UNIVERSITY OF SOUTHAMPTON

ON DYSPNOEA

IN

ADVANCED CANCER

by Louis Henry Heyse-Moore MRCP

Doctor of Medicine

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MEDICINE I

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ABSTRACT

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The literature on dyspnoea in advanced cancer is reviewed. In a study of 968 patients, dyspnoea was shown to be common and commonly severe. Survival was inversely proportional to severity and prevalence. Established methods of measuring dyspnoea - visual analogue scales (VAS) and word and numeric scales were tested. A new measure of dyspnoea, the Dyspnoea Assessment Questionnaire (DAQ) was developed incorporating qualitative as well as quantitative aspects of dyspnoea. It correlated well with the VAS. Dyspnoea was less well controlled than pain. Another new measure, the Dyspnoea Exertion Score (DES) did not correlate with VAS scores. Measurement of psychological status by the Crown-Crisp Experiential Index (CCEI) showed raised scores for anxiety, obsessionality and depression for terminal cancer patients. In dyspnoeic patients, only anxiety levels were higher than in the non-dyspnoeic. Lung and pleural tumours, smoking and the hyperventilation syndrome (HVS) were risk factors for dyspnoea. The Hyperventilation Provocation Test (HVPT) was used to diagnose HVS. CCEI anxiety scores were higher in HVS than in either non-HVS or dyspnoeic patients. HVS was diagnosed in 1 in 5 patients tested. In conclusion: dyspnoea is a major problem in advanced cancer; a new method of measuring it was developed; HVS is a common cause.

Dedication

In memory of my father

Page 127, para 3, line 1 - "Days" should read "Weeks".

Page 127, para 4, line 1 - "168" should read "68".

Page 128, row 8 of table - "Days" should read "Weeks".

Page 167, para 6, line 1 - "Days" should read "Weeks".

Page 168, whole of para 1, to read: "COAD. The median time (26 weeks) indicates that dyspnoea is not only common and often severe but also often long-lasting, with an attendant chronic restriction of mobility."

Page 186, conclusion No.16, line 2 - "Days" should read "Weeks".

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ACKNOWLEDGEMENTS

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Appendix 9 - From Heyse-Moore LH et al. How much of a problem is dyspnoea in advanced cancer? - permission granted by Edward Arnold; similarly figs 12 and 14.

The author would also like to thank the many people, too numerous to mention individually, for their support and advice. In particular my thanks to Professor JBL Howell for acting as my supervisor; to Vernon Ross, my research assistant; to Mark Mullee for statistical and computing advice; to Dr R Hillier and Dr G Thorpe for their help with this project and for kind permission to study their patients at Countess Mountbatten House; to Dr Lees, the junior doctors and all the ward staff for their help in data collection; to Mrs J Toomer, Mrs S Adcock and Mrs Theresa Clark for typing of forms and the manuscript; to Dr Guyer for advice on chest x-rays; to Dr Gallagher for carrying out post mortems on patients studied; to the Sisters of Charity, St. Joseph's Hospice for their help and support during preparation of the manuscript; to the Friends of Countess Mountbatten House for purchasing computers used in this study; to Cancer Relief Macmillan Fund for underwriting the costs of my post, of a research assistant and secretarial support; to Vitalograph Ltd for their loan of vitalograph spirometry equipment; and finally to all the patients who generously agreed to take part in this study.

ABBREVIATIONS

Those in common medical use are not listed here.

ABBREVIATION	FULL NAME	PAGE REFERENCE
AVIS	Average Interval Score	101
AVCS	Average Class Score	101
AVSS	Average Severity Score	101
CCEI	Crown-Crisp Experiential Index	60, 231
CP	Cortical Perception	41
DAQ	Dyspnoea Assessment Questionnaire	99, 209
DES	Dyspnoea Exertion Score	103,213
DQQS	Dyspnoea Quality-Quantity Score	103
DWS	Dyspnoea Word Score	107
HVPT	Hyperventilation Provocation Test	55
HVS	Hyperventilation Syndrome	33, 47
ME	Magnitude Estimation	64
MMPQ	McGill-Melzack Pain Questionnaire	65, 215
MRC	Medullary Respiratory Complex	41
NWC	Number of Words Chosen	65
NWCS	Number of Words Chosen Score	101
OHFO	Oral High Frequency Oscillations	95
PDI	Transdiaphragmatic Pressure	31
PDIMAX	Maximum Transdiaphragmatic Pressure	31
PPI	Present Pain Intensity	65
PRI(S)	Pain Rating Index (Sum)	65
PRI(R)	Pain Rating Index (Rank)	65
PTSS	Percentage Total Severity Score	103
SBW	Score of Best Word	101
SFMPQ	Short-form Melzack Pain Questionnaire	66, 217
STSS	Short Total Severity Score	101
TCS	Total Class Score	101
TIS	Total Interval Score	101
TSS	Total Severity Score	101
VAS	Visual Analogue Scale	61
VASMe D	Mean 24 hour VAS dyspnoea - Doctor Assessment	105

ABBREVIATIONS (cont'd)

ABBREVIATION	FULL NAME	PAGE REFERENCE
VASMe N	Mean 24 hour VAS dyspnoea - Nurse Assessment	106
VASMe 7	Mean VAS dyspnoea for previous week	108
VASMe 24	Mean 24 hour VAS dyspnoea - Patient Assessment	103
VASMax 52	Worst VAS dyspnoea for previous week	107

CHAPTER 1 INTRODUCTION

> "I actually feel that I am not going to come through it..... I thought I was going to die before anyone got there..... You've got to fight for that last gasp of breath..... It's very very frightening when you're on your own."
>
> (from a conversation with a patient with breast carcinoma and lung metastases).

Albert Schweitzer said that "pain is a more terrible lord of mankind than even death itself."[1] Dyspnoea, and the fear of suffocation, as shown in the above quoted conversation, may be if anything worse and demands effective relief which at present is not always met.

The literature on dyspnoea in advanced cancer is still sparse and much has to be inferred second hand from research done in a general medical setting. Anecdotal evidence is still often the only source justifying clinical practice.[2]

For these reasons the author decided to study the epidemiology, measurement and causes of dyspnoea to provide a foundation on which future research into treatment could be built.

1.1 Goals

The overall goals of the study were as follows:

1. To review the literature on dyspnoea in advanced cancer.
2. To study its epidemiology.
3. To investigate present methods of measuring dyspnoea in terminal care and to assess their relative merits.

4. To develop a new method of measuring dyspnoea taking into account qualitative as well as quantitative aspects.
5. To investigate the place of the following factors in the aetiology of dyspnoea: site of primary cancer, lung metastases, the hyperventilation syndrome and psychological status.
6. To study changes in dyspnoea over time.

1.2 Hypotheses

1. Dyspnoea is a common and major problem in advanced cancer.
2. Patients, doctors and nurses do not always agree as to the presence and degree of dyspnoea.
3. Words employed by patients to describe their dyspnoea may be used to provide a score of its severity.
4. The comprehensiveness of measurement of dyspnoea may be increased by taking into account qualitative as well as quantitative factors.
5. The hyperventilation syndrome is a common and under-recognised cause of dyspnoea in advanced cancer.
6. Anxiety and depression levels are higher in dyspnoeic than non-dyspnoeic patients.
7. Dyspnoea is at present less effectively relieved than pain.

CHAPTER 2 LITERATURE REVIEW

2.1 Definitions

Dyspnoea

Comroe[3] defined dyspnoea as "difficult, laboured, uncomfortable breathing; it is an unpleasant type of breathing, though it is not painful in the usual sense of the word. It is subjective, and, like pain, it involves both perception of the sensation by the patient and his reaction to the sensation."

Heim et al[4] define dyspnoa as "the unpleasant feeling of difficulty or inability to breathe, based on the perception of real, threatened or fantasied impairment of ventilation." This definition indicates that not only is dyspnoea subjective but that the same stimulus causing dyspnoea "may be experienced and reported differently by different persons or by the same person at different times"[4]. This is because each person's previous experience is unique to them and hence can modify their perception of their bodily sensations. An example of this is anticipatory nausea and vomiting in patients receiving chemotherapy[193].

For patients with terminal cancer, symptom relief is paramount. Hence for the purposes of this study, any definition of dyspnoea must take this into account. So, although dyspnoea means literally "difficult breathing" it will here be taken to mean distressing respiratory difficulty. This means that the severity of a patient's dyspnoea is what he or she says it is. It also implies that although dyspnoea is often associated with patho-physiological changes such as hypercapnia, this is not universal.

Thus the dyspnoea of the hyperventilation syndrome may occur with normal lung function. Conversely, patients with acidotic hyperventilation may not feel distressed by their breathing and hence not be symptomatic.

Dyspnoea then has the following components:

1. A sensation linked *uniquely* to respiration. (Therefore chest pain due to a pathological rib fracture and brought on by respiration is not included).
2. Awareness of respiration.
3. Difficulty with respiration.
4. An affective component of distress.

This distressing difficulty may involve the act of breathing, or it may occur when the breath is held. In the second case the difficulty occurs because of the conflict between the desire to breathe, and the voluntary decision not to do so. The opposite of dyspnoea is eupnoea, that is, breathing characterised by a lack of sensations[42].

Breathlessness

According to Howell[5], "breathlessness can be defined as an awareness of the act of breathing, usually occurring when ventilation or the effort required to ventilate the lungs is excessive." He distinguishes between normal sensations and abnormal symptoms related to breathing: the first occurs when "normal people become aware of their breathing, either by consciously focussing attention upon it, or when it is so increased by exercise that it obtrudes into consciousness"; the second applies "when awareness of breathing occurs in unexpected circumstances, such as at rest without conscious attention, or with mild exertion; it is immediately recognised as abnormal ..... Despite the sensations being 'normal' their occurrence under abnormal circumstances leads to their becoming symptoms."

In this thesis, the word 'breathlessness' will apply in three ways - firstly, as one of the words patients may use to describe their dyspnoea, secondly as the word used when asking the patient about his or her dyspnoea, and thirdly as the word used in the various measurement scales to be applied to patients in this study.

So respiration and its disorders may be expressed diagramatically as in fig 1.

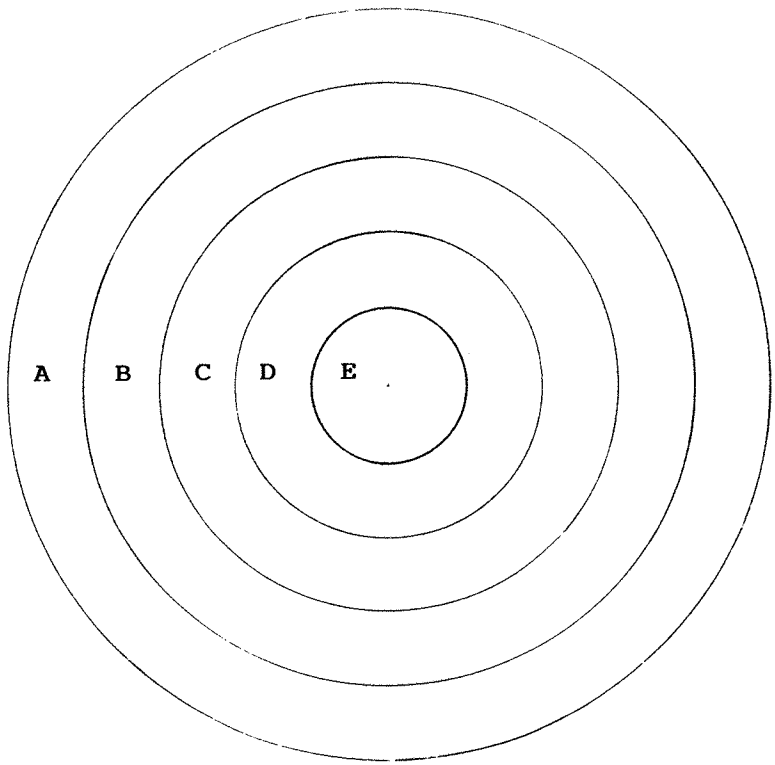
It is important to distinguish breathlessness and dyspnoea from tachypnoea (a respiratory frequency that is greater than normal at rest), from hyperpnoea (a respiratory excursion that is greater than normal at rest) and from hyperventilation (increased ventilation due to either tachypnoea or hyperpnoea, or both).

Another breathing pattern that might be confused with dyspnoea is periodic breathing, where respirations wax and wane either in amplitude or in frequency; a form of this is Cheyne-Stokes breathing[6] where there are alternating periods of hyperpnoea and apnoea (each lasting about 15-20 seconds) although the respiratory frequency does not alter, and the patient is not usually distressed. The pathophysiology will be discussed further on (see p 24).

Kussmaul respiration (hyperventilation due to metabolic acidosis) may also be mistaken for dyspnoea but can be distinguished because the respirations are not difficult and distressing.

The Hyperventilation Syndrome (HVS)

This condition has not been clearly defined. Thus, the results of a questionnaire completed by participants at a symposium on respiratory psychophysiology showed no



A = Respiration normal or abnormal

B = Breathlessness

C = Difficult breathing

D = Difficult distressing breathing (Dyspnoea)

E = Asphyxia

Fig 1. Venn diagram of relationships of respiration and its disorders

consensus[7]. The clearest definition the authors could obtain was that this syndrome is "characterised by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced in whole or in part by voluntary hyperventilation." This, however, lacks the qualities needed for an operational definition that would allow precise diagnosis. Two other factors - an increased sensitivity to hypocapnia[8] and reproduction of symptoms on hyperventilation[9,10,11] - which help to clarify the diagnostic criteria, will be discussed further later (see p 55).

Advanced Cancer

Countess Mountbatten House (CMH) like other terminal care units provides care for people dying of cancer. Within this group however, there is some heterogeneity. Firstly, 'cancer' here implies any neoplasm which clinically behaves in a malignant fashion, including for example histologically benign brain tumours. Secondly, although the diagnosis has usually been confirmed histologically, at times patients are accepted with no histological confirmation if it is clinically obvious that the patient has advanced cancer and is too frail to stand investigations that would not in any case change the management. Thirdly, patients may be referred who are in theory curable, but who have refused treatment. Fourthly, although most patients admitted have a short prognosis, measured in days or weeks, a few live much longer[12]. McCusker[13] defines the terminal care period as one where there is a progressive malignancy and where treatment won't significantly increase the survival. She points out that this period should not be confused with the point where life-expectancy is estimated to be short since a patient may die within several months but have a treatable malignancy. In her study the length of the terminal care period varied from 1-1320 days (Median 45 days, Mean 94 days).

Although most patients referred to hospices move from treatment to control the tumour, to terminal care for control of symptoms, a few go the other way as well. In many patients, these categories overlap.

For the purposes of this thesis, any patient admitted to CMH will be deemed to have 'advanced cancer'.

2.2 Etymology

The roots of words used to describe breathing and its problems shed some light on our perception of dyspnoea, especially from the aspect of emotional distress.

Dyspnoea comes from the Greek "dys" and "pnoia" meaning "difficult breath". Breathlessness derives from the old English "braeth" (which itself comes from the Indo-European "bhretos", "bhre" meaning "burn") and the old English "ness" implying a state or condition[14]. The connotation with "burn" evokes how in Genesis the Holy Spirit is symbolised by a divine wind and in Acts by a flame[15]. The words used for breath in Latin (Spiritus), Greek (Pnoia) and in Hebrew (Ruach) double up as the words used for spirit. Hence it can be seen how breathing was linked in these cultures with the very essence of a person's life, and it is not surprising then that even today, problems with breathing may be perceived as a threat to life itself, hence at times engendering extreme anxiety.

In present day English, this duality still occurs. Thus "Inspiration" means both to breathe in and to be inspired. Expiration means to breathe out, but to expire means to die.

Finally, "Cancer" from the latin for "crab"[13] suggests the sense of being inexorably trapped in the pincer-like growth of a tumour (particularly should it be a lung cancer).

2.3 Epidemiology

Frequency

Estimates of the overall rate of occurrence of dyspnoea in advanced cancer vary (see table 1)[2,16-25].

AUTHOR(S)	YEAR	INCIDENCE (I) & PREVALENCE (P)
Eaton-Smith[16]	1961	I = 2/33 = 6.1%
Saunders[17]	1967	I = 32% of 1100 pts.
Hinton[18]	1967	I = 17/102 = 16.7% (including non-cancer pts)
Hardy & Pritchard[19]	1977	I = 17/117 = 14.5%
Wilkes[20]	1984	I = 42% (including non-cancer pts)
Heyse-Moore[2]	1984	I = 179/381 = 48%
Twycross & Lack[21]	1986	I = 51%
Reuben & Mor[22]	1986	I = 70.2% of 1754 pts in last 6 weeks life
Wachtel et al[23] (Same study)	1988	P = Increased as death approached Measured at 2 week intervals: 49% ___ 55% ___ 64%.
Hockley et al[24]		I = 18/26 = 69.2% (patients with terminal cancer on a respiratory ward)
Higginson & McCarthy[25]	1989	I = 18/86 = 21% (Dyspnoea as main symptom

Table 1. Frequency of dyspnoea in terminal cancer.

The higher rates reported in more recent studies may reflect improved methods of data collection particularly by using a prospective design. Even these figures are probably underestimates as a number of patients would be unable to take part because of being confused or too ill. However it is this group of patients who are more likely to be dyspnoeic since Reuben and Mor[22] have shown that prevalence of dyspnoea increased as patients approached death. Certainly, dyspnoea can now be seen to be one of the commonest symptoms in terminal cancer.

Anorexia	90%
Weight loss	84%
Dyspnoea	64%
Pain	60%
Constipation	52%
Nausea and vomiting	44%

Table 2. Prevalence of commonest symptoms in terminal cancer. Modified from Wachtel et al.[23]

Severity

Hardy and Pritchard[19] in 1977 reported that in a study of 117 consecutive patients with terminal cancer of whom 17 were dyspnoeic, 8/17 (47.1%) had unrelieved constant dyspnoea, 6/17 (35.3%) had unrelieved inconstant dyspnoea and 3/17 (17.6%) were relieved.

Table 3 shows the range of severity of dyspnoea in a study using a five point verbal scale.

Symptom severity	No. patients	%
Horrible	51	8.4
Severe	92	15.1
Moderate	69	11.3
Mild	138	22.6
None	260	42.6

Table 3. Severity of dyspnoea, mean 7 days before death. From Reuben and Mor[22].

It should be noted that dyspnoea was rated as 'severe' or 'horrible' in 23.5% of the sample, showing that this symptom is not only common, but commonly severe. This is borne out by Lunt et al[26] in a study comparing two hospices and a district general hospital (table 4). They used different wording: extremely, very, moderately, slightly, or not breathless.

Setting	Mean worst level of dyspnoea on a 5 point scale.	Proportions severe or worse (%)
DGH	2.92	16/36 (44)
Hospice 1	2.19	6/33 (18)
Hospice 2	2.44	10/30 (33)

Table 4. Lunt et al.[26] Severity of dyspnoea in the 3 days before admission. 1985. DGH = District General Hospital.

Finally, Higginson and McCarthy[25] found that 18/86 (21%) of terminal cancer patients gave dyspnoea as their main symptom. On a 6-point verbal scale, they showed a trend for dyspnoea to decrease but then to worsen in the last week of life. These figures did not, however, reach statistical significance.

Duration

No data on duration of dyspnoea in terminal cancer patients were discovered in the literature; one study[25] however did report that where dyspnoea had been the main presenting symptom (13 patients), the median length of time in care was 3 weeks with 4 of these patients surviving more than 8 weeks.

Age

The mean age of dyspnoeic patients with terminal cancer has been reported as 67.0 years[22] compared to 66.9 years in the non-dyspnoeic. A more detailed analysis[23] of the same study shows that in the last two weeks of life, 65.3% of patients aged 21-64 yrs were dyspnoeic, compared to 64.8% aged 65-74 yrs and 61.7% aged >75 yrs. Hence, no link between age and dyspnoea status has been demonstrated.

Sex

Author(s)		% Dyspnoeic Male	Female	All	Patient Nos.
Heyse-Moore[2]	(I)	57	39	48	381
Wachtel et al[23]	(P)	63.2	65.0	64.0	1119
Haram[24]	(P)	55.0	40.8	47.3	not stated

Table 5. Frequency of dyspnoea by sex. Terminal cancer patients. I = Incidence, P = Prevalence.

The studies detailed in table 5 suggest that dyspnoea may be commoner in men than women.

Other epidemiological factors

Other factors such as socio-economic status, race, place of abode, asbestos exposure and smoking do not appear to have been specifically studied in dyspnoeic patients with advanced cancer, although they have, of course, been investigated in patients with respiratory diseases in general[28].

Countess Mountbatten House receives patients from Southampton and Portsmouth, both of which have large, long-established docks, where dockers in the past had to work with asbestos. It is not surprising, therefore, that the diagnosis of pleural mesothelioma secondary to asbestos exposure is not uncommon in patients admitted to CMH. Epidemiological data on this will be presented (see p 150).

The prevalence of HVS in advanced cancer has not been studied. In general medical practice a prevalence of 6-11% has been reported[46].

2.4 Mechanisms

Various theories have been advanced as to how dyspnoea is generated. In considering these theories, it is important to ask whether they can lead to better treatment of dyspnoea. It is assumed in the following discussion that measures to treat the cause of the dyspnoea are the first line of management. However when this is impossible, as with an inoperable lung carcinoma, symptomatic measures must be used.

Length-Tension Inappropriateness

Campbell and Howell[30] noted that if breathing is hindered, ventilatory needs are at first unchanged, but an increased effort is needed to maintain the same level of ventilation. Thus the relationship between the demand for, and the effort of, breathing is changed. They proposed that it is this imbalance which leads to dyspnoea, through alterations in the length and tension of the respiratory muscles.

To understand the mechanism for this, it is necessary to consider how muscle contraction is controlled. Motor signals from the brain pass down the spinal cord to the motor nerve cells supplying the muscle to be stimulated. From here, signals pass down two sets of motor neurones: the alpha motor neurones which supply the main (extrafusal) muscle fibres; and gamma efferents (small motor neurones) which supply the intrafusal fibres of the muscle spindle, the sense organ for the stretch reflex, which is in parallel with the extrafusal fibres[29].

The alpha motor nerves are part of the executive system, the main pathway for muscle contraction. The gamma system is supervisory, providing a feed-back mechanism for fine tuning of muscle contraction, through annulo-spiral endings which are sensitive to stretch. If these endings are stimulated, signals pass up the 1a sensory fibres which synapse in the spinal cord with the alpha motor nerve cell supplying that muscle. Thus misalignments in the states of contraction or stretching between the extra- and intra-fusal fibres can be harmonised through this feed-back loop, as shown in fig 3.

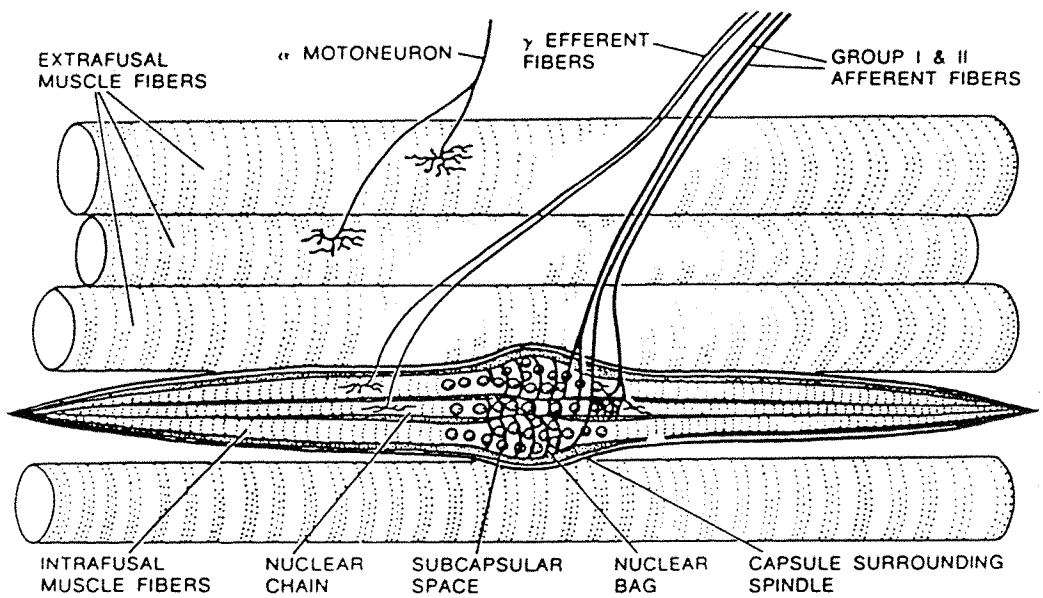


Fig 2. Muscle spindle

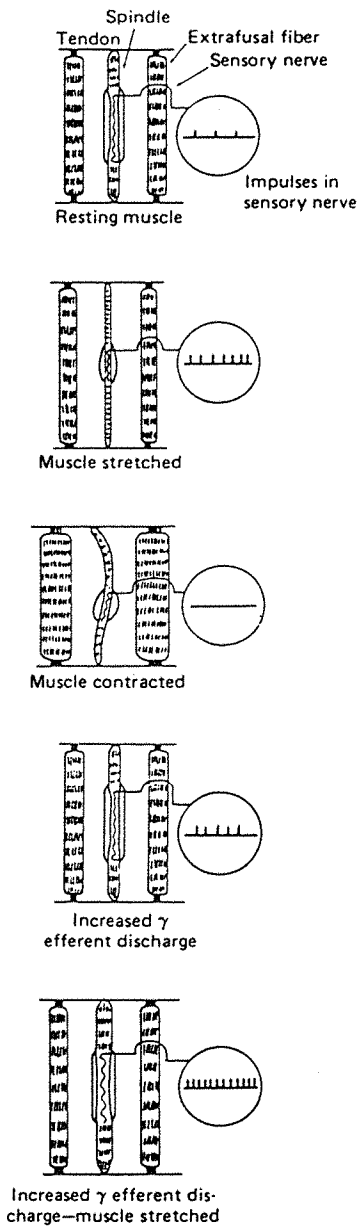


Fig 3. Muscle spindle discharge - effects of various conditions

How then is this applicable to respiration and dyspnoea? Consider the sequence of events during breathing:

A motor command to breathe travels from the respiratory centre to the respiratory muscles causing contraction of both the extra-fusal fibres and the muscle spindle. If there is no hindrance to breathing, the degree of contraction will be similar in both, and there will therefore be no change in the annulo-spiral receptor and hence no change in the sensory output from this receptor.

