countries is bound to be fraught with uncertainty.—I am, etc.,

GEOFFREY EDSALL

Department of Microbiology,
London School of Hygiene and Tropical Medicine,
London W.C.1

1 Osler, W., *The Principles and Practice of Medicine*. New York, Appleton, 1892.

SIR,—I was interested to read your leading article (26 May, p. 436) in which the different presentations of typhoid within developed temperate countries and undeveloped African countries was attributed to variations in infective, emotional, cultural, and religious backgrounds. Several years ago I had the opportunity of working in a mixed European and Asian community during an outbreak of typhoid. Psychiatric symptoms occurred in no more than 10% of cases, and there was no apparent difference in the incidence of these symptoms between the two racial groups.

One patient presented initially with severe anxiety and agitation accompanied by pain in the neck and thoracic spine, another presented with hypomanic symptoms, and three others with the more characteristic mental confusion and delirium, associated with headache and pyrexia. As you point out, the true diagnosis may be obscured by these psychiatric manifestations and the management of the case made more difficult.—I am, etc.,

R. A. BILLINGS

Department of Rheumatology
Guy's Hospital,
London S.E.1

Infection with E.B. Virus

SIR,—We would like to comment on one point in your leading article (31 March, p. 757) in which you state that "a common virus aetiology for [infectious mononucleosis and acute lymphatic leukaemia] appears to be improbable, for more than half of leukaemic children examined have been found not to show antibody to E.B. virus." While we do not dispute the conclusion expressed, we feel some comment should be expressed about this line of reasoning.

At the 42nd Annual Meeting of the Royal College of Physicians and Surgeons of Canada in January of this year we presented a case of acute childhood leukaemia in which a patterned inverse relationship in fluctuation between serum IgM and the absolute blast count in the peripheral blood was frequently observed. We had speculated that this might represent a faltering response in the humoral immune system to specific leukaemia antigen (? virus). This is in line with the theories of Schwartz *et al.*,[1] who have postulated that the absence of antibodies in patients with acute lymphoblastic leukaemia to leukaemia antigens is part of the disease syndrome. It is interesting that these patients may have an impaired ability to mount an IgM antibody response to poliovirus.[2]

In proving or disproving the thesis that inability to produce antibodies to leukaemia antigen is an integral part of lymphoblastic leukaemia, experience with an out-bred strain of animals (for example, cats) might prove useful—if, that is, one can draw analogies between these situations. The sequential estimation of anti-FeLV titres in cats naturally and experimentally infected with leukaemia might help to elucidate this point. The assistance of our veterinary colleagues might be valuable.—We are, etc.,

J. E. PARKER
R. A. ROCKERBIE

North Vancouver,
British Columbia

1 Schwartz, S. O., Greenspan, I., Brown, E. R., *Journal of the American Medical Association*, 1963, **186**, 106.
2 Ogra, P. L., Sinks, L. F., Karzon, D. T., *Journal of Pediatrics*, 1971, **79**, 444.

Duration of Action of Beta-blocking Drugs

SIR,—Dr. S. G. Carruthers and others (21 April, p. 177) draw attention to the duration of action of beta-adrenergic blocking drugs and present useful data comparing the decay in blood practolol level with the decline in beta-blockade.

Under the circumstances, however, we wonder whether their use of the term "pharmacological half-life" is appropriate. After the distribution phase practolol levels decline exponentially and the rate of this decline may be expressed as a half-life. If there was a direct relationship between practolol level and response, then the decay of beta-blockade would also be exponential. However, their data and those of others[1 2] show a near-linear relationship between response and the logarithm of practolol concentration. It follows that if the blood level falls exponentially, the response will diminish at a constant rate—that is, as a zero order process. In this type of decay process the time taken for response to fall from 20% to 10% would be twice as long as the change from 10% to 5%.

