epidemiological grounds the case against the food-borne hypothesis is still open.—I am, etc.,

H. P. FERRER.

Department of Social and Preventative Medicine, University of Manchester.

Adjuvants to L-dopa for Parkinsonism

SIR,—Notwithstanding the generally satisfactory response of Parkinsonian patients to L-dopa, undesirable side-effects and the high cost of the drug have led to attempts to reduce dosage with the aid of other agents. Success in this field has been reported using dopa-decarboxylase inhibitors,[1] which, since they do not pass the blood brain barrier, act so as to prevent peripheral "wastage" of dopa. However, these preparations have not yet become generally available, and it was thought that mention of two other attempts to enhance the effectiveness of relatively small doses of L-dopa, albeit unsuccessful, might be of practical and theoretical interest.

The following schema shows some of the pathways by which dopa is converted to its various end products; the enzymes involved are bracketed. Dopa — (dopa-decarboxylase) — dopamine.

Pathway 1. — Dopamine — (dopamine beta-oxidase) — noradrenaline.

Pathway 2. — Dopamine — (monoamine oxidase) — dopac — (catechol-*o*-methyltransferase) — homovanillic acid.

Pathway 3. — Dopamine — catechol-*o*-methyltransferase) — methoxytyramine — (monoamine oxidase) — homovanillic acid.

Since pyridoxine is a co-factor in the enzymatic activity of dopa decarboxylase, alterations in concentration of this vitamin might be expected to influence conversion of dopa to dopamine. The administration of pyridoxine has been reported to have reduced the anti-Parkinsonian effectiveness of a given dose of L-dopa.[2] On the assumption that this was due to enhanced extracerebral (and hence therapeutically undesirable) conversion of L-dopa to dopamine it was decided to combine L-dopa therapy with the anti-tuberculosis drug isoniazid, which causes marked depletion of body stores of pyridoxine.

Five Parkinsonian patients were maintained on 1-2 g., L-dopa for a week and their status recorded with regard to akinesia, rigidity, and tremor. Isoniazid (5 mg./kg.) daily was added, and the patients observed for a period of 10 days. No change in clinical signs was noted. Another trial involved an attempt to inhibit the enzyme dopamine beta-oxidase (*Pathway* 1 above) by administration of disulfiram (Antabuse). This has been shown experimentally to increase dopamine levels in the caudate nucleus, hypothalamus, and brain stem with marked reduction of brain stem noradrenaline.[3] It has also diminished motor restlessness in cats induced by previous medication with L-dopa, pheniprazine (a monoamine oxidase inhibitor), and reserpine.[4] Four Parkinsonian patients stabilized as above on 1 g., L-dopa daily were given antabuse 0·5 g., t.i.d. for 9 days together with ascorbic acid (a potentiator of the Antabuse block by virtue of its action as a reducing agent.) Again, no improvement could be related to combined therapy

An explanation for this disappointing result probably lies in evidence that not more than 3% of exogenous dopamine is metabolized to noradrenaline,[5] so that even if total enzymatic block had been achieved the corresponding increase of dopamine would probably have been only marginal. The hoped-for but unrealized aims of these trials were to obtain greater effectiveness from low doses of L-dopa by adding other agents in quantities known to be therapeutically safe. It is possible that higher dosage levels in experimentally induced extrapyramidal syndromes in animals would throw light on the mode of action of L-dopa, perhaps less simple than has hitherto been believed.

Another theoretical means of increasing dopamine stores would be by blocking the enzyme catechol-*o*-methyltransferase which leads eventually to the formation of homovanillic acid (*Pathway* 3 above). Pyrogallol is a catechol-*o*-methyltransferase blocking agent, but seems to be too toxic for trial in humans.—I am, etc.,

J. BRAHAM.

Department of Neurology, Tel-Hashomer Government Hospital, Israel.

REFERENCES
1 Tissot, R., *Presse Médicale*, 1969, **77**, 617.
2 Duvoisin, R., *et al.* quoted by Cotzias G. C., Papavasiliou, P. S., and Gellene, R. *New England Journal of Medicine*, 1969, **281**, 272.
3 Goldstein, M., and Nakajima, K. *Journal of Pharmacology and Experimental Therapeutics*, 1967, **157**, 96.
4 Reis, D. J., Moorhead, D. T., and Merlino, N., *Archives of Neurology*, 1970, **22**, 31.
5 Rutledge, C. O., and Jonason, J., *Journal of Pharmacology and Experimental Therapeutics*, 1967, **157**, 493.

