Papers and Originals

ANTIBIOTICS REVISITED: PROBLEMS AND PROSPECTS AFTER TWO DECADES*

BY

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Most of my active life in microbiology and infectious diseases has been during the past two decades, and thus has coincided with the general availability of antibiotics for patient-care. Ten years ago, at the invitation of Sir Alexander Fleming, I presented in London our group's work on combined antibiotic action (Jawetz, 1952). After another decade of widespread use of antibiotics it may be appropriate to take stock of the benefits that have accrued and the problems that have reached prominence. Any attempt to adequately review this large field would obviously be doomed. Therefore I have chosen instead to present some isolated topics taken from my personal experiences in the United States.

As a first broad topic I should like to examine the question: To what extent are antibiotics panaceas? To what extent is it possible to prescribe a particular antimicrobial drug without concern for the aetiology of the disease process?

Drug Selection

In clinical meetings one often hears the words: "The patient received antibiotics but failed to respond." Surely this is a meaningless statement. Did the patient receive tetracycline, neomycin, penicillin, or chloramphenicol? Each of these drugs has a specific clinical and pharmacological effect. Perhaps the patient failed to respond because the wrong antimicrobial drug was prescribed. The statement, "the patient received antibiotics," probably dates from the time when penicillin was the main available antibiotic. Administering an antibiotic usually meant giving penicillin. The specific meaning of "the patient received antibiotics" was lost as more and more different antimicrobial drugs became available. Many physicians felt that all these drugs had similar effects because they all acted on microbes—and to most doctors microbes are a hazy, ill-defined recollection of medical-school days. This uncertainty was enhanced by concentrated advertising which claimed almost universal efficacy for each proprietary drug.

The pronouncements of pharmaceutical houses often encouraged the physician's belief that if 3-blindmycin—a drug described in the *Lancet* (1956) as being elaborated by *Micrococcus moribundus*, or embalmers' blight—was effective in one infection, it was probably effective in all infections, no matter what the aetiological agent. Whatever the merits of 3-blindmycin as an antimicrobial agent, it eventually was employed as a tonic for the patient, a placebo for his anxious relatives, and a tranquillizer for the physician. And yet, as a first step in rational selection of drugs we must accept the fact that antibiotics are not tonics. Their therapeutic activity depends solely on their ability to inhibit or kill micro-organisms. Before administering such a drug the physician must therefore convince himself that the patient suffers from a microbial infection.

As a second step it is necessary to acknowledge that each antimicrobial drug has a specific effect on a limited number of micro-organisms. Before selecting a drug the physician must therefore formulate a specific aetiological diagnosis on clinical grounds. The skilled physician's "best guess" can be correct with surprising frequency. Having arrived at a specific clinical diagnosis, the physician can then select a suitable drug aimed at the aetiological micro-organism.

But is it really rationally possible, from the hundreds of antimicrobial drug names, to choose a specific drug for a specific bug? This question requires an answer in two parts. (*a*) While there are hundreds of drug names, there are actually only a few classes of useful antimicrobial agents; the most important ones are these: penicillins, streptomycins, chloramphenicol, tetracyclines, erythromycins, neomycins, polymyxins, sulphonamides. A physician needs to know only *one* representative of each class and should forget about the conflicting advertising which claims superiority for one member of a class over another. (*b*) Each physician can devise for himself a short list of specific primary and secondary indications for each representative of a class of drugs. My current version of such a list is given in the Table. It makes no claim for universal acceptability or permanent validity. However, if the physician follows his own rules, given in *his* list, and rejects the frequent personal and community pressures to alter them, he can greatly simplify the decision on which drug to use and when to use it (Jawetz, 1962).

The physician's initial aetiological diagnosis on clinical grounds permits prompt selection of a drug to institute therapy. Before administering antimicrobial drugs suitable specimens are often obtained to permit the isolation of specific micro-organisms in the bacteriological laboratory. The isolation of a significant organism may confirm the physician's original impression and support his choice of drug. Conversely, it may force a change in antimicrobial therapy. The identification of the aetiological micro-organism is often far more meaningful than "sensitivity tests" to antimicrobial drugs.

