Thorax 1990;45:982-984

LETTERS TO THE EDITOR

BCG vaccination of schoolchildren in England and Wales

We read with interest the article by Drs V H Springett and I Sutherland (February 1990;45:83-8) and would like to support from our own experience in Avon their conclusion that when the school BCG scheme is stopped the consequences will not be "epidemiologically disastrous" for young adults.

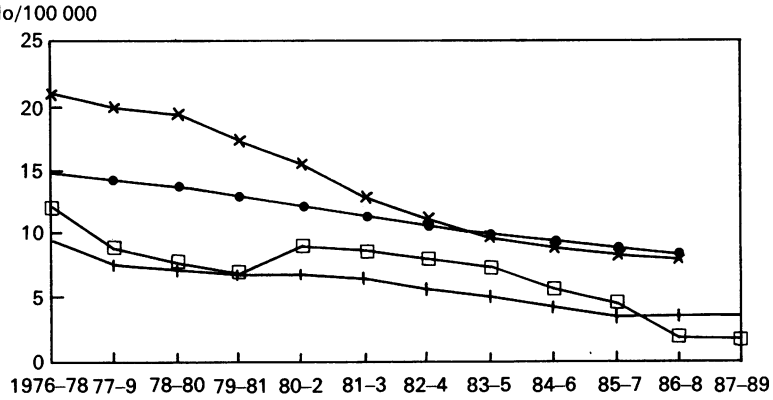
Tuberculosis notification rates in Avon have always been lower than the rates for England and Wales and thus it was one of the first area health authorities to discontinue routine BCG vaccination in children in 1976, except for at risk neonates. Recently we have reviewed all cases of tuberculosis in Avon (except Bath) since 1976 from the notification register and Hospital Activity Analysis. The accompanying graph shows respiratory tuberculosis notification rates for all ages and all (respiratory and other) tuberculosis notifications for the 15-24 year age group in England and Wales and Avon. In view of the wide fluctuation in yearly rates among the 15-24 year age group in Avon due to very small numbers, we have calculated all the rates as a three year rolling average from 1976-8 to 1987-9. As expected, the notification rates among the 15-24 year age group in Avon—that is, the group most affected by the policy change—show a slight increase in 1980-2 and subsequent slowing of the rate of decline. On the whole, however, it would appear that cessation of routine BCG vaccination in 1976 had no significant deleterious effect on the tuberculosis notification rate in Avon.

No routine tuberculin skin tests have been performed in Avon since 1976, so we propose to do a tuberculin sensitivity survey in children aged 12-13 years to determine the current natural conversion rate in Avon.

The results will give a measure of the transmission of the infection in the community and provide us with valuable information at a time when there is considerable debate about the future policy of the schools BCG vaccination programme.

SYED AHMED
W J POULSOM
Frenchay Health Authority, Frenchay Common, Bristol BS16 1ND

1 Office of Population Censuses and Surveys. *Key population and vital statistics.* Series VS: Nos 3-15. London: HMSO, 1976-88.
2 Office of Population Censuses and Surveys. *Statistics of infectious diseases.* Series MB2: Nos 3-15. London: HMSO, 1976-88.



Tuberculosis notification rates/100 000 population: respiratory tuberculosis at all ages and all tuberculosis at 15-24 years from 1976-8 to 1987-9. ●——● All ages, England and Wales; ×——× 15-24 years, England and Wales; +——+ All ages, Avon; □——□ 15-24 years, Avon.

Concentrations of cefixime in bronchial mucosa and sputum

Dr D R Baldwin and colleagues (May 1990; 45:401-2) have presented data on concentrations of the new oral cephem antibiotic cefixime in blood, sputum, and bronchial biopsy material. The concentrations of cefixime were below the assay limit in 13 of the 28 sputum specimens tested, but higher ones were noted in the bronchial biopsy specimens. Because of these findings, the authors believed that cefixime might have a role in the treatment of acute exacerbations of chronic bronchitis.

