questioning. The story of unexplained abdominal pain in the mother or other members of the family tends to support the diagnosis.

Treatment with antidepressants, either the tricyclic group or monoamine oxidase inhibitors, is frequently effective in eliminating the abdominal discomfort. In most cases regardless of age the relief is permanent unless there is renewed stress causing repeated anxiety in the child. The condition may be disabling, since the depressed child cannot function adequately either socially or at school. The underlying emotional problems often remain unsuspected, and frequent short absences from school lead to poor school work and antipathy on the part of the teachers.

There is reluctance to use antidepressant drugs in children, but in this type of recurrent abdominal pain they are certainly no more dangerous than a laparotomy and may be much more beneficial.—We are, etc.,

EVA FROMMER.
DENNIS COTTOM.

St. Thomas's Hospital,
London S.E.1.

REFERENCES

1 Conway, D. J., *Great Ormond Street Journal*, 1951, **1**, 99.
2 Apley, J., *The Child with Abdominal Pains*. Oxford, Blackwell Scientific, 1959.
3 Frommer, E. A., in *Recent Developments in Affective Disorders*, ed. A. Coppen and L. A. Walk, p. 117. *British Journal of Psychiatry, Special Publication*, No. 2, 1968.

Paraquat Toxicity

SIR,—In paying tribute to Otto Warburg (obituary 15 August, p. 409), Drs. D. M. Stokes and D. A. Walker (22 August, p. 462) could have pointed out that while the "legendary biochemist" might well have been ignorant of the toxic effects of paraquat (methyl viologen) he would certainly have been aware of its unusual electrochemical properties. In this respect paraquat and some related dipyridyls have a long and honourable history as redox indicators.[1,2]

In support of their hypothesis on the mechanism of paraquat toxicity Drs. Stokes and Walker quote an article by Dr. J. C. Gage,[3] but in fact they do so out of context. Gage showed that the resting respiration of intact rat liver mitochondria was virtually unaffected by paraquat and diquat, probably because of their inability to penetrate the mitochondrial membrane. This finding appears to preclude the suggestion of Drs. Stokes and Walker that bypassing of the mitochondrial electron transport chain is a plausible mechanism of action of paraquat.

We agree with Drs. K. Fletcher and A. A. B. Swan (12 September, p. 646) that there is no parallel between Warburg's theory of carcinogenesis and paraquat toxicity. Any attempt to explain the apparently specific effect of paraquat, as opposed to diquat, on lung fibroblasts should take into account the substantial difference in their redox potentials,[4] since diquat is electrochemically more active than paraquat. However, since reduction might occur in vivo only as far as the free radicals, this consideration may not be important.

Dr. J. McEvoy (12 September, p. 647) is, of course, right to emphasize that his patient suffering from diquat poisoning showed no evidence of any lung lesion. A recent report[5] of fatal diquat poisoning, however, indicates that this compound may indeed produce "changes in the lungs similar to those reported for paraquat."—We are, etc.,

S. S. BROWN.
P. F. GIBSON.

University Department of
Clinical Chemistry,
Royal Infirmary,
Edinburgh.

REFERENCES

1 Michaelis, L., *Biochemische Zeitschrift*, 1932, **250**, 564.
2 Michaelis, L., and Hill, E. S., *Journal of General Physiology*, 1933, **16**, 859.
3 Gage, J. C., *Biochemical Journal*, 1968, **109**, 757.
4 Brian, R. C., *Chemistry and Industry*, 1965, 1955.
5 Schönborn, H., *et al.* in *Summary Proceedings of the Fourth Congress of Poisons Control Centres*, Basko Polje Makarska), Jugoslavia, September, 1970, p. 14.

Clofibrate, Fibrinolysis, and Platelet Stickiness

SIR,—Nobody would question the effects of clofibrate on serum lipids described in "Today's Drugs" (12 September, p. 632); but that clofibrate "corrects decreased fibrinolysis" is extremely doubtful, and that "abnormal platelet stickiness . . . [is] altered toward normal values" requires qualification.