Over-reliance on "Sensitivity Tests"

Although laboratory methods for the selection of drugs active against the micro-organism isolated from the patient can occasionally be an invaluable aid, the reliance on sensitivity tests is greatly overemphasized. Often such tests may be unnecessary or even misleading. Unless the sensitivity test result bears a definite relationship to the clinical problem it hinders more than it helps. When purveyors of drugs shower clinical laboratories with free antibiotic disks they know that these disks will be used. No matter how absurd the report to the physician may be, it may influence his choice of drug. Let us assume that formaldehyde disks are made available under some attractive name. Surely some laboratories will employ them. Since formaldehyde fixes bacteria, "sensitivity" to such disks would be universal and the laboratory would report

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A Specific Indication for Each Antimicrobial Drug

Drug	Primary Indication. Drug of first choice in these infections	Secondary Indication. Possible drug of choice in these infections
Penicillin G	Pneumococcus, streptococcus, gonococcus, treponema, penase-neg. staphylococcus*, clostridia, anthrax, *Proteus mirabilis*	Bacteroides, actinomyces†, salmonella
Streptomycin†	Mycobacteria (e.g., *M. tuberculosis*), Pasteurella (e.g., *P. pestis*), enterococcus (with penicillin)	Klebsiella, *H. influenzae*, coliforms¶, Brucella
Chloramphenicol	Salmonella, *Haemophilus influenzae*	Penase-pos. staphylococcus‡, coliforms¶, proteus
Erythromycin group (e.g., erythromycin propionate; triacetyloleandomycin) ..	None	Penicillin substitute, streptococcus, penase-pos. staphylococcus‡
Tetracycline group (e.g., tetracycline hydrochloride; demethylchlortetracycline) ..	Shigella, brucella, bacteroides, Eaton agent, psittacosis-L.G.V.-trachoma viruses	Klebsiella, coliforms¶, R.T.I.§
Sulphonamide group ..	Meningococcus, coliforms in previously untreated U.T.I.‖	Shigella. actinomyces†, R.T.I.§
Neomycin group (neomycin, kanamycin) ..	Topical in mixed infections	Coliforms¶, proteus, penase-pos. staphylococcus‡
Polymyxin group (polymyxin B, colistin) ..	Topical in Gram-negative bacterial infections; pseudomonas	Coliforms¶
Methicillin, oxacillin ..	Penase-pos. staphylococcus‡	
Nitrofurantoin ..	Recurrent U.T.I.‖	

* Penase-negative staphylococcus : staphylococcus producing no penicillinase
† Often administered in combination with another drug.
‡ Penase-positive staphylococcus : staphylococcus producing penicillinase.
§ R.T.I. = Respiratory-tract infection, including sinusitis, otitis, bronchitis, pneumonitis, with mixed bacterial flora.
‖ U.T.I. = Urinary-tract infection.
¶ Hospital-borne coliform infections are often treated with drug combinations—e.g., neomycin + chloramphenicol, or streptomycin + tetracycline.

"organisms sensitive to formaldehyde." Some physician receiving such a statement, and having implicit faith in laboratory reports, will inject formaldehyde into his patient. This admittedly will fix the patient's bacteria, but it will also fix the patient. This imaginary sequence is only a small step from to-day's reality. I have seen laboratory reports stating "pneumococcus from sputum sensitive to methenamine mandelate," a drug which acts by virtue of releasing acid and formaldehyde into the urine without any systemic action (Waterworth, 1962). A physician receiving the laboratory report "staphylococcus from blood culture sensitive to nitrofurantoin ('furadantin')" was tempted to administer the drug systemically. Since that drug is active only in the urine, his patient continued to have staphylococcal bacteriaemia—albeit with sterile urine!

Similar misleading laboratory information is often applied to some important infections which require bactericidal drug action for cure. Antibiotic disk tests estimate bacteriostatic effects but give no indication of the bactericidal ability of drugs. In bacterial endocarditis, acute osteomyelitis, sepsis in the debilitated patient, and several other disorders, bactericidal drugs are essential to eradicate infection. Therefore the results of disk tests cannot guide therapy in these conditions and suitable tests for bactericidal drug effects must be used (Jawetz and Brainerd, 1962). Moral: Laboratory tests are helpful only if applied judiciously and interpreted sensibly.

At this point perhaps you will agree that the rules for drug selection which I have listed are obvious and certainly have not changed in the past two decades. Like many other simple principles in medicine these obvious rules are violated daily. There exists a truly monumental abuse and waste of antimicrobial drugs. This statement is readily supported if one examines patients' records and critically questions the need for antimicrobial drugs. It readily becomes apparent that only a small proportion of the antimicrobial drugs given to patients every day is given on proper indication.

