therefore be entirely feasible for the therapy of infections with highly sensitive organisms such as gonococcus, group A streptococcus, or pneumococcus, and its relatively low sensitizing potential would tend to recommend it for such uses. However, experience with oral penicillin therapy of acute gonorrhoea, in which one is dealing with the most sensitive of these organisms, has not proved as satisfactory as with the intramuscular forms. Moreover, in sick patients suffering from severe infections in which large doses are required, it is often difficult to administer, and, in addition, may also entail gastro-intestinal disturbances similar to those encountered with other antibiotics (erythromycin, carbomycin, and the broad-spectrum antibiotics) when it is given in similar or larger total amounts. Oral penicillin cannot, therefore, be recommended as a dosage form of choice in the treatment of severe infections due to organisms which are only of low or moderate sensitivity to that antibiotic.

In approaching the problem of dosage and the choice of a parenteral form of penicillin for the treatment of infections with organisms that are only slightly or moderately sensitive, one must consider (1) the nature of the lesion, particularly with respect to the accessibility of the organisms within that lesion to penicillin reaching it from the circulating blood; (2) the density of the bacterial population at that site; and (3) the possibility of intervention of host or immune factors to aid in disposing of small numbers of residual organisms. For most of the background of our understanding of this subject we are indebted to the laborious and carefully designed studies of Eagle and his co-workers. He has established the rationale of large and intermittent dosage and the need for achieving concentrations in the blood which are many times the minimum *in vitro* inhibiting concentration, and also the necessity for long-continued treatment in order to eradicate established foci of infection in which there are large numbers of organisms. The experiments of Weinstein and his co-workers extended these findings and showed that if a sufficiently high concentration is achieved in the tissue fluids, effective concentrations can be reached within fibrin foci, and these concentrations will then drop more slowly than those of the surrounding tissue fluids.

From these observations, and from the very rapid rate of excretion of penicillin by the kidney, one may conclude that the intermittent intramuscular injection of the aqueous sodium or potassium salts is preferable to the repository preparation for the treatment of deep and walled-off foci of infection. Obviously, the longer the antibiotic remains in the repository site the flatter will be the curve of the concentrations within the blood and tissue fluids; also, the high gradient necessary to penetrate the walled-off foci is less readily achieved by such repository preparations. On the other hand, repository forms may be useful even for deep foci of infection, whenever the organisms are sufficiently sensitive and there is adequate access to tissue fluids, as may be the case in syphilitic or haemolytic streptococcal infections.

The same reasoning which has led to these conclusions also offers some rationale for the use of inhibitors of renal excretion of penicillin, such as probenecid ("benemid"), to raise the peak levels and sustain high concentrations between intermittent intramuscular injections; it could also be used as an argument for the support of the intermittent rapid intravenous injections as opposed to continuous intra-

venous injection during probenecid administration for the purpose of obtaining high peaks of concentrations in the treatment of subacute bacterial endocarditis or of walled-off foci of infection with organisms of low sensitivity.

Streptomycin

Although streptomycin remains the major mainstay in the treatment of tuberculosis, two important features have led to renewed interest in this agent and an increase in its systemic use in many non-tuberculous infections. One is the use of smaller doses (1 or 2 g. a day) and shorter courses, which minimize the occurrence of the major toxic effects of this antibiotic on the eighth nerve; the other is the use of streptomycin in combination with other agents, particularly with large doses of penicillin, which has resulted in an increase in its effectiveness against relatively resistant Gram-positive organisms, coupled with a reduction in the rate and degree of emergence of streptomycin-resistant variants. The latter usage is best typified in the treatment of bacterial endocarditis due to organisms which are only slightly sensitive to either penicillin or streptomycin separately. It is important, however, to avoid the use of streptomycin alone in such cases, lest resistant variants emerge rapidly during such use and subsequently interfere with the successful application of the combined therapy.

The rapid bactericidal action of streptomycin has, in our experience, been most helpful in the early acute stage of severe infections with Gram-negative bacilli, particularly in Friedländer's pneumonia, although the character of the necrotizing lesion in the latter has militated against its continued effectiveness and against its success in completely eliminating the organisms. Resort must then be had to other antibiotics to which the residual organisms are sensitive. Streptomycin is still useful either alone or together with other antimicrobial agents in the treatment of meningitis, infections of the urinary tract, and other severe infections with susceptible organisms; also, used together with penicillin and/or sulphonamides, it still has an important place in the prevention and treatment of generalized peritonitis. The importance of alkalization of the urine in enhancing the effectiveness of streptomycin in the treatment of urinary tract infections cannot be overemphasized.