We have studied 20 patients with an acute exacerbation of chronic bronchitis, 10 receiving 200 mg cefixime twice daily for seven days and 10 a 400 mg dose once daily. Sputum was cultured before, during, and after the treatment; concentrations of cefixime were measured microbiologically in serum and purulent sputum at standard times after the first drug dose. Mean peak serum concentrations of 2·5 mg/l after 200 mg and 6·2 mg/l after 400 mg were found, though one patient had no antibiotic in the blood despite supervised administration. Four patients given 200 mg and two given 400 mg showed no detectable concentrations in the sputum; the mean sputum concentrations in the other patients were 0·08 and 0·23 mg/l. Penetration from blood to sputum averaged just under 4%. The MIC_{90} values for *Streptococcus pneumoniae* rose from 0·25 mg/l (before treatment) to 4 mg/l (after treatment) and those for *Branhamella catarrhalis* from 0·06 to 0·5 mg/l.

Five of the 10 patients given 200 mg doses and four of those receiving 400 mg cefixime were assessed as treatment failures. *S pneumoniae* was responsible in four patients, *B catarrhalis* in three, and *Haemophilus influenzae* combined with *B catarrhalis* in one other. The patient with no cefixime in blood or sputum also represented a treatment failure. No unwanted drug effects were noted.

Our conclusion therefore differs from that of Dr Baldwin and his colleagues. In view of the above findings and our previous unfortunate experiences with cefuroxim axetil[1] and cefaclor[2] we believe that no oral cephalosporin has yet been found which is suitable for patients with acute purulent exacerbations of chronic bronchitis, for the following reasons: (1) poor or irregular absorption, (2) poor penetration into infected sputum, (3) instability in the presence of (*B catarrhalis*) β lactamases, (4) development of relative resistance during treatment, and (5) the high cost in relation to the results achieved.

F P V MAESEN
R COSTONGS
Department of Respiratory Diseases
B I DAVIES
Department of Medical Microbiology

De Wever Ziekenhuis, PO Box 4446, 6401 CX Heerlen, The Netherlands

1 Davies BI, Maesen FPV, Teengs JP. Cefuroxim axetil in acute purulent exacerbations of chronic bronchitis. *Infection* 1987;15:253-6.
2 Maesen FPV, Geraedts WH, Davies BI. Cefaclor in the treatment of chronic bronchitis. *J Antimicrob Chemother* (in press).

AUTHORS' REPLY The results of Dr Maesen and colleagues differ from those of a randomised double blind multicentre study[1] which compared cefixime 400 mg daily with amoxycillin 500 mg twice daily. A clinical cure was found in 13 of 22 patients treated with cefixime (59%) compared with 14 of 24 treated with amoxycillin (58%). All patients in the cefixime group and all but one in the amoxycillin group improved. All the 25 pathogens isolated were eradicated by cefixime whereas 24 of 29 were eradicated by amoxycillin. This study has the advantage of providing a comparison with established treatment.

With regard to the apparent rise in minimum inhibitory concentrations for the pretreatment and post-treatment isolates of *Moraxella* (previously *Branhamella*) *catarrhalis*, Dr Maesen and colleagues have not stated whether their MICs were obtained in parallel from pretreatment and post-treatment isolates or on different occasions. This is important when MIC data are being compared. The MIC_{90} values given are within the expected range for both β lactamase and non-β lactamase producers[2] and the observed differences could therefore be attributable to methodological factors. We would also point out that their use of the term MIC_{90} may be incorrect when so few strains have been included.

A recent paper[2] compared the relative in vitro activity of 39 antibiotics on 74 clinical isolates of *M catarrhalis*, of which 58 were β lactamase producing strains. The MIC_{90} of cefixime was 0·5 mg/l for both β lactamase and non-β lactamase producing strains, indicating that cefixime is relatively stable in the presence of β lactamase. The rise in MIC values for the pneumococci is curious but could be explained if the pretreatment and post-treatment isolates were not the same strains (that is, were not typed serologically). The mechanism of resistance is not clear as alteration in penicillin binding proteins, possibly by transformation, is very unlikely in four patients over such a short time period.

In view of the favourable in vitro activity of cefixime, it may have a role in the treatment of chronic bronchitis, particularly where resistance patterns preclude first line drugs.

