

# Decreased Chemoreceptor Sensitivity and Chronic Obstructive Lung Disease

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In New Zealand, as in many other parts of the world, chronic bronchitis and obstructive lung diseases are common causes of disability and are the causes of a large number of admissions to our hospitals. It is evident that cigarette smoking is the main aetiological factor in this high incidence of bronchitis (Lambert and Reid, 1970; de Hamel and O'Donnell, 1971). As a result of the better understanding of the functional abnormalities involved as well as of improved therapy with antibiotics, bronchodilator drugs and physical methods for clearing the obstructing secretions, we are now seeing many ambulant patients with chronic carbon dioxide retention complicating obstructive lung diseases.

In recent years there has been renewed interest in the reasons for the elevated arterial carbon dioxide tension ( $P_{a,CO_2}$ ) in these patients and for their diminished ventilatory response to an increasing alveolar carbon dioxide tension ( $P_{A,CO_2}$ ). It is 50 years since this diminished ventilatory response to an additional acute rise of carbon dioxide tension was demonstrated (Scott, 1920). Subsequent investigations have shown that in some patients mechanical factors associated with the obstructive disease are responsible for the decreased response to the increased  $P_{a,CO_2}$  (Richards *et al.*, 1958; Brodovsky *et al.*, 1960) while in others there is impairment of the usual responsiveness of the respiratory centre (Prime and Westlake, 1954; Flenley and Millar, 1967; Lane and Howell, 1970). If mechanical limitation is the dominant cause of the elevated  $P_{a,CO_2}$  the patient is likely to sense an increased work of breathing although only a limited increase of alveolar ventilation is obtained for this work. In the absence of this sensation of an additional drive to the respiratory muscles from an increasing carbon dioxide stimulus, a patient is likely to be unaware of his rather perilous state. For some years patients with severe obstructive lung disease have been described as 'fighters' and 'nonfighters' (Robin and O'Neill, 1963) or 'pink and puffing' and 'blue and bloated' (Scadding, 1963). Recently, Lane and Howell (1970) have shown that an

impaired chemosensitivity to increasing carbon dioxide tension may be an aetiological factor underlying this descriptive classification.

This article describes observations made on 13 patients with chronic obstructive lung disease and carbon dioxide retention. Details of the patients are summarised in Table 1 (p. 58). The results are also described in 10 subjects free from evidence of cardiopulmonary disease and of an age distribution similar to the patients under review. Chemoreceptor sensitivity in the presence of obstructive lung disease is discussed and a case report included which demonstrates the serious consequences of an impaired responsiveness to both increasing carbon dioxide and hypoxia. All our 13 hypercapnic patients had chronic bronchitis but the chest X-rays in five (KE, JL, EMcF, CB and RD) suggested the presence of emphysema. Carbon monoxide transfer and lung volumes which are helpful in the differentiation of the bronchitic and emphysematous types of obstructive chest disease were not measured in most of these patients and are not discussed. The ventilatory response to increasing carbon dioxide was assessed by the rebreathing method with the subjects seated. During this rebreathing period we used an intraoesophageal balloon to measure the end inspiratory and end expiratory intrathoracic pressures for each breath. The average pressure difference per breath over each 30 seconds of the rebreathing test period was multiplied by two to allow its expression per minute. An increase of this calculated value provided an index of an increase in respiratory muscle activity which was compared with the change in  $P_{A,CO_2}$  in each half minute over the same period. We used this index of 'pressure drive' per mm increase of  $P_{A,CO_2}$  as an estimate of the output of the respiratory centre. An impaired sensitivity of the respiratory centre to an increasing  $P_{A,CO_2}$  was concluded if the value for calculated intrathoracic pressure increase fell more than 20 per cent below the lowest value for a normal subject in our group (4.5 cm H<sub>2</sub>O/min/mm  $P_{A,CO_2}$ ). A similar method was used in the patient described in some detail to assess the sensitivity to hypoxia but in that assessment a direct arterial sampling of blood was performed to obtain the  $P_{a,CO_2}$ , a needle being left in place during the procedure. During the assessment for hypoxia, patients rebreathed from a circuit filled with air while the end-tidal  $P_{A,CO_2}$  was maintained at 38 mm by controlling the access to the carbon dioxide absorber. The rate of fall of  $P_{O_2}$  was monitored with an oxygen electrode in the balloon of a Rahn-Otis end-tidal sampler.