The decay of pharmacological effect would be better expressed as the decrease in response per unit of time.—We are, etc.,

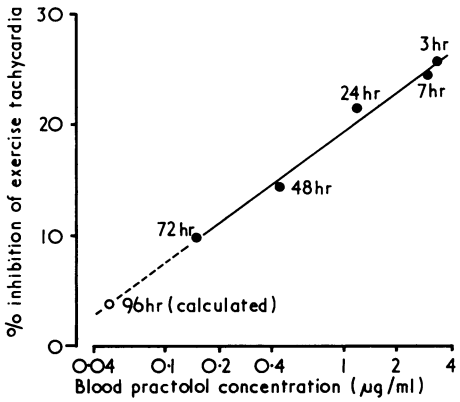
C. R. KUMANA
T. R. D. SHAW

Department of Cardiology and
Clinical Pharmacology,
St. Bartholomew's Hospital,
London E.C.1.

1 Gibson, D. G. *Postgraduate Medical Journal*, 1971, supplement (January) **47**, 16.
2 Schneck, D. W., Aoki, V. S., Kroetz, F. W., and Wilson, W. R., *Clinical Pharmacology and Therapeutics*, 1972, **13**, 685.

SIR,—Dr. S. G. Carruthers and his colleagues (21 April, p. 177) have produced valuable evidence that in man the action of beta-blocking drugs is more prolonged than had been suspected hitherto, and they rightly point out that practolol need be administered only once daily to achieve its therapeutic effect. They draw attention, however, to an apparent discrepancy between the blood practolol level and the reduction in exercise tachycardia achieved in a group of healthy volunteers following administration of a single dose of 400 mg.

On the theoretical basis, the effect of any drug ought to be a function of the logarithm of its concentration, a fact which seems to have been ignored in many published correlations between blood levels and drug effects in man. A log. concentration/effect plot of the data given by Dr. Carruthers and his colleagues (3-72 hr), shown in the figure, yields an almost perfect straight line ($r = 0.99$) in support of the theory. This relationship is also seen in the individual data, which have been kindly provided by the authors. Furthermore, calculation of the drug's blood



elimination half-life (15·1 hr) enables one to predict that the mean blood level at 96 hr after dosage should have been 0·049μg/ml (presumably below the sensitivity of the method used). On the basis of the log. concentration/effect plot shown, this should have produced 4·2% reduction in exercise tachycardia. This is close to the value actually observed (2·3%).

These observations indicate that the effect produced by practolol is consistent with its blood level. The reported discrepancy disappears and it is therefore unnecessary to implicate tissue binding to explain its prolonged action. Indeed, tissue binding is unlikely because the drug's distribution volume (100 l.), derived from the blood concentration data, is just that which would be predicted from its basic nature, its ionization constant (pKa) of 9·1, and its distribution into body water alone. It is apparent that measurement of a blood practolol level should provide a reliable prediction of its therapeutic effect.—I am, etc.,

S. E. SMITH

Department of Pharmacology,
St. Thomas's Hospital Medical School,
London S.E.1

Outpatient Maintenance of Chronic Schizophrenics with Long-acting Fluphenazine

SIR,—The letter from Drs. G. R. Daniel and A. A. Schiff (28 April, p. 244) raises an issue of importance concerning the extent to which results of therapeutic drug trials can be generalized. In each of the studies cited by them we were able to supplement the results of a controlled trial by data which gave some indication of the proportion of patients to whom the results might apply.

In the trial of oral phenothiazines[1] our conclusions were not based solely on the results of the 35 schizophrenic patients in the trial, as implied by Drs. Daniel and Schiff, but on a consideration of the outcome in all 116 acutely ill patients who were admitted to hospital during an 18-month period. For example, two groups of patients were not allowed by their doctors to enter the trial. Of the 11 who were thought to need no preventive medication only three relapsed whereas out of the 15 who were thought to need (and did actually receive) continuous medication 10 relapsed. We concluded that maintenance medication was clearly useful in the group of patients with an intermediate prognosis who did enter the trial, but that the trial results could not with confidence be applied to all acutely ill schizophrenic patients. We discussed the choice of therapeutic strategies in our paper

and would not wish to change the opinions expressed there.

