biturates are markedly longer-acting than phenobarbitone in gross overdosage. If, however, a classification is used which is based on speed of onset, this will be relevant in all contexts. The speed of onset of effect is a function of fundamental physicochemical properties, particularly lipid solubility,¹ and will hold irrespective of the dose taken. Thus thiopentone is always "ultra-quick-acting," pentobarbitone always "quick-acting," phenobarbitone relatively "slow-acting." It is, of course, the same property of lipid solubility that prevents renal elimination of the "quick-acting drugs" in the unmetabolized state and renders their action in gross overdosage so prolonged.

I felt also that an additional point might have been made—namely, that barbiturate poisoning need now scarcely ever occur. With the advent of hypnotics, such as nitrazepam, which are effective but almost completely safe, barbiturates need not be prescribed except for use in hospital, where their administration can be properly supervised.—I am, etc.,

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Intermittent Methohexitone

SIR,—As a dental practitioner with many years' experience in the use of methohexitone for conservative dental procedures, I was extremely interested to read both the leading article and the paper on this subject (31 May, pp. 525 and 540), the paper published in the *British Dental Journal* of 3 June by the same authors, and the ensuing correspondence. The authors of this report on the physiological responses to methohexitone are to be complimented on the scope and thoroughness of their investigation, which can only result in improved patient safety through increased understanding of the pharmacological actions of this drug.

However, after clinical experience of many thousands of personal administrations of methohexitone, this report appears to be more a study of the effects of overdosage (in some cases gross overdosage) and extreme prolongation of operating time, rather than a study of the correct use of intermittent methohexitone in low dosage for operations of short duration. In my own practice, this technique is used solely to produce sedation and amnesia (routinely supplemented with short-acting local analgesia) for operative procedures not exceeding 20 minutes. The total dosage administered is rarely in excess of 200 mg., with an average nearer 100 mg. For longer procedures diazepam, diazepam/methohexitone,¹ or the intravenous pre-medicant technique of Jorgensen are used.

Apart from the enormous dosages and overextended operating times employed by the authors of the current study, certain

other discrepancies are apparent which lack satisfactory explanation.

No adequate comparisons are made with other methods currently used in the treatment of dental patients. For example, it is claimed that in 45% of the patients treated contrast media placed on the tongue and swallowed entered the bronchial tree, as revealed on later chest radiographs. Apart from the figure of 8.5% quoted by workers at the University of Sheffield (14 June, p. 691) (itself a widely differing result) and the unsubstantiated statement by the Birmingham author in the *British Dental Journal* of 3 June that "this manoeuvre does not result in contrast media being found in the chest of normal subjects," no real evidence has been documented to my knowledge showing that contrast media is never found in the bronchial tree of conscious patients undergoing prolonged treatment under local analgesia (where mouth packing is seldom carried out), or other methods commonly used, for example, N₂O/O₂. Without such comparisons, it is difficult to accept that such findings are restricted solely to the use of methohexitone for conservation, even in the large dosages employed in the present study, where it would be surprising indeed if depression of the laryngeal reflexes did not occur.

An important finding which should be borne in mind by all those using intermittent methohexitone is that concerning cardiovascular responses. It is stated that methohexitone in total dosages exceeding 200 mg. produced widespread and permanent peripheral vasodilatation with a noticeable reduction in peripheral resistance, requiring greatly increased cardiac output to maintain normal blood pressure. (For reasons which are unclear, this figure is put at 150 mg. in the *B.D.J.* article.) It is also noted that if peripheral resistance was suddenly increased in response to pain the raised cardiac output into the rising resistance system caused severe hypertension.

The meaning of this latter statement is somewhat obscure, as if dosages of methohexitone in excess of 200 mg. produce a permanent reduction in peripheral resistance might one not reasonably expect the peripheral response to a painful stimulus to be similarly obtunded? Here again no comparisons are made with other drugs used routinely as oral and intramuscular premedicants for both dental and general surgical procedures, or with other general anaesthetic agents used in equivalent dosage for similarly prolonged durations. It might perhaps be of interest to learn the degree of hypertensive response which occurs, for example, in highly apprehensive and fully conscious patients undergoing the extirpation of a hyperaemic pulp or the surgical removal of a difficult impacted lower third molar where successful local analgesia has not been obtained.

Postoperative orthostatic hypotension was recorded in two-thirds of the patients studied. Yet again no comparisons are given. It would in fact be surprising if patients treated with any method (including local analgesia) in a fully supine position for periods averaging 74 minutes did not also exhibit some degree of orthostatic hypotension upon being asked to stand up—although it must be agreed that this effect was undoubtedly enhanced by the great dosages of methohexitone administered.