If, however, there is hindrance to breathing, the rate of shortening of the extra-fusal fibres will be slower than that of the intra-fusal muscle fibres of the spindle and hence there will be a misalignment of the 2 systems with stretching of the annulo-spiral receptor and hence increased sensory firing.

This sensory nerve firing will stimulate the alpha motor nerve cell supplying the extra-fusal fibres of the same muscle. The resultant increased tension and shortening in the extra-fusal fibres will overcome the hindrance to breathing and realign the 2 systems, hence stopping the excess annulo-spiral receptor firing.

Campbell and Howell suggest that signalling from misalignment of the two systems also relays to the respiratory centre in the brain stem. Projection of this signal, together with projection of the motor command from the respiratory centre, to consciousness, allows a comparison of the demand for ventilation and the result achieved. In hindered breathing, there will be a mismatch, and it is this discrepancy, they propose, which gives rise to the sensation of breathlessness.

It is beyond the scope of this thesis to review the evidence for and against this theory. Since parts of it are based on known anatomical and physiological facts and

parts are speculative, it continues to be debated[32]. However, it is relevant to see if it throws light on the management of dyspnoea.

Firstly, the motor neurones of the gamma efferent system are regulated by descending tracts from a number of areas in the brain[31]. This is why anxiety causes an increased discharge. In a dyspnoeic patient, therefore, a vicious circle ensues: the muscle spindle mismatch leads to a sense of dyspnoea and hence anxiety resulting in increased gamma-efferent discharge and increased spindle mismatch. So measures to reduce anxiety such as relaxation exercises or sedatives may help to break this cycle.

Secondly, benzodiazepines inhibit the activity of neurones in the brain and spinal cord by potentiating the neural inhibition mediated by gamma-aminobutyric acid (GABA), thus reducing gamma-efferent discharge, and hence spindle mismatch.

Thirdly, opioids will reduce the sensitivity of the respiratory centre[34] to sensory signals from the muscle spindle. They could also reduce the sensitivity of the area of the cortex receiving signals from the respiratory centre.

Fourthly, in HVS there may be an increased cortically generated motor neurone discharge[5] coupled with bizarre peripheral afferent information arising from muscle receptors responding to gross respiratory dysrhythmias[35] and hence intermittent spindle mismatch. In addition, the hypocapnia generated will increase neuronal excitability [36,37] and thus further sensitise the gamma-efferents. So, treatment of HVS (see p 92) will mitigate these effects.

Developments of the Length-Tension Inappropriateness Hypothesis

Howell[5] has modified the length-tension inappropriateness hypothesis to take account of new evidence. Thus, Killian and Campbell[38] showed that the magnitude of respiratory sensations induced by added loads depended on peak muscular force, duration of inspiration and respiratory frequency.

So the Golgi tendon organ, the muscle sensory receptor sensitive to tension appears to be implicated in respiratory sensation. Further, they suggest that the respiratory pattern generated in response to respiratory loading, does so to minimise the respiratory sensation (hence dyspnoea) rather than respiratory work rate.

Also Plum[39] has proposed a behavioural system of respiratory control with alternative or additional central sources of motor commands in situations other than quiet resting breathing. This is associated with so-called corollary discharges between the source of the motor command and the area of the cortex subserving respiratory awareness and so a centrally generated sense of effort[5,207]. The main implication of this is the current view that there is a direct cortico-spinal pathway for the motor command to breathe in the awake state[5].

Hence, there may be a learned, maladaptive, cortically generated breathing pattern which can override automatic respiratory control from the brain stem, leading to excessive breathing and therefore symptoms of HVS[5] as discussed on p 29. This will be considered further (p 47).

J-receptor stimulation

Paintal[40] has demonstrated the existence in cats of type J (juxta-alveolar) lung receptors (formerly called K-deflation receptors) sensitive to a rise in interstitial pressure or volume. In addition, slowly adapting pulmonary stretch receptors and rapidly adapting or irritant receptors have been described[41]. Paintal[41] has pointed out that stretch receptors are not the source of a dyspnogenic signal since they are maximally stimulated during inspiration, which actually *relieves* respiratory distress. He postulates that it is therefore the J receptors which are the source of dyspnogenic signals travelling via the vagus nerve to the brain[42].

If this is true, then reducing the increased firing of these receptors (stimulated for example by pulmonary oedema) should reduce dyspnoea. Inhalation of a local anaesthetic such as bupivacaine[43] might therefore help. This will be considered in further detail on p 80.

Diaphragmatic fatigue

Roussos and Macklem[44] demonstrated that when a subject breathing against resistance generates a transdiaphragmatic pressure (Pdi) of more than about 40% of maximum (Pdi_{max}), then the diaphragm becomes fatigued (i.e. where $Pdi/Pdi_{max} > 0.4$). Below 40%, respiration could be maintained indefinitely. They suggest that, since in respiratory disease Pdi/Pdi_{max} may exceed 0.4, respiratory muscle fatigue plays a part in the sensation of dyspnoea. They also showed that to some extent, diaphragmatic fatigue can be compensated for by other respiratory muscles taking over temporarily.

Therapeutically, therefore, it is important that dyspnoeic patients be taught to breathe as efficiently as possible to gain the maximum benefit from the least possible

effort. Although Leith and Bradley[43] have reported that respiratory muscle training increases static strength and endurance, this is less likely to be of benefit to patients with advanced cancer, since many are losing weight and muscle bulk rapidly.

Any measure which reduces airways resistance, such as the use of bronchodilators in asthma, will reduce Pdi and hence reduce the likelihood of muscle fatigue.

Some dyspnoeic patients become very frightened and restless and hence increase their metabolic rate. This may worsen their dyspnoea by increasing their oxygen requirements; indeed, Roussos and Macklem[44] did show that hypoxia shortened the time to onset of diaphragmatic fatigue. So measures such as sedatives to reduce anxiety, and hence oxygen requirements, may be of use here, as will oxygen given therapeutically.

Similarly, treatment of other causes of a raised metabolic rate, such as antipyretics for pyrexia and transfusions for anaemia, may help (see pp 84 and 91).

Cortical perception of dyspnoea

This will depend on:

1. Quantitative factors; that is the amount of the incoming signal to the cortex. The perception threshold is also important; thus, an asthmatic may be sensitised to even minimal dyspnogenic signals which another person would not recognise as such. This is considered in more detail on p 37.

2. Qualitative factors; it may be that dyspnoea is made up of a number of different but allied sensations, each with their own group of cortical receptors. Hence, different causes of dyspnoea may stimulate different

receptor groups leading to different sensations. This would explain the diversity of language patients use to describe their dyspnoea.

The Hyperventilation Syndrome (HVS)

Why do people with this syndrome overventilate? Usually, respiratory changes are homoeostatic, tending to restore the *milieu interieur* of blood gases and pH to normal when some event, such as exercise, causes changes in these indices. With hyperventilators, however, the opposite applies; they start from a position of normality and excessive ventilation leads to divergence from this situation.

The precipitating factors causing hyperventilation [9,10,11,46,48] may be:

1. Organic disease
2. Physiological
3. Environmental stress
4. Psychological
5. Habit
6. Increased sensitivity to hypocapnia

These factors generate feed-back loops[9,10,35,48] (fig 4).

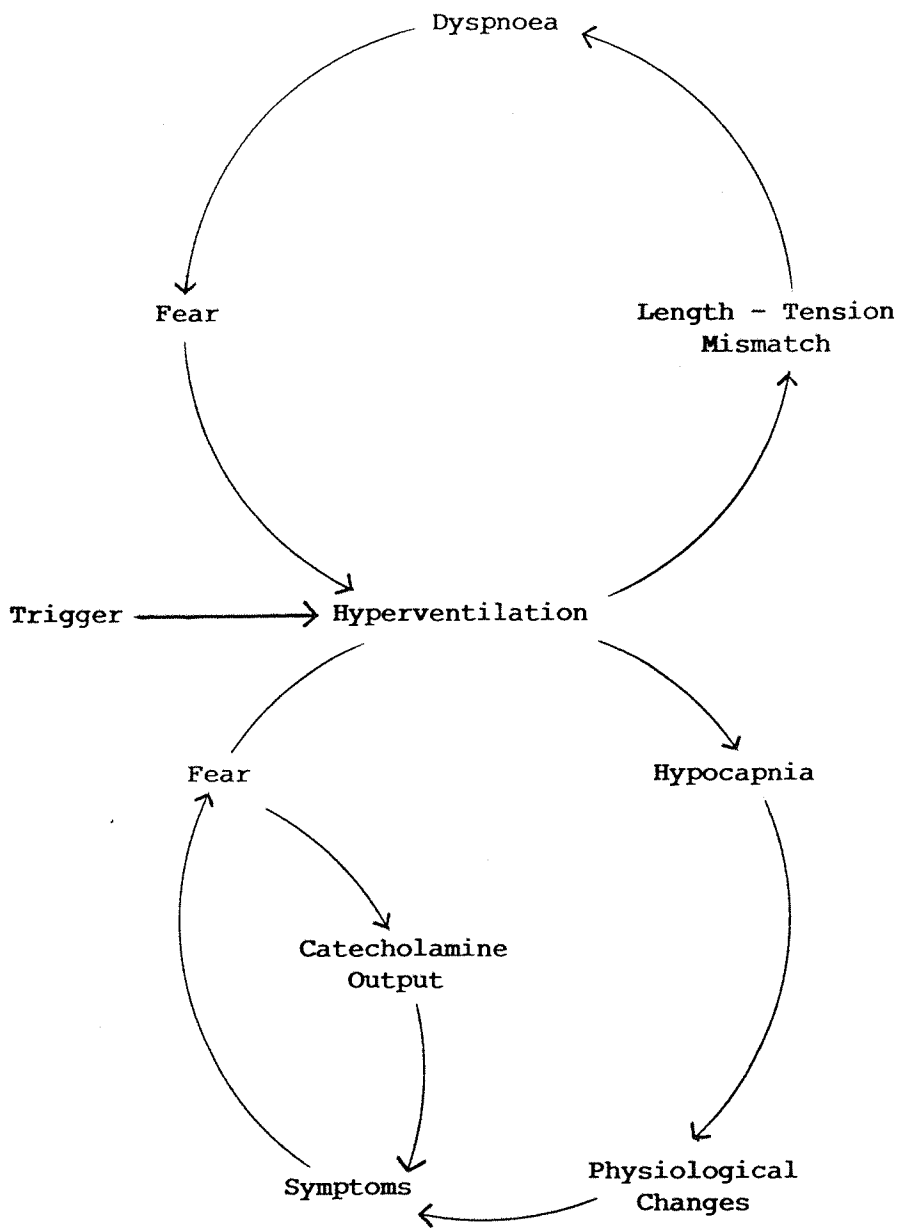


Fig 4. Hyperventilation - sequence of events

The way in which hyperventilation causes dyspnoea through a length-tension mismatch in the respiratory muscles has been described on p 29. The gross respiratory dysrhythmias noted by Burns and Howell[35] in patients with what they termed disproportionate breathlessness (in other words hyperventilators) may be thought of as being due to variations in the level of perceived threat and hence physiological responses (including hyperventilation) of the individual. In addition, homoeostatic mechanisms, such as the inhibitory effect of hypocapnia on the respiratory centre, tend to reduce respiration. The interplay of these factors thus leads to irregular breathing.

The triggers to hyperventilation will now be considered in more detail. Organic causes are listed in table 6[9,46,75].

Physiological factors causing hyperventilation include exercise, altitude acclimatisation, and heat[46].

Glynn et al[47] have also demonstrated that chronic pain acts as a respiratory stimulant causing chronic hyperventilation.

Environmental stress may be real (as with fear brought on by choking) or imagined (as with fear of the dark). In either case, the result is the same - the 'fight or flight' reaction[9], which includes increased respiration needed to meet the resulting increased oxygen demands, and also to excrete the excess carbon dioxide produced[46]. Since in western society the 'fight or flight' reaction is often repressed, the increased ventilation becomes inappropriate and hypocapnia may result, leading to the feed-back loops shown in fig 4, and hence dyspnoea.

Patients who are anxious for other reasons will be predisposed to the above sequence. Thus, in these patients, the trigger may be environmental[35], or due to an interaction between the environment and their internal

Cardiovascular

- Congestive cardiac failure
- Cardiac valve lesions
- Myocardial infarct pain
- Dissecting aortic aneurysm
- Pulmonary embolus

Respiratory

- Asthma
- Chronic obstructive airways disease
- Pulmonary hypertension
- Pneumothorax
- Respiratory dyskinesia
- Interstitial lung disease
- Tumour emboli

CNS

- Brain stem lesions (anoxia haemolysis, infarct, tumour)
- Encephalitis

Gastrointestinal

- Peptic ulcer
- Gastric retention
- Splenic flexure syndrome
- Hiatus hernia

Metabolic

- Pyrexia

Urogenital

- Retention of urine

Hepatic

- Cirrhosis
- Hepatic failure
- Hepatic coma
- Cholecystitis
- Gall stones

Endocrine

- Grave's disease
- Hyperparathyroidism
- Phaeochromocytoma
- Diabetic neuritis

Musculoskeletal

- Pseudomyasthenia

Drugs

- Digoxin intoxication
- Salicylate overdose
- Alcohol withdrawal

Table 6. Organic causes of hyperventilation. From Jones[9], Pfeffer[46] and Hardonk and Beumer[75].

psychological state. For example, a patient who is admitted to a hospital ward, where he had previously had an unpleasant procedure such as chemotherapy carried out, may become anxious and hyperventilate even though the external environment is not of itself threatening. Similarly, HVS has been noted in patients with depression, hysterical reactions and obsessional personality traits[35].

It would not be surprising, therefore, that patients with advanced cancer, and the associated constellation of negative emotions such as fear and depression, may hyperventilate.

This sequence may also begin from the other end: chronically anxious people found to have cancer may as a result become more anxious and hyperventilate.

MacEvoy[51] has discussed the role of signal detection theory in the subjective interpretation of symptoms. She points out that, in theory, when the threshold of seeing a light flash is measured, below a certain intensity there will be no response to the stimulus, but above this point, the light will be detected, as shown in fig 5 [a].

In practice, at a given stimulus intensity, sometimes the light is detected and sometimes not. As the intensity rises, the eye detects an increasing percentage of the light flashes, till above a certain point, all flashes are visible (fig 5[b]).

With a dyspnogenic signal, the same will apply. Some people will be more sensitive to such signals, and hence be more likely to experience dyspnoea, than others.

In addition, the psychological interpretation of weak signals and whether they are due to the external stimulus or to background 'noise' varies with individuals.

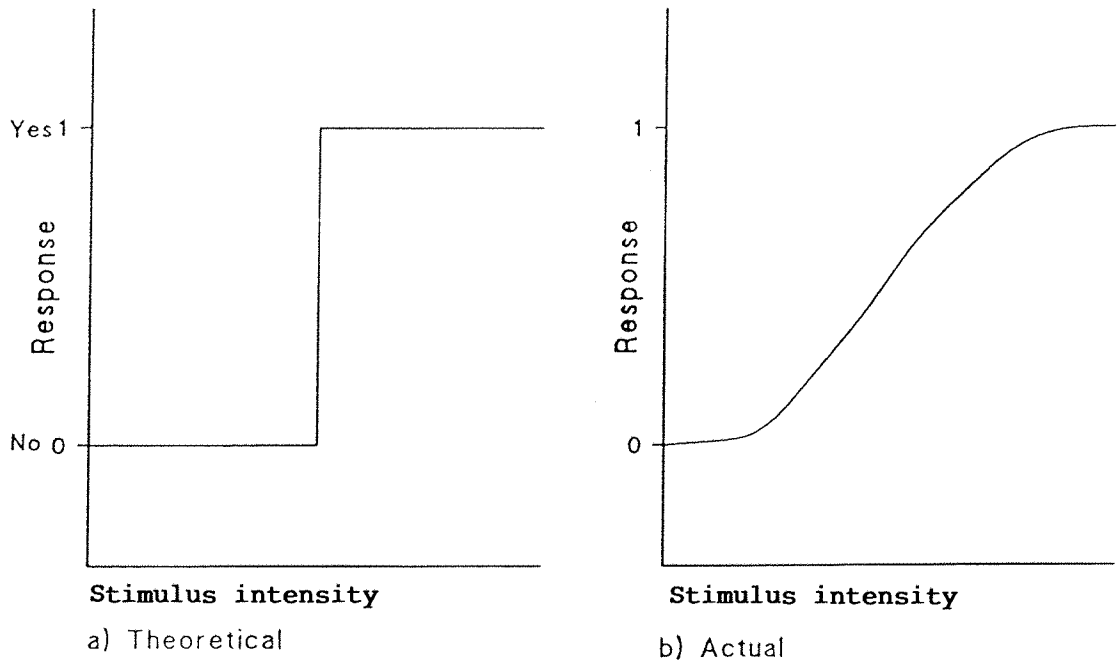


Fig. 5 Signal Detection

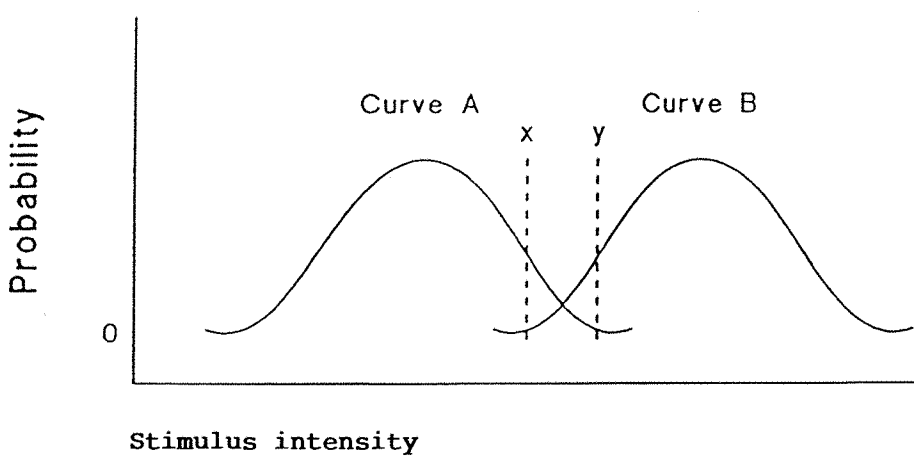


Fig 6. Interpretation of signal detection
Curve A = Background noise
Curve B = Noise + signal
x and y = Points of overlap

As can be seen in fig 6, between the points x and y there is an overlap of the two curves, and hence this may be interpreted psychologically as being due either to background noise totally, or to the dyspnogenic signal and background noise combined curve, or to a mixture of the two. Hence some people will interpret weak dyspnogenic signals as dyspnoea whereas others will not.

Fourthly, whatever the trigger, hyperventilation may become a habit persisting even in the absence of any stressor, whether external or internal.

Finally, Howell[50] and Jones[9] have pointed out that individuals vary widely in their sensitivity to hypocapnia, some developing symptoms within a few seconds when hyperventilating, others seeming virtually insensitive. This was borne by their findings that symptoms developed more rapidly in those with HVS than with controls[9,50]. Fig 6 shows how this increased sensitivity could lead to dyspnoea.

Hence, therapy of HVS must be aimed at treating any organic causes, removing environmental stressors, alleviating psychological distress and breathing retraining. This last is theoretically simple but practically difficult for, just as it takes time to learn a habit, so it takes time to unlearn it.[36]. Howell[50] has also stressed the importance of insight gained by the patients when they find their symptoms reproduced on voluntary hyperventilation. This understanding gives patients a sense of control over what can be a frightening experience, since they know that by reducing ventilation, they can abort an attack. Because hypocapnia plays an important part in the genesis of this syndrome, raising blood CO_2 levels by using a rebreathing bag[50] during acute attacks will help.

2.5 Causes

These may be considered at various levels using systems theory[52,53] (see fig 7).

1. The Pathogen

In cancers with known triggers such as smoking or asbestos, exposure will have occurred many years before and so no longer be relevant to causation.

2. The Pathology

The pathogen initiates an anatomical or physiological change which may cause dyspnoea through stimulation of sensory neurones (see fig 8, p 45). This may, however, be silent for months or years. Thus it is only when a lung cancer is large enough to affect the mechanics of ventilation or neurological signals to the brain that dyspnoea ensues.

Many classifications have been proposed[28,54] based on aetiology, exertion, types of ventilatory discomfort or time factors. These, however, relate to dyspnoea from any aetiology. In advanced cancer, certain causes predominate. These are tabulated in appendix 7.7 (p 256).

The following major categories pertain[2,55,56]:

- Increased ventilatory demand.
- Decreased ventilatory capacity.
- Neural stimulation.
- Psychogenic.

With increased ventilatory demand, there is a raised metabolic rate leading to increased oxygen consumption. It may not cause dyspnoea of itself but may tip the balance in someone with a reduced respiratory reserve.

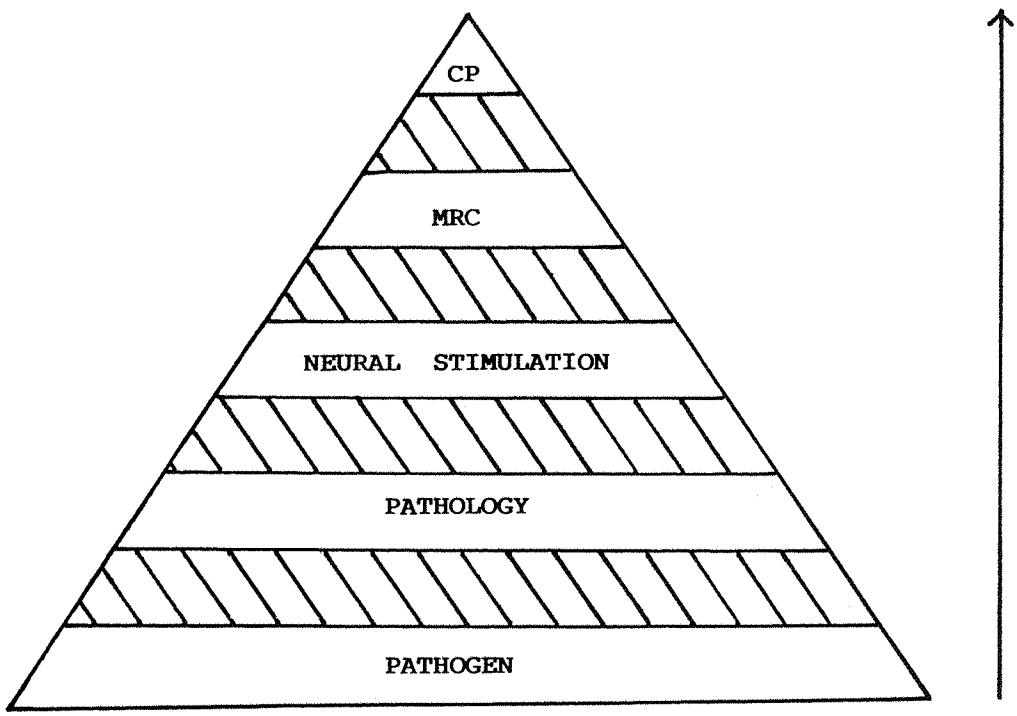


Fig 7. Systems view of causation of dyspnoea

MRC = Medullary Respiratory Centre

CP = Cortical Perception

In decreased ventilatory capacity, there is often ventilation-perfusion inequality and so hypoxaemia, either because an area of lung is not ventilated but is perfused (eg collapse) or because there is ventilation but no perfusion (eg pulmonary embolism).

Also, increased lung stiffness is common, adding to the amount of respiratory muscle work needed to maintain a normal PO_2 (eg lymphangitis carcinomatosa).

When there is a loss of elastic lung recoil (eg emphysema) both inspiratory and expiratory muscle effort is needed, so increasing the work of ventilation.

Painful chest lesions such as pathological fractures of the ribs may prevent full inspiration causing a fall in the PO_2; respiratory muscle efforts to compensate for this may then be frustrated by pain.

If respiratory muscles are completely paralysed as with C3 cord transection[58] or by tubocurarine[57], dyspnoea does not occur since length-tension mismatch does not take place. Muscular dysfunction, as with carcinomatous myopathy, however may be associated with dyspnoea[59].

Neural stimulation may be peripheral affecting the lung J receptors (eg pneumonia) or central, affecting the respiratory centre (eg raised intracranial pressure).

Psychogenic factors, namely anxiety, depression, hysteria and obsessional personality have all been linked with dyspnoea and HVS[11,35]. Apart from increasing cortical awareness of respiratory difficulty, anxiety may also worsen dyspnoea by increasing ventilatory demand and by raising respiratory muscle tone (see p 29).

There are a number of research reports of causes of dyspnoea in advanced cancer.

Thus, 3 reports[60,61,62] describe dyspnoea from lymphangitis carcinomatosa secondary to stomach and breast carcinomas. Dyspnoea from the mechanical effects of thoracic tumours has also been described - Mahler et al[63] describe a patient with a tumour of the left main bronchus where further narrowing and hence dyspnoea occurred when the patient lay on his right side. Thomas[64] describes dyspnoea and hyperinflation of the right lung due to check-valve obstruction by a tumour of the right main bronchus. Olumide et al[65] report 5 cases of rapidly progressive dyspnoea from superior mediastinal compression by malignant lymphoma.

Two studies[66,67] report pulmonary oedema and dyspnoea secondary to high doses of opioids in patients with metastatic cancer. This is a known complication of heroin overdose[66] and may be due to stimulation by opioids of mast cells to produce leukotrienes and histamine, leading to increased pulmonary vascular permeability. Kerr[68] documents a single case of dyspnoea and orthopnoea with no evidence of pulmonary oedema in a man with metastatic carcinoma of the prostate which disappeared when the slow-release morphine tablets he was taking were discontinued. Nisbet et al[69] reporting on orthopnoea due to bilateral diaphragmatic paralysis mention malignancy as one possible cause.

Lastly, Reuben and Mor[22] found that dyspnoea in terminal cancer patients was significantly associated with carcinoma of bronchus, lung and pleural metastases, other respiratory disease and cardiac disease (the last 2 categories were not elaborated further). Also, in 23.9% no risk factor for dyspnoea was found - they thought the 'debility of terminal cancer' was the cause (but no mention of HVS as a possible aetiology was made). They also found that dyspnoea was *less* common in patients with colorectal carcinomas.

