Drug combination has been a much debated subject. Controversies in this field have arisen, I believe, from our failure to translate scientific principles into pragmatic policies. When two or more drugs are to be given they can be prescribed separately or as a combination if one is available. Although multiple drug therapy has been decried in general the principal target of criticism has been the so called “fixed combinations”. To be fair it must be admitted that most critics have accepted combined drug therapy as rational in certain situations, e.g., tuberculosis, hypertension and hormonal contraception. But besides these there are several other circumstances in which the concomitant use of two or more drugs is necessary, desirable and justifiable. Let us briefly examine some of them before considering the pros and cons of combinations.

The Perspective

First, a majority of patients have multiple symptoms (12) which cannot be relieved by means of a single drug—even if all are due to one specific aetiology. For example, streptococcal tonsillitis gives rise to fever, headache, dysphagia and dry cough. Penicillin G alone would control the infection and eventually relieve all symptoms. But the patient desires prompt relief from his suffering, which it is the doctor’s primary duty to provide, and so an analgesic-antipyretic and perhaps an antitussive linctus are also called for. Secondly, a patient may carry only a single diagnostic label but may in addition have some complicating or aggravating factors. Thus hypertensive patients and those with a peptic ulcer frequently have an anxious personality. To relieve their anxiety it is then necessary to give a sedative or a tranquilliser as an adjunct to specific therapy. Thirdly, a patient may have more than one disease, e.g., diabetes and hypertension or diabetes and arthritis. Use of two or more drugs at the same time is then unavoidable. Finally, and this is a very common event in practice, a precise diagnosis either cannot be made or is not feasible owing to lack of facilities, money and time. To illustrate, a red eye may be due to allergy or infection, diarrhea may be due to dietary indiscretion or infection, and acute bronchitis may be due to streptococci and pneumococci alone or mixed with H. influenzae. It is no doubt laudable and scientifically sound to strive to make a precise diagnosis, but is it worthwhile in every case in the context of our socio-economic milieu? Would it not be a practicable proposition and, as Lasagna (7) puts it, a “respectable idea” to
“cover more therapeutic bets” with more than one drug? Do we really need to do, and do, a precise diagnosis in every patient we see if the possible causes can be dealt with by the concomitant use of safe drugs? I do not for a moment doubt that it would be highly scientific to do so, and justifiable in a research situation or when some of the drugs to be used are very toxic, but does it otherwise stand to reason in the stark realities of life?

The Fixed Combinations

Having reviewed the circumstances requiring combined drug therapy, let us now examine the charges levelled against fixed combinations.

The first and the most important objection to multiple drug therapy is the possibility of adverse drug interactions. Their nature, mechanisms and clinical significance have been increasingly appreciated during recent years (3, 4, 11, 14) and voluminous compilations of reported and possible interactions have been published (6). But this applies as much when two or more drugs are used separately as when they are used in a fixed combination. When drugs are given separately but concomitantly, or mixed as and when required, the physician needs to think of interactions not only among the active ingredients but also among the excipients, diluents, solvents and preservatives used in the different formulations. For example, if tetracycline is given orally with some other tablet or capsule which contains calcium carbonate as an excipient or filler, but which is not known to the physician since it is not disclosed on the label, the absorption of tetracycline can be impaired and result in a diminished therapeutic response. Witness also the rapid deterioration of sodium ampicillin which occurs when the drug is added to intravenous infusions of dextrose solution (2). As a matter of fact the fixed combinations have an advantage in this respect because the manufacturer has of necessity to ensure that the product is stable and that there are no physical or chemical incompatibilities. Further, at least some clinical data are available on marketed combinations, and that provides a reasonable safeguard against entirely unexpected interactions.

The second objection is that fixed combinations preclude the adjusting of doses of individual ingredients from patient to patient or in the same patient from time to time. Ostensibly this is a rational objection, but how often do we really have to individualise the dose? I concede that it is essential to do so in the case of drugs such as digoxin, and therefore even though digoxin and chlorothiazide are often used together no one has ever marketed a fixed combination of the two. However, in the case of many commonly used drugs, e.g., non-narcotic analgesics, sedatives, minor tranquillisers, antacids, anticholinergics and antidiarrheals, precise regulation of the dose is not required as a high percentage of patients responds satisfactorily to the average dose. As such, what the combinations of such drugs need to provide is a dose of each ingredient which is in the usual effective dose range. If smaller doses are used, there must be acceptable evidence of synergistic or supra-additive effect between two or more ingredients.

The third objection to fixed combinations is that when they are used to “cover bets”
one of the ingredients may be superfluous and, while not contributing to the therapeutic effect, may expose the patient to possible side effects. Again this criticism would apply to combined therapy in general irrespective of whether the drugs are prescribed separately or as a fixed combination. In situations like this the physician is expected to be aware that one of the drugs would inevitably be "going along for the ride" (8) and to weigh the pros and cons of this prescription.

At this point it would be proper to examine two case reports cited by Madan (10) as illustrations of therapeutic misadventures caused by the use of fixed combinations. The first case is that of an 18 year old girl who suffered from agranulocytosis due to chronic ingestion of an antidiarrheal mixture containing sulphaguanidine. The original case report (16) reveals that the mixture was a combination of sulphaguanidine 2 g., pectin 0.225 g., kaolin 3 g. and tincture of opium 0.08 ml. in each 15 ml. It was prescribed by the girl’s father, himself a physician, for “intermittent cramps in the lower part of the abdomen which were followed by loose stools”. Perhaps initially the mixture was given to cover a probable infection. However, although investigations including x-ray studies had revealed no abnormality the mixture continued to be given almost once a week for two full years. It is inconceivable that the physician used it without knowing, or trying to know, its composition; but if he did he has to blame himself rather than the mixture. In all fairness it must also be disclosed that the mixture was promoted for “nonspecific diarrhea”—a totally unjustifiable claim which nonetheless does not absolve the physician of his responsibility to know what he was prescribing. Stevens (16) who first reported the case has also commented: “Irresponsibility cannot be solely blamed on the pharmaceutical manufacturer, for products such as this one require prescription”. Thus this is an example of a good combination (e.g., good for acute bacillary dysentery) badly promoted and irresponsibly prescribed.

