Drug Antagonism

SIR,—In treating a lady aged 77 years with L-dopa for a long standing Parkinsonism, I was delighted with the results. Three months later, however, when the patient was on a dosage of 500 mg four times daily, I had occasion to put the patient on chlorthalidopoxide (Librium) in a dose of 10 mg three times daily. To my amazement she regressed within 24 hours to her original Parkinsonian state. The L-dopa was being continued at the time. As the only significant factor was the exposure of the patient to chlorthalidopoxide, I stopped that drug. Within 36 hours her progress was back to her previous state.

Since then I have come across other patients who have been tried on L-dopa but it has failed to have an effect on the disease. Two of these had a definite history of having been on chlorthalidopoxide or a combination drug at the time. I wonder how many "failed L-dopa" cases there are in Britain because of chlorthalidopoxide or combinations of this drug.—I am, etc.,

LEWIS MACKIE

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Halothane Hepatitis

SIR,—The current attack and defence of halothane in relation to liver toxicity by Dr. P. Sharpstone and others (20 February, p. 448) and Dr. T. H. S. Burns and Dr. M. W. Johnstone (29 May, p. 523) could lead, if you will allow it, to another generation of debate on the question of which is better for the patient: (1) one toxic drug which will produce all or nothing that the surgeon requires from anaesthesia, or (2) a multitude of drugs which can be given in non-toxic dosage to produce any or all of the facets of anaesthesia as required by the surgical conditions.

I am voicing no new thought but merely re-stating the opinions of very many authors during the last 25 years, too numerous to quote references in a short letter.

My opinion favours the multidrug technique—namely, induction by intravenous short-acting barbiturate, maintenance of sleep by unpolluted nitrous oxide and oxygen, intravenous analgesics as required, and manual assistance of respiration in the non- or partially curarized patient (mechanical in preference to manual ventilation in the fully curarized patient). May I remind readers that the above technique is applicable throughout the whole age scale from neonatal to geriatric patient.

May I also point out to anaesthetists that those who are skilled and experienced in multi-drug techniques are better equipped for work in intensive therapy units than those whose experience has been limited to the administration of a single drug.—I am, etc.,

DONALD BLATCHLEY

London W.4

Dental Emergencies

SIR,—The attention of my Committee has been drawn to Appendix VI of the Annual Report of Council on "Gaps in Medical Care" and the item on dental emergencies (*Supplement*, 8 May, p. 88).

It should be pointed out that with regard

to the final paragraph "The agonizing toothache touring London on a Sunday", the dental profession in Inner London have always been willing to provide an emergency service, subject of course to the availability of the necessary facilities such as premises, adequate ancillary staff, and appropriate payment for services.

This is, however, a national problem and when the question of emergency dental treatment has been raised by questions in the House of Commons successive Ministers of Health have stated in their replies that they do not consider that the provision of an emergency service is necessitated by demand. Therefore, until the policy of the Department of Health and Social Security is changed, it does not seem that such a service can be provided.

In any event, the larger hospitals in London have an emergency dental service.—I am, etc.,

IVOR DOMB

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London W.C.1

Atheroma: A New Hypothesis

SIR,—Correspondence (8 May, p. 335) following your detailed leading article (3 April, p. 2), suggests that there has been incomplete appreciation of some of the observations and arguments in our communication.¹

We request therefore an opportunity briefly to state some of the salient points and to emphasize certain important conclusions which appear to have been overlooked.

(1) It has proved possible to identify regions in the arterial system which experience relatively high or low wall shear.

(2) A distinction has been made between man and animals on "stable" diets, termed as being in a quasi steady state, and animals in which there has been abrupt marked change of diet, leading to sudden massive alteration of plasma levels of lipid, etc., termed as being in a transient situation.

(3) In man and certain animals in a quasi steady state, early atheromatous lesions have been shown to occur preferentially in regions known to experience low wall shear.

(4) This distribution is inconsistent with the hypothesis of mechanical damage to the arterial wall by the flowing blood; such a hypothesis implies the occurrence of lesions in high shear regions, which are spared in the quasi steady state.

(5) In certain animals studied in a transient situation, the early lesions have been shown to occur preferentially in regions known to experience high wall shear.

(6) It is shown in the communication how the diffusion of material, in either direction between the blood and the arterial wall, may be significantly influenced by wall shear. Shear facilitates diffusion by enhancing the concentration gradient, which drives the diffusion. In the case of diffusion from wall to blood, material which has diffused out is effectively swept away. In the case of diffusion in the reverse direction, shear makes the material more readily available, close to the wall.

(7) If the material composing early atheromatous lesions in man, and in animals in a quasi steady state, were diffusing from the blood to the wall, then it would accumulate preferentially in high shear regions. However, this distribution is not observed, hence

such a hypothesis is unacceptable. The distribution of early lesions in man and animals in the quasi steady state is instead consistent with the hypothesis that materials which have been synthesized in the wall are diffusing out from wall to blood. As expected, such diffusional efflux will be inhibited in low shear regions.

