Correspondence

Letters to the Editor should not exceed 500 words.

Endomyocardial Thickening

SIR,—The interesting report by Dr. M. Black and Dr. J. M. Fowler (13 March, p. 682) is a useful reminder that the endocardium can sometimes become thickened and fibrotic in obscure cases of cardiac failure. It is a pity, therefore, that the patients were described as cases of "endomyocardial fibrosis," because this term, although it is anatomically correct, was originally given by workers at Kampala, Uganda, to a peculiar disease which had been found in Africans.¹ As more has become known about this disease it has been found to have reasonably consistent clinical, epidemiological, and morbid-anatomical characteristics.² It differs significantly from the two other diseases which occur in Africa, in both of which the endocardium may be thickened in patches—Becker's "cardiovascular collagenosis,"³ and the "African cardiomyopathy" which has been reported from South Africa⁴ and Southern Rhodesia,⁵ and is commonly seen in Nigeria and other West African countries. Dr. Black and Dr. Fowler seem rather too ready to group together all cases of obscure heart disease with patchy thickening of the endocardium under the general title of endomyocardial fibrosis. Davies⁶ showed that this could not be done.

Although the term "endomyocardial fibrosis" is merely descriptive and anatomical, it should be used with restraint: if it is not, extravagant ideas may be allowed to develop that endomyocardial fibrosis—as described originally at Kampala, and lately at Ibadan, Nigeria—has a "world-wide

distribution." Dr. Black and Dr. Fowler are prepared to believe that this is so, but what evidence there is suggests that it is not.

Let this letter might appear to be dominated by a semantic problem, I should like to suggest that a study of the geography of obscure forms of heart disease, and of endomyocardial fibrosis in particular, is very important in attempting to understand their aetiology. Although future work may possibly show that the endomyocardial fibrosis described from Uganda is not solely a tropical and a subtropical disease, it is remarkable that it is relatively common in the hot and wet regions of the Tropics, where it has been described often in spite of meagre medical services, and yet is exceedingly rare in other parts of the world where medical services are much more advanced. Just as a possible aetiology of Burkitt's tumour was suggested from a study of its distribution in Africa, so the agent which causes endomyocardial fibrosis may be revealed by studying the geographical distribution of this peculiar cardiac disease.—I am, etc.,

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Combining the Antidepressant Drugs

SIR,—Dr. William Sargent in his letter to you (23 January, p. 251) states that he believes "it is generally safe" to combine antidepressants like phenelzine (Nardil) and desipramine (Pertofran) "in proper dosages with great benefit to many patients." One recalls his previous letter on "Antidepressant Drugs and Liver Damage" (28 September, 1963, p. 806) in which he casts doubt on "the dangers supposed to arise from combining certain groups of" antidepressives, and the "supposed deaths from liver damage" attributed to iproniazid (Marsilid). Would he argue that there is no causal relationship between lung cancer and smoking because not all those who smoke develop a bronchial carcinoma?

Recently in Perth, Western Australia, a woman aged 29, who had for some months been treated with phenelzine 15 mg. three times per day, was put on imipramine (Tofranil) 25 mg. by intramuscular injection three times per day. After the third dose she developed hyperpyrexia, a generalized rigidity, and became comatose. Antidepressants were withdrawn, and with treatment she recovered.¹ Fatal hyperpyrexia in the

course of antidepressant therapy has been reported by L. W. Bowen,² and Stanley and Pal.³ Professor Ayd mentioned several earlier and similar cases as long ago as 1961.⁴

There is evidence of the therapeutic value of these antidepressant drugs,⁵ but it is essential also to know the risks entailed by their use in order to weigh these risks against the probable benefits. Accordingly we report that two deaths have occurred in Perth in patients given the usual therapeutic doses of amitriptyline (Tryptanol) who then took alcohol.⁶ One of us (M. F. L.) undertook experiments to discover whether amitriptyline (0.017 mg./10 g. body weight) potentiates the effects of ethyl alcohol. Mice were used because they have to date given reliable prediction of interaction of drugs with ethyl alcohol in man. These experiments indicated that amitriptyline potentiates the effect of alcohol on the righting reflex (possibly increasing the hazard caused by those who "drive and drink") and that it greatly increases the mortality caused by large doses of alcohol. Several cases of adynamic ileus have been reported in association with amitriptyline therapy⁷⁻¹⁰ as well as cases of urinary retention followed by death from ascending pyelonephritis with imipramine therapy,¹¹ precipitation of latent schizophrenia,¹² etc.