3. Afferent neural signalling

This has been discussed in detail in the section on mechanisms. Therapeutically, it implies blocking excessive neural signalling to the respiratory centre and cerebral cortex and so symptomatically relieving dyspnoea. This will have no effect on the pathology causing the dyspnoea. Fig 8 shows the ways signals reach the cortex[35,56,59,198].

4. The cortical perception of dyspnoea

This has been discussed on pp 28 and 37.

In many patients with terminal cancer, several different causes of dyspnoea coexist and it may be impossible to say which is causing what degree of dyspnoea. Only by treating each cause sequentially and observing any improvement can distinctions be made.

2.6 Clinical Features

Since dyspnoea is, like pain, subjective, it can *only* be discovered by asking patients about their breathing. It is not enough to note, for example, tachypnoea clinically and then assume the patient is dyspnoeic - he probably is, but not necessarily.

Respiratory sensations

What then does dyspnoea feel like? Guz[70] describes five different types of respiratory sensation:

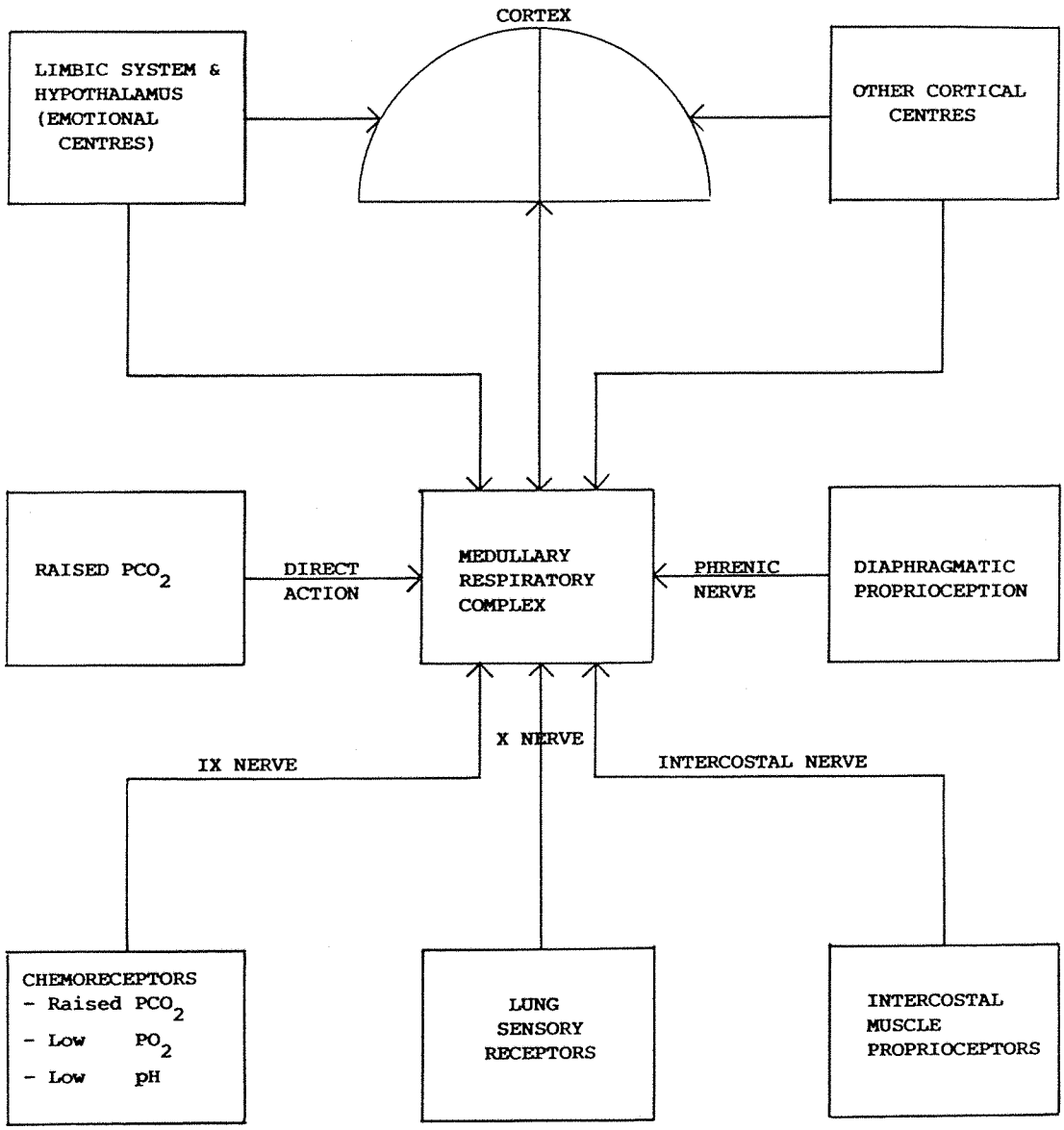


Fig 8. Routes of dyspnogenic signalling to the brain

1. Breath-holding sensation - this is a thoracic sensation of discomfort developing with time and coinciding with the onset of diaphragmatic contractions that become more and more powerful till the subject can no longer resist the urge to inspire.

2. The sensation arising from inhalation of CO_2 - this is a feeling of not being able to breathe deeply enough, or air hunger.

3. Tracheo-bronchial irritation - this is a raw irritation in the anterior chest and lower neck brought on, for example, by a tracheostomy tube or with influenza.

4. Obstructed breathing - this is a poorly localised sense of obstruction sometimes described as coming from the neck, sometimes the chest.

5. Dyspnoea or breathlessness - this applies to patients with respiratory disease and is either like exercise-induced dyspnoea - but felt at an inappropriately low workload or even at rest - or is a sense of tightness in the chest. It is as though there is an excessive drive to breathe.

While the above categories seem clear, the author has found that in practice patients often have difficulty in describing their dyspnoea or may use phrases and sentences rather than single words (see quotation p 12). This is borne out by McEvoy[71], who noted hundreds of statements by patients about their breathlessness - for example:

"I take too much air in"
"My body seems to want to breathe air in from other parts of my body, then I shake"
"I feel a barrier like its cutting off my air passages"
"I've literally died a number of times"
"Like someone sitting on your chest"

She divided these into 14 categories such as "Descriptive of sensation" or "Descriptive of emotion". From these it was found that patients with disproportionate breathlessness (HVS) were more likely to experience symptoms of hyperventilation and the emotional and affective aspects of breathlessness. Associations of words describing dyspnoea with particular diagnoses were not demonstrated. Dyspnoea is therefore less likely than pain to reveal diagnostic descriptions. For example, contrast the quotations from patients above with the typical history of central crushing chest pain radiating to the left arm during myocardial infarction.

Diagnostic descriptions of dyspnoea

However, certain aspects of a patient's description of their dyspnoea may help in diagnosis as in table 6.

Dyspnoea in HVS

Grossman and de Swart[73] found that the following descriptions of dyspnoea were commoner in HVS than non-HVS patients:

1. Unable to breathe deeply enough
2. Suffocating feeling
3. Faster or deeper breathing than normal
4. Need for air

Burns and Howell[35] found the following characteristics of breathlessness to be significantly commoner in patients with disproportionate breathlessness than in a control group.

1. Poor relationship of breathlessness to exertion
2. Acute hyperventilation attack present
3. Breathlessness experienced at rest

Aspect of dyspnoea	Description	Diagnosis
Quality	- Wheeze	Asthma
	- Chestiness	Respiratory infections
Timing[72]	- Sudden onset	Pneumothorax Pulmonary embolus Arrhythmia. Pulmonary oedema.
	- Onset over hours	Pneumonia. LVF. Asthma
	- Over days/weeks	Pleural effusion Enlarging Ca bronchus
	- Over months/years	COAD. Fibrosis Lungs. Anaemia.
	- Intermittent	Asthma. LVF
Time of day	- Paroxysmal Nocturnal Dyspnoea	LVF
	- Early morning	Asthma
Positional	- Orthopnoea	Pulmonary oedema
	- On one side	Check valve effect by bronchial tumour
Respiratory cycle	- Breathing in worse	HVS
	- Breathing out worse	Organic disease
Precipitating factors	- Cold air	Asthma
	- Drug induced	Cytotoxics/Pneumonitis Steroids/CCF Opioids/pulmonary oedema
Improvement	- Treatment trial (eg salbutamol)	eg Asthma
Activity	- Worse after exercise	Asthma
	- Dramatic improvement when rests	Pulmonary HT
Associated symptoms	- Pleuritic chest pain	Pleural invasion by tumour
	- Pain in distribution C8 T1 T2	Pancoast tumour

Table 6. Examples of diagnostic aspects of dyspnoea as a symptom of organic disease

4. Describe main difficulty as getting air in
5. Breathlessness clearly episodic, fluctates even within minutes
6. Breathlessness varying with social situation
7. Gross recent increase of breathlessness
8. Not improved by periods of stopping smoking
9. Breathless during conversation
10. Breathlessness relieved by sedatives or alcohol
11. Morning worsening of breathlessness, if present, is not relieved by bringing up sputum
12. Breathlessness worse in evenings

Associated symptoms in HVS

These are protean (see table 7) and may cause the sufferer to be investigated fruitlessly for organic pathologies[10]. The mechanisms whereby these symptoms occur are complex, but may be summarised as follows[10,36,37]:

1. Increased neuromuscular excitability
Hypocapnia leads to loss of intracellular CO_2 and hence alkalosis, which in turn leads to increased intracellular ionised calcium, partly by release of bound intracellular calcium from, for example, the mitochondria and partly by influx of extracellular calcium into the cell. The resultant hypocalcaemia leads to increased neuromuscular excitability and hence symptoms such as paraesthesia and muscle tremors.

Profound alkalosis causes intracellular anaerobic glycolysis and reverses the situation because of lactic acid production. The resulting low intracellular pH leads to profound weakness and even coma eventually.

2. Cerebral artery vasoconstriction
This is due to hypocapnia and leads to symptoms such as dizziness and faintness.

CVS
Tachycardia
Pounding heart
Irregular heart beat
Precordial pain
Tight chest
Heavy chest
Raynaud's phenomenon

CNS
Dizziness
Faintness and fainting
Tingling hands/feet/face
Visual disturbances
Tetany (rare)
Cramps
Headaches
Floating/sinking feelings
Numbness
Buzzing head
Lack of concentration
Fits
Irritability
Pain threshold increase

Fatigue
Tiredness
Fatiguability
Weakness
Exhaustion
Sleep disturbance
Nightmares
Reduced performance

GIS
Globus hystericus
Dysphagia
Abdominal pains
Dry mouth
Aerophagy and belching
Heartburn
Abdominal bloating

Emotion
Crying
Anxiety/Panic/Fear of dying/
Fear of madness
Tenseness
Unreality/Depersonalisation
Hallucinations

Musculoskeletal
Tremors hands
Muscle pains
Tetany
Tight muscles
Dysphonia

Temperature related
Chills
Flushing
Sweating
Fever
Warmth in head

Table 7. Non-respiratory symptoms of HVS[10,35,73,74].

3. Coronary artery vasoconstriction
This is due to raised intracellular ionised calcium; angina and dysrrhythmias may ensue.

4. The Bohr effect
Hypocapnia causes a shift to the left of the oxygen - haemoglobin dissociation curve reducing the amount of oxygen available to the tissues and also its rate of transfer. Hence the faintness and angina described above may worsen.

5. Catecholamine output
This is partly an effect of raised intracellular ionised calcium and partly related to the fear often associated with HVS. The resultant sympathetic dominance may cause, for example, sweating, muscle tremors, tachycardias, chest pain and dysrrhythmias.

Other significant factors in HVS include[35]:

- past mental illness
- Family history respiratory or mental illness
- Stress factors such as bereavement, marital disharmony or recent surgical operation
- Lifelong excessive health consciousness
- Obsessional personality

Clinical examination

Dyspnoea, being a symptom, cannot be deduced with certainty from examination, although of course, signs such as tachypnoea or hyperpnoea are likely to be present. The signs elicited will be those of the underlying pathology (see appendix 7.7). Since the lesions causing dyspnoea are likely to be advanced in terminal cancer, the

corresponding clinical findings may be gross, as with severe stridor from mediastinal lymphadenopathy and tracheal stenosis.

Clinical findings in HVS

These have been described as follows[7,10,11,35,75]:

1. Respiratory system
   Attacks hyperventilation
   Noisy expiration and inspiration of oral origin (eg lips) disappears on distraction
   Rapid shallow breathing (dog breathing, thoracic breathing)
   Sighing respirations (with or without inspiratory laryngeal stridor)
   Chest kept expanded all the time
   Accessory muscles of respiration being used
   Grossly irregular breathing pattern
   Respirations return to normal when relaxed or distracted
   Yawning
   Non-productive cough
   Frequent clearing of throat
   Normal breath sounds and percussion note

2. Cardiovascular
   Tachycardia
   Dysrrhythmia
   Raynaud's phenomenon
   Flushing

3. Neuromuscular
   Brisk reflexes
   Dilated pupils
   Tremors

Muscle hypertonia
Tetany
Chvostek's sign positive
Trousseau's sign positive

4. Other
Sweating
Dysphonia
Crying

Lewis and Howell[7] when they questioned delegates at a respiratory conference found that many thought HVS more common in women. Lum[36], however, found the sex incidence to be almost exactly equal.

In addition to the above signs, the author has noted:
a) Mouth wide open
b) Sitting bolt upright
c) If breathing quietly, respiratory rate and frequency increases markedly when approached by staff or visitors.

These clinical findings can be deduced from the pathophysiology described on p 49. Not all signs will be present in each individual and none are of themselves diagnostic.

Investigations

Investigations for dyspnoea are only indicated when they may make a difference to the management of a dying patient[76]. Two factors are important: firstly, is the wish not to inflict unnecessary distress on a dying patient; secondly, most units providing terminal care are separate geographically from hospitals and hence tests such as chest x-rays would necessitate an ambulance journey, which a frail patient would not stand well. In

these circumstances, an empirical therapeutic trial may also be diagnostic[76] (as with glucocorticosteroids for dyspnoea from lymphomas affecting the lungs).

Some useful investigations are listed in table 8.

Test		Examples of Indications
Chest x-ray	-	Is there a pleural effusion large enough to tap? Is there lymphangitis carcinomatosa treatable by steroids[196]?
Sputum culture	-	To establish antibiotic sensitivity in pneumonia
Spirometry	-	Is there reversible airways obstruction?
Haemoglobin	-	Is there anaemia sufficient to cause dyspnoea which would be helped by transfusion?
ECG	-	Establishing the type of dysrrhythmia and hence its treatment may relieve cardiac decompensation and hence dyspnoea.

Table 8. Investigations for dyspnoea

It is debatable whether a V/Q scan is likely to be helpful [56] because the risks of treating pulmonary emboli by anticoagulants in the terminally ill, who may be at risk from haemorrhage for several reasons such as blood dyscrasias, may outweigh the benefits of preventing further emboli and the ensuing increase in dyspnoea. Similarly, blood gas estimation is unlikely to alter management (see p 73).

Investigations in HVS

1. The Hyperventilation Provocation Test (HVPT)
This has been widely used in various forms. Its essence is the reproduction of symptoms thought to be due to hyperventilation, by voluntary hyperventilation [7,36,50,73,75,77]. The time needed for the HPVT to produce symptoms is usually less than 3 minutes[36,75] but up to 30 minutes may be needed to reproduce chest pain[36], although this may have its dangers in causing dysrrthymias.

Howell[50] and Jones[9] have demonstrated that 20 deep breaths is enough to reproduce symptoms and can discriminate between hyperventilators and controls. Psychological challenge under hypnosis[78] has also been used to provoke hyperventilation, as has a "think test"[77] where patients are asked to think about the circumstances of a previous attack and the feelings and sensations experienced - this may then precipitate hyperventilation.

2. Estimation of blood gases
This may be either by arterial sampling, or by measuring end-tidal PCO_2 (PET CO_2) levels of expired air, which correlate well with arterial PCO_2 levels[75].

Although a raised pH and low PCO_2 might be expected in hyperventilation[48], this is not always so. Lum[10], found that about one third of cases had equivocal or low-normal levels PET CO_2. Hardonk and Beumer[75] found no difference between HVS patients and controls of PET CO_2 levels at rest, or during hyperventilation.

However, PET CO_2 levels during and after HVPT do reveal differences between HVS patients and controls. Thus Hardonk and Beumer[75], measuring PET CO_2 levels before, during and after 3 minutes hyperventilation, found the rate of recovery of PET CO_2 after testing HVS patients to be significantly slower than normals. They proposed a

ratio measurement of resting PET CO_2 levels to PET CO_2 levels post hyperventilation. They found that after 3 minutes recovery, this ratio discriminated completely between HVS and non-HVS patients, a level greater than 1.5 suggesting HVS. They also found that controls would have a period of post HVPT apnoea, but that this was absent with HVS. Next they showed that although HVS patients and controls had the same respiratory frequency (Rf) post recovery, the total expired volume in HVS patients was much higher. This uncoupling of Rf from volume was characteristic of HVS. Finally, computer analysis of symptoms did not reveal a diagnostic pattern in the words used.

Howell[50] found that the time taken to develop symptoms (t) during HVPT was inversely related to the fall in PET CO_2 (Delta PCO_2) in normal volunteers. A measure of sensitivity to hypocapnia (SCO_2) was developed such that:

$$SCO_2 = \frac{\text{Delta } PCO_2 \times t}{100}$$

A low SCO_2 implied high sensitivity to hypocapnia and vice-versa. In a group of HVS patients, SCO_2 scores were significantly lower than controls[9].

Nixon and Freeman[77] measured PET CO_2 levels when using the "think test" described above. They set a figure for Delta PCO_2 = or > 10 mmHg for > 1 minute as indicating HVS. When this test was compared with the HVPT, it was significantly more sensitive.

3. Spirographs

The following respiratory patterns typical of HVS have been described:

- Grossly irregular pattern[35]
- Deep respirations[35]
- Absence of post HVPT apnoea[75]

4. ECG findings in HVS
The following have been described[11,36,48,79]:

- ST segment depression (sometimes elevation): this may be reproduced by voluntary hyperventilation or intravenous epinephrine and is prevented by CO_2 inhalation or intravenous KCL
- T wave inversion (or isoelectric)[79]
- Tachycardia
- Ventricular and atrial ectopics
- Long QT interval
- Supraventricular tachycardia

Lewis[48] describes how ECG changes of tachycardia and longer QT intervals in normals during HVPT tend to be reversed even while hyperventilating, as though there is a compensatory mechanism; this however is absent in HVS.

5. Psychometric Testing in HVS
Burns and Howell[35] using a variety of psychological questionnaires such as the Maudsley Personality Inventory, found an association with anxiety, depression and hysteria. A psychological history also revealed a link with obsessional personality, excessive health consciousness and past mental illness. Jones[9], using the Crown-Crisp Experiential Index (CCEI)[80] also demonstrated an association between sensitivity to hypocapnia and anxiety, depression and phobia. Perfectionism[50] has been linked as well. Lum[10] mentions a connection with Type A personality.

6. Blood Chemistry

Hypophosphataemia in HVS is recognised[11,75] and thought to be due to a shift of phosphate from the extracellular to the intracellular compartments as a result of metabolic changes induced by alkalosis. Variable values for serum potassium, chloride and calcium have been found[75], although since low levels of ionised calcium are associated with tetany (as in hypoparathyroidism) it might have been expected that there would be a link with HVS. No alterations are found in blood sugar levels or serum magnesium and sodium[11,75].

7. Inhalation of CO_2

Abolition of symptoms by using a rebreathing bag or by inhalation of a 5% CO_2 mixture may be used diagnostically[75].

8. Diagnosis by exclusion

Investigations may fail to reveal any organic or psychological pathology[7,81], although of course HVS may coexist with, for example, asthma[75].

In summary then, the following are the most useful tests in discriminating HVS from other causes of dyspnoea:

a) The HVPT
- reproduction of symptoms
- the "Think Test"
- slow recovery PET CO_2 post HVPT
- $\frac{\text{resting } PETCO_2}{PETCO_2 \text{ 3 mins post HVPT}} > 1.5$
- Post HVPT apnoea absent
- uncoupling of respiratory frequency from total volume
- SCO_2 low

b) Blood Gases - raised pH and low PCO_2 in the absence of organic pathology

c) Abolition of symptoms by inhalation CO_2.

Differential diagnosis of dyspnoea

The following may be confused with dyspnoea:

Tachypnoea
Hyperpnoea
Hyperventilation
Periodic respiration
Cheyne-Stokes breathing
Kussmaul respiration

These have been considered in section 2.1.

Differential diagnosis of HVS

a) Any organic cause of dyspnoea
b) Since HVS can present with an extraordinary range of symptoms (see p 50), it may mimic a wide variety of organic illnesses. Lewis[48] lists 30 different organic illnesses with which patients with HVS originally presented before the correct diagnosis was made. Examples were: coronary heart disease, asthma, epilepsy, peptic ulcer, arthritis, hyperthyroidism.
c) Conversely, misdiagnosis of diabetic ketoacidosis as HVS has been described[84].
d) If HVS coexists with an organic pathology, such as asthma, a therapeutic trial eliminating one cause (eg with bronchodilators) may clarify which is causing dyspnoea. It should also be noted that during asthma attacks a hypocarbic respiratory alkalosis (due to

ventilation/perfusion mismatch) results, together with hypoxaemia (which worsens as the degree of obstruction increases[83].

Psychometric Tests in dyspnoea

No studies were found in the literature on the assessment of psychological status in dyspnoeic patients with advanced cancer. However, the Crown-Crisp Experiential Index (CCEI)[80,85] has been used for patients with HVS[9].

The CCEI (see Appendix 7.3) consists of 48 questions which can be answered in 5 or 10 minutes and from which can be drawn scores for six psychological indices - free-floating anxiety, phobic anxiety, obsessionality, somatic concomitants of anxiety, depression and hysterical personality. The combined scores provide a measure of general emotionality or "neuroticism". Hence it provides a quick assessment of psychological state. It has been validated and found to be objective and reliable[85].

The following points should be borne in mind concerning its use in patients with advanced cancer:

1. Questions eliciting somatic concomitants of anxiety such as indigestion, sickness, excessive sweating and fluttering of the heart will not distinguish between emotional origins of these symptoms and organic causes common in terminal cancer. High scores may therefore be expected irrespective of anxiety levels.

2. Depression occurs frequently in patients with advanced cancer[86]; hence scores for this sub-scale are likely to be high.

3. The hysteria sub-scale has been found to measure extraversion as well as hysterical personality[85]. Low scores might therefore be expected in cancer patients struggling to come to terms with their illness[86].

2.7 Measurement

Since dyspnoea is subjective, its measurement depends on the patient's own assessment rather than objective physiological measures such as spirometry. The following have been described:

1. Visual Analogue Scales (VAS)
2. Stimulation tests
3. Magnitude estimation
4. Numeric scaling
5. Verbal scaling
6. Activity scaling
7. Voice changes

1. Visual Analogue Scales (VAS)

These were first used for measuring feelings as early as 1921[87]. They were not widely used till 1968 since when they have become increasingly popular.

Aitken[88], in 1969, proposed a 100 mm horizontal line at each end of which are the extremes of the feeling in question. Thus, Zealley and Aitken[89] used a VAS with "normal mood" as one end of the scale and "most depressed" at the other as a measure of depression. Patients were asked to mark where on this scale their level of depression was.

The advantages of VAS for measuring subjective feelings are[88,89]:

1. Simple, quick and easy to use.
2. Can be used frequently to assess change.
3. Provides more sensitive detection of changes than say 5 point word scales.
4. Less bias is introduced from individual likes and dislikes of words or numbers used in other scales.
5. Reliability: thus Zealley and Aitken[89] found good correlation between patients' assessment of their manic-depressive illness and that of staff.
6. Repeatability: Aitken[88] found that subjects who had breathed against resistance gave similar VAS scores for dyspnoea for similar resistances on different occasions. In another study[90], reproducibility for individuals of VAS scores for breathlessness induced by standard exercise tests was good over a week ($p < 0.001$). Even after a year, there was significant reproducibility ($p < 0.01$).
7. Good correlation with other types of scale: thus, for chronic cancer pain, correlation between VAS measurements and the McGill-Melzack Pain Questionnaire was good[91].

Disadvantages of the VAS are:

1. Different subjects will have had differing experiences, both quantitatively and qualitatively, of the feeling in question. Hence if the top end of a VAS for dyspnoea is "extremely breathless"[90], this may mean different things to different people.

2. Even when the top end of a VAS for breathlessness is anchored by relating it to a standard respiratory stimulus such as exercise to exhaustion, or breathing 8% CO_2, there is wide inter-subject variability[90]. Provided, however, this is borne in mind, changes in scores are valid measures that can be studied statistically[87].

In palliative medicine, the VAS has been used particularly to measure pain[91,92] but also other symptoms such as mood, appetite, nausea and sleep[92]. Although dyspnoea in advanced cancer has been measured by VAS[26,93], this scale has more often been used in non-malignant respiratory disease such as chronic obstructive airways disease[93,94] and asthma[94], or in physiological experiments with normal subjects[90].

One problem with the VAS is that, in some of the studies[90,93,94] already quoted, it was used to measure dyspnoea only at the time the scale was presented to subjects. In the terminal care setting, however, dyspnoea levels over a period of time are important in assessing success of symptom control; further, any recent exertion by the patient may distort the measurement. These problems may be bypassed either by ensuring that patients have been resting, or by asking them to indicate the average level of breathlessness they have experienced over, say, the previous day, an approach used successfully by Lunt et al[26].

2. Stimulation Tests

Here, dyspnoea is induced either by standard exercise on a treadmill[94], or by inducing hypercapnia or hypoxia[95]; it is then measured on a VAS or numeric scale. The bottom end of the VAS scale is anchored by "not at all breathless", for example at rest, and the top end by relating it to an activity in daily life which induces severe breathlessness and is easily recalled by the patient[94]. Hence this ensures an objective index for quantifying the sensation of dyspnoea. It may be used to assess changes in dyspnoea after the standard stimulus, whether less because of treatment or more if the disease process worsens.

These would not generally be suitable in palliative medicine as many patients will be too ill to perform the manoeuvres needed.

