childhood when the cell population is small and when it can be treated vigorously with sufficient drugs to kill all the leukemic cells. A few years ago acute leukemia of childhood was a disease of three to four months (Tivey 1954). It was not so long ago that a leading article in the *Lancet* (1964) pointed out that few had survived this disease for more than two years. Quite recently Burchenal (1965), in a report for the Task Force, had found 101 patients with known acute leukemia who had survived five to fourteen years. Sixty-four of these patients have no sign of the disease. I suspect that these are patients who received chemotherapy at a time when they had small cell populations. Our ability to reproduce these successes is limited by the fact that leukemic cell populations during clinical relapse are probably often above one trillion, while chemotherapy often becomes too toxic when enough is given to kill these numbers of cells. The present studies with drug combinations cannot be extended to the treatment of all leukemic patients at this time. These combinations have been given in a study of a few patients with a quality of patient support not generally available. Toxicity is severe. Combinations of two drugs are, I believe, approaching complete leukemic cell destruction in about 1 % of leukemic children.

In summary, then, the point of this study of cell kinetics in leukemic mice and children is that for the first time it provides a measure of what proportion of the leukemic cells can be destroyed by drugs. The skilful use of this measure will permit a precise assessment of each new therapy. Every little improvement in management of the leukemic patient brings us a little closer to the goal of complete kill of leukemic cells with less toxicity for the patient. These improvements will come not only from the discovery of new drugs but also from present research on platelet and white cell replacement; on prevention of infection by reverse isolation and better antibiotics for pseudomonas and fungal infections; and especially from better ways of using old antileukemic drugs as their pharmacology, alone and in combination, is understood.

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Drug Combinations in Antibacterial Chemotherapy

by Professor Mary Barber MD[1]
(*Postgraduate Medical School of London*)

Abstract
Double chemotherapy for the treatment of bacterial infections has been recommended for many reasons, of which the most important are the following: (1) To achieve a synergic effect. (2) To delay the emergence of resistant strains. (3) To prevent superinfection. (4) To treat relatively inaccessible bacteria. (5) To treat mixed infections. (6) To treat undiagnosed infections.

Combinations which have a truly synergic effect *in vivo* are those which show bacteri*cidal* synergy *in vitro*. Bacteri*cidal* therapy is of great practical importance in conditions which are inaccessible to the natural defences of the body, or where they are deficient. If in such cases the infecting bacterium is not readily killed by a single drug, then combinations should be tried. There are no absolute rules and double bactericidal sensitivity tests should always be carried out on the infecting strain, but the most likely combination to show this type of synergy is a penicillin and streptomycin.

If a bactericidal drug is combined with an agent which is only bacteristatic, the killing effect may be antagonized, since many bactericidal drugs only kill rapidly multiplying cells. Again there are no absolute rules, but antagonism is particularly liable to occur when the bactericidal agent is one of the penicillins and is very unlikely to occur when it is a polymyxin, since this kills resting bacteria.

Drug combinations to delay the emergence of drug-resistant strains should be considered for infections due to staphylococci and coliform bacilli, particularly in hospitals, and when it is desired to use drugs to which these bacteria readily develop resistance.

Drug combinations may also be the most efficient treatment for mixed infections and may be necessary for the treatment of fulminating infections pending bacteriological diagnosis. The combination of nystatin with a tetracycline may be necessary to prevent candidiasis if tetracycline therapy has to be prolonged.

The use of antibiotic combinations for the treatment of bacterial infections has been the subject of many reviews (Garrod 1953, 1964, Chabbert

[1]Professor Barber died in a road accident on September 11, 1965. Enquiries regarding her paper may be addressed to the Secretary to the Department of Bacteriology, Postgraduate Medical School, London.

1953, Dowling 1957, Jawetz 1958, Lacey 1960). All the authors take the view that double chemotherapy is only justified for certain specific reasons, and condemn factory-made mixtures of antibiotics, on the grounds that it is important to prescribe the two antibiotics in appropriately chosen doses. Moreover, the trade name of a mixture often gives no indication of the drugs it contains and may suggest to the uninitiated that it is a new antibiotic, rather than a mixture of two well known ones.

