showed crystal clear fluid under normal pressure. Microscopic examination showed no cells, and the protein content was 35 mg./100 ml.

It was thought that the hypertensive crisis might be a consequence of the drug therapy. In case the administration of pethidine was a contributory factor, she was treated with a forced acid diuresis and a minimal urine pH of 4.8 was obtained. The blood pressure started to fall and by 10 hours after the ingestion of Mucron it had reached a level of 130/70. The blood pressure remained normal during the rest of her stay in hospital, and on follow-up one month later she was normotensive and asymptomatic apart from a mild depression.

Sympathetic amines contained in preparations for the symptomatic relief of nasal congestion are made up in free- or slow-release forms. Tonks and Lloyd¹ reported two cases taking monoamine-oxidase inhibitors in whom the use of a slow-release form of phenylpropanolamine resulted in the development of a severe headache, and in one case status epilepticus, but only slight elevation of blood pressure. A marked rise in blood pressure was shown experimentally by Dr. Cuthbert and colleagues, using phenylpropanolamine in the free form in subjects taking monoamine-oxidase inhibitors. The present patient supports their suggestion that severe hypertensive crises may be seen more commonly with amines in their free form than with slow-release preparations. On the other hand there may be little difference in the incidence with which both types give rise to severe headache.—We are, etc.,

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R. M. BUCKLE.

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REFERENCE

- ¹ Tonks, C. M., and Lloyd, A. T., *Brit. med. J.*, 1965, 1, 589.

Hypertension from Cold Remedies

SIR,—The paper published by Dr. M. F. Cuthbert and others (15 February, p. 404) prompts me to report the case history of a patient seen recently in Leeds.

A 36-year-old woman was admitted with a history of severe headache of sudden onset three hours previously. This was associated with vomiting and photophobia; in addition, she probably had a fit while still at home, after which she remained drowsy and confused, but was still complaining frequently of the headache, which was mainly frontal and vertical. She had some neck stiffness and a positive Kernig's sign. The plantar responses were extensor, but there were no focal signs in the nervous system, although later she developed a transient right hemiparesis. She was normotensive, and full physical examination did not reveal any further abnormal signs. A lumbar puncture confirmed subarachnoid haemorrhage, and cerebral angiography suggested the possibility of a left posterior communicating aneurysm. She was managed conservatively in view of some uncertainty in the x-ray findings and because of her long-standing somewhat hysterical personality. There was no evidence of recurrent bleeding, and she made a complete recovery.

Questioning revealed that she had been taking phenelzine 30 mg. daily for six months, and that a few hours before her subarachnoid haemorrhage she had taken two Mucron tablets. This proprietary nasal decongestant contains 30 mg. phenylpropanolamine in each tablet, plus vitamin C, phenacetin, and ippecacuanha.

Although we (like Tonks and Lloyd in their cases of encephalopathy in similar circumstances¹) did not observe the blood pressure to be raised, it seems likely that sudden severe hypertension caused by the interaction of phenelzine and phenylpropanolamine resulted in the rupture of a berry aneurysm. About three hours passed before the onset of the headache after taking the Mucron and a further three hours before the blood pressure was taken. It is feasible that six hours is long enough for the blood pressure to have risen to dangerously high levels and fallen again. Dr. Cuthbert's experiments on himself with a monoamine oxidase inhibitor and phenylpropanolamine were quite rightly cut short with phentolamine, and so we do not have any evidence as to how long to expect the blood pressure to remain raised in such circumstances.

I would like to thank Dr. R. N. Tattersall for his permission to publish the details of this case history.

—I am, etc.,

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REFERENCE

- ¹ Tonks, C. M., Lloyd, A. T., *Brit. med. J.*, 1965, 1, 589.

Awareness during Anaesthesia

SIR,—In this day and age of light anaesthesia, any reminder that the patient receiving a general anaesthetic expects to be unaware of the surgical procedure, and have no recollection of it, is welcome. However, perhaps the picture is not so gloomy as Drs. J. Wilson and D. J. Turner (1 February, p. 280) suggest.

A reported study¹ described 20 consecutive cases anaesthetized using atropine 0.6 mg., thiopentone 1.0–2.0 mg./lb. bodyweight, nitrous oxide 3.5 l./min.; oxygen 1.5 l./min. into a semiclosed circle absorber system, relaxants, and artificial ventilation 50–150% in excess of the Radford Nomogram value. Words of established emotional significance, in the form of a story, were tape recorded and repetitively applied to the patients through insulated earphones at times varying from 10–90 minutes after the induction of anaesthesia. On the second or third postoperative day the patients were visited by an experienced interviewer who was unaware of the precise details of the study. The interview was designed to annotate a predesigned protocol. No evidence indicating recall of auditory stimuli could be obtained, nor did any patients provide evidence of distress.