3. Magnitude estimation (ME)

This is a variant of stimulation tests. Subjects are given a standard respiratory stimulus[96] and are told that this level of breathlessness corresponds to the standard number "10". The respiratory stimulus is then changed and patients estimate the change in breathlessness. Thus, if they felt twice as breathless, they give a score of 20, and so on. As with stimulation tests, this test is not generally suitable in palliative medicine.

4. Numeric scales

Here, the subject is asked to choose a number corresponding to their dyspnoea from a scale, e.g. 0-5, where 0 means no dyspnoea and 5 maximum dyspnoea. The advantage of this scale is a higher response rate in very ill patients[26]; its disadvantage is that it may be less sensitive than a VAS[26,87,89]. However, it correlates well with VAS measures[26,89].

5. Verbal scales

The subject chooses from a word scale of intensity. Thus, Aitken[88] describes a category scale of Absent, Minimal, Mild, Moderate, Severe, Extremely severe, corresponding to a numeric scale of 0-5.

Advantages of this scale are simplicity and ease of use, and that it can be repeated frequently. Its disadvantages are[88] that the same word may mean different things to different people and there is no certainty that subjects

will give equal values to each category, so that a particular word may represent a large change to one person and a small change to another.

Further, a verbal scale is, like all the scales so far mentioned, a measure of intensity which takes no account of qualitative differences. Thus, if one person describes their breathlessness as "choking" and another as "distressing", how can a quantitative scale discriminate between the two? A useful analogy here is the difference between monochrome and colour[97].

Melzack and Torgerson[98] have approached this problem for pain measurement by obtaining words describing pain from the clinical literature and asking subjects to assign each of 78 words to different classes. They then asked groups of doctors, patients and students to assign an intensity score for each word and used the mean values thus obtained as a measure of the intensity of pain for each word. Patients were then presented with a questionnaire, the McGill-Melzack Pain Questionnaire (MMPQ) in which the 78 words were divided into 3 classes (sensory, affective and evaluative) and 20 subclasses. Patients were asked to choose one word from each subclass which best described their pain, or leave a subclass out if no word fitted. (See Appendix 7.2). Four different types of scoring were obtained[97]:

1. The Pain Rating Index (PRI[S]) as the sum of the mean values of all the words chosen.
2. The Pain Rating Index (PRI[R]) based on the sum of the rank values of the word chosen in each class.
3. The Number of Words Chosen (NWC).
4. The Present pain intensity (PPI). This is the score of the word chosen as describing the intensity of the patient's pain at the time of administration of the questionnaire from a number-word scale of 0-5.

These various measures were found to correlate well with each other, to provide quantitative data that could be analysed statistically and to be sensitive to differences in methods of pain control.

In addition, a short-form McGill-Melzack Pain Questionnaire[99] (SF-MMPQ) has been developed, where 15 words (in the same three classes as the MMPQ) describing pain, are each ranked on a scale of intensity of 0 to 3 corresponding to verbal scaling of None, Mild, Moderate, Severe (see Appendix 7.2). For each of the three classes scoring systems similar to the PRI[S] and PPI of the long questionnaire were developed and were found to provide similar information. The SF-MMPQ has therefore the advantage of simplicity and of being quicker to administer, although it does not provide as much information as the MMPQ.

Dyspnoea in advanced cancer does not appear to have been studied in these ways; indeed no studies were found even listing words used by dyspnoeic patients, McEvoy[71] has, however, analysed phrases used.

6. Activity Scales

Severity of dyspnoea may be measured by scales related to activity. Thus, Fletcher[54] has used the following scale in emphysema:

Grade 1: Is the patient's breath as good as that of other men of his own age on walking, and on climbing hills or stairs?

Grade 2: Is the patient able to walk with normal men of his own age and build on the level but not able to keep up on hills or stairs?

Grade 3: Is the patient unable to keep up with normal men on the level, but able to walk about a mile or more at his own speed?

Grade 4: Is the patient unable to walk more than about 100 yards on the level without rest?

Grade 5: Is the patient breathless on talking or undressing, or unable to leave his house because of breathlessness?

Many patients with terminal cancer will be classed as Grade 4 or 5, and hence the lower end of the scale may not be sufficiently sensitive.

Another scale, based on the Jones Index,[72] classifies acute breathlessness and hence is more discriminatory where exertion is severely limited by dyspnoea:

Grade I: Able to do housework or job with difficulty.

Grade II: Confined to chair/bed but able to get up with moderate difficulty.

Grade IIb: Confined to chair/bed and only able to get up with great difficulty.

Grade III: Totally confined to a chair or bed.

Grade IV: Moribund.

However, this scale makes no mention of the activity level that *brings on* dyspnoea; also moribund patients cannot give any indication of whether they feel short of breath.

The advantage of these scales is that they can indicate the level of disruption of a patient's everyday life by dyspnoea.

7. Voice changes

Mohler[100] has shown that voice pitch (measured as the fundamental frequency, F_o) rises with increasing ventilation and dyspnoea, due to the elastic vocal folds of the larynx changing, allowing air shunts through the arytenoid aperture, and hence creating a falsetto voice.

This measurement would be difficult in terminal care for the following reasons:

1. Voice pitch is higher with anxiety[100], and this symptom is common in patients with advanced cancer.

2. Laryngeal changes due to age, carcinoma, recurrent laryngeal nerve palsy or loss of laryngeal muscle bulk from cachexia, are common and will affect the voice.

3. A baseline voice pitch when the patient is not dyspnoeic is needed for comparison, which would not be available since patients are already breathless when first seen.

2.8 Treatment

Management of dyspnoea in advanced cancer will often be the same as in general medicine[28] and will not be discussed further. However, some treatments require special consideration[2]; they may be palliative, that is treatment of a correctable pathology such as pneumonia, or symptomatic, meaning only inhibition of the dyspnogenic neural signal from the periphery to the brain. A list of treatments available is set out in appendix 7.8.

1. Palliative drug measures

a) Antibiotics

Although these may relieve dyspnoea from pneumonia in advanced cancer they are not universally indicated, as they may prolong a patient's dying rather than living. Factors to consider[2] are:

i) Physical state
Patients who have abnormal lungs and reduced respiratory function, who are unable to cough properly, whose immune status is low, who are bed-bound or who are moribund are unlikely to respond well. A patient who is already dyspnoeic and develops a respiratory infection which is treated with antibiotics may on recovery be left even more dyspnoeic due to further lung damage.

ii) Social factors
Patients may want treatment for the following reasons:
- to be well enough to attend an important family event such as a wedding
- to gain time to sort out business affairs or a will
- to gain time to heal family rifts
- to gain time to work through emotional or spiritual distress
- in the hope of staving off death, or even of cure

Conversely, they may feel ready to die and not wish for any further treatment.

Equally, their families may be involved in these decisions.

Sometimes, patients are too ill to make such decisions, and they may have no family. Hence, each case must be considered individually and if antibiotics are not given, other symptomatic measures used are necessary.

No studies were found on the frequency of prescription and success of antibiotics for dyspnoea in advanced cancer or which one to choose.

However, chloramphenicol 250-500 mg 6 hrly has been recommended[2] for the following reasons:

1. Bacterial resistance is uncommon.
2. It is active against anaerobic infections such as might be found distal to a bronchus stenosed by tumour.
3. The risk of pancytopaenia (1 in 30,000 courses[101]) in patients whose median life expectancy is only two weeks[12] is minimal.

b) Glucocorticosteroids

These may help dyspnoea as follows:

1. Relief of bronchospasm[199].
2. Reduction of tumour oedema in lung or mediastinal neoplasms and hence relief of airways compression[104].
3. Relief of lymphangitis carcinomatosa[196].
4. Direct anti-tumour effect on lymphomas affecting the lungs[102].
5. Relief of leuko-erythoblastic anaemia due to marrow invasion by tumour and in which the tumour is responsive to steroids (eg lymphomas)[202].
6. To prevent inflammatory swelling during radiotherapy to lung fields[2,204]. Although steroids may reduce the effect of radiotherapy on the lung tumour[204], this is not a major consideration in the terminally ill.

Dexamethasone 8 mg/24 hours or Prednisolone 60 mg/24 hrs may be prescribed on the assumption that a high dose is needed to reduce tumour oedema within the thoracic cavity, in a similar way to treatment of oedema from brain tumours[103]. It is not certain, however, which is the best

dose level. Thus, Hanks et al[104] used doses of dexamethasone of 4-16 mg/24 hrs and of Prednisolone 10-30 mg/24 hrs in terminal cancer patients for a wide variety of indications, including airways obstruction. However, Regnard et al[107] recommend 24 mg IV. The short prognosis[12] of hospice patients usually obviates the problems of taking high dose glucocorticosteroids long term, such as osteoporosis or moon face. However, other unwanted effects such as proximal myopathy or psychoses may occur in the short term.

c) Cytotoxics and Hormones

These are not often used in terminal care. A study at St Christopher's Hospice[105] showed 1.6% of admissions were receiving cytotoxics, and 6% hormones.

Possible indications for palliative chemotherapy include: Cyclophosphamide for small cell carcinoma of lung[105], and cytotoxic agents such as bleomycin to be instilled into the pleural cavity after drainage of a pleural effusion[108]. However, Berry[109] reported that only in 18% of a group of patients with small cell lung cancer, was dyspnoea improved by chemotherapy.

Hormones such as tamoxifen in breast cancer may reduce the size of lung metastases and hence relieve dyspnoea[2,205].

2. Symptomatic drug measures

a) Opioids

These may have the following effects on dyspnoea and respiration:

1. Reduced medullary respiratory centre sensitivity to CO_2.[110]

2. Inhibition of the pontine respiratory centre causing reduced respiratory frequency[110].
3. Reduced discharge from peripheral chemoreceptors (eg carotid body)[191].
4. In guinea-pigs, vagal stimulation causes release of neuropeptides from the sensory nerve endings into the bronchi and hence bronchoconstriction. Belvisi et al[111] have shown that this effect is blocked by opioids implying opioid receptors on these sensory nerve endings.
5. In surgically resected human bronchi in vitro, capsaiacin causes release of neuropeptides from sensory nerves into the bronchi and hence mucus secretion. This is blocked by morphine[112].
6. Santiago and Edelman[113], reviewing opioids and breathing, report a number of other effects:
   a) Enkephalins may stimulate J receptors (and hence increase respiratory frequency), and may cause pulmonary vasoconstriction and also asthma.
   b) Opioids can cause release of histamine from mast cells peripherally[66], and also tracheal constriction. In addition, they may bolster immune defences in the lung.
7. The tranquillising effect of opioids[114] will, by reducing anxiety, break the vortex of dyspnoea and anxiety aggravating each other. Opioids also increase tolerance to pain even when perception of the pain is little changed[114]. Hence it might be possible that a similar mechanism applies to dyspnoea.
8. If ventilation is painful, as with pathological rib fractures, opioids will reduce the pain and hence make respiration easier.
9. Acute left ventricular failure is improved by opioids. The mechanism is unknown, but may be due to peripheral vascular dilatation reducing cardiac work[114].
10. Patients with chronic pain (including cancer pain) have been shown to hyperventilate[115] leading to a low $PaCO_2$, but normal pH, suggesting metabolic compensation. Relief of the pain was associated with a return of

$PaCO_2$ to normal levels (but with no change in the pH) and hence decreased ventilation. Thus, opioids may indirectly reduce respiration in this way.

Clinically, frequency and depth of respiration[110] are decreased, as is any associated anxiety[114].

Opioids are widely used in palliative medicine for subjective relief of dyspnoea[2,107,117,118,119]. However, they can cause serious respiratory depression[114] and may therefore be avoided in case of respiratory failure or pneumonia.

This fear has not been found to be a problem in terminal care for a number of reasons[2]:

a) Dyspnoeic patients taking morphine do not necessarily die quickly. Rather, the respiratory cripple may improve his mobility so much that the risks of being bed bound (pulmonary emboli, pneumonia, pressure sores) are avoided. Thus, Light et al[120] found that oral morphine substantially increased exercise capacity in patients with chronic obstructive airways disease and led to a reduced perception of breathlessness for a given level of ventilation.

b) Walsh[121] investigated 20 terminally ill patients taking regular morphine. Twelve had chronic obstructive airways disease and 8 carcinoma of the bronchus. Only 1 had a raised $PaCO_2$. Similarly, Bruera et al[122] found a highly significant reduction of dyspnoea after a dose of intramuscular morphine but no significant change in respiratory frequency or effort, in PaO_2 or in end-expiratory PCO_2. This applied for patients both on regular morphine and not. This was however an open study. Walsh also found that during continuous monitoring[123] of a patient taking morphine regularly, the respiratory rate and $PaCO_2$ did not change before and after a dose of morphine.

c) Oral opioids are probably associated with lower peaks and less rapid changes in plasma levels than if given parenterally[121], and hence would be less likely to lead to significant respiratory depression.

d) Dyspnoea may cause restlessness and increased ventilatory effort thus leading to high energy and oxygen consumption. Opioids will reduce anxiety and hence reduce oxygen needs.

e) In some patients, ventilation is set too high. For example, lymphangitis carcinomatosa stimulates J receptors and hence increases the drive to breathe. Opioids may here simply bring ventilation back to normal.

The same principles of opioid administration as for pain control apply[124]. These are:

1. Regular dosage to *prevent* return of the symptom.

2. Titration of dose against effect. Thus, morphine 2.5 mg 4 hrly may be started and the dose gradually increased stepwise by about 50% each day or two till the dyspnoea is relieved. If drowsiness occurs, the dose should be held stable till this wears off.

   Henteleff[119] has developed a dyspnoea protocol for treatment of terminally ill patients. This uses the respiratory rate as a guide to whether morphine dosage should be increased, decreased or not changed, and hence obviates any fear of overdosage and respiratory depression (table 9).

   Dosage of opioids for dyspnoea is said to be lower than that needed for pain, but this does not appear to have been proven.

Respirations	Action
Over 30/min	increase morphine
15-30/min	increase for distress: continue if comfortable at rest
12-15/min	no change
less than 12/min asleep, but over 12/min on being awakened	reduce morphine
less than 12/min despite waking	Naloxone 0.4 mg 1M stat, hold morphine, notify physician. Repeat naloxone 0.4 mg 1M q 10 min up to twice then q 60 min until respirations over 12/min.

Table 9. Control guide for treatment of dyspnoea with morphine (Henteleff[119]).

3. Use oral medication in preference to injections. However, Cohen et al[133] found that 7 out of 8 patients, with severe dyspnoea from terminal lung cancer, were relieved symptomatically using a regime of bolus IV morphine 1-2 mg every 5-10 minutes followed by a continuous IV infusion with the hourly dose equivalent to 50% of the cumulative bolus dose. Seven of the 8 patients died during this therapy (mean study time = 30 hrs, range 16-87 hrs). The authors were uncertain as to whether the morphine shortened survival or not. As opposed to this, acute tolerance may develop to intravenous diamorphine[200] and this method is therefore best restricted to urgent treatment of severe dyspnoea.

4. Nebulised morphine 5 mg given over 15 minutes[107] has been recommended. This may work by a local action[111,129], but it is also significantly absorbed and so will have some systemic effect[128]. Its

bioavailability, however, is low[192] - 4.8% for a 10 mg dose - which would reduce the likelihood of systemic toxicity. Low doses have been shown to improve exercise endurance in patients with chronic lung disease[129].

5. Adjuvant medication is commonly needed so that 2 drugs with different modes of action against dyspnoea will act synergistically and hence may allow a lower dose of each than if either were prescribed alone. An example is the use of glucocorticosteroids and morphine for dyspnoea from lymphangitis carcinomatosa.

6. A number of authors[107,116,117,118,119] report reduction of dyspnoea by opioids but give no figures as to how many patients benefited or how the dyspnoea was measured. However, Robin and Burke[125], using a single patient randomized double blind trial of hydromorphone against placebo, found a marked improvement of dyspnoea by the opioid, as measured by an index indicating degree of impairment of various daily activities. Johnson et al[126] report decreased breathlessness in patients with chronic obstructive airways disease, as measured by VAS, with dihydrocodeine. Woodcock et al[127] found a similar improvement.

7. Good analgesia will of itself reduce the chronic hyperventilation induced by intractable pain[115].

8. Finally, Bruera et al[122] noted that the dyspnoea-relieving effect of subcutaneous morphine wore off after about 2 hours, whereas analgesia in the same patients lasted longer. Hence more frequent doses of morphine might be needed for dyspnoea than for pain.

Treatment of opioid overdosage

Provided the guidelines outlined above are followed, overdosage is unlikely to be a problem[121]. For patients where the respiratory frequency is only slightly below

normal, coached breathing[130], where the doctor or nurse stays with the patient, keeps him awake, and so prevents reduced ventilation, may be all that is needed. In the author's experience, using naloxone to reverse respiratory depression has hardly ever been necessary. It may occasionally be needed where a nerve block has markedly reduced pain levels and hence removed the respiratory stimulant effect of pain, thus precipitating hypoventilation[131]. 0.1-0.4 mg naloxone IV is given, titrating dose against effect, and repeated if necessary[206]; a balance must be struck between antagonising opioid respiratory depression and its analgesia, otherwise pain may return. Naloxone is short-acting which means that too high a dose is quickly metabolised. However, this also means that its opioid antagonist effect may wear off before the opioid has been metabolised, and so the patient must be observed over several hours to see if further naloxone is needed[206].

b) Psychotropics

These may alleviate dyspnoea in the following ways:

1. Reduced anxiety
2. Muscle relaxation: as discussed on p 29, benzodiazepines may potentiate GABA neural inhibition in the brain and spinal cord and hence decrease muscle spindle mismatch thus reducing dyspnoea.
3. Treatment of depression

The following have been used:

i Diazepam

Chronic administration of diazepam has been found to reduce the sensation of dyspnoea and increase exercise tolerance[132] in patients with the "pink puffer" syndrome. However, Stark et al found no improvement in exercise-induced dyspnoea in normal subjects by diazepam[134]. Woodcock et al[135] suggested that diazepam

was contraindicated in fixed airways obstruction either because of drowsiness or because one of their patients taking diazepam died during an exacerbation of breathlessness and they were uncertain as to whether diazepam contributed to this. They were, however, using very high doses (5 mg tds and 10 mg nocte). Jones and Cameron[146] similarly found no benefit. Flumazenil[137] is a specific benzodiazepine antagonist for overdosage but is only used in intensive care situations, needing close monitoring, and therefore is not suitable for hospice use.

ii Promethazine

Woodcock et al[135] found that promethazine 25 mg tds and 50 mg nocte reduced breathlessness and improved exercise tolerance without altering lung function in pink puffers. Stark et al[134] also found a minor trend of reduction in exercise induced breathlessness in healthy subjects by promethazine but this did not reach statistical significance. Jones and Cameron[136] found no improvement by promethazine of dyspnoea in patients with chronic airflow limitation during exercise.

iii Alcohol

Woodcock et al[135] found that alcohol improved exercise tolerance and reduced dyspnoea in patients with chronic lung disease. Bar-Or et al[138] found that beta-endorphin levels in patients with acute intoxication were significantly raised and therefore suggested this as the mechanism of alcohol's effect on dyspnoea.

iv Antidepressants

Sedative antidepressants such as amitryptiline might be expected to reduce dyspnoea by an anxiolytic effect. Depression itself has been shown to be associated with dyspnoea[35,139] as part of its somatic presentation; further, treatment with antidepressants[139] led to resolution of the dyspnoea.

v Nabilone

Relief of dyspnoea by nabilone is probably due to two factors: firstly, adrenergic and anticholinergic effects on the airways, and secondly a central sedative effect[107,140]. It does, however, have significant toxicity[140] (such as drowsiness, confusion, hallucinations or psychoses[141]) and it has therefore been suggested that it should only be used in patients who have not responded to opioids[140], and that the dose should be low (200 mcg tds)[107] as compared with the usual antiemetic dose (1-2 mg bd)[141]. The lower doses have to be specially made by a pharmacist as 1 mg is the lowest strength capsule commercially available.

c) Atropinics

Hyoscine Hydrobromide has the following effects[2,143] relevant to dyspnoea:

1. Reduced secretion from all exocrine glands. This will therefore reduce bronchial secretions in terminal bronchopneumonia.

2. Relaxation of smooth muscle and hence bronchodilatation.

3. It is markedly sedative. However, in the elderly it may cause the anticholinergic syndrome[142] (excitement, ataxia, hallucinations, behavioural abnormalities and drowsiness) and so should not be given by itself but with another sedative drug such as diamorphine or chlorpromazine.

4. Amnesia: this is of use if the terminally ill patient survives a respiratory crisis.

The dose is 0.4-0.8 mg IM 4 hrly. Tachyphylaxis is said to occur but has not in the author's experience been a problem. Hyoscine may also be used in the syringe driver (0.8-2.4 mg/24 hr). Atropine is not usually used because of its neuro-excitatory effects.

d) Muscle relaxants

In theory muscle relaxants such as dantrolene or baclofen would reduce dyspnoea through an effect on length-tension respiratory muscle mismatch. No studies on this were found. Diazepam has already been considered (see p 77).

e) Local Anaesthetic Inhalation

If dyspnoea is mediated by lung J-receptors (see p 31) nebulised inhaled local anaesthetics might prevent firing of these sensory receptors and hence reduce dyspnoea[43]. To do this, particle size would have to be small enough to reach alveoli where the J receptors are sited - the majority of particles must be less than 4 micrometres (um) diameter[43]. Lunt et al measured particle diameters in three commercially available nebulisers and found that they were mostly above this limit[43].

Two methods of dealing with this have been described. Lunt et al[43] dehydrated particles and hence reduced their size by passing them through an electrically heated tube using an air pump. The other approach is to nebulise fluids with an ultrasonically vibrating metal plate[2] producing particle sizes of about 4 um diameter, or with a jet nebuliser (mean diameter particles 1.5 um)[93].

Both Bupivacaine[43,144,145] and Lignocaine[44,107,140,147] have been used, either for dyspnoea or cough, with variable results. Some report reduced dyspnoea with bupivacaine[43,144,145] or with lignocaine[140,148], while

others report mostly no improvement with lignocaine[93,147] or even increased airways resistance[147]. One study with asthmatics showed a bimodal response with increased airways resistance initially due to bronchial irritation and reduced resistance after about 45 minutes[146] due to a membrane stabilising effect on bronchiolar smooth muscle, and hence bronchodilation.

Why are there there variable results? Firstly, nebulisers producing particles too large to reach alveoli will not work; thus Winning et al[144] found that the majority of partides of ^{99m}Technetium labelled bupivacaine with aerodynamic mass median diameter = 4.77 um were deposited in the large airways on lung scan, whereas Hamilton et al[149] found that smaller particles (mass median diameter = 0.9 um) of ^{99m}Technetium labelled bupivacaine were mostly deposited peripherally in the alveoli.

Secondly, bronchoconstriction may be induced masking any bronchodilator effect[146].

Thirdly, as particles travel down the airways they may become rehydrated in the moist atmosphere, and hence with an increasing diameter tend to fall out in the larger airways[150]. The isotope studies just mentioned, however, suggest this is not a major factor[144,149].

Fourthly, if only small amounts of local anaesthetic solution are reaching the alveoli, the concentration of that solution may be critical in determining any effect. Doses that have been used are shown in table 10.

Drug	Strength (%)	Dose (ml)	Time (mins)	Authors
1. Lignocaine	20	2.5	8	Santolicandro[148]
	10	4	15-20	Howard et al[147]
	5	Not stated	20	Stark et al[93]
	4	1	10	Weiss et al[146]
	2	5	15-20	Regnard et al[107]
2. Bupivacaine	5	5	10	Winning et al[144]
	0.5	Not stated	Not stated	Lunt et al[43]

Table 10. Dosages of nebulised local anaesthetic

Unwanted effects are bronchocontriction[146], pharyngeal numbness[147], vocal paresis[147], and abolition of the cough reflex[147]. The problems caused by the absent cough reflex may be circumvented by using small diameter particles[145], possibly because of a laminar flow effect down the airways[151]. However, fasting for 1 hour after administration has been recommended[107] to prevent aspiration. A case of fatal bronchospasm (probably anaphylactic) after topical 10% lignocaine, given before bronchoscopy, has been described[152].

f) Oxygen and Helium

Oxygen may relieve dyspnoea either physiologically by improved arterial PO_2 levels and hence reducing respiratory work for example in "pink puffers"[153] or psychologically (see p 19) the oxygen being seen as the breath of life.

It is not usually first-line management for dyspnoea in advanced cancer, except in acute situations[2] for various reasons[2,56,140]:

i) the oxygen cylinder and mask may be distressing to the patient or his watching family.
ii) the hazards of suppression of anoxic drive in chronic bronchitics, although the use of low concentrations (24%) of oxygen obviates this problem.
iii) problems of maintaining domiciliary supplies.
iv) Cylinder dependance - the patient has to be accompanied by his cylinder at all times.
v) Dry mouth.

Helium-oxygen (He-O_2) mixtures have been recommended for dyspnoea due to tracheal obstruction[107], since they are less dense than air and hence reduce the work of breathing[154]. Thus Boorstein et al[155] describe a case of asthma and tracheal angio-oedema refractory to conventional bronchodilator treatment which improved on a He (80%) - O_2 (20%) mixture.

Neither oxygen nor He-O_2 appears to have been evaluated for use in palliative care.

g) Prostaglandin inhibitors

O'Neill et al[156] have demonstrated in a double-blind randomised study that indomethacin significantly reduced the sensation of breathlessness in healthy volunteers during different levels of standardised exercise, as compared with placebo; ventilation and oxygen uptake were not affected. The mechanism is uncertain, though the authors point out that prostaglandins are generated in the lungs, and that vagal nonmyelinated C fibres (many of which terminate as juxta-alveolar (J) receptors) are

stimulated by prostaglandins. Prostaglandin inhibitors might therefore decrease receptor stimulation and hence reduce breathlessness[40].

Aspirin, another prostaglandin inhibitor, reduces pyrexia and so metabolic rate and oxygen consumption. Dyspnoea might therefore be alleviated, though this does not appear to have been tested.

h) Beta-adrenergic blockade

Metoprolol has been reported as useful in treating HVS[157], reducing excessive ventilation and hence relieving hypocapnia. The deleterious effects of beta-blockers in asthma and heart failure must however be borne in mind.

i) Relief of other symptoms

Just as the pain threshold may be lowered by factors as discomfort, anxiety, depression or isolation[124], so the same could apply for dyspnoea. Hence control of other symptoms may raise the "dyspnoea threshold" and so reduce dyspnoea.

j) Doxapram[137]

This is only used in intensive care units to stimulate ventilation in acute respiratory failure. It is not indicated for dyspnoea in advanced cancer.

k) Aminophylline

This not only relieves bronchospasm and heart failure, but also acts as a respiratory stimulant[158].

