

The grey area of effort syndrome and hyperventilation: from Thomas Lewis to today

ABSTRACT—Lewis* used the diagnosis 'effort syndrome' for subjects whose ability to make and sustain effort had been reduced by homeostatic failure. A major element was depletion of the body's capacity for buffering the acids produced by exercise. In his view this systems disorder was not to be regarded as a specific organ disease, and losing sight of the metabolic element would foster the invention of fanciful, unphysiological diagnoses. His views were dismissed because normal resting plasma bicarbonate levels were considered by others in that era to exclude serious depletion of the body's total capacity for buffering the effects of exertion. Today, effort syndrome is still a useful diagnosis for a condition of exhaustion and failure of performance associated with depletion of the body's buffering systems. Other elements associated with homeostatic failure are now recognised, principally emotional hyperarousal and hyperventilation. Their physiological interrelationships are described. Effort syndrome is amenable to recovery through rehabilitation, and it may be a mistake to treat chronic fatigue syndrome and unspecific illness without including it in the differential diagnosis.

Adaptation requires the individual to maintain the internal systems in an orderly and stable condition irrespective of the variations of the external environment. The defences of order and stability include the capacity of the homeostatic system for self-regulation under pressure; and the freedom to use personal and social skills to evade or outwit environmental challenges that might overwhelm homeostatic competence. These defences differ considerably from one person to another, and they can be exhausted by over-use. Pickering [1] thought it inherently probable that over-use, 'the unduly intense or sustained use of normal homeostatic adaptive patterns designed for phasic or short-term use' contributed to the pathogenesis of troublesome disease states in man, eg hypertension. He agreed with Wolf and Wolff [2] that the misuse of the adaptive systems was often associated with 'a sustained state of over-reaction to the minor stresses of daily life'.

PETER G F NIXON, FRCP
Honorary Consulting Cardiologist, Charing Cross Hospital, London

The first purpose of this paper is to provide a reminder that in his 'effort syndrome' Lewis [3] delineated the clinical picture of adaptive failure with over-reaction to stressors. The second is to recall his interest in the part played by buffer-base depletion resulting from chronic overbreathing. The third is to indicate the need for a wider investigation of carbon dioxide regulation in the chronic fatigue and ill-health syndromes that are as common today as effort syndrome was in Lewis's era. As far as we know, some might be effort syndrome disguised by a proliferation of new hypotheses that have never been trimmed by Occam's razor.

The soldier's heart

Lewis studied soldiers in the first world war who failed to make and sustain the effort required of them. He identified two major groups; those who were incapable of adapting to heavy or protracted environmental challenges, and those who were worn out by overuse.

The performance-arousal curve

Lewis's approach is well represented by the performance-arousal curve (Fig 1). The individual in an up-slope position can improve his performance by arousal to greater effort, but on the downslope, beyond the

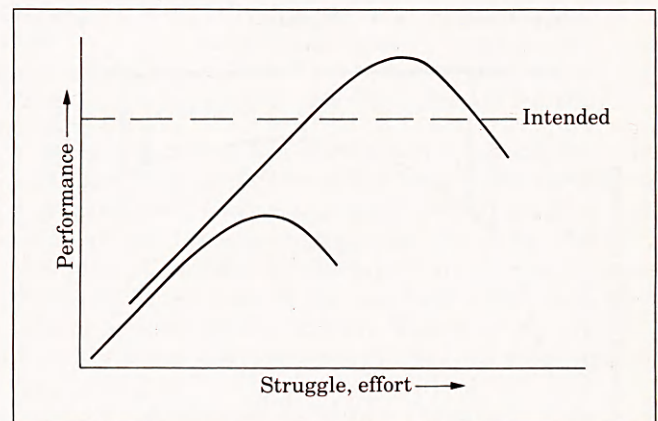


Fig 1. Performance-arousal curves as models of Lewis's approach to triage in effort syndrome.

* Sir Thomas Lewis CBE MD DSc FRCP FRS, born 1881, died 1945. Physician and Director of Department of Clinical Research, University College Hospital, London.

limits of homeostatic tolerance, performance fails. Some individuals (lower curve) have a lower potential for performance and a lower threshold for 'going over the top' than the hardier (upper curve), but the differences are of degree, not of kind. Even the heroic have their limits and suffer from effort syndrome when they go 'over the top'. Lewis pointed out that the differences in symptomatology which exist between health and effort syndrome are largely differences of degree; but there is no sharp line of division. Experience taught Lewis that it was more useful to maintain this concept of a grey area than to attempt to make a specific disease out of effort syndrome. He also emphasised that it is not peculiarly a soldier's malady but one of the commonest disorders seen among men, women, and children in civilian practice.