The next question I wish to examine concerns the possible harmful or beneficial effects of the large-scale use of antimicrobial drugs on the individual or on society. Many antimicrobial drugs are remarkably non-toxic and well tolerated. However, virtually all of them are capable of producing allergic or toxic reactions. The decision to use a drug in spite of potential side-effects must be made in each individual case. To arrive at such a decision the physician must weigh the risk of using the drug and inducing a drug reaction against the risk of harming the patient seriously by not using the drug. If a given drug promises to be the sole life-saving agent available, allergic reactions can often be overcome and toxic side-effects controlled. Sometimes the risk of toxic drugs must be explained to the patient. This was illustrated in Professor Garrod's case of bacterial endocarditis where the use of neomycin was essential for the cure (Havard, Garrod, and Waterworth, 1959). The question of "deaf or dead" was resolved by the patient in favour of eradicating the infection at the risk of deafness.

Emergence of Resistance

To illustrate emergence of resistance among microorganisms permit me to tell a fable (Fig. 1). Once upon a time there was an island covered with short grass and populated by a million short-legged dachshunds. They were happy, there was plenty of food, and when opposite sexes met they reproduced to propagate the happy race. But one day the grass began to grow tall and taller. The poor short-legged dachshunds could no longer find food and they grew thin and sad. They could no longer find one another and soon the race became extinct. However, among the million short-legged dachshunds there was one freak—a long-legged dachshund. He had been shunned by his confrères and had lived alone in his hideout. On the short-grass island the long-legged dachshund had been exposed to predators and barely managed to survive. But when the grass grew taller the long-legged dachshund began to enjoy himself. He could peer over the top, could find food, and grew fatter as the short-legged ones starved. One day he was overjoyed to meet a long-legged lady dachshund. They had a family and their offspring populated the tall-grass island ever after.

The high level of drug (the tall grass) does not create resistant (long-legged) microbes, for they are either spontaneous mutants of a susceptible species or members of a naturally occurring resistant species. But the selection pressure of the drug favours elimination of the susceptible

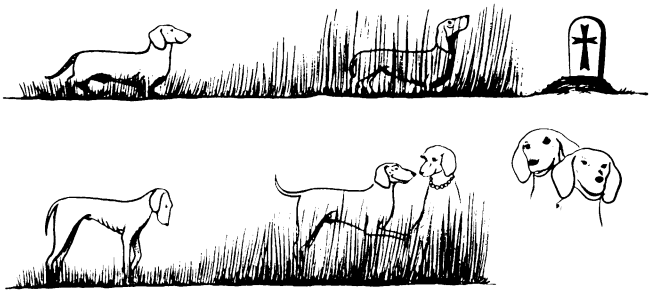

FIG. 1.—The short-legged and the long-legged dachshunds.

micro-organisms and survival and propagation of the most resistant ones. It may be worth while to illustrate these events as the physician observes them in a single patient and in a human population living in a relatively closed environment.

A 20-year-old student nurse (Fig. 2) had arrived at our hospital for training with the knowledge that she had inactive rheumatic heart disease with mitral insufficiency. Two weeks before the chart begins she noticed a paronychia and squeezed some pus out. The night before admission she suddenly felt very ill and feverish. On the morning of admission she had a high fever, and appeared severely toxic and septic. Blood cultures were drawn and tetracycline was started, without any apparent clinical improvement. Blood cultures subsequently yielded 500–800 colonies/ml. of *Staphylococcus aureus*, resistant to tetracycline and penicillin. A new drug, erythromycin, to which the organism appeared sensitive *in vitro*, had just arrived at the hospital. The drug was administered in full doses intravenously and orally. Soon there was symptomatic improvement, less fever, and blood cultures contained less than one colony of the same organism per ml. After three days of erythromycin therapy the patient suddenly became much worse, and blood cultures again yielded 600 colonies of staphylococci per ml. Embolic phenomena appeared, and in spite of desperate therapeutic efforts the patient died of a massive cerebral embolism. The staphylococcus isolated prior to erythromycin therapy was inhibited *in vitro* by 0.5 μg./ml. The strain obtained three days later required more than 20 μg./ml. for inhibition, an apparent fortyfold increase in resistance to that drug.

