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.,

S. S. DAVIS
M. MITCHARD

Department of Pharmacy,
University of Aston

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.,

E. BUTFIELD

Principal,
West End Hospital Speech Therapy Training School

London W.1

1. Beyn, E. S., and Shokhor-Trotsky, M. K., *Cortex*, 1966, 2, 96.
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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.,

A. J. G. SWANSON

Surgical Paediatric Department,
Western General Hospital,
Edinburgh 4

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.

has to be calculated from the erythrocyte counts and the haematocrit.

Studies on 500 healthy persons indicate that the older age groups, regardless of sex, have higher M.C.V. than the younger age groups. It is quite conceivable that anoxia produced by chronic lung troubles in older age groups, though asymptomatic clinically, may have produced larger M.C.V., as has been observed by Surgeon Commander Lambert and Mr. Morris, who stated smokers have larger M.C.V. than non-smokers. I am puzzled, however, by the fact that there is no sex difference in the studies done here. It appears to me that there are more smokers in the male group than in the female group (and therefore the M.C.V. should be larger in the male than in the female group). No age differences were observed of haemoglobin or haematocrit values by our studies.

The M.V.C. of 500 Healthy Individuals According to Sex and Age Groups

Age Group	Male	Female
16-19 ..	89.5 ± 8.6	89.6 ± 7.6
20-29 ..	90.0 ± 8.7	90.4 ± 8.9
30-39 ..	91.9 ± 6.7	91.2 ± 12.4
40-49 ..	92.5 ± 9.4	91.6 ± 8.7
50 and above	93.0 ± 10.3	93.1 ± 8.7
Average ..	91.4 ± 9.2	91.3 ± 9.4

Each group consists of 50 individuals.

The Difference of the M.C.V. in Different Age Groups

Age Group	16-19	20-29	30-39	40-49	50 and above
20-29	d: 0.46 t: 0.528 p > 0.5				
30-39	d: 2.36 t: 3.049 p < 0.005	d: 1.90 t: 2.429 p > 0.02			
40-49	d: 3.02 t: 3.321 p < 0.005	d: 2.56 t: 2.793 p < 0.01	d: 0.66 t: 0.801 p > 0.4		
50 and above	d: 3.50 t: 3.660 p < 0.001	d: 3.04 t: 3.157 p < 0.005	d: 1.14 t: 1.302 p > 0.1	d: 0.48 t: 0.481 p > 0.8	

Each group consists of 50 healthy male individuals.
d: Difference of the means.
t: Student's t
p: Probability

These studies also indicate that the M.C.V. by the Coulter S is higher than the generally accepted values: 82-92 μ^3 ,² or 76-96 μ^3 .³ The larger M.C.V. values by the Coulter S have also been observed recently by Silver and Frankel.⁴ Their values range 83.6 to 99.2 μ^3 on 200 determinations of male and female blood donors and student nurses. The lower M.C.V. values by the manual methods appear to be due to less precise determinations of the erythrocyte counts.—I am, etc.,

TAKASHI OKUNO

Lutheran General Hospital and
School of Medicine,
University of Illinois,
U.S.A.

- 1 Sharp, A. A., and Ballard, B. C. D., *Journal of Clinical Pathology*, 1970, 23, 327.
- 2 Wintrobe, M. M., *Clinical Hematology*, 6th edn. Philadelphia, Lea and Febiger, 1967.
- 3 DeGruchy, G. C., *Clinical Hematology in Medical Practice*, 2nd edn. Philadelphia, F. A. Davis, 1964.
- 4 Silver, H., and Frankel, S., *American Journal of Clinical Pathology*, 1971, 55, 438.

Mandarin Nail Syndrome

SIR,—From time to time changes in cosmetic practice bring their own bad effects on the hair, skin, and nails to those who follow the current trends. Recently I have seen several patients, both young and older women, who present with painful lesions of one or more nail beds, generally associated with some discoloration extending in variable distances from the free margin of the nail to the lunular. At times the nail plates are shed.

This is often mistaken for an infection of the nail plate by fungus, yeast, or mould, though no micro-organisms are recovered. Needless to say, systemic or local treatment will not help in any way, because the changes are brought about through purely mechanical means. The long nail acts as a lever and promotes a force great enough to rupture the connexion between the nail bed and the nail plate, and often produces small haemorrhages as well. This process is frequently repeated, and the separation of the nail plate from the bed progresses until the nail may be lost.