After World War I, Kerr *et al* [4] considered that up to one-third of patients seen in general practice were suffering from the effects of struggle. A diagnosis of anxiety neurosis might be made, but essentially they were trapped in a vicious circle, emotional arousal creating physiological disturbances and visceral sensations which, in turn, raised the level of anxiety. The sympathetic nervous system became increasingly labile, and the nervous system increasingly irritable from the effects of hyperventilation and tissue alkalosis.

Soley and Shock [5] investigated effort syndrome and concluded that hyperventilation due to anxiety and effort was an adequate cause of its symptoms, at that time listed under diagnoses such as soldier's heart, disordered action of the heart (DAH), neuro-circulatory asthenia or Da Costa's syndrome.

In World War II, neither Wood [6] nor Friedman [7] accepted Lewis's view of the aetiological importance of buffer salt depletion.

Buffer salt depletion

Lewis's investigation suggested that:

'Owing to a deficiency of certain blood constituents, it is said to approach more nearly towards an acid reaction than is normal when small quantities of carbon dioxide (CO₂) or lactic acid (such as are produced by exercise) are added to it. This approach to an acid reaction is at once signalled by breathlessness, the respiratory centre being extraordinarily sensitive to the blood reaction.'

His theory of 'buffer salt depletion' [6] was rejected by those who found plasma bicarbonate levels in the lower range of normal values and did not appreciate that the resting plasma bicarbonate level is an inadequate predictor of the body's acid-base responses to effort. Today this 'approach to an acid reaction' can be observed simply and directly by recording end-tidal (end-expiratory) CO₂ levels during conventional exercise testing.

Over-reaction to minor stresses

Lewis [8] warned that ignoring the buffering fault would encourage clinicians to 'attribute effort syndrome wholly to the instability or irritability of the ner-

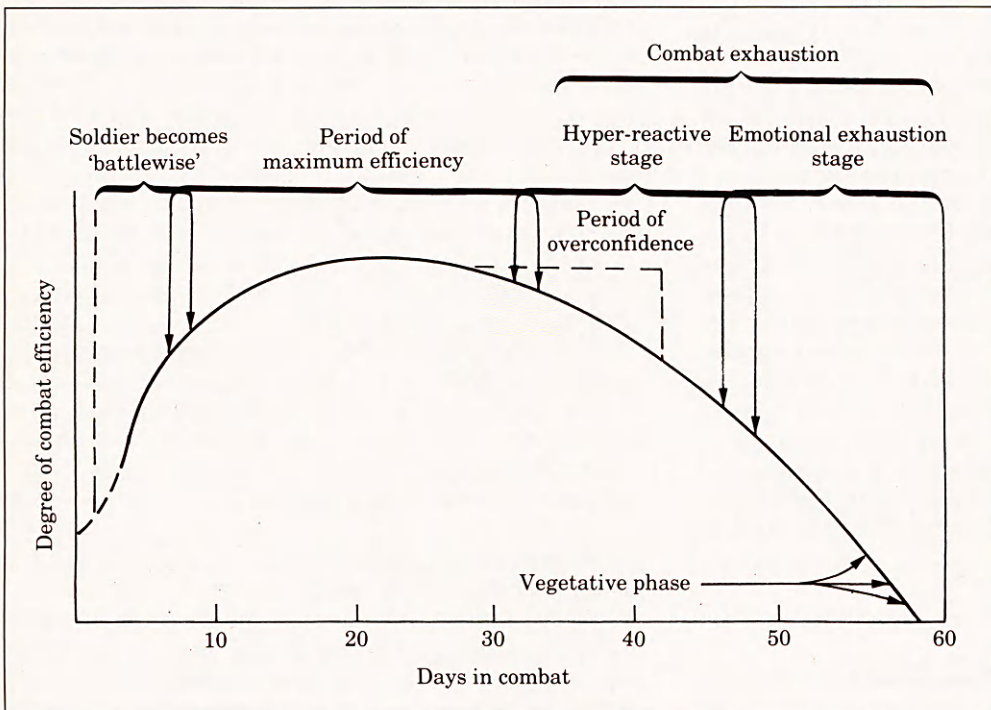


Fig 2. Performance-arousal curve model of human function in battle. A portrayal of the relation of stress and the development of combat efficiency (heavy black line) of the average American soldier [2].

vous system', overpromote the diagnosis of neuro-circulatory asthenia, and foster a pejorative view of the patient. Notwithstanding Lewis's warning against ignoring the buffering deficit, much is written today about exhaustion (fatigue syndrome) and unspecific ill health without mention of the hyperventilation or effort syndrome that would open the door to rehabilitation.

