the treatment of gastric ulceration in Chinese subjects."

The purpose of my letter, however, was not to discuss the merits (or otherwise) of carbenoxolone but to share with readers some recent developments in the area of drugs in the treatment of gastric ulceration.—I am, etc.,

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¹ Fung, W. P., et al., *Annals of the Academy of Medicine, Singapore*, 1973, 8, 359.

Wartime Penicillin

SIR,—The Personal View by Dr. Terry Hamblin (10 August, p. 407) states that he is reminded "of the wartime doctor forced to watch children dying of pneumonia, while the penicillin to save them went to cure the troops' gonorrhoea." Such a reminiscence is wholly imaginary (in any case the author was rather young at the time) and should not be allowed to pass unchallenged. As a wartime consulting surgeon to the Central Mediterranean Forces I know that in the Italian campaign at least the use of both calcium and sodium penicillin was carefully controlled, as both, but particularly the latter, were in short supply. They were used exclusively for the wounded.—I am, etc.,

HAROLD EDWARDS

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Coroners and the Public Interest

SIR,—It does indeed seem hardly right that in the recent dental fatality you refer to (10 August, p. 374) the B.M.J.'s request for the depositions should have been turned down by the Westminster coroner. As a private individual I have seldom had such requests ignored or refused and have usually been sent a complete photocopy of the proceedings free of charge. But I have always made it clear that my purpose in requesting the information was to elucidate the causes of collapse in these cases with a view to preventing future tragedies.

It should, however, be realized that inquest proceedings in these dental fatalities are of little diagnostic value unless supplemented through direct personal communication with those in the surgery when the collapse occurred, as has been previously pointed out both by myself (3 February 1973, p. 293) and by Dr. M. P. Coplans and Mr. I. Curson (13 January 1973, p. 109). Too much credence also tends to be placed on the views of the expert witness. Whatever value it may have for the coroner a single unchallenged medical opinion, and one that in a coroner's court is not allowed to be challenged by anyone with medical competence, should not be accepted outside that court.—I am, etc.,

J. G. BOURNE

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Amitriptyline and Imipramine Poisoning in Children

SIR,—Dr. H. J. S. Matthew (29 June, p. 726) gives us the impression that he read only part of our letter (18 May, p. 386). We indeed gave the result of in-vitro experiments to substantiate our statement that the amount

of imipramine recovered in the dialysate is not so small as has been supposed. In fact, we had been stimulated to do the experimental work by the reports of others¹⁻³ and by our own experience⁴ of successfully treating by haemodialysis cases of massive overdose of imipramine—despite poor recovery of the drug in the dialysate. A most striking finding was that imipramine apart from being "cleared" by the dialysis membrane is rapidly taken up by the plastic material (polyvinylchloride) of the extracorporeal blood-line system. We suppose that this uptake, which after three hours of dialysis amounts to 60-70% of the drug's initial value, explains the poor recovery of imipramine in the dialysate in clinical dialysis. It will possibly offer a new therapeutic approach to the management of imipramine poisoning.

By refusing, on the one hand, to accept haemodialysis in the treatment of imipramine poisoning until its efficacy can be proved, and by ignoring, on the other hand, experimental evidence of the value of dialysis Dr. Matthew unfortunately has contributed to the confusion in the field of acute poisoning—a field in which he himself is obviously engaged.⁵ We would be sorry if this letter of ours should be considered only to enrich the folklore of poisoning.—We are, etc.,

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- ¹ Harthorne, J. W., Marcus, A. M., and Kaye, M., *New England Journal of Medicine*, 1963, 268, 33.
- ² Bland, D. C., and McQuaid, A., *Clinical Trials Journal*, 1966, 3, 425.
- ³ Bauditz, W., and Bartelheimer, H. R., *Archiv für Toxikologie*, 1970, 26, 133.
- ⁴ Asbach, H. W., et al., *Current Topics in Intensive Care Medicine*, 1974, 1, 212.
- ⁵ Matthew, H., *British Medical Journal*, 1971, 1, 519.

Methoxyflurane Nephrotoxicity

SIR,—May we make a couple of remarks further to your timely leading article on methoxyflurane nephrotoxicity (4 May, p. 239)? Firstly, we believe an important aspect of our recent study in man¹ relates to the differences in methoxyflurane metabolism and renal sensitivity to inorganic fluoride. These individual differences have been supported in an animal model.² Furthermore, enzyme induction by phenobarbitone causes a doubling of metabolism and thus increased nephrotoxicity.³ The widespread potential of drugs to cause enzyme induction makes it difficult to predict which patients may be induced. Thus our recommendation for dosage restriction¹ is purposely well below the toxic level to allow for the unforeseen addition of factors such as nephrotoxic antibiotics, enzyme induction, and individual variations in metabolism and renal sensitivity.