#### RESULTS

The normal subjects showed a ventilatory response to the increasing  $P_{A,CO_2}$  of  $1.39 \pm 0.63$  l/min/mm  $P_{A,CO_2}$ . Of the 13 patients with chronic obstructive



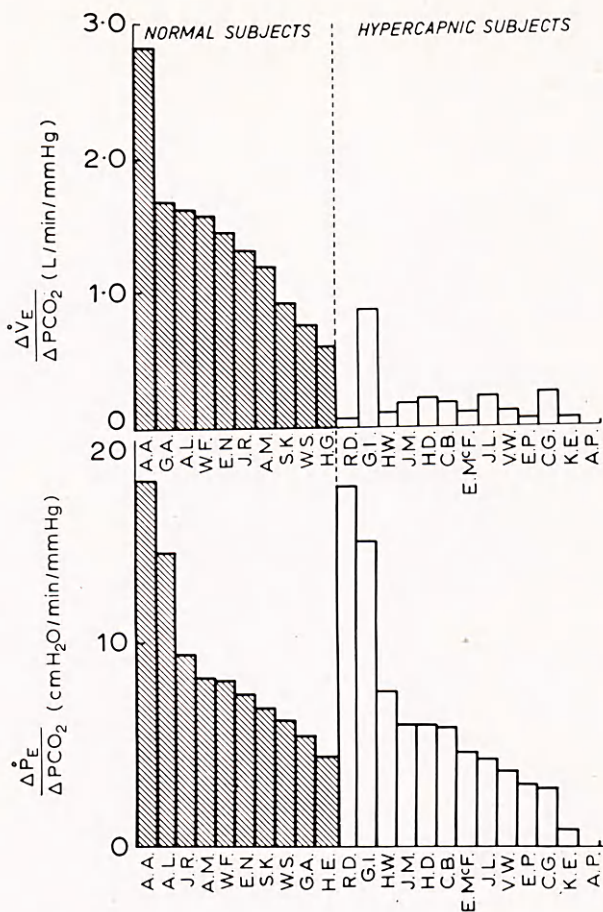


Fig. 1. Changes in minute ventilation,  $V_E$ , and of end expiratory-end inspiratory absolute intrathoracic pressure differences (average per half minute  $\times$  resp. freq. and expressed per minute),  $P_E$ , per mm increase in  $P_{A,CO_2}$  during the same half minute of the rebreathing tests in 10 normal and 13 hypercapnic subjects.

lung disease and hypercapnia, 12 showed responses below those of all the normal subjects and the mean response for the group was  $0.14 \pm 0.08$  l/min/mm  $P_{A,CO_2}$ . Among the normal subjects the lowest value for the intrathoracic

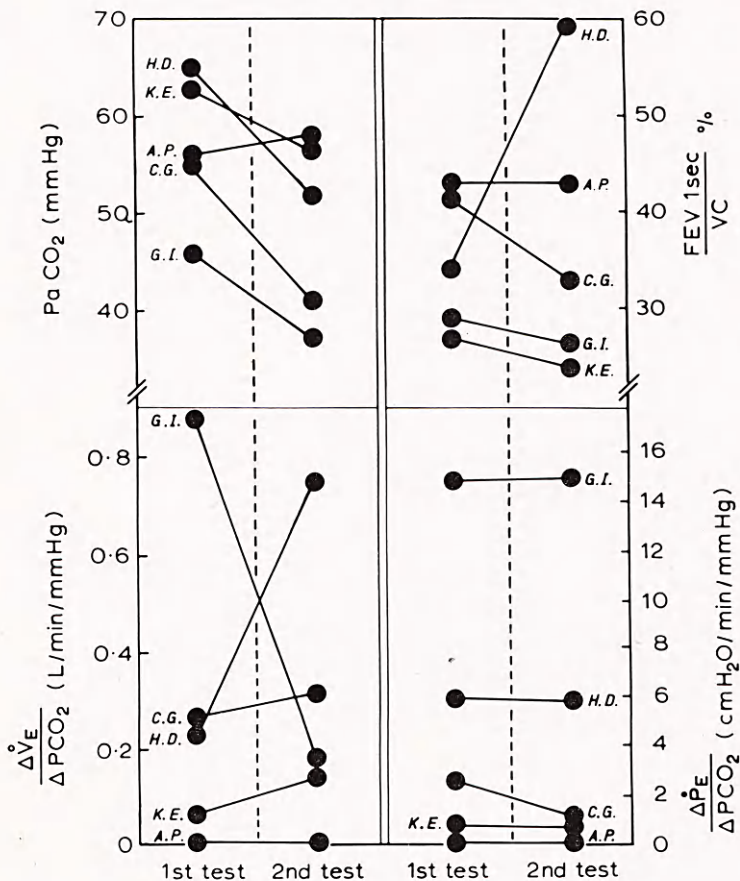


Fig. 2.  $P_aCO_2$ ,  $FEV_{1sec}/VC\%$ , increase in minute ventilation and intrathoracic pressure differences (as in Fig. 1) in 5 patients with hypercapnic and chronic obstructive lung disease when first assessed and again about 1 year later.

pressure 'output' was  $4.5$  cm  $H_2O/min/mm P_{A,CO_2}$  (Fig. 1). Six of the hypercapnic patients showed values below this and in the two subjects KE and AP the response was trivial or absent.

Five of the hypercapnic patients were re-assessed about one year later.

With the rebreathing carbon dioxide stimulus the transpulmonary pressure drive per mm  $P_{A,CO_2}$  was decreased slightly in one subject but unchanged in four (Fig. 2). This relationship changed little in spite of varying significant

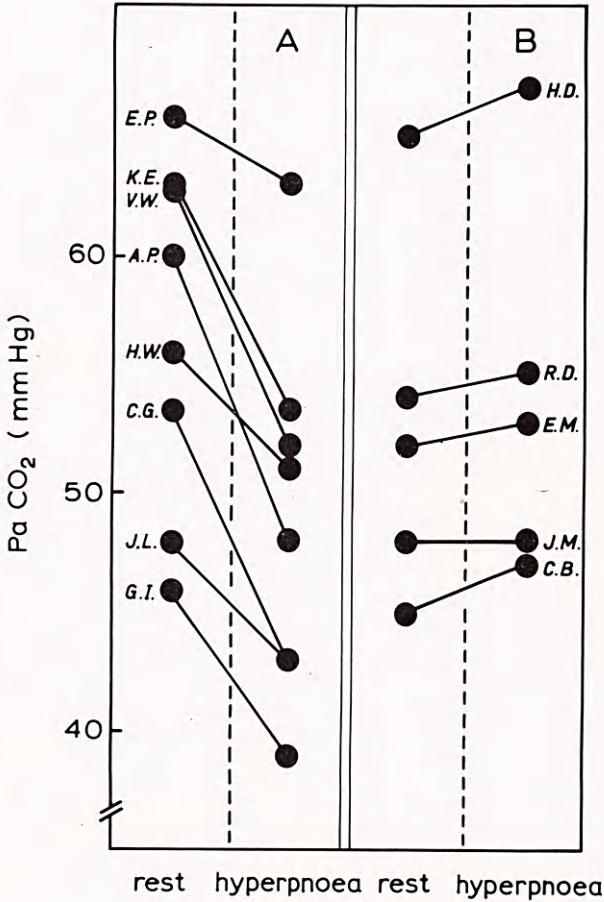


Fig. 3. Changes of  $P_{a,CO_2}$  in the 13 hypercapnic patients of Table 1 following 2 minutes voluntary hyperpnoea. (A) those showing a decrease of  $P_{a,CO_2}$ , (B) those showing no decrease.

changes of the  $FEV_1/VC$ ,  $P_{a,CO_2}$  or of the ventilatory response per mm  $P_{A,CO_2}$  (Fig. 2).

