fortiori a paragraph, to open with functional or attention-catching words.

The principle I am defending is the same that applies in choosing the titles of articles. All authorities agree that functional words should occupy the initial or strong position. Thus "Retinoblastoma: a study of the natural history and prognosis in 268 cases" is a better title than "A study of the natural history and prognosis in 268 cases of retinoblastoma"; "Acute myeloid leukaemia treated according to the Hammersmith protocol: a preliminary report" is preferable to "A preliminary report of treatment of acute myeloid leukaemia according to the Hammersmith protocol".

Similarly, "The possible role of nitrosamines in the genesis of oesophageal carcinoma has been suggested by Magee and Barnes and McGlashan *et al*" (12 July, p 61) is a more enticing beginning for a paragraph than "Magee and Barnes and McGlashan *et al* have suggested a possible role of nitrosamines in the genesis of oesophageal carcinoma" would have been. On the other hand, instead of "A recent North American survey has re-examined the problem of chest pain in smokers" (15 November, p 368) I should have preferred "The problem of chest pain in smokers has been re-examined in a recent North American survey". This example also shows one of the pitfalls to which too strict avoidance of the passive can lead. A problem can be examined in a survey, but could a survey, even a computerised one, examine a problem? Examination calls for conscious intellectual effort.

My second point is to recall Sir George Wilson's warning¹ against the misuse of "develop," as in "the patient developed pancreatitis." The patient did not develop pancreatitis; pancreatitis developed in the patient. One develops photographs. An investigator develops disease in experimental animals. But one does not develop disease in oneself—unless one is a self-experimenter, a psychopath, or a cigarette smoker. I expect it was with this third exception in mind that you (13 December, p 607) wrote of smokers "who have already developed chronic bronchitis or coronary artery disease."

Finally, it is disquietening to note in how many otherwise respectable American journals the word "data" is treated as a singular noun. It is true that neuter plural nouns took singular verbs in classical Greek, but I doubt if the perpetrator of "This data was carefully analyzed" was under the influence of deep reading in Plato and Thucydides. He would not have spelled "analysed" with a z.

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¹ Wilson, G, *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, 1965, 24, 280.

Long-stay mental hospital population

SIR,—The terrible chronicity rate, causing so much suffering to the patients and relatives concerned, reported by Dr Thomas Bewley and Dr Eamonn Fottrell and others (p 675) at Tooting Bec Mental Hospital needs an explanation.

Can a lot of it be due to lack of intensive treatments when the patients were admitted there or elsewhere earlier in their illness? Will these authors also tell us how many now "chronic" schizophrenics and affective states had insulin, electric conversion therapy, the phenothiazines, and finally a modified lower medial leucotomy before being con-

demned to a lifetime of suffering in the chronic wards of Tooting Bec?

When Tooth and Brooke¹ and also Baker² made their calculations on the emptying of mental hospitals, so criticised by Dr Bewley and his colleagues, they had already found, for instance, that over 40% of 10 000 supposedly chronic patients had been able to leave mental hospitals following mostly modified lower medial leucotomies.³ Baker had worked with me, and learnt also at Banstead, what can now be achieved by the use of intensive physical treatments and not "giving up" before *all* such treatments had been used.

Unless we know about the treatment of all these supposedly chronic patients this paper loses most of its value as a guide to whether or not we shall be able to close our mental hospitals and use general hospital units instead.

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¹ Tooth, G C, and Brooke, E M, *Lancet*, 1961, 1, 710.

² Baker, A A, *Lancet*, 1969, 1, 1090.

³ Tooth, G C, and Newton, M P, *Leucotomy in England and Wales 1942-1954*. London, HMSO, 1961.

The third man

SIR,—In his interesting letter about the Everest expedition (10 January, p 92), Dr C R A Clarke mentions the curious sensation of two climbers that their snow-hole bivouac had been shared by a third. Some claim that this is a well-recognised phenomenon in near-exhausted travellers, and it inspired T S Eliot to write in "The Waste Land":

Who is the third who walks always beside you?
When I count, there are only you and I together
But when I look ahead up the white road
There is always another one walking beside you.

