storage of chemical products and increased publicity of the potential dangers of chemical agents.⁶ Legislation in Canada and the United States will shortly make safety containers mandatory for drugs and household products.^{2,5}

In November 1969 the Liverpool Regional Hospital Board agreed that the Palm-N-Turn container should be introduced into the region and that this programme should start in Birkenhead. It is hoped that child-resistant containers will be adopted in other areas and that their use may be made compulsory throughout the country as soon as possible.—I am, etc.,

D. H. S. REID.

Children's Hospital,
Birkenhead, Cheshire.

REFERENCES

- 1 Breault, H. J., *Pediatrics*, 1967, **40**, 159.
- 2 Breault, H. J., personal communication, 1970.
- 3 Stracener, C. E., Scherz, R. G. and Crone, R. I., *Pediatrics*, 1967, **40**, 286.
- 4 Scherz, R. G., Latham, G. H. and Stracener, C. E., *Pediatrics*, 1969, **43**, 84.
- 5 Hughes, J. R., *New England Journal of Medicine*, 1970, **282**, 981.
- 6 Baltimore, C. L., and Meyer, R. J., *Pediatrics*, 1968, **42**, 312.

War Surgery in Nigeria

SIR,—I was very interested in the article by Mr. G. W. Odling-Smee (6 June, p. 592), particularly noting his views on major limb wounds in which fractures are combined with soft tissue injuries. I hope his advocacy of the use of immediate internal fixation in compound fractures is not taken at its face value without full reference to the paper by Dudley *et al.*¹ which he quotes. Too often one sees these injuries closed under tension or by unsafe local flaps and encased in plaster for six weeks with disastrous results. If internal fixation is to be used particularly when there is a skin defect there must be available "a team seized with the urgency of skin cover."¹ Trueta's work² and that of his predecessors and followers has frequently been mis-read or only half read by those responsible for the care of compound injuries, and the application of the principle of delayed primary skin cover too often ignored in the past, in war and peace.—I am, etc.,

B. S. CRAWFORD.

Plastic and Jaw Department,
Hallamshire Hospital,
Sheffield, Yorks.

REFERENCES

- 1 Dudley, H. A. F., Knight, R. J., McNeur, J. C., and Rosengarten, D. S., *British Journal of Surgery*, 1968, **55**, 332.
- 2 Trueta, J., *The Treatment of War Wounds and Fractures*. London, Hamish Hamilton 1939.

Ergotamine Tartrate in Migraine

SIR,—I am surprised that Dr. D. S. Freestone (6 June, p. 599) should be puzzled by the ineffectiveness of ergotamine tartrate shown by Dr. W. E. Waters (9 May, p. 325). The wonder is that the investigation, using a homoeopathic dose instead of a therapeutic dose, was ever undertaken.

For many years I, like Dr. Waters, followed the usage of textbooks and gave a dose of 1 or 2 mg. followed by 1 mg. half hourly. I was quite convinced that ergotamine

tartrate was a drug of little value, except in so far as there was no other more effective drug in tablet form unless one happened to have discovered that a particular patient responded to some less conventional treatment, such as 400 mg. of sodium amylal.

One day I chanced to pick up a manual¹ in which I read that the American usage is to give 5 mg. initially followed by 2 mg. half hourly, if necessary up to the usual maximum dose of 10 mg. in a day. I now find that a single dose of 5 mg. is all that is needed to abort an attack of migraine in almost any patient unless vomiting necessitates an injection.—I am, etc.,

T. D. FITZGERALD.

Sheerness, Kent.

REFERENCE

- 1 Rahway, N. J., Merck, 1966, *Merck's Manual of Diagnosis and Therapy*. 11th ed.

Nifuratel for Trichomonal Vaginitis

SIR,—Drs. B. A. Evans and R. D. Catterall (9 May, p. 335) quote an early study by Dr. J. Delnon and myself on nifuratel¹ at the obstetrics and gynaecology clinic of the University of Berne. In further trials on 485 patients² I was able to compare the trichomonacidal activity of nifuratel (Magmilor; in Switzerland Macmilor) with that of metronidazole (Flagyl), referring also to my previous experiments with the latter product.³

The conclusions I came to are quite different from those reached by Drs. Evans and Catterall. In fact, in 1965-6, I observed that the cure rate attained by metranidazole was about 68%, and that by nifuratel about 80%.