The reasons suggested for double chemotherapy are: (1) To achieve a synergic effect. (2) To delay the emergence of resistant strains. (3) To prevent superinfection. (4) To treat relatively inaccessible bacteria. (5) To treat mixed infections. (6) To treat undiagnosed infections. In addition some people have recommended the use of two drugs in order to achieve good therapeutic results with small doses of drugs which would be too toxic to use in larger doses, but this has not proved to be of much practical value.

The first three of these reasons are the most important and will be discussed at length. The last three are briefly referred to below.

Inaccessible Bacteria

The most important example of this is in relation to the treatment of brucellosis with streptomycin. *Brucella* spp. tend to be intracellular and streptomycin does not readily penetrate cells. Shaffer *et al.* (1953) showed that *Brucella suis* was about 25,000 times less sensitive to streptomycin when injected in leucocytes than when free. This is probably the reason why combined therapy with tetracycline and streptomycin is more effective in the treatment of brucellosis than is treatment with streptomycin alone. *Myco. tuberculosis* also tends to be intracellular and since isoniazid readily penetrates cells, combined treatment with isoniazid and streptomycin is to be recommended, quite apart from the problem of drug resistance.

Mixed Infections

In mixed infections a single narrow-spectrum antibiotic may be effective, but, if not, two antibiotics, for example benzylpenicillin and streptomycin, are often more efficient, and may also be cheaper, than a broad-spectrum antibiotic.

Undiagnosed Infections

It is important to make a bacterial diagnosis before starting antibiotic treatment whenever possible. In the seriously ill, however, early treatment is important and must be started as soon as appropriate specimens have been sent to the bacteriological laboratory. The selection of antibacterial drugs for such cases is difficult. If the infection has developed in hospital, the antibiotic sensitivity pattern of likely infecting organisms may be known. Sometimes the clinical picture may give a lead. For blind antibiotic therapy in very ill patients treatment with methicillin, ampicillin and polymyxin is possibly the widest bactericidal combination.

BACTERICIDAL SYNERGY AND ANTAGONISM

Jawetz & Gunnison (1953) in one of their now classic papers on 'Antibiotic Synergism and Antagonism' defined 'synergism' as 'the ability of two antimicrobial drugs acting together to increase markedly the rate of *early bactericidal* [my italics] action, as compared to the rate with either drug alone, and to kill greater numbers of bacteria or to cure experimental or clinical infections more effectively than could be expected from simple algebraic summation of single drug effects'. Simple summation was termed 'addition' and any combined effect less than the sum was called 'antagonism'. It will be seen from this definition that Jawetz & Gunnison were concerned with the bactericidal, not the bacteristatic, effect of drugs and it has been found in practice that it is synergy of this type which operates *in vivo*.

In special cases a combination of drugs may be qualitatively as well as quantitatively different from the action of either drug alone. Thus the combination of penicillin and streptomycin acting together against enterococci is more effective than any concentration of either drug separately. When this is not the case, it is sometimes difficult to establish whether a combination is synergic or only additive, and most investigators use the term synergy only when the excess over addition is gross.

As pointed out by Buttle (1956), in antibacterial chemotherapy the term synergy is used in the same sense as the term 'potentiation' is used in general pharmacology. Bacteriologists following Bigger (1950) reserve the latter term for the effect which 'a substance which is not itself antibacterial may exercise on an antibacterial agent'.

As a result of studies of the action of various combinations of antibacterial drugs Jawetz & Gunnison (1952, 1953) formulated a law which can be briefly summarized as follows:

Bactericidal + bactericidal drug – may be synergic
Bactericidal + bacteristatic drug – may be antagonistic
Bacteristatic + bacteristatic drug – additive

Table 1 lists the commonly used antibacterial drugs according to their antibacterial spectrum and indicates those which are bactericidal.