Comment.—Obviously, the microbial population in this unfortunate patient originally consisted of short-legged erythromycin-sensitive staphylococci. As these were suppressed by the drug, the long-legged resistant mutants came to the fore and "took over." In chronic infections—for example, endocarditis, osteomyelitis, tuberculosis—erythromycin, novobiocin, or streptomycin used singly may permit the rapid emergence of resistant bacteria. Therefore the use of these drugs singly is contraindicated under such circumstances.

Fortunately the emergence of resistance within a given patient occurs relatively infrequently. By contrast, the emergence of drug-resistant organisms is observed more

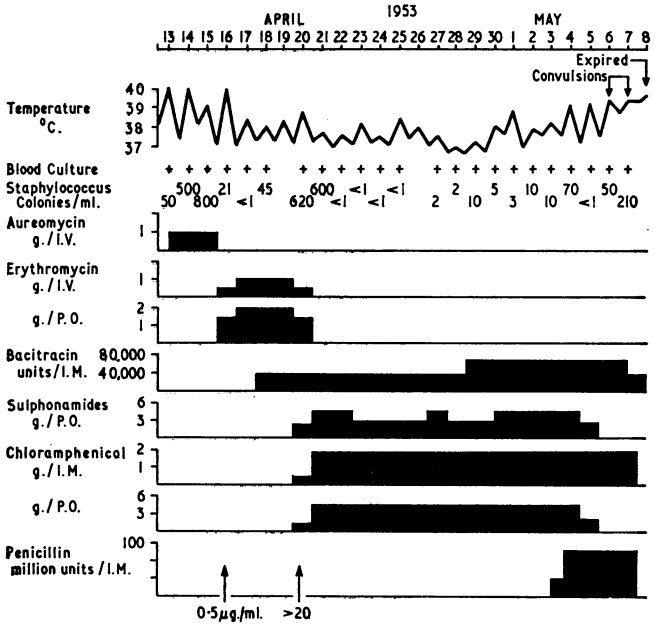

Fig. 2.—Emergence of microbial resistance within a student nurse, aged 20, with rheumatic heart disease, mitral insufficiency, and bacterial endocarditis due to *Staphylococcus aureus*.

regularly in human populations living in a closed environment which contains a high concentration of drug.

At a large city hospital (Fig. 3) it was noted that more than 55% of staphylococci cultured from patients, physicians, nurses, and attendants were insusceptible to penicillin. It was therefore decided to abandon the use of that drug and to substitute a new drug, erythromycin, to which all staphylococci in that hospital were susceptible *in vitro*. As erythromycin was used on a large scale there occurred a striking rise in the incidence of erythromycin-resistant staphylococci. Five months after the change in drug about 75% of the staphylococci cultured from

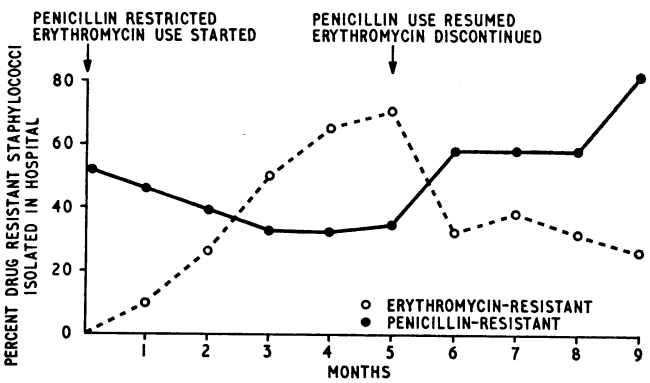

Fig. 3.—Emergence of microbial resistance in a hospital population. (Lepper *et al.*, *J. Lab. clin. Med.*, 1953, **42**, 832.)

patients, physicians, nurses, and attendants in that hospital were erythromycin-resistant and the drug had obviously lost its usefulness. Its use was then discontinued and penicillin was restored. Within one month the incidence of erythromycin-resistant organisms had been cut in half; but even in the absence of selection pressure by the drug some resistant organisms persisted. This sequence has been observed with virtually all antimicrobial agents which are used in large amounts in a closed environment (Bauer, Perry, and Kirby, 1950). Whenever a new drug saturates a hospital population, long-legged organisms resistant to that drug are favoured in colonizing the population. This sequence may lead to rapid loss of effectiveness of drugs in hospitals. Restrictive control of drug use may avert this development and may even reverse the trend to some extent (Barber, Dutton, Beard, Elmes, and Williams, 1960). Cutting the grass short favours the short-legged organisms but regrettably cannot be expected to result in the complete elimination of the long-legged ones.

