provoked bleeding demanding curettage thus allows early diagnosis and may explain why, in the study of Smith *et al.*⁴ deep myometrial invasion was found in 1% of cases but in 18% of controls with endometrial carcinoma.¹⁰

As it is unlikely that retrospective studies will be able definitively to establish the relationship of oestrogens to endometrial carcinoma prospective surveys to elucidate this problem fully are urgently needed. In our prospective studies we have performed pretreatment curettage and then monitored the endometrial response to unopposed oestrogen and combined oestrogen/progestogen regimens, curettage being repeated at intervals during therapy. In a double-blind, randomised, placebo-controlled crossover study endometrial hyperplasia was diagnosed in 23% of patients after unopposed oestrogens but in no patient after placebo.¹¹ In further longitudinal studies^{12,13} extending for nearly three years dose-dependent hyperplasia was diagnosed in 13-36% of patients during unopposed cyclical oestrogen therapy, atypical hyperplasia developing later than, and perhaps from, cystic glandular hyperplasia. The urinary and plasma oestrogen levels during therapy¹³ were in and above the range associated with the mid-cycle ovulatory peak (indicating that the term "hormone replacement therapy," much used in your article, is inappropriate). The development of both cystic glandular and atypical hyperplasia, in view of the oestrogen levels, is not illogical and we find that, in order effectively to relieve menopausal symptoms oestrogens have to be given at dosages which promote endometrial hyperplasia.

Our final disagreement with your article relates to the value of progestogens in preventing endometrial hyper-stimulation. Although endometrial carcinoma has been reported during sequential therapy,¹⁴ such anecdotal reports should not be included in a serious debate. Combination oestrogen/progestogen therapy (as in oral contraception) has not resulted in an epidemic of endometrial cancer, and progestogens per se are destructive to endometrial cancer.^{15,16} In our studies^{12,13} the subsequent addition of a progestogen for five or seven days each calendar month not only reversed oestrogen-induced hyperplasia to normal endometrium in all cases but also reversed pretreatment hyperplasia. Furthermore, hyperplasia was diagnosed in only one (2%) of patients solely given sequential therapy. Progestogens therefore act in a protective role. It is probable that this protective effect is exerted in at least two ways. Progestogens induce regular endometrial shedding and in our studies the absence of vaginal bleeding during unopposed oestrogen therapy was associated with a higher incidence of endometrial hyperplasia. In the premenopausal woman progesterone lowers the endometrial levels of both oestradiol and progesterone receptors¹⁷ and increases the oestradiol dehydrogenase levels.^{18,19} Oestrogenic stimulation of the endometrium which is mediated through the receptor mechanism is therefore depressed. Also, the enzymatic conversion of the more active intra-uterine oestrogen, oestradiol, to the less active oestrone is accelerated and these actions of progesterone may be synergistic. Our preliminary data suggest that similar mechanisms operate in the postmenopausal woman given progestogens.²⁰

We believe that the addition of a progestogen will protect against endometrial hyper-stimulation. Whether the progestogen should be given sequentially or continuously is still to be determined.

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- ¹⁸ Pollow, K, *et al.*, *Journal of Endocrinology*, 1975, **67**, 131.
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SIR,—I think you were unwise to come down so heavily on one side of a very controversial issue (23 July, p 209). A first leading article in the *BMJ* carries considerable weight and might be expected to review both sides of a controversy before reaching a final conclusion one way or the other.

Like most retrospective studies, the reports which you cite could all be criticised on one ground or another and usually on several grounds. There is the problem of the criteria for histological diagnosis of cancer; the problem of the adequacy of the hospital records on which most of the studies were based; the problem of why the oestrogen cases were started on oestrogens in the first place; the problem of the adequacy of the control series; and the question whether oestrogen-treated patients are more likely, because of bleeding, to be diagnosed. No doubt other correspondents will draw your attention to this and other weaknesses in the case against oestrogens.

Of more importance, however, is the fact that many comparable studies have failed to establish any association between oestrogen therapy and endometrial cancer. You could not be expected to review this voluminous literature in extenso, but you would surely have been wise at least to quote the paper by Lauritzen,¹ who presents both sides of the case but cites many studies which have failed to show the association in question. It is an unfortunate feature of the news media in general that bad news seems to carry more weight than good news, but this selective attention to sensational positive reports at the expense of less exciting negative reports should surely not be allowed to penetrate the scientific field.

This is not to deny that there may exist an association between oestrogen therapy and endometrial cancer which, if it is established, is surely likely to be dose-related and attributable to continuous rather than intermittent therapy, as has been shown in rabbits.² The proper stance for the profession at the present stage is surely neither to accept nor to reject the hypothesis which you enunciate so clearly

in your leading article but to use oestrogens (the clinical value of which you seem to under-rate) in the smallest dose required to achieve their purpose, to keep the patients under close supervision, and to collect as much information as possible on this important issue. We must hope that gynaecologists and pathologists in Britain are already mounting retrospective studies comparable to those carried out in the United States. There are already plans afoot to organise a multicentre prospective trial in the United Kingdom, but it will probably be many years before this yields any results. In the meantime a concerted effort to obtain endometrial aspirates from postmenopausal women who have been on oestrogens for a prolonged period might yield important information relatively quickly.