A fatal case of subarachnoid haemorrhage which occurred during the use of intermittent methohexitone is reported by the authors in the *British Dental Journal* of 3 June, inferring that the technique was to blame. Perhaps it may be of interest to note that a similar case occurred in New Zealand in recent years—following the administration of a local analgesic containing adrenaline. It would seem that one should tread warily before making inferences of this kind, particularly as subsequent correspondence has revealed further details of this case, including the fact that the patient had a pre-existing cere-

bral aneurysm and was also given a local analgesic containing noradrenaline (7 June, p. 630).

It is not my intention to attempt to belittle this very impressive and valuable study, which I most sincerely hope will be extended with equal fervour to other methods in current use for the treatment of dental patients. But it must also be firmly pointed out that in my own opinion this was a study of methohexitone overdosage, and the incorrect application of an extremely valuable technique. As the authors themselves state in the *British Dental Journal*: "it would be unfortunate indeed if an excellent drug fell into disrepute due to its misuse"—which is precisely what has been achieved by this study.

After reading in a local newspaper that "dentists here are using a drug labelled a killer by a team of British doctors, who have also warned that people in Britain are dying at the rate of one every three months simply because they had their teeth filled"—a headline which has greatly distressed many of my patients—might I also be permitted to make the observation that the method used in this undoubtedly excellent study in fact bears very little resemblance to the technique as it is routinely practised in New Zealand.—I am, etc.,

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Degenerative Tropical Neuropathy and Diet

SIR,—We note the points raised by Dr. A. F. Tuboku-Metzger (26 April, p. 249). One of us (B. O. O.) has pointed out previously that, although yams, beans, maize, and millet and other food items which contain cyanogenetic alkaloids are sometimes eaten in the "endemic" areas in Nigeria where the degenerative tropical neuropathy is common, there is no other food item which is consumed in large quantities and as regularly as cassava. We have also noted that a form of cassava preparation called "purupuru" commonly eaten in these areas contains 4–6 mg. of hydrocyanic acid per 100 g. of dry weight, compared with "gari," which contains 0.1–2 mg. HCN per 100 g. of dry weight.^{1,2} The hydrocyanic acid content of foodstuffs, which Dr. Tuboku-Metzger wrote about, is therefore variable. Deaths from acute cyanide poisoning resulting from eating improperly processed raw cassava roots are known to occur in this part of the world. An adult consuming 750 g. of purupuru per day will be exposed to at least 30 mg. of cyanide. The lethal dose of cyanide in man is 60 mg.³ A variable rate of hydrolysis of cyanogenetic glycosides may explain why some foods like cassava constitute a more important source of dietary cyanide,⁴ as the ease of hydrolysis of these glycosides varies from source to source.

We accept that the amount of hydrocyanic acid that can be safely consumed varies from person to person, and appears to be affected

by the variety of other foods eaten. This will explain why it is not everyone on a high cassava diet who suffers from neuropathy. Availability of first-class proteins may be important, in view of the qualitative changes demonstrable in the plasma amino-acid pattern in the tropical degenerative neuropathy.⁶ It is also possible that other nutritional deficiencies are important in the pathogenesis. There is clinical and biochemical evidence of riboflavine deficiency in these patients.¹

All the questions raised by Dr. Tuboku-Metzger have been discussed in detail in an earlier paper,¹ and lack of space does not justify a repetition. We would like, however, to mention briefly that one of us (B. O. O.) has now successfully induced ataxia in Wistar rats fed on a diet of cassava for 18 months. The plasma thiocyanate level in these animals when killed was higher than in the controls. Concentration of rhodanese in the liver in affected rats was lower than in the control group, but the difference is not statistically significant. Single nerve fibre preparations of peripheral nerves show segmental demyelination which we have described in biopsy specimens from patients.⁷ These results will be published in greater detail elsewhere.—We are, etc.,

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Pain in the Neck

SIR,—Dr. D. A. H. Yates gave an excellent summary of the cervical spine's diseases and mechanical problems (28 June, p. 807). Although he places due emphasis on the diseases which cause pain in the neck, a greater emphasis than is usual in medical writings on this subject is given to mechanical factors and to nervous tension factors. Mechanical and nervous tension factors are present in at least 75% of the patients who attend my department complaining of neck pain. He also stresses that forcible manipulations are best avoided and that gentle traction, rotation, and mobilization techniques are more appropriate. I heartily concur and consider that the rule should be to use the minimum of force consistent with achieving the objective—not the maximum of force, as is often used in some schools of manipulation.