There is now much evidence that inorganic fluoride is the primary cause of the acute renal lesion. In an animal model doses of fluoride and oxalic acid approximating that which results from methoxyflurane anaesthesia were injected. At this dosage only inorganic fluoride produced renal functional and pathological abnormalities characteristic of methoxyflurane nephrotoxicity.³ The mechanism of fluoride nephrotoxicity is suggested by recent ob-

servations of graded reductions in renal medulla sodium concentration related to increased medullary inorganic fluoride concentration. These changes were associated with increased urine flow rate.⁴ Abolition of the hyperosmotic interstitium in the medulla would explain both the inability to concentrate and dilute urine observed in man.¹ However, it seems likely that fluoride may have quite widespread effects on different portions of the nephron.³—We are, etc.,

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- ¹ Cousins, M. J., and Mazze, R. I., *Journal of the American Medical Association*, 1973, 225, 1611.
- ² Mazze, R. I., Cousins, M. J., and Kosek, J. C., *Journal of Pharmacology and Experimental Therapeutics*, 1973, 183, 481.
- ³ Cousins, M. J., et al., *Journal of Pharmacology and Experimental Therapeutics*, 1974, In press.
- ⁴ Whitford, G. M., and Taves, D. R., *Anesthesiology*, 1973, 39, 416.

Cullen's Sign, Hepatoma, and α -Fetoprotein

SIR,—Drs. T. A. Mabin and M. Gelfand have recently reported (16 March, p. 493) the occurrence of Cullen's sign in two patients with an α -fetoprotein-positive, hepatocellular carcinoma. They suggest that in African patients this sign may be more commonly associated with primary hepatoma than with pancreatitis or ectopic pregnancy. In the last five years the only patient with Cullen's sign admitted to our department had a ruptured hepatocellular carcinoma. This patient was known to have cirrhosis of the liver and the presence of a haemorrhagic ascitic fluid positive for α -fetoprotein suggested the correct diagnosis. A more detailed description of this patient has been published.¹ Our data confirm the association between Cullen's sign and hepatocellular carcinoma and emphasize the importance of the determination of α -fetoprotein in both serum and ascitic fluid for establishing the correct diagnosis.—We are, etc.,

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Section of Clinical Immunology,
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- ¹ Levo, Y., Pick, A. I., and Ben-Bassat, M., *Harefuah*, 1973, 85, 161.

Therapeutic Starvation

SIR,—Dr. J. A. Innes and others reported (18 May, p. 356) results of long-term follow-up of therapeutic starvation which differ somewhat from our observations.¹ In contrast with the evaluation of Innes and co-workers we had a control group. Our study compared the long-term results among 50 obese south-western American Indians who underwent an initial fasting programme and subsequent conventional therapy with another group of the same ethnic composition matched for sex, age, initial weight, and diabetic status but receiving only low-calorie conventional management. For each of the seven years of follow-up an increasingly greater percentage of the fasted patients than of the control subjects weighed less than originally. The ultimate change in mean weight was statistically significant ($P<0.05$)

for the fasting group (-8.7%) but not for the conventional managed patients ($+0.5\%$). Proportionate weight loss was greater for men than for women, for the 30-49 years age group than for the younger or older subjects, for diabetics than for non-diabetics, and for persons whose weight exceeded 250 pounds (114 kg). The initial fasting programme improved the long-term results of conventional low-calorie dietary treatment for obesity.—We are, etc.,

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1 Sievers, M. L., and Hendrikx, M. E., *Health Services Reports*, 1972, 87, 530.

Frustrations in Community Paediatrics

SIR,—Though working in a completely different field to Dr. Terry Hamblin (10 August, p. 407) his feelings of frustration with the status quo echo mine. As a clinical medical officer in community medicine (my new title since reorganization) I have tried to give good service in the often forgotten but important area of community paediatrics. I looked forward to reorganization as a time of expansion with developmental paediatrics coming to the fore and the opportunity to carry out real preventive medicine among the babies and children of today who are, of course, tomorrow's adults.

Four months after reorganization I have seen my work virtually nullified as facilities such as special school places, nursery care, physiotherapy, and speech therapy services dwindle while waiting lists lengthen. Add to this very inadequate secretarial help, little or no equipment, and total administrative chaos where there are three doing one person's job is it surprising that morale among health visitors, district nurses, psychologists, and others as well as doctors is at an all-time low?—I am, etc.,

P. E. NEWTON

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Aspirin and What Else?

SIR,—I was interested to read the leading article (6 July, p. 5) entitled "Aspirin and What Else?" The writer has done a real service by speaking in favour of an invaluable drug, which it is fashionable recently to criticize for little or no valid reason. Not long ago in a series of cases aspirin was exonerated from causing analgesic nephropathy. Attempts have been made to hang this label round aspirin's neck without justification.