The original Atromid (clofibrate plus androsterone) was reported by Srivastava *et al.*[1] to increase fibrinolytic activity in arteriopathic patients; subsequently Goodhart and Dewar,[2] using Atromid-S, stated that this effect occurred only in patients with hypercholesterolaemia. My colleagues and I found Atromid to increase fibrinolytic activity temporarily, the effect lasting for not more than three months.[3] When we studied clofibrate alone (Atromid-S)—that is, without androsterone, the dilute blood clot lysis times of five out of six patients which were within normal limits before treatment actually prolonged during treatment with the drug[4] in other words, fibrinolytic activity was reduced. Sweet *et al.*,[5] using the euglobulin lysis time, found clofibrate to have no effect on fibrinolytic activity, irrespective of hypercholesterolaemia. We believe that the temporary fibrinolytic effect of the original Atromid was due to its high content of androsterone, since we have shown that androgens temporarily increase fibrinolytic activity.[6]

Several workers, notably Carson *et al.*,[7] have shown that clofibrate reduces platelet stickiness over the short term but in none of these studies was the drug given for more than two months. In a study lasting nine months my colleagues and I found that while clofibrate initially reduced platelet stickiness, this effect was lost after six months' treatment. Our findings therefore fail to confirm that clofibrate has any worthwhile long-term effect on two of the "thrombogenic abnormalities" mentioned in your article; and also raise the possibility that in some patients the effect of the drug on fibrinolysis may be unfavourable.—I am, etc.,

G. R. FEARNLEY.

Gloucestershire Royal Hospital,
Gloucester.

REFERENCES

1 Srivastava, S. C., Smith, M. J., and Dewar, H. A., *Journal of Atherosclerosis Research*, 1963, **3**, 640.
2 Goodhart, J. M., and Dewar, H. A., *British Medical Journal*, 1966, **1**, 325.
3 Hocking, E. D., Chakrabarti, R., Evans, J., and Fearnley, G. R., *Journal of Atherosclerosis Research*, 1967, **7**, 121.
4 Chakrabarti, R., and Fearnley, G. R., *Lancet*, 1968, **2**, 1007.
5 Sweet, B., Rifkind, B. M., and McNicol, G. P., *Journal of Atherosclerosis Research*, 1965, **5**, 347.
6 Fearnley, G. R., and Chakrabarti, R., *Journal of Clinical Pathology*, 1964, **17**, 328.
7 Carson, P., McDonald, L., Pickard, S., Pilkington, T., Davies, B., and Love, F., *Journal of Atherosclerosis Research*, 1963, **3**, 619.

Cholera in Britain

SIR,—I found your leading articles on cholera (12 September, p. 601, and 3 October, p. 2) concise and useful. I was sorry, however, that you did not make more of the opportunity to remind the profession of the necessity in this jet age of making sure that a geographical history is taken from every patient. This could be the best protection against the consequences of spread of an imported disease such as cholera. The profession and the public seem to be becoming slightly more aware of the medical risks of going abroad, but it would appear that some of those concerned in the logistics of travel do not always face up to their responsibilities.

I have in front of me a cutting from a recent London evening paper in which it is said: "Tourists who ignored warnings to have inoculations, then picked up diseases like typhoid and cholera were criminally irresponsible, the Association of British Travel Agents said today."[1] It seems to me a bit hard to put the blame on the public in this way. Surely the agents should make sure that their passengers are informed and protected before they travel to any endemic or suspect area.

I detect some complacency about cholera appearing in Europe which, in this context, includes the United Kingdom. For example, another cutting, this time from a German paper, says: "Keine Cholera Gefahr für Europa." This is in keeping with the frequently expressed view that cholera is today not a serious community risk to the sophisticated world, where high standards of sanitation and hygiene and an adequate public health infrastructure make its spread unlikely. This may be so in the big cities and towns, where the chances of spread by infected water or food, or by personal contact are probably minimal. Nevertheless, I doubt its relevance in some slum areas and country villages in which the sanitation or lack of it sometimes seems to me to be as potentially encouraging to the vibrio as anything I have seen in the tropical world. Wherever there is dirt, squalor, and bad sanitation there could be some spread of cholera brought in by travellers from endemic regions or from areas where there are outbreaks.