Lacey (1958) divided synergic and additive combinations of drugs into the following six classes according to their presumptive sites of

action, presumptive routes by which they reach the site and the presumptive chemical sequence blocked:

(1) Same site, same route.
(2) Same site, different route.
(3) Different sites, same sequence.
(4) Different sites, convergent sequences.
(5) Different sites, different sequences, overlapping routes.
(6) Different sites, different sequences, different routes.

Classes (1) and (2), in which the two drugs have the same site of action, are usually only additive. When two drugs have different sites of action the combination is frequently synergic. When two drugs act at different sites on the same sequence or metabolic pathway, the action of the combination is referred to as sequential blocking. Examples of this are the action of antifolics and antithymines on *Str. fæcalis* and the action of sulphonamides, antifolics and antipurines on *Proteus vulgaris*. In combinations of this type and also those of class (4) the drugs usually show a one-way cross-resistance. Although combinations of classes (3) and (4) are of great theoretical interest and are almost always synergic, at present none such has been found which is suitable for the treatment of bacterial infection. As already indicated, for practical purposes, we are concerned with bacteri*cidal* synergy and in fact all combinations used for their synergic effect in antibacterial chemotherapy belong to class (6).

It is impossible to predict that any two drugs will invariably have a synergic effect with different strains of bacteria, even when the latter are all of the same species. Nevertheless, it is now clear that the most likely combinations to be synergic are those in which a penicillin or bacitracin is combined with one of the streptomycin group. The penicillins and bacitracin all act primarily on the bacterial cell wall and a recent paper by Plotz & Davis (1962) suggests a mechanism whereby these drugs may have a synergic effect when combined with one of the streptomycin group. These investigators studied the effect of penicillin and streptomycin against *Esch. coli* when the cells were first treated with one antibiotic and then exposed to the second in fresh medium. They found that brief exposure to penicillin hastened the subsequent killing of the cells by streptomycin and the uptake of streptomycin by the cells was also shown to have been more rapid. On the other hand, preliminary treatment with streptomycin had no effect on subsequent killing by penicillin. On the basis of these results the authors suggested that synergy between penicillin and streptomycin depends on penicillin damaging the cell membrane, thus increasing the access of streptomycin.

A remarkable example of synergy, which is at present quite unexplained, is the combination of polymyxin with a sulphonamide or trimethoprim

Table 1
Antibacterial agents for clinical use

Group I (*for Gram-positive bacteria and Gram-negative cocci*)	*Group II* (*broad-spectrum*)	*Group III* (*for Gram-negative bacilli*)
Penicillins ●	Tetracyclines	Streptomycin ●
Ampicillin ●	Chloramphenicol	Kanamycin ● ▲
Cephalosporins ●		Neomycin ● ×
Erythromycin ■		Polymyxin ●
Lincomycin		Colistin
Novobiocin ■		
Fucidin		
Vancomycin ● ▲		
Ristocetin ● ▲		
Bacitracin ● ×		
Sulphonamides		

● Antibiotics which are actively bactericidal
■ Antibiotics which are sometimes bactericidal in high concentrations
▲ Highly toxic drugs to be reserved for special purposes
× Drugs too toxic for systemic use but valuable for local treatment including intestinal antisepsis (since they are not absorbed from the alimentary tract)

(2,4-diamino-5-(3,4,5,-trimethoxy-benzyl)-pyrimidine) against *Proteus* spp. Polymyxin alone has little or no activity against organisms of this genus and sulphonamides and trimethoprim are only bacteristatic. The combination of polymyxin with either of the two latter is active against all species and, particularly with trimethoprim, is frequently bactericidal. This and other examples of synergy are described by Garrod & Waterworth (1962).

Antagonism

Penicillins: Bactericidal antagonism is liable to occur when a bactericidal drug is combined with one that is only bacteristatic, but this is not invariably the case. The reason why penicillins are antagonized by bacteristatic drugs is fairly clear. The penicillins inhibit the formation of the bacterial cell wall, so that when growth takes place the cells die by lysis, but when the cells are not growing they are not killed. If a penicillin is combined with tetracycline the latter prevents multiplication of the cells and therefore interferes with the killing effect of the penicillin. This can be readily demonstrated *in vitro* (*see* Garrod & Waterworth 1962) and Lepper & Dowling (1951) have shown that, in the treatment of bacterial meningitis, benzylpenicillin plus tetracycline is less effective than benzylpenicillin alone.