(8) The preferential accumulation of material in high shear regions in transient studies, the "mirror-image" of the quasi steady state distribution, is consistent with the diffusion of accumulating materials from blood to wall. The requirement is that the plasma levels of the accumulating material exceed the wall levels.

(9) Concerning the association of atheroma with hypertension, it is possible, as mentioned in the communication, that this is an illustration of the influence of wall shear on diffusion; blood velocity and arterial wall shear will be reduced if there is arterial dilatation associated with the elevation of blood pressure, and a normal flow rate. A similar mechanism might operate in syphilitic aortitis.

We are anxious to draw attention to one other aspect of our communication. We are particularly concerned that the proposed shear dependent mass transfer hypothesis should not be misconstrued as solely invoking wall shear, or haemodynamics, as affecting atherogenesis; the hypothesis links haemodynamics and biochemical factors. The communication points out that the evidence is consistent with wall shear being a major controlling factor in the rate of development of the early stage of the atheromatous process. However, it clearly further argues that the progression of the process will also be retarded by any means which reduces the accumulation of atheromatous material by influencing its rate of net production or diffusion. Manifestly this includes, in addition to wall shear, such local factors as the nature and availability of precursor, the rate of synthesis and degradation or removal of accumulating material, and such overall factors as the transport system for the materials in the body.—We are, etc.,

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¹ Caro, C. G., Fitz-Gerald, J. M., and Schroter, R. C., *Proceedings of the Royal Society, Series B*, 1971, 177, 109.

Oestrogens in Oophorectomized Women

SIR,—One aspect of the treatment of postmenopausal women using oestrogens for replacement therapy has as yet not been discussed in the literature. I have found continuous daily therapy of synthetic oestrogenic compounds similar to those given by Dr. S. Gow and Professor I. MacGillivray (10 April, p. 73) to be unacceptable to most "normal" postmenopausal women—that is, those with intact gonads. They develop a variety of clinical symptoms that suggest a cumulative action of the drug. In support of this view, in one patient the eosinophilic vaginal smears persisted six weeks after treatment had ceased. However, there is as yet no satisfactory scientific parameter on which this form of treatment can be based¹ and additional factors affecting the treatment

of postmenopausal women cannot be excluded—for example, stress, parity, and diet, also the persistence of enzymic activity in the ovaries^{2,3} or possibly in the uterine body.

I found that hysterectomized and oophorectomized women tolerate continuous treatment for a longer period than "normal" women. Intermittent therapy (thrice weekly) with all forms of oestrogenic substances is the treatment now used in this clinic. This therapy is based on empirical rules.

It would be a great asset if we could evaluate the menopause in a more precise manner to establish or confirm oestrogen lack as the cause of the various postmenopausal symptoms, and research is proceeding along these lines in this clinic.—I am, etc.,

GEOFFREY DOVE

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- ¹ Dove, G. A., Morley, F., Batchelor, A., and Lunn, S. F., *Journal of Reproduction and Fertility*, 1971, **24**, 1.
- ² Yin, P. H., and Sommers, S. C., *Journal of Clinical Endocrinology and Metabolism*, 1961, **21**, 472.
- ³ Novak, E. R., Goldberg, B., Jones, G. S., and O'Toole, R. V., *American Journal of Obstetrics and Gynecology*, 1965, **93**, 669.

Decline of the Necropsy

SIR,—The writer of your leader "Decline of the Necropsy" (24 April, p. 181) must surely have had his tongue in his cheek. In compliment to my clinical colleagues it should be made clear that the decline of the hospital necropsy has arisen since surgeons now send their specimens to the pathologist while the patient is still alive, and advances such as antibiotic therapy have converted necropsies on medical patients to studies in degeneration rather than infection.

As for "hack operations"—firstly, these frequently involve the honour and liberty of the subject; insurance, compensation, and legacies; and the reputation of one's colleagues. The same cannot be said of routine hospital necropsies.

Secondly, the principle envisaged by your writer could be extended further. Surgeons might be released from removing normal appendices in nursing homes, gynaecologists from performing routine abortions in private clinics, and physicians from fussing over private neurotics anywhere; these gentlemen would not then be "condemned to neglect more important hospital duties." Moreover there is no reason why a barrister should waste his valuable time attending court for a plea in mitigation in respect of some peculiarly revolting villain; solicitors should not be asked to conduct conveyancing; indeed one can continue ad infinitum.

Although admittedly I must now eschew the higher flights of chemistry and viro-bacteriology nonetheless a fundamental interest in haematology has not prevented me from considering myself a better "pathologist" because on occasion I look at sections and even make postmortem examinations. Indeed, I have come to the view that apart from the occasional (very occasional) surgical biopsy it is the coroner's necropsy alone in which the full skill, learning, and responsibility of the pathologist (as distinct from technical and scientific procedures) is seen to full advantage.—I am, etc.,

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Blue Valve Syndrome

SIR,—Your leading article "Blue Valve Syndrome" (8 May, p. 294) gives a rather incomplete picture of a condition which must, by now, be familiar to all pathologists interested in the heart. This is presumably the condition originally described in 1958 by Fernex and Fernex,¹ which is not uncommon in general hospital necropsy material, at least in this region.² Apart from the familial cases, this abnormality is seen mainly in the elderly and was found in 1% of necropsies on patients over 50 in this hospital.