Prophylaxis of Venous Thrombosis

SIR,—In an article on diagnostic accuracy in venous thrombosis (18 April, p. 142) it is claimed that the ^{125}I-labelled fibrinogen test is too complicated and time-consuming to be used as a routine procedure for screening high risk patients. This is true of the technique used by the authors. However, it has now been superseded in most centres in Britain by the ratemeter.[1] The test is performed by a technician or physiotherapist and takes only a few minutes. We have now arrived at the situation where we could argue with equal force that a haemoglobin estimation is too complicated and time-consuming. The article adds no new information to what has already been published[2 3] and confirmed by others.[4]

In the second article by the same authors on dextran-70 in the prophylaxis of postoperative venous thrombosis (18 April, p. 144) it was disappointing to see the unequivocal support which they have given to the idea that dextran-70 is an efficient method of prophylaxis in preventing postoperative venous thrombosis. In a recent symposium[5] devoted entirely to this subject the evidence from many centres regarding the usefulness of dextran-70 was conflicting. We have been unable to show any significant reduction in the incidence of deep vein thrombosis in a group of 58 surgical patients who received dextran-70, when compared with a control group receiving no prophylactic measures.[5] In addition, the dangers of this therapy in high risk patients, very often elderly patients undergoing major operations, must be emphasized. In our series, two patients developed alarming symptoms and dextran-70 had to be discontinued. One patient developed acute massive pulmonary oedema and died, and the other developed acute heart failure from which he recovered.

In the absence of really effective prophylaxis, treatment is still an important feature. It is much more effective when carried out at the earliest possible moment in those patients where thrombi are spreading from the calf into the larger veins. It is in this group that there is a real danger of pulmonary embolism.[6] To accomplish this at the present moment the best method is to screen all patients "at risk" with the ratemeter, and to institute treatment at the proper time.—We are, etc.,

V. V. KAKKAR.
J. T. G. RENNEY.
A. N. NICOLAIDES.

King's College Hospital Medical School, London S.E.5.

REFERENCES
1 Kakkar, V. V., Nicolaides, A. N., Renney, J. T. G., Friend, J. R., and Clarke, M. B., *Lancet*, 1970, **1**, 540.
2 Flanc, C., Kakkar, V. V., and Clarke, M. B., *British Journal of Surgery*, 1968. **55**, 742.
3 Kakkar, V. V., *Annals of the Royal College of Surgeons of England*, 1969, **45**, 257.
4 Negus, D., Pinto, D. J., Le Quesne, L. P., Brown, N. and Chapman, M., *British Journal of Surgery*, 1968, **55**, 835.
5 Symposium on Use of Dextran-70 (Macrodex) in Prevention of Deep Vein Thrombosis. February, 1970.
6 Renney, J. T. G., Kakkar, V. V. and Nicolaides, A. N. Paper delivered to the Surgical Research Society of Great Britain and Ireland, meeting January 1970.
7 Kakkar, V. V., Howe, C. T., Flanc, C., and Clarke, M. B., *Lancet*, 1969. **2**, 230.

Use of Broad-spectrum Antibiotics

SIR,—I have recently received a number of wall charts entitled *The Beecham Range of Penicillins*, for display in our hospital wards, presumably as a guide to treatment for the junior medical staff. Under the column entitled "Indications" there are several entries with which many bacteriologists would not agree, but one of the entries under Ampiclox Neonatal (ampicillin and cloxacillin) prompts me to write to you.

This broad spectrum combination is advocated for "Treatment of confirmed or suspected infections in neonates including Pneumonia, Septicaemia, '*Failure to thrive*'" (my italics). It is the recommendation for the empirical use of such a powerful combination of drugs which I find particularly disturbing. Antibiotics are already used uncritically enough in man. The Swann report[1] endorsed the disquiet previously expressed about the disastrous results of their indiscriminate use in calves, with the consequent selection of enteric pathogens with multiple drug resistance. There is no reason for supposing that human infants are immune to similar effects.

Apart from this probable long-term influence of the indiscriminate use of these valuable drugs there is, I think, another real danger in adopting such recommendations. Administration of broad-spectrum antibiotics results in a profound alteration in the normal flora of the body and renders the patients especially susceptible to colonization by multiply resistant organisms, particularly *Pseudomonas sp.*, *Staph. aureus*, and *Candida sp.*, and many bacteriologists believe that patients on such drugs should be nursed in isolation. This is seldom possible,