A serious question may be raised whether the generally prevailing use of dihydrostreptomycin in preference to streptomycin has a sound basis. It now seems clear that dihydrostreptomycin tends to produce a predominantly auditory-nerve damage which may be insidious and delayed in its onset and usually is irreversible; streptomycin, on the other hand, gives rise predominantly to vestibular dysfunction, which may be recognized early, and at that stage, if the treatment has stopped, may be reversible. Any difference in antimicrobial activity of the two agents *in vitro* or in experimental animals is probably slight, but it appears to be predominantly in favour of streptomycin, while no appreciable difference has been demonstrated in the clinical activity of these two forms. Is it not, therefore, more appropriate to consider streptomycin the first choice in therapy as between these two forms, with dihydrostreptomycin reserved for continuing the treatment when it is imperative to do so with evidence of sensitization, or possibly after symptoms of vestibular damage are first recognized? It is possible, however, that this problem may be resolved by the combined use of the two forms if present indications of the much lower toxicity of this combination are more firmly established.

The Tetracyclines

Now that the chemical kinship of "aureomycin" and "terramycin," which had long been suspected, has been fully established, it is appropriate to consider these two agents together and also to include the third one, tetracycline, which chemically has been divested of the distinguishing portions of the structure of each of the other two. Preliminary observations in our laboratory and clinic would

point to a very close similarity in the antibacterial action of these three analogues *in vitro* and *in vivo*. The differences which have been noted *in vitro* seem to be related chiefly to the instability of aureomycin outside of the body, and the clinical differences appear to be related primarily to the lower toxicity of tetracycline.

The relative clinical efficacy of tetracycline may be extremely difficult to evaluate, just as we have found great difficulty in establishing any clear and overall differences in efficacy between aureomycin and terramycin. On the other hand, there seems little doubt that in isolated individual patients, there appears to be a gross and distinguishable difference in activity between the two latter agents, favouring the one or the other, and there may also prove to be such a difference in occasional patients or infections with respect to tetracycline and either or both of the other chemically related substances. From the point of view of toxicity, only the untoward gastro-intestinal effects lend themselves to comparison. Data thus far available would indicate that the use of tetracycline is accompanied by a significantly lower incidence of gastro-intestinal symptoms than is the use of aureomycin in comparable doses and in similar patients. Terramycin, in our clinic, has regularly produced an appreciably greater incidence of gastro-intestinal symptoms than aureomycin, particularly the diarrhoea associated with displacement of the faecal flora by resistant staphylococci.

The tetracycline antibiotics are still highly effective against infections with a wide variety of Gram-positive and Gram-negative bacteria, including many types of bacterial meningitis. In our experience and in many other hospitals *intravenous* aureomycin has also proved to be the most effective single antimicrobial agent in the treatment of acute diffuse peritonitis. One interesting phenomenon that has been noted is the apparently striking efficacy of *intravenous* aureomycin in the treatment of peritonitis due to *Salmonella typhosa* and resulting from perforations of the bowel or of the gall-bladder complicating chloramphenicol-treated typhoid fever.

The tetracyclines are highly effective against all rickettsial infections, and they appear to be the most effective agents available against the psittacosis-lymphogranuloma-trachoma group of organisms. The effectiveness of all antibiotics against trachoma, however, has recently been questioned in some quarters. The popular misconception about the efficacy of these agents against "viruses" had led to many conflicting reports on their use in many diseases known or presumed to be of viral aetiology. In general, it is probably fair to state that no clear-cut proof of the effectiveness of these agents in uncomplicated viral infections has yet been brought forth. Moreover, although most workers have felt that the efficacy of aureomycin in the treatment of cases of primary atypical pneumonia of the type associated with cold agglutinins has been proved, some doubts have also been raised in this regard.