It may well be that the condition proceeds to intractable heart failure, but this process probably takes many years. Histories of loud mitral systolic murmurs for 20 years before the final illness are not uncommon, and about a third of the cases that I have seen died of non-cardiac disease. Clinicians should be aware that mucoid degeneration predisposes to "spontaneous" rupture of the chordae tendinae as well as to endocarditis (both infective and non-bacterial thrombotic), but apart from these complications the mitral incompetence seems to be relatively well tolerated in the age group in which it is most often found.

Finally, may I protest against perpetuating this new term "blue valve syndrome". It seems to have been coined on the basis of a single case by authors³ whose review of the literature was confined to four American papers. In my experience of over 50 cases the colour is more accurately described as pearly-grey and emphasis on the occasional blue tinge would only add to the number which are incorrectly labelled rheumatic valvular disease. There is undoubtedly a place for a short, recognizable name for this comparatively common condition but Fernex and Fernex's original term "mucoid degeneration" is as short, and considerably more accurate than the term "blue valve".—I am, etc.,

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- ¹ Fernex, M., and Fernex, C., *Helvetica Medica Acta*, 1958, **25**, 694.
- ² Pomerance, A., *British Heart Journal*, 1969, **31**, 343.
- ³ McCarthy, L. J. and Wolf, P. L., *American Journal of Clinical Pathology*, 1970, **54**, 852.

Beta-adrenergic Blocking Drugs

SIR,—Your leading article on "Beta-adrenergic Blocking Drugs" (30 January, p. 243) raises some fundamental questions in this rapidly expanding field. The first is the distinction between intrinsic sympathomimetic activity and selectivity. There is good pharmacological evidence, in both animals and man, that practolol has a cardio-selective action. However, it is quite possible that an agent with intrinsic sympathomimetic activity could achieve a selective effect if sympathetic tone were higher in the heart than in the bronchial smooth muscle. It has been shown for agents with intrinsic sympathomimetic activity that where sympathetic tone is low, no change in function results, but where tone is high beta blockade occurs.¹ This is supported by the comparative study on airway function in asthmatics done by Connolly and Batten.² It would appear from their study that a drug does not have to be cardioselective to have less effect on airway resistance. In any case

whether drugs are cardioselective and/or have intrinsic activity, they may still provoke asthmatic attacks in sensitive subjects, and at present there is no beta-blocking drug which is free from side effect.

The leading article comments on a paper in the same issue by Sandler and Pistevos (p. 254). In this paper, considerable falls in blood pressure were seen after intravenous oxprenolol given for the treatment of dysrhythmias after myocardial infarction. It is unfortunate that oxprenolol was administered as bolus injections in amounts up to 6 mg. As the drug is approximately equipotent with propranolol, it is not surprising that a bolus injection might cause hypotension. The main therapeutic conclusion is that any effective beta-blocking drug when given intravenously should be injected slowly with extreme caution, as there is no known beta-blocking drug which would be free from the risk of provoking hypotension in such a situation.

Another major problem in evaluating the newer beta-blockers is obtaining an accurate estimate of their beta-blocking potency versus propranolol in man. This is especially true of the cardioselective drug practolol, where the standard test, which is prevention of isoprenaline tachycardia, becomes difficult to interpret.

In the therapeutic situation practolol has been evaluated extensively in angina. In only one published study so far³ where practolol has been compared with propranolol in the same patients it seems that practolol was approximately one tenth as potent as propranolol. In the same symposium, Prichard⁴ also stated that the maximum effect that could be obtained in angina with practolol was less than that which could be obtained with propranolol. Therefore it becomes difficult to interpret the frequency of side-effects such as bronchospasm and heart failure, because part of the apparent therapeutic advantage of practolol may be due to the fact that it is being used in doses which do not produce the same degree of beta blockade.

It would seem to me that there is a strong case for doing double-blind cross-over trials in angina, using the newer drugs oxprenolol and practolol, in an attempt to assess their relative potency, and side effects due to beta blockade, such as hypotension and bronchospasm.—I am, etc.,

J. W. PATERSON

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- ¹ Dollery, C. T., Paterson, J. W., and Connolly, M. E., *Clinical Pharmacology and Therapeutics*, 1969, **10**, 765.
- ² Connolly, C. K., and Batten, J. C., *British Medical Journal*, 1970, **2**, 515.
- ³ Prichard, B. N. C., Lionel, N. D. W., and Richardson, G. A., *Postgraduate Medical Journal*, 1971, **47**, Supplement, p. 59.
- ⁴ Prichard, B. N. C., *Postgraduate Medical Journal*, 1971, **47**, Supplement, p. 112.

Breath-activated Aerosol

SIR,—I should like to report a small study of a new breath-activated, pressurized inhaler. This device (Autohaler) has been developed in an attempt to overcome the problems which some patients experience in synchronizing the delivery of a metered dose of bronchodilator drug with the beginning of a deep inspiration.¹ To obtain maximum benefit from a pressurized inhaler, the dis-