Today Lewis would find support for his views in publications which conclude that the increased sensitivity and over-reaction to sensory stimuli are secondary responses to disordered habituation [9], to alkalosis and hypocapnia [10,11], and to high levels of emotional arousal associated with both reduction of regulatory inhibition of the sympathetic nervous system and asymmetry of its input to the heart [12,13]. Common symptoms are hyperacusis, photophobia, paraesthesiae, and irritability with people.

Although he had made the point that the symptoms of effort syndrome resembled the effects of exercise in the healthy, Lewis was well aware that factors other than physical effort were aetiologically important. He wrote about the role of tension and anxiety of mind, arduous work, irregularity of habits in feeding and sleeping, and exposure of the body to wet and cold.

Metabolic consequences of hyperventilation

The definition of hyperventilation is precise: it is an increase of alveolar ventilation beyond metabolic requirements. Carbon dioxide is eliminated faster than it is produced by the tissues. The overbreathing might be the result of altitude, certain diseases and toxic conditions, and some drugs. It can be obtained voluntarily by overriding the normal control of ventilation, and involuntarily it is a consequence of high levels of emotional arousal [14]. Voluntary 'hysterical' or manipulative overbreathing probably accounts for less than 1% of cases. It is the involuntary, emotionally driven type that involves us most as clinicians.

The immediate consequences of hyperventilation are a fall of pressure of carbon dioxide in the arterial blood below the normal range of 36–45 mmHg (hypocapnia), and a rapid shift of the acid-base balance towards alkalosis [14]. An acute hypocapnic state can be reached in less than a minute. If the overbreathing were to be maintained the homeostatic regulation of the acid-base balance would be challenged by the continuing loss of carbonic acid from the system. Protection of pH is obtained by the excretion of alkalis into the urine. This is injurious if it is carried beyond tolerance because potassium [15] and phosphates are also lost [16,17]; this loss is itself a cause of fatigue. Physical activity is limited because lactic and other acids produced by exercising skeletal muscle are buffered less completely than normal, with the consequence that the muscles ache. The unbuffered acids reach the central circulation. As Lewis said, this 'approach to an acid reaction is at once signalled by

breathlessness'. The reactive overbreathing contributes to the vicious circles that help to perpetuate hyperventilation.

The catecholamine and cortisol elements of the concomitant emotional arousal can cause magnesium diuresis: this reduces opposition to the intracellular calcium overloading which is an important consequence of respiratory alkalosis [18]. The rise of the $\text{Ca}^{++}/\text{Mg}^{++}$ ratio increases the tone of the body's muscular tubing and thereby promotes cerebral, coronary and peripheral vascular constriction, bronchial constriction, and muscular disorders of the gut and urogenital systems [19].

The variable outcome of a period of hyperventilation

The outcome of a given act of hyperventilation is unpredictable because it is governed not only by the rate, depth, and duration of the overbreathing but also by pre-existing conditions such as the level of emotional arousal, the depletion of the alkaline buffering systems, and the prevailing conditions of sensitivity and reactivity to stimulation [9–13]. It is affected by reduction of cerebral blood flow and the Bohr effect (oxygen release from haemoglobin) [20]; failure of perception of hypocapnia [21]; anxiety caused by somatic symptoms that have no apparent relationship to the breathing; and activation of vicious circles of emotional arousal and overbreathing.

Thus the forced hyperventilation test is unreliable: in the reassuring presence of the physician an act of hyperventilation is unlikely to produce the symptoms it might in a frightened woman on a lonely road at night. On the other hand, recalling episodes of high emotional arousal, particularly where anger is involved, can trigger a severe and prolonged bout of hypocapnia in the susceptible [22]. Individuals with an emotional impediment called 'alexithymia' cannot respond to imagery testing in this way [13].

Chronic hyperventilation with impairment of buffering

It takes a great deal of overbreathing to deplete the alkaline buffering systems to the level where even light physical activity can cause a shift towards acidosis and stimulate the respiratory centre as Lewis described. At this level of metabolic derangement the anaerobic threshold for exercise is low, and fatigue and muscular aching a prominent symptom. The diagnosis can be made by using capnography during exercise testing (see below).