There is, however, clear evidence of a decreasing efficacy of aureomycin and terramycin in the treatment of some staphylococcal infections; this is associated with an increased incidence of staphylococci resistant to these agents. The decrease in effectiveness, however, seems to be limited primarily, or perhaps entirely, to nosocomial infections with staphylococci or to such infections acquired during the course of treatment with one of these agents, and they may in fact be confined to hospitals in which either or both of these agents have been very widely used. There is also a suggestion of a decrease in the effectiveness of the tetracyclines in the treatment of infections with some coliform organisms, particularly *Aerobacter aerogenes*.

Chloramphenicol

The clinical activity of this agent overlaps most of the range of infections which are favourably influenced by the tetracyclines. Chloramphenicol appears to be appreciably less effective against infections with Gram-positive organisms and probably also against the psittacosis-lymphogranuloma-trachoma group of infections. It is somewhat

more effective against some of the Gram-negative bacillus infections, particularly those due to salmonellae and many of the *Proteus* organisms. It is also about as effective as the tetracyclines in rickettsial infections. Chloramphenicol is highly effective in *Haemophilus influenzae* meningitis, and is considered by some authors to be the agent of choice in this disease.

Of prime interest is the fact that although chloramphenicol is generally much less active than penicillin and significantly less active than the tetracyclines against staphylococci *in vitro*, strains of moderate or high resistance to chloramphenicol are rarely encountered. As a result, chloramphenicol has recently proved to be highly useful in the treatment of serious infections due to staphylococci that are resistant to penicillin and to the tetracyclines.

In the treatment of salmonella infections, although chloramphenicol is generally considered to be the agent of choice, it must be conceded that this has been clearly demonstrated only with respect to the clinical response of patients with typhoid fever. Even in this disease, however, the efficacy of chloramphenicol leaves much to be desired, for the most frequent complications in this disease—namely, relapse, perforation, haemorrhage, cholecystitis, and the carrier state—are not entirely prevented; possibly some of them, particularly relapses, have not been reduced at all in frequency even by prolonged therapy with adequate or large doses. In other serious salmonella infections in humans, as in *Salmonella typhi-murium* infections in mice, there is to my knowledge little evidence of any striking and lasting therapeutic benefit from chloramphenicol.

One is hardly justified at this time in leaving the discussion of the clinical use of chloramphenicol without expressing some opinion concerning the severe and fatal bone-marrow depressions which have been attributed to this agent. Extreme views have been expressed on this subject; some have felt that the sale of the drug should be entirely prohibited, while others have even manifested serious doubts that chloramphenicol has been conclusively proved to be the cause of any of the cases of bone-marrow depression which have been attributed to it. Judging solely from the published data, however, it seems difficult to escape the conviction that at least a significant proportion of the cases of blood dyscrasias that have been described may reasonably be attributed to the use of this drug, but that, on the whole, this complication is rare considering the frequency with which chloramphenicol has been used. It also seems reasonable to recommend, as did the National Research Council's *ad hoc* committee, that this agent should not be used repeatedly for minor indications, for prophylaxis, or where any risk at all would be difficult to justify. On the other hand, in the treatment of those significant and serious infections for which chloramphenicol is clearly preferred or indicated on the basis of its known clinical performance, there seems no reason to hesitate to use it.

It has generally been recommended that frequent blood counts be made if chloramphenicol is to be used. Actually such counts, if done at frequent intervals during an initial course of treatment of the average duration, can hardly yield information of value, since by far the majority of cases of blood dyscrasias that may arise probably would show little change until some time after treatment is discontinued. It is possible, of course, that some appropriate test may be devised which would reveal the earliest evidence of such potential trouble, and haematologists should be encouraged in every way to attempt to find such a test. However, a rapid drop in the total leucocyte or neutrophil count in the blood is often encountered in the first few days of treatment in many serious infections and accompanies a favourable clinical response; this is usually followed by a gradual return of the count to normal levels, even while treatment is being continued. Such findings should suggest further observation, but not discontinuance of the drug, unless it no longer is indicated for treatment of the disease. On the other hand, in view of the importance of the problem and the paucity of thoroughly authenticated data, physicians should be encouraged to make complete blood studies

before treatment with this or other potential bone-marrow depressants is initially undertaken, and again later, particularly before subsequent courses of treatment with such agents. Logistically, however, the probability of encountering abnormal findings that are significant and indicative of future serious trouble are extremely small, judging from the very low incidence of this serious complication. Initial counts, however, are significant in order to rule out antecedent blood dyscrasias.