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¹ Lauritzen, C, *Clinical Obstetrics and Gynecology*, 1977, **4**, 145.

² Meissner, W A, Sommers, S C, and Sherman, G, *Cancer*, 1957, **10**, 500.

The understanding of chronic bronchitis

SIR,—Much ink has been spilt on the definition of chronic bronchitis, and an article by Dr C M Tinker in your latest insert (Intake No 50) sums up the present position. However, the emphasis of his article and its omissions introduce an element of mysticism into the subject. My own interest in the subject is as an ex-chest physician and present geriatrician who now sees fair numbers of both respiratory cripples and also very old chests in non-bronchitics.

A signal omission in Dr Tinker's article is the recognition of the degree of pulmonary fibrosis in many bronchitic lungs. On x-ray the lung fields may show numerous small "reticular" opacities in the periphery, especially in the middle and lower zones. Years ago, at the Brompton Hospital, Professor Lynne Reid demonstrated peribronchiolar abscesses in serial projections of microscopic sections of such lungs, and it must be the fibrotic scars of such abscesses that are seen on x-ray. The lung damage so caused will cause bronchiolar distortion, ventilatory disturbance, and broncho-pulmonary shunting. Dr George Simon used to say that one should always be prepared to study a chest x-ray with a hand lens, but a seeing eye is all that is needed to detect these lesions. With regard to the presence of bronchospasm, this disappears in chronic respiratory insufficiency and the sputum often becomes permanently mucoid. Thus no benefit is obtained from antibiotics or bronchodilators. Incidentally, it is unfortunately not true that all these respiratory cripples are smokers or ex-smokers.

The second factor which needs more emphasis is emphysema. As a geriatrician I frequently see emphysematous lungs in sensible old people who deny bronchitis, some but not all of whom are smokers. It appears to me that the elastic fibres in the lung ultimately fatigue with coughing—and all of us cough occasionally. In bronchitis the process occurs early, in non-bronchitic smokers rather later, and last of all in non-bronchitic non-smokers. This must equate with the known fall in forced expiratory volume which occurs with aging.

"Chronic bronchitis" is shorthand for a disease complex which changes as the individual ages. It may be largely asthmatic in childhood and adolescence, quiescent in early adult life apart from exercise-induced asthma and distended lung fields on x-ray, then with a period of both spasm and recurrent infection in middle life, and finally with varying symptoms of chronic respiratory insufficiency. The blue bloater and pink puffer are only different ends of the same spectrum, presumably related to the individual's tolerance of carbon dioxide retention. The amount of clinical or radiological emphysema may be very small, and it would be more rational to label such cases "chronic restrictive lung disease" rather than "chronic obstructive airways disease" when fibrosis is severe.

If medical students could think of bronchitis along such lines, more effort might be devoted to controlling infection in middle life, and less to the futile use of steroids and bronchodilators when the lung has become a bag of scar tissue.

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Antibiotics in respiratory infections

SIR,—There are certain statements in Dr I Gregg's article dealing with antibiotics in respiratory infection (Intake No 50, published by Abbot Laboratories Ltd, insert in *BMJ*, 9 July) which we feel require comment.

(1) "*Almost* (our italics) all strains of *Streptococcus pyogenes* have remained sensitive to penicillin." To our knowledge resistance to penicillin in this species has *never* been reported.

(2) The suggestion that ampicillin is more effective than benzylpenicillin against most strains of *Staphylococcus aureus* implies that ampicillin is active against penicillin-resistant strains of this organism. Resistance to penicillin in *Staph aureus* is dependent upon the production of β -lactamase, which is equally active against ampicillin, the use of which therefore could not possibly be indicated in the treatment of infections due to such strains.

(3) The suggestion that amoxycillin seems to be superior to ampicillin in the treatment of exacerbations of chronic bronchitis because of its ability to penetrate into bronchial secretions has never been put to the test in a controlled clinical trial and must therefore be regarded as conjectural.

(4) The author surely does not think that *Strep pyogenes* and *Staph aureus* are the commonest causes of bacterial pneumonia.

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Stability of measles vaccine

SIR,—Drs M D Coulter and B M Jones (9 July p 120) question the stability of measles vaccine and its distribution through the post. As part of the MRC Measles Vaccine Trial 1964 the stability of the vaccine in field conditions was investigated by this institute. Samples of vaccine used in clinics were returned to us in the post at the end of each

session. Vaccine was received from the 32 areas throughout England and Wales. Of the 45 samples tested, only one vial had a serious loss of potency. Samples "lost in the post" and "left out of the refrigerator" still retained adequate potency to stimulate immunity. However, vaccine does lose potency if not properly handled and we would like to join with Professor J A Dudgeon (2 July p 44) and Dr J K Anand (11 June p 1533) in stressing the importance of complying with the instructions issued by the manufacturer.