1) Progesterone

This has been reported as stimulating ventilation in obese men with the Pickwickian syndrome[203], possibly by a peripheral action, increasing the ventilatory response to hypoxia.

3. Palliative Procedures

a) Radiotherapy

Berry reports that this may be useful in relieving dyspnoea in patients with carcinoma of the bronchus not only with small cell histology (45% improved) but also of any histology[109] (45% improved). A split-course technique giving 20 Gy in 5 fractions over 4 days is recommended followed 4 weeks later by a further similar dose if there is sufficient improvement with the first course to warrant further treatment. This avoids long drawn-out and hence tiring daily fractions of radiotherapy over 6 weeks in patients with very short prognoses.

Radiotherapy to lung metastases is not usually indicated as they are often radioresistant. However some highly radiosensitive tumours such as lymphomas, seminomas and nephroblastomas, will respond[159]. A maximum dose of 15 gy in 6 fractions over 3 weeks to both lungs has been recommended, as higher doses may produce acute radiation pneumonitis.

Mehta et al[160] have used endobronchial irradiation with Iridium-192 for palliation of malignant airways obstruction. Thirty (83.3%) of 36 patients with dyspnoea improved symptomatically. Median implant time was 50.5 hrs.

Radioactive gold grains have been implanted following diathermy resection of obstructing bronchial tumour[161]. Symptomatic relief was obtained, though no details were given. External beam irradiation (20 Gy in 3 weeks)[108] has been used to prevent recurrence of pleural effusions, but is of limited value as the wide field of irradiation limits the total dose.

b) Laser therapy

Bronchial carcinomas, whether primary or secondary, causing airways obstruction, may be resected using lasers. The most widely used technique is photoresection using the neodymium yttrium aluminium garnet (Nd:YAG) laser[162,163]. The beam is transmitted through a quartz fibre which itself can be passed down the biopsy channel of a fibreoptic bronchoscope. It is particularly useful in dyspnoeic patients who have had maximum radiotherapy.

Response is immediate, there is no systemic toxicity, and treatment may be repeated. Hetzel[162] quotes a respiratory symptoms response rate of 45 (76%) out of a group of 59 patients, with improvement in the peak expiratory flow rate (PEFR) in 37 (63%). PEFR may increase as much as 512% due to lung re-expansion. Antibiotics may be needed for infected secretions distal to the obstruction. Tracheal stenosis causing stridor responds particularly well. In some cases, reopening the obstructed bronchus may be ineffective due to tumour also compressing the blood supply, so that ineffective ventilation of an under-perfused lung simply increases the dead space[163].

Photodynamic therapy is less likely to be of use: here, haematoporphyrin derivative is injected and preferentially retained by tumour cells. When stimulated by light from an argon-dye or gold vapour laser, the drug is activated and has a cytotoxic effect through production of singlet oxygen[162]. Although more selective, it takes several days

to produce tumour necrosis and bronchoscopy is usually needed to remove slough blocking the bronchus. Further, other rapidly dividing cells may retain the drug, haemorrhages may occur and photosensitivity rashes have been reported.

c) Stents

Tracheobronchial obstruction from tumour has been successfully relieved by either silicone[164] or expandable metal stents[165].

Silastic stents were reported in one study[164] to stay in place for up to 18 months (mean = 4.4 months). However progression of the tumour beyond the tube did occur in 2 out of 11 cases.

Expandable metal stents are more flexible than silastic tubes, a smaller surface area is in contact with airways mucosa and there is minimal risk of occluding a bronchial orifice if the stent migrates. They are better for long-term placement as the stent hooks are fixed to the bronchial wall and make removal difficult. Simmonds et al[165] quote a case history of a man with squamous cell carcinoma of the bronchus with compression of both main bronchi whose dyspnoea and respiratory indices improved after stenting.

d) Pleural taps

Pleural effusions are common in patients with primary or secondary malignant neoplasms of the lung or pleura and may - though not always - cause dyspnoea. The following methods of drainage have been described[166]:

1. Simple drainage

2. Large-bore closed-tube thoracostomy chest drainage, followed by pleurodesis with a sclerosing agent. Cytotoxic sclerosants may also work by destroying tumour cells.
3. Small-bore catheter chest drainage (eg the Bonnano catheter[167]) and pleurodesis. This is a less distressing procedure than using large bore chest drainage tubes[166].

Indications for drainage[2] are:

1. Where the effusion is the main cause of dyspnoea
2. If a previous tap has relieved dyspnoea
3. As part of further active treatment (although this is unlikely to be frequent in patients with advanced cancer).

Problems with tapping pleural fluid include:

1. The effusion may recur rapidly (within an average of 3-4 days[166,168] after simple drainage). However, some may take several weeks to return[168].
2. Toxic effects of agents used for pleurodesis (see table 11) and their high cost.
3. Even a simple drainage may be distressing to a very ill, frail patient, let alone tube drainage.
4. Repeated taps are often needed, as draining more than 1.5 litres at a time may precipitate acute heart failure[108].

Hence, the following protocol is suggested:

1. Simple drainage, and repeat if patient fit enough.
2. If rapid reaccumulation and the patient can tolerate the procedure drain to dryness using a small bore cannula, and instil bleomycin, which is the agent of choice[108]. The patient is moved to several different positions over the next 4 hours, followed by further drainage over 24 hours and removal of the cannula[168].

3. An alternative is to connect the cannula to a continuous drainage bag and leave in situ. This would be most suitable for patients with short prognoses who are not ambulant[170].

Sclerosant	Comments	Dosage
Talc	Needs a general anaesthetic and thoracoscopy. Pain and pyrexia may follow. Response rate 90%. Best for those with longer prognoses.	-
Bleomycin	No tissue necrosis if injected in wrong place. No bone marrow toxicity Fever and chills. Response rate 60%	5 mg test dose followed by 30 - 60 mg.
Tetracycline	Severe local pain	500 mg dissolved in 20 ml 0.25% bupivacaine.
Thiotepa	Bone marrow suppression Local irritation	10-65 mg which may be repeated at 1-2 weekly intervals.
Corynebacterium Parvum	Only fine needle aspiration needed. Fever, mild pain. Nausea and vomiting	7-14 mg may be repeated 1-4 weekly intervals

Table 11. Main agents used for pleurodesis.

Sources: Mansi and Hanks[167], Walsh et al[166], Mosley[168], Regnard and Davies[169], Hoy[56].

e) Pleurectomy

This may occasionally be indicated in patients with recurrent effusions and a long prognosis[108]

f) Paracentesis

Drainage of ascites will relieve pressure on the diaphragm and hence reduce dyspnoea. Sclerosing agents are less successful here. For patients with longer prognoses, a peritoneo-venous shunt such as the Denver Shunt may be of use[56].

g) Drainage of Pericardial effusion

Dyspnoea may occasionally result from pericardial effusion and tamponade. Drainage is technically more difficult than for pleural effusions and more hazardous[108], and should therefore only be carried out in a unit experienced in this technique with appropriate life-support facilities[56], and in patients with longer prognoses. It is therefore rarely indicated in palliative medicine.

h) Drainage of pneumothoraces

Pneumothoraces may be caused by primary lung or oesophageal carcinomas, by metastatic lung tumours and by subpleural sarcomatous deposits[194]. They are probably underdiagnosed in palliative care because investigations may be contraindicated in the very frail dying patient. They may occur after pleural taps, though this is almost always of no clinical significance, will resolve spontaneously and so needs no treatment.

i) Blood transfusions

Anaemia is common in advanced cancer and may be from multiple causes. If dyspnoea occurs as a result, a transfusion with packed red cells may help. The author has found that this only sometimes is of use and runs the risk of circulatory overload in very frail patients. Transfusion, as a symptom control measure, does not appear to have been evaluated in palliative medicine.

j) Physiotherapy

This may help in various ways:

1. Bronchial secretions narrow the airways and hence increase the work of breathing. Coughing up sputum may alleviate this: postural drainage, percussion, vibration, coughing exercises and forced expiration have all been used. If there is little sputum, however, chest physiotherapy (postural drainage, percussion and vibration) may be positively harmful[195] by causing bronchospasm and transient hypoxaemia.

   Although coughing exercises are effective, they may cause dynamic compression of the airways by inducing high transmural pressures and so inhibit mucociliary clearance[195]. This problem can be overcome by using the "forced expiration technique" where patients expire forcefully from middle to low lung volumes while maintaining an open glottis[195]. However, both these procedures may be beyond a very weak terminally ill patient in which case gentle postural drainage with humidified air to reduce mucus viscosity, may be all that is feasible[171].

2. Breathing exercises.
HVS and its symptoms, including dyspnoea, may be alleviated by breathing retraining, teaching the patient to change from fast panting thoracic breathing to slow diaphragmatic breathing[10,172,173]. This may be aided by asking the patient to insert a short pause after each respiratory cycle, and to place one hand on the chest and the other on the abdomen so that the first moves less than the second.[173] The reason that this prevents overbreathing is that the ventilation-perfusion ratio is much higher at the apices than the bases of the lungs, so that although blood flow is much greater at the bases, uptake of oxygen and excretion of CO_2 is relatively less than at the apices[174,197]; a change to diaphragmatic breathing takes advantage of this.

Lum[10] has found that 75% of a series of over 1000 patients with HVS were completely symptom free at 12 months after treatment, 20% were mostly relieved, and 5% intractable. Treatment took between 1 and 6 months.

By contrast, hypercapnic hypoxic patients will benefit from increasing their thoracic breathing.

3. Insight therapy
Howell[50] has recommended explanation to the patient with HVS of the pathophysiology of HVS followed by asking them to take 20 deep breaths which usually evokes their symptoms, including dyspnoea. This insight allows them to gain control of their behavioural overbreathing. No figures were given on success rates.

4. Rebreathing CO_2
Acute attacks of HVS may be rapidly abolished by use of a rebreathing bag[50] or breathing a 5% CO_2 mixture[75].

5. Humidified Air
   This will loosen viscous bronchial secretions and aid coughing[171], whether by humidifiers, inhalations or nebulisers.

k) Psychological therapies

Dyspnoea and psychological distress are often closely related[9,10,35,48]. Various therapies to reduce this distress may help dyspnoea indirectly.

1. Relaxation exercises[86,175]
   The subject progressively relaxes different muscle groups, with or without initially tensing them. This is often combined with breathing exercises, as already described[175,176]. Relaxation decreases physiological arousal, tension headaches and insomnia, and also reduces anxiety, enhances coping ability and interrupts obsessive negative thinking[175]. Massage may be a useful adjunct[175].

2. Visualisation/Guided Imagery[175,176]
   The subject is asked to bring to mind a pleasant and peaceful scene from his or her past and remember it in as much detail as possible, including sights, sounds, smells and so on.

3. Hypnosis[175]
   The subject enters an altered state of consciousness in which he or she becomes more open to suggestion, for example that his or her breathing is becoming progressively easier.

4. Transcendental Meditation[175]

5. Biofeedback[175]

The subject is given information as to how tense their muscles are through electromyography, for example with finger or frontalis muscle electrodes[177,178]. This is often combined with relaxation or visualisation exercises.

6. Behavioural and cognitive approaches

Breathing exercises, relaxation exercises and biofeedback are all forms of behavioural therapy, while insight therapy, visualisation, hypnosis and meditation are cognitive treatments.

Malatesta et al[179] describe the successful use of behavioural reconditioning for a patient with brain stem dysfunction and repeated respiratory arrests who was suffering from panic attacks with suffocation phobia when being weaned off the ventilator.

Moorey and Greer[86], using adjuvant psychological therapy (APT), a form of behavioural and cognitive therapy, report reduced anxiety and depression in cancer patients (which might therefore be of use in dyspnoea).

7. Counselling and Psychotherapy

These therapies may be lengthy and so, while they can resolve inner conflicts and so be of help for anxiety and dyspnoea, they are less likely to be of use for the terminally ill with very short prognoses. Further, Rosser et al[180] did not find that dyspnoea from chronic obstructive airways disease improved with supportive or analytical psychotherapy.

4. Symptomatic Procedures

a) Cold air

A bedside fan directing a current of air against the cheek relieves terminal dyspnoea[181]. Cold air or cold solutions applied to the face, nasal mucosa or pharynx are known to reduce ventilation probably through stimulation of the trigeminal nerve[182,183]. Schwarzstein et al[183] showed that a flow of cold air directed at the cheek reduces breathlessness induced by an inspiratory resistive load and hypercapnia without significant reduction in total ventilation.

b) Acupuncture

Jobst et al[184] have shown in a randomised controlled trial, reduced breathlessness scores (VAS) and increased 6 minute walking distance in patients with COAD when treated with traditional Chinese acupuncture as compared with placebo acupuncture.

c) Oral high-frequency oscillations (OHFO)

George et al[185] have demonstrated reduced ventilation with no change in PCO_2, along with reduced breathlessness, in patients with COAD by using OHFO, where high frequency air oscillations were superimposed on tidal breathing by using a loudspeaker attached to a mouthpiece. This technique remains experimental.

2.9 Evaluation

Efficacy of individual treatments has already been indicated. There are few global assessments. Lamerton[186] found that 36% of a group of 289 home care patients at St Joseph's Hospice in London obtained good relief from dyspnoea. Higginson and McCarthy[187] found no improvement over time in dyspnoea scores in a series of 18 patients with terminal cancer. It might be, however, that untreated, these patients' scores would have worsened.

CHAPTER 3 METHODS

Three cohorts of patients were studied:

1. Preliminary study
2. Main study
3. Hyperventilation study

Data collection was carried out by the author and a research assistant.

3.1 Preliminary Study (Cohort 1)

This was undertaken to provide an initial assessment of how much of a problem dyspnoea is in advanced cancer, concentrating on prevalence, severity, survival and site of primary carcinoma.

The admission notes of all patients (N = 303) admitted to Countess Mountbatten House between 14.10.86 and 31.5.87 (229 days) were studied retrospectively for the following information: name; date of birth; age; sex; date(s) of admission(s), discharge(s), readmission(s) and death; site(s) of primary carcinoma(s), and whether dyspnoeic or not on admission. Severity of dyspnoea was assessed from the history taken by the admitting doctor as absent (0), mild (1), moderate (2) or severe (3) in the last 219 patients. Evidence for the diagnosis of the primary carcinoma and presence or absence of lung metastases was recorded in the last 233 patients.

Information was stored initially on a card index system and later transferred to computer for analysis (see p 111).

Results from this study were published (see appendix 7.9).

3.2 Main Study (Cohort 2)

Data were collected prospectively from patients admitted to CMH between 7.9.87 and 7.2.89 (519 days) to carry out more detailed investigations into the epidemiology of dyspnoea, to compare different methods of measuring dyspnoea, to test and validate two new measures of dyspnoea (the Dyspnoea Assessment Questionnaire or DAQ and Dyspnoea Exertion Scale or DES) and to investigate some causes of dyspnoea - with special reference to HVS. Information was also obtained on treatment given, but this does not form part of this thesis.

A protocol was submitted to the Southampton Ethical Committee and approval obtained. During part of the study, due to the increased numbers of patients referred to CMH, there was an age limit set on patients accepted for clinical care. Between 19.4.88 and 3.7.88 (75 days) only patients less than 70 years of age were admitted, and between 4.7.88 and 3.1.89 (183 days) only those less than 75 years old were admitted. There was no age limit for the remaining 261 days of the study.

Criteria for eligibility of patients

Inclusion criteria were:

1. Patients with advanced cancer.
2. Patients of either sex from age 18 years on.
3. Patients willing to give written consent.
4. Both dyspnoeic and non-dyspnoeic patients. The DAQ was only presented to dyspnoeic patients.

Exclusion criteria were:

1. Patients too frail to take part.
2. Confused patients.
3. Patients with expressive or receptive dysphasia.

Development of Dyspnoea Assessment Questionnaire (DAQ)

Present methods of measuring dyspnoea rely on quantitative scales only (see p 61). How patients describe breathlessness, however, includes qualitative differences such as between "choking" and "tight". By analogy, present methods are equivalent to monochrome, but patients descriptions equate to colour. A questionnaire was therefore developed along similar lines to the McGill-Melzack Pain Questionnaire[97] to take account of both aspects.

Fourteen doctors, 7 from CMH and 7 from the department of medicine at Southampton General Hospital, were asked to provide a list of all the words they could think of to describe dyspnoea (see appendix 7.1). A total of 164 words was obtained. Initially an attempt had been made to ask patients for words describing dyspnoea, but they were not able to, or would use long phrases. Of the words submitted by the doctors, 21 were rejected initially for the following reasons:

- Too technical for patients to understand
- Too esoteric, that is not likely to be within the vocabulary of patients
- Ambiguous words
- Synonyms for other words in the initial list
- Words not describing dyspnoea
- Words part of word/phrase already on list

This left 143 words which were divided into 5 classes and 27 subclasses. As this was an unwieldy number, a further questionnaire (see appendix 7.1) was circulated to 47 doctors comprising the original 14 and 33 from other hospices in Great Britain. Thirty-three replies were received. They were asked the following about the 143 words:

1. Is each word a valid descriptor of dyspnoea?
2. Assign a number on a scale of severity of 0-5 for each word
3. Is the classification, as it stands, valid for each word?
4. If the siting of a word in the classification is not considered valid, where else in the classification system would you place a word?

From the completed questionnaires, a severity score for each word was obtained by averaging the individual scores returned. Only words where there was 85% or greater agreement that a word was thought a valid descriptor of dyspnoea were chosen. This left 43 words in 5 classes and 16 subclasses. For all these words, there was greater than 85% agreement that their classification of the words was valid (see appendix 7.1).

The 43 words were then grouped into 16 categories corresponding to the subclasses (the classes were ignored as they were of no additional benefit). Dyspnoeic patients were then presented the DAQ (see appendix 7.1) and asked to look at each category in turn and choose the word from each category which best described their breathlessness. If no word in a category fitted, they were to leave that group blank and move on to the next. Finally, they were asked which of all the words presented best described their dyspnoea. Some patients had difficulty in concentrating and so these were presented with cards, one at a time, with only one category of words per card.

Knowing the severity scoring for each word previously obtained, and the words chosen by the patients, scores were calculated for each patient. Several different ways of computing these scores were tried and compared with an established method of measuring dyspnoea, the visual analogue scale (VAS) for validation.

The scores derived were:

1. Number of Words Chosen Score (NWCS)
2. Total Severity Score (TSS) - the sum of the severity scores of all words chosen, rounded off to 1 decimal place.
3. Average Severity Score (AVSS) - the average of the severity scores of all words chosen.
4. Total Class Score (TCS) - the words in each category of the DAQ were listed in ascending order of severity as obtained above, and correspondingly assigned a class score (see appendix 7.1). Thus in category 10, 'shallow' has a class score of 1, 'heaving' 2, 'panting' 3 and 'gasping' 4. The class scores of all words chosen were then summed.
5. Average Class Score (AVCS) - the average of the class scores of all words chosen.
6. Score Best Word (SBW) - the severity score of the word the patient felt best described his/her breathlessness.
7. Total Interval Score (TIS) - this takes account of the different numbers of words in each category. It assumes a minimum score of 0 in each category if no word is chosen, and a maximum score of 5 which is in the interval above the highest scoring word in that category. Thus for a 1 word category, that word scores 2.5, for a 2 word category, those words score 1.67 and 3.33 and so on as shown in fig 9. Interval scores for all words chosen were summed, and rounded off to 1 decimal place.
8. Average Interval Score (AVIS) - the average of the interval scores of all words chosen.
9. Short-Total Severity Score (STSS) - this was calculated to see if a rapid bedside assessment of dyspnoea could be developed. The 14 most popular words chosen by patients (see results p 132) were taken and only these words were used in calculating each patient's severity score from words they had already chosen in completing the DAQ.

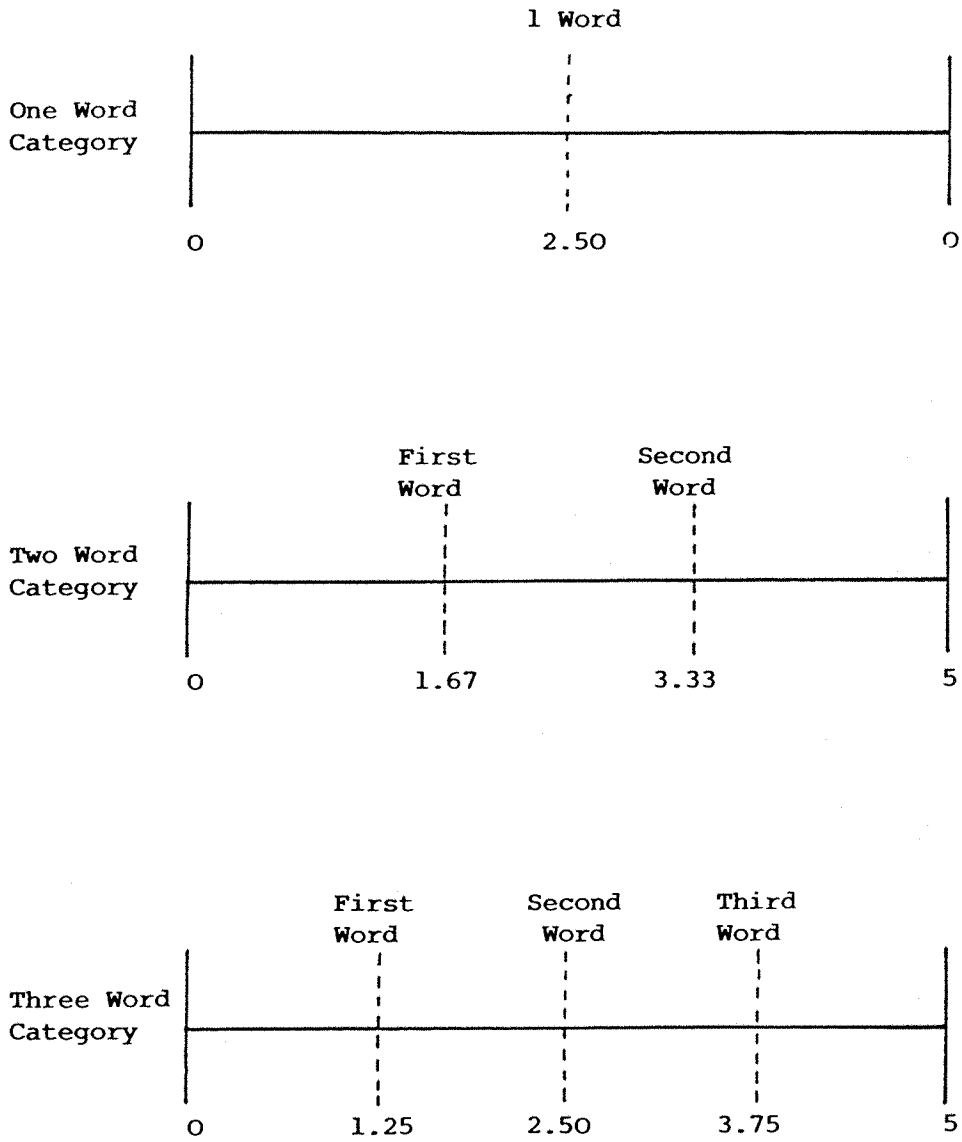


Fig 9. Interval scoring method examples

10. Dyspnoea Quality-Quantity Score (DQQS) - since the VAS measures predominantly quantity, and the DAQ quality, the two scores were combined and the mean calculated, so that $DQSS = \frac{PTSS + VASMe\ 24}{2}$

where PTSS is the TSS score as a percentage of maximum. The maximum possible TSS score, obtained by choosing the highest scoring word in each category, is 55.06 (see appendix 7.1). For calculation of the PTSS, the scores used are to 2 decimal places. Then, when the DQQS has been derived, the final figure is rounded off to 1 decimal place.

VASMe 24 means the patient's view of the average level of dyspnoea over the last 24 hours as measured by VAS.

Development of Dyspnoea Exertion Scale (DES)

Various scales have been developed to measure the relationship of dyspnoea to exertion (see p 66). However, these are often not appropriate for terminal cancer patients, who are usually very frail and have very restricted mobility. Thus very few would be considered Grade I on the Pneumoconiosis Research Unit Scale[54] (Is the patient's breath as good as that of other men of his own age and build at work, on walking and on climbing hills or stairs?). Most will tend to come at the bottom of the scale (Grade V - Is the patient breathless on talking or undressing, or unable to leave his house because of breathlessness?). Therefore this scale would be not sensitive enough to assess exertional dyspnoea in advanced cancer.

