Guest Editorial

POLYPHARMACY—MORE SINNING THAN SINNED AGAINST

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THEN AND NOW

In ancient times, the practice of medicine required artful prescribing of a multitude of ingredients which were compounded skillfully to cater to the needs of individual patients; and the patient was inundated with a deluge of drugs. In 1785, William Withering advocated the treatment of dropsy in these words "medicines of the de-obstruent, tonic antispasmodic, diuretic and evacuate kinds". His instructions required the use of "pills of Myrrh and white vitriol; and if costive, a pill with calomel and sloes". However, the possibility of therapeutic incompatibility resulting from the coadministration of a variegated confetti of such medicaments was recognized as early as 1825 when John Ayrton Paris of Great Britain wrote in the introduction to his famous text-book, Pharmacologia, that "we have copious catalogues of formal recipes, and many of unexceptionable propriety, but the compilers do not venture to discuss the principles upon which they are constructed, nor do they explain the part which each ingredient is supposed to perform in the general scheme of formula. Substances may be medically inconsistent which are chemically compatible".

Since Paris levelled this charge mildly, but in no uncertain terms, against the practice of polypharmacy or multiple drug therapy, much water has flown under the bridge and tremendous strides have been made in the development of new drugs. Today more of our drugs are tailored to attack the root-cause of disease or the fundamental mechanisms of its pathophysiology so that it is often possible to eradicate the disease or suppress the entire symptom-complex with one durg alone. However, even a cursory glance at the treatment charts of the hospitals or private patients reveals that only a few patients escape medication with more than one drug. Further, there are many fixed-dose combinations of drugs available in the market, the rationale claimed for which is the enhancement of benefit to the patient while the actual aim is the augmented profits made by the manufacturers.

MANUFACTURER'S MOTIVES

In vindication of this viewpoint, let us take the example of a newly discovred antimicrobial agent which has one or more of the following features: dubious efficacy; narrow spectrum of activity; undesirable properties. Because of commercial interest in such a discovery, the manufacturer produces fixed-dose combinations which contain the new drug as one of the

ingredients. In fact, with many congeners available in each field, the number of combinations and permutations which can be, and are, marketed together is astronomic. In a survey of the West German therapeutic scene in the fifties (13) it was revealed that, of the 6000 proprietary preparations marked by 565 different firms, most of them contained several pharmacologically active ingredients. Five or six was the rule, and more than ten was not infrequent. One pharmaceutical company had included twenty-two different substance in one tablet. In our country, confusion is worse confounded. Any attempt at statistical analysis will be a Herculean task. Anyway, such fixed-dose combinations are vigorously promoted by fanciful advertisements. The colourful brochures and pamphlets, which sing the siren song of the purveyor of pills, dominate the thoughts and beliefs of the prescriber. The psychological appeal that three drugs of established therapeutic value are better than two which, in turn, are better than one is difficult to resist (12) and the physician feels secure in the numerical strength of drugs used. I seek the indulgence of my readers for any irrelevance and irreverence to our profession if I highlight this sense of pseudo-security of the physician by citing the dialogue between little Linus and his Pal, as depicted in a cartoon by the famous Charles Schulz :

Pal : You seem very secure today, Linus.

Linus : I am. I *feel* quite secure.

Pal : Where do you think the source of this security lies.....in the thumb you are sucking, in the blanket you are wearing or in the pose you are assuming.

Linus : I would say it is a combination of ingredients.....not unlike a doctor's prescription.

SOME CASE REPORTS

Whatever the spirit and intent of using multiple ingredients in fixed ratios, it is increasingly realized that the increasing therapeutic misadventures with such combinations are ever-increasiag. In the April, 1969 issue of the Archives of Internal Medicine (17), a case is reported of an 18 year old girl with agranulocytosis which was caused by chronic ingestion of a proprietary mixture containing sulphaguanidine. The mixture was prescribed for diarrhoea by the patient's father, a physician. Another physician's 4-year old daughter had complete deafness resulting from the administration of streptomycin-penicillin mixture which was prescribed by a paediatrician colleague (3). These are not isolated or stray examples of the adverse effects of a totally unnecessary and wholly unwarranted ingredient of a combination. In fact, the ravages wrought by such combinations are staggering in proportion and frightening in variety (10). There are numerous reports in literature of the sins committed by polypharmacy. Not only this, there must be many more victims of fixed-dose combination of drugs which have never been reported for obvious reasons. To my mind, the publicized cases which we come across in journals and monographs represent merely the tip of the floating ice-berg with much of the information lying beneath the surface of our awareness since it (information) is buried or cremated along with the patients. If Shakespeare was alive today,

he would as well have said for Polypharmacy, "Tremble, thou wretch, thou has within thee undivulged crimes" (King Lear, Act III, Scene 2).