The other case is that of a physician’s 4 year old daughter who became deaf owing to the administration, as stated by Madan (10), of “streptomycin-penicillin mixture” by a pediatrician colleague of the girl’s father. Reference to the original report (5) tells us that the mixture contained procaine penicillin and dihydro-streptomycin. Now dihydrostreptomycin is no longer used parenterally owing to its toxic effect on the cochlear division of the 8th nerve, and so the combination was obviously a bad one. What is surprising, however, is that it was prescribed by a specialist for “recurrent impetigo”—a condition known to be caused by streptococci, sometimes mixed with staphylococci, and fully responsive to penicillin G alone irrespective of the presence or absence of staphylococci (17). This then is an example of a bad combination used with all disregard to scientific principles.

I may now point out some practical advantages of fixed combinations viz., economy, convenience and avoidance of dosage errors. These must be considered valid reasons for their use (8) as long as medicine is practised not as a detached impersonal science but as a socially oriented profession.
The Drug Efficacy Study

Much of the recent furore about fixed combinations arose when the Drug Efficacy Study carried out in the U.S.A. by the National Academy of Sciences—National Research Council (NAS-NRC) was published. By and large the study has been a useful essay and has shed light on some of the irrational therapeutic practices. Problems have arisen, however, because many accept the Study blindly and seek to apply it dogmatically. I think the experts who took part in the Study themselves also never intended it to be so accepted or applied. Lasagna, who was one of the panel chairmen and may therefore be expected to know the truth, has openly admitted (9) that the panels chosen had “parochial biases”, that “the study was of necessity imperfect” and that “its magnitude precluded exhaustive attention to detail”. So far these revelations do not appear to have been refuted. He has also said (7) that personal experience and bias did influence the consensus of opinions expressed by the panels and that in many instances the basis was “more like shifting sand than hard bedrock”.

A fact which I believe must be considered in interpreting the NAS-NRC Study is that experts often disagree among themselves. See for example the survey made by McMahon (12). The opinions of professors as well as private practitioners were invited on 20 popular fixed combinations. Except in one instance the professors could not be unanimous. In this state of affairs would it be prudent to regard any small panel’s view as the final truth? To illustrate the fallacy of a dogmatic attitude let me take the example of the much criticised fixed combinations of penicillin and streptomycin. The NAS-NRC panel has opined (13) that they are ineffective in bronchitis, bronchiectasis and other respiratory infections. According to some British experts, however, respiratory infections involving *H. influenzae* and diffuse aspiration bronchopneumonia can be treated with 300 mg. (500,000 units) of benzyl penicillin and 0.5 g. of streptomycin intramuscularly twice a day (1). If a fixed combination can provide these doses, and such combinations do exist, it should be considered a rational combination for the indications mentioned. Where do these divergent views of experts leave us?

The Solution

As I said at the beginning we have so far failed to translate scientific principles into pragmatic policies. A time has now come to make good this failure if we want to disprove the cynical comment often bandied about, viz., in medicine the practice is often different from theory. And this must be done not through dogmatisation but, as Spalton (15) has said, through the “free process of scientific publication, debate and education”. That this is an attainable goal I have no doubt—provided of course that all of us, i.e., academicians, practitioners, manufacturers and legislators, try sincerely to do our bit.

REFERENCES

Armed with the necessary data, the Drug Efficacy Sciences-National Research Council drug study was an important essay, providing a useful, if not universally accepted, framework for evaluating drug efficacy. However, challenges have arisen in the process of applying the findings, as I will explain later. For some experts, the study was initially met with skepticism due to the acknowledged biases, and the need for exhaustive attention to detail.

When personal biases and subjective opinions are expressed by the panels and the experts, the consensus is often less than uniform. In this state of equipoise, the study's ultimate success or failure hinges on the ability to create an environment where the experts are expected to be so accepted or applied. Therefore, the study advocates exhaustive attention to detail.

A notable exception to the equipoise shown by the NAS-NRC Study is the survey made by McMahon (12). He surveyed 20 popular fixed combinations, noting the absence of unanimity in recommendations. The survey revealed that the fixed combinations are not always the best solution, as each combination is evaluated by the study's experts. This raises the question of whether the fixed combinations are truly the best option for patients.

To translate scientific principles into practice, we must ask ourselves how we can prove the efficacy of these combinations. Should we consider the fixed combinations as a rational combination of experts' opinions or as unattainable hard work? The answers to these questions will shape our approach to drug combinations.

The National Academy of Sciences' report on drug combinations provides guidance on the evaluation of fixed combinations. The report lists 17 references, including studies that evaluate the efficacy of different drug combinations. These studies highlight the importance of careful evaluation and the need for a comprehensive approach to drug combinations.

In conclusion, the challenge of drug combinations lies in balancing the need for scientific rigor with practical applicability. The fixed combinations, while not universally accepted, can serve as a useful framework for evaluating drug efficacy. However, the experts' opinions must be applied with caution, and the need for exhaustive attention to detail must be recognized.

References: