LETTERS TO THE EDITOR

Respiration in dystrophia myotonica

The interesting paper by Dr J E Clague *et al* (March 1994;**49**:240–4) contains some results and conclusions which are at variance with earlier studies.

Firstly, their results showed that the ventilatory response to carbon dioxide in these patients was lower than in the controls, but the difference was not significant. Several earlier studies showed clear evidence of a reduction in the slope of the ventilatory response.[1 2] In addition, one study showed that the magnitude of this reduction was related to the severity of respiratory muscle weakness.[2] I would therefore submit that the first conclusion in the abstract of the paper that "moderately severe global respiratory muscle weakness does not appear to influence the ventilatory response to rising carbon dioxide tension" is incorrect.

It should also be pointed out that the authors do not actually quote data confirming "global respiratory weakness" as they only report maximum *inspiratory* pressures (MIP). In this condition this may lead to underestimation of the severity of muscle weakness since previous studies in dystrophia myotonica have shown that maximum expiratory pressures tend to be relatively more impaired than inspiratory pressures.[2 3] Weakness of expiratory muscles might also be relevant to the sensation of discomfort during carbon dioxide rebreathing. Clague *et al* assessed this by asking the question "how difficult is it to breathe?" They equate the answers with *inspiratory* effort sensation and go on to examine the relation between this index and various factors including MIP. In the unnatural situation of ventilation stimulated by carbon dioxide both inspiratory and expiratory muscles are usually active, and therefore the sensation may not be determined solely by inspiratory effort. It might have been worth also exploring the relation between the effort sensation and expiratory muscle weakness.

A further point where the results appear to be at variance with earlier data relates to the variability of the timing of resting breathing. The authors found no difference from normal in the variation of the duration of individual breaths. Previous work has, however, commented on patients with marked variation from breath to breath. The explanation for the discrepancy may lie in the technique used, since subjects in the study of Clague *et al* used a mouthpiece and noseclip, while studies showing marked variability of breath timing[2 3] used more surreptitious monitoring of chest wall movement which probably gives a fairer reflection of undisturbed resting breathing.

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1 Begin R, Bureau MA, Lupien L, Bernier J-P, Lemieux B. Pathogenesis of respiratory insufficiency in myotonic dystrophy. *Am Rev Respir Dis* 1982;**125**:312–8.
2 Serisier DE, Mastaglia FL, Gibson GJ. Respiratory muscle function and ventilatory control. I. In patients with motor nuerone disease. II. In patients with myotonic dystrophy. *Q J Med* 1982;**51**:502–26.
3 Gillam PMS, Heaf PJD, Kaufuren L, Lucas BGB. Respiration in dystrophia myotonica. *Thorax* 1964;**19**:112–20.

AUTHOR'S REPLY We were interested to read Professor Gibson's letter which raises several important points. He is quite correct in stating that we did not include the maximum expiratory pressure data as we followed the normal convention of relating inspiratory effort sensation to maximum inspiratory pressures. This approach has been developed in Hamilton (Canada) and Cleveland (USA) but the subject table should certainly have contained the MEP data which was 56 (16) cm H_2O for the myotonic group compared with 156 (23) cm H_2O for our normal subjects. As can be seen the patient values are significantly below the age-matched controls and are very similar for both inspiration and expiration. This is the basis for the statement about global respiratory muscle weakness and we apologise for this omission.

We were surprised to see no significant difference in the ventilatory responses to carbon dioxide between our patients and the control subjects. We suspect this reflects the selection of our patients which we specified in the methods section. As can be seen, we did not study the most severely affected myotonic patients and, in particular, there were no subjects with diaphragm weakness – a difference between our patient group and that of Professor Gibson which he cites in his reference 2.

We have conducted a subsidiary analysis adopting the same approach of pooling data that we used in our analysis of effort sensation. If this is done with the independent variable being ventilation, then a just significant effect of maximum inspiratory pressure can be seen ($p>0{\cdot}05$) and this explains a very small amount of the variability in the ventilatory response to carbon dioxide. This analysis was removed for reasons of space during the revision of the paper.

Our point is that the ventilatory response to carbon dioxide is likely to be a continuum, with the most severely affected patients certainly having a reduced ventilatory response but many patients who are affected by dystrophia having preserved responses. Hence the problem is one of degree and other complicating factors, rather than an intrinsic defect always associated with the disease.

We have analysed the inspiratory effort sensation for both global and expiratory muscle weakness and found no difference in the conclusions from those listed in the paper. This is not surprising, given the similarity of the MIP and MEP results. We know of no data looking at the patterns of activation of the expiratory muscles during carbon dioxide rebreathing in patients with dystrophia myotonica. However, we doubt if this is substantially different from that seen in healthy humans.

Finally, we agree that the breathing pattern data we report are different from those obtained using non-invasive means of monitoring ventilation and we have suggested in paragraph 2 of the discussion why this may be so. Some of our patients showed substantial variability in their respiratory cycle duration when monitored awake as part of a sleep study described elsewhere. We were impressed by how easily these effects were abolished by a modest dead space. This may reflect an influence of a different set point for the apnoeic threshold in these patients that might be worth further systematic study.

However, these intriguing changes in ventilatory control do not seem to influence the capacity of the individual to assess sensation unless that patient is confronted by an increased inspiratory load to breathing.

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Sympathomimetics and airway hyperreactivity

In commenting upon whether the use of sympathomimetics is associated with hyperreactivity of asthmatic airways to inhaled spasmogens, Drs Taylor and Sears and Drs van Schayck and van Herwaarden (February 1994;**49**:190–1) categorise the effect of sympathomimetics (at therapeutic dose levels) as small. Their opinions may be valid when histamine or methacholine are used for assessment of airway responsiveness, but it is possible that larger effects might have been observed if other test spasmogens had been used. For instance, it is known that regular use of terbutaline resulted in an increased sensitivity to the spasmogenic actions of adenosine monophosphate that was greater than the corresponding change in sensitivity to methacholine.[1] Recently, similar differential changes have been observed in allergic patients whose sensitivity to allergen, after regular use of salbutamol, was exaggerated to a greater extent than to methacholine.[2]

Clinical observations of differential changes in sensitivity of intact airways to spasmogens were anticipated by an experimental analysis of the changed responsiveness of the airways in sensitised guinea pigs during exposure to antigen.[3] In these animals, responsiveness of the airways to seven distinct spasmogens was measured before and after infusion of antigen. As in humans,[4] the magnitude of increased responsiveness was greater for some spasmogens than for others, with peptidoleukotrienes (LTC_4 and LTE_4) and bradykinin being particularly sensitive indicators of increased responsiveness during an acute allergic reaction in the guinea pig. Of possible interest to clinical investigators was the finding that, following prolonged exposure to salbutamol, the exaggerated responsiveness of the airways to LTC_4 and LTE_4 that accompanies a mild allergic reaction was further intensified. Thus, a substantial proportion of animals (78 of 235) became either too responsive for evaluation or died during exposure to antigen or LTC_4, even though concomitant responsiveness to histamine, acetylcholine, serotonin, and prostaglandin $F_{2\alpha}$ was diminished significantly.[5] A reduced response to certain spasmogens reflected a continued bronchodilator response to infused salbutamol, and these findings therefore explain the paradox of hyperreactivity to inhaled antigen without corresponding hyperreactivity to histamine as had been reported earlier but not understood.[6] No mechanism has been established to account for this differential; however, it may be a manifestation of the properties of the (supposedly inert) enantiomer that comprises 50% of salbutamol, since induction of ex-