Erythromycin and Carbomycin

The antimicrobial spectrum of these two antibiotics appears to be almost identical qualitatively, but against most of the susceptible strains of bacteria erythromycin appears to be appreciably more active than carbomycin. The antibacterial spectrum of both agents resembles closely that of penicillin, but they are said to be active also against rickettsias and against the psittacosis-lymphogranuloma-venereum group of organisms. Pharmacologically, erythromycin and carbomycin differ greatly. Oral administration of erythromycin, especially with alkali, yields rather high concentrations in blood and urine. Significant concentrations of carbomycin, however, are not readily demonstrable in the blood, except in patients with jaundice, and, although rather high concentrations are found in the bile, very little active carbomycin is recovered from the faeces and urine.

Erythromycin seems to be somewhat less effective than penicillin against most infections with Gram-positive organisms and much less effective against gonococcal infections. Its major usefulness has been in the treatment of staphylococcal infections, particularly those resistant to penicillin, aureomycin, and terramycin, and the results in such cases have, on the whole, been encouraging. Failures in patients with endocarditis have been associated with development of resistance in the staphylococci during the course of treatment. Similarly, the development of resistance seems to be the major cause of most of the failures of erythromycin treatment in cases of enterococcal and *Streptococcus viridans* endocarditis; only rarely have such cases responded favourably to treatment with this agent alone. In these cases, better results may possibly be obtained by the use of erythromycin in combination with penicillin, streptomycin, or bacitracin, which may increase the activity and delay or prevent the development of resistance in the infecting organism.

The results of the use of carbomycin in the treatment of infections with bacteria that are susceptible to it *in vitro* have, generally speaking, not been very favourable, and, on the whole, they have been quite inferior to those obtained with erythromycin in similar cases. Indeed, in the treatment of pneumococcal pneumonia the appearance of bacteraemia and the development of purulent complications, including meningitis, during the course of treatment with maximum tolerated doses of carbomycin suggest that this antibiotic should be avoided at least in this disease. It has also proved disappointing in the treatment of staphylococcal infections. Of interest, however, are reports indicating that carbomycin may be effective in the treatment of amoebiasis and in cases of granuloma inguinale (Donovanosis).

Bacitracin, Polymyxin, and Neomycin

These three agents are grouped together because their inherent toxicity when they are used parenterally has greatly limited their use in systemic diseases. Each, however, has been successfully used by the intramuscular route in important and serious infections when others have failed.

Systemic bacitracin has proved particularly useful, alone or with penicillin or other antibiotics, in the treatment of a few cases of bacterial endocarditis and in other cases due to Gram-positive organisms resistant to other antibiotics. Occasional successes have also been reported in meningitis and brain abscess due to similar organisms; in these conditions it is said to be devoid of local irritation, thus permitting topical application, intrathecally, intraventricularly, and into brain abscesses. The local irritation from intramuscular injection, however, may be quite marked, but this is minimized by including procaine with the diluent and by limiting

individual injections to 25,000 units or less. The nephrotoxicity of bacitracin, which is inherently related to its activity, is generally transient; it has also been limited to some extent by improvements in manufacture, but chiefly by keeping the average daily dose in adults down to 100,000 units or less, maintaining the urine at a neutral or slightly alkaline pH, and avoiding systemic treatment or using it with great caution in patients who already have reduced renal function.

Polymyxin B, likewise, has found special uses, locally and systemically, in the treatment of infections with strains of *Pseudomonas* and other Gram-negative bacilli which are resistant to other forms of treatment. As with bacitracin, the nephrotoxicity has been either avoided or transient, or kept at a minimum by proper dosage, and in children the drug has not been much of a problem when properly used. The local irritation and slight fever from intramuscular injections has been found to be much lower in purified preparations of polymyxin B and more recently in preparations of polymyxin E. The paraesthesias, however, are still a particularly prominent feature of treatment in adults, but do not seem to be very important in infants and children.

Neomycin is probably the most toxic of these agents when used systemically, producing renal and auditory damage with sufficient frequency and severity to justify its use in this manner only under circumstances which warrant great risks. The toxicity is minor when the dose is kept at 1 g. a day and given for brief periods. When so used, it may be of value in some infections with organisms sensitive to this antibiotic, but considered to be resistant to other agents.