A similar type of antagonism is also seen when a penicillin is mixed with chloramphenicol. The sulphonamides do not appear to antagonize penicillins, possibly because their bacteristatic action is too slow and is usually preceded by a period of multiplication. Erythromycin and novobiocin give variable results depending on the concentration. In low concentrations they are bacteristatic and may antagonize the penicillins. In high concentrations they are often bactericidal

and when mixed with benzylpenicillin in such concentrations they are indifferent or sometimes even synergic. All the penicillins are similarly antagonized by bacteristatic drugs and the effects are particularly marked with methicillin (*see* Garrod & Waterworth 1962).

Streptomycin group: With streptomycin and the related antibiotics, neomycin and kanamycin, the position is not quite so clear-cut as with the penicillins. Garrod (1948) found that streptomycin, like the penicillins, only killed staphylococci in conditions that permitted multiplication. Manten & Meyerman-Wisse (1962), on the other hand, consider that streptomycin can kill resting cells and is therefore not necessarily antagonized by bacteristatic agents. In practice, at least in the test-tube, bacteristatic drugs appear to be antagonistic to the action of streptomycin about as frequently as to that of benzylpenicillin (*see* Chabbert 1953, Chabbert & Patte 1960, Garrod & Waterworth 1962).

Polymyxins: The polymyxins are certainly exceptions to the rule that bactericidal drugs are antagonized by bacteristatic agents. They act by interfering with the permeability of the protoplast membrane and are lethal to resting and multiplying cells.

Practical Application

Possible synergy or antagonism is of practical importance in the treatment of infections which only respond to a bactericidal agent, that is to say in conditions where the natural defences of the body are unable to deal with the small number of bacteria left after treatment with a bacteristatic drug. This applies to infections such as bacterial endocarditis or meningitis, where the lesions are not readily penetrated by phagocytes, or to any infections in patients with blood diseases or other pathological conditions leading to inadequate body defences.

When for any of these reasons bactericidal chemotherapy is considered to be of paramount importance, two general rules should be observed. First, a bactericidal drug other than a polymyxin should not be used in combination with a bacteristatic drug, unless laboratory tests have shown that the two are not antagonistic. Secondly, if no single suitable drug can be found which is bactericidal for the infecting microbe, *in vitro* tests with likely combinations should be carried out.

Apparent Synergy with Benzylpenicillin against Penicillinase-producing Staphylococci

In 1960 Herrell and his colleagues reported synergy between benzylpenicillin and erythromycin against penicillinase-producing staphylococci that were also resistant to erythromycin. Using an agar dilution method and a fairly small inoculum they tested 56 strains of staphylococci to each of these antibiotics separately and to both together. With erythromycin alone all strains grew in 1,000 μg/ml and with benzylpenicillin alone the minimum inhibitory concentration ranged from 12·5 to 100 units/ml. With the two antibiotics together all strains were inhibited by 0·8–3·1 μg/ml of each, and the mixture was bactericidal. In a further study (Herrell *et al.* 1962) these observations were confirmed and 3 patients with infections due to staphylococci resistant to both antibiotics separately were successfully treated with the combination.

Godtfredsen *et al.* (1962) noted that the new steroid antibiotic, Fucidin (sodium salt of fusidic acid), had a synergic effect on benzylpenicillin against penicillinase-producing staphylococci but not against penicillin-sensitive strains. Apparent synergy was further studied by Barber & Waterworth (1962). They found that the synergic effect depended on the rate at which the staphylococci could inactivate benzylpenicillin and was not seen at all with highly active penicillinase-producers.

This phenomenon has been elucidated by Waterworth (1963). She pointed out that with erythromycin-resistant staphylococci of the dissociated type (*see* Garrod 1957) only a small minority of the cells are resistant and that the position with Fucidin is somewhat similar, since with nearly all strains of *Staph. aureus* a large inoculum contains a few Fucidin-resistant cells. She carried out experiments which showed that synergy between benzylpenicillin and Fucidin only occurred in tests with a large inoculum and depended on the fact that the Fucidin was able to inhibit the growth of most cells so that the destruction of benzylpenicillin in the mixture was delayed for two to four hours. When the small number of Fucidin-resistant cells began to grow they were killed by the surviving penicillin. Similarly she showed that the synergy between benzylpenicillin and erythromycin only occurred with penicillinase-producing strains which also showed resistance to erythromycin of the dissociated type, and depended on the erythromycin delaying the inactivation of benzylpenicillin long enough for the latter antibiotic to kill any erythromycin-resistant cells.

In practice this means that the synergy between benzylpenicillin and Fucidin or erythromycin is extremely limited. It does not operate with very highly active penicillinase-producing strains and, in the case of erythromycin, the strain must also show resistance to this antibiotic of the dissociated type. Fucidin and erythromycin both antagonize the bactericidal action of penicillinase-resistant penicillins such as methicillin.

DRUG-RESISTANCE AND SUPERINFECTION

In the Individual Patient

The use of two drugs in combination to delay the emergence of a drug-resistant strain is now a well established principle and is almost universally used in the treatment of tuberculosis. A change in the drug sensitivity of an infecting bacterium during a single short course of treatment does not in fact occur very frequently. On the bacterial side the only organisms likely to show such a change are staphylococci and coliform bacilli. When antibiotics have to be given for long periods the danger is increased, and is particularly great in the case of tuberculosis, since tubercle bacilli are nearly as adaptable to antibacterial drugs as are staphylococci and coliform bacilli.

Although staphylococci appear to be able to develop resistance to almost any antibiotic, this usually only follows continued use of the antibiotic in a hospital where strains are spreading from patient to patient. With streptomycin, erythromycin, novobiocin and Fucidin, however, resistance develops so rapidly that a gross change in sensitivity of an infecting strain is not infrequent after antibiotic treatment of less than a week's duration. For this reason streptomycin was long ago abandoned for staphylococcal infection. Since the discovery of the new penicillins, erythromycin, novobiocin and Fucidin are rarely used, but, if they are, there is a clear case for giving two of them together.

It is less certain to what extent double chemotherapy is desirable from this point of view for infections due to coliform bacilli. Undoubtedly they can develop resistance to streptomycin within a day or so of the onset of treatment. With other antibiotics the position has been less well studied than with staphylococci.

Another use of drug combinations is to prevent superinfection. In practice the only form of superinfection likely to be prevented in this way is that due to candida. Infection with this organism is liable to occur when broad-spectrum antibiotics, particularly tetracycline, are given, especially if treatment is continued for more than a week. When tetracyclines have to be administered for long periods the addition of nystatin is worth considering. Alternatively, a preparation of antibiotic-resistant lactobacilli administered orally helps to prevent superinfection. The practice of combining tetracycline with the highly toxic antibiotic amphotericin, in a single preparation, is to be deplored.

In a Hospital Community

In most large hospitals antibiotics are used extensively in wards where cross-infection is liable to take place, so that the emergence of drug-resistant strains is encouraged. The best way to deal with this situation is to prevent cross-infection and limit the use of antibiotics. But the first is difficult, if not impossible, in most existing hospital buildings and the use of antibiotics will almost certainly remain high, even if they are reserved for the treatment of patients likely to benefit directly from their administration.

In hospitals where drug-resistant staphylococci are a serious problem, universal double chemotherapy for all infections in the hospital has been suggested, at least as a temporary measure (Barber *et al.* 1960, Chabbert 1959). But there are obvious objections. Double chemotherapy is bound to increase the total consumption of antibiotics in the hospital and, apart from cost, this increases the frequency with which hospital bacteria come into contact with each antibiotic. Moreover, the policy might favour the spread of *Ps. pyocyanea* in hospitals, since this organism tends to be resistant to nearly all the commonly used antibacterial drugs.