A new scale was therefore devised with questions weighted towards distinguishing dyspnoea at low levels of exertion: the Dyspnoea Exertion Scale (DES). Scoring was derived on a 0-5 scale, 5 implying the worst level of dyspnoea (see appendix 1). This scale was presented to the patient as

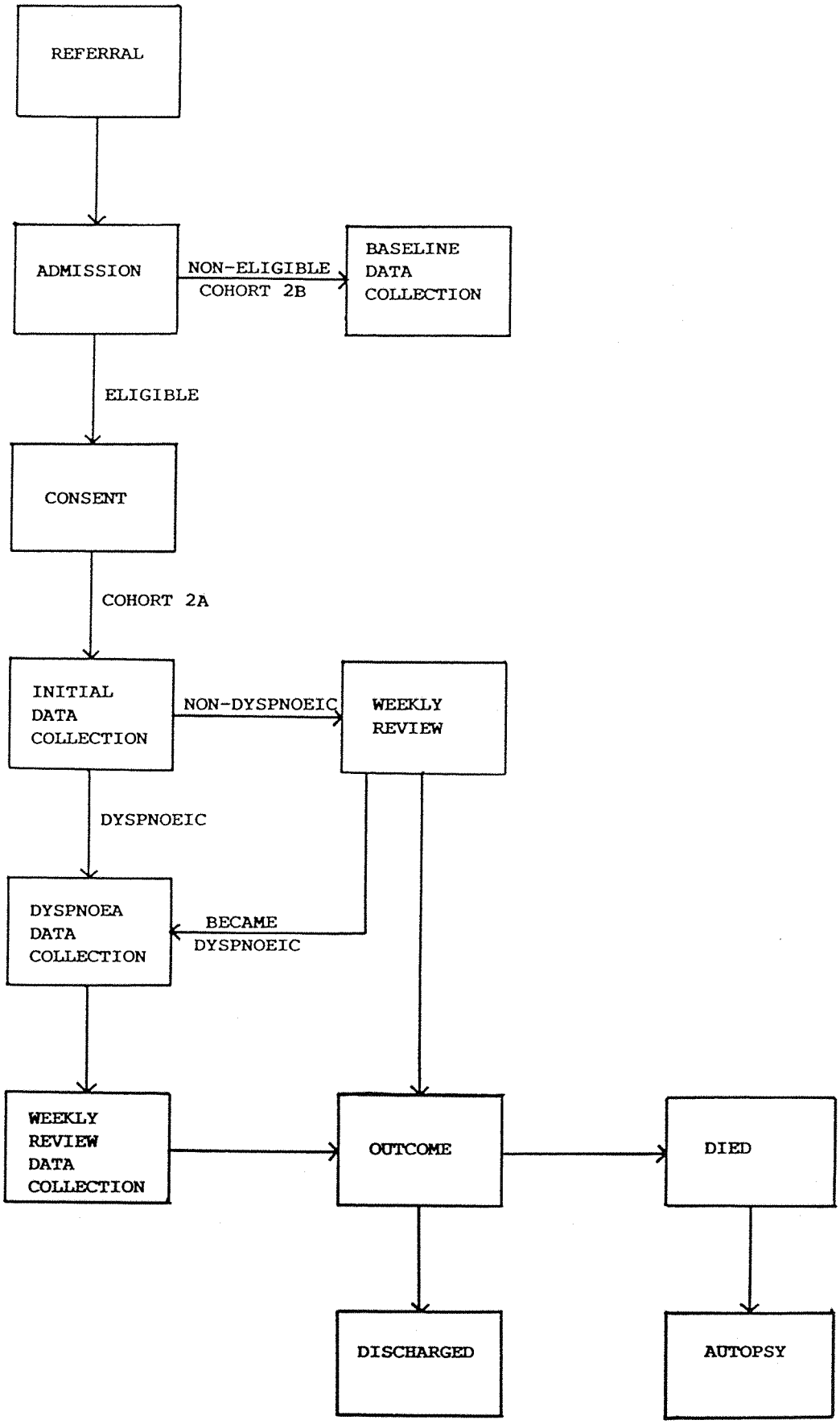


Fig 10. Main study method flow diagram

part of the data collection on dyspnoea (see appendix 7.4, Dyspnoea Questionnaire 1, question 3).

Scores obtained were then compared with a VAS of the patient's dyspnoea for validation.

Entry procedure for Main Study (see fig 10)

Patients referred for admission to CMH came either from home or hospital. For hospital referrals, a chest x-ray (CXR) was requested before admission, if not already done in the last two weeks because x-ray facilities were not available on site at CMH.

On admission, the admitting doctor decided whether each patient was eligible to participate or not, and asked if the patient would be prepared to take part in a research study. If not eligible (Cohort 2B) then the same data (baseline data) were collected from the notes as in the preliminary study, except that the patient was asked directly whether (s)he was breathless, and the doctor was asked to complete a VAS of his/her impression of the average level of breathlessness the patient had experienced over the last 24 hours (VASMe D).

If the patient was eligible (Cohort 2A) the research assistant or the researcher was informed. The patient was approached, details of the study explained using a standardised format, and written consent obtained (appendix 7.3).

The data sheets in appendix 3 - 'demographic data', 'case notes', 'treatment record', 'non-drug therapy for SOB', 'investigations at CMH', 'nurse's questionnaire', 'doctor's questionnaire' and the Crown-Crisp Experiential Index (CCEI)[85] were completed using the following sources:

Case notes
Treatment sheets
Laboratory results
Admitting nurse
Admitting doctor
Patient (for demographic data, investigations, CCEI and establishing dyspnoea status).

A full blood count (FBC), biochemistry and CXR were performed where clinically indicated and not recently done. Urinalysis and measurement of pulse rate, respiratory rate (RR) and temperature were carried out by the research assistant, as was spirometry (pre- and post salbutamol) and measurement of height and weight where the patient's condition permitted.

Although the CCEI is designed to be self-administered, the research assistant usually had to help in its completion due to the patient's frailty and difficulties in concentration. The CCEI was chosen as a measure of the psychological state of the patient as it was quick and easy to complete (about 5 minutes being needed) and also measured a wide range of psychological parameters.

The VAS completed by the admitting nurse was entitled VASMe N, meaning the nurse's view of the average level of the patient's dyspnoea over the last 24 hours.

From 1.9.88, a physiotherapy record was kept of whether the patient had had relaxation exercises, breathing exercises, postural drainage or percussion.

If the patient was not dyspnoeic, nothing further was done at the initial interview. If dyspnoea was present, then the following data sheets were completed with the patient (see appendix 7.4 for blank examples):

a) 'Dyspnoea Questionnaire 1: qualitative and quantitative aspects'. With this, two types of VAS were completed, the average level of breathlessness over the last 24 hours (VASMe 24) and the worst level over the last week (VASMax 52). A standard explanation used by Guz[90] in measuring dyspnoea with a VAS was given to the patient (see appendix 7.4) and the scales completed. Questions 2 (Dyspnoea Word Scale [DWS]) and 3 (Dyspnoea Exertion Scale [DES]) of the questionnaire were completed by presenting the patient with separate cards with the questions typed on them for them to choose the answer that fitted. With visually impaired patients, these questions were read out.

b) 'Dyspnoea Questionnaire 2 - Causes'.

c) 'Dyspnoea Assessment Questionnaire'.

d) 'Hyperventilation Test - Results'. Subjects with FEV_1 > 1 litre and suspected of having HVS had an HVPT carried out. One litre was chosen as a safe cut-off point. It was discovered that few patients fitted these criteria, which were therefore progressively revised as follows:

-	from 18.7.88	FEV_1 > 0.8 litres
-	from 1.9.88	All dyspnoeic patients whatever level of FEV_1 and whether suspected of HVS or not
-	from 9.12.88	All patients

The last modification allowed HVPT to be carried out on non-dyspnoeic patients as a comparison. The risk to patients of carrying out an HVPT with an FEV_1 < 1 litre was considered minimal (in practice, no patients had any problems with this).

This completed collection of admission data. Next, at weekly intervals, both the dyspnoeic and non-dyspnoeic patients were reviewed.

Dyspnoeic patients, were asked whether their breathlessness had changed (see appendix 7.5), and a repeat DAQ was performed, along with another VAS for the average level of dyspnoea over the last week (VASMe 7). Non- dyspnoeic patients were asked if they had become breathless - if so, the dyspnoea-related questionnaires were completed as described above. If not, no further action was taken. Patients continued to be followed up weekly until they were either discharged or died, in which case a post-mortem was requested from the relatives and where they agreed, signed consent obtained. Finally, the treatment record (see appendix 7.3) was updated.

If a patient was readmitted, and had previously been entered into the study, the following data were collected:

for dyspnoeic patients:

- VASMe 24 and VASMax 52
- DAQ
- Treatment record
- Blood tests and CXR if clinically indicated
- CCEI

for non-dyspnoeic patients:

- the same, but excluding VASMe 24, VASMax 52, DAQ

As before, patients were reviewed weekly.

Data collected covered a wider field than that studied in this thesis.

3.3 Hyperventilation Study (Cohort 3)

This was undertaken to find out how common HVS is in patients with advanced cancer. A positive HVPT was taken as diagnostic of HVS. Although HVPT's were performed in the main study (Cohort 2A), epidemiological analysis could not be carried out because:

a) patients entered to the study were not from consecutive admissions
b) only 24 of the 155 patients in the study had an HVPT done.

Hence, a third cohort was studied to provide epidemiological data (see fig 11).

All patients admitted between 19.12.89 and 16.3.90 (87 days) were studied. Appendix 7.6 sets out eligibility criteria.

The admitting doctor completed the baseline data sheet (see appendix 7.6) for all patients detailing age, sex, primary carcinoma, presence of lung metastases, other lung pathology and whether breathless or not. If the patient was ineligible, no further action was taken.

For eligible patients, the test was explained to them (see HVPT instructions, appendix 7.6) and written consent obtained. As in the main study, the patients were asked to take 20 deep breaths; they were then asked if they noticed any sensations or symptoms, and if so, whether they had experienced these before in association with breathlessness.

The test was taken as positive if the 20 deep breaths reproduced symptoms previously experienced in association with breathlessness.

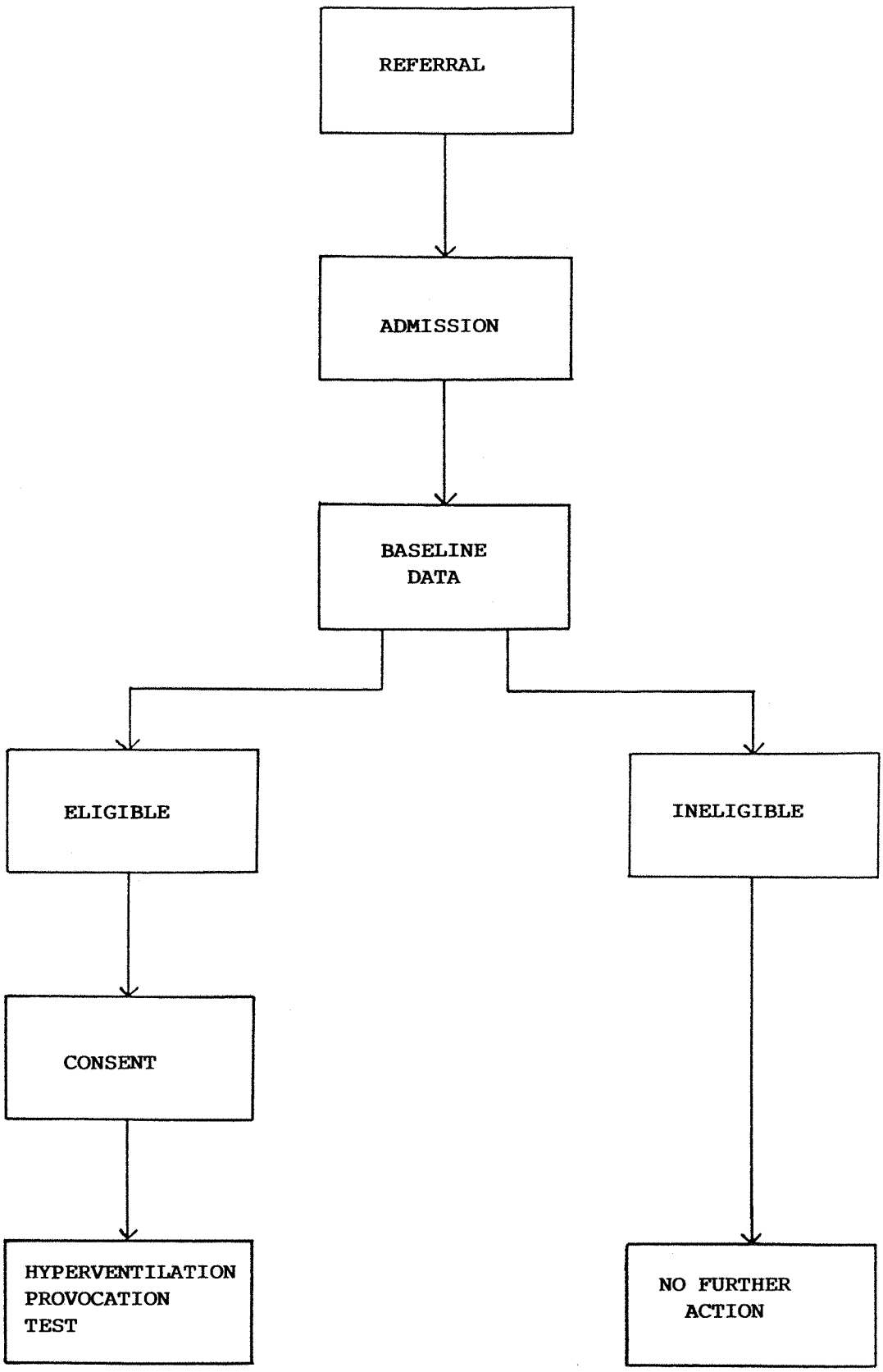


Fig 11. Hyperventilation study method flow diagram

3.4 Method of Analysis

Data obtained from these three studies were initially stored on an IBM PCXT 286 computer and analysed using an Ashton-Tate Dbase III plus software programme. Further analyses were performed on an IBM 3090-150 mainframe computer of the University of Southampton and an IBM-compatible PC using the statistical packages, BMDP, SAS and SPSS PC plus.

The statistical tests used were chi-square test (with Yates' continuity correction factor when applicable), Kaplan-Mier survival analysis, Mann-Whitney U tests and Spearman's rho. All tests were two-tailed unless otherwise stated.

In discussing the results obtained, for simplicity, and following convention, 5% or less probability ($p \leq 0.05$) is taken as indicating statistical significance. It is recognised however that this is an arbitrary figure.

CHAPTER 4 RESULTS

4.1 Patient Numbers Studied

These are detailed in table 12.

Cohort		Patient Numbers	Number Admissions	Study Period (days)
1	Preliminary study	303	355	229
2A	Main study (eligible)	155	251	519
2B	Main study (ineligible)	385	448	
3	Hyperventilation study	125	125*	87
	TOTALS	968	1179	835

Table 12. Patient numbers and study period (*Readmissions were not recorded in hyperventilation study).

In Cohorts 1, 2A and 2B, 211 of the 843 patients (25.0%) were readmitted at least once.

Prevalence of dyspnoea on admission is shown in table 13.

DYSPNOEA

Cohort	Nos. assessed for dyspnoea	Present (% of those assessed for dyspnoea)	Absent	Unknown	Totals
1	292	162 (55.5)	130	11	303
2A	155	71 (45.8)	84	0	155
2B	299	253 (84.6)	46	86	385
2 (all)	454	324 (71.4)	130	86	540
3	105	62 (59.0)	43	20	125
TOTAL	851	548 (64.4)	303	117	968

Table 13. Prevalence of dyspnoea on admission.

4.2 Age

	DYSPNOEA			
Cohort	Present	Absent	Unknown	Total
1	66.3	65.8	62.4	65.9
2A	63.9	64.3	-	64.1
2B	63.7	61.2	64.9	63.7
3	67.7	67.0	61.0	66.4

Table 14. Mean ages (years) and dyspnoea status

Patients in the main study had lower mean ages, which reflected the age restriction policy in operation for admissions to CMH during part of the study (see p 98).

In the preliminary study, mean ages in those with dyspnoea were not significantly different from the non-dyspnoeic, as shown in table 15.

Dyspnoea status	No. patients	Mean ages	Standard deviation
Non-dyspnoeic	130	65.8	12.6
Dyspnoeic	162	66.3	11.6
All (including unknown status)	292 (+11) = 303	65.9	12.0

Table 15. Association between dyspnoea and age. $t = 0.39$, $df = 290$, $p = 0.69$, CI for the difference in population means = -3.40, 2.27. (Patients with unknown dyspnoea status (N = 11) excluded from analysis). Cohort 1.

Table 16. Prevalence of dyspnoea by sex

Cohort	Sex	Dyspnoeic (%)	Non-dyspnoeic	Dyspnoea status unknown	Dyspnoea status known	All
1	M	87 (61.3)	55	5	142	147
	F	75 (50.0)	75	6	150	156
	All	162 (55.5)	130	11	292	303
2A	M	37 (46.2)	43	0	80	80
	F	34 (45.3)	41	0	75	75
	All	71 (45.8)	84	0	155	155
2B	M	132 (86.8)	20	47	152	199
	F	121 (82.3)	26	39	147	186
	All	253 (84.6)	46	86	299	385
3	M	31 (54.4)	26	5	57	62
	F	31 (64.6)	17	15	48	63
	All	62 (59.0)	43	20	105	125
Total	M	287 (66.6)	144	57	431	488
	F	261 (62.1)	159	60	420	480
	All	548 (64.4)	303	117	851	968

Overall, gender was not significantly associated with presence or absence of dyspnoea (X^2 = 1.65, df = 1, p = 0.20, difference in proportions = 4.5%, 95% CI for difference in proportions = -2% to 11%), although in the preliminary study, the association was close to significance at the 5% level (X^2 = 3.31, df = 1, p = 0.07, difference in proportions = 11.3%, 95% CI [confidence interval] = 0% to 23%).

4.4 Socioeconomic status (SES)

	SES	N	Dyspnoeic	Not Dyspnoeic	% Dyspnoeic
1	Professional	26	11	15	42.3
2	Intermediate	21	8	13	38.1
3.1	Non-manual skilled	26	12	14	46.1
3.2	Manual skilled	48	25	23	52.1
4	Partly skilled	2	0	2	0
5	Unskilled	0	0	0	0
6	Inadequately described occupations	15	7	8	46.7
7	Armed Forces	6	2	4	33.3
8	Unknown	11	6	5	54.5
	TOTAL	155	71	84	45.8

Table 17. Prevalence of dyspnoea on admission by SES. Cohort 2A. (X_2 = 1.71, df = 7, p = 0.97). "Unskilled" not included in figures as none recorded in trial.

4.5 Race

In the main study (Cohort 2A) 154 (99.4%) of patients were white and 1 (0.6%) Asian. Relationship to dyspnoea could not therefore be assessed.

4.6 Abode

Abode (UK)	N	Dyspnoeic (%)	Non-dyspnoeic
Urban (= Town or city)	141	65 (46.1)	76
Rural (= village or country)	14	6 (42.9)	8
Total	155	71 (45.8)	84

Table 18. Prevalance of dyspnoea by abode (UK) (X_2 = 0.002, df = 1, p = 0.96, 95% CI = -23% to 30%). Cohort 2A.

Abode (countries)	N	Dyspnoeic	Non-dyspnoeic	% Dyspnoeic
UK only	119	61	58	51.3
UK and abroad	36	10	26	27.7
Total	155	71	84	45.8

Table 19. Prevalence of dyspnoea by abode (countries) (X_2 = 5.243, df = 1, p = 0.02, difference in proportions = 23.6%, 95% CI = 6% to 41%). Cohort 2A.

Place of abode in the UK did not affect prevalence of dyspnoea (table 18). However, patients who had lived abroad were less likely to be dyspnoeic (table 19). Of the 36 who had lived abroad, 25 (69.4%) had lived in tropical or sub-tropical countries, 4 (11.1%) in a wide variety of countries while in the army or navy, 5 (13.9%) in Europe and 2 (5.6%) in the U.S.A.

4.7 Survival

Data on survival were kept for Cohorts 1, 2A and 2B. Of the 843 patients in these groups, 821 (97.4%) had died when analyses were carried out.

Mean survival was longer in Cohort 2A. Overall, however, dyspnoeic patients appear to have a shorter survival than non-dyspnoeic (table 20).

This is confirmed in Cohort 1 where survival analysis (see fig 12) demonstrates a significant difference ($p = 0.04$). Further, fig 13 suggests that as the prevalence of dyspnoea increases, survival decreases; patients surviving less than one day from admission had a prevalence of 82.1%.

In Cohort 1, the last 219 patients were assessed as to the severity of their dyspnoea by studying the history taken by the admitting doctor, and from this assigning dyspnoea scores of 0 (absent) 1 (mild), 2 (moderate) or 3 (severe). (See table 21). Of the 219, 213 (97.3%) had died at the time of analysis of the data (16.9.88), 1 was still alive, the death records of 5 were unavailable, and 10 were too ill to be assessed.

There is a clear inverse relationship between severity of dyspnoea and median survival (table 21). Also, overall median survival (11.0 days) in this cohort was much shorter than mean survival (34.7 days). Similarly in Cohort 2A, overall mean survival was 70.6 days, and median survival was 34.5 days, (range = 532 days, SD = 91.8 days, N = 150). Survival analysis comparing the four levels of dyspnoea showed a highly significant ($p < 0.001$) inverse relationship (fig 14).

Table 22 shows that of all the dyspnoea measures tested in Cohort 2A (a non-randomised sample) only the DQQS showed a

Cohort	Dyspnoeic		Non-Dyspnoeic		Unknown		TOTALS	
	Nos.	Mean survival (days)	Nos.	Mean survival (days)	Nos.	Mean survival (days)	Nos.	Mean survival (days)
1	157	33.2	126	38.8	11	8.8	294	34.7
2A	69	78.1	81	64.0	0	-	150	70.6
2B	251	35.1	43	47.9	83	42.2	377	38.1
2A+B	320	44.4	124	58.4	83	42.2	527	47.3
Total	477	40.7	250	48.5	94	38.3	821	42.8

Table 20. Survival and Dyspnoea Status

Severity Dyspnoea (0-3)	Male n	Male %	Male Median Survival (days)	Female n	Female %	Female Median Survival (days)	Both sexes n	Both sexes %	Both sexes Median Survival (days)
0	42	19.2	19.0	48	21.9	24.0	90	41.1	21.0
1	23	10.5	14.0	28	12.8	18.0	51	23.3	17.0
2	26	11.9	9.0	17	7.8	7.5	43	19.6	8.0
3	13	5.9	5.0	12	5.5	2.0	25	11.4	3.0
Not assessed	4	1.8	6.5	6	2.7	3.0	10	4.6	3.0
Total	108	49.3	11.0	111	50.7	11.0	219	100.0	11.0

Table 21. Comparison of prevalence and severity of dyspnoea with survival and gender. Cohort 1. Calculations of median survival excluded 5 patients for whom death records were unavailable - 2 males and 1 female with severity of 0, and 1 male and 1 female with severity of 2.

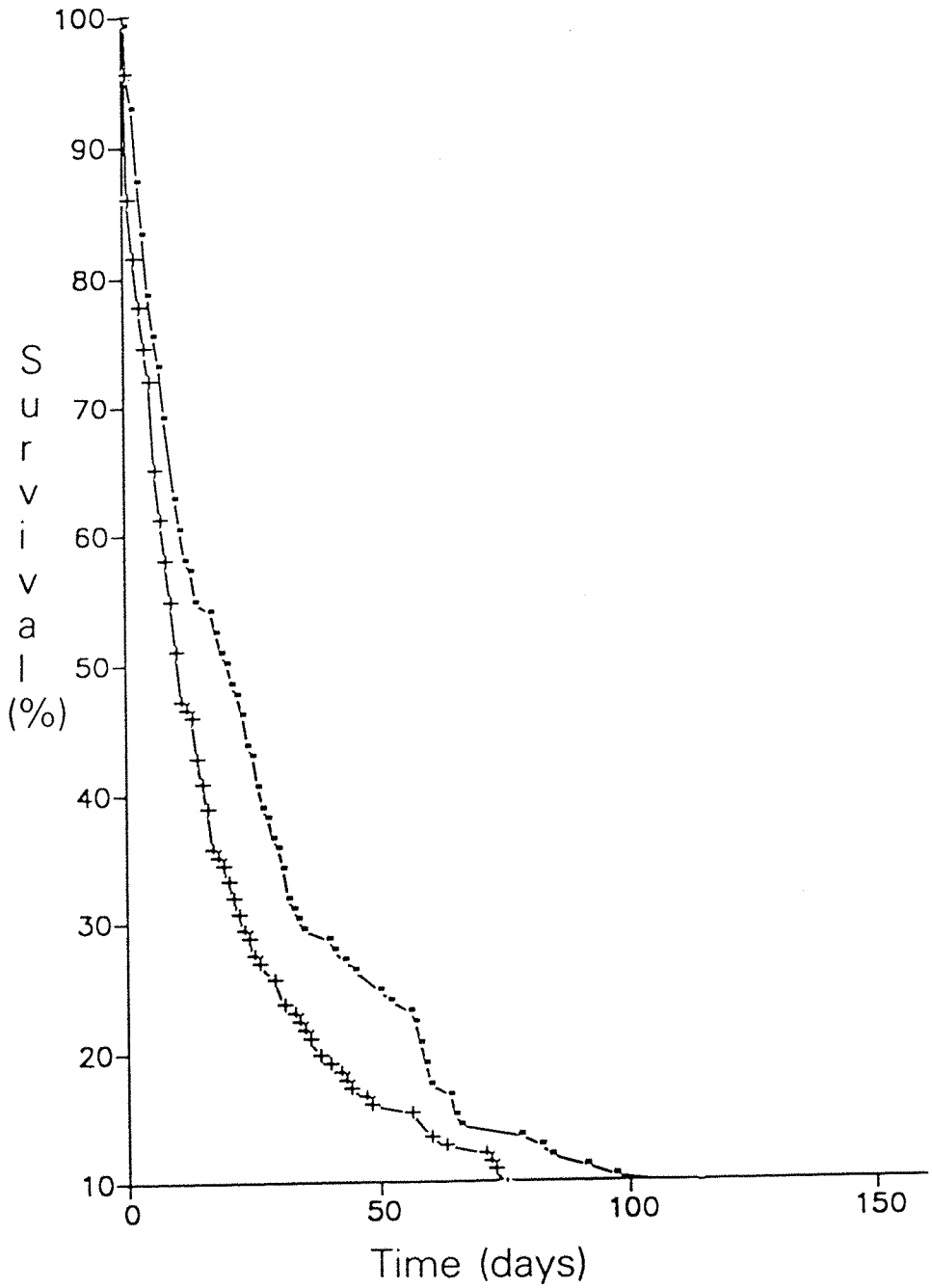


Fig 12. Survival analysis comparing presence (-x-) with absence (-■-) of dyspnoea (log-rank X^2 = 4.27, df = 1, p = 0.04)

