Correspondence

Letters to the Editor should not exceed 500 words.

Keeping the Heart Going

SIR,—In your editorial entitled "Keeping the Heart Going" (19 June, p. 1566) we believe that incorrect emphasis has been placed upon the risks of the production of ventricular fibrillation by pacing on the T wave in patients who have returned to sinus rhythm.

All proved instances of ventricular fibrillation, in our experience, have occurred only with the epicardial system of pacing, and only in the immediate post-thoracotomy period.¹ It seems that the risk of ventricular fibrillation is highest when the threshold for the production of ventricular fibrillation is lowered from superficial myocardial damage caused by stitching the electrode on to the epicardium and from alterations in pulmonary ventilation due to the thoracotomy. Another factor was probably the unnecessarily high power of the earlier units.

Now that we use endocardial jugular systems for long-term pacing, thereby avoiding a thoracotomy, the risk of ventricular fibrillation must be greatly reduced, and we have never seen it in our experience of over 100 patients treated by endocardial pacing.—We are, etc.,

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REFERENCE

- ¹ Sowton, E., *Brit. Heart J.*, 1965, 27, 311.

Thrombosis and Anticoagulants

SIR,—Drs. L. Poller and Jean M. Thomson (5 June, p. 1475) state, "There is a clinical impression that fresh thrombotic attacks are more likely to occur shortly after anticoagulant treatment is stopped." The evidence is stronger than a mere impression. During the three months following withdrawal of anticoagulant therapy from 61 patients with cerebrovascular disease I observed an incidence of 3.2 cerebrovascular accidents per 100 patient-months, as compared with 1 during the time on therapy and 2 during the fourth to twelfth month after stopping treatment.¹

The possibility of this difference occurring by chance was 1 in 50.—I am, etc.,

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REFERENCE

- ¹ Marshall, J., *Circulation*, 1963, 28, 329.

Interstitial Pulmonary Fibrosis

SIR,—We were glad to see the article by Dr. Margaret E. A. Turner-Warwick and Dr. Deborah Doniach on auto-antibody studies in interstitial pulmonary fibrosis (3 April, p. 886). This appears to confirm our previously published findings,¹ details of which have now appeared in the May issue of the *Annals of the Rheumatic Diseases*.² In our series we excluded cases with clinical rheumatoid arthritis, but still found occasional unexpected radiological evidence of rheumatoid changes.

We were very interested in what Dr. Turner-Warwick and Dr. Doniach had to say about the correlation of the duration of lung symptoms with the presence of rheumatoid factor. We have been repeating the tests for rheumatoid factor on some patients now for over two years and have observed that where a change in the titre occurs it is usually to a less positive one; we have not yet come across a case which progressed to clinical rheumatoid arthritis as reported by Lee and Brain.³

We note that Drs. Turner-Warwick and Doniach found the antinuclear factor test positive in 28% of their cases. Only 12 of our 19 cases have been tested for A.N.F. These were done by Dr. Geoffrey Taylor, of the Manchester Royal Infirmary, and were all negative. This might perhaps be explained by a difference in sensitivity of the A.N.F. test as performed by different laboratories. The 4% of positive sera in the control group described suggests that the test as used by the authors is rather over-sensitive.

Fluorescent-antibody studies on post-mortem lung from one of our patients showed gamma-globulin lining the alveoli. The interpretation of this finding, which may merely represent terminal exudation of serum proteins, is, at the moment, impossible.—We are, etc.,

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REFERENCES

- ¹ Ward, R., and Stalker, R., *Lancet*, 1964, 2, 477.
- ² ———, *Ann. rheum. Dis.*, 1965, 24, 246.
- ³ Lee, F. I., and Brain, A. T., *Lancet*, 1962, 2, 693.

Screening Tests for Carcinoma of the Cervix

SIR,—I was very interested in Drs. C. B. Cameron and O. A. N. Husain's paper on 6-phosphogluconate dehydrogenase (12 June, p. 1529). In our own previous published series¹ we had three cases of carcinoma-in-situ, two of which were not associated with an elevated level of 6-phosphogluconate dehydrogenase, one of the cases not associated with an elevation of 6-phospho-

gluconate dehydrogenase showed micro-invasion, while the other did not. The one case associated with an elevated level showed micro-invasion. We have now collected nine cases of carcinoma-in-situ, of which five were not associated with an elevation of 6-phosphogluconate dehydrogenase. Of the five cases with no enzyme elevation, four of these showed micro-invasion.

It would seem that we are in disagreement as to how reliable a guide 6-phosphogluconate dehydrogenase is to the presence of invasive carcinoma. This may be due to a lack of a clear definition as to what groups of workers mean by invasive carcinoma. If the enzyme is to detect the "quiescent" from "incipient invasive," surely it must detect micro-invasion. It would be useful if one could clarify the meaning of the term "invasive" when used in reference to the use of 6-phosphogluconate dehydrogenase. If it can only reliably detect clinical invasive or stage I carcinoma, it has a very limited usefulness.