During the night the subject commonly awakens between midnight and three am with anxiety or panic, sweating, restlessness, and palpitations. This is because sleep has reduced ventilation and permitted a shift towards acidosis which triggers the hyperventilation response. During the day there is restlessness and inability to be still because muscular relaxation with-

out the appropriate reduction of ventilation produces a bout of hypocapnia [23,24].

The breathing behaviour

In hyperventilation with impairment of buffering the breathing usually appears effortless and unobtrusive [25]. The predominant movement is upper thoracic. The depth and rate can be seen to rise and fall with variation of emotional arousal, giving a clue to topics that cause emotional upset, and the rhythm can be disturbed by breath-holding or respiratory tics such as sighs, yawns, sniffs, and coughs. Aerophagy is common. The thorax can be over-inflated to a point that precludes the inspiration of anything more than a small fraction of the tidal volume. This can cause tachypnoea and terror. The pain from the overdistended chest is commonly regarded as cardiac, particularly where the hyperventilation is causing *angor animi* through cerebral vasoconstriction, or paraesthesiae with pain in the arm(s). Many are taken to hospital and risk invasive intervention and lifelong labelling as heart patients, particularly where the ST and unspecific T-wave ECG changes of hyperventilation are mistaken for ischaemia. Patients with ischaemic heart disease may hyperventilate when exhausted, and when they do so run the risk of surgical intervention [26].

The borderland between health and disease

In this grey area the individual can undergo profound alterations of health and performance and adaptability without showing evidence of concrete disease. It is clearly desirable to develop yardsticks for changes to assist in diagnosis and rehabilitation.

The performance-arousal curve is a useful model for representing the 'gradient from the healthy man to him who is seriously unwell' [3], and also for classifying the information we have today (Fig 3) [27].

The performance-arousal curve today

The curve represents the continuum from health and healthy fatigue through exhaustion and ill health to the point P of sudden discontinuous or catastrophic change due to breakdown of homeostatic control. Unfortunately arousal cannot be quantitated, but the perception of it as a determinant of health and performance (the ability to do what has to be done) has heuristic value: for example, in rehabilitation, the curve can act as a chart for plotting the position and course of a patient in the grey area in a way that can be understood by therapists from different disciplines.

Lader [28] described arousal as a continuum extending from drowsiness at one extreme, through alertness and conditions of excitement to the extremes of revulsion, rage, panic, and ecstasy at the other. Fig 3 is drawn with a peaked top because most patients can pinpoint the time when an emotional upset, an event

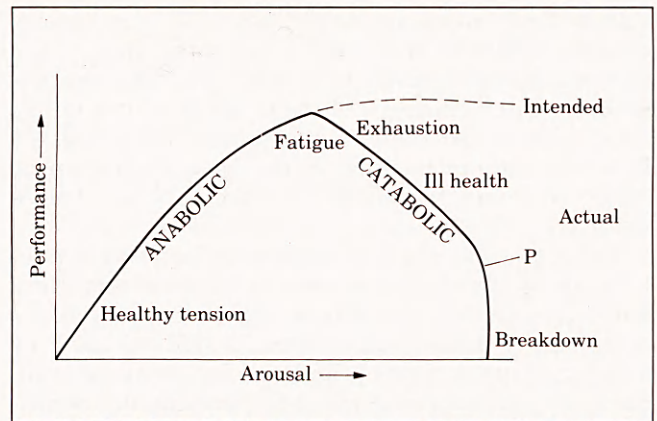


Fig 3. A performance-arousal curve for rehabilitation. P represents the catastrophic cliff-edge of breakdown.

or trauma, marked their going 'over the top' from customary upslope traits of performance and health into downslope states of exhaustion and ill health. The 'intended' dotted line is drawn to emphasise the fact that people on the downslope may focus their minds on closing the gap between what they can do and what they think is intended of them, and struggle harder, but succeed in little more than moving deeper into homeostatic disorder. This predicament probably acts as a breeding ground for hyperventilation-related illness.

The affect in the downslope disorders tends to be high and labile, switching rapidly but unpredictably through denial, fear, panic, frustration, anger, despair, and 'giving in—giving up'.

Since Lewis's day many more downslope disorders (Fig 3) have been clarified.

Sympathetic activity and hypocapnia

It is often assumed that overbreathing is an automatic consequence of sympathetic activation, but the two are independently triggered [13,29]. They act synergistically, and may create vicious circles of interaction: sympathetic stimulation amplifies the respiratory response to given levels of arterial carbon dioxide [30], and hypocapnia increases sympathetic activity [31]. Chronic hyperventilation itself increases the sensitivity of the respiratory centre, and this may be the reason why the anxious hyperventilator finds it difficult to hold his breath.

