Correspondence

Nebulised pentamidine as treatment for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome

SIR,—Dr Miller and his colleagues (July 1989;**44**:565–9) report that nebulised pentamidine when delivered by a Respirgard II nebuliser is more effective in the treatment of *Pneumocystis carinii* pneumonia than when delivered by an Acorn nebuliser.

They state, however, that the mass median aerodynamic diameter (MMAD) of the aerosol produced by the Acorn is 2·6 μm. This means that 50% of the aerosol mass is contained in droplets of less than 2·6 μm and 50% of the aerosol mass is contained in droplets of 2·6 μm or more. It is therefore a physical impossibility for 46% of the particles to be less than 3·9 μm, as the authors state. If this latter figure is correct, then the MMAD of the aerosol must be 3·9 μm or more. The correct size of the aerosol is critical to the interpretation of this study. Newman and colleagues have shown that the MMAD of the Acorn nebuliser, when measured in the same manner, ranges from 4·5 to 5·7 μm.[1] It seems likely that Dr Miller and his colleagues have miscalculated the MMAD.

Only one patient from the group treated by Acorn nebulisers was seen to have oozing and contact bleeding at bronchoscopy, whereas four patients from the Respirgard group, which delivers a smaller droplet aerosol, were noted to have these findings. It is therefore difficult to implicate the pentamidine as the cause of these abnormalities, as the larger aerosol (delivered by the Acorn nebuliser) would be expected to produce a greater upper airway deposition, and so cause more rather than less mucosal irritation. Moreover, the authors state that the diagnosis of pneumocystis pneumonia was made by bronchoscopy before pentamidine was started (with the exception of one patient treated empirically). How is it then possible for the nebulised pentamidine to have caused the mucosal friability attributed to it?

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1 Newman SP, Pellow PGD, Clarke SW. Droplet size distributions of nebulised aerosols for inhalation therapy. *Clin Phys Physiol Meas* 1986;7:139–46.

AUTHOR'S REPLY

We are grateful to Dr Summers for pointing out a typographical error in our manuscript. As he points out, it is physically impossible for the droplet dispersion to be as described. In fact 64·5% and not 46·5% of the droplets were less than 3·9 μm. We believe that our calculations of the MMAD are correct. Using the Acorn nebuliser at a flow rate of 8 l/min we obtained an MMAD of 2·1 μm and GSD of 2·9 with saline, and an MMAD of 2·6 μm and GSD of 2·9 with pentamidine (100 mg/ml). The group quoted by Dr Summers report that an Acorn nebuliser running at 8 l/min nebulising saline produces an MMAD of 2·3 μm and not 4·5–5·7 μm.[1]

We report four patients from group 2 with bronchial oozing and a further patient with bronchial oozing and haemoptysis and in group 1 two patients with ooze and a further patient with ooze and haemoptysis. Unfortunately, with editorial pruning details of the bronchial bleeding have been lost. We in fact described bronchial oozing as the bronchoscope was being positioned in peripheral bronchi before bronchoalveolar lavage.[2] In the patients in whom we reported bronchial bleeding pentamidine had been started pending the bronchoscopic result. At the time of bronchoscopy one patient had received six doses of pentamidine, two patients four doses, one patient two doses, and a further patient a single dose of pentamidine (group 2 patients). In group 1 patients one patient had received three doses, one two doses, and one a single dose of pentamidine at the time of bronchoscopy. Our explanation for this apparent difference in incidence of side effects is that possibly the Acorn, because of the greater heterodispersity of aerosol droplets, in fact enables a smaller proportion of the delivered dose to reach the peripheral airways and so cause the local toxic effect.

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1 Clay MM, Pavia D, Newman SP, Clark SW. Factors influencing the size distribution of aerosols from jet nebulisers. *Thorax* 1983;**38**:755–9.
2 Miller RF, Semple SJG. Bronchial bleeding with nebulised pentamidine. *Lancet* 1988;ii:1488.

Antibodies to neutrophil cytoplasmic antigens in Wegener's granulomatosis and other conditions

SIR,—I read the excellent article by Dr DJ Harrison and colleagues (May 1989;**44**:373–7) with interest, but would question whether the quoted sensitivity of their neutrophil autoantibody test for Wegener's granulomatosis is the most appropriate one to choose.