D R BALDWIN
J M ANDREWS
J P ASHBY
R WISE
D HONEYBOURNE
Clinical Investigation Unit, Dudley Road Hospital, Birmingham B18 7QH

1 Kiani R, Johnson D, Nelson B. Comparative multicentre studies of cefixime and amoxycillin in the treatment of respiratory tract infections. *Am J Med* 1988;**85**(suppl 3A): 6–13.
2 Doern GV, Tubert TA. In vitro activities of 39 antimicrobial agents for *Branhamella catarrhalis* and comparison of results with different quantitative susceptibility test methods. *Antimicrob Agents Chemother* 1988; 32:259–61.

Clinical correlates of angiographically diagnosed idiopathic pulmonary hypertension

We read with great interest the report by Dr H H Gray and his colleagues (June 1990;45: 442–6). Several points are raised which, we feel, merit comment and, hopefully, clarification. The most critical one is the distinction between what we prefer to call major vessel chronic thromboembolic pulmonary hypertension and small vessel idiopathic pulmonary hypertension.

This distinction has major management implications. The most vital one is that chronic thromboembolic pulmonary hypertension is potentially subject to surgical correction by thromboendarterectomy; idiopathic pulmonary hypertension is not. Furthermore, as Dr Gray and colleagues note, medical management of the latter often is not successful, with transplantation as the "final option." We have evaluated and followed more than 220 patients with major vessel, chronic thromboembolic pulmonary hypertension who have undergone pulmonary thromboendarterectomy[1]; our experiences in making this diagnosis may be germane.

One of the central problems in determining the diagnosis has been the terminological confusion created by the World Health Organisation classification of idiopathic pulmonary hypertension, a classification which has outlived its usefulness. Particularly troublesome is the uncertainty introduced by the "thromboembolic" subcategory.

We would submit that a "1990s" classification would be "small vessel pulmonary hypertension" and "large vessel thromboembolic pulmonary hypertension." In the first category are patients whose pulmonary hypertension arises from obstruction in the small, distal "resistance" vessels of the lung. Various lesions cause such obstruction, as has been amply demonstrated. Among these are so called "thrombotic" lesions. In our view patients with such lesions should no longer be described as having thrombo*embolic* pulmonary hypertension as no evidence for embolism has been offered. More likely, such lesions arise in situ from endothelial injury.

In the second category are patients whose pulmonary hypertension arises from obstruction of the large *elastic* arteries (main, lobar, segmental). These organised obstructing thrombi arise, in virtually every patient, from embolisation of venous thrombi. This distinction is not only pathogenetically more useful; it is also operationally critical. Patients in the second category can be substantially aided (even "cured") by thromboendarterectomy; patients in the former category cannot.

Other considerations follow once this distinction is made: anticoagulation in true thromboembolic ("large vessel") hypertension is, in our view, essential. The same can be said of Greenfield filter placement, to protect against further embolism in patients with substantial, large vessel thromboembolic pulmonary hypertension. As Mansour *et al* and others have noted, the morbidity and mortality of this procedure is negligible (in contrast with caval ligation or plication). In small vessel hypertension the value of anticoagulation is much less certain and filter placement is not indicated in the absence of venous thrombosis. We agree with Dr Gray and colleagues that differentiating the two conditions is difficult and frequently impossible on clinical grounds. We have, however, found a much higher frequency of a history compatible with deep venous thrombosis or pulmonary embolism (over half of all patients) in cases of major vessel obstruction (perhaps this is because one of us has taken the history in each of these cases).[2] There also is one distinctive physical finding in large vessel thromboembolic pulmonary hypertension: a flow murmur (as in congenital pulmonary artery branch stenosis), due to partial obstruction by a chronic thrombus; one or more of these murmurs can be heard *over the lung fields during breath holding* in some 30% of patients. We have not heard such murmurs in patients with small vessel pulmonary hypertension.

As Dr Gray and colleagues have suggested, the perfusion lung scans and pulmonary angiograms in these two groups differ substantially. In regard to perfusion lung scans, we have not found segmental or larger perfusion defects in patients with small vessel pulmonary hypertension. All patients with major vessel chronic thromboembolic pulmonary hypertension have had one (usually more and larger) such defect. (But commonly the perfusion scan defects *underestimate* the extent of major vessel obstruction.)