In his own notes on the poem Eliot says, "The lines were stimulated by the account of one of the Antarctic expeditions (I forget which, but I think one of Shackleton's): it was related that the party of explorers, at the extremity of their strength, had the constant delusion that there was *one more member* than could actually be counted."

I cannot recall having seen this mentioned in medical literature before. Has it ever been noted and investigated by any psychiatric authority?

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Commercial and NHS factor VIII concentrates

SIR,—One of the inevitable dangers of a journalistic approach to medical problems is that limitations in time (radio or television) or space (newspapers or periodicals) may give rise to a selection of comments made by experts which, when taken out of context and put together for a programme or article, are misleading. This probably arose during the ITN television series "World in action" in which two consecutive programmes attempted to deal with the availability of factor VIII concentrates for haemophilia patients in the United Kingdom.

There is no doubt that the import into the United Kingdom of factor VIII concentrates derived from external sources, however well screened for hepatitis viruses, represents an unequivocal pathway by which

the level of a potentially lethal virus into the whole community is being deliberately increased. Although the absolute magnitude of this problem was exaggerated and overdramatised by the television programmes, nobody with direct or indirect responsibilities for this phenomenon would wish to belittle the serious nature of the moral and practical dilemmas which face us all.

Perhaps the most important misleading feature of the second television programme was the impression given that the recent and specific injection of £500 000 by the DHSS into the blood transfusion services will have worked its way through by mid-1977, and by that time the necessity to purchase further supplies of factor VIII concentrates will be eliminated. Our own experience indicates that this will not occur, not least because the present NHS production target for factor VIII concentrates is too low. What seems more certain, however, is that by mid-1977 we shall begin to understand that the problems are multifactorial, a good deal more complex than hitherto appreciated, and only partly related to the haemophiliac. In the meantime we would be well advised not to raise the expectations of the patients, their relatives, and the staff of the regional haemophilia centres beyond the certainty that things will improve very slowly, and at the same time look at the problem once again.

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Sodium valproate and platelet function

SIR,—Dr A Richens and Dr S Ahmed (1 November, p 255) and Jeavons and Clark¹ have shown that sodium valproate reduces the frequencies of seizures in epilepsy. The drug is likely to be widely used and, while reported side effects have so far been minor, there has been one report² of a prolonged bleeding time in four out of five patients who also showed coagulation abnormalities. The prolonged bleeding time was attributed to defective platelet function, but one patient was thrombocytopenic. We have therefore studied the effects of sodium valproate on platelet function and coagulation to determine the clinical significance of these findings.

Sodium valproate was added to citrated plasma from six healthy adults to give final concentrations of 0.2, 1.0, and 5.0 g/l corresponding to one, five, and 25 times the therapeutic level. Platelet adhesiveness to glass beads, platelet factor 3 release, and ristocetin- and collagen-induced aggregation were normal. Inhibition of the secondary phase of platelet aggregation following normal primary aggregation with adenosine diphosphate (2.4×10^{-6} mol/l), adrenaline, and thrombin was demonstrated in all six plasmas at 25 times the therapeutic level and, with thrombin, in three plasmas at the therapeutic level. Standard tests of coagulation (prothrombin, partial thromboplastin, thrombin, Reptilase, and Stypven times) were normal at all three concentrations.

Platelet function tests were also performed on 23 patients (aged 4-22 years) taking sodium valproate. Inhibition of the secondary phase of aggregation following primary aggregation with adenosine diphosphate, adrenaline, or thrombin was demonstrated in six patients, five of whom were taking sodium valproate as the sole anticonvulsant.

The bleeding time (Ivy method) was, however, normal in all 23 patients studied. None of the patients in this small series was thrombocytopenic.

It is unlikely that this acquired platelet function defect will be of clinical significance, but until further experience is gained with this agent it would seem advisable to measure the bleeding time and platelet count before major surgery in patients taking sodium valproate.

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1 Jeaons, P. M., and Clark, J. E., *British Medical Journal*, 1974, 2, 584.