It was of interest that four of the six hypercapnic patients who showed an impaired respiratory centre output as indicated by the intrathoracic pressure

changes during the carbon dioxide rebreathing test were able to reduce their  $P_{a,CO_2}$  with voluntary hyperpnoea whereas only two of the seven (HW and GI) with a predominantly ventilatory impairment were able to do this (Fig. 3). Three of the patients (AP, HD and JM) increased their  $P_{a,CO_2}$  by 8 mm or more while breathing 100 per cent oxygen for 11 minutes.

ILLUSTRATIVE CASE HISTORY

AP, now aged 62, was admitted to hospital four times between 1953 and 1968 with impaired consciousness due to respiratory failure. This semi-coma had been caused twice by pneumonia and twice by an exacerbation of bronchitis.

TABLE 1. Normal subjects and patients with chronic obstructive disease and elevated arterial  $P_{CO_2}$

Subject	Age & Sex	FEV <sub>1</sub> L	FEV VC%	$P_{aCO_2}$	pH	$P_{O_2}$
AP*	57 M	1.12	42	60	7.32	51
CG	65 M	1.20	52	56	7.30	70
KE	41 F	0.51	27	63	7.32	43
EP	54 F	0.35	35	66	7.37	39
VW	59 F	0.36	33	63	7.37	63
JL	72 M	0.55	41	48	7.33	40
EMcF	60 M	0.66	17	52	7.33	71
CB	60 M	0.51	49	45	7.37	65
HD	69 M	0.61	34	65	7.37	38
JM	73 M	0.75	31	48	7.33	67
RD	43 M	0.44	28	54	7.34	49
HW	67 F	0.43	24	56	7.32	63
GI	53 M	0.98	28	46	7.39	71
NORMALS						
HE	50 M	3.10	80			
WS	73 M	3.20	82			
SK	52 M	3.36	76			
AM	50 M	3.11	70			
JR	68 M	2.51	70			
EN	41 M	3.65	70			
WF	47 M	2.98	70			
AL	87 M	2.73	70			
GA	51 M	3.59	70			
AA	58 M	3.01	87			

(Arterial blood gases were not measured in the normal subjects)

\*Refer illustrative case history.

He smoked about thirty cigarettes daily and his weight varied between 196 and 220 lb. He has had episodes of secondary polycythaemia which had been noted in this type of patient by earlier authors (Fishman *et al.*, 1966). The results of spirometry are listed in Table 1 (AP). His predicted vital capacity was 4.2 litres. His  $P_{a,CO_2}$  on admission has varied from 66 to 92 mm Hg and his



$P_{a,O_2}$  from 40 to 60 mm Hg. Papilloedema has been noted on three admissions. Chest X-rays have shown some cardiac enlargement and varying degrees of parenchymal infection. Although his ventilation did increase on physical exercise and with voluntary hyperpnoea (which lowered his  $P_{a,CO_2}$ ) there was no change in ventilation or in the intrathoracic pressure differences in response to a change of  $P_{A,CO_2}$  from 50 to 95 mm Hg or  $P_{a,O_2}$  from 60 to 40 mm Hg during assessment in the laboratory (Fig. 4a and 4b). His respiratory illness with its

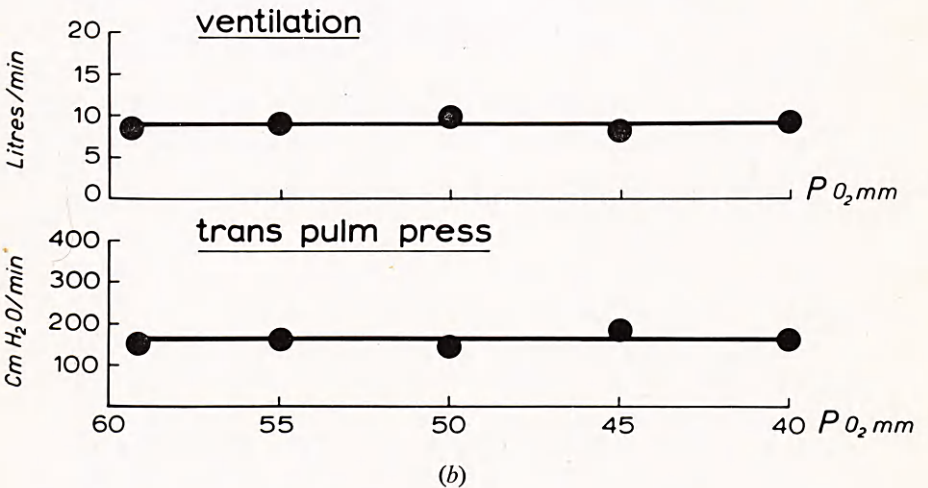
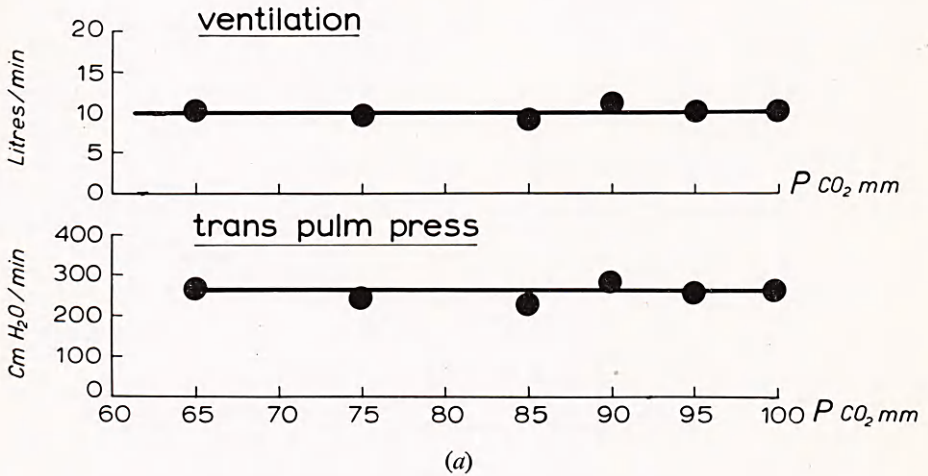


Fig. 4. Minute ventilation and transpulmonary pressure per minute (as in Fig. 1) in patient AP, (a) during increasing  $P_{A,CO_2}$  of the rebreathing test (b) during increasing hypoxia with  $P_{A,CO_2}$  constant at 38 mm.

intermittently severe disturbances of blood gases and impairment of consciousness have not been associated with any breathlessness. The absence of breathlessness as a warning signal of the serious changes of hypoxia and hypercapnia is likely to have contributed significantly to his lapses into near fatal semi-coma.

#### DISCUSSION

The rebreathing method of Read (1967) has enabled the ventilatory response to carbon dioxide to be assessed in a few minutes in contrast to the more prolonged steady state method. When using this easily performed technique we have also measured intra-oesophageal pressure. This has enabled us to obtain information for the further differentiation of the possible reasons for the impairment of the ventilatory sensitivity to the carbon dioxide stimulus in patients with severe obstructive lung diseases and carbon dioxide retention. The ventilatory response to a rising  $P_{A,CO_2}$  will show what breathing the patient can achieve, but if the ventilatory response is impaired no information is obtained concerning the several possible causes of this. While the inspiratory work of breathing has not been calculated in these patients an increased drive to inspiration has been indicated by an increase of the intrathoracic pressure differences over each half minute of the increasing carbon dioxide stimulus. An increase in the calculated 'intrathoracic pressure response' at this time has been accepted as evidence of an increased drive to the respiratory muscles from a stimulated respiratory centre.