Depression of parasympathetic activity by hypocapnia permits sympathetic dominance and explains the prevalence of sinus tachycardia, overactive heartbeat, cold hands, and sweating axillae in hyperventilators [3,20].

The sympathetic system's loss of cerebral cortical inhibition and the asymmetry of its input to the heart promote cardiac arrhythmia, coronary vasoconstriction, and myocardial repolarisation disorders [12,13].

Some metabolic responses to stress

During relatively easy tasks the sympathetic nervous system is aroused. With challenging tasks the adrenal medulla begins to secrete catecholamines. On the downslope, where the individual is carried beyond the boundaries of physiological tolerance by more prolonged, severe, unfamiliar or stressful effort, or put into predicaments not permitting control over aversive stimuli, the pituitary-adrenocortical system comes into play and cortisol is secreted. This has a lipogenic effect and catalyses the action of the catecholamines on target organs [32,33]. Catecholamine secretion in everyday life can reach phaeochromocytoma-like levels [34], and the plasma cholesterol rise 50–60% above baseline [35]. Where these neuroendocrine influences overwhelm insulin, the catabolic effects foster diabetes mellitus, obesity, hypertension, hyperlipidaemia, and atherosclerosis [36]. Sterling and Eyer [37] provide an excellent description of the pathways by which anabolic influences and immune competence are diminished and catabolic processes increased at the high and more sustained levels of arousal. These processes are aggravated by sleep loss [38].

Hyperventilation and non-specific illness

There is an expansion of interest in the grey area of unspecific illness or 'medical symptoms not explained by disease' [39], and a proliferation of self-interest groups promoting their own notions of causation of ill health. Hyperventilation is usually omitted from differential diagnosis, probably because it is regarded as a pejorative label and tantamount to an accusation of neurosis or malingering, or possibly because it is assumed to be an innocuous byproduct of anxiety.

The failure to consider hyperventilation has been lamented by a number of writers [4,5,16,40–43]. Lum [20] believed that hyperventilation had an important if not primary role in 40% of patients attending a general physician's clinic in 1969. The proportion is probably greater today. In about 50% of patients attending cardiological clinics the symptoms are not explained by disease, and effort syndrome is a useful diagnosis because it opens the door to rehabilitation. Patients with coronary disease can acquire effort syndrome,

and the likelihood of surgical treatment is increased if the hyperventilation-induced symptoms and ECG changes are not recognised [24]. The coupling of emotional arousal with hyperventilation in exhaustion can trigger cardiovascular destabilisation and dynamic conditions such as coronary vasoconstriction or spasm and arrhythmia [27], as may be seen, for example, in unstable angina, syndrome X, or the switching on of a paroxysmal tachycardia.

Ill-defined neurological disorders with paraesthesiae, facial pain, tinnitus, hyperacusis, or photophobia, and ischaemic symptoms without organic disease are common, as are anxiety states, phobic disorders, and panic. 'Fibrositis' is also common and usually yields to correction of the sleep disturbance and buffer depletion [27]. In a study of a popular 'myalgic' fatigue syndrome with a supposedly viral aetiology, symptoms of effort syndrome antedated the real or purported viral infection by a mean period of 2.3 years [44].

Diagnosis of hyperventilation syndrome

Questionnaires have been designed to pick up hyperventilation as a marker or mediator of illness, but their value has declined now that their symptom lists have been appropriated by single-interest groups applying them to alternative diagnoses.

Plasma bicarbonate analysis

It was Wilson, Levine and Edgar [45] who dismissed Lewis's theory of causation of effort syndrome. They did not consider the possibility that the competence of the body's buffering systems and the acid-base responses to exercise cannot be predicted from resting plasma bicarbonate values [46–48]. One wonders what opportunities for research and clinical intervention have been lost through the continuing acceptance of this dismissal [49,50].

