Lung Biopsy

SIR,—Your leading article on lung biopsy (6 June, p. 555) cannot be allowed to pass without comment. To say that "owing to the indifferent contribution it has made in assisting diagnosis over the years the method has now been virtually abandoned" suggests that your leader writer cannot be familiar with either the paper by Steel and Winstanley¹ or with current practice in a number of hospitals all over the world.

Quite contrary to the view quoted above, I believe that trephine biopsy has made a great contribution to the diagnosis of diffuse lung disease, and the procedure has converted me from being a keen advocate of open lung biopsy to an ardent supporter of the much simpler technique.

To suggest that the procedure is more alarming or more liable to morbidity than a formal thoracotomy under general anaesthesia in an operating theatre seems to me to be pushing the objection of trephine biopsy beyond the limits of reason.—I am, etc.,

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REFERENCE

- 1 Steel, S. J., and Winstanley, D. P., *Thorax*, 1969, 24, 576.

SIR,—Your leading article "Lung Biopsy" (6 June, p. 555) seems to call for comment. Far from being "virtually abandoned," trephine biopsy with a high-speed air drill is the method of choice at the London Chest Hospital, and is being increasingly used in teaching hospitals and thoracic units in Britain and abroad. In a recent account¹ we reported 119 trephine biopsies, of which

85% were diagnostically significant, and the total has now grown to 182. Complications were not serious. The incidence of pneumothorax was 26%, but only a quarter of these patients needed an intercostal tube. There was no instance of pleural infection. In contrast, Gaensler *et al.*² carried out 106 lung biopsies by open thoracotomy under general anaesthesia. They used an intercostal tube as a routine and their complications, though few, were more serious than those we encountered.

The only feature of trephine biopsy which could be regarded as "alarming" is the whistling noise produced by the air drill, and this should be familiar to anybody who has visited the dentist in recent years. Premedication is unnecessary and local anaesthesia is used. After biopsy patients are fully mobile within half an hour and can usually leave hospital the following day. There is thus a considerable saving in operating theatre time and hospital bed occupancy.

We feel that lung biopsy should not be entirely restricted to patients in whom there is a prospect of finding a treatable condition. In industrial lung disease, for example, diagnosis has more than merely therapeutic value, and in any patient there is always the possibility of finding something totally unexpected.—We are, etc.,

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REFERENCES

- 1 Steel, S. J., and Winstanley, D. P., *Thorax*, 1969, 24, 576.
- 2 Gaensler, E. A., Moister, M. V. B., and Hamm, J., *New England Journal of Medicine*, 1964, 270, 1319.

Pseudo-obstruction of the Large Bowel

SIR,—In the Current Practice article (6 June, p. 583), Mr. P. K. Caves and Dr. H. A. Crockard refer to pseudo-obstruction of the large bowel. The term pseudo-obstruction of the intestine was used by Naish and his colleagues¹ to describe a syndrome of intermittent intestinal obstruction, often associated with malabsorption without organic cause. Pathologically, these cases show marked hypertrophy of the smooth muscle of the bowel wall and, in the cases in which it has been examined, pathological changes in the myenteric plexus.² The lesion is permanent and does not recover. The treatment is excision of the affected segment, if practicable.

The cases which Mr. Caves and Dr. Crockard describe appear to be those of acute colonic dilatation of varying aetiology, most of which recovered completely. This is manifestly a different condition. The terminology of obstruction without organic cause is already confused, but perhaps it would be less so if the name "pseudo-obstruction" were confined to the condition originally described by Naish, and acute dilatation or some other similar term used for the type which recovers with or without treatment.—I am, etc.,

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Anxiety and Investigations

SIR,—Your leading article entitled "Anxiety and Investigations" (16 May, p. 377) on the use of diazepam omitted to mention one of the common side effects of intravenous administration of sedative doses of this drug, namely amnesia. This has frequently been reported in the literature.¹⁻³

We recently carried out a volunteer trial in the laboratory⁴ and found dense amnesia for at least 10 minutes and mildly impaired learning more than 30 minutes after injection. Considerable care should, therefore, be taken not to release outpatients until their powers of memory return, which is probably at least half an hour after the acute effects of the drug have passed off. Since the effects of the intravenous administration of this drug appear to dissipate variably over a period of some hours, it would also be advisable before undertaking such procedures to warn the patient and his escort of the need to make arrangements to

prevent possible indiscretions during this period.—We are, etc.,

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P. F. R. CLARKE.

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REFERENCES

- 1 Brown, S. S., and Dundee, J. W., *British Journal of Anaesthesia*, 1968, 40, 108.
- 2 Fox, G. S., Wynands, J. E., and Bhambhani, M., *Canadian Anaesthetic Journal*, 1968, 15, 281.
- 3 O'Neil, R., and Verrill, P. J., *British Journal of Oral Surgery*, 1969, 7, 12.
- 4 Clarke, P. R. F., Eccersley, P. S., Frisby, J. P., and Thornton, J. A., *British Journal of Anaesthesia* (in press).

