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

which are poorly matched to the demand unit. While a frequency mismatch between patient and pacemaker may be uncommon, a combination of this with borderline amplitude may explain the increased incidence of inappropriate fixed-rate pacing in sick sinus syndrome.

Thus, in summary, failure of inhibition of demand pacemakers may be expected to be more common in patients with sick sinus syndrome than in those with heart block because of a greater likelihood of myocardial infarction causing a fall in amplitude of the input signal to the pacemaker. Patients with sick sinus syndrome and a normal scalar QRS duration may have a sensed QRS in which the frequency distribution does not match the demand pacemaker.—We are, etc.,

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1 Radford, D. J., and Julian, D. J., *British Medical Journal*, 1974, 3, 504.
2 Sutton, R., Chatterjee, K., and Leatham, A., *Lancet*, 1968, 3, 645.
3 *British Medical Journal*, 1973, 2, 677.
4 Sutton, R., in *Cardiac Pacing*, ed. H. J. T. Thalen, p. 421. Assen, van Gorcum.
5 Norman, J., and Sutton, R., 10th International Conference on Medical and Biological Engineering (1973).

Indomethacin-aspirin Interaction

SIR,—We were interested in the paper by Dr. P. M. Brooks and others (12 July, p. 69), as their observations on the effect of aspirin on indomethacin plasma levels are similar to those of Champion *et al.*[1] but different to those of Jeremy and Towson,[2] and different also to our own.[3 4]

Jeremy and Towson found that aspirin given "concurrently" decreased indomethacin absorption. Champion *et al.* found "concurrent" administration of buffered aspirin (Bufferin) did not significantly decrease indomethacin absorption. Dr. Brooks and colleagues found that soluble aspirin (300 mg aspirin, 30 mg citric acid, 100 mg calcium carbonate, and 3 mg saccharin sodium) given concurrently did not significantly decrease indomethacin absorption. We found that pretreatment with, and simultaneous administration of, a buffered aspirin (Bufferin) increased the rate of indomethacin absorption.

Simultaneous administration of certain antacids with an acidic anti-inflammatory agent, naproxen, has been shown significantly to increase naproxen absorption (Segre *et al.*[5]). Ambre and Fischer[6] have shown that coadministration of a weakly acidic coumarin drug with magnesium hydroxide produced higher and earlier peak plasma levels than when the drug was given with water.

Possibly the concurrent use of buffered aspirin by Champion *et al.* and partially buffered aspirin by Dr. Brooks and colleagues accounts for the difference between their results and those of Jeremy and Towson, who apparently used a plain aspirin preparation. We have suggested that the increased rate of absorption of indomethacin found in our studies was due to the simultaneous administration of a buffered aspirin, perhaps causing local changes in gastric pH, thereby possibly increasing the dissolution rate of indomethacin. Perhaps Dr. Brooks did not administer the two drugs simultaneously; the results would be consistent with this.—We are, etc.,

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1 Champion, G. D., *et al.*, *Clinical Pharmacology and Therapeutics*, 1973, 13, 239.
2 Jeremy, R., and Towson, J., *Medical Journal of Australia*, 1970, 2, 127.
3 Garnham, J. C., *et al.*, *British Journal of Clinical Pharmacology*, 1974, 1, 178.
4 Garnham, J. C., *et al.*, *European Journal of Clinical Pharmacology*, 1975, 8, 107.
5 Segre, E., *et al.*, *New England Journal of Medicine*, 1974, 291, 502.
6 Ambre, J. J., and Fischer, L. J., *Clinical Pharmacology and Therapeutics*, 1973, 14, 231.

Sexual Life after Gynaecological Operations

SIR,—In his paper on sexual life after gynaecological operations (14 June, p. 608, and 21 June, p. 680) Mr. A. G. Amias suggests (in Part I) that "some of the poor results of hysterectomy can be directly attributed to the harmful effects of newspaper medicine," and also that "erroneous notions about the operation are fostered by opinionated and ill-informed comment in the lay press."