The leading article refers rightly to the large amounts of aspirin consumed by the population, which would be impossible were it not such a safe drug. It is interesting to consider the problem the other way round and pose the question: What other drug could be taken in equal amounts that would give rise to less trouble than aspirin? It could well be that some of the major haemorrhages supposedly caused by aspirin are in fact cases of von Willebrand's disease, which is hinted at in this article. They might also be due to thrombocytopenia or to purpura due to other drugs or senility—or

even to subclinical scurvy. Should such a patient start to bleed from any cause and feel unwell the drug he is likely to resort to is aspirin, which may then be blamed as the sole causative agent for the haemorrhage.—I am, etc.,

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Acute Myelofibrosis and Chromosome Damage after Procarbazine Treatment

SIR,—Acute myelofibrosis is an unusual variant of myelofibrosis characterized by an acute onset, anaemia, and thrombocytopenia. The spleen is not palpable and lymph nodes are not enlarged. A total of about 10 cases have been published. The course is rapidly progressive, death usually occurring within eight months after diagnosis.¹

Recently we have seen a 66-year-old patient who developed acute myelofibrosis. After being treated for six months with procarbazine (a hydrazine derivative) for Peyroni's disease he developed hypoplasia of the bone marrow. This was first attributed entirely to a direct toxic effect of the drug, but the bone marrow biopsy specimens showed that myelofibrosis was also partially responsible for the pancytopenia and the rapid deterioration of the patient's condition. Chromosome preparations of blood showed 28.8% aneuploid cells and 6.8% cells with structural abnormalities such as breaks, deletions, translocations, and dicentric in the metaphases (see fig.) but no marker chromosome was found. The patient died eight months after the appearance of the symptoms. Necropsy showed a slightly enlarged spleen (315 g) and a normal-sized liver. The histological findings showed extramedullary haemopoiesis. The penis showed the typical signs of Peyroni's disease.

In the present case three factors can be considered in relation to the chromosomal abnormalities: (a) the patient's age, (b) the procarbazine medication, and (c) the acute myelofibrosis. A relationship between increasing age and the development of chromosomal abnormalities is generally accepted.² In males of the age of this patient the relationship is expressed in a decrease of euploid cells to minimally 93.9%, with 3.4% of the cells showing structural defects (acentrics, dicentrics, and translocations). In our case both aneuploidy and structural abnormalities were present in a much higher frequency. Thus the patient's age could not be the sole cause of the observed abnormalities.

With regard to the induction of chromosomal abnormalities by procarbazine it should be mentioned that alkylating agents, as well as actinomycin and other cytostatic drugs, are known to induce chromosomal

damage.³ In cytogenetic studies with 1-methyl-2-benzyl-hydrazine (MBH), another hydrazine derivative, chromatid translocations have been observed in three types of mouse ascites tumours *in vivo*⁴ but no abnormalities have been found *in vitro*.⁵ Procarbazine has also failed to produce chromosomal damage in leucocytes *in vitro*. This does not exclude the possibility of *in vivo* activation, but positive evidence of *in vivo* mutagenic effects of procarbazine on chromosomes is lacking.

Previous studies on chromosomes in acute myelofibrosis^{6,7} have shown a high percentage of translocated chromosomes in peripheral blood and bone marrow cells. Chromosomal abnormalities in chronic myelofibrosis have also been reported.^{8,9}

Recently a carcinogenic effect of methyl hydrazine, a third hydrazine derivative, has been shown in Syrian golden hamsters¹⁰ and in mice.¹¹ Procarbazine is usually given in combination with other cytostatic drugs in Hodgkin's disease. This makes it very difficult to relate a myeloproliferative disease or carcinoma developing in a patient with Hodgkin's disease on a multiple drug regimen to procarbazine.

The possibility of the induction of acute myelofibrosis and chromosomal damage by procarbazine in our patient has to be considered seriously. The prescription of procarbazine in benign disorders such as Peyroni's disease¹² and Dupuytren's disease¹³ may well prove to involve more risk than is believed at present.—We are, etc.,

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- Lewis, S. M., and Szur, L., *British Medical Journal*, 1963, 2, 472.
- Brown, W. M., Court, et al., *Chromosome Studies on Adults* (Eugenics Laboratory Memoir No. XLII). London, Cambridge University Press, 1966.
- Hampel, K. W., *Internationale Zeitschrift für klinische Pharmakologie, Therapie und Toxikologie*, 1968, 1, 332.
- Therman, E., *Cancer Research*, 1972, 32, 1133.
- Rutishauser, A., and Bollag, W., *Experientia*, 1963, 19, 131.
- Mitus, W. J., Coleman, N., and Kiosoglou, K. A., *Archives of Internal Medicine*, 1969, 123, 192.
- Slyck, E. J., van, Weiss, L., and Dully, M., *Blood*, 1970, 36, 729.
- Engel, W., et al., *Humangenetik*, 1968, 6, 335.
- Kiosoglou, A. K., Mitus, W. J., and Dameshek, W., *Blood*, 1966, 28, 241.
- Toth, B., and Shimizu, H., *Cancer Research*, 1973, 33, 2744.
- Toth, B., *International Journal of Cancer*, 1972, 9, 109.
- Aboulker, P., and Benassayag, E., *Journal d'Urologie et de Néphrologie*, 1970, 76, 499.
- Saurm, M., and Lebeuf, M., *Bulletin de la Société Française de Dermatologie et de Syphiligraphie*, 1971, 78, 523.

Structural abnormalities (arrowed) found in blood cultures of patient with acute myelofibrosis: (a) chromatid breaks; (b) translocated D-chromosome (normal D-elements); (c) a dicentric chromosome (quinacrine fluorescence), probably a (4;10)-trans location.