The difference between these results and those recently reported in your journal may be explained by differences in experimental method and by the environment of the patients. Important factors in any consideration of awareness and recall associated with surgery are the sounds available to the patients, their interpretation of them, and the significance of that interpretation to the patient. As the authors indicate, if patients are anaesthetized the problem doesn't arise. However, if the surgical situation demands particularly light anaesthesia, perhaps partial isolation of the patient from auditory stimuli is of value during the operative period. Also the appropriate auditory stimuli provided by

good nursing care immediately the patients are even dimly aware of their environment will have a lasting effect on their overall impression of the surgical experience.—I am, etc.,

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REFERENCE

- ¹ McIntyre, J. W. R., *Canad. Anaesth. Soc. J.*, 1966, 13, 495.

Ampicillin and Urticaria

SIR,—I read with interest the papers dealing with adverse reactions to drugs in your issue of 1 March (p. 527), and, in particular, that by Dr. Natalie Hurwitz and Professor O. L. Wade (p. 531). In their summary the authors suggest that "larger surveys of adverse reactions in relation to drug usage would make a useful contribution to the problem." In common with most other pharmaceutical manufacturers, we maintain extensive coverage of the international medical and allied scientific literature on our drugs, including a continuous survey of adverse reactions and side-effects. I feel, therefore, that it may be of general interest to present our findings with ampicillin, which was reported by Dr. Hurwitz and Professor Wade as having produced eight maculopapular pruritic rashes in 103 patients treated, an incidence of 7.8%.

Our most recent figures show that a total of 13,638 patients treated with ampicillin have been reported in the published clinical literature. Of these, 383 (2.8%) experienced skin reactions of various kinds. The description and incidence of rashes varies from observer to observer; careful observation of the patient and post-treatment follow-up tends to produce a higher reported incidence. Of the rashes recorded in the literature 58 were described as urticarial, 23 as macular, and 114 as maculopapular (including the so-called "morbilliform" type); 19 patients exhibited other types of rash, and 169 skin reactions were of an unspecified nature.

The rashes reported during ampicillin therapy fell into two broad categories—that is, urticarial and erythematous. Urticaria is generally regarded as a sign of true penicillin hypersensitivity, and there is no evidence to suggest that ampicillin is associated with a higher incidence of this type of rash than other penicillins. The majority of the erythematous rashes are apparently ampicillin-specific and do not indicate true penicillin hypersensitivity. They commonly start as a faint erythema, often with a centrifugal distribution. They are usually macular or maculopapular, and are less irritant than urticaria and often controlled with antihistamines. In many cases the rash fails to develop further and usually disappears quickly when ampicillin is withdrawn; in some patients it may even disappear without discontinuation of the antibiotic. In a few cases, however, it becomes a generalized severe erythema, sometimes with slight fever. Though the rash may arise during the course of therapy, sometimes as early as the first day, it often develops about five days after the end of treatment, and for this reason has been called the "fifth-day rash."¹ Subsequent courses of the antibiotic may not necessarily reproduce the reaction. In a limited number of patients with this type of rash investigated so far we have been unable to demonstrate circulating reaginic antibodies in the serum. It is now well established that

patients with glandular fever almost invariably develop a rash if given ampicillin,²⁻⁵ and the same is true to a lesser extent for some other antibiotics.

A survey of the literature shows that there has been a particularly high incidence of rashes in patients treated with ampicillin for *Salmonella* infections. It has been postulated that some of the rashes may be produced by endotoxin released by rapid lysis of bacteria, though there is little evidence to support this. Many of these patients received high dosage, but we have been unable to show a significant relationship between dosage and incidence.

An intensive investigation is being undertaken in an attempt to provide information on many of the unexplained features of the rash associated with ampicillin therapy.—I am, etc.,

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Beecham Research Laboratories,
Brentford, Middx.

REFERENCES

- 1 Stevenson, J., and Mandal, B., *Brit. med. J.*, 1966, **1**, 1359.
- 2 Pullen, H., Wright, N., and Murdoch, J. M., *Lancet*, 1967, **2**, 1176.
- 3 Pullen, H., Wright, N., and Murdoch, J. M., *Lancet*, 1968, **1**, 1090.
- 4 Patel, B. M., *Pediatrics*, 1967, **40**, 91.
- 5 Gabbert, W. R., and Hopwood, Ann H., *J. Ky med. Ass.*, 1968, **66**, 967.

Jakob-Creutzfeldt Disease

SIR,—The statement in your leading article (1 March, p. 528) that the term "Jakob-Creutzfeldt disease" has been erroneously used by British neurologists and physicians for many years is simply not true. There is no evidence whatsoever that the cases so recognized by neurologists in Britain at least up to 1954 were not in general similar clinically and pathologically to the five patients described by Jakob. The fact that Spielmeier, the renowned German neuropathologist, suggested the term "Jakob-Creutzfeldt disease" for what you wish to describe as "corticostriatonigral degeneration" you seem now to consider of no importance. It is surely folly to change without reason the name of a disease or syndrome, as it only confuses the student and hinders the advance of knowledge. The clinical condition which you label "Jakob-Creutzfeldt disease" and which has been transmitted to a chimpanzee was never described by either of these authors. It would be lamentable if our literature were allowed, in any degree, to become a mixture of unreality and make-believe, in the justification of which it becomes necessary to discredit our distinguished predecessors.—I am, etc.,