CONCLUSIONS

Combinations of two antibiotics showing bactericidal synergy are of great importance in the treatment of bacterial endocarditis and other infections where bactericidal therapy is necessary, when the infecting bacteria are not readily killed by a single drug. The most likely combination to be synergic is benzylpenicillin and streptomycin, but there are no absolute rules and double sensitivity tests should always be carried out with the microbe concerned. Bactericidal antibiotics, other than a polymyxin, are frequently antagonized by bacteristatic drugs, particularly tetracycline and chloramphenicol, so that such combinations should be avoided in conditions needing bactericidal therapy, unless tests have shown that there is no antagonism with the infecting organism.

Drug combinations may also help to delay the emergence of resistant strains and in this connexion should be considered in the treatment not only of tuberculosis, but also of infections due to staphylococci and coliform bacilli. The addition of nystatin may be useful for the prevention of candidiasis when long-term treatment with a broad-spectrum antibiotic is necessary.

Drug combinations may be preferable to the use of broad-spectrum antibiotics for the treatment of mixed infections. Finally, they may be essential for the blind treatment of fulminating infections pending bacteriological diagnosis.

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Section III

Chairman
The Rt Hon Lord Cohen of Birkenhead MD

Panel Discussion: Drug Interaction in Relation to Acute Poisoning

Lord Cohen: The first question is: *What is the Commonest Form of Drug Interaction in Acute Poisoning?*

Dr R Goulding (*Guy's Hospital, London*): There is no simple answer to this because, as far as we can see from enquiries made to us nowadays, polypharmacy, or polytherapy, is so common that we hardly ever see acute poisoning attributable to one agent. There may be one principal agent, but there are nearly always three, four or five that may be involved as well. Naturally the most spectacular of the interactions are those in people on monoamine oxidase inhibitors who are given something else and then something dramatic happens. But there are all sorts of interactions beyond that. The commonest cases of poisoning from drugs are undoubtedly attributable to those agents which are used for mental trouble or used in psychiatric practice. It is interesting that the plea has been made by a number of eminent psychiatrists that we should encourage them in the use of certain of these drugs because, by treating successfully patients with depression, they will save people from the grave by their own hand. In my opinion, and figures of suicide rate lately collected support this, they are merely putting drugs in the hands of people who want to kill themselves.

Professor M D Milne: I entirely endorse Dr Goulding's views. I think the main trouble for the clinician is to discover what the poisoning agent is. One gets a bewildering amount of polypharmacy in would-be suicides and I think it prevents any scientific therapy other than symptomatic treatment in many cases. Only if you really know the chief poison, such as phenobarbitone, can you say 'we must hæmodialyse or give specific treatment'.

Lord Cohen: On the regretful assumption that alcohol is a drug: *In What Position on the Table does Alcohol and Barbiturate Interaction come into this Acute Poisoning?*

Dr Goulding: I have always regarded this explanation as a kindness on the part of the pathologist giving evidence in the Coroner's court, because then the death becomes an accident and not a deliberate measure. I have no doubt that if a sufficient quantity of alcohol is taken with a sufficient quantity of barbiturate it would have an additive effect, but it is unjustifiable to assume that a person has died by accident just because he has had one or two glasses of sherry and then taken a few barbiturate tablets. I do not think that is the case.

Lord Cohen: The next question is: *What Types of Drugs can Cause Bleeding in Patients Already on Anticoagulants and What is the Explanation?*

Dr J J Burns: Pharmacology textbooks point out the hazards of giving large doses of salicylates in conjunction with various coumarin anticoagulants. Salicylates have an effect on prothrombin synthesis and thus they can have an additive or perhaps synergistic effect to the action of dicoumarol and this drug combination may lead to bleeding. Recent reports indicate that phenylbutazone potentiates the action of warfarin, and this can lead to an exaggerated prothrombin response. This effect appears to result from an