I would like to disagree about movements at the occipito-atlantal and atlanto-axial joints. Although it is widely thought that nodding takes place at the occipito-atlantal joint, in fact a greater range of flexion-extension occurs at the atlanto-axial joint. On

average the ranges are 10° at the occipito-atlantal joint compared with 15° at the atlanto-axial joint in adults.—I am, etc.,

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Hormonal Management of Breast Cancer

SIR,—Dr. B. A. Stoll has ably summarized much clinical experience on the hormonal treatment of advanced breast cancer (3 May, p. 293). In the discussion of male breast cancer the author alludes to the effectiveness of castration, and mentions as possible secondary therapies corticosteroids, major endocrine ablation, and oestrogens, experience with the latter generally having been disappointing. Considering the small number of patients with this disease treated in any one institution, two patients recently treated with progestins are noteworthy, and are described below.

A 61-year-old man, previously reported,¹ developed local recurrence in the left thoracic wall four years after mastectomy. Orchiectomy resulted in objective regression and control of the disease for two years; diethylstilboestrol 15 mg. daily having been added subsequently. While on this treatment for nine months, progression of disease with extension to pleura and bones prompted a trial of 5-fluorouracil and triethylenethiophosphoramide (Thio-tepa). One year later the patient was hospitalized in a markedly deteriorated state with fever, anaemia, ulcerations, and bleeding from the chest wall. Medroxyprogesterone acetate (Depo-Provera) 100 mg. i.m. three times weekly was begun, and six weeks later, because of no objective change, diethylstilboestrol 15 mg. daily was added. On this progestin-oestrogen combination almost total regression of local nodules was noted, associated with a return of well-being. After six months of treatment, disease exacerbation occurred, and the patient died three months later. It is likely that the response was secondary to progestin-oestrogen treatment, since the patient was previously oestrogen resistant.

An 80-year-old man had a right radical mastectomy, March 1967; the axillary lymph nodes were positive for carcinoma. One year later atrial fibrillation and a right pleural effusion were identified, and he received digoxin and diuretics with no effect. In October 1968 he was hospitalized for dyspnoea and bilateral pleural effusions; no other signs of congestive heart failure were present. A right thoracentesis revealed a straw-coloured fluid with a specific gravity of 1.022, and pleural biopsy confirmed metastatic carcinoma. Osteoblastic metastases were present in the pelvis and lumbar spine. Bilateral orchiectomy was therefore performed (30 October 1968). The following month he required readmission for recurrent accumulation of pleural fluid and rapid atrial arrhythmias refractory to digitalis and propranolol. Because of his precarious state he was begun on medroxyprogesterone acetate 100 mg. three times weekly on 22 November 1968. He showed gradual improvement with slowing of the heart rate and no further need for thoracentesis. He continues to be active and asymptomatic, although in the past month further progression in bony metastases has been observed. One cannot exclude a delayed response to orchiectomy in the improvement noted while on progestin.

In addition to the above, one other patient with bone metastases and hypercalcaemia received medroxyprogesterone acetate.¹ Because of further rise in serum calcium the drug was discontinued after three doses, and orchiectomy was performed. A satisfactory re-

sponse to progestins prior to castration was reported by Geller, Volk, and Lewin² in a 61-year-old man; inhibition of testicular hormone secretion as a result of decreased pituitary gonadotrophins induced by the 17-alpha hydroxyprogesterone caproate (Delalutin) was believed to have been instrumental in producing the remission. However, a response after orchiectomy and adrenalectomy to progesterone-oestrogen combination has also been reported³; this experience is analogous to that seen in women receiving similar therapy following major ablation, as cited by Dr. Stoll. Possibly reflecting the personal experience of the contributor (Kendall Emerson, jun.), Harrison's *Principles of Internal Medicine* mentions that "progestational compounds may be of value" in this disease.⁴

In view of these preliminary observations, progestins with or without oestrogen should receive further trial in the treatment of male breast carcinoma. Because they lack androgenic activity relative to the other progestins, possible androgen-mediated stimulation of tumour growth would be best avoided by using derivatives of 17-alpha hydroxyprogesterone.—I am, etc.,

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Cardiomyopathies

SIR,—At a time when cardiomyopathies are becoming more frequently diagnosed it was refreshing to read your recent leading article (7 June, p. 589).

I appreciate that the author was probably only attempting to review the recent publication by the International Society of Cardiology referred to, and therefore kept within the limits set by that publication. I was, however, disappointed that the possible "tie-up" between such conditions as eosinophilic leukaemia and endomyocardial fibrosis was not mentioned. Indeed, the short comment about endomyocardial fibrosis appeared to dismiss any such connexion. The common features of eosinophilic leukaemia, endomyocardial fibrosis, and one or two other conditions are fully discussed in a recent article in the *American Journal of Medicine*.¹

May I hope for a further leading article giving the British view on what appears to be a truly international problem in the field of cardiomyopathies?—I am, etc.,

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