The major uses of bacitracin and also of polymyxin and neomycin, at present, seem to be their local application in the treatment of infected wounds and dermatological lesions. Their low irritating and sensitizing potential when used in this manner has made them especially suited for these purposes. Moreover, such usage is particularly appropriate because of the higher sensitizing potential of most of the antibiotics that are more commonly used for systemic therapy. The reports of such topical use, which have come primarily from dermatologists and surgeons, are generally favourable, but they are often difficult to evaluate. These antibiotics have been used separately and in various combinations, often all three of them together and sometimes with streptomycin. When so used they exert a powerful bacteriostatic and bactericidal effect on a wide range of bacterial species.

Each of these three antibiotics is also very poorly absorbed from the gastro-intestinal tract. Advantage is taken of this property for their use in reducing the bowel flora. Various combinations of bacitracin, polymyxin, neomycin, and streptomycin have proved as effective as any other agents previously used for this purpose. Neomycin in particular seems to be favoured at the moment by some authorities in this field because of its broad antibacterial range and its rapid action. It is less active than bacitracin against clostridia and other Gram-positive organisms, so that the two of them have been used successfully together. Bacitracin and polymyxin likewise cover a wide range of activity, which, however, does not include the *Proteus* organisms.

Special Uses

A few remarks about the use of antimicrobial agents in some selected situations may be appropriate, though it is appreciated that one can hardly do justice to those subjects in a presentation of this sort.

Urinary Tract Infections

First, in urinary tract infections, a critical survey of current reports suggests that there may be a declining efficacy of the available agents. This may be more apparent than real, and may be due in part to the fact that much more is expected of antimicrobial agents than is justified on the basis of their known activities. The cases in which there are partial or total failures keep returning, and temporary relief is followed by further relapses or reinfections,

either with resistant strains or, more often, because the underlying and predisposing factors have not been or cannot be corrected. Eventually one is left with a group of patients who have residual infections which resist all available agents until some new one with a slightly different action appears. This may again give temporary relief. Infections with *Pseudomonas*, *Proteus*, and *Enterococcus*, and more recently an increase in *Aerobacter* infections, seem to be most frequently encountered in such resistant cases. A similar situation exists among patients with chronic bronchopulmonary suppurative lesions in which organisms not usually considered to be respiratory pathogens are now being found with increasing frequency as a result of the repeated elimination of the common respiratory pathogens by the use of increasing amounts and varieties of antimicrobial agents.

Bacterial Endocarditis

The problem of therapy in cases of bacterial endocarditis in which blood cultures are persistently negative has recently received special prominence because of the higher mortality in such cases as compared with that in patients with positive blood cultures. Needless to say, appreciation of the seriousness of this disease, of the need for prolonged and intensive treatment, and of the importance of a thorough knowledge of the aetiological agent is not only desirable but almost imperative for the proper conduct of such therapy. This is necessary not only for the choice of the agent but for the determination of dosage and duration of treatment; and it emphasizes the importance of making every effort to identify the aetiological agent before treatment is begun.

In patients in whom bacterial endocarditis is at all suspected, it is particularly important, therefore, that the usual tendency to give penicillin or other antimicrobial agents be avoided until proper blood cultures have been taken. Such treatment may not only reduce the chances of subsequently obtaining positive blood cultures but may even render it impossible to do so. Moreover, there is evidence that such treatment, which is usually inadequate to produce a cure, may appreciably increase the difficulty in subsequently obtaining a cure even when positive blood cultures are obtained and large doses of properly selected agents are then given. However, after proper cultures have been made and while awaiting the results, it may be desirable or even imperative to begin treatment. In such cases the preferred antimicrobial treatment would seem to consist of large doses of penicillin given in the aqueous form by intermittent intramuscular injection and supplemented by moderate doses of streptomycin. The dose of penicillin can be increased steadily after several days if the response still seems inadequate, and probenecid may also be added. If evidence of infection continues, and no bacterial agent has been forthcoming to provide the basis for a rational change, treatment becomes essentially a matter of trial and error, and the present tendency to use multiple agents often prevails.

