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CORRESPONDENCE

Correspondents are urged to write briefly so that readers may be offered as wide a selection of letters as possible. So many are now being received that the omission of some is inevitable. Letters should be signed personally by all their authors.

Kinetic Classifications of Antitumour Drugs

SIR,—In the design of modern combination drug schedules for the treatment of various malignant diseases attempts have been made to apply certain principles of cell cycle kinetics.[1-3] The success of this approach for advanced head and neck cancer has been reported by L. A. Price and others (5 July, p. 10). In the current literature there are two main kinetic classifications of antitumour drugs, which are essentially in agreement. Unfortunately, their terminology has caused considerable confusion. It is essential that a clear definition is made between the use of the terms "phase specific" and "cycle specific," as originally proposed by Bruce *et al.*,[4 5] and the later introduction by Skipper[6] of the terms "cell cycle stage specific" and "cell cycle stage non-specific." Basically "phase specific" agents are comparable with "cell cycle stage specific" agents, while "cycle specific" agents may be equated with "cell cycle stage non-specific" agents.

These terms may be defined as follows: (1) "Phase specific" or "cell cycle stage specific" agents exert their maximal effects on cells at a specific phase of the cell generation cycle. Examples are cytosine arabinoside, hydroxyurea, 6-mercaptopurine, methotrexate, vinblastine, and vincristine. (2) "Cycle specific" or "cell cycle stage non-specific" agents kill in all phases of the cell cycle to a similar extent but have less effect on cells out of cycle. Examples are actinomycin D, B.C.N.U., cyclophosphamide, daunorubicin, 5-fluorouracil, and melphalan.

The important point clinically is that the addition of agents from the second group to drug combinations will be additively toxic to the bone-marrow, whereas the addition of agents from the first group is less likely to increase the marrow toxicity of the combination, provided the drugs are given over periods not exceeding 48 hours. Since combination chemotherapy is being increasingly used we feel that an accurate knowledge of this classification is important in avoiding severe toxicity to normal tissues, and preliminary evidence already suggests that the clinical use of this classification permits the design of less toxic antitumour schedules without loss of therapeutic effect.[1 3 7-9]—We are, etc.,

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1 Price, L. A., and Goldie, J. H., *British Medical Journal*, 1971, **4**, 336.
2 Price, L. A., *Proceedings Third Lilly Symposium on the Vinca Alkaloids in the Chemotherapy of Malignant Disease*, ed. W. I. H. Shedden, p. 35. Altrincham, Cheshire, John Sherraff, 1973.
3 Atkinson, M. K., McElwain, T. J., *Proceedings Third Lilly Symposium on the Vinca Alkaloids in the Chemotherapy of Malignant Disease*, ed. W. I. H. Shedden, p. 77. Altrincham, Cheshire, John Sherraff, 1973.
4 Bruce, W. R., Meeker, B. E., and Valeriote, F. A., *Journal of National Cancer Institutes*, 1966, **37**, 233.
5 Bruce, W. R., *Canadian Cancer Conference*, 1966, **7**, 53.
6 Skipper, H. E., *National Cancer Institutes Monographs*, 1971, **34**, 2.
7 Price, L. A., *et al.*, *Proceedings International Symposium on Cancer of the Head and Neck*, Montreux, Switzerland, 1975.
8 Price, L. A., *et al.*, *British Medical Journal*, 1975, **3**, 10.
9 Goldie, J. H., and Price, L. A., in preparation.

Sick Sinus Syndrome

SIR,—It is interesting to note in the paper of Radford and Julian[1] that two of 19 patients who had implanted demand pacemakers for the treatment of the symptoms of sick sinus syndrome showed failure of inhibition—that is, reversion to inappropriate fixed-rate pacing. This incidence was higher in the sick sinus syndrome patients than in the remainder of the pacemaker clinic, which we have also observed. At least two mechanisms are possible in such cases: the amplitude of the sensed spontaneous QRS may fall to a level below the maximum sensitivity of the unit, or the frequency content of the spontaneous QRS may be discordant with the unit despite adequate amplitude.

Amplitude fall has been described in acute myocardial infarction.[2] The aetiology of sick sinus syndrome is more commonly thought to be coronary artery disease than is the case in patients requiring pacing for heart block.[1 3] Thus acute myocardial infarction may also be expected to be more common and may account for a critical fall in amplitude of the spontaneous QRS. The possibility of acute ischaemia without infarction causing a similar phenomenon has just been investigated in our laboratory and no fall in QRS amplitude was found (Sutton, unpublished data), suggesting that infarction rather than ischaemia must occur to produce failure of inhibition of a demand pacemaker as a result of reduced QRS amplitude.

A change in frequency content of the spontaneous QRS has also been observed during myocardial infarction[4] and associated with inappropriate fixed-rate pacing leading to ventricular fibrillation. We have recently investigated a patient with sick sinus syndrome[5] and a scalar QRS of 0·08 seconds' duration whose demand unit showed inappropriate fixed-rate pacing 72 hours after electrode insertion. Using a filter system sensed spontaneous QRS showed considerable energy at 70 Hz, a higher frequency than that usually found in patients with chronic block. Though this finding was not considered to explain the failure of inhibition fully it was thought that these patients may often have spontaneous QRS of frequencies