therefore remains largely unknown. On the other hand, the terms "alive" or "dead" do not give an account of the whole phenomenon. For example, the patient described by Dodge and Curie² benefited from decompression and lobectomy, and was the only one of the 37 cases reported by Haymaker *et al.*³ which survived. Nevertheless, the death of the same patient was later reported⁴ and I wonder whether this case could be used to illustrate the success or failure of surgery.

	No. of Cases	Alive	Dead
Untreated	268	63	205
Treated	101	49	52
Surgery only	28	11	17
IDU* only	25	13	12
ARA C** only	8	7	1
Steroids only	19	9	10
Steroids + surgery	2	1	1
IDU or ARA C + surgery	12	4	8
IDU or ARA C + steroids	3	2	1
Steroids + surgery + IDU or ARA C	3	2	1
Poly-I.C.***	1	0	1

*Idoxuridine.

**Cytosine arabinoside.

***Semisynthetic RNA which induces interferon production.

It must be stressed that in the untreated group recovery is usually slow and often takes weeks, if not months. In many cases in the treated group, however, the first signs of recovery appeared within 72 hours, an improvement noted by Dr. Upton himself in his case no. 1.⁵ It is true, nevertheless, that a careful reading of the literature shows that there is no valid evidence that any one treatment is much better than the others.

In a patient described by Gurwith *et al.*⁶ there was marked deterioration while on dexamethasone, but there was rapid recovery after idoxuridine therapy. In other cases (personal communication) idoxuridine is of no help, but external decompression and lobectomy may have a striking beneficial effect. I also have seen patients who deteriorated despite surgical intervention but responded within 30 hours to idoxuridine infusion.

The importance of brain oedema as a contributory cause of death has been clearly recognized.⁷⁻⁹ One must therefore agree with Dr. Upton when he asks that chemotherapy be combined with either surgical or "medical" decompression. For reasons which have already been put forward^{10,11} the use of steroids alone appears hazardous, and I would like to make a plea that if dexamethasone is to be used it should always be combined with antiviral chemotherapy.

Acute necrotizing encephalitis is the most frequent type of encephalitis in adults encountered in our latitudes; the problem is not only, therefore, of academic interest. At the symposium on herpes encephalitis held in Manchester earlier this year a working party was established with a view to encouraging multicentre retrospective and prospective studies into the problems inherent in the treatment of this disease. I hope that such a co-operative undertaking will help us in the future to treat our unfortunate patients more successfully.—I am, etc.,

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¹ Rappel, M., *Postgraduate Medical Journal*, in press.
² Dodge, P. R., and Cure, C. W., *New England Journal of Medicine*, 1956, 225, 849.

- ³ Haymaker, W., Smith, M. G., van Bogaert, L., and de Chenar, C., in *Viral Encephalitis* ed. W. S. Fields and R. J. Blattner, p. 95, Springfield Thomas, 1950.
- ⁴ Booth, C. B., Okazaki, H., and Gaulin, J. C., *Neurology*, 1961, 11, 619.
- ⁵ Upton, A. R. M., Barwick, D. D., Foster, J. B., *Lancet*, 1971, 1, 290.
- ⁶ Gurwith, M. J., Harman, C. E., and Merigan, T. C., *California Medicine*, 1971, 115, No. 6, 63.
- ⁷ Pierce, N. F., Portnoy, B., Leeds, N. E., Morrison, R. L., and Wehrle, P. F., *Neurology*, 1964, 14, 70.
- ⁸ Page, L. K., Tyler, H. R., Shillito, J., *Journal of Neurosurgery*, 1967, 27, 346.
- ⁹ Delmas-Marsalet, P. M., Bergouignan, M., Castaing, R., du Pasquier, P., and Vital, C., *Bulletin de l'Académie de Médecine (Paris)*, 1968, 192, 316.
- ¹⁰ Longson, M., and Beswick, T. S. L., *Lancet*, 1971, 1, 749.
- ¹¹ Rappel, M., *et al.*, *Journal of the Neurological Sciences*, 1971, 12, 443.

Trimethoprim-sulphamethoxazole in Folic Acid Deficiency

SIR,—Drs. I. Chanarin and J. M. England (11 March, p. 651) have drawn attention to the dangers of trimethoprim-sulphamethoxazole therapy in megaloblastic anaemia. We also have observed these dangers and the following case may be of interest.

A 72-year-old woman was admitted because of a severe urinary tract infection. She had a previous history of diabetes mellitus, rheumatoid arthritis, and primary hypothyroidism, which had been treated by diet, analgesics, and thyroxine respectively. To this was added trimethoprim-sulphamethoxazole (Septrin) for the urinary infection, because the patient claimed to be allergic to ampicillin. While this therapy continued, investigation was instituted for the severe megaloblastic anaemia which had been discovered on admission. In view of the previous history, pernicious anaemia was considered the most likely diagnosis, but B₁₂ deficiency was excluded by the presence of a normal serum level (170 pg/ml), free acid in the gastric juice (pH 2.3), and the lack of response to vitamin B₁₂ therapy (Fig.).