Clinical and bacteriological cures in a few cases of bacterial endocarditis of known and varied aetiology have been reported during treatment with chloramphenicol, terramycin, or aureomycin, particularly the latter, but these agents are not the antibiotics of choice in such infections. In the majority of reports of their use in such cases, marked inhibition of the infection, with clinical improvement and negative cultures, occurred—sometimes for prolonged periods during treatment—only to be followed by relapses of symptoms and bacteraemia after these drugs were discontinued. In most of these cases the subsequent administration of the same antibiotic in combination with others, or the use of other combinations, particularly massive doses of penicillin plus streptomycin, has resulted in cures. One possible cause of failures of treatment with aureomycin and terramycin has been the difficulty of sustaining treatment with the desired doses for long periods. From current clinical indications this may be more feasible with tetracycline, and better results may be forthcoming in some cases if, indeed, this was an important factor in the earlier failures. Development of resistance in originally sensitive organisms during

the course of treatment has only rarely been found responsible for failures of therapy with these antibiotics, in contrast to the findings in cases treated with erythromycin.

Meningococcal Infections

Meningococcal infections appear destined to increase in prevalence during the coming years. There is no evidence to indicate that the sulphonamide drugs, particularly sulphadiazine, have as yet been displaced as the most effective agents in the treatment of infection with this organism. The occurrence of sulphonamide-resistant strains, if they have been encountered, must be extremely rare. However, the general tendency of physicians to inject procaine penicillin, or some other repository form of penicillin, into all patients with fever may result in an increase in the number of failures in the treatment of this disease. Moreover, although the use of huge intramuscular doses of soluble preparations of penicillin may be effective in the treatment of meningococcal meningitis, such a regimen hardly seems warranted and can hardly be recommended as the treatment of choice if the sulphonamides are equally or more effective.

Hormone Therapy

In connexion with the problem of meningococcal infections, any increase in their prevalence is inevitably associated with an increase in the occurrence of cases of the so-called Waterhouse-Friderichsen syndrome. Since the adrenal hormones have been generally accepted as an integral part of the treatment of this condition, it seems appropriate to raise the question of the use of adrenal hormones in infection. This subject was reviewed by Thomas,¹ and more recently by Kass and Finland.² Among certain groups of clinicians interested in this subject there are apparently widely divergent views which, because of the paucity of adequately controlled data, are quite difficult to reconcile. There are those who feel that such hormones should be given to all patients with severe infections in order to hasten the symptomatic recovery while awaiting the more lasting and curative effects of antibiotics. Others, aware of the increase in severity of infections which may result, and which may reduce the effectiveness of antimicrobial therapy, have felt that the risk is unwarranted, unnecessary, and only rarely justified, and that the few unfavourable results may more than balance any temporary and apparent advantages. The middle course is taken by those who, recognizing the dangers, have limited the use of the hormone treatment to the first day or two while antibiotics are being given, in the hope of obtaining the maximum benefits from the hormones while incurring a minimum of risks from their use.

There is general agreement that in experimental infections cortisone and A.C.T.H. enhance infections of almost all types. It is also clear that this enhancement of infection or decrease in resistance to infection is quite non-specific with respect to the microbial aetiology of the disease and is even independent of multiplication of the organisms themselves, since it can be demonstrated in the increase in necrotic action of bacterial toxins alone. There is also abundant evidence that many types of human infections are aggravated by treatment with A.C.T.H. and cortisone, and that such treatment also gives rise to spontaneous infections with organisms that are normally saprophytic, or renders clinically active other infections which may be latent. This enhancement of infection, however, is associated with certain non-specific alterations in the clinical manifestations of infection which include a drop in temperature and increase in the general appearance of well-being which are known to be the direct results of hormone therapy and which occur in spite of advancing infections. These non-specific effects make it difficult and sometimes impossible to evaluate the course of the infection or to recognize the occurrence of new and complicating infections.

Proper evaluation of the hazards involved in the hormone therapy of infections is still not possible, and awaits care-

fully controlled clinical and bacteriological studies on a large number of cases. The difficulties of evaluating results of such usage are increased by the fact that full advantage is usually taken of the beneficial effects of antibiotics during the administration of the hormones. Indeed, the realization of the prospect of enhancing an infection generally leads to the use of multiple antibiotics, and in large doses, along with the hormones.

With respect to the specific problems presented by the Waterhouse-Friderichsen syndrome it is well to point out that in spite of the readiness of most clinicians to admit the need for adrenal hormones in this condition there is little or no acceptable proof that an adrenal insufficiency is a major or an important factor in this disease. Certainly it has never been clearly demonstrated that there is any residual adrenal insufficiency in patients who recover from this disease with or without hormones. There is also little evidence that there is any specific difference in adrenal activity in this disease as compared with that in other severe infections or toxæmias in which there is definite evidence of increased adrenocortical activity. With respect to the hypotensive or shock-like phase of this syndrome, the question may properly be raised whether this may not be better managed by the use of agents specifically directed against the hypotension, while awaiting the specific curative effects of the antibacterial agents.