Chemoprophylaxis

At this point I should like to mention chemoprophylaxis. The best time to treat infections is at their very beginning. Micro-organisms are then multiplying at a high rate, optimally susceptible to drug action. Tissue responses are still minimal and reversible without necrosis, obstruction, or the need for drainage. At such an early stage of infection there are usually no specific diagnosable signs or symptoms. Either the individual appears entirely well or—at most—he suffers from non-specific systemically produced manifestations. A drug specifically directed against the offending micro-organism might well abolish the infectious process and not permit it ever to reach the level of specific clinical disease. In some rare instances this sequence probably takes place and true prevention of disease results. An example might be the dramatic reduction in incidence of mastoiditis coincident with the widespread use of antimicrobial drugs for "earaches." The

majority of these are undoubtedly caused by catarrhal otitis which would subside spontaneously. In a minority, bacteria (haemolytic streptococci, pneumococci) are involved which might produce suppuration and, in the absence of early adequate drainage, might progress to mastoid cells. This type of very early treatment can prevent a clinical disease and may be one of the "hidden benefits" of antibiotic abuse.

Similarly, true chemoprophylaxis—that is, the administration of an antimicrobial drug *prior* to infection—may succeed. Specific chemoprophylaxis is effective in gonorrhoea, syphilis, meningococcaemia, plague, streptococcal and rickettsial infections, and some others. The unifying concept of all effective chemoprophylaxis is the use of a drug specifically directed against one particular micro-organism of uniform susceptibility. Conversely, prophylactic drug administration is doomed to failure if it attempts to banish the entire microbial flora of the environment. Trials of prophylactic drugs to prevent bacterial pneumonias in unconscious or post-operative patients or those with impending cardiac decompensation have regularly ended in failure (Petersdorf, Woodward, Feinstein, and Browder, 1961). The prophylactic drug suppressed the more susceptible microbes but did not hinder, and even favoured, the growth of the most resistant types. As a result, chemoprophylactic drugs not only failed to prevent bacterial complications of non-bacterial disease but often induced more severe and intractable infections. A striking case will illustrate this point.

A 58-year-old man (Fig. 4) tended his lawn and suddenly noticed a painful swelling in his groin. He diagnosed an inguinal hernia and visited our out-patient department, where his diagnosis was confirmed and he was scheduled for an elective herniorrhaphy. When he entered the hospital his pre-operative physical examination indicated that he was in excellent general condition except for his hernia. One observer thought he might have minimal Parkinsonism. While not exhibiting grossly unusual tremors, rigidity, or shuffling gait, he did have an inexpressive, possibly mask-like face. (However, this may have to be disregarded because he is a retired police sergeant.)

The herniorrhaphy was performed with ease. Upon its completion the surgeon ordered full doses of oral tetracycline. The patient had an uneventful course for three days. On the fourth day he suddenly developed nausea, vomiting, and diarrhoea. Because of the fear of enterocolitis, tetracyclines were discontinued when a rectal swab revealed many staphylococci. The following day the patient had a high fever, felt acutely ill with severe chest pain, and had obvious signs of pneumonitis. The lung involvement progressed to extensive pneumonia with pneumatoceles, pleural effusion, and finally lung abscesses. The organism cultured from sputum, pleural fluid, and blood was a *Staphylococcus aureus* resistant to penicillin and tetracycline. The patient was extremely ill for two weeks in spite of intensive antimicrobial treatment of the staphylococcal pneumonia; then he improved very slowly. He was discharged 11 weeks after the surgical procedure, with a lung abscess still not entirely healed.

Comment.—What did the surgeon have in mind when prescribing post-operative tetracycline? He probably felt that an individual with possible Parkinsonism might fail to turn, cough, or ventilate well post-operatively and consequently might be more likely to develop pulmonary infection. Tetracycline was used to ban the potential pathogens and prevent infection.

What actually did happen? As a result of full doses of systemic tetracycline given for several days, parts of the normal flora of the respiratory tract and gut were suppressed. This created a partial void—and such a void is always promptly filled by drug-resistant organisms prevalent in the environment. Thus the stage was set for the establishment of large numbers of staphylococci (or of Gram-negative rods) and the subsequent likelihood of the development of infection by these organisms.