The key test is, of course, the pulmonary angiogram. It is quite distinctive in the two conditions. In small vessel pulmonary hypertension patent and normally tapering elastic arteries are seen, with "pruning" of the small, distal vessels (that is, no "capillary" blush). In large vessel chronic thromboembolic pulmonary hypertension various patterns are seen in the central arteries: frank obstruction, peculiar taperings and irregularities, webs, and bands. These many patterns reflect the variability in the way in which central (main, lobar, segmental) thrombotic occlusions organise and recanalise. Direct fibreoptic angioscopy helps diagnosis occasionally.

We concur that lung biopsy does not help to distinguish the two conditions. All the small vessel lesions "characteristic" of small vessel pulmonary hypertension can be found in major vessel thromboembolic pulmonary hypertension and in other disorders associated with pulmonary hypertension.[3] Biopsy therefore may obfuscate rather than elucidate the diagnosis. History taking, lung scanning, pulmonary angiography, and angioscopy are the most useful techniques for obtaining a diagnosis.

Because of the major management implications of making the correct diagnosis, we hope that the confusion evoked by "mixing" large vessel thromboembolic pulmonary hypertension with small vessel pulmonary hypertension (in which thrombotic lesions may occur) can be dissipated; patients with the former, potentially remediable, condition can then be recognised and managed appropriately.

KENNETH M MOSER
PETER F FEDULLO
WILLIAM R AUGER
University of California, San Diego Medical Center, San Diego, California 92103-1990, USA

1 Nicod P, Moser KM. Primary pulmonary hypertension: the risk and benefit of lung biopsy. *Circulation* 1989;**80**:1486–8.
2 Moser KM, Auger WR, Fedullo PF. Chronic major-vessel thromboembolic pulmonary hypertension. *Circulation* 1990;**81**:1735–43.
3 Pietra GG, Edwards WD, Kay M, *et al*. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 59 patients in the National Heart, Lung, and Blood Institute primary pulmonary hypertension registry. *Circulation* 1989;**80**:1198–206.

AUTHOR'S REPLY We welcome the comments of Professor Moser and his colleagues, whose experience in the field of idiopathic pulmonary hypertension is well known. Our paper was a retrospective review of patients presenting with unexplained pulmonary hypertension and as such suffers from certain weaknesses. Our finding of a lower incidence of prior deep venous thrombosis or pulmonary embolism in the group with asymmetrical pulmonary arteriopathy than that in Professor Moser's group, and the absence of pulmonary flow murmurs in the case records, may represent one of these weaknesses as the incidence of these findings would almost certainly be higher in a prospective study when someone with a particular interest in the subject makes the clinical assessment.

We agree entirely with their comments concerning the distinction between patients with idiopathic pulmonary hypertension. The histological differentiation into the three WHO categories (primary plexogenic, thromboembolic, and pulmonary veno-occlusive disease) may be difficult and indeed makes the assumption that there are in fact three separate disease entities, whereas it may be that a range of diseases exists. Such a differentiation is often clinically unhelpful and, as clinicians, we agree that until the aetiologies of idiopathic pulmonary hypertension are more clearly defined it may be more helpful to make distinction between patient groups based on therapeutic options. The distinction that Professor Moser and his colleagues use in dividing patients into those with small and large vessel pulmonary obstruction has a lot to recommend it from a therapeutic point of view and has the additional advantage that patients are not given a diagnostic label that is based on speculation about the causes of their pulmonary hypertension. If the causes of idiopathic pulmonary hypertension become clearer and if an imaging or pathological technique becomes available that reliably separates patients into these aetiological groups, the patient can be given an accurate diagnosis. Until then a distinction based on therapeutic groupings would have more practical benefit.

HUON H GRAY
Wessex Cardiothoracic Centre, Southampton General Hospital, Southampton SO9 4XY
JOHN M MORGAN
Brompton Hospital, London SW3 6HP

Antemortem recognition of brain metastases in malignant mesothelioma

Drs M Huncharek and J Muscat report that antemortem diagnosis of central nervous system metastases from pleural mesothelioma is rare, with only three reports of antemortem diagnosis (July 1990;45:571). I suspect that this is due to underreporting rather than to the rarity of the condition. Indeed, on the day I read the article I received a necropsy report