The use of the intrathoracic pressure changes as an indication of the efferent activity of the respiratory centre in these patients is dependent on there being no mechanical limitation to an increase of these pressures. In two of the hypercapnic patients (KE and AP) there was little or no increase in ventilation or in intrathoracic pressure during the increasing  $P_{A,CO_2}$  but both were able to increase their ventilation voluntarily and reduce their  $P_{a,CO_2}$ . Among the others tested, the increase of intrathoracic pressure 'drive' during the rebreathing test was similar in the normal subjects (range 75–220 cm  $H_2O$ /min/mm  $CO_2$ ) and in the hypercapnic patients (75–220 cm  $H_2O$ /min/mm  $CO_2$ ) indicating that the impairment in the latter subjects was not due to a mechanical limitation of the chest wall. Some of the hypercapnic patients achieved this through an increased frequency of breathing. The validity of this as a method of assessment is also supported by the lack of improvement of the intrathoracic pressure 'drive' per mm  $P_{A,CO_2}$  in the five patients retested, in spite of there being in three of them an improved ventilatory response to the  $P_{A,CO_2}$ . Among the hypercapnic patients there was increased blood buffering for the  $H^+$  ion changes with an increased serum bicarbonate and polycy-



thaemia in some. However, this was insufficient to account for the impaired responses to carbon dioxide.

The possibility that the relief of arterial hypoxia in some of the patients during the rebreathing test might account for the impaired sensitivity to carbon dioxide was ruled out since there was no relationship between the responses to  $P_{A,CO_2}$  and the changes observed in the arterial  $P_{CO_2}$  or  $P_{O_2}$  during the oxygen breathing.

In all but one of the hypercapnic patients the intrathoracic pressure change (cm  $H_2O$ /min/mm  $P_{A,CO_2}$ ) was proportionately greater than the ventilatory response (l/min/mm  $P_{A,CO_2}$ ). Thus, in general, a mechanical impairment to ventilation was responsible at least in part for the reduced ventilatory response whether the sensitivity of the respiratory centre to the increasing carbon dioxide was normal or reduced. A comparison of the pressure responses of EP (3.1 cm  $H_2O$ /min/mm  $P_{A,CO_2}$ ), CG (2.8 cm  $H_2O$ /min/mm  $P_{A,CO_2}$ ), KE (0.8 cm  $H_2O$ /min/mm  $P_{A,CO_2}$ ) and AP (0 cm  $H_2O$ /min/mm  $P_{A,CO_2}$ ), with those of the normal subjects (Fig. 1, lower sections) showed these responses to be well below those of the normal subjects. This low ventilatory response was influenced by a poor sensitivity of the respiratory centre to carbon dioxide. Patient AP showed no pressure response at all to the carbon dioxide and in KE this was only trivial.

Among our normal subjects the values for the ventilatory response per mm increase of  $P_{A,CO_2}$  were mostly below the average values for normal subjects obtained by Read (1967), Anderton *et al.* (1964) and Lloyd *et al.* (1958). Only two of our subjects were less than fifty years old. Occasionally, subjects with healthy lungs have been encountered with a low sensitivity to carbon dioxide (Lambertsen, 1960) but we have regarded the finding of a severely impaired sensitivity in 2 of our 13 hypercapnic subjects as of probable significance and related to the obstructive lung disease. At least two others showed moderate impairment. We cannot be certain of the relationship of this impairment to the obstructive disease. Only one of these four patients was overweight. Flenley and Millar (1967) demonstrated a decreased mechanical work of inspiration during an increasing carbon dioxide stimulus in six of eight patients with chronic ventilatory failure. Lane and Howell (1970) studying patients with chronic airways obstruction, but not all in ventilatory failure, showed that an impaired output of inspiratory work in response to carbon dioxide was more commonly seen in patients of the bronchitic type ('nonfighters') than in obese 'fighters' of the emphysematous type. These were the patients who were also less likely to admit to dyspnoea. Our results did not fit in with this when our patients were classified on clinical and radiological grounds, although we did not assess carbon monoxide transfer or lung volumes