May we submit that the time has come for a critical reappraisal of antidepressive drug therapy? Perhaps such drugs should be reserved for the treatment of mild cases of depression, for there is much evidence that modified E.C.T. is still the best, the least time-consuming, and the most economical treatment for moderate-to-severe endogenous depressions.^{13 14}

Surely combinations of antidepressant drugs are best avoided, and, in our view, the amitriptyline group should not be prescribed for elderly patients who may develop ileus. Patients should be advised not to take alcohol when on these drugs, pending further investigation.—We are, etc.,

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Vertebral-artery Thrombosis and Oral Contraceptives

SIR,—The success and the resultant popularity of oral contraceptives have been marred a little of late by the suspicion that the "pill," as it has come to be known, may occasionally be responsible for some undesirable side-effects. The most serious incidents, a number of which were reported lately,¹⁻⁴ are related to vascular thromboses to which women taking oral contraceptives may become liable for reasons adduced by Egeberg and Owren.⁴ It is such an incident, which ended fatally, I wish to report.

A 26-year-old mother of two children, who always enjoyed good health in the past, had been taking Anovlar (4 mg. of norethisterone acetate and 0.05 mg. of ethinylloestradiol) for about six months. She was admitted as an emergency with a history of sudden onset of headache over the vertex, which was followed by pain in the right side of the neck, numbness in the right side of her face, and sensation of coldness in the right halves of her lips. She was subjectively giddy, and when trying to climb the stairs was ataxic. Then she fainted, and on coming round she had diplopia and hyperacusis in both ears. These two symptoms persisted and by the time she arrived in hospital she began to feel numbness and "pins and needles" in the left leg and arm.

On examination she was fully conscious and orientated, but was rather disturbed and hiccupping. There was evidence of right lateral rectus paralysis and of complete facial weakness of the lower motor neurone type on the same side. The left corneal reflex was depressed and sensation over that side of the face was impaired. Hearing to whisper was depressed on the right side and Weber was lateralized to the left. The left upper limb was weak and its tone slightly increased. There was left hemihypoesthesia and no impairment of vibration sense. Deep reflexes were brisker on the left side and all abdominal reflexes were absent. The left plantar was extensor and the right one was equivocal. The rest of the neurological examination was negative. There was no cardiac abnormality and the blood-pressure was 120/80 mm. Hg. A diagnosis of vascular "episode" giving rise to progressive lesion of the right paramedian area of the pons was made. She soon developed a complete left hemiplegia and dysarthria, and gradually became deeply unconscious. This was associated with generalized increase in tone and opisthotonos, and at this stage both plantars became extensors. She then gradually regained consciousness.

A lumbar puncture yielded clear fluid at a pressure of 80 mm. of water. There were six red blood cells per c.mm. in the cerebrospinal fluid, the protein content of which was 29 mg./100 ml. Later there was a further temporary lapse of consciousness following which she was transferred to the Midland Centre for Neurosurgery. The angiography which was performed there was interpreted as being indicative of a block in the lower part of the basilar artery. She developed a spastic tetraplegia and her condition deteriorated, although she retained consciousness almost to the end. She died after a total illness of over seven weeks.

Post-mortem examination showed an antemortem thrombus firmly embedded in the last inch of the right vertebral artery. No other obstruction was found and other cerebral vessels were normal. There was softening in the right side of the pons.

Search of the recent medical literature failed to reveal a single instance of spontaneous thrombosis in the intracranial part of the vertebral artery in a young person. In the instance here reported there was no history of injury and no abnormality was found in the arterial tree of the brain apart from the thrombotic lesion. It is possible, therefore, that the contraceptive which this patient had been taking predisposed her to the fatal thrombosis.

I am grateful to Dr. A. M. Nussey, under whose care this patient was admitted, for permitting me to publish this case, and for his advice. Also I should like to thank Dr. J. S. McKinnell for his report on the necropsy findings.

—I am, etc.,

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Lymecycline

SIR,—If one, reasonably, assumes that the figures reported in the Tables of the paper by Dr. A. Pines and his colleagues (12 December, p. 1495) are the true ones and that some disagreements with those quoted in the text (p. 1496, 2nd column, line 9; 27 instead of 21; p. 1497, 1st column, lines 4 and 8 from bottom: 60 instead of 69 and

60 instead of 66) are just due to misprints, the following facts are worth mentioning:

(1) The statement that "lymecycline was superior to tetracycline hydrochloride in tolerance" is supported only by the evidence set out in Tables IV and V, according to which side-effects were seen in 13 out of 66 patients during treatment with lymecycline and in 23 out of 69 patients during treatment with tetracycline.