Prophylaxis

There is little doubt that, in the U.S.A. at least, the total volume of antimicrobial agents used in prophylaxis or for minor and irrelevant indications exceeds by manyfold the total amount used in the treatment of infections for which they are specifically indicated. In the recent report on the use of one agent at a large community and teaching hospital it was revealed that 65% of the patients received that agent solely for prophylaxis, and many of the same patients had been given other antibiotics at the same time. It is obviously impossible to evaluate such usage. A few words concerning some of the more specifically directed prophylactic uses of antimicrobial agents may be in order.

In evaluating prophylaxis it is desirable to know, first, the objective and how that can best be measured; second, the best method of accomplishing that objective; and, third, the price that must be paid, not particularly in dollars and cents, but in terms of serious side-effects. As to the objectives, one may differentiate several types of uses.

(1) Mass prophylaxis of short duration and for a specific purpose, as in the use of sulphadiazine in the elimination of meningococcal infections and carriers.

(2) Mass prophylaxis on a continuous basis, as in the attempt to minimize acute respiratory infections through the administration of sulphadiazine.

(3) Individual prophylaxis on a continuous basis, as in the use of sulphonamides or penicillin in the prevention of recurrences of rheumatic fever indirectly through the prevention of haemolytic streptococcal infections.

(4) Individual but brief prophylaxis against specific infections, as in the use of oral penicillin following venereal exposures or perhaps in the prevention of ophthalmia neonatorum.

(5) Individual prophylaxis, given in a more prolonged or intensive course, in the hope of preventing various infections, as in the use of antimicrobial agents: (a) in the preparation for bowel resections or immediately after such resections; (b) in women during or after long and complicated delivery; (c) after catheterization or instrumentation of the urinary tract, or after operations in this region; (d) in relation to tooth extraction or dental manipulations in patients with valvular or congenital cardiac defects in the hope of preventing subacute bacterial endocarditis; and (e) during the early phases of management of burns and other potentially infected surface wounds.

The use of antibiotics in the treatment of common colds and acute simple undifferentiated respiratory diseases or in non-streptococcal pharyngitis may perhaps also be included in the latter category because this amounts essentially to the prophylaxis of complicating bacterial infections. On the other hand, early treatment of streptococcal infections

¹ *Ann. Rev. Med.*, 1952.

² *Ann. Rev. Microbiol.*, 1953.

as a means of preventing attacks of rheumatic fever or glomerulonephritis may be considered in a different category, since one is here dealing with an already established infection for which one is administering specific treatment.

The different types of prophylactic uses do not lend themselves equally to proper evaluation. From available data, however, one may easily conclude that the two most successful of these uses have been the mass prophylaxis of meningococcal infections by the administration of a short course of sulphadiazine and the individual prophylaxis of gonococcal infections by the use of single oral doses of penicillin immediately following exposure. The success of these procedures is based on the fact that in these situations one is dealing with specific bacteria against which the prophylactic agents have proved efficacy to a marked degree under the particular conditions in which they are used. Moreover, under these conditions the untoward effects are minimal.

The success of individual prophylaxis of streptococcal infections and recrudescences of rheumatic fever by continuous administration of sulphonamides or penicillin is more difficult to measure, but seems fairly well established. Although this involves a greater risk of untoward effects, that seems warranted in view of the nature of the disease one aims to prevent. In this connexion it may be pointed out that the choice of the optimum agent has not been clearly defined. It may therefore be worth considering that, although penicillin may be slightly more effective for the purpose, it may still be preferable to use another agent, like a sulphonamide, which is adequate for the purpose. Should an infection then occur it is less likely to be resistant to penicillin, which would then be available, and more likely to be effective in the treatment of that infection.