The recent circular letter from the Chief Medical Officer (C.M.O. 16/70) has rightly drawn the attention of medical officers of health to the risks of imported cholera infection. The warning should be extended also to the general practitioners who are likely to see the suspect patients first, and to the travelling public, who should be informed about specific regions and vac-

cinated if necessary; in any case, they should be instructed on return to tell their doctors where they have been and when.—I am, etc.,

BRIAN MAEGRAITH.

Liverpool School of Tropical Medicine, University of Liverpool.

REFERENCE

1 *Evening News*, 23 September 1970.

Embryonal Tumours in Childhood

SIR,—I should like to draw the attention of your readers to two therapeutic trials, in Wilms's tumour (nephroblastoma) and neuroblastoma, currently being undertaken by the Medical Research Council's working party on embryonal tumours in childhood.

The trial of treatment of neuroblastoma is designed to investigate whether the regression that sometimes occurs in this disease is a consequence of an immune reaction developed against the tumour, and if so whether this immunity can be increased by immunotherapy. There is experimental evidence that neuroblastomas contain tumour-specific antigens against which an immune reaction may be stimulated,[1] and also that the immune system is more likely to succeed in eradicating a tumour when the number of residual malignant cells in the body is low.[2] It is therefore important that immunotherapy should follow a period of chemotherapy, and in this trial it is proposed to treat patients with vincristine and cyclophosphamide for this purpose, after initial surgery and radiotherapy if indicated. The working party considered that the most suitable groups of patients for such a trial are as follows: (1) all patients over the age of one year with neuroblastoma, except those with a primary lesion confined to the cervical region; (2) all patients under the age of one year with metastatic disease.

The trial of treatment in nephroblastoma is designed to assess the relative efficacy of vincristine and actinomycin D as agents in the treatment of nephroblastoma after surgery and radiotherapy. There is now increasing evidence[3] that the prognosis of nephroblastoma is improved by the use of actinomycin D for periods of two years following surgery and radiotherapy. There is also evidence[4] that vincristine, a drug which is relatively less toxic than actinomycin D, is efficacious in treating metastatic disease. It is therefore planned to conduct a controlled clinical trial in children over the age of one year with stage I, IIa, and IIb (American classification) disease in an attempt to compare the effectiveness of the two drugs in the long-term treatment.

Further information may be obtained from the secretaries of the working party, Dr. P. Morris Jones (at the Royal Manchester Children's Hospital, Pendlebury, Manchester, M27 1HA) and Dr. Dorothy Pearson (Christie Hospital and Holt Radium Institute, Withington, Manchester, 20).

I would, of course, be very happy to discuss these trials with any clinician who is asked to treat patients with either of these conditions, and who feels they might be suitable for these trials.—I am, etc.,

R. S. ILLINGWORTH.

Children's Hospital, Sheffield, Yorks.

REFERENCES

1 Hellström, I., Hellström, K. E., Pierce, G. E., and Yang, J. P. S., *Nature*, 1968, **220**, 1352.
2 Bill, A. H., and Morgan, A., *Journal of Pediatric Surgery*, 1970, **5**, 111.
3 Wolff J. A., Krivit, W., Newton, W. A., and D'Angio, G. J., (1968). *New England Journal of Medicine*, 1968, **279**, 290.
4 Sullivan, M. P., *Cancer Chemotherapy Reports*, 1968, **52**, 481.

Emphysema in Coalworkers

SIR,—The correlation survey between the pathological, physiological, and radiological findings pertaining to emphysema in 247 coalminers and ex-miners reported by Dr. R. Ryder and others (29 August, p. 481) is of particular importance to the understanding of respiratory disability in coalminers. Their finding suggest that disability is related more to the emphysematous changes than to dust reticulation or simple pneumoconiotic changes. I would like to draw attention to the mounting evidence that fumes from shotfiring underground (nitrous fumes) can cause emphysema.

In 1960 a number of North Staffordshire coalminers were found to be suffering from acute or subacute pulmonary oedema after exposure to the fumes from a new type of explosive (Hydrox shells).[1] Follow-up studies over the past ten years of not only these men but also coalminers with a history of excessive exposure to the fumes from conventional powder shots, have shown a high proportion of miners exposed to fumes from shotfiring developed severe disabling emphysema.