I feel that one must remember that the hexose monophosphate shunt may well be increased in malignant tissue, as has been shown,^{2,3} but where 6-phosphogluconate dehydrogenase is not rate limiting the enzyme will not necessarily be increased. This might certainly apply in the early stages of carcinoma-in-situ. Such a situation in which the enzyme became rate limiting would not necessarily develop at the same time as invasion of the stroma of the cervix.

An analogy can be drawn from McLean's⁴ work on the carbohydrate metabolism of the lactating mammary gland. During the early stages of lactation the yield of ¹⁴C-labelled carbon dioxide from glucose labelled in the carbon-one position with ¹⁴C is increased ninefold, while the increase in 6-phosphogluconate dehydrogenase activity is only two-fold. The proportionally greater increase in hexose-monophosphate-shunt activity compared with the increase in 6-phosphogluconate dehydrogenase is maintained throughout lactation. Surely a similar relationship may apply to carcinoma-in-situ and the early invasive stages of cervical carcinoma, and, though pathway activity is increased, the enzyme activity may not be.—I am, etc.,

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REFERENCES

- ¹ Muir, G. G., Canti, G., and Williams, D., *Brit. med. J.*, 1964, 2, 1563.
- ² Abraham, S., Hill, R., and Chaikoff, I. L., *Cancer Res.*, 1955, 15, 177.
- ³ Emmelot, P., Bosch, L., and Van Vals, G. H., *Biochim. Biophys. Acta (Amst.)*, 1955, 17, 451.
- ⁴ McLean, P., *ibid.*, 1958, 30, 303.

Deaths from Prolonged Ingestion of Phenacetin

SIR,—Although Spühler and Zollinger described "Primary Chronic Interstitial Nephritis" attributable to phenacetin in 1953,¹ it was not until January 1964 that Sanerkin and Weaver reported the first death

in this country due to prolonged ingestion of phenacetin.² Shortly afterwards, a second case was described by Jacobs in May 1964.³ Sanerkin and Weaver suggested that serious phenacetin nephropathy might be more common than is generally supposed, and their view is amply justified by the fact that I have found three cases of death due to chronic necrosis of the renal papillae within the space of four months from February 1965 to June 1965. Each of these three cases was associated with a history of prolonged ingestion of an analgesic compound containing phenacetin, and each case has shown no evidence of diabetes mellitus and no evidence of obstruction in the urinary tract.

Case 1.—On 22 February 1965 a young woman aged 35 was admitted to Southend General Hospital in coma and died before a clinical diagnosis could be made. At necropsy there was marked necrosis of the renal papillae. Histology confirmed chronic necrosis of the renal papillae, together with chronic interstitial nephritis. I recalled the observation of Sanerkin and Weaver that inquiries should be made in such cases regarding the ingestion of phenacetin, and the inquiries of the Coroner's Officer revealed that the deceased had taken approximately 16 tablets of Veganin (each tablet containing 250 mg. of phenacetin) each day over a period of six years.

Case 2.—Shortly after I had reported the first case described I received the histological sections of bilateral granular kidneys from a woman, aged 60 years, on whom I performed a necropsy on 2 February 1965. The kidneys showed chronic necrosis of the renal papillae and chronic interstitial nephritis. Macroscopically, the kidneys were uniformly grossly contracted and each weighed 40 g. Re-examination of the kidney fragments taken for histology showed naked-eye papillary necrosis. The cause of death was uraemia, and I subsequently questioned the patient's daughter, who told me that her mother had taken about 15 tablets of Codis (each tablet containing 4 grains (260 mg.) of phenacetin) each day over about six years.

Case 3.—In April 1965 a man aged 68 years was admitted to Southend General Hospital with anaemia and a high blood urea. Since he had a painful hip, I suggested that inquiries should be made regarding the taking of analgesics. Although the man was confused, he did admit to taking Codis every night for a long time. This patient died on 6 June. The Coroner's Officer found 120 Codis tablets in the deceased's home and ascertained that the man had obtained Codis tablets in consignments of 400 at one time. The acquaintances of the deceased knew that he had taken tablets regularly, but they were not aware of the nature of these tablets.

Sanerkin and Weaver reported Aschoff bodies in the myocardium of their case, and it is of great interest to note that the young woman aged 36 showed an acute myocarditis on histological examination.

A complete description of these three cases will be incorporated in a paper, but I think it is desirable to report as quickly as possible the occurrence of three deaths associated with the prolonged ingestion of phenacetin which have been seen within the space of four months in one hospital.

The present knowledge regarding phenacetin nephropathy has been reviewed recently in the *B.M.J.* (13 March, p. 673), and though there may be some doubt as to whether phenacetin itself is the active principle producing nephropathy, the circumstantial evidence is surely now strong enough to make it essential that Great Britain should follow the example of Sweden, where the sale of phenacetin has been restricted to medical prescription since February 1961.