In my experience, the activity of nifuratel in bacterial and mycotic infections was satisfactory in cases of mixed aetiology and in preventing mycotic superinfections, which often occur after treatment with metranidazole.—I am, etc.,

M. ARNOLD.

Baar, Switzerland.

REFERENCES

- 1 Arnold, M., and Delnon, J., *Therapeutische Umschau und medizinische Bibliographie*, 1965, **22**, 490.
- 2 Arnold, M., *Therapeutische Umschau und medizinische Bibliographie*, 1966, **23**, 356.
- 3 Arnold, M., and Berger, M., *Gynaecologia*, 1961, **152**, 238.

SIR,—Drs. B. A. Evans and R. D. Catterall draw some rather rash conclusions from their comparison of anti-trichomonal activity between nifuratel and metronidazole (9 May, p. 335). The authors do not appear to have considered what is known of the epidemiology of trichomoniasis. The most detailed and up-to-date statistical data indicates that the incidence of trichomonas is about 10-15% in women generally and 70-75% in prostitutes.

Drs. Evans and Catterall neither treated the male partners nor considered the possibility of re-infection in the 12-week period which elapsed between the end of treatment and their last control. The fact that four patients presented with a gonorrhoeal

infection during treatment is in itself very significant in this connexion.

Another questionable point is that the side-effects ascribed to nifuratel were general allergic reactions which occurred without any local intolerance, despite repeated insertions of pessaries into the vagina. The side-effects mentioned by the authors are more likely to be attributable to other drugs administered concurrently (penicillin, etc.) or taken by the patients in question.

These observations of mine are based on six years' experience with nifuratel (Magmilor) in hundreds of cases,¹ where I observed quite different results with no local or systemic side-effects. Treating trichomoniasis with nifuratel I attained approximately 93% recovery, which is a rate in agreement with that achieved by many authors in other countries. I stopped using metronidazole as the success rate was less than 70%.—I am, etc.,

ITALO SAGONE.

Milan, Italy.

REFERENCE

- 1 Sagone, I., *Minerva Ginecologica*, 1965, **17**, 654.

Pre-ulcerative Buruli Lesions

SIR,—In our recent paper on "Clinical Features and Treatment of Pre-ulcerative Buruli Lesions" (16 May, p. 390) it was not made clear that the five cases described were investigated bacteriologically, and that *Mycobacterium ulcerans* was isolated from the excised lesions in each case. We have commented¹ previously on bacteriological findings in lesions of different histological types.—I am, etc.,

IAN PHILLIPS.

Member of Uganda Buruli Group.

St. Thomas's Hospital,
London S.E.1.

REFERENCE

- 1 Uganda Buruli Group, *Lancet*, 1969, **1**, 111.

Sleep and Drug Overdose

SIR,—For some years I have followed Dr. Ian Oswald's work on sleep and related problems with interest and admiration so it is with some dismay that I read the article on late brain recovery processes after drug overdose (9 May, p. 318).

It may be that raised paradoxical (R.E.M.) sleep rebound indicates prolonged turnover of proteins in the cerebrum,¹ but it occurs in a variety of conditions—amphetamine withdrawal, barbiturate withdrawal, overdose with tricyclic drugs, and after "E.C.T. overdose." Dr. I. Haider and Dr. Oswald show that in Case 1 after an overdose of Mandrax R.E.M. sleep returned to normal according to their chart in 31 days, but in Case 4 after two episodes of overdose with nitrazepam the R.E.M. remained abnormal for 33 days and more than 42 days.

In their third last paragraph they say that "nitrazepam is to be preferred to its contemporary rivals" because of its safety, but then go on to make a statement that indicates that co-ordination, emotional stability, and good judgement need not be

expected in patients who are conscious after overdosage of nitrazepam.

I find this quite confusing, and as a clinician who prescribes both nitrazepam and methaqualone I cannot see how judgements as to "safety" in overdosage can be equated with "preference," presumably as such preference must take into account the effectiveness of a drug in normal dosage for a specific purpose—in this case induction of sleep.—I am, etc.

