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

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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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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

published.³ The failure to demonstrate higher levels of this activity in our mouse test—injecting the animals with chronic idiopathic thrombocytopenic purpura plasma—needs to be further elucidated.

It was a pity that Dr. Penington did not classify his positive cases. Although deficiency in feed-back inhibition could be considered in thrombocytopenia, my colleagues demonstrated that the giant-cell content of the protected areas of x-ray treated mice can be increased with "positive" plasma (received after irradiation) even in animals adjusted to normal platelet levels by means of syngeneic thrombocyte transfusions.⁴

Comparing the thrombopoietic effects of from 0.4 to 2.0 ml. subcutaneously administered plasma samples using his isotope bioassay method Dr. Penington states that "the results presented are the first in which a dose-response relationship has been established." We investigated dose-response curves in several cases.² There were five different doses from 0.015 ml. to 0.240 ml. given intravenously. Platelet count increases higher than those quoted by Dr. Penington were produced five to eight days after the plasma injection. Bone marrow megakaryocytes were also investigated. At least some pathologically active human plasma samples initiated a significant bone marrow and splenic megakaryocytosis, with a shift to the left in recipient mice already one day after the appropriate stimulus. The same pattern of changes followed the administration of "positive" mouse plasma. Several conditions of platelet physiopathology were, later, investigated and bone marrow changes, in general, were in accordance with expectations, except post-splenectomy thrombocytosis.⁵

It is surely unfair to disparage extensive previous work because some preliminary results with a seemingly more precise method diverged; especially as Penington's new method, used independently by others,⁶ appears to be a real advance.—I am, etc.,

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Glaucoma

SIR,—I feel sure that practitioners who have read Mr. S. Romano's article on primary glaucoma (16 May, p. 407) will be grateful for his conciseness and clarity. He has, however, confined the article to glaucoma in the adult.

I think a description of primary glaucoma ought to remind the reader of the congenital form, which is not an uncommon condition. It may be classified apart from glaucoma associated with rarer diseases occurring in fetal or neonatal life, and which diseases exhibit either purely ocular defects or these together with systemic abnormalities.

Most cases of congenital glaucoma are sporadic but a small percentage show an autosomal recessive trait. Mechanical impairment of aqueous outflow, with a

resultant rise in intraocular pressure, produces early symptoms and their recognition is important. They appear before the physical signs and are an intolerance of bright light, blepharospasm, and epiphora. Later the signs appear of a hazy cornea in an enlarged eye which feels hard when palpated, becomes somewhat injected, and in which the optic disc may be seen to be cupped. The treatment is essentially surgical, supplemented where necessary by miotics, and the correction of refractive errors.

Since the prognosis depends on not only early treatment but also early recognition of the disease, one should therefore consider the possibility of congenital glaucoma when one is asked to see an infant who is persistently photophobic and irritable, and an ophthalmic opinion may be very welcome.—I am, etc.,

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Illustrated Lectures

SIR,—Having just returned from a medical conference at which the majority of the speakers used slides during their talks, I wonder if I might have the courtesy of your columns to draw attention to the uselessness of the bulk of these slides because of their illegibility.

Since many participants at such conferences travel far and at much—usually public—expense in order to attend, it would

seem desirable that as much as possible of what is addressed to them should be assimilable.

High quality slides require the specialist medical illustrator's skill. But if the following points are borne in mind, any speaker can produce useful slides.

Make as few points per slide as possible; more than five is probably too many. Use several slides instead.

Represent the information in diagrammatic form if at all feasible, rather than in words and numbers. Simple histograms and graphs are most effective, using thick lines. Omit everything that is not essential.

If using a typewriter, the area to be photographed should be no larger than 3.5 in. × 5 in. (appr. 9 cm. × 12.5 cm.)—assuming a pica typeface with 10 characters to the inch. An electric typewriter with carbon ribbon is most desirable.¹

Lettering on larger originals than the size mentioned should be clearly legible when the original is viewed from a distance equal to eight times its largest (that is diagonal) dimensions—for quarto paper, from over 4 yards (3.7 m.).

Positive—that is black on white—slides are on the whole more legible than negative.²—I am, etc.,

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Diazepam and Neuromuscular Transmission

SIR,—Drs. S. A. Feldman and B. E. Crawley have recently reported that diazepam potentiates the neuromuscular blockade produced by gallamine (9 May, p. 336). This is in contrast to the findings of Hunter¹ who investigated diazepam and tubocurarine.

In order to determine whether diazepam affects transmission at the neuromuscular junction we have investigated its activity upon the rat phrenic nerve-diaphragm

preparation in vitro. Diazepam in concentrations between 2 and 16 × 10⁻⁵M potentiated tache inhibition was compared with the original control contraction height prior to diazepam pretreatment. However if this percentage inhibition was expressed in terms of the contraction height after diazepam pretreatment a slight potentiation of neuromuscular blockade was seen (13%).

In order to determine whether diazepam increased contraction height pre- or post-

Neuromuscular blockade produced by tubocurarine before and after pretreatment with diazepam. (T=tubocurarine 10⁻⁴M; D=diazepam 4 × 10⁻⁵M.)

contractions elicited by supramaximal stimulation of the phrenic nerve. This effect was dependent upon concentration and, at the highest concentration examined, a 50% increase in contraction height was seen.

Neuromuscular blockade produced either by tubocurarine or by gallamine was not potentiated by diazepam when the percen-

synaptically diazepam was added to the tissue bath with a high concentration of tubocurarine, and the muscle was stimulated directly. A sustained increase in contraction height was observed as before.

It is concluded that diazepam does not potentiate the effects of competitive neuromuscular blocking agents in vitro in