I thank Mr. G. Y. Jerman, H.M. Coroner for the County Borough of Southend-on-Sea, for permission to publish the details of the first and third cases.

—I am, etc.,

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- Spühler, O., and Zollinger, H. U., *Z. klin. Med.*, 1953, 151, 1.
- Sanerkin, N. G., and Weaver, Corinna M., *Brit. med. J.*, 1964, 1, 288.
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Abuse of Digitalis

SIR,—I should like to comment on one point of Dr. H. D. Friedberg's letter (19 June, p. 1611) in which he warns against the indiscriminate giving of potassium to patients with digitalis intoxication. Amongst the evidence of potassium loss, which he postulates as a prerequisite for giving potassium, he includes estimation of serum levels. It should be appreciated, however, that potassium loss need not be reflected in a lowered serum level. Electrocardiographic features suggesting hypo- or hyperkalaemia agree well with serum-potassium concentrations only if the latter are markedly abnormal (below 2.3 or over 6.7 mEq/litre).¹ Whether the clinically relevant factor is the intracellular potassium concentration or the intra/extracellular gradient seems still controversial.² From the practical point of view the salient consideration is that a normal serum-potassium level should not be regarded as a contraindication to the exhibition of potassium, which may be life-saving, provided there are other reasons to assume potassium depletion and the compound is given with the necessary precautions.—I am, etc.,

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REFERENCES

- Dreifus, L. S., and Pick, A., *Circulation*, 1956, 14, 815.
- Holzmann, M., *Klinische Elektrokardiographie*, pp. 390 seq., 4th ed., 1961. Thieme, Stuttgart.

Carcinogenesis of Isoniazid in Mice

SIR,—Your editorial (12 June, p. 1508) on the carcinogenic action of isoniazid in mice and its "apparent" lack of effect in man treads dangerous ground. Similar special pleading could be used to ensure that no chemical (drug, food additive, or pesticide) was withheld from the environment until there was substantial evidence that it induced cancer in man. Results in animals are certainly not proof of carcinogenicity in man. However, experience tells us that (with one possible exception) every chemical known to induce cancer in man also gives rise to tumours in one or more species of experimental animal. It would seem prudent, therefore, in our present state of knowledge to regard all animal carcinogens as potentially dangerous to man.

The suggestion that "it seems highly improbable that so striking a sequel would not have been recorded" may be grossly misleading. Environmental carcinogens have a habit of remaining hidden unless they are actively sought out. The position is further complicated by the fact that the same

chemical effects different tissues in different species.¹ There is no certainty that if isoniazid induces tumours in man these will be leukaemias or carcinomas of the lung as in mice.

The clinician prescribing isoniazid has to balance the manifest value of the drug in combating tuberculosis against the possible danger. Nobody wishes such a valuable drug to be withheld, but until a careful and controlled analysis of the causes of death of patients treated with isoniazid is made² a rational assessment of the risk, if any, is impossible.—I am, etc.,

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REFERENCES

- Bonser, G. M., *Acta Un. int. Cancr.*, 1962, 18, 538.
- Roe, F. J. C., Boyland, E., and Haddow, A., *Brit. med. J.*, 1965, 1, 1550.

Transferable Antibiotic Resistance

SIR,—Your leading article under this heading (22 May, p. 1325) indicates that a new aspect of resistance to antibiotics could now be important, and although its implications have only so far been demonstrated in the laboratory, its relationship to clinical and field experience must be followed up.

There is one aspect of salmonella infection in calves in particular which could indicate that therapy in these animals is unlikely to have an effect on the human population. Infection of the calf with salmonella can occur in a number of ways—they can be infected by an excretor cow, infection can be transmitted through the faeces of another calf by contact with contaminated food or drinking-water, or even the milk fed to calves may contain the organisms. Although infection in calves can be a serious clinical entity, it has been found that the majority of recovered calves clear themselves completely of infection, so that after 12 weeks of age few of the original infected group remain carriers of the organisms.

Field¹ and his colleagues examined over 2,000 healthy cattle entering various abattoirs for slaughter, and salmonella organisms were isolated from 18 (0.8%). It seems likely, therefore, that, although young calves may develop clinical signs of salmonellosis and receive antibiotic therapy during the early stages of life, the number of those treated calves which will show evidence of salmonella when they go for slaughter at nine to ten months or later will be very small. It would appear, therefore, that the therapy of calves could reduce rather than increase the salmonella risk to human beings.

In the case referred to by Dr. Anderson where resistance was encountered following the use of ampicillin in the treatment of calves suffering from *Salmonella typhimurium*, 80 out of 130 calves in one house were passing the organisms, so that a very heavy infection was encountered. All 130 calves were treated with ampicillin at a therapeutic level of 8 mg./kg. for five days, and a dramatic response was obtained to therapy. In addition there was a marked reduction in the number of calves which were found to be passing salmonella organisms. Despite this