in all subjects, which would have been necessary for more precise classification into bronchitic or emphysematous types.

Chronic exposure to hypoxia at high altitude during adult life results in a marked reduction of the ventilatory response to hypoxia and this is a function of the number of years of the hypoxia (Weil *et al.*, 1971). There has been much interest as to whether such an impaired ventilatory response to hypoxia can be acquired. Patients having their hypoxaemia and cyanosis improved by the surgical correction of a tetralogy of Fallot have been studied with conflicting results (Sørensen and Severinghaus, 1968; Edelman *et al.*, 1970). In only one of our subjects did we assess the ventilatory response to increasing hypoxia and it was absent when the  $P_{a,O_2}$  was reduced to 40 mm. We did not know whether this loss was acquired and, if so, whether it could be related to the severe functional abnormality of his ventilation. Flenley and Millar (1967) have demonstrated some impairment of the ventilatory response to hypoxia in two bronchitic patients with elevated  $P_{a,CO_2}$  values.

Whether or not our patient, AP, described in the illustrative case history, has suffered his impaired chemoreceptor sensitivity to hypercapnia and hypoxia as a complication of or as an adaptation to the severe arterial blood gas changes of his disease is undetermined but our own and published evidence indicates that such impairment is present in a number of patients with chronic obstructive lung disease. This patient and KE were obviously severely affected with a poor response to a rising  $P_{A,CO_2}$  but we considered that at least four of our 13 hypercapnic patients showed significant impairment. Our patient's case history demonstrates the complications to which these patients are prone and the apparent non-respiratory type of clinical illness with which they, as 'nonfighters' may present. The need for early therapy for an exacerbation of bronchitis in patients with serious obstructive lung disease is well recognised. Unfortunately, patients with a seriously impaired chemoreceptor sensitivity are likely to be late in presenting for therapy in the absence of the usual increase in breathing that would be expected from the disturbance of their blood gases. In such patients a readily available method of assessment as has been described may be of particular value in drawing attention to their more perilous state.

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#### American Boatmen

In the latter part of the last century, and for the first fifteen or twenty years of the present, the commerce of the Interior Valley was carried on in flat boats, which floated with the current, and in keel boats, and barges, which were, by oars, setting poles, and cordells, propelled against it. Flat boats still continue in use, but the others are no longer employed. The principal voyages were from the Ohio River to New Orleans; and the watermen who performed them, constituted a peculiar class: First. They were, for a long period, exposed to a river atmosphere. Second. Their exposure to the weather was incessant. Third. Their diet consisted chiefly of bread and meat. Fourth. They drank whisky to excess. Fifth. Those who returned by the river, were compelled to labor in the most toilsome manner, and were often in the water. Sixth. Those who traveled back by land, performed a journey of a thousand miles on horseback or on foot, encamping at night in the open air.

In this occupation many died of fevers, contracted from lying through the night at the river banks, or at New Orleans; and rheumatism or pulmonary diseases were the lot of others; but the majority were strong and hardy—none being more so, than those who performed the long overland journey from New Orleans, to the middle portion of the Ohio River, on foot. Since the general introduction of steamboats, the flat boat hands no longer return by land; but on the lower decks of those boats, where many of them yield to dissipation, and the mortality is, I presume, quite as great as among those of former times.

(From Daniel Drake's *Principal Diseases of North America*, 1850.)