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** It is true that W. Spielmeier suggested that the term Jakob-Creutzfeldt disease should be applied to a neurological syndrome characterized by the slow development of a Parkinsonian-like picture, often associated with dementia, signs of corticospinal tract degeneration, and amyotrophy in the limbs. More recently, however, many neurologists have come to the conclusion that the cases which Jakob and Creutzfeldt originally described almost certainly represented a different diagnostic entity from that referred

to by Spielmeier. The general consensus of opinion among many neuropathologists in Britain and the majority in the U.S.A. is that the term Jakob-Creutzfeldt disease is more properly used to identify a syndrome characterized by rapidly progressive dementia developing in the presenium, often associated with myoclonus, and by a spongiform type of degeneration in the cerebral cortex seen at necropsy. The matter is still controversial, but majority opinion seems to be leaning towards the view expressed in our leading article rather than towards the more traditional British use of this diagnostic title as stressed by Dr. Nevin.—ED., *B.M.J.*

Cerebral Malaria

SIR,—I agree with Dr. P. W. Hutton (1 March, p. 578). I see no major difference between quinine and the 4-amino-quinolines (in the absence of parasite resistance) in the treatment of cerebral complications of falciparum malaria, so long as reasonable care is taken during administration to avoid the precipitation of medical shock.

Recent discussions (25 January, p. 256) indicate some misunderstanding of the processes involved in the development of coma, which is primarily due to incompetence of the cerebral circulation following leakage of protein and water through the endothelial walls of the small brain vessels. Quinine and chloroquine (and the corticosteroids for that matter) reverse this process, acting as anti-inflammatory agents; the restoration of the circulation leads to return of consciousness, often in a few hours. The antiparasitic activity of the drugs at this stage is not a factor in the immediate clinical response. We are lucky to have two such powerful schizonticides which are equally active anti-inflammatory agents.

May I say how pleased I was to read Dr. Hutton's warning on falciparum malaria as it occurs in the United Kingdom. It is time the public and the profession appreciated the potential risks of overseas travel in this respect.—I am, etc.,

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New B.N.F.

SIR,—I should like to draw attention to what, in my view, is a possibly lethal error in the "Classified Notes for Prescribers" in the new edition of the *British National Formulary*.¹ I refer to p. 76, where speaking about chlorpromazine it says, "It is, however, very effective in more severe agitated states, especially in the elderly in whom other drugs may cause confusion. Single injections (300 mg. or so) can be used to control acutely disturbed patients." It is not absolutely clear from the context whether this dosage is recommended only for the elderly, or for any acutely disturbed patients. However, none of my colleagues have ever used more than 150 mg. in a single injection, the usual maximum being 100 mg., while the manufacturers, who admittedly tend to err on the conservative side, recommend only "25–50 mg. in an injection."²

Dr. P. S. Nemetz (18 January, p. 186) has recently drawn attention to the danger of injecting even 100 mg. of chlorpromazine in the elderly: "There is great potential for postural hypotension with brain softening, myocardial infarction, syncope with trauma, and even irreversible shock and death." He stresses that intramuscular injections have four or five times the potential of an oral preparation, and in my own experience it is rarely necessary to exceed a total oral daily dosage of 150 mg. in elderly patients. Intramuscular doses of 300 mg. would clearly be dangerous.—I am, etc.,

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REFERENCES

- 1 *British National Formulary*, 1968. British Medical Association and Pharmaceutical Society of Great Britain, London.
- 2 May and Baker, *Largactil in Psychiatry*, 1967, 7th edition, p. 26. Dagenham, Essex, May and Baker Ltd.

B.N.F. Recommendations

SIR,—The *British National Formulary* 1968 makes admirable recommendations about the abbreviations which should be used in prescribing. Perhaps a future addition would advise on the rationalization of the terms "b.d.," "t.d.s.," "i.d.," "q.d.s.," "q.i.d.," "nocte," and others which are commonly used on prescription sheets, especially in hospitals.

A complete standardization of terminology in prescriptions should be useful for pharmacists, doctors, and nurses. In the interests of accuracy, simplicity, and safety in prescribing today the writing of prescriptions is too important a matter to be left to the whims and fancy of individual doctors.—I am, etc.,

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D. A. SPENCER.

Transfusion and Perforation

SIR,—In reply to Dr. D. J. Formby (8 March, p. 643), who suggests a possible link between the use of citrated blood and perforation of the gut, we can confirm that our cases were transfused with citrated blood, as we believe is the practice in the majority of British centres. We accept that acidosis may occur in these infants. In our original article (9 November, p. 349) we postulated that hypoxia may play a part in the aetiology, and one knows that hypoxia is usually followed by a fall in pH. If acidosis is the chief factor, however, it is surprising that perforation is not seen more often in those conditions known to produce hypoxia and a fall in pH in the newborn, such as respiratory distress syndrome and cyanotic congenital heart disease. In our experience, however, the incidence of perforation of the bowel in these conditions seems to be low.

From the records of this hospital over a period of seven years we have found four more similar cases in addition to those already