Drs Coulter and Jones quote Dr Christine L Miller (11 June p 1532) as saying "10% of vaccinated children have lost immunity 12 years later." I would not make this deduction from any of Dr Miller's statements. The protection rates reported for the trial ranged from 84% to 95% throughout the first five years.¹ If 90% of vaccinated children are still protected after 12 years it would indicate that the initial protection has been well maintained.

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Standards and Control,
London NW3¹ Measles Vaccine Committee of the Medical Research
Council, *Practitioner*, 1971, **206**, 458.

ECT on television

SIR,—It seems that once again we have been subjected by the media to a biased piece of viewing, part of the ever-popular establishment knocking game in which professional expertise is denigrated. I refer to the "Panorama" programme of 18 July on electric convulsion therapy (ECT), an eminently safe and very widely used procedure which has saved countless lives (since depression, the treatment of which is its main function, is the chief cause of suicide). Of the countless grateful sufferers all over the world whose illness has been alleviated by ECT what were we shown? One woman with, I suspect, a long-standing neurosis who blamed her poor concentration (a common symptom of such an illness) on one course of ECT some years before—a youth who had suffered from an acute psychotic breakdown after taking LSD and had been effectively treated by ECT but complained that he hadn't signed a consent form.

Sensible people must surely realise that well-trained professionals are not going to continue administering a treatment for many years if it does not work. What would be the point? What a pity the BBC producer could not realise the same—but perhaps that would not have been so newsworthy. One could cite the same argument against appendicectomy—that not everyone does well afterwards and some have the operation unnecessarily. The example of psychiatrists' "foolishness" cited in the programme—that insulin coma therapy had now been discontinued despite its claim that it had been useful over many years—showed the lack of understanding of the subject very clearly. Insulin coma therapy was indeed effective but somewhat hazardous, and was replaced eventually by electroplexy for the very reason that the latter proved to be safer and more effective.

The Society of Clinical Psychiatrists is shortly to publish a report on "Public Relations in Psychiatry." As chairman of the study group which produced this report I have frequently been appalled by the way the mass media are able to present such biased pro-

grammes and are allowed to get away with it. Just who does advise them? We are strongly advocating the setting up of a public relations officer for psychiatry who can give official guidance and rebuttals where necessary to such bodies, but perhaps to hope that such advice would be heeded is vain.

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Diagnosing familial hypercholesterolaemia in childhood

SIR,—Dr D J Betteridge and his colleagues draw attention (9 July, p 127) to their paper¹ on the regulation of 3 hydroxy-3-methylglutaryl coenzyme-A reductase (HMG CoA reductase) activity in type II hyperlipoproteinaemia. We were aware of the article, which reports on measurement of the enzyme activity in fresh leucocytes from first- and second-degree relatives of an index patient with familial hypercholesterolaemia (FH), but we consider that their data failed to support the hypothesis that the diagnosis of FH can be made by measurement of HMG CoA reductase activity in the system they used.

This hypothesis can be tested only by identifying affected individuals by independent criteria. In the family studied there were no obligate heterozygotes, but the index patient and his brother (II₅), having tendinous xanthomata and hypercholesterolaemia, had a very high probability of being affected. In the remaining live members of the family serum cholesterol concentration was the only independent criterion available. The sister (II₄) had a serum cholesterol (8.58 mmol/l (331 mg/100 ml)) elevated more than two standard deviations above the expected mean for her age and therefore had a high probability of being affected. Only one of the offspring (III₁₁) of the probable heterozygotes tested (III₆, 7, 8, 9, 10, and 11) had a serum cholesterol above the upper limit quoted by the authors (5.9 mmol/l (228 mg/100 ml)).

In order to test the association of FH with HMG CoA reductase activity and to determine the discriminating power of the test it is essential to examine only the first-degree relatives of known heterozygotes all of whom have the same 1 in 2 chance of carrying the mutant gene. Thus of the individuals likely to be affected three (II₇ and 5 and III₁₁) had incomplete suppression and one (II₄) had normal enzyme regulation. Of the first-degree relatives of heterozygotes likely to be unaffected (II₃, I₁, II₆, 7, 8, 9, and 10) four had normal enzyme regulation (I₁, II₃, III₅ and 6) and three had incomplete suppression (III₈, 9, and 10). Only in the index patient and his relatives II₅ and III₁₁ were the cholesterol level and enzyme activity concordant in indicating a heterozygote. There appears to be no more than a chance association between the enzyme activity and cholesterol levels in this family.

Dr Betteridge and his colleagues mention in their letter that they have recently found discordance between HMG CoA enzyme activity and serum cholesterol levels in a man heterozygous for FH and suggest that this could be explained by heterogeneity of the mutant gene causing FH. This explanation cannot be used to explain the discordance in