Capnography

Capnography is a technique which allows air from a nostril to be drawn through a rapid infrared CO₂ analyser and the result registered continuously on a recorder. When proper precautions are taken, the

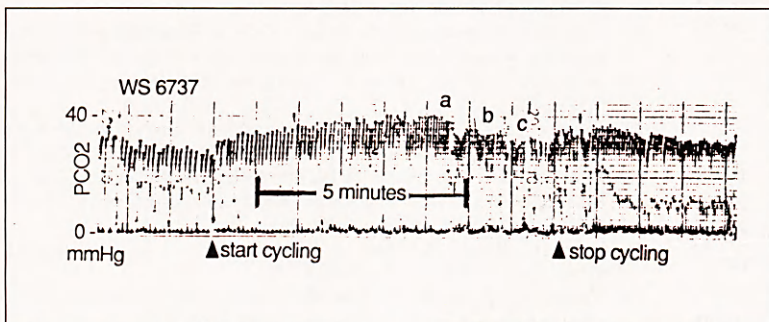


Fig 4. Capnogram: Middle-aged man with effort syndrome seated on a bicycle ergometer. Anticipatory overbreathing reduces the end-tidal pCO₂ from 34 to 26mmHg. Arrival at the anaerobic threshold after five minutes light effort is signalled by aching legs (a) and a fall of pCO₂ from acidotic stimulation of the respiratory centre. Chest pain occurs at (b), exhaustion at (c).

end-tidal portion (Pet CO₂) of the cycle provides a reading within about 1mmHg of the simultaneous arterial pCO₂ tension [51]. The apparatus can be used to record resting Pet CO₂ levels, less than 35mmHg indicating hypocapnia [14,51], and the responses to challenges such as forced hyperventilation, imagery (the think test) [22,40] and exercise [52]. In chronic hyperventilation subjects are usually unaware of hypocapnia [21,40,41].

Before the variables affecting the outcome of a period of hyperventilation were appreciated the diagnostic use of capnography was made difficult by uncritical use of the forced hyperventilation test; and by an insistence that the pCO₂ should constantly be less than 30mmHg, an error pointed out by Lum [51]. The use of a range of challenges makes it easier to form an opinion as to whether the CO₂ regulation is closely wedded to the metabolic needs of the body or distracted from it to the detriment of health and performance, by emotional arousal, buffer depletion, and other disorders of homeostatic regulation.

Capnography during exercise testing is particularly useful in effort syndrome because the onset of leg pain or discomfort, signalling Lewis's approach to an acid reaction, is seen to be followed swiftly by falling pCO₂, overbreathing with or without chest pain, and exhaustion: these are signs of arrival at the anaerobic threshold which is reduced in effort syndrome by depletion of the alkaline buffering systems (Fig 4).

Management with SABRES

A cardiac rehabilitation service based upon Lewis's and Mackenzie's principles [3,54] appeared to accommodate the needs of effort syndrome pretty well in the 1960s and 1970s. It took into account the need for sleep, arousal management, breathing, the balance of rest and effort and the recovery of self-esteem (acronym SABRES) [55-57]. Rejection of rehabilitation began in the 1980s when proselytising self-interest groups, fostering beliefs in allergic and viral aetiologies, increasingly demanded 'cures' for what they insisted were 'diseases', and rejected beliefs in recovery through learning and training. Medical failure to produce a concrete diagnosis aggravated the position. Cynicism and lack of commitment removed a well-designed intervention, with the consequence that the recovery rate might be falling from the 70% claimed by Lum [20] for hyperventilation-related disorders towards the 15% reported by Grant [58].

Conclusions

Lewis should be given full credit for describing effort syndrome, identifying the key role of depletion of the body's buffering systems, and asserting that neurasthenia, the 'over-reaction to the minor stresses of everyday life', had a physical, metabolic basis.

There is sufficient evidence to justify the inclusion

of non-invasive CO₂ testing in the investigation of fatigue syndromes and unspecific ill-health as well as in functional cardiovascular disorders. The demonstration of hyperventilation and low anaerobic threshold for effort invites intervention by rehabilitation.

Traditional methods of rehabilitation, such as the regimen described by T Lauder Brunton [59], available still in continental Europe, might need to be rediscovered for effort syndrome. It is unlikely that palliative drug therapy and prolonged rest can be successful if the depletion of the buffering systems, the hyperarousal and the hyperventilation are ignored.