This does not mean that the patient might not have developed pneumonia without receiving tetracycline. However, the chances are great that the pneumonia would have been caused by a drug-sensitive member of the normal flora and would have responded promptly to specific treatment. Thus "chemoprophylaxis" in this instance certainly did not prevent infection and probably helped to establish the worst type of infection.

Prospects

In spite of the emerging resistance among some bacterial species, available antimicrobial drugs continue to be remarkably effective against many of the most common pathogens. Among uniformly susceptible species of micro-organisms such as pneumococci, gonococci, or haemolytic streptococci there has been only a slight change in behaviour toward antimicrobial drugs, or none at all. It may be hoped and expected that this behaviour will continue for years to come.

On the other hand, the study of infectious diseases in a modern general hospital indicates that the overall prevalence of infections has not fallen substantially from that occurring in the past. Some infections that were common in past decades, such as tuberculosis, diphtheria, and scarlet fever, have decreased in incidence to very low levels. Both the type of infection and the nature of the infected patient have changed. In the present pattern, micro-organisms indigenous to the host are increasingly common causes of infectious disease. There is an apparent increase in the number of infections due to such organisms as enterococci, staphylococci, and Gram-negative rods such as coliforms, pseudomonas, and proteus. Regrettably, these micro-organisms are particularly adaptable to environmental changes and are frequently somewhat resistant to existing antimicrobial drugs. New, more effective

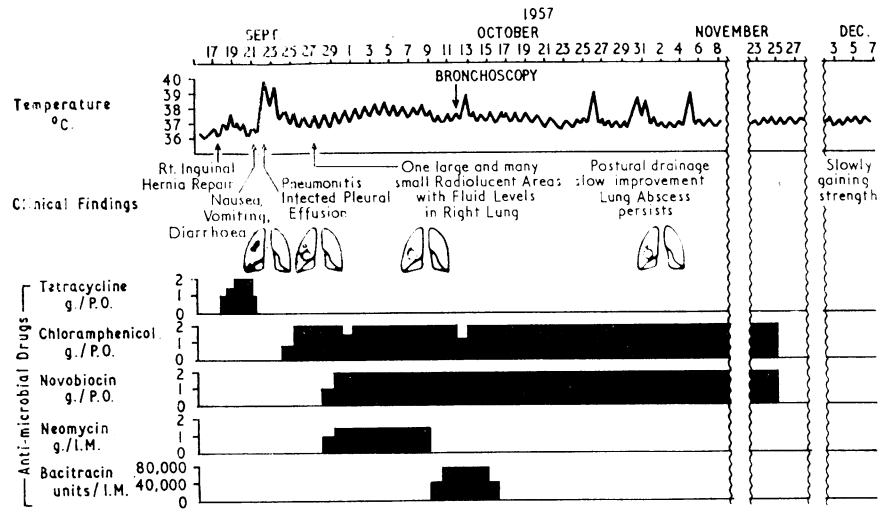

FIG. 4.—Harmful effect of "antibiotic prophylaxis" in a surgical patient. This man developed staphylococcal pneumonia and lung abscesses after the prophylaxis.

drugs are needed to deal with such endogenous micro-organisms, which are "opportunists" infecting debilitated patients rather than primary pathogens.

The search for truly different new antibiotics has been disappointing. The massive screening of antibiotic-producing organisms has yielded the same types of drug molecules over and over, but there has been a dearth of new agents which offer the hope of clinical applicability. One wonders whether the reservoir of naturally occurring antimicrobial agents revealed by present-day technical methods may have been exhausted. The initiative may have passed to the chemists. The recent demonstration of antiviral activity of synthetic analogues of nucleic acid building-blocks places the development of systemic antiviral drugs in the realm of the possible. Synthetic molecules such as the nitrofurans and the semi-synthetic newer penicillins suggest that we may hope for the development of drugs with "tailor-made" activity against the more troublesome endogenous micro-organisms. Such hopes may not be fulfilled in the near future, and for the present we must try to employ available drugs to best advantage. In part, this means judicious and restrained use of drugs to minimize the further emergence and spread of resistant organisms. In part, it may require the selection of drug combinations which manifest greater activity than their individual components.