This difference in frequency is said to be significant at the 5% level of χ^2 . In fact the χ^2 value calculated on the 2x2 table

Treatment	Side-effects	No Side-effects	Total
Lymecycline ..	13	53	66
Tetracycline hydrochloride ..	23	46	69

is 2.548 with correction for continuity (clearly appropriate to samples of this size) and 3.208 without correction: both values are lower than 3.841, significant value at 5% level for 1 degree of freedom, and the former one does not even reach the 10% level. Therefore the difference between the two groups in incidence of side-effects is not significant, unless the authors have any other reason, not stated in the paper, in favour of the alternative hypothesis.

(2) The paper reports that "the [side-] effects described were mainly nausea, vomiting, and a burning sensation in the mouth, throat, or abdomen." In an attempt to evaluate the hypothesis of a better tolerance of lymecycline, it thus seems reasonable to take into account the incidence of "previous gastric condition" in the two groups of patients initially treated with the two antibiotics, as reported in Table I, viz., 4 out of 41 in those treated with lymecycline and 13 out of 49 in those treated with tetracycline hydrochloride. If the per cent. incidence of "gastric condition" before treatment is compared with the side-effects during treatment, one obtains:

Treatment	Previous Gastric Condition	Side-effects
Lymecycline ..	10%	20%
Tetracycline hydrochloride ..	27%	33%

There is no need for any statistical analysis to see, from these figures, that any clinical impression of a better tolerance to lymecycline may be entirely due to the fact that the "gastric condition" of the patients treated with tetracycline hydrochloride was worse since the beginning of treatment. Statistically, it can be demonstrated that the heterogeneity of the two groups of 41 and 49 patients with respect to their "previous gastric condition," although not significant as pointed out by the authors, is nearer to significance than the heterogeneity of the two groups of 66 and 69 patients with respect to their side-effects.

In conclusion, the differences in incidence of side-effects observed during treatment with lymecycline and with tetracycline hydrochloride may be explained by either chance alone or the pre-existing "gastric condition" or both. The hypothesis that any of the two treatments is better tolerated cannot thus be taken as demonstrated.—I am, etc.,

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** We regret the misprints referred to by Dr. Stratford. His letter has been shown

to Dr. A. Pines and his colleagues, who reply as follows:

When first treatments with lymecycline or tetracycline hydrochloride are compared, there is a definite significant difference in side-effects at the 5% level of χ^2 :

Incidence of Side-effects With First Treatments

	Tetralysal	Tetracycline	Total
Side-effects ..	7	20	27
No side-effects ..	34	29	63
Total ..	41	49	90

When the incidence of side-effects with either drug is calculated according to which drug was given first, the significance is at the 2% level of χ^2 :

First Treatment			
Either Drug Showing	Tetralysal	Tetracycline	Total
Side-effects ..	8	22	30
No side-effects ..	33	27	60
Total ..	41	49	90

Side-effects were more likely to occur when tetracycline hydrochloride was given first. Six of the nine later treatments were instances where side-effects occurred with the second drug following side-effects already encountered with the first drug:

Side-effects by First and Second Treatments

	Drug A		Drug B		Total
	Side-effects	No Side-effects	Side-effects	No Side-effects	
Drug A					
Side-effects ..	4	—	4	2	10
No side-effects ..	—	17	9	10	36
Drug B					
Side-effects ..	2	1	7	—	10
No side-effects ..	1	16	—	17	34
Total ..	7	34	20	29	90

Thus it seems that these six patients were particularly sensitive to tetracycline types of drugs and that there was a carry-over of the hypersensitivity from the first to the second drug. Lymecycline suffers in comparison because those patients first showing side-effects with tetracycline were more likely to show side-effects with lymecycline than vice versa. Dr. Stratford is correct in that the difference in total side-effects, including those switched, is not significant: the asterisks on 13 and 20 were due to a misunderstanding by one of us. To test the significance of the total incidence of side-effects would be inappropriate and misleading because of the above points.

Out of 30 patients who had side-effects with initial treatment, six had previous gastric conditions: 11 out of 60 with no side-effects had previous gastric trouble. Obviously there is no correlation of side-effects with previous gastric conditions.

Side-effects were more frequent with tetracycline hydrochloride than with lymecycline: neither chance nor pre-existing gastric conditions could be the explanation.—Ed., B.M.J.

* All P values have been computed with χ^2 (using Yates's correction for continuity in two-by-two tables) testing the null hypothesis.