2 Sutor, A. H., and Jesdinsky-Buscher, C., *Medizinische Welt*, 1974, 25, 447.

SI units

SIR,—We wrote to you previously (17 May 1975, p 389) protesting against the introduction of the mole and pascal as units of measurement in clinical medicine. We therefore think it appropriate to inform you that the East Anglian Regional Medical (Advisory) Committee has reluctantly concluded that, despite the reservations expressed from many quarters in the medical journals and in correspondence with our committee, the pace of change has been so great that the East Anglian Region can no longer maintain its stand against the new units. Accordingly the committee has advised that the new units should be introduced in the hospitals in the region. Naturally we have stressed the dangers inherent in the changeover and have emphasised the need for adequate education of all concerned and for carefully phased and monitored implementation.

We wish to make known our belief that the professional organisations which advised the DHSS on this matter acted without adequate consultation with those who carry responsibility at the bedside and in the laboratory. We have accordingly written to these august bodies expressing our disapproval and venturing to suggest that in future such far-reaching decisions should be made only after wider consultation with appropriate members of the medical profession.

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Ischaemic necrosis of lesser curve of stomach

SIR,—We read with interest Dr P D Mohr's letter (13 December, p 650) concerning ischaemic necrosis of the lesser curvature of the stomach following highly selective vagotomy, but we cannot accept that interruption of the vasa nervorum accompanying the vagus could possibly jeopardise the viability of the lesser curvature. These vessels are branches of the left gastric artery, which is routinely ligated in many forms of gastric surgery. Indeed Appleby¹ has advocated ligation of the coeliac axis for gastric malignancy and reported 13 cases without loss of viability of the stomach. Forty years ago Wilson-Hey performed a "four-point gastric ligation" for duodenal ulceration in

over 300 patients in which the four major arteries to the stomach were ligated without ischaemic necrosis ensuing.

Vagotomy will certainly reduce gastric mucosal blood flow, and patients with gastric ulcers on the lesser curvature have low mucosal flow rates,² but the mucosa of the lesser curvature in the dog is as well perfused as other areas of the stomach.³ Autoradiographs of the rat stomach after administration of ⁸⁶Rb Cl, using the indicator fractionation technique of Sapirstein,⁴ have also failed to demonstrate a diminution in the perfusion of the lesser curvature.⁵

In-vivo study of the microvasculature of the gastric mucosa shows a rich syncytium of communicating vessels which is capable of shunting blood towards or away from any particular area provided suitable conditions of vessel control exist.^{6,7}

It is well known that the stomach has an almost unrivalled resistance to ischaemic damage. We wonder whether either excessive use of diathermy along the lesser curvature might be responsible for perforation, oedema, and ensuing ischaemic necrosis of ligation of small areas of serosa, including submucosal vessels, might have similar consequences after highly selective vagotomy.

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1 Appleby, L. H., *Cancer*, 1953, 6, 704.

2 Taylor, T. V., et al., *British Journal of Surgery*, 1975, 62, 788.

3 Delaney, J. P., *American Journal of Digestive Diseases*, 1965, 10, 201.

4 Sapirstein, L. A., *American Journal of Physiology*, 1958, 193, 161.

5 Taylor, T. V., MD Thesis, University of Manchester, 1975.

6 Barlow, T. E., Bentley, F. H., and Walder, D. N., *Surgery, Gynecology and Obstetrics*, 1951, 93, 657.

7 Taylor, T. E., and Torrance, H. B., *Gut*, 1975, 16, 781.

Massive intoxication with metoprolol

SIR,—Beta-adrenergic-blocking agents are extensively used in Sweden as prophylactic therapy in angina pectoris and as basic treatment for hypertension in young adults. Despite the widespread use of these substances, poisoning is rare. It is therefore of interest to report a case of massive intoxication with the new β_1 -receptor blocking drug metoprolol (Seloken, Betaloc, Lopresor). The drug is devoid of intrinsic activity and has very little membrane-stabilising activity.