Our group has been concerned with the theoretical and practical basis of combined antibiotic action for many years. There has been no definitive advance in understanding of the fundamental mechanisms involved in combined antibiotic action since our last review (Jawetz, 1958). The selection of useful drug combinations remains largely empirical, but, in our hands at least, it has been very helpful in the management of individual patients desperately ill with infections caused by resistant microbes. A limiting feature of combined antibiotic action is the strain-specific behaviour of drug combinations. It is impossible to generalize that this or that pair of drugs exhibits "synergistic" or enhanced effect. Each drug combination has to be specifically selected for its enhanced activity against a given strain of micro-organism from a specific patient. Laboratory methods for such specific selections have been developed (Jawetz, Gunnison, Coleman, and Kempe, 1955; Chabbert, 1957), and are available at medical centres. By such methods we have successfully managed a number of infections caused by micro-organisms resistant to available single drugs. The following case is an example of hospital infection by an "opportunist" microbe effectively treated with a specifically selected drug combination.

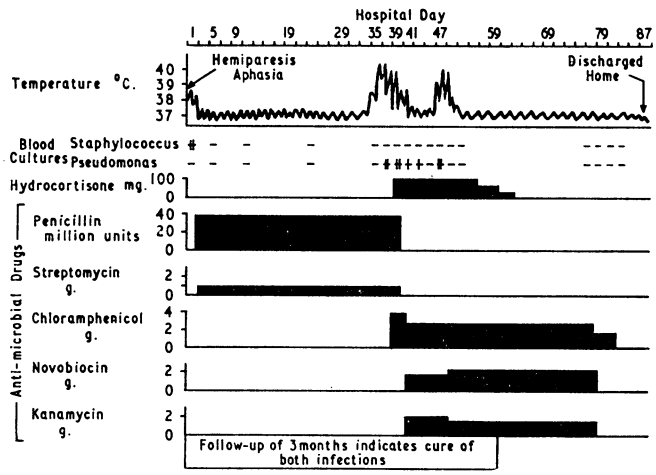

FIG. 5.—Iatrogenic hospital infection treated with selected antibiotic combinations. In this patient staphylococcal endocarditis was followed by bacteriaemia due to *Pseudomonas-achromobacter* organism.

A 36-year-old man (Fig. 5) entered hospital with a diagnosis of staphylococcal endocarditis on the basis of history, physical signs, and blood cultures. He responded well to treatment with large doses of penicillin and streptomycin, a mixture selected as strongly bactericidal for his strain by laboratory tests. After four weeks of treatment he suddenly developed high septic fever and intermittent fall in blood-pressures. Many blood cultures grew organisms of the Pseudomonas-Achromobacter family. These organisms were inhibited to some extent by several drugs, but only a combination of kanamycin, novobiocin, and chloramphenicol was rapidly bactericidal *in vitro*. When the patient received this combination his serum diluted 1:5 became bactericidal *in vitro* for the infecting organisms; and after an initially stormy course cure was achieved.

Comment.—There can be little doubt that the superinfection with particularly resistant Gram-negative organisms was eradicated thanks to the use of a carefully selected drug combination and by the well-controlled administration of potentially toxic drugs. But where had the patient acquired the superinfecting organisms? A detailed epidemiological study was done (Lee and Fialkow, 1961). The same organism was recovered from 14 additional patients—all on one floor of the hospital—and therefore christened "Bacillus tenth-flooris." Its source turned out to be a jar of cotton pledgets soaked in benzalkonium chloride, used to wipe the skin prior to venepuncture. Benzalkonium is strongly adsorbed by cellulose or protein fibres and its antibacterial properties are reduced or lost (Plotkin and Austrian, 1958). Consequently, the jar in question on the tenth floor of the hospital actually contained cotton pledgets in dirty water which permitted the growth of pseudomonas-like organisms and mediated iatrogenic infection of the patients. This incident forced our hospital to abandon the "modern" benzalkonium compounds as disinfectants and to return to the use of 70% alcohol for the cleansing of skin—an antibacterial agent introduced three-quarters of a century ago.

This sequence of events recalls the Hunterian Society debate of November 17, 1952 (*Brit. med. J.*, 1952). The proposition was debated "that the continued advance in medicine will produce more problems than it solves." The proposition carried by 59 votes to 47. The developments in the last decade provide no basis for disagreement with the majority vote.

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