early postoperative feeding when safe and practicable.

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¹ Bevan, J C, and Burn, M C, *British Journal of Anaesthesia*, 1973, **45**, 115.

² Kelnar, C J H, *British Medical Journal*, 1976, **1**, 751.

³ Thomas, D K M, *British Journal of Anaesthesia*, 1974, **46**, 66.

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Mechanism of action of antiallergic drugs

SIR,—We should like to reply to the criticisms of our hypothesis on the mechanism of action of antiallergic drugs (3 April, p 820) made by Mr C J Vardey and Dr I F Skidmore (7 August, p 369). They refer to the lack of correlation between the ability of antiallergic drugs to inhibit cAMP phosphodiesterase and their ability to inhibit the anaphylactic release of histamine.¹ However, the enzyme was isolated from human lung tissue (mostly non-mast cells) while histamine was released from rat peritoneal mast cells. Thus we would argue that the lack of correlation between effects in different tissues from different species is neither surprising nor evidence against the hypothesis. Indeed, there is good reason to believe that cAMP metabolism is controlled differently in the two tissues. Isoprenaline, a well-established stimulant of adenylate cyclase, potentially inhibits histamine release from human lung² but inhibits histamine release from rat peritoneal cells only weakly, if at all.^{3,4} Evidence on the mechanism of action of antiallergic drugs is, therefore, difficult to interpret unless it is obtained using pure mast cell preparations from a single species.

The time courses of inhibition of histamine release by antiallergic drugs and phosphodiesterase inhibitors show less disparity than Mr Vardey and Dr Skidmore suggest because studies so far published have been incomplete. In fact, cromoglycate, doxantrazole, and theophylline show close similarity in the time course of inhibition of histamine release.⁵

The lack of synergism between β -adrenergic receptor stimulants and antiallergics in rat mast cell studies is, again, not surprising because of the relative insensitivity of these cells to β -agonists.

There is, as yet, no additional evidence to support the hypothesis that antiallergics inhibit histamine release by maintaining a high level of cAMP within the cell which in turn inhibits calcium transport across the cell membrane. However, it is not contradicted by the work quoted by Mr Vardey and Dr Skidmore.

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¹ Fullerton, J, Martin, L E, and Varley, C J, *International Archives of Allergy and Applied Immunology*, 1973, **45**, 84.

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Thyrotoxic vomiting

SIR,—Dr F D Rosenthal and his colleagues (24 July, p 209) draw attention to this symptom and suggest that it is a rare feature of severe thyrotoxicosis.

Six months ago I saw a patient similar to their reported cases who had thyrotoxicosis with severe and persistent vomiting. Since then I have recorded the incidence and severity of this symptom in new cases of thyrotoxicosis and have been surprised to find that of eight consecutive patients, only two had no nausea or vomiting. One patient complained of a constant feeling of nausea, two patients had occasional vomiting, up to twice weekly, and three suffered from frequent vomiting, particularly on rising in the morning. There was no correlation with other symptoms, physical signs, or biochemical results.

It is my impression that nausea and vomiting are common symptoms of thyrotoxicosis, unrelated to severity and possibly caused by a direct effect of thyroid hormones on the medulla. In all my cases these symptoms were rapidly abolished by carbimazole.

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Lung cancer and smoking: Is there proof?

SIR,—You state in your leading article (21 August, p 439) that I "must be virtually alone, however, in asserting that the usual hypothesis is 'a catastrophic and conspicuous howler.'" This latter phrase, quoted by *The Times* correspondent,¹ is in fact not mine: it was written by R A Fisher and published in the *BMJ* in 1957.² The full quotation reads: "I do not relish the prospect of this science [statistics in medical research] being now discredited by a catastrophic and conspicuous howler." I should add that I share Fisher's apprehension.

Other inaccuracies in your leading article are too numerous to be discussed adequately in a short letter, but perhaps you will permit me to mention two of them briefly. The claim that the secular trends in the sex ratio of mortality from lung cancer "provide no support for the constitutional view" is based on an unpublished, superficial, and incomplete examination of the evidence. You also state that, on the constitutional view, the enormous secular increase in lung cancer rates has to be attributed entirely to improvements in diagnosis. This is incorrect. In the first place constitutional and (smoking) causal hypotheses are not mutually exclusive. But if it could be established that sex-specific and age-specific death rates from lung cancer have genuinely increased in the course of the century we should need to consider at least the following additional hypotheses, singly or in any combination: (1) the frequency of genes predisposing to lung cancer has increased; (2) mortality from competing causes of death—for example, from fatal infectious diseases genetically associated with lung cancer—has diminished; and (3) extrinsic carcinogens unconnected with smoking, such as oncogenic viruses, have made an increasing impact.³

As I see it,³ two main difficulties of interpretation plague this field: (1) the phenomenon of self-selection: smokers, ex-smokers, and non-smokers and even Mormons and Seventh Day Adventists are not selected randomly from

the general population; (2) the often demonstrated unreliability of the clinical diagnosis of lung cancer. Clinical diagnostic error has changed from drastic underdiagnosis at the beginning of the century to overdiagnosis in recent years.³ Although studies of monozygotic twins discordant for smoking habits are not entirely free from ambiguities of interpretation, they provide the best available control in human populations of the genetic variable.³ I am pleased to see that you show a greater awareness of interpretational problems than, for example, the 1971 report of the Royal College of Physicians, *Smoking and Health Now*.

The clinician takes responsibility for the advice he gives his patients, but in turn he must rely on the opinions of experts whose duty it is to analyse the evidence as objectively and rigorously as possible. Many studies, including the crucial ones of twins, show that smoking helps to cause prolonged cough and morbidity from chronic bronchitis. In my view this causal connection must be regarded as established. However, in the case of cigarette-associated cancers I have given reasons³ for doubting the orthodox (causal) interpretation. You argue that the public expression of such doubts might encourage some people to smoke cigarettes. But if the orthodox causal hypothesis is incorrect the feelings of guilt and anxiety induced in habituated cigarette smokers by anti-smoking campaigners are unfortunate and unnecessary. Because of the difficulty of drawing up an accurate balance sheet it is, as you say, of more than academic importance that we get our interpretations as nearly correct as possible.

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¹ Hodgkinson, N, *The Times*, 18 August, 1975, p 2.

² Fisher, R A, *British Medical Journal*, 1957, **2**, 298.

³ Burch, P R J, *The Biology of Cancer. A New Approach*. Lancaster, Medical and Technical Publishing, 1976.

Out-of-hours calls in general practice

SIR,—I note that Dr M G F Crowe and his colleagues (26 June, p 1582) deal initially with a large proportion of requests for out-of-hours calls by rendering advice over the telephone. In their article they point out that they have the advantage over the deputies in the Sheffield study¹ that they usually know the patients already and have immediate access to their NHS records. Even this advantage does not, in my view, provide a "fail-safe system." All general practitioners know that in assessing incoming telephone calls requesting visits one has to take into account the possibility of a failure by the caller to mention some factor which is medically significant but to a layman insignificant. There is also the possibility of human error on the part of the doctor in failing to ask one crucial question, the answer to which may totally alter the doctor's decision as to whether to visit or not. Equally, in giving "advice over the telephone with the proviso that the patient could ring again if the recommended treatment did not help" the doctor has to take into account infinitely varying reactions of callers to this advice. Some patients are put off too long; others ring again before the treatment has had time to work; yet others misunderstand the message and interpret it as meaning "do not worry; nothing is wrong."

A number of cases of this kind regularly appear before service committees and in the