In our study of fluphenazine decanoate (17 March, p. 633) 78 chronic schizophrenic patients aged under 65 attending St. Olave's Hospital constituted all those with the defined characteristics in the catchment area known to be on the drug. Eight of them could not, for various reasons, be adequately managed on fluphenazine decanoate alone and did not enter the trial. During a 15-month period six of the 34 patients receiving active fluphenazine relapsed (including one who dropped out and relapsed). Assuming that a similar number among the 36 on placebo would have relapsed had they been receiving active medication, it can be estimated that 20 patients out of 78 (26%) could not be managed adequately on fluphenazine decanoate alone. This estimate takes no account of the unknown number of patients who may have begun fluphenazine injections but for various reasons did not continue and were therefore not included in our original group of 78.

So far as Drs. Daniel and Schiff's remarks on the dose level are concerned, it should be pointed out that our patients received a minimum level of 25 mg monthly. The dose could have been adjusted at the monthly visits if the clinicians in charge of the patients had wished. In fact, most relapses were fairly sudden. There was no evidence in the case-note describing the previous routine visit of any prodromal deterioration which might have given a clue that an increase in dosage was necessary. Our results suggest that the drug is effective in low doses.

In view of the hazards of long-term phenothiazine treatment, which have not yet been fully explored so far as injected fluphenazine is concerned, we would suggest that these drugs must be used in a cautious and balanced way. Our papers indicate their value in preventing relapse in many patients, but they also indicate that not all patients are likely to benefit and that some patients may not need to take maintenance medication at all.—We are, etc.,

S. R. HIRSCH
J. P. LEFF
J. K. WING

Institute of Psychiatry,
London S.E.5

1 Leff, J. P., and Wing, J. K., *British Medical Journal*, 1971, 3, 599.

Meningococcal Meningitis

SIR,—The article by Dr. J. Stevenson which dealt with bacterial meningitis (19 May, p. 411) was timely. Though Dr. Stevenson notes that meningococcal infection is still the main cause of pyogenic meningitis, he states that its position is now less dominant than it once was vis-à-vis the other two main causes—*Streptococcus pneumoniae* and *Haemophilus influenzae*. I have recently drawn attention[1] to a recrudescence of meningococcal meningitis since 1967 which is apparent in the statistics of mortality, notifications, and hospital discharges as well as in the number of isolations reported by the Public Health Laboratory Service which he quotes. The latest information indicates that this trend is continuing and may indeed be accelerating. The number of notifications of acute meningitis specified as meningococcal in the December quarter of 1972[2] was 189 and the provisional figure for the March quarter of 1973 is 360. These compare with 115 and 185 notifications respectively in the corresponding quarters of the year before. In 1971 the estimated total number of hospital discharges[3] ascribed to meningococcal infection passed the 1,000 mark for the first time since 1964. The number of isolations reported by the P.H.L.S. rose from 519 in 1971 to 601 in 1972, and the latest cumulative total for this year stood at 395 as compared with only 280 at the corresponding time last year.[4]

Dr. Stevenson refers to the hazard of delay in reaching the correct diagnosis in the home or in hospital. It may be that a greater awareness of the trend revealed by these statistics will help clinicians to be on their guard.—I am, etc.,

PETER M. LAMBERT

Office of Population Censuses and Surveys,
Medical Statistics Division,
London W.C.2

1 Lambert, P. M., *Community Medicine*, 1973, 129, 279.
2 *Registrar General's Quarterly Return for England and Wales, Fourth Quarter, 1972*. London, H.M.S.O., 1973.
3 Department of Health and Social Security and Office of Population Censuses and Surveys, *Report on Hospital In-patient Inquiry for the Year 1971*, Part I. London, H.M.S.O. In preparation.
4 Public Health Laboratory Service, 1973 (unpublished).