The treatment is obvious: the nail should be cut very short to minimize further damage to the nail bed. Filing should be avoided, and the patient reassured that the nails will grow out normally when they are given a chance.—I am, etc.,

E. J. MOYNAHAN

Guy's Hospital,
London S.E.1

Action of Disodium Cromoglycate

SIR,—In a recent review of the possible mechanisms of action of disodium cromoglycate Cox¹ has pointed out that a conflict of opinion exists concerning the ability of the drug to alter the sensitivity of the airways of asthmatic subjects to challenge with histamine. Altounyan² in adults and Dickson³ in children have both shown that the fall in forced expiratory volume in one second (FEV₁) after a histamine aerosol was diminished after a period of regular treatment with disodium cromoglycate. Recently, however, Ryo and colleagues⁴ failed to demonstrate any significant effect when the drug was given either chronically or acutely before histamine challenge in adult asthmatics. I have obtained similar evidence in childhood asthmatics who were being investigated during a clinical trial of disodium cromoglycate.

Forty asthmatic children who had taken no drugs for the previous eight hours each inhaled histamine acid phosphate solution (0.03 or 0.1%, according to previously determined sensitivity) for two minutes from a Wright's nebulizer. FEV₁ was measured before and at ½-1 minute intervals after the challenge. When the FEV₁ had returned to the initial value a capsule was administered in a single-blind fashion, either of disodium cromoglycate or of a placebo (lactose with sodium sulphate). After 10 minutes histamine challenge was repeated. Histamine sensitivity was diminished both by disodium cromoglycate and by placebo (see Table) but the difference between the two forms of treatment was not significant. There was a diminution in the fall in FEV₁ of 35% after placebo and of 34% after disodium cromoglycate. Thus the effect of disodium cromoglycate was no greater than the effect of a placebo.

Mean Fall in FEV₁ (%) after Histamine Aerosol

Control	Placebo	Control	D.S.C.G.
46.0	30.0	34.0	22.5
t = 3.22	t = 3.96		
n = 7	n = 33		
p < 0.01	p < 0.001		

The results of this study and that of Ryo and colleagues⁴ differ from those of Altounyan² and Dickson,³ suggesting that there may be a difference between the modes of action of disodium cromoglycate given acutely and chronically. The present study also differs from that of Kerr and his colleagues,⁵ who found that the effect of intravenous histamine on airways was diminished by disodium cromoglycate. This would suggest that the mechanism of action of intravenous histamine on the lung is different from that of the inhaled drug, and that it might be more profitable to explore this difference than to assume, as do Kerr and his colleagues,⁵ that a difference does not exist.—I am, etc.,

M. SILVERMAN

Department of Paediatrics,
Institute of Diseases of the Chest,
London S.W.3

- 1 Cox, J. S. G., *British Journal of Diseases of the Chest*, 1971, 65, 189.
- 2 Altounyan, R. E. C., in *Disodium Cromoglycate in Allergic Airways Disease*, ed. J. Pepys, and A. W. Frankland. London, Butterworths, 1970.
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- 4 Ryo, U. Y., Kang, B., and Townley, R. S., *Journal of Allergy*, 1971, 47, 96.
- 5 Kerr, J. W., Govindaraj, M., and Patel, K. R., *British Medical Journal*, 1970, 2, 139.

Head Injuries in Children

SIR,—From the prominence devoted to benign intracranial hypertension in your leading article (22 January, p. 196) it is clear that you consider this condition to have a close relationship with head injury. The reasons for your belief have not been given. Scant support for it is to be found in Grant's paper¹ from which you quote. The contention that air studies are unnecessary in children with benign intracranial hypertension begs the question, for how can a firm diagnosis be made without the measurement of intraventricular pressure and gas replacement?

Dr. J. H. Burkinshaw (5 February, p. 378) raises other issues. Of course clinical observation of the head-injured patient is of vital importance, but skull radiographs may give useful information which cannot be obtained by other means. In particular, it must be stressed that anticipation of complications after head injury is more than half the battle, and anything which helps is to be welcomed. One of Dr. Burkinshaw's two (and only two) indications for routine skull radiography is "to confirm a clinical diagnosis of depressed fracture of more than trivial degree." This is dangerous stuff. Very occasionally there may be an obvious dent in the head over a depressed fracture, but much more commonly there is a haematoma which effectively conceals what is underneath. Why can routine skull radiography help in management? The following are a few conditions which can be demonstrated by this investigation:

(1) A fracture line crossing the course of a meningeal artery or dural venous sinus. In