Folate deficiency was confirmed as the cause of the anaemia by a low serum folate (1.7 µg/ml) and a dietary history showing a daily intake of only 4.1 µg per day approximately. We were very disturbed to find a marked fall in the haemoglobin and platelet count after ten days of Septrin (Fig.). It seemed very likely that the patient's folic acid deficiency anaemia had been aggravated to a dangerous degree by the Septrin. It would

seem that caution is indicated in using this drug in any patient in whom folic acid deficiency is suspected.—We are, etc.,

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Anticonvulsant Drugs, Folate Deficiency, and Metabolic Bone Disease

SIR,—Dr. Roger Williams and his colleagues (23 October 1971, p. 202 and 29 January, p. 297) reported similar significant inverse correlations between urinary glucaric acid excretion and (1) the level of serum calcium and (2) the degree of folate deficiency in drug-treated epileptic patients. Both sets of data were interpreted as supporting the hypothesis that anticonvulsant bone changes and anticonvulsant folate deficiency are due to enzyme induction.

There are some difficulties in explaining the anticonvulsant folate changes on the basis of enzyme induction. There is evidence that diphenylhydantoin is a more powerful "antifolate" drug than phenobarbitone.¹ This would imply, according to the induction hypothesis, that diphenylhydantoin is a more powerful enzyme inducer than phenobarbitone, which does not appear to be the case. Indeed, the data presented by Drs. G. H. Spray and D. G. Burns (15 April, p. 167) clearly suggest that phenobarbitone has a more marked enzyme inducing effect than diphenylhydantoin. Despite this the only group of their animals in whom liver folate fell was that on diphenylhydantoin.

There is no convincing evidence yet that folate is required for drug hydroxylation. If this were true one would expect an increase in the urinary excretion of 5-(p-hydroxyphenyl)-5 phenylhydantoin following the administration of folic acid to folate-deficient epileptic patients being treated with diphenylhydantoin. However, Olesen and Jensen² indicated that the excretion of this metabolite actually decreases after the administration of folic acid.

Alternative theories of anticonvulsant-induced folate deficiency for which there is some evidence are impairment of folate transport³ or inhibition of co-enzyme function.^{4,5}

The explanation for the drug-induced

bone changes also remains uncertain, but an alternative to the enzyme induction hypothesis deserves consideration in view of the report of Ragab *et al.*⁶ that the folate antagonist, methotrexate, can produce osteoporosis with some features similar to those produced by anticonvulsants. (Dent, personal communication). Could not the bone disease in epileptic patients also be related to the effects of anticonvulsant drugs on folate metabolism? Certainly there is a great deal of clinical overlap between the folate and metabolic bone changes in epileptic patients, as the similar correlations with urinary glucaric acid excretion would suggest, and as would be expected if both are dose-related complications.—I am, etc.,

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- 1 Reynolds, E. H., Mattson, R. H., and Gallagher, B. B., *Neurology (Mineap.)*, 1971, 21, 394.
- 2 Olesen, O. V., and Jensen, O. N., *Acta Pharmacologica et Toxicologica*, 1970, 28, 265.
- 3 Woodbury, D. M., and Kemp, J. W., *Psychiatry, Neurologia, Neurochirurgia*, 1971, 74, 91.
- 4 De Wolff, F. A., Hillen, F. C., Sprangers, W. J. M., Suijkerbuijk-Van Beek, M. M. A., and Noach, E. L., *Archives Internationales de Pharmacodynamie et de Therapie*, 1971, 194, 316.
- 5 Spector, R. G., *British Journal of Pharmacology and Chemotherapy*, 1972, 44, 279.
- 6 Ragab, A. H., Frech, R. S., and Vietti, T. J., *Cancer*, 1970, 25, 580.

Research in Psychiatry

SIR,—The question posed by your thoughtful leading article on research in psychiatry (8 April, p. 61) is of serious concern and your suggestions are most pertinent. We must look at every way of making psychiatric research more effective.

May I suggest one location for psychiatric research that is neglected but should not be overlooked: the mental hospitals. The bulk of specialist psychiatric treatment is, in Britain, still based on these institutions and their extramural extensions. May I illustrate the excellent opportunities for research which they afford from the record of the hospital in which I work. Professor Michael Shepherd's original essay in epidemiological psychiatry,¹ which was based on this hospital and forecast most trends in mental hospital population of the last decade, shows to what good account administrative records can be turned. He has also pointed out the deficiency of the 'prime material' for research in clinical psychopharmacology, particularly in the evaluation of new drugs which, I believe, can be met from suitable mental hospitals. At St. John's, among completed projects, we have undertaken evaluations of reserpine,² chlorpromazine,³ imipramine,⁴ the effect of recent neuroleptics on movement of patients⁵ and the psychological correlates of their action.⁶

With a modest investment in staff and equipment a considerable contribution to the pharmacology of imipramine has been completed.