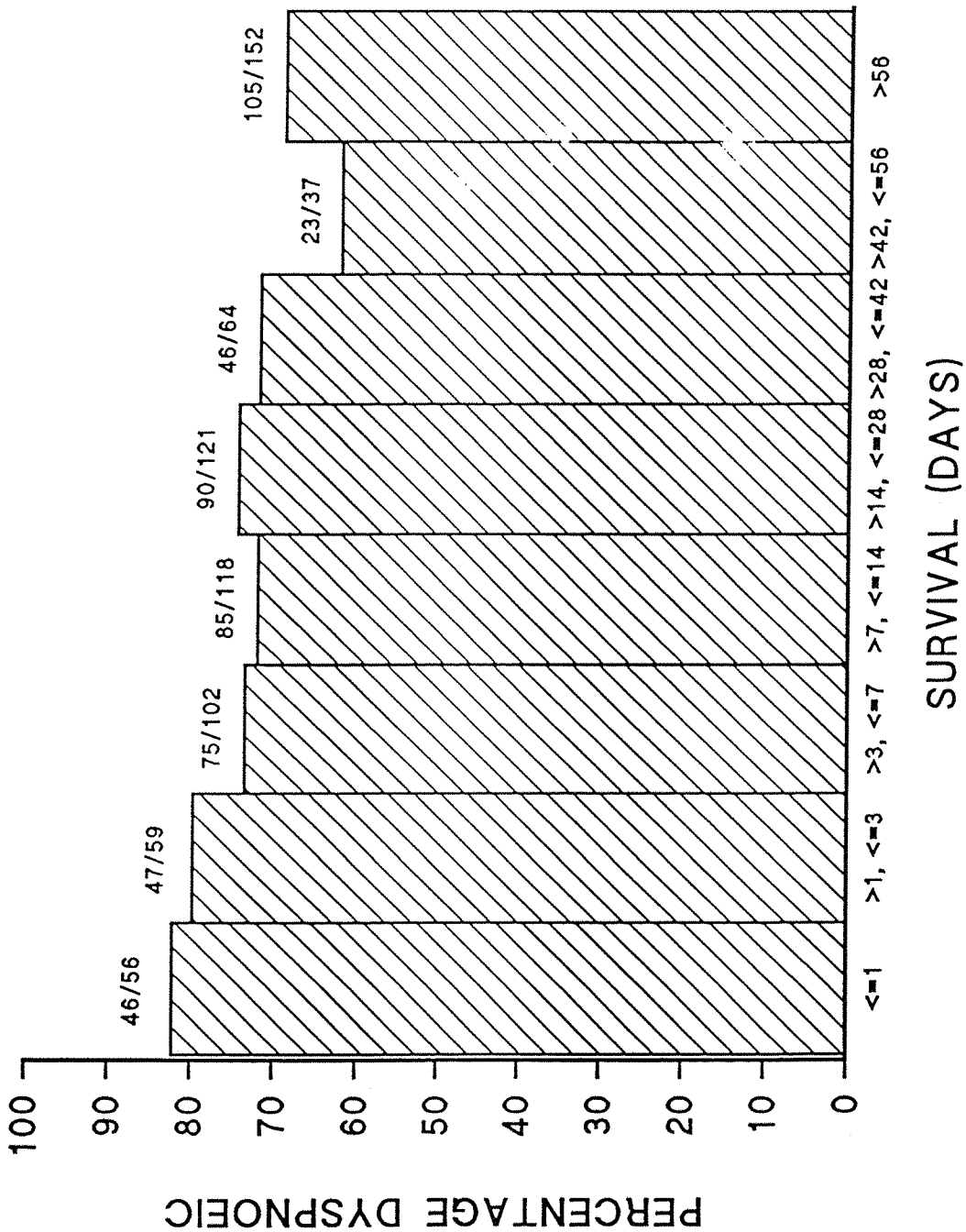


Fig 13. Survival and prevalence of dyspnoea

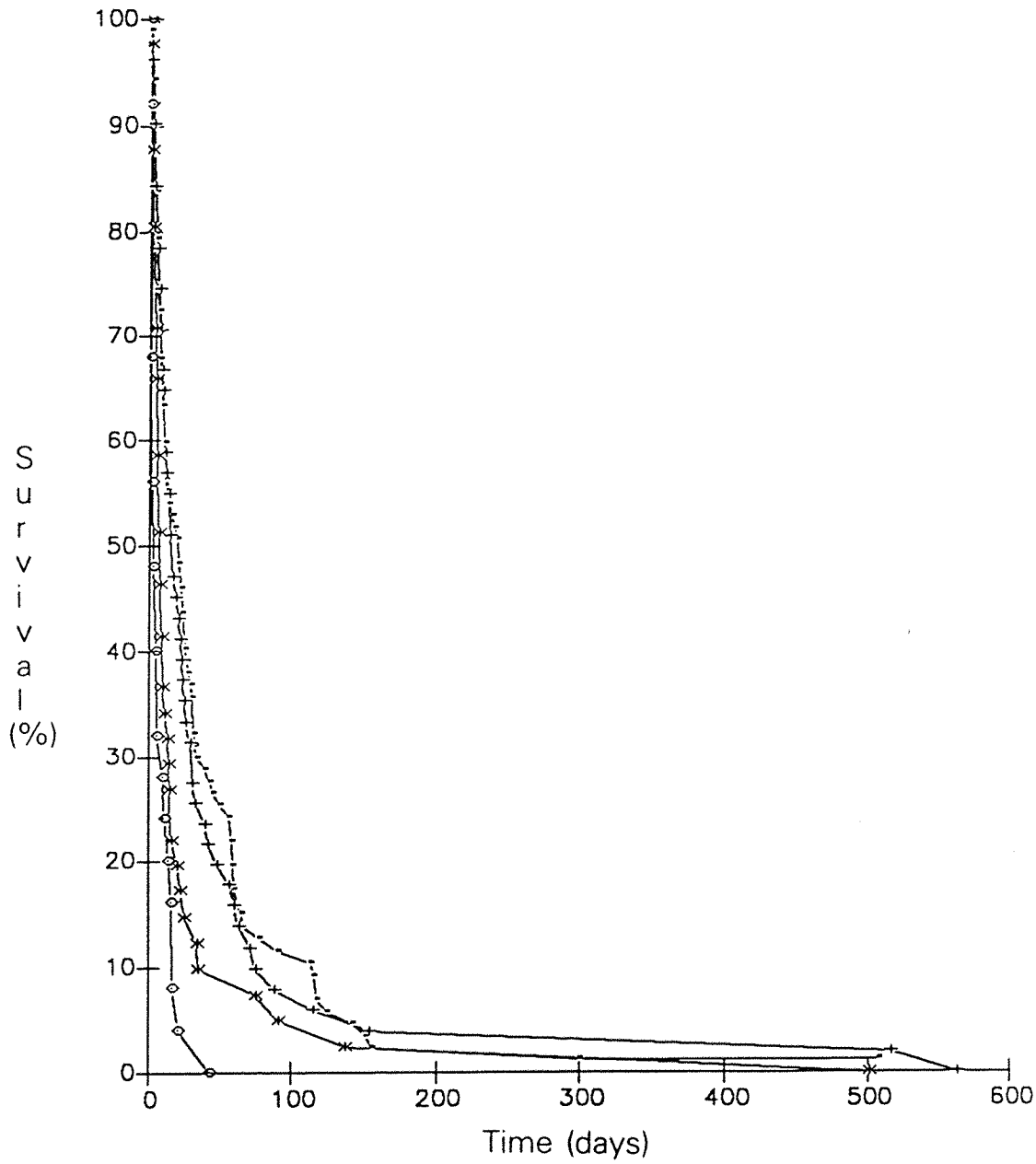


Fig 14. Survival and severity of dyspnoea:
-■- = severity of 0; - + - = 1; - x - = 2;
- 0 - = 3 (log-rank X^2 = 31.52, df = 3, p 0.001)

significant negative correlation with survival. However, the various DAQ scores did show higher negative correlation coefficients than the VAS scores. The DAQ results are analysed in detail further on (see p 130).

Dyspnoea measure	Correlation coefficient [rho]	N	P value
VASMe 24	0.06	147	0.270 NS
VASMe N	-0.11	120	0.214 NS
VASMe D	-0.14	132	0.117 NS
DAQ - TSS	-0.24	61	0.063 NS
DAQ - TIS	-0.23	61	0.075 NS
DAQ - STSS	-0.23	61	0.078 NS
DAQ - DQQS	-0.26	61	0.044 *

Table 22. Correlations dyspnoea measures and survival. Cohort 2A.

Next, the relationship between survival and primary site of cancer was analysed (table 23). No statistically significant association was found. Similarly, no link was found between the presence of lung metastases and survival (log rank $X^2 = 0.31$, df = 1, P = 0.58). Further figures on primary site of cancers are shown on p 146.

Primary Site Cancer	Dyspnoea Present n	Present %	Present Median Survival (days)	Absent n	Absent %	Absent Median Survival (days)	Total n	Total %	Total Median Survival (days)
Bronchus	44	15.6	11.0	17	6.0	11.0	61	21.6	11.0
Breast	29	10.2	11.0	18	6.4	15.5	47	16.6	14.0
Colon & Rectum	13	4.6	8.0	17	6.0	18.0	30	10.6	10.5
Prostate	10	3.8	42.5	9	3.2	45.0	19	6.7	45.0
Stomach	8	3.5	12.5	9	3.2	31.0	17	6.0	25.0
Other	53	18.7	11.0	56	19.8	22.5	109	38.5	16.0
Total	157	55.5	11.0	126	44.5	20.5	283	100.0	14.0

Table 23. Relationship between prevalence of dyspnoea, primary site of cancer and survival. Cohort 1. (For primary site of cancer and survival, log rank $X^2 = 6.42$, df = 5, p = 0.27).

4.8 Measurement of dyspnoea

In Cohort 1, severity of dyspnoea was assessed from the admitting doctor's history as described on p 119. Table 21 shows that 11.4 % of all admissions were rated as severely dyspnoeic, equivalent to about one admission per week, since there were 576 admissions to CMH in 1987.

Table 24 shows that doctors and nurses tended to mark dyspnoea scores much lower on average than patients (difference in mean scores VASMe D v. VASMe 24 = 19.5% difference in mean scores VASMe N v. VASMe 24 = 24.6%). However, doctors and nurses were more likely to mark a patient as dyspnoeic than the patients themselves (difference in proportions doctors v. patients = 42.2% difference in proportions nurses v. patients = 40.8%).

The median time dyspnoeic (26 days) was markedly shorter than the mean (196.1 days).

Of the 168 patients in Cohort 2A who had VASMe 24 > 0, 16 had VASMe 24 scores *higher* than the VASMax 52. (As the VASMax 52 is the worst level of dyspnoea over the last week before admission, it should by definition be either the same as or higher than the VASMe 24).

DYSPNOEA MEASURE	N (%) dyspnoeic	Mean (% of maximum)	Median	Range	S.D.	Theoretical maximum
VASMe N	106 (85.5)	31.6 (31.6)	23.0	93.0	25.5	100.0
VASMe D	119 (86.9)	33.1 (33.1)	26.0	99.0	29.3	100.0
VASMe 24	68 (44.7)	56.2 (56.2)	56.0	99.0	28.9	100.0
VASMax 52	71 (46.7)	65.2 (65.2)	69.0	97.0	25.6	100.0
VASMe 7	12 (30.0)	61.4 (61.4)	62.5	60.0	19.6	100.0
DWS	53 (37.3)	2.4 (48.0)	2.0	4.0	0.9	5.0
DES	60 (41.7)	3.1 (62.0)	3.0	4.0	1.3	5.0
Time dyspnoeic (days)	51 (32.9)	196.1	26.0	4314.0	664.9	-
DAQ SCORES						
NWCS	62 (40.0)	8.1 (50.6)	9.0	16.0	4.6	16.0
TSS	62	23.8 (43.2)	23.7	51.3	14.6	55.1
AVSS	62	2.7 (57.4)	2.7	3.6	0.8	4.7
TCS	62	14.5 (33.7)	13.5	37.0	10.0	43.0
AVCS	62	1.7 (28.3)	1.7	4.5	0.7	6.0
SBW	62	2.7 (57.4)	2.6	4.5	1.1	4.7
TIS	62	19.1 (36.3)	19.0	45.1	12.5	52.6
AVIS	62	2.1 (48.8)	2.3	3.4	0.7	4.3
STSS	62	13.7 (34.5)	14.2	29.5	8.1	39.7
DQQS	62	48.1 (48.1)	50.1	95.5	25.2	100.0

Table 24. Dyspnoea scores, Cohort 2A. Dyspnoeic patients only.

Temporal factors

Changes in dyspnoea over time in Cohort 2A were studied. In 56 patients, weekly dyspnoea status (VASMe 7) was reviewed once; in 14, twice; in 5, 3 times; in 1, 4 times; and in 1, 5 times. The remaining 99 patients were not followed up for a number of reasons, principally because they had become too ill or died.

Dyspnoea Status	N	(%)
Not dyspnoeic on admission(s) or review(s)	35	(62.5)
Dyspnoeic on admission(s) and when reviewed	15	(26.8)
Became dyspnoeic after admission	2	(3.6)
TOTAL	56	(100)

Table 25. Dyspnoea status on and after admission. Cohort 2A.

To see if dyspnoea improved as a result of treatment at CMH, patients who were dyspnoeic on admission and reviewed were studied (table 26).

Scores	Dyspnoea levels		
	VASMe 24	VASMe 7 (1st review)	VASMe7 (2nd review)
Mean	48.6	44.6	47.0
Median	46.0	44.0	47.0
N	15	15	2

Table 26. Changes in dyspnoea levels over time for patients dyspnoeic on admission. Cohort 2A.

Of the 15 patients who were dyspnoeic on admission, 9 (60%) improved (mean reduction in VAS = 27.3%) and 6 (40%) worsened (mean increase in VAS = 31.0%). Percentage here means number of mm change on a scale of 100 mm.

With regard to presence or absence of dyspnoea, table 27 (p 131) and fig 13 (p 123) suggests that patients closer to death are more likely to be dyspnoeic, such that, although the overall prevalence of dyspnoea on admission was 72.9%, 82.1% of those surviving less than 1 day after admission were dyspnoeic.

The figures on dyspnoea in table 27 were from the doctors' assessment in each cohort for uniformity.

Dyspnoea Assessment Questionnaire (DAQ) results

The development of the DAQ has been described on pp 99-103. The initial word list of 164 words, how these were reduced to 43 words, how these were classified, how the various scoring methods were developed and the keys to the scorings, and the questionnaire itself, are set out in appendix 7.1 to prevent this results section becoming too cumbersome.

Sixty-two dyspnoeic patients in Cohort 2A completed the DAQ on their first admission. Table 28 ranks the words chosen in order of popularity. The 14 most popular words were used to develop the Short-Total Severity Score (STSS) as described on p 101. Table 29 (p 133) ranks the categories of words, and table 30 (p 134) the 'best words'.

COHORT	SURVIVAL (Days) [Dyspnoeic/All]								
	≤ 1	>1 ≤3	>3 ≤7	>7 ≤14	>14 ≤28	>28 ≤42	>42 ≤56	>56	Totals
1	22/28	13/23	26/44	29/52	25/46	13/26	5/11	24/53	157/283
2A	0/0	4/4	7/8	18/20	26/29	7/10	8/8	44/53	114/132
2B	24/28	30/32	42/58	38/46	39/46	26/28	15/18	37/46	251/294
Total	46/56	47/59	75/102	85/118	90/121	46/64	23/37	105/152	517/709
Total %	82.1	79.7	73.5	72.0	74.4	71.9	62.2	69.1	72.9

Table 27. Survival and doctor's assessment of dyspnoea status.
See also fig 13, p 123.

Rank	Category	Word	No. times chosen	% maximum
1	4	Uncomfortable	45	72.6
2	2	Variable	36	58.1
3	6	Wheezy	29	46.8
4	13	Distressing	28	45.2
5	16	Chesty	27	43.5
6	11	Disabling	22	35.5
7	1	Bad	20	32.3
8	8	Tiring	18	29.0
9	8	Exhausting	16	25.8
9	9	Short of breath	16	
11	3	Tight	15	24.2
11	10	Shallow	15	
13	9	Breathless	14	22.6
13	14	Dreadful	14	
15	8	Fatiguing	12	19.3
15	12	Worrying	12	
17	3	Restricting	11	17.7
17	5	Noisy	11	
17	9	Puffed	11	
20	7	Rattling	10	16.1
20	10	Panting	10	
20	10	Gasping	10	
23	9	Out of breath	9	14.5
23	15	Stifling	9	
25	1	Awful	8	12.9
25	15	Suffocating	8	
27	3	Constricting	7	
27	7	Bubbling	7	11.3
27	12	Frightening	7	
27	12	Panic	7	
31	12	Scaring	6	
31	13	Intolerable	6	9.7
31	15	Choking	6	
34	1	Severe	4	
34	1	Unbearable	4	6.4
34	3	Compressing	4	
34	10	Heaving	4	
38	15	Asphyxiated	3	4.8
39	9	Winded	2	3.2
39	12	Terrifying	2	
41	12	Fearful	1	1.6
41	15	Drowning	1	
43	15	Strangling	0	0.0

Table 28. DAQ. List of words chosen in order of frequency. First admissions. Maximum possible frequency = 62. 4 patients did not choose any words. The 14 most popular words were used to develop the STSS.

Rank	Category No.	Category	No. times chosen	% maximum
1	9	Air quantity	52	83.9
2	8	Energy	46	74.2
3	4	Pain	45	72.6
4	10	Respiratory effort	39	62.9
5	3	Constrictive pressure	37	59.7
6	1	Intensity	36	) 58.1
=	2	Temporal	36	)
8	13	Depression	34	54.8
9	6	Dry sound	29	46.8
10	15	Suffocation	27	) 43.5
=	16	Illness	27	)
12	12	Fear	25	40.3
13	11	Loss of power	22	35.5
14	7	Wet sound	17	27.4
15	14	Dread	14	22.6
16	5	Sound quantity	11	17.7

Table 29. DAQ categories ranked by frequency chosen. 62 patients.

Rank	Best Word	SBW (Score Best Word)	No. choosing	% choosing
1	(Short of breath	2.48	5	11.6
	(Distressing	3.12		
3	(Variable	2.12		
	(Uncomfortable	1.85	4	9.3
	(Tiring	2.36		
6	(Restricting	2.67		
	(Exhausting	3.94	3	7.0
	(Panic	4.51		
	(Suffocating	4.30		
10	(Tight	2.91		
	(Out of breath	2.61		
	(Shallow	2.36	2	4.6
	(Worrying	2.61		
	(Frightening	3.73		
	(Chesty	2.33		
16	(Bad	3.03		
	(Severe	3.79		
	(Awful	3.85		
	(Constricting	3.09		
	(Wheezy	3.00		
	(Rattling	3.48	1	2.3
	(Puffed	2.51		
	(Disabling	3.64		
	(Scaring	3.36		
	(Stifling	3.30		
	(Choking	4.12		
27	(Unbearable	4.73		
	(Compressing	3.00		
	(Noisy	2.76		
	(Bubbling	3.18		
	(Fatiguing	3.06		
	(Winded	2.82		
	(Breathless	3.03		
	(Heaving	3.21		
	(Panting	3.24	0	0
	(Gasping	3.97		
	(Fearful	3.54		
	(Terrifying	4.51		
	(Intolerable	4.42		
	(Dreadful	3.58		
	(Strangling	4.09		
	(Drowning	4.18		
	(Asphyxiating	4.61		

Table 30. DAQ best words ranked by frequency chosen. 62 patients. 5 patients did not choose a best word.

Comparisons different measures dyspnoea

The VASMe 24 was used as the standard by which to compare other measures as shown in table 31.

Dyspnoea Measure	No. pairs observations	Correlation Coefficient (Spearman's rho)	p value
VASMe N	122	0.51	< 0.000
VASMe D	134	0.60	< 0.000
VASMax 52	152	0.94	< 0.000
DWS	59	0.51	< 0.000
DES	61	0.20	0.114 (NS)
DAQ NWCS)		0.41	0.001
TSS)		0.45	< 0.000
AVSS)		0.44	< 0.000
TCS)		0.42	0.001
AVCS)		0.42	0.001
SBW)	62	0.37	0.003
TIS)		0.45	< 0.000
AVIS)		0.36	0.004
STSS)		0.41	0.001
DQQS)		0.83	< 0.000 *

Table 31. Correlations dyspnoea measures with VAS 24. * DQQS correlation not valid as VAS 24 score used to calculate it.

All measures, except the DES correlated highly significantly. Of the various DAQ measures, the best were the TSS and TIS.