The terms sensitivity and specificity of a diagnostic test were introduced by Jacob Yerushalmy[1] in an epidemiological setting when the diagnosis of the patient was known and the accuracy of the test was evaluated in retrospect. This type of sensitivity and specificity, subsequently called nosological,[2] is of limited direct value in diagnosis when the patient presents with a finding or group of findings and the test is used to help confirm or exclude a diagnosis.[2,3] In these circumstances the diagnostic specificity (positive predictive value) and sensitivity (negative predictive value) are more appropriate. When the test is applied in clinical practice these values can be

Wegener's granulomatosis

	Positive (D)	Negative ($\bar{D}$)	
Positive (F) ANCA test	18	3	Diagnostic specificity P(D|F) = 18/21 86%
Negative ($\bar{F}$)	5	214	Diagnostic sensitivity P($\bar{D}$|$\bar{F}$) = 214/219 98%
	Nosological sensitivity P(F|D) = 18/23 78%	Nosological specificity P($\bar{F}$/$\bar{D}$) = 214/217 99%	

Nosological and diagnostic sensitivity and specificity of the test for antibodies to neutrophil cytoplasmic antigens (ANCA)

used to assess the likelihood of disease according to the result of the test so long as the probabilities of disease in the diagnostic setting and in the patients studied for the paper are similar.

On the other hand, nosological values of sensitivity and specificity are of limited direct relevance to the practising physician, who would need to convert these probabilities to the clinically relevant probabilities using Bayes's formula. This conversion is to a large extent dependent on the prior probability of disease in the clinical population studied and this is rarely known. There is a lot to be said for collecting data in a realistic clinical setting, as the authors have done, and quoting diagnostic specificity and sensitivity, rather than evaluating a new test in a group of patients who are known to have the disease in question and comparing this with the results in a group of normal people. In these circumstances the nosological value would be more appropriate.

Taking the bright, coarsely granular pattern as positive, the authors found that the result of the test was positive in 18 patients with Wegener's granulomatosis and in three who did not have the disease. The result was negative in five patients who had active Wegener's granulomatosis and in 214 other patients, in most of whom, from the limited details given, Wegener's granulomatosis might have been initially suspected but was not subsequently confirmed. On the basis of these figures (table) the nosological sensitivity is 78%, the nosological specificity 99%, the diagnostic sensitivity 98%, and the diagnostic specificity 86%. It would seem that the authors have quoted the nosological sensitivity with the diagnostic specificity. I would suggest that it would be more appropriate for them to have quoted the diagnostic sensitivity of 98%—which, as an added bonus, looks even better than the quoted sensitivity of 78%.

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1 Yerushalmy J. Statistical problems in assessing methods of medical diagnosis, with special reference to *X*-ray techniques. *Pub Health Rep* 1947;**62**:1432–49.
2 Wulff HR. *Rational diagnosis and treatment*. 2nd ed. Oxford: Blackwell, 1981:80–102.
3 Feinstein AR. The haze of Bayes, the aerial palaces of decision analysis and the computerised Ouija board. *Clin Pharmacol Ther* 1977;**21**:482–96.

AUTHOR'S REPLY I am grateful for the clear explanation of nosological versus diagnostic sensitivity and specificity. In our report we aimed to show primarily the significance of a positive result in the test for antibody to neutrophil cytoplasmic antigens as a diagnostic aid for Wegener's granulomatosis. A sizeable proportion of biopsy proved cases, however, were antibody negative—hence our reluctance to quote a diagnostic sensitivity, or negative predictive value, of 98% because of the danger of a delay in diagnosis as a result of undue weight being attached to a negative result. Prompt diagnosis and early treatment are essential to prevent long term complications in Wegener's granulomatosis,[1] and negative laboratory results should not be assumed to exclude the diagnosis if there is persistent suspicion on clinical grounds.[2]

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1 Harrison DJ, Simpson R, Neary C, Wathen CG. Renal biopsy and anti-neutrophil antibodies in the diagnosis and assessment of Wegener's Granuloma. *Br J Dis Chest* 1988;**82**:398–404.
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Book notices

Textbook of Respiratory Medicine. Vol 1. JF Murray, JA Nadel, eds. (Pp 1167; £65·75.) Philadelphia: Saunders, 1989. ISBN 0 7216 1439 6.

In recent years the comprehensive textbook of general medicine, aimed at the practising physician, has made a dramatic comeback—largely, I suspect, being used for a brief overview of areas outside the everyday experience of the reader. But this reviewer realises that over the same period he has relied very little on the larger textbooks in his own speciality of respiratory medicine. This new multi-author textbook presents over 2000 double column pages of information in two volumes (but there are two larger North American multi-volume textbooks on respiratory medicine). The contributors are well known academic leaders in their subjects, mainly from the United States but with representatives from England, Canada, and Australia. About one third of the textbook is devoted to basic science and techniques and the remainder to clinical topics, which are arranged separately under conventional headings but with