Such work has been made possible by the help of the Oxford Regional Hospital Board, the M.R.C., a grant from the Nuffield Provincial Hospitals Trust, and the generosity of drug firms. The handicaps in attracting such support outside university centres are great, however, and what can be accomplished is subject to serious limitations. The chief of these is the impossibility of obtaining sustained support as

opposed to support for individual projects. In this respect I believe your view that "there is no evidence that promising developments have been starved of support" needs qualification.—I am, etc.,

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- 1 Shepherd, M., *The Major Psychoses in an English County*, London, Chapman and Hall, 1957.
- 2 Watt, D. C., *Journal of Neurology Neurosurgery and Psychiatry* 1958, 21, 297.
- 3 Shepherd, M., and Watt, D. C., *Journal of Neurology Neurosurgery and Psychiatry* 1956, 19, 232.
- 4 Elkes, A., *Mode of Action of Imipramine*, M. D., Thesis, London University, 1958.
- 5 Shepherd, M., Goodman, N., and Watt, D. C., *Comprehensive Psychiatry*, 1961, 2, 11.
- 6 Allport, D. A., Crookes, T. G., and Watt, D. C., *Neuropsychopharmacology*, Amsterdam, 1964, 3, 93.
- 7 Crammer, J. L., and Rolfe, B., *Psychopharmacology*, 1970, 18, 26.

Private Practice

SIR,—How sad it was to read the letter from Mr. J. R. Kirwan, vice-president of the British Medical Students' Association (20 May, p. 464), in which he criticized the views Professor C. A. Wells (6 May, p. 346) expressed on the role of private practice in enhancing the experience and teaching training of consultants.

As a general practitioner I would endorse Professor Wells's views wholeheartedly, and would suggest that Mr. Kirwan will find when he comes to practise medicine, as he so surely will do in the near future, that those consultants who have experience of private practice have on the whole a far better and more understanding relationship with the general practitioner.

Similarly, it is rarely the private patient who wastes the doctor's time, as he is having to pay for the privilege. I wish the same could be said for a section of the population that regards the Health Service as an organization to be exploited to the ultimate for every trivial problem, whether medical or not, to the detriment of those who are really sick.

Perhaps it will surprise Mr. Kirwan to discover that there are those who do not share his views, but who are no less dedicated to the service of medicine and resent his implication that because a doctor will see private patients he must necessarily give less care to those who are not.—I am, etc.,

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Accidents and Fatigue in Small Boats

SIR,—Tens of thousands of people are now taking to the sea around these islands and last year some 3,000 had to be rescued. Further, there are many unexplained losses of small boats, and there are deaths from such conditions as hypothermia which might be avoided by a better understanding of the problems. Anyone who has talked to yachtsmen will be struck by the frequency with which they make serious errors of judgement when fatigued, or may experience gross misinterpretation of their surroundings and even have visual hallucinations. Really too many people are involved in this activity for one to ascribe these phenomena to some

peculiarity of yachtsmen. Rather one must look at the activity itself.

In sailing small boats the yachtsman is expected to perform a highly accurate task when exposed to unpleasant conditions in which he may be feeling wet, cold, seasick, and very tired. Also, he may have anxieties about the suitability of his boat or because he has his family on board, not to mention all the anxieties that beset people in ordinary life. It is not surprising, therefore, that the yachtsman is subject to special physical and mental stresses. One such example I heard of recently was that a party having crossed the Channel and being very fatigued, sailed north-west into Poole Harbour, which is flanked by low-lying land, under the impression that they were sailing up the Needles Channel which runs north-east and is flanked by white cliffs and a castle.

There are studies in progress in this department on the general question of fatigue among sailors and also into clothing and stores. I would like to ask readers for the benefit of their experience and advice on these matters under, among others, the following headings:

(1) Details of errors of any kind occurring in the course of handling small boats, and also of any odd experiences.

(2) Details of any small boat accidents at sea in which readers may have been involved professionally or even as victims.

(3) Any general observations about these problems, for example, about protective clothing, provisions, and medical supplies; and advice and personal experiences which could be made available to a wider public.

All details supplied would be regarded as confidential insofar as nothing that could identify an individual would be disclosed, but, of course, the intention is to provide information which will help others in the future.—I am, etc.,

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Sir Paul Chambers's Inquiry

SIR,—Dr. A. A. Gildersleve (20 May, p. 469) questions the logic of some of the conclusions of Sir Paul Chambers in his report (*Supplement*, 6 May, p. 45).

Dr. Gildersleve asks if it is logical to destroy the General Medical Services Committee and Central Committee for Hospital Medical Services if, as Sir Paul admits, they are so well informed. This question misses two central issues of criticism in the report—namely, these committees are autonomous, and not accountable to the Representative Body, and they contain non-members of the B.M.A., and are elected mainly by bodies which are not part of the B.M.A.

Doubtless, Dr. Gildersleve read Section X, para. 6 of the report, in which Sir Paul says: "... members of existing committees should be elected, if they are willing, to serve on the new committees. Thus it is hoped that some members of ... the C.C.H.M.S. ... [and] ... G.M.S.C. ... will be willing to be nominated for election under the new system." (*Supplement*, 6 May, p. 64). If this occurs, then the new committees will retain the best of the old which Dr. Gildersleve thinks will be destroyed. The new committees will, in addition, be composed wholly of B.M.A. members, and answerable to the R.B.