types suggests that these facts are causally related. Coughing, a regular accompaniment of smoking in many people, may be a contributory factor in the detachment of ciliated epithelium.

These may be some of the "other possible factors" postulated by Dr. Glass to which smokers are more liable than non-smokers.—I am, etc.,

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Antibiotic Combination in Staphylococcal Infections

SIR,—A recent *in vitro* study¹ has shown the advantages of kanamycin and cephalothin or kanamycin and methicillin in combination against methicillin-resistant strains of *Staphylococcus aureus*. It was suggested that combination therapy be initiated against all methicillin-resistant strains while awaiting the outcome of the appropriate *in vitro* tests. Others have recently extended this recommendation and have suggested combination therapy in all serious staphylococcal infections even before it is known whether or not the infecting strain is methicillin-resistant.^{2,3} Before accepting this latter recommendation, especially since infections with methicillin-resistant strains are uncommon, it is important to know whether antagonism occurs when the combination is used against methicillin-sensitive strains of *Staph. aureus*.

Ten strains of methicillin-sensitive coagulase-positive *Staph. aureus* isolated from clinical specimens were used to investigate this possibility. Pure cultures were obtained by transfer of single-colony isolates. Routine disc sensitivity tests were done on all strains according to the method of Bauer and Kirby.⁴

Routine tube dilution minimal inhibitory tests (M.I.C.) were performed simultaneously, comparing kanamycin, cephalothin, and kanamycin/cephalothin. All tests were made of an inoculum of 10^7 organisms per ml. using tryptose-phosphate broth; tubes were read for macroscopic turbidity after 18 hours of incubation. Subcultures of 0.01 ml. of all clear tubes were made on to agar plates; the concentration of antibiotic which yielded no growth was considered to be the minimal bactericidal concentration (M.B.C.), although this test guarantees only that there are less than 10^2 survivors/ml. With two strains, dynamics of growth were studied

in the presence of antibiotics singly and in combination, with counts of colony-forming units made at 0 time, 1, 2, 4, and 24 hours. The rate of killing over the first four hours is thought to be particularly important in evaluating antibiotic combinations.^{5,6}

The patterns of antibiotic resistance and the M.I.C. and M.B.C. are shown for all 10 strains in the Table. On the basis of minimal bactericidal concentrations, the combination was of some advantage in five cases, but in the others was only as effective as cephalothin used alone. Nine of the 10 strains were killed in 0.5 $\mu\text{g./ml.}$ of each of the agents in combination.

Growth curve characteristics of strain 2576 are shown in the Figure and illustrate some synergism. The second strain tested in this fashion showed no difference in the rate of killing between the combination and cephalothin or methicillin used alone.

Against a large inoculum of a methicillin-sensitive strain of *Staphylococcus aureus*, the kanamycin/cephalothin combination, in concentrations easily attainable in the blood stream, shows greater bactericidal activity than either agent used alone.

In these studies of 10 methicillin-sensitive strains of *Staph. aureus* there were no evidences of antagonism. Since cephalothin and kanamycin are bactericidal in different ways, it would be predicted that there would be no antagonism and that synergism might occur.^{5,6}

On the basis of these tests, it seems reasonable to consider using the kanamycin/cephalothin or kanamycin/methicillin combinations when confronted with a life-threatening staphylococcal infection. If disc tests show sensitivity to methicillin, the kanamycin may be stopped, although some experts prefer the combination in endocarditis, regardless of sensitivity to methicillin. If

the infecting strain is methicillin-resistant, the combination could be used until appropriate *in vitro* tests confirm its efficacy.—I am, etc.,

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Dysmenorrhoea

SIR,—Mr. A. Davis (11 November, p. 357) supports Muir's hypothesis that dysmenorrhoea results from myometrial ischaemia due to hypercontraction of the uterus, but this view is not supported by the studies of Wilson and Kurzrok.¹ Severe ischaemia of the uterus often occurs during the early hours of the puerperium and is not associated with pain.^{2,3} Pain indistinguishable from dysmenorrhoea can be provoked in all women by means of chemical, mechanical, and electrical stimulation of the cervix uteri. A simple and precise method for measuring the critical electrical stimulus which when applied to the cervix causes pain was described in your columns.⁴ If these results are confirmed a foundation for dysmenorrhoea will be established.

A lowered threshold to pain arising in the uterus does not mean, as Mr. Davis suggests, that "it's all up here." He is well aware that but a small proportion of signals arising in the periphery reaches consciousness, for there are many "censors" in the nerve pathways concerned. The operation of these censors can be affected either way by impulses both from the higher centres and from the periphery. Further, the actual cells in the apperception area can similarly be affected. There is no need to stress the point that it is the destination of the signals which determines their message. Experimental studies^{5,6} show that the effects caused by stimulating the hypogastric nerve vary with the hormonal state of the subject.

Such a concept would explain why the same individual can have both painful and painless periods, the degrees of intensity of the pain, why women complaining of severe dysmenorrhoea may have painless periods when admitted to hospital for investigation, as well as the undoubted benefit derived from the varied and multitudinous methods of treatment, ranging from exercise, hygiene, and spinal manipulation to presacral neurectomy. It would also explain why any and all of these treatments may prove unavailing.—I am, etc.,

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Minimal Inhibitory (M.I.C.) and Minimal Bactericidal Concentrations (M.B.C.) Obtained with Ten Methicillin-sensitive Strains of *Staphylococcus Aureus* against Kanamycin, Cephalothin, and the Kanamycin/Cephalothin Combination

Strain	Antibiogram*	Kanamycin		Cephalothin		Kana/Ceph	
		M.I.C. $\mu\text{g./ml.}$	M.B.C. $\mu\text{g./ml.}$	M.I.C. $\mu\text{g./ml.}$	M.B.C. $\mu\text{g./ml.}$	M.I.C. $\mu\text{g./ml.}$	M.B.C. $\mu\text{g./ml.}$
2994	P	32	32	<0.25	0.5	<0.25/0.25	0.5/0.5
3024B	Ch, T	64	128	<0.25	0.5	<0.25/0.25	0.5/0.5
3076	P, E, S, Ch, T	64	64	<0.25	4	<0.25/0.25	4/4
2572	P, Ch, T, K	>128	>128	<0.25	0.5	<0.25/0.25	0.5/0.5
1893	P	32	32	0.5	1.0	<0.25/0.25	0.5/0.5
2529B	P, S, T	16	16	<0.25	0.5	<0.25/0.25	<0.25/0.25
2024	P, T	128	128	<0.25	0.5	<0.25/0.25	0.5/0.5
2560	Sensitive to all	32	64	<0.25	0.5	<0.25/0.25	<0.25/0.25
2562	P	32	32	<0.25	1.0	<0.25/0.25	0.5/0.5
2576	P	16	64	<0.25	1.0	<0.25/0.25	0.5/0.5

* Refers to antibiotics to which the strain is resistant on testing with high concentration discs according to the method of Bauer et al.⁴. Antibiotics tested were: Penicillin G (P), Erythromycin (E), Streptomycin (S), Chloramphenicol (Ch), Tetracycline (T), Kanamycin (K), Cephalothin (C), and Methicillin (M).