The 19-year-old son of a hypertensive patient under treatment with metoprolol was admitted to this hospital after a reported intake of 200 50-mg tablets of metoprolol—that is, a total of 10 000 mg or 160 mg/kg body weight. On admission he was conscious and had peripheral cyanosis. The heart sounds were weak. The pulse was palpable in the femoral artery but not in the radial artery. The blood pressure was not registrable. The heart rate was 60–70/min. ECG showed sinus rhythm with normal AV conduction and normal S-T segment and T waves. Blood gas determination showed base excess —5 mmol (mEq)/l, pH 7.41, P_{CO_2} 3.9 kPa (29 mm Hg), and standard bicarbonate 20 mmol (mEq)/l. The patient was treated during the first few hours with 2 l of balanced electrolyte solution (Ringer's solution) and the acidosis was corrected with 150 mmol of sodium bicarbonate. Intravenous administration of 7 mg metaraminol and 6 mg of glucagon raised the blood pressure to 115 mm Hg

systolic in 10 minutes. Another fall in blood pressure to 75 mm Hg systolic one hour later was successfully treated with a further dose of 3 mg metaraminol intravenously. The blood pressure then stabilised at a level slightly above 100 mm Hg, which was the patient's usual level.

The initial treatment included gastric lavage, which yielded a cloudy product containing food and tablet residues. During the first six hours there was some fluid retention, which was treated with frusemide. Twelve hours after admission the patient was quite comfortable and without any signs of cardiovascular depression.

The plasma level of metoprolol two hours after admission was 12 200 ng/g plasma, at seven hours 9400 ng/g, and at 10 hours 5700 ng/g. After a single dose of 100 mg to healthy volunteers the maximum plasma concentration has been found to be about 100 ng/g plasma on average.¹ To judge from the plasma levels almost all of the ingested dose (10 000 mg) must have been absorbed.

In animal experiments the lethal dose has been found to be 2000–3000 mg/kg in the mouse and rat and at least 10 times lower in the dog.² This difference in oral toxicity between the species is explained by the difference in bioavailability, which is 10 times higher in the dog than in the rat.³ The bioavailability of metoprolol in man is similar to that in the dog.^{3,4} The dose of 160 mg/kg body weight ingested by the patient in this case must therefore be near the lethal dose. Plasma levels of metoprolol have been analysed in dogs after oral doses up to 10 mg/kg. The maximum plasma level was 1200 ng/g one hour after administration. The concentration found in the patient—12 200 ng/g—three to four hours after ingestion is therefore what would be expected from the dog data and dose taken.

Earlier reports on suicidal attempts have documented a relatively low toxicity of this type of drug. One patient survived 900 mg of prazosin⁵ and another 2000 mg of propranolol.⁶ In both cases modest signs of cardiac depression were reported.

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2 Bodin, N.-O., et al., *Acta Pharmacologica et Toxicologica*, 1975, 36, suppl V, p 96.

3 Borg, K. O., et al., *Acta Pharmacologica et Toxicologica*, 1975, 36, suppl V, p 104.

4 Regardh, C.-G., et al., *Acta Pharmacologica et Toxicologica*, 1975, 36, suppl V, p 45.

5 Karhunen, P., and Hartel, G., *British Medical Journal*, 1973, 2, 178.

6 Wermut, W., and Wojcicki, M., *British Medical Journal*, 1973, 3, 591.

Lactic acidosis after glucose infusion

SIR,—Dr A C Ames and others (13 December, p 611) report that after the infusion of glucose, sorbitol, or fructose to women with ketosis in labour there was an increase in blood lactate but an accompanying fall of acetoacetate and 3-hydroxybutyrate levels. The most marked increase in lactate followed the infusion of 30% glucose. In contrast, infusion of normal saline produced a fall in lactic acidosis with little significant change in the level of ketones. Dr Ames and his colleagues conclude, therefore, that while it is known that increased lactic acidosis may occur with fructose, the infusion of sorbitol or glucose should likewise be administered with caution to women in labour because of the hazard of a base deficit in the fetus.