Might we be given references to support this? We normally expect to find such references to other published material drawn upon for learned articles; why should we not be given them when they derive from the lay press? I am particularly interested since for nine years I have been writing a regular medical column for the 6m. readers of *Woman's Own*—a far from negligible section of the lay press. So I can say with some confidence that this magazine certainly has not during this time produced "erroneous notions about the effects of the operation [of hysterectomy]." Nor, to my knowledge (obviously I take a close professional interest in the matter), have other women's magazines. On the contrary, I have, like my medical journalist colleagues, been at some pains to reassure readers that the operation certainly is not the end of the road as far as sexual satisfaction or enjoyable living is concerned, while at the same time making the point that neither is it a panacea for all ills—that it cannot, for example, cure an unhappy marriage or a clumsy lover—a point with which few doctors will disagree.

That there is a need for such articles in widely read popular magazines is undoubted. A very large section of the readership writes to us seeking "the reduction of fear, anxiety, and guilt by explanation and sympathy" which Mr. Amias says is so vital, yet which they fail to obtain from the people who perform their operations and look after them during recovery. May I therefore suggest to Mr. Amias that he has not perhaps studied the lay press of which he is so scornful quite as carefully as he might have done? Perhaps, on this occasion, we have been treated to "opinionated and ill-informed comment" published in the *medical* press.—I am, etc.,

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*** We showed Mrs. Rayner's letter to Mr. Amias, whose reply is printed below.—ED., *B.M.J.*

SIR,—Mrs. Rayner is welcome to leaf through the pages of "Doctor's Own," but would she kindly note that my words were aimed at practising doctors whose job it is to see and treat real patients face-to-face every day. They will not require references to remind them of countless people frightened by a "medical" item in the press—such a common experience that no one sets down chapter and verse every time it happens. The main purpose of my paper, however, was not to assail Mrs. Rayner or her paper but to urge the medical profession itself to explain as well as prescribe.

The need for this is underlined by the glimpse Mrs. Rayner affords us of her own prose style on the effects of hysterectomy. We are treated to an array of bland generalizations complete with the obligatory female snigger at "a clumsy lover," which no doubt impresses her 6m. proxy patients but not, I suspect, a worried woman with a problem unique to herself. The "need for such articles in . . . popular magazines" is very genuinely doubted by me. To satisfy Mrs. Rayner's yearning for a reference may I dedicate the following to her from an unimpeachable (lay) source: "The lady doth protest too much, methinks."[1]—I am, etc.,

A. G. AMIAS

1 Shakespeare, W., *Hamlet*, act III, scene 2, line 242, *c.* 1601.

Normal Sexual Response

SIR,—I have read Professor R. W. Taylor's interesting paper (7 June, p. 543) and wish to challenge large parts of its content as being erroneous, unsubstantiated (because it is largely not open to substantiation), and containing more that is fantasy than fact.

In the first place Professor Taylor makes the grievous but common error of divorcing "sexual activity," from "reproductive activity." This error is entirely fundamental as it relies on the hedonistic quality of the sexual act instead of the "whole thing" of reproduction, of which coitus is the physiological linking mechanism. The reproductive act is a whole physiology in its own right, commencing at spermatogenesis and oogenesis, linking at coitus, and terminating (for the male) in ejaculation and (in the female) at parturition.

Professor Taylor then makes the modern error of making the male and the female similar, as he states clearly in his opening paragraph. Nothing could be farther from the truth. The male and female are not homologous but heterologous—that is, "of equivalent nature, but different in sex." He then goes on to describe certain physiological responses—the erection of the nipple and/or clitoris during coitus—that are no part of my experience nor those of my patients. Quite frankly I don't believe a word of it. The clitoris is in fact a functionless vestigal remnant of an organ inappropriate and useless to its owner's sex (like the male nipple). Again, it is heterologous with the penis, not homologous with it, as is usually (but wrongly) believed.

Finally, without defining it, Professor Taylor implies that orgasm in the female is similar to, or homologous with, orgasm in the male. Again this is absurd. Orgasm is the climax of the sexual act. In the male this is characterized by the expulsion of the