Development of New Drug Dosage Form

SIR,—We would like to reply to the criticisms of Dr. J. C. Garnham (22 January, p. 249) on the flow chart development of a new drug dosage form (8 January, p. 102).

The term "drug" can be applied to the crude preparations of vegetable origin, but more aptly refers to active pharmacological principles; and, as such, drugs are rarely, if ever, used in clinical practice. The clinician handles and administers a drug preparation—that is, a medicine. One can therefore refer to the discovery of a new drug, to its isolation, or to its synthesis but cannot refer to its development. What is developed is a drug preparation or drug dose form. As to the meaning of biochemical pharmacology: the subject of biochemical pharmacology can be subdivided into studies on pharmacological effects at the biochemical level, which are now more often referred to as pharmacodynamic studies, and action of biochemical processes on the drug—that is, drug metabolism which includes activation, inactivation, detoxification, lethal synthesis, etc. The study of pharmacokinetics, on the other hand, is a mathematically based and not biochemically based discipline. Pharmacokinetics is defined as the quantification of processes involved in the absorption, distribution, metabolism, and excretion of drugs.

Pharmacokinetic studies are carried out in both healthy volunteers and patients and attempts are made to correlate pharmacokinetic characteristics with pharmacological response, but though much time, effort, and expense have been devoted to discovering new drugs the investigation of physiological and pharmaceutical factors that modify drug response have been neglected. The choice between healthy volunteers and sick patients for pharmacokinetic studies has been the source of active discussion. It is obvious that clinical evaluation must be carried out in patients. Blood and urine samples can be collected routinely and information from steady state drug level data be obtained.

Of course it is probable that absorption, metabolism, and excretion of a drug will be changed by disease. It is possible but improbable that if preparation A is shown to be superior to preparation B in healthy volunteers there will be marked changes in the relative values obtained in patients. It is possible that both preparations A and B could prove to be unsuitable in the patient and a new formulation have to be designed—for example, to promote absorption.

As to the time and cost implications of the flow chart, one cannot sacrifice safety to efficiency or economy. The flow chart for the development of a new drug dosage form is based upon similar charts currently being used in at least two pharmaceutical companies.¹ It suggests a procedure by which information required in a submission to the Committee on the Safety of Medicines may be obtained with the least delay.

At the present time our methods of delivering drugs to the target site are extremely primitive. After the drug is absorbed into the blood stream it is distributed round the body to the areas where it is required. In most cases the distribution is not selective and the whole body may be swamped with drug, leading to side effects and adverse reactions. It is now well known that difference in formulation can affect the release and absorption of drugs and that chemically equivalent dosage forms may not be equivalent

in terms of biological availability. Good formulation can enhance the stability and efficacy of a drug, whereas poor or inadequate formulation can render a potentially active drug completely inactive. It is obviously foolish to spend time on developing a drug dose form before the drug has been administered to man, but it is reasonable to begin to investigate the physical and chemical characteristics of compounds which early animal studies have indicated as potentially useful. It is then possible to prepare drug dosage forms of approved drugs and to proceed to clinical evaluation with the minimum of delay.—We are, etc.,

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¹ Nineman, A. W., M. & B Pharmaceutical Bulletin, 1970, 19, 2.

Speech Therapy for Hemiplegics

SIR,—The article on rehabilitation of hemiplegia (January, p. 94) infers that there is no definite proof that the results of speech therapy are better than "nature." There is some evidence available, however, that dysphasic patients recover more quickly with the help of speech therapy, and reach a higher standard of language facility.¹⁻⁶

From my experience of working intensively with cardiovascular accident aphasics over a long period of time in the past, I do know of their desperate plight and that of close members of the family concerned. The speech therapist, with her specialized knowledge of language, psychology, psychopathology, neurology, and phonetics, etc., is in a better position than anyone else to aid human communication in aphasia. Ideally the speech therapist should work intensively as a member of a highly specialized medical and paramedical rehabilitation team.

Perhaps it should be stressed that British speech therapists have not been very willing to take part in research where a division is made between observation of patients treated and those left untreated, as they have felt strongly that all dysphasics need help.—I am, etc.,

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- ¹ Beyn, E. S., and Shokhor-Trotsky, M. K., *Cortex*, 1966, 2, 96.
- ² Grewel, F., and Greene, M. C. L., *Psychiatrica, Neurologia, Neurochirurgia*, 1968, 71, 469.
- ³ Hagen, C., *The Effect of Speech and Language Therapy on Communication Disordered Stroke Patients*. American Speech and Hearing Convention, New York, 1970.
- ⁴ Maruszewski, M., *International Journal of Psychology*, 1969, 4, 73.
- ⁵ Perry, P. S., and Boswell, N. S., *Long Term Score Changes on the Peabody Picture Vocabulary Test (PPVT) by Adult Aphasics*. American Speech and Hearing Convention, New York, 1970.
- ⁶ Vignolo, L. A., *Cortex*, 1964/65, 1, 344.

Novel Crush Injury

SIR,—I should like to bring to your notice an uncommon injury sustained in a most unusual fashion.

Though mention has been made previously of injuries due to "Klackers" (11 September 1971, p. 643) the severity of injury which may be suffered has not been stressed in

medical literature. The following case history demonstrates the remarkable force present at the time of impact of the two "Klackers."

A left-handed, 12-year-old boy was playing with these "Klackers" and while the two heavy balls were concluding their downward arcs ready to ricochet one from the other, the unfortunate fellow unwittingly interposed his right thumb in their flight path. The consequences to his distal phalanx were severe. The digit swelled up and became painful, necessitating a visit to a casualty department, where primary treatment to the thumb was given.

Some 17 days later he was referred by his own general practitioner to us for admission with the complaint of an exquisitely tender, grossly inflamed, and swollen thumb which was discharging pus at its point. An x-ray showed a displaced fracture of the distal phalanx. More interesting, however, was the appearance of the bone fragments, which displayed the appearance of osteomyelitis (Fig.).

Treatment was, as advocated by Harris,¹ by drainage as well as high dosage of cloxacillin to which the penicillinase-producing *Staphylococcus aureus* grown was sensitive. In spite of this it was not until the loose distal fragment was removed that the thumb began to heal. Histology of the bony fragment confirmed the changes of acute osteomyelitis. One further feature of interest in this case was that this boy was receiving long-term penicillin treatment as prophylaxis after rheumatic fever.

Osteomyelitis of the digits is uncommon especially in children—even trauma to the thumb is only 12% of all digit-tip trauma.² This boy had the misfortune to be one of the few and therefore had a period of six weeks' illness, three weeks as an inpatient, and two operations, all as a result of his inaccuracy with his "Klackers."

I am grateful to Mr. W. G. Scobie for his permission to present this case.

—I am, etc.,

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- ¹ Harris, N. H., *British Medical Journal*, 1962, 1, 1440.
- ² Horner, R. L., *Surgical Clinics of North America*, 1969, 49, 1373.

Red Cell Size and Age

SIR,—I was interested in Surgeon Commander R. J. W. Lambert and Mr. J. E. W. Morris's letter about "Red Cell Sizes and Air Composition" (18 September 1971, p. 706), since we have been studying here the M.C.V. (mean corpuscular volume) by using the Coulter Model S.¹ The advent of the Coulter S has enabled us to measure directly the size of red cells. Otherwise, the M.C.V.