THE AMERICAN VIEWPOINT

Recently, the Council on Drugs of American Medical Association (2) reaffirmed its long-standing position that the "use of fixed-ratio combination of all drugs, antibiotics included, is, with few exceptions, neither a sound nor judicious practice". For example penicillin plus sulphonamide or penicillin plus streptomycin are often prescribed in fixed-dose combinations (11). One of the most common indications for the use of the former combination is mixed bacterial infections like bronchiectasis, peritonitis, urinary tract infection and chronic otitis media. However, this combination is of doubtful value for following reasons : (i) many different strains and species of bacteria are associated with these infections; (ii) patterns of anti-microbial sensitivity are highly variable; and (iii) total antimicrobial activity of the combination may be less than the sum of individual activities of its ingredients. Further, use of the combination places the patient in "double jeopardy", that is, he is exposed to the toxic effects of both the drugs which, in the words of Friend (5), are "double-edged swords". Also, it is impossible to adjust individual doses in individual patients (1). Hence, it is strongly urged by the National Academy of Sciences of U.S.A. (15) to refrain from the use of fixed-dose combination of sulphonamides and penicillins. Similarly, after considering the pros and cons, it is the clear verdict of the said Academy that the combination of streptomycin and penicillin "no longer belongs in the therapeutic armamentarium".

THERAPEUTIC INCOMPATIBILITY—ANOTHER HAZARD

Besides the problem of fixed-dose combination of drugs, we are, at least we should be, deeply concerned with the additional problem of therapeutic incompatibilities resulting from drug interactions when two or more substances, which are not in fixed ratios, are given to the patient. In the present era of drug explosion when we have a vast array of new potent drugs with radically different structures, with which many of our practising physicians have not had the time or opportunity or inclination to educate themselves, the problem of drug interactions, expected or unexpected, has assumed gigantic proportions.

The mechanisms underlying these interactions are both complex and varied, and the possible and potential number of interactions is limitless. One drug may alter the action of another by modifying its absorption, transport, storage, biotransformation, action on receptor sites or excretion (6, 14). It is not possible in this article, nor is this the purpose, to discuss these mechanisms and to enumerate the various categories of interactions between various drugs. However, some prominent examples of undesirable interactions are cited: monoamine oxidase inhibitors with narcotic analgesics and adrenergic drugs; tolbutamide with sulphonamides; streptomycin and neomycin with neuromuscular blocking agents; anticoagulants with butazolidine derivatives; thyroxine with methandrostenolone; ephedrine

with ergonovine and oxytocin; digitalis with chlorothiazide; reserpine with ether; tetracycline with calcium and iron; phenothiazines with narcotics; probenecid with aspirin; alcohol with antihistaminics etc (4, 16).

PLEA FOR RATIONALITY

It is to be emphasised that the turbulence created by the plethora of therapeutic incompatibilities resulting from the practice of polypharmacy should not becloud our judgment in using drug combinations in certain clinical situations viz., tuberculosis, bacterial endocarditis, endotoxin shock, mixed infections of skin and wounds, hypertension, epilepsy and fluid retention (7, 9). Further, drug interactions may occasionally be beneficial in reducing the intensity and frequency of adverse reactions (8).

However, it is reiterated that the choice of a combination on rational basis is more infrequent than frequent; and multiple drug therapy is often overdone, unnecessary and avoidable. If "the curse of polygamy is many mothers-in-law", that of polypharmacy is multiple drug reactions. Unlike King Lear, who, in the words of Shakespeare, was "more sinned against than sinning", polypharmacy is more sinning than sinned against. It was never more true than now what Osler said, "If many drugs are used for disease, all are insufficient". Whenever possible, and it will be more often than not possible, the commercial coercion and psychological appeal in prescribing "not just one drug but multiple of medically proven ingredients" must be resisted.

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The baneful features of controversy develop chiefly, I believe, from the use of language which expresses emotional attitudes rather than intellectual considerations. If differences between investigators are discussed strictly on the intellectual level there is no reason for the development of a sense of injury, no reason for later enmity. Properly conducted, a polemic may leave both the original investigator and his critic with the conviction that they have been concerned with the advancement of science. The desire for conquest, the impulse to engage in triumphal exaltation is absent. Also the emahasis on observed facts may lead to further work of a more refined character and thus to new and unanticipated discoveries.—**Walter Bradford Cannon : "The Way of an Investigator ; A Scientist's Experiences in Medical Research, New York, W. W. Norton & Company, Inc. 1945 p. 100.**