References

- 1 Pickering GW. *High Blood Pressure*. London: Churchill, 1955.
- 2 Wolf S, Wolff HG. A summary of experimental evidence relating life stress to the pathogenesis of essential hypertension in man. In: *Hypertension*. (Bell ET, ed). Minneapolis: University of Minnesota Press, 1951; p288.
- 3 Lewis T. *The soldier's heart and the effort syndrome*. London: Shaw and Sons, 1918.
- 4 Kerr WJ, Dalton JW, Glibe PA. Some physical phenomena associated with the anxiety states and their relation to hyperventilation. *Ann Intern Med* 1937;**2**:961-92.
- 5 Soley MH, Shock NW. The etiology of effort syndrome. *Am J Med Sci* 1938;**196**:840-51.
- 6 Wood P. Da Costa's syndrome (or effort syndrome). *Br Med J* 1941;**1**:767-72, 805-11, 845-51.
- 7 Friedman M. Studies concerning the etiology and pathogenesis of neurocirculatory asthenia. Part i. *War Medicine* 1944;**6**:221-7. Part ii. *Am Heart J* 1945;**30**:325-32. Part iii. *ibid* 1945;**30**:478-91. Part iv. *ibid* 1945;**30**:557-66.
- 8 Lewis T, Cotton TF, Barcroft J, et al. Breathlessness in soldiers suffering from irritable heart. *Br Med J* 1916;**2**:517-9.
- 9 Gruzelier JH, Nixon PGF, Liddiard D, et al. Retarded habituation and lateral asymmetries in electrodermal activity in cardiovascular disorders. *Int J Psychophysiology* 1986;**3**:219-26.
- 10 Lum LC. Hyperventilation and anxiety state. *J R Soc Med* 1981;**74**:1-4.
- 11 Stead EA. Hyperventilation. *Dis Mon* 1960;**1**:31.
- 12 Wolf S. Psychosocial forces in myocardial infarction and sudden death. *Circulation* 1969;**39** (suppl 4):74-81.
- 13 King JC. *Sympathetic and hypocapnic pathways between the brain and the heart: implications for health care*. MSc thesis. Roehampton Institute, University of Surrey, 1991.
- 14 Grossman P, Wienties CJ. Respiratory disorders: asthma and hyperventilation syndrome. In: *Handbook of clinical psychophysiology*. (Turpin G, ed), Chichester: Wiley, 1989; pp519-54.
- 15 Knoche JP. Hypokalaemia. *Adv Intern Med* 1984;**30**:317-35.
- 16 Magarian GJ. Hyperventilation syndromes: infrequently recognised common expressions of anxiety and stress. *Medicine* 1982;**61**:219-36.
- 17 Weiner H. Stressful experience and cardiorespiratory disorders. *Circulation* 1991;**83** (suppl 2):2-8.
- 18 Ginsburg R, Bristow M, Schroeder J, et al. Potential pharmacologic mechanisms involved in coronary artery spasm. In: *Drug-induced heart disease*. (Bristow M, ed), Amsterdam: Elsevier, 1980; pp451-65.
- 19 Ribeiro LGT, Lefer AM. Etiology and pathology. In: *Coronary artery spasm* (Chahine RA, ed), New York: Futura, 1983;p46.
- 20 Lum LC. The syndrome of habitual chronic hyperventilation. In: *Modern trends in psychosomatic medicine*, 3 (Hill OW, ed), London: Butterworth, 1976; pp196-230.
- 21 King JC, Rosen SD, Nixon PGF. Failure of perception of hypocapnia. *J R Soc Med* 1990;**83**:765-7.
- 22 Nixon PGF, Freeman LJ. The 'think test': a further technique to elicit hyperventilation. *J R Soc Med* 1988;**81**:277-9.

