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.,

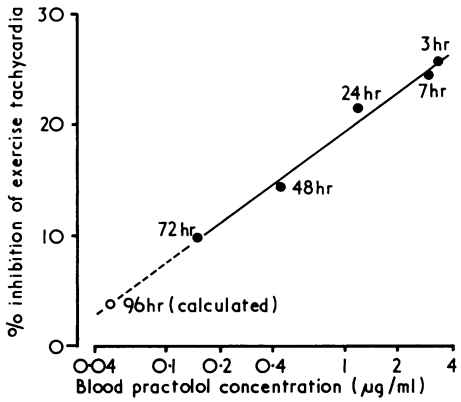
C. R. KUMANA
T. R. D. SHAW

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