SIR,—Your leading article entitled "Anxiety and Investigations" (16 May, p. 377) omits one useful action of diazepam which contributes to its success in conservative dentistry and possibly in other investigations. When given intravenously in doses in the region of 1 mg./5kg., Keilty and Blackwood¹ found a high incidence of amnesia for an intra-oral injection given two to three minutes later, and this was confirmed by O'Neil *et al.*² using a slightly higher dose of diazepam. This amnesia is very transient, but patients remain quiet and the operation can be continued under local anaesthesia.

As stated in your survey cardiovascular effects of this dosage are minimal. In fact, Brown and Dundee³ found that the intravenous injection of doses of 0.61–0.8 mg./kg. diazepam did not produce a fall in systolic pressure in excess of 20 mm Hg.—I am, etc.,

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REFERENCES

- 1 Keilty, S. R., and Blackwood, S., *British Journal of Clinical Practice*, 1969, 23, 365.
- 2 O'Neil, R., Aellig, W. H., and Laurence, D. R., *British Dental Journal*, 1970 (in press).
- 3 Brown, S. S., and Dundee, J. W., *British Journal of Anaesthesia*, 1968, 40, 108.

Phenylketonuria

SIR,—Your leading article on phenylketonuria (6 June, p. 553) ends by stating that in some regions centralization of the biochemical investigations of infants in whom two screening tests have been positive may be necessary, but that subsequent treatment and supervision should be possible locally if adequate facilities are available.

The differential diagnosis of phenylketonuria from other causes of high blood phenylalanine levels can be very difficult, and it is a serious error to treat an infant unnecessarily with a low phenylalanine diet. We, therefore, believe that the diagnosis should in all cases be confirmed in one of a small number of centres specializing in the diagnosis and management of the inborn errors of aminoacid metabolism.¹⁻²

The management of the established case is also difficult, and requires a team of experts including a dietician with paediatric experience and a biochemist with a special interest in these aminoacid disturbances in addition to the paediatrician. A psychologist

and child psychiatrist are also needed for the regular assessment of the child's developmental progress and to help with the emotional problems which arise commonly in children requiring a special and rather unpalatable diet for many years.

The greatest danger in treatment arises from brain damage, and even death, resulting from too severe restriction of dietary phenylalanine, and we have had children referred to us in whom it seemed likely that severe mental retardation was the result of such dietary mismanagement. A regular prompt laboratory service for phenylalanine estimations is thus essential.

We, therefore, suggest that centralization of the processing of the screening procedure, confirmation of the diagnosis, and management of the established case should all take place in one of a small number of special centres. Such centralization of management does not necessarily involve frequent visits to the centre after the initial inpatient stay. An appropriate sample of blood or plasma for the estimation of phenylalanine can be sent by post. Since the dietitian will be known already to the mother, any dietary change required in the light of the result can be made without delay by 'phone or by post. We have controlled the management of many children in this way and, in general, have encountered excellent co-operation from the local paediatrician and general practitioner.

Phenylketonuria is rare; only about 90 patients are born in the United Kingdom each year. If our management is to be adequate and if, in addition, research is to be carried out to improve methods of diagnosis and management, centralization is essential.

For complicated surgical procedures, such as open heart surgery, the profession is beginning to realize that centralization leads to better results and is more economical. Similarly, we should recognize that there are certain rare medical disorders whose management is complicated and that patients suffering from them benefit from being referred to a special centre. Phenylketonuria is one of them.—We are, etc.,

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REFERENCES

- 1 Medical Research Council Working Party on Phenylketonuria, *British Medical Journal*, 1968, 4, 7.
- 2 Department of Health and Social Security, *Screening for early detection of phenylketonuria*. Circular H.M. (69) 72. London, H.M.S.O., 1969.

Liquorice and Addison's Disease

SIR,—The report by Dr. D. I. M. Siegler concerning a patient suffering from autoimmune Addison's disease with hypercalcaemia (30 May, p. 522) is incomplete in that it omits to mention that the patient had a liking not only for salt but also for liquorice. The sodium-retaining properties of this sweet protected her from clinical adrenal insufficiency in the heat of Aden, where she lived as a soldier's wife, and also masked many of the physical signs of this disease—for example, pigmentation. This is

the second patient I have encountered in which the ingestion of large amounts of liquorice has enabled a patient with Addison's disease to escape from the clinical results of adrenal failure for a long period of time. One can speculate as to whether her penchant for liquorice, as well as her appetite for salt, arose from some subconscious intuition as to the therapeutic value of these substances in her disease.