J. M. MACGREGOR.

Department of Neurology,
Groote Schuur Hospital,
Cape Town, S. Africa.

REFERENCE

- ¹ Oswald, I., *Nature*, 1969, 233, 893.

Susceptibility to Aspirin Bleeding

SIR,—Your leading article (23 May, p. 436), which accompanied the paper of Dr. D. J. B. St. John and Mr. F. T. McDermott (23 May, p. 450), refers to the controversial nature of the role of acid in aspirin-induced gastrostaxis, but fails to point out the equally controversial nature of some of your other statements. Thus, the opening sentence implies that aspirin is a proved and primary cause of a substantial proportion of acute gastrointestinal bleeds. In fact, the evidence is not strong enough to support such an unequivocal statement. Some publications certainly suggest that such may be the case, but the evidence adduced is circumstantial, with the major references quoted as "proof" resting their case on the finding that patients admitted to acute medical wards with haematemesis and melaena had somewhat more commonly taken aspirin during the preceding week than patients admitted to the same units for other reasons. Valman *et al.*¹ are typical in that 56% of their cases with an acute bleed had taken some aspirin, while aspirin had been taken by only 32% of the control group. There are many reasons for not jumping to the too obvious conclusion. For example, the vague symptoms of discomfort and malaise with which a developing bleed may be associated would tend to cause many people to seek relief with their old standby, aspirin. Smith² stated that a history of higher incidence of recent ingestion of aspirin is not proof that aspirin is the causal agent of massive haemorrhage, and Waterson³ could find only three patients out of 165 where aspirin could possibly be incriminated as the cause of bleeding. More recently, Halmagyi in Ontario⁴ was unable to find any causal relationship between drugs and upper gastrointestinal haemorrhage in his series of 425 cases.

Among difficulties in the way of accepting the hypothesis that aspirin is a direct cause of acute bleeds are: the non-reproducible nature of the phenomenon in the same subject⁵; the numerous controlled studies which indicate that the increase in faecal blood loss due to repeated large doses of aspirin is distributed about a mean of 3-4 ml./day, and the lack of evidence to justify extrapolation to the high figures associated with haematemesis and melaena; and the fact that in cases of massive aspirin overdosage obvious blood is rarely, if ever, found in the gastric aspirates.

Again, your statement that 10-15% of

persons taking aspirin continually lose enough blood to develop iron-deficiency anaemia is not well supported by the world literature (and not supported at all by the reference you quote). Baragar and Duthie⁶ concluded that the great majority of patients with rheumatoid arthritis can tolerate regular aspirin without serious blood loss or development of anaemia. This is not surprising since the average man replaces red cells equivalent to 40 ml. of blood daily, and has the ability, when the need arises, to increase this rate 6 to 9 fold. There is enough iron in the normal daily dietary intake to permit the generation of 23-29 ml. of blood.

With respect to the use of aspirin in people with bleeding diatheses involving platelets, such as von Willebrand's disease, there is mounting evidence that even moderate doses of the drug may prolong bleeding time.⁷ However, this effect does not so far appear to bear any relationship to the sort of gastric bleeding referred to in your leading article.⁸⁻⁹ Leonards and Levy¹⁰ state that gastrostaxis is a local effect and is not related to the prolongation of bleeding time produced by aspirin.

Progress is being made towards aspirin formulations with less risk of adverse effects on the gastric mucosa, and recent sophisticated studies have established that extra blood loss on administration of plain aspirin is approximately halved by substitution of a soluble preparation.⁹

It is important that a balanced view be taken with regard to the deficiencies of aspirin therapy. Here is a rare example of an efficacious drug which has been proved to be relatively safe, whether taken sporadically as self-medication for aches, pains, and fevers, or when prescribed for the treatment of certain common and crippling rheumatoid diseases where dosage is high and continuous.—We are, etc.,

GARETH BLANE,

Clinical Research Co-ordinator.

GORDON R. FRYERS,

Managing Director,

Reckitt and Colman Pharmaceutical Division,
Hull, Yorks.