Of the first 100 coalminers—mainly from North Staffordshire—all with a history of excessive exposure to either Hydrox or conventional powder shots, more than 70 men show clear physiological evidence suggestive of emphysema. Many of them are respiratory cripples and among those who have died there has been necropsy evidence of advanced emphysema as well. None of these 100 coalminers had progressive massive fibrosis. Twenty-two miners had radiological evidence of simple pneumoconiosis. However, many of these miners with simple pneumoconiosis together with evidence of both excessive fume exposure and emphysema were very seriously disabled, whereas the disability resulting from simple pneumoconiosis alone is seldom serious.[2] My impression is that emphysema in coalminers is associated with far more disability than simple pneumoconiosis, and the degree of emphysema relates more often to a history of excessive fume exposure than to the presence of punctate or micronodular opacities.

The above observations should be considered together with recent animal toxicological studies from America.[3 4] These and other investigations have shown that various animal species develop severe irreversible emphysematous changes, without acute toxic or acute pulmonary manifestations, some ten to twenty weeks after continuous inhalation of 15-25 p.p.m. NO_2 fumes. Though the nitrous fume hazard in British coalmines was investigated in detail between 1935 and 1942,[5 6] current data about this hazard to which coalminers may be exposed are sadly lacking. However, the miners referred to have, in all probability, been exposed to similar or higher concentrations of nitrous fumes; not continuously, as in the animal investigations, but intermittently over months or years.

I am not suggesting that all coalminers are more prone to develop emphysema. The 100 coalminers[7] mentioned in this letter were at special risk as regards exposure to fumes from shotfiring underground. The majority of these men were involved in development work in poorly ventilated areas; that is, contract workers engaged in hard heading, ripping, or crutting; overmen, shotfirers, or their assistants; or certain categories of face workers working in the return air roads. So far 20 of the 100 coalminers I have seen have been accepted as suffering from nitrous fume poisoning (Prescribed Disease No. 17).

It would be interesting to know how many of the 247 coalminers reported by Dr. Ryder and colleagues had evidence of both emphysema and an excessive exposure to the fumes from shotfiring. In particular, it would be of interest to know the emphysema state and the probable past fume exposure of the small group of 20 men they mention who had been refused compensation by the Pneumoconiosis Panels and who died within four years. Recently, I was asked to examine ten severely disabled coalminers who had been repeatedly refused compensation for pneumoconiosis. My own observations revealed no appreciable evidence of pneumoconiosis, but five of these ten men had advanced emphysema and a clear past history of excessive exposure to fumes from shotfiring.—I am, etc.,

M. C. S. KENNEDY.

Department of Respiratory Physiology, City General Hospital, Stoke-on-Trent.

REFERENCES

1 Kennedy, M. C. S., *Poumon et le Coeur*, 1960, **16**, 1139.
2 Gilson, J. C., and Hugh-Jones, P., *Medical Research Council. Special Report Series*, 1955, No. 290.
3 Freeman, G., Haydon, G. B., *Archives of Environmental Health*, 1964, **8**, 125.
4 Haydon, G. B., Davidson, J. T., Lillington, G. A., and Wasserman, K., *American Review of Respiratory Diseases*, 1967, **95**, 797.
5 Haldane, J. S., and Graham, J. I., *Interim Report on the Production of Nitrous Fumes during Shot-firing in Relation to Alleged Silicosis*, British Colliery Owners Research Association, 1935.
6 Graham, J. I., and Runnicles, D. F., *Medical Research Council. Special Report Series*, 1943, No. 244, p. 187.
7 Kennedy, M. C. S., *Nitrous Fume Poisoning, Coalminers, and Shotfiring*, in preparation.

Double-blind or Not?

SIR,—In your leading article (12 September, p. 597) you extol the merits of the double-blind trial. Yet at the same time you admit that a doctor's enthusiasm for a remedy may enhance its value to the patient "such factors may well affect the patient's clinical course." Thus in advocating the double-blind technique you are willing to negate the duty of a doctor to do his utmost for his patient.

It is true that you insist that a double-blind trial should be both necessary and ethical, and you will doubtless use this phrase glibly to evade criticism. But in fact these criteria can seldom be fulfilled, and advocates of "scientific medicine" who subject their patients to such experiments must