- 23 Ley R. Panic attacks during relaxation and relaxation-induced anxiety: a hyperventilation interpretation. *J Behav Ther Exp Psychiatry* 1988;**19**:253-9.
- 24 Ley R. Panic attacks during sleep: a hyperventilation-probability model. *J Behav Ther Exp Psychiatry* 1988;**19**:181-92.
- 25 Okel BB, Hurst JW. Prolonged hyperventilation in man. *Arch Intern Med* 1961;**108**:157-62.
- 26 Freeman LJ, Nixon PGF, Legg C, Timmons BH. Hyperventilation and angina pectoris. *J R Coll Physicians Lond* 1987;**21**:46-50.
- 27 Nixon PGF. Human functions and the heart. In: *Changing ideas in health care* (Seedhouse D, Cribb A, eds), Chichester: Wiley, 1989; pp31-65.
- 28 Lader L. Psychophysiological parameters and methods. In: *Emotions, their parameters and measurement* (Levi L, ed), New York: Raven Press, 1975: p361.
- 29 Ley R. Blood, breath and fears: a hyperventilation theory of panic attacks and agoraphobia. *Clinical Psychology Review* 1985;**5**:271-85.
- 30 Schaefer KE. Respiratory pattern and respiratory response to CO₂. *J Appl Physiol* 1958;**13**:1-14.
- 31 Groen JJ. The measurement of emotion and arousal in the clinical physiological laboratory and in medical practice. In: *Emotions, their parameters and measurement* (Levi L, ed), New York: Raven Press, 1975, pp727-46.
- 32 Henry JP, Stephens PM. *Stress, health and the social environment*. New York: Springer-Verlag, 1977.
- 33 van Doornen L. Stress and the dynamics behind hypertension, cholesterol and atherosclerosis. In: *Behavioural observations in cardiovascular research* (Appels A, ed), Amsterdam: Swets and Zeitlinger, 1991: pp79-106.
- 34 Kagan AR, Levi L. Health and environment—psychosocial stimuli: a review. *Soc Sci Med* 1974;**8**:225-41.
- 35 Dimsdale JE, Herd JA. Variability of plasma lipids in response to emotional arousal. *Psychosom Med* 1982;**44**:413-30.
- 36 Brindley DN, Rolland Y. Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in atherosclerosis. *Clin Sci* 1989;**77**:453-61.
- 37 Sterling P, Eyer J. Allostatis: a new paradigm to explain arousal pathology. In: *Handbook of life stress, cognition and health* (Fisher S, Reason J, eds), Chichester: Wiley, 1988: pp629-49.
- 38 Adam K, Oswald I. Sleep helps healing. *Br Med J* 1984;**289**:1400-1.
- 39 Creed F, Mayou R, Hopkins A, (eds). *Medical symptoms not explained by organic disease*. London: Royal College of Psychiatrists & The Royal College of Physicians, 1992.
- 40 Lewis BI. Chronic hyperventilation syndrome. *JAMA* 1954;**155**:1204-8.
- 41 Lewis BI. Hyperventilation syndrome. *Calif Med* 1959;**91**:121-6.
- 42 Rice RL. Symptom patterns of the hyperventilation syndrome. *Am J Med* 1950;**8**:691-700.
- 43 Engel GL, Ferris EB, Logan M. Hyperventilation: analysis of clinical symptomatology. *Ann Intern Med* 1947;**27**:683-704.
- 44 Rosen SD, King JC, Nixon PGF. Is chronic fatigue syndrome synonymous with effort syndrome? *J R Soc Med* 1990;**83**:761-4.
- 45 Wilson FN, Levine SA, Edgar AB. The bicarbonate concentration of the blood plasma in cases of irritable heart. *Heart* 1920;**7**:62-4.
- 46 Edwards RHT. Personal communication, 1993.
- 47 Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis. *N Engl J Med* 1991;**324**:1394-401.
- 48 Jones NL. *Blood gases and acid-base physiology*. New York: Thieme, 1987: pp161-5.
- 49 Paul O. DaCosta's syndrome or neurocirculatory asthenia. *Br Heart J* 1987;**58**:306-15.
- 50 Wooley CF, Stang JM. Samuel A. Levine and his world war 1 experience. *Am J Cardiol* 1988;**62**:952-6.
- 51 Collier CR, Affeldt JE, Farr AF. Continuous rapid infrared CO₂ analysis. *J Lab Clin Med* 1955;**45**:526-39.
- 52 Chambers JB, Kiff PJ, Gardner WN, et al. Value of measuring end-tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing. *Br Med J* 1988;**296**:1281-5.
- 53 Lum LC. Hyperventilation syndromes in medicine and psychiatry: a review. *J R Soc Med* 1987;**80**:229-31.
- 54 Mackenzie J. The soldier's heart. *Br Med J* 1916;**1**:117-9.
- 55 King JC. Hyperventilation—a therapist's point of view. *J R Soc Med* 1988;**81**:532-6.
- 56 King JC. Cardiac rehabilitation. In: *Occupational therapy and physical dysfunction* (Turner A, Foster M, Johnson SE, eds), Edinburgh: Churchill Livingstone, 1992: pp763-78.
- 57 Nixon PGF. Behavioural management and rehabilitation after acute myocardial infarction. In: *Behavioural Medicine: International Perspectives* (Byrne DG, Caddy GR, eds), New Jersey: Ablex, 1992: pp121-52.
- 58 Grant RT. Observations on the after-histories of men suffering from the effort syndrome. *Heart* 1926;**12**:121-42.
- 59 Lauder Brunton T. *Collected papers on circulation and respiration*. London: Macmillan, 1916: pp451-72, 637-60.

Address for correspondence: Dr P G F Nixon, 43 Weymouth Street, London W1N 3LD.