REFERENCES

- ¹ Valman, H. B., Parry, D. J., and Coghill, N. F., *British Medical Journal*, 1968, 4, 661.
- ² Smith, M. J. H., in *The Salicylates: An International Symposium*, ed. A. St. J. Dixon. London, Churchill, 1966.
- ³ Waterson, A. F., *British Medical Journal*, 1955, 2, 1531.
- ⁴ Halmagyi, A. F., *Surgery, Gynecology and Obstetrics*, 1970, 130, 419.
- ⁵ Parry, D. J., and Wood, P. H. N., *Gut*, 1967, 8, 301.
- ⁶ Baragar, F. D., and Duthie, J. J. R., *British Medical Journal*, 1960, 1, 1106.
- ⁷ Quick, A. J., *American Journal of the Medical Sciences*, 1966, 252, 265.
- ⁸ Kuiper, D. H., Overholt, B. F., Fall, D. J., and Pollard, H. M., *American Journal of Digestive Diseases*, 1969, 14, 716.
- ⁹ Leonards, J. R., and Levy, G., *Clinical Pharmacology and Therapeutics*, 1969, 10, 571.
- ¹⁰ Leonards, J. R., and Levy, G., in press, 1970.

**We disagree with Drs. Blane and Fryers that there is not enough "proof" that aspirin can be a clinical problem, in terms of both acute and occult bleeding. In the study by Valman and others¹ the incidence of aspirin ingestion among patients admitted for haematemesis and melaena was greater than among patients admitted to a general medical ward with pneumonia,

fever, and chest pain. The difference was highly significant ($P < .001$). The control group had as much, if not more, cause for taking aspirin for symptomatic relief as had the patients who were bleeding. In view of the welter of evidence, dating from Douthwaite and Lintott's observations in 1938,² that aspirin has a direct haemorrhagic effect on the human gastric mucosa, the most reasonable conclusion from these data is that aspirin caused the erosions. This is not to deny that other factors are involved. Excessive blood loss is the single most important cause or iron deficiency.³ Patients with rheumatoid arthritis are commonly anaemic and aspirin-induced occult bleeding is likely to be an important factor in some of them.⁴

Drs. Blane and Fryers imply that easier gastric absorption of aspirin will result in less mucosal damage. In fact it is formulations that are not absorbed in the stomach but are absorbed lower down, such as enteric-coated aspirin, that cause less occult bleeding. Aspirin is a very useful drug but it does cause trouble, and research into an aspirin preparation free from gastric side-effects would be welcomed.—ED., B.M.J.

REFERENCES

- ¹ Valman, H. B., Parry, D. J., and Coghill, N. F., *British Medical Journal*, 1968, 4, 661.
- ² Douthwaite, A. H., Lintott, G. A. M., *Lancet*, 1938, 2, 1222.
- ³ Green, R., *et al.*, *American Journal of Medicine*, 1968, 45, 336.
- ⁴ Croft, D. N., and Wood, P. H. N., *British Medical Journal*, 1967, 1, 137.

Pseudo-obstruction of the Large Bowel

SIR,—I see that yet another clinical entity has emerged. I refer to the condition of "Pseudo-obstruction of the Large Bowel" described under Current Practice by Mr. P. K. Caves and Dr. H. A. Crockard (6 June, p. 583).

Large bowel obstruction is a clinical syndrome characterized by abdominal distension, constipation, colicky lower abdominal pain, and with the typical x-ray findings of dilated large bowel. A careful analysis of the case histories of the four examples of "pseudo-obstruction" described in this paper reveal that they all had the criteria of large bowel obstruction, and indeed they all underwent laparotomy for this condition, though no mechanical cause for obstruction could be found at operation. There is therefore no case for labelling this condition "pseudo-obstruction" simply because no mechanical cause could be found. The patients were undoubtedly suffering from functional obstruction of the colon, but the obstruction was real enough.

The pathogenesis of functional obstruction of the intestine has until recently been poorly understood. There are two known mechanisms: vascular and neurogenic. A vascular aetiology can apparently be excluded in these patients, so we are left with a neurogenic cause, or, as it is more popularly called, paralytic ileus. Ileus is a sympathetic reflex which may affect the intestinal tract in whole or in part,¹ and the colon is the portion of the intestinal tract under the greatest influence of the sympathetic nervous system and with the least parasympathetic contribution. The colon therefore will be maximally affected by a sympathetic reflex, the small intestine