Treatment of Bacterial Meningitis

SIR,—Dr. J. Stevenson (19 May, p. 411) suggests cephaloridine as an alternative treatment in cloxacillin-resistant neonatal staphylococcal meningitis. This is an unexpected suggestion and I would be interested in the evidence on which it is based. According to Garrod and O'Grady[1] "there is always cross-resistance between methicillin, cloxacillin and cephaloridine and staphylococci proved to be resistant to either of these penicillins may be assumed to be resistant to cephaloridine."

Is there any evidence that the in vivo activity of cephaloridine against cloxacillin-resistant staphylococci is different from its activity in sensitivity tests in vitro?—I am, etc.,

J. S. CARGILL

Department of Bacteriology,
Royal Infirmary,
Glasgow

1 Garrod, L. P., and O'Grady, P., *Antibiotic and Chemotherapy*, 3rd edn., p. 461. Edinburgh and London, Livingstone, 1971.

Prescribing Mandrax

SIR,—As my main interest in the last 30 years has been continually learning and teaching the skilled selective use of physicial treatments of psychiatric patients, I hope I may comment on the proper clinical use of Mandrax and methaqualone in view of some of the things said about them in your columns, such as Dr. P. R. Smith's letter (2 June, p. 552) reporting that his committee had been told, and seems to believe that "addiction could be rapid and that withdrawal symptoms are just as bad as heroin." He asks for a voluntary ban on its use in as many parts of the country as possible.

I have used various forms of continuous sleep treatment since 1940 on several thousands of patients, and recently patients have been kept under narcosis for two or more months while intensive electric convulsion therapy can also be given; the longest course of narcosis has been over four months. Large amounts of phenothiazines have been used, but sedatives have to be given as well. We have finally fallen back in the last 500 or more patients on the use of Mandrax or methaqualone in preference to other sedatives such as barbiturates, chloral, Mogadon (nitrazepam) etc. as it seems to produce less withdrawal symptoms and tendency to addiction than the barbiturates and it works so well. At present I have 10 patients on this regimen at a nursing home, if any "committee" doctor would like to check up on clinical realities; and there are hundreds and hundreds of clinical records to consult at St. Thomas's and Belmont Hospitals.[1]

I have also used Mandrax as a sedative for many years and find it often preferable to the barbiturates as regards addiction, and more effective as a sedative than Mogadon. No addiction (the taking of rapidly increasing doses and a severe withdrawal syndrome) has been seen except in the young, in psychopaths, or in very ill depressed people, who needed more antidepressants and not increasing sedation. If one uses Mandrax or Mogadon, one should give only one tablet if possible as a sedative at night, with additional antidepressants given at the same time (amitriptyline or trimipramine 50-150 mg) to stop early waking; one should not just increase sedatives. One can also start with Mogadon, and use Mandrax only if the former does not work, *in preference* often to the barbiturates.

And, please Sir, no more suggested drug bans. But more *B.M.J.* articles on the skilled selective clinical use of drugs, and fewer articles on non-clinically useful double-blind sample results.—I am, etc.,

WILLIAM SARGANT

London W.1

1 Sargant, W., and Slater, E., *An Introduction to Physical Methods of Treatment in Psychiatry*, 5th edn. Edinburgh and London, Churchill Livingstone, 1972.

Eclampsia and Social Change in the Tropics

SIR,—I suggest that Dr. D. Jenkinson (26 May, p. 487) may be able to correlate the ability of Zambians to speak English with increased social status and prosperity on the one hand and a tendency to be older and heavier at the time of their first pregnancy and to gain more weight during pregnancy on the other.

In the U.K. the incidence and severity of pre-eclampsia in primigravidae increase with increasing age, weight, and weight gain during pregnancy. This is also the case in Yorubas in Western Nigeria,[1] but they are younger, lighter, and gain much less weight during pregnancy than in the U.K. and the incidence and severity of hypertension during pregnancy are correspondingly less. However, the blood pressure frequently rises for the first time during labour, so that the combined incidence of hypertension in pregnancy and labour is very similar. The incidence of eclampsia in Yorubas is probably greater than in the U.K. because of the rapidity in which the condition can develop during labour. On the other hand, the risk for the baby is greater in the U.K. because