Addison's disease is indeed a rare cause of hypercalcaemia. The doctors in the metabolic department of this hospital, who have a considerable experience of hypercalcaemia, had not previously encountered Addison's disease as a cause. Indeed the real cause of the hypercalcaemia of this patient would have escaped recognition had she not been shown at the hospital's weekly staff meeting.—I am, etc.,

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Susceptibility to Aspirin Bleeding

SIR,—Your leading article (23 May, p. 436) on susceptibility to aspirin bleeding emphasizes a number of important points, notably the problem of defining the causes of susceptibility to aspirin-induced bleeding. However, the initial claim that 25% of cases of haematemesis and melaena in the London area are caused by aspirin is unjustifiable. In the source paper¹ there were 56% of recent aspirin-takers among those with acute bleeding compared with 32% in controls. The excess of 24% could represent the effect of aspirin if the control and bleeding series were comparable, but here there is cause for doubt. The control series used by Valman and his colleagues would appear to be identical with that of Parry and Woods,² and the latter authors emphasize that the proportions of aspirin-takers in their control series varied from 25 to 50% according to the diagnostic grouping used. If 50% were appropriate, and there are no means of judging, then the excess of aspirin-takers in the test group would fall to 6%.

The problems of ensuring comparability between test and control groups in investigating the role of aspirin in inducing acute gastrointestinal bleeding have been commented upon by others,³⁻⁵ and it seems clear that the complete comparability has yet to be achieved. The dyspeptic patient used as a control may have given up aspirin because it made his abdominal symptoms worse, while the patient with a stroke or coronary thrombosis may have forgotten the, to him, insignificant event of taking aspirin shortly before admission. On the other hand, the patient with haematemesis or melaena may have taken aspirin because he mistook for a 'flu-like illness the faintness initially induced by the bleeding.

The difficulties could be solved if patients with so-called aspirin-induced bleeding could be proved to be consistently susceptible but in fact, as you say, when they have been re-challenged with aspirin they appear to be no more liable to occult bleeding than control subjects.³ This anomaly could be explained if a combination of aspirin and another factor were needed to induce acute bleeding. Alcohol would seem to be an obvious accessory factor, but though it ac-

centuates occult bleeding there is no clear evidence that it alters liability to acute haemorrhage.

The general epidemiological evidence suggests that aspirin may be a causal factor in inducing bleeding but it is not unequivocal. In a paper recently published by you, Dr. K. F. R. Schiller and his colleagues⁶ found that during three successive quinquennia the rate of admission to the Radcliffe Infirmary for haematemesis and melaena remained constant. During that time the proportion of individuals recorded as taking drugs, predominantly aspirin, beforehand was found to have quadrupled. This disparity might only reflect the recent interest in aspirin as a cause of bleeding; however, it is also noteworthy that the proportions of patients with gastric and duodenal ulcer did not fall as might have been expected if aspirin-induced acute ulceration had become an increasing problem.—I am, etc.,

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University of Nottingham.

REFERENCES

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- 2 Parry, D. J. and Wood, P. H. N., *Gut*, 1967, 8, 301.
- 3 Allibone, A., and Flint F. J., *Lancet*, 1958, 2, 1121.
- 4 Davis, J. S., *Lancet*, 1958, 2, 1121.
- 5 Salter, R. H., *American Journal of Digestive Diseases*, 1968, 13, 38.
- 6 Schiller, K. F. R., Truelove, S. C., and Williams, D. G., *British Medical Journal*, 1970, 2, 7.

Thrombopoietin

SIR,—Thrombopoietin being a "bee in my bonnet" since 1957, I read with great interest the preliminary communication by Dr. D. G. Penington (7 March, p. 606). He states that in the experiments of my colleagues and myself increases in the platelet counts of animals receiving different plasma samples are "relatively small, of the order of 20 to 25% over the resting platelet count." In fact, our papers show that only increases of 30% or more over the resting counts were considered as "positive." In addition, we demonstrated that elevation of the circulating platelet count in several conditions is preceded, in man as in animals, by the appearance of higher levels of this apparently specific factor. This plasma factor cannot be dialysed, runs with beta-globulins, and is easily destroyed by trypsin.¹ It is likely that other plasma factors function in the later stages of thrombocytopoiesis. Availability of thrombopoietin alone does not, therefore, guarantee the undisturbed maturation of cells of the megakaryocyte series and, conversely, if a certain plasma factor is able to induce thrombocytosis, this factor may or may not be thrombopoietin as such.

We never stated that the plasma thrombopoietic activity is elevated in "essential" thrombocythaemia. On the contrary, we stated that seven out of seven apparently "essential" cases gave negative responses in our mouse test.² The simplest way to demonstrate elevated thrombopoietin levels is to test plasma samples from severely thrombocytopenic patients. More than 100 cases of thrombocytopenia were tested in our laboratories, and the fact that some samples of thrombocytopenic plasma exhibit elevated thrombopoietic activity has already been