Mass prophylaxis on a continuous basis has been only partially successful, but for the purpose for which it was designed it has served as well as was possible at the time. Such continuous prophylaxis is inevitably accompanied by a much greater risk of untoward effects, some of which may be serious. The experiences with such usage in the U.S. Armed Forces during the second world war taught us the danger of the replacement of the prevalent flora by organisms resistant to the prophylactic agent being used. This phenomenon has more clearly been exemplified, on a different scale and under different circumstances, by the spread of penicillin-resistant staphylococci in hospitals where they are widely and continuously used.

In the experience with sulphadiazine prophylaxis during the second world war it was fortunate that the severe infections with sulphadiazine-resistant streptococci occurred just at a time when penicillin became available, so that the potentially serious consequence of the fact that sulphadiazine was no longer effective in these cases was mitigated by the use of penicillin. This emphasizes the importance of choosing for prophylaxis an agent which is effective, but which is different from the one that must be relied on for the treatment of severe infections that may arise during such prophylaxis.

Individual prophylaxis for specific purposes is of course the major excuse for the widespread use of antibiotics. It is also the most difficult to evaluate. No attempt will be made to do so, but a brief comment on one of the more accepted uses which is considered to be fully justified may be in order—namely, the use of penicillin during dental manipulations in patients with valvular or congenital heart disease for the prevention of bacterial endocarditis. Although the principle of this usage is generally accepted, there is considerable difference of opinion regarding the dosage to be used, whether it is necessary to give the antibiotic before the actual procedure, for how long before and for how long after that procedure. The controversies may stem from the fact that the objective is not entirely clear. For example, if the aim is to eliminate the potential blood-stream invaders from the dental foci it would require large doses given over a long period prior to the dental procedures; only a brief period of treatment would then be

required after the actual operation, unless one were dealing with an infection which had not been entirely eradicated at the time, when resort must be had to more prolonged use of similar large doses. On the other hand, if the aim is merely to clear the blood stream of the organisms which invade just at the time of the dental procedure, a single relatively small dose given at or shortly before that time should suffice.

Obviously one cannot hope to prevent all blood-stream invasions from dental foci, since presumably such invasion takes place during inevitable daily procedures, such as the mastication of food and the brushing of teeth. If one should wish to prevent or to minimize the dangers of such invasions one might be tempted to use continuous therapy throughout the life of the individual. Of the extremes that have been advocated, the use of the single small dose reduces or prevents the immediate bacteraemia and is obviously associated with the least risk of sensitization and other reactions, and also offers the smallest risk of replacing the oral or dental flora by the potential causative organisms of endocarditis, which may be resistant to penicillin, whereas the more prolonged treatment with the largest doses offers the greatest potential risks in these respects, although it may best serve the purpose of reducing or eliminating dental infections.

The final answer to this problem cannot be given, for there seems to be no acceptable evidence that any cases of bacterial endocarditis have actually been prevented by any type of prophylaxis. On the other hand, there are at least a few cases of bacterial endocarditis, fairly well authenticated, which have followed extractions under prophylaxis of various types. Of particular interest is the fact that in the patient who received the largest doses and for the longest period the endocarditis which followed was caused by the most resistant organism. Here is further support for the general idea that the prophylactic agent of choice for any given purpose should be different from the one on which it may be necessary later to place chief reliance for cure of infections that might occur. Put another way, a less active agent may suffice for prophylactic purposes but may not prove adequate for treatment, should that become necessary.

Omnibiotics

The physician in practice, and many of his patients as well, are constantly on the look-out for some simple substance or formula which can be applied with universal success. The busy practitioner is particularly desirous of having some major weapon on which he can always rely to be successful in all types of infections, and which would thus relieve him of the responsibility and trouble involved in the complicated or even simple diagnostic procedures. Whenever such a cure-all has been offered it has usually been grasped with enthusiasm and widely and indiscriminately applied. The disappointment which invariably has followed has always been proportional to the magnitude of the unwarranted promises and claims that had been held out. On the other hand, the discriminate choice of therapeutic agents only on the basis of proper indication and proved efficacy for the desired purpose, though perhaps more difficult to practise, may in the long run be less disappointing and more rewarding.

Summary and Conclusions

This has been an attempt to bring out in a critical manner some of the current problems in the use of the antibiotics at present available. Many of the opinions that have been expressed will undoubtedly meet with honest and justifiable disagreement, for they express only the deductions made by me on the basis of my own experience. There is one conclusion, however, with which few will dissent—namely, that there still remain many problems in the treatment and prevention of infectious diseases which have not been solved by the antibiotics at present available.