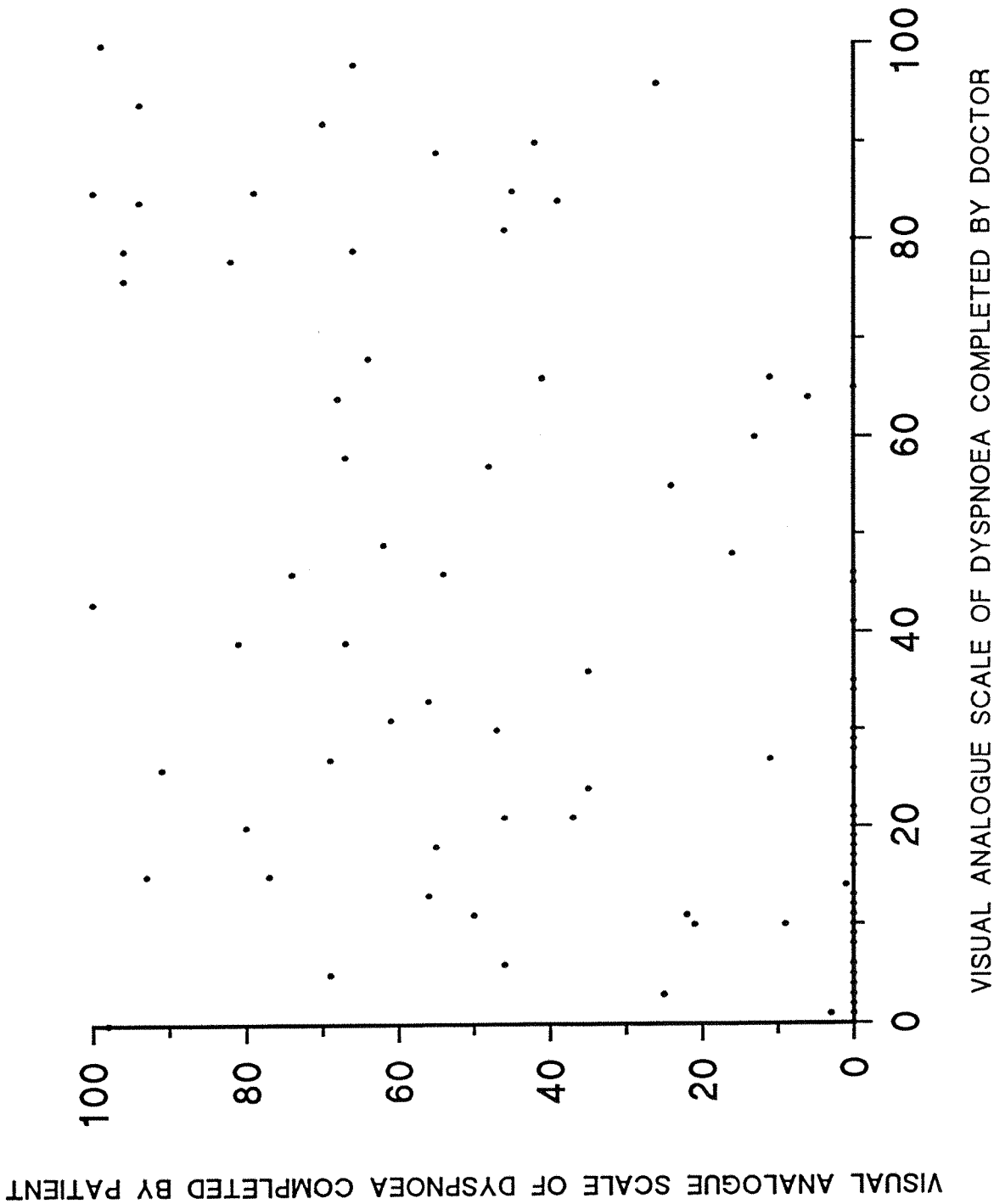


Fig 15. Scatterplot of VASMe 24 and VASMe D

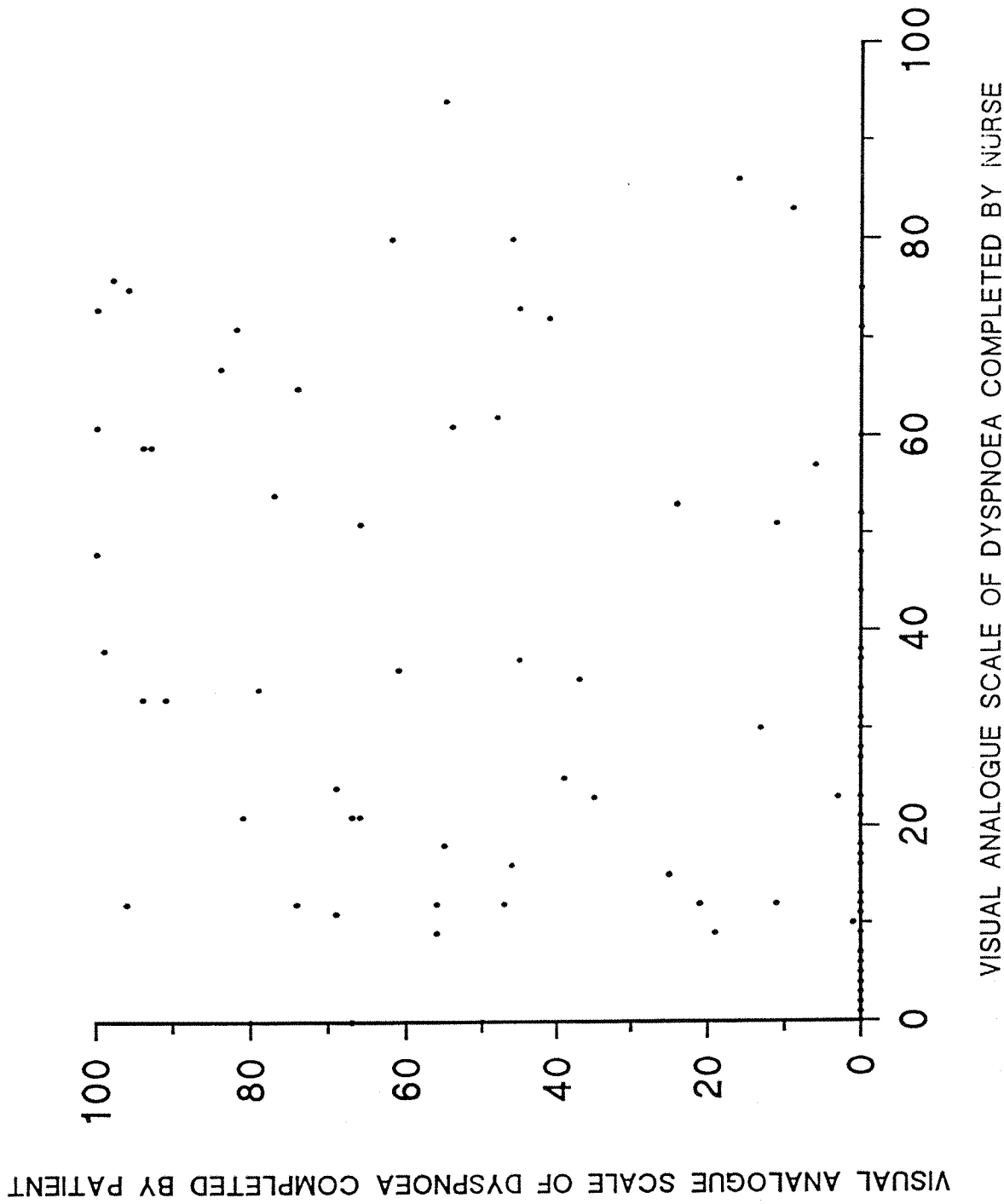


Fig 16. Scatterplot of VASMe 24 and VASMe N

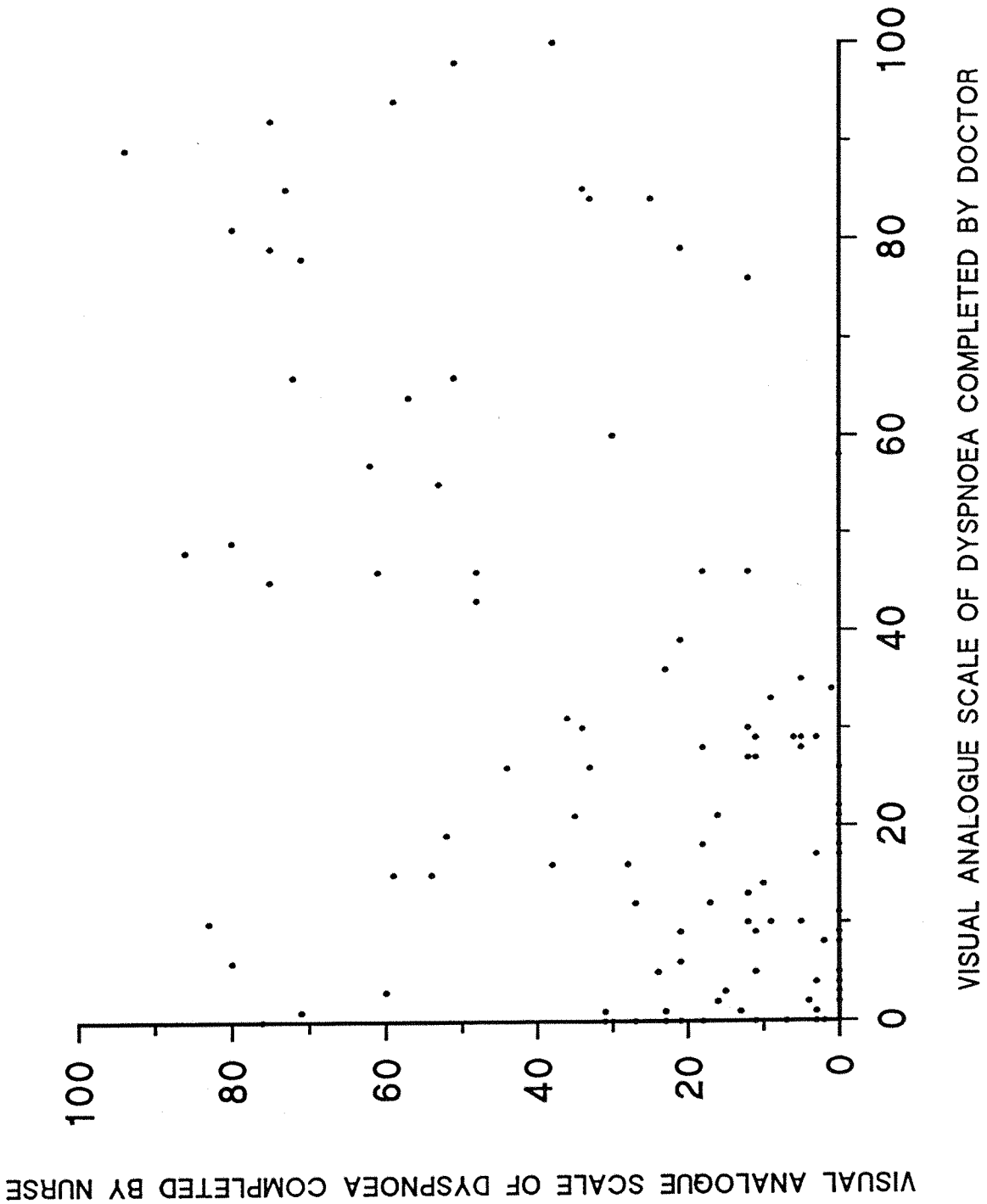


Fig 17. Scatterplot of VASMe D and VASMe N

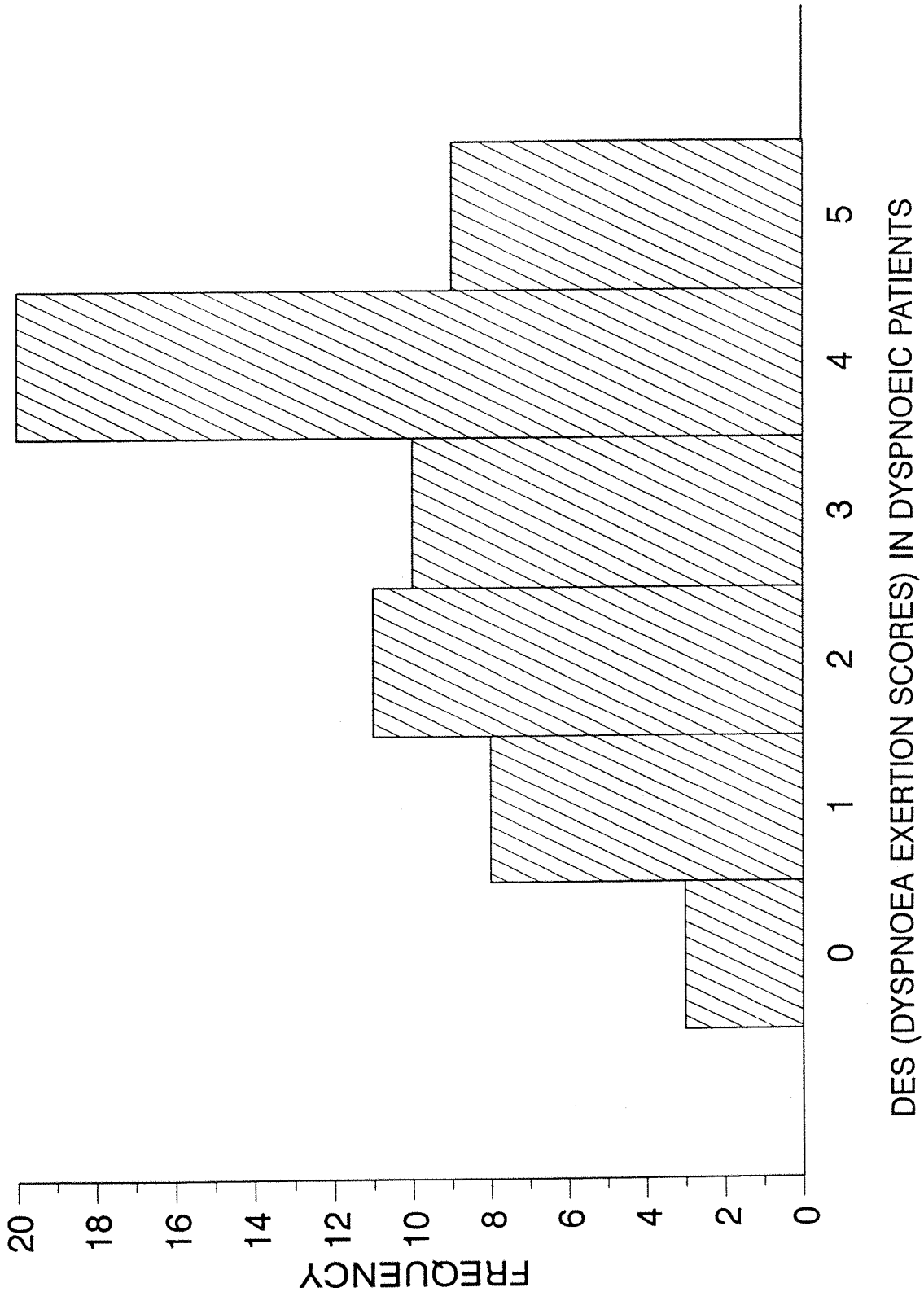


Fig 18. Frequency histogram for dyspnoea exertion scores (DES)

The closest correlation was between VASMax 52 and VASMe 24 (both measures from the patients themselves). Doctors' and nurses' VAS scores also correlated significantly ($r = 0.44$, $p = < 0.001$, $N = 114$).

Scatterplots comparing VASMe 24, VASMe D and VAS N are shown in figs 15, 16 and 17.

For patients who were dyspnoeic, the bar chart (fig 18) of the DES shows that the distribution was skewed towards the higher scores, with a score of 4 ("I become breathless on talking") being the most commonly chosen.

4.9 Psychological Status

The Crown-Crisp Experiential Index (CCEI)[85] was completed on 150 patients (first admissions). It measures six psychological indices: Free-floating Anxiety (A), Phobic Anxiety (P), Obsessionality (O), Somatic Anxiety (S), Depression (D) and Hysteria (H).

CCEI subset	Scores Mean	Median	Range	SD
A	5.5	5.0	16.0	4.0
P	4.9	4.0	15.0	3.5
O	8.2	8.0	14.0	3.2
S	8.6	9.0	14.0	3.5
D	5.3	5.0	15.0	2.8
H	3.4	3.0	14.0	3.1

Table 32. CCEI scores N = 150. Theoretical maximum scores each subset = 16.

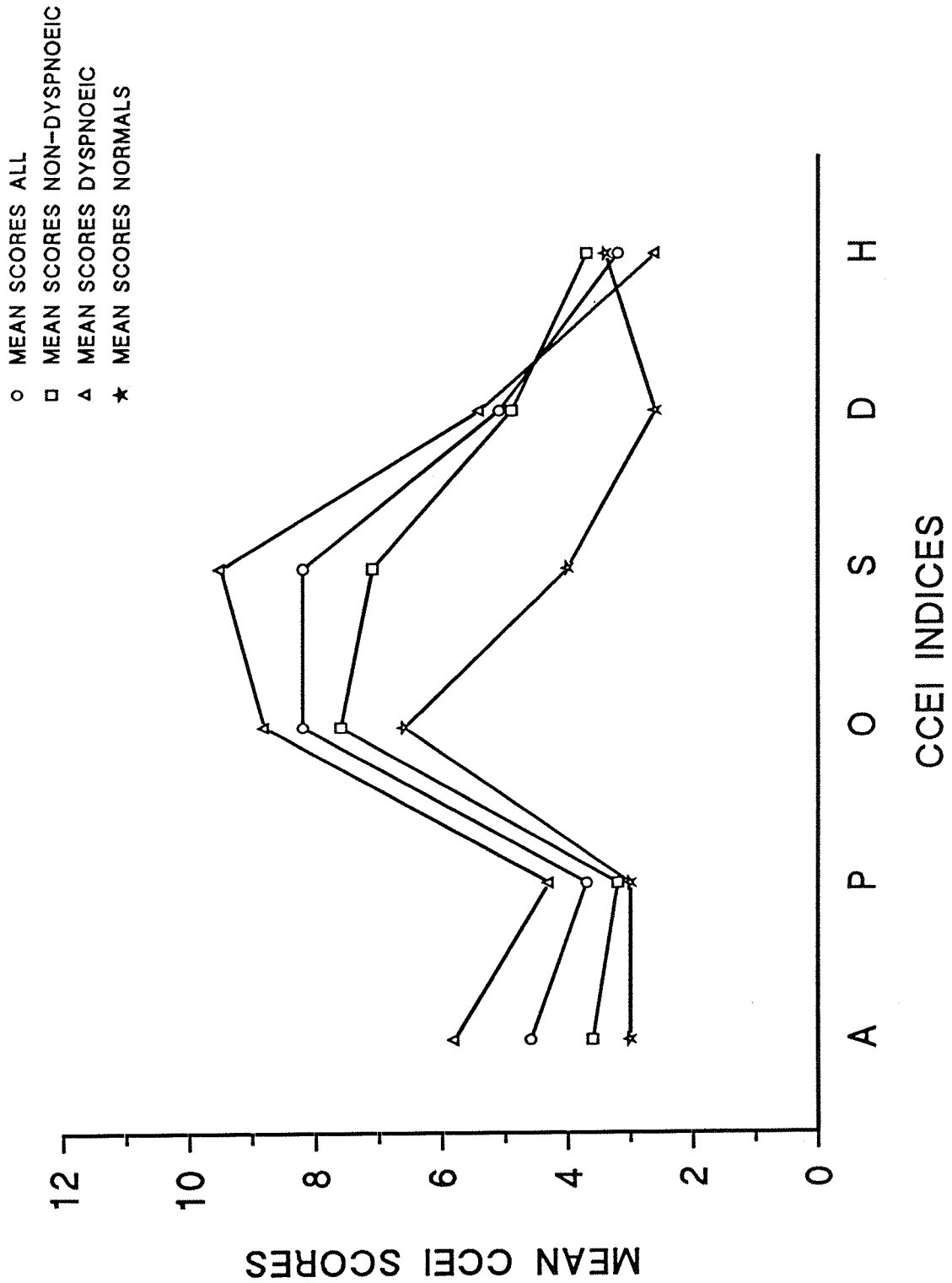


Fig 19. Mean CCEI scores and dyspnoea (males)

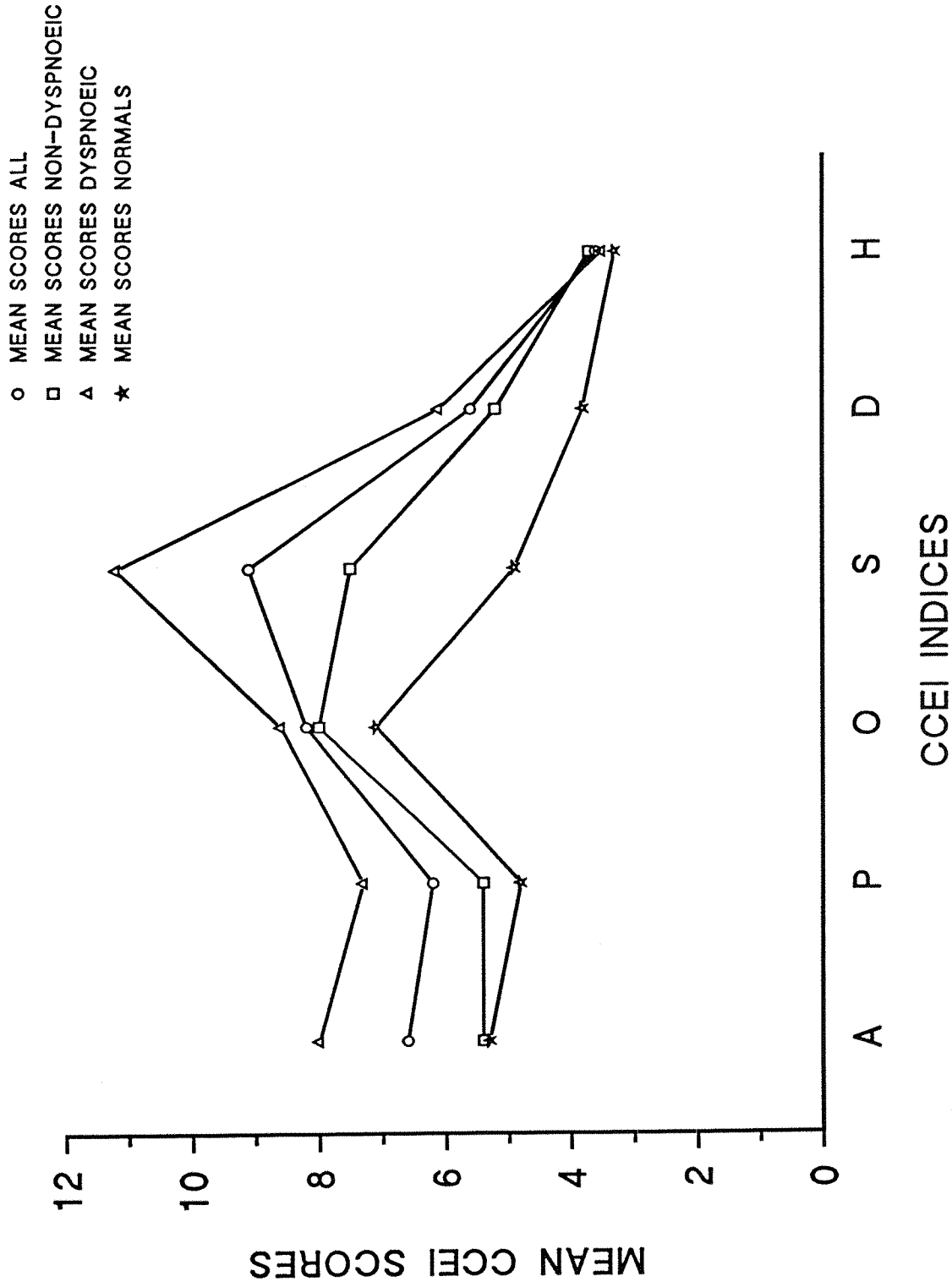


Fig 20. Mean CCEI scores and dyspnoea (females)

Group	Sex	N	A	P	O	S	D	H
ALL	M	79	4.6	3.7	8.2	8.2	5.1	3.2
	F	71	6.6	6.2	8.2	9.1	5.6	3.6
NON-	M	43	3.6	3.2	7.6	7.1	4.9	3.7
DYSPNOEIC	F	39	5.4	5.4	8.0	7.5	5.2	3.7
DYSPNOEIC	M	36	5.8	4.3	8.8	9.5	5.4	2.6
	F	32	8.0	7.3	8.6	11.2	6.1	3.5
NORMALS	M	310-328	3.0	3.0	6.6	4.0	2.6	3.4
	F	347-368	5.3	4.8	7.1	4.9	3.8	3.3

Table 33. Relationships mean CCEI scores to dyspnoea. Cohort 2A. Normals from Crown and Crisp 1979[85]. Maximum possible score for each index = 16.

The range of figures given for the numbers of normals in table 33 is because Crown and Crisp pooled the figures from several studies[85], but did not give the overall numbers, only the overall means.

Figs 19 and 20 and table 33 demonstrate that all the CCEI indices except hysteria worsen in dyspnoeic patients. Phobic anxiety scores were higher in dyspnoeic females than males. Depression scores only increase slightly in the dyspnoeic. Table 34 shows that free-floating anxiety, phobic anxiety and somatic anxiety scores are significantly higher statistically in dyspnoeic patients than those non-dyspnoeic.

CCEI Subset	Dyspnoea Status						U Value	P Value
	VASMe 24 > 0 (N = 66)			VASMe 24 = 0 (N = 82)				
	Mean	SD	Median	Mean	SD	Median		
A	6.8	4.1	6.0	4.5	3.7	3.5	1829.5	0.001*
P	5.7	3.7	5.0	4.5	3.2	3.5	2102.0	0.019*
O	8.7	3.2	9.0	7.8	3.0	8.0	2260.5	0.084NS
S	10.3	3.1	11.0	7.3	3.1	7.0	1409.0	0.000*
D	5.7	2.6	6.0	5.1	3.0	5.0	2323.0	0.137NS
H	3.0	2.9	2.0	3.7	3.3	3.0	2358.0	0.174NS

Table 34. Comparison of CCEI scores and dyspnoea status. Cohort 2A. Mann-Whitney test. N = 148. 5 patients did not have a CCEI done. 2 patients not assessed as to VASMe 24 score. * = significance. NS = not significant.

Figures 19 and 20 are shown as linear graphs to conform with how Crown and Crisp[85] presented their data, although the figures for each of the indices are separate from each other.

DAQ Dyspnoea Measure	CCEI subsets. Correlation coefficients (p values)					
	A	P	O	S	D	H
TSS	0.25 (0.055)	0.01 (0.920)	0.09 (0.473)	0.44 (0.000)*	0.16 (0.211)	0.27 (0.030)*
TIS	0.22 (0.085)	-0.03 (0.811)	0.10 (0.432)	0.40 (0.001)*	0.15 (0.230)	0.28 (0.026)*
STSS	0.09 (0.478)	-0.07 (0.600)	-0.04 (0.780)	0.32 (0.011)*	0.12 (0.360)	0.20 (0.131)
DQQS	0.10 (0.457)	-0.01 (0.926)	-0.01 (0.943)	0.24 (0.066)	0.05 (0.684)	0.24 (0.065)

Table 35. DAQ dyspnoea measures and CCEI subsets - Correlations. (N = 61). Spearmans rho.

Table 35 shows comparisons between levels of dyspnoea as measured by the DAQ and the CCEI indices. Only values for somatic anxiety and hysteria showed statistically significant correlation.

The relationship between CCEI scores and survival was analysed (table 36) but no link was shown.

CCEI measures	Correlation (Spearman's rho) coefficients	p value
A	0.13	0.125
P	0.07	0.400
O	-0.04	0.601
S	0.04	0.662
D	0.04	0.627
H	0.01	0.937

Table 36. Correlations CCEI scores and survival. Cohort 2A. N = 145.

4.10 Site of Primary Carcinoma

Site	Dyspnoeic N (%)	Non-dyspnoeic N	Totals N
Bronchus	126 (78.3)	35	161
Colon	61 (55.0)	50	111
Breast	76 (71.7)	30	106
Prostate	32 (57.1)	24	56
Ovary	32 (60.4)	21	53
Stomach	24 (54.5)	20	44
Pancreas	19 (67.9)	9	28
Oesophagus	19 (73.1)	7	26
Haematological malignancies	16 (69.6)	7	23
Bladder	13 (61.9)	8	21
Primary brain tumours	9 (45.0)	11	20
Cervix	12 (66.7)	6	18
Pleural mesotheliomas	12 (80.0)	3	15
ENT malignancies	9 (60.0)	6	15
Kidney	9 (75.0)	3	12
Malignant melanoma	4	4	8
Body of uterus	5	2	7
Skin (excluding melanomas)	2	4	6
Sarcomas	4	2	6
Hepatomas	1	1	2
Spinal cordoma	1	0	1
Mycosis fungoides	0	1	1
Penis	1	0	1
Thyroid	1	0	1
Fallopian tube	1	0	1
Urethra	1	0	1
Mediastinal teratoma	1	0	1
Carcinoid colon	1	0	1
Unknown primary site	26 (57.8)	19	45
Multiple primaries	22 (56.4)	17	39
TOTALS	540 (65.1)	290	830

Table 37. Sites of primary carcinoma and dyspnoea status. All cohorts. Patients with unknown dyspnoea status excluded. For the 9 most frequent malignancies, with all others counted as "other carcinomas", $X^2 = 27.20$, $df = 9$, $p < 0.01$.

Diagnosis	All patients Dyspnoeic & Non-dyspnoeic N	Mean VASMe 24	Dyspnoeic Only N	Mean VASMe 24
Colon	31	19.4	9	66.7
Bronchus	29	47.1	21	65.0
Breast	22	38.9	14	58.4
Prostate	17	9.1	4	38.5
Ovary	14	14.9	4	52.0
Bladder	7	15.9	2	55.5
Stomach	6	18.7	2	56.0
Pleura	5	29.8	3	49.7
Pancreas	4	6.5	2	13.0
OVERALL	152	25.1	68	56.2

Table 38. Relationship commonest primary carcinomas to mean VASMe 24. Patients with 2 primaries included. Cohort 2A.

From table 37 (p 146) it can be seen patients with carcinomas of lung, breast, oesophagus and kidney, and with pleural mesotheliomas, were more likely to be dyspnoeic. Those with carcinomas of colon, prostate and stomach, with primary brain tumours and with multiple primary sites were less likely to be dyspnoeic.

Table 38 shows that for all patients, mean VASMe 24 was higher than the overall mean with carcinomas of breast and bronchus and pleural mesothelioma. However, this includes non-dyspnoeic patients. When only the dyspnoeic patients are studied, the mean VASMe 24 scores are much higher throughout, though those dyspnoeic with carcinomas of the prostate and pancreas had the lowest mean VASMe 24 scores in this category.

Method of diagnosis of the primary site is shown in table 39 below.

Diagnosis	Cohorts 1 (%)	2A (%)	2B (%)	TOTALS (%)
Histology	182 (78.1)	114 (73.5)	193 (50.1)	489 (63.3)
Other investigations	39 (16.7)	41 (26.4)	174 (45.2)	254 (32.9)
No record	12 (5.1)	0 (0)	18 (4.7)	30 (3.9)
Totals	*233 (100)	155 (100)	385 (100)	773 (100)

Table 39. Method of diagnosis of primary carcinoma Cohorts 1 and 2. * In Cohort 1, the first 70 of 303 patients did not have method of diagnosis recorded.

Evidence for diagnosis of primary site was not recorded in Cohort 3.

Lung and Pleural Metastases

Diagnosis	Cohorts 1	2A	2B	TOTALS
Chest X-ray	34	26	20	80
Histology	1	3	2	6
Other investigations	10	15	14	39
Totals (% of overall numbers)	45 (19.3)	44 (28.4)	36 (9.3)	125 (16.2)
None detected or not investigated	188	111	349	648
Overall	233	155	385	773

Table 40. Method of diagnosis of lung and pleural metastases.

Cohort	Lung/pleural metastases + = present - = absent	Dyspnoeic	Non-dyspnoeic	All
1	+	34	10	44
	-	128	120	248
2A	+	26	18	44
	-	45	66	111
2B	+	24	5	29
	-	229	41	270
3	+	18	1	19
	-	42	44	86
Totals	+ (%)	*102 (12.0)	34 (4.0)	136 (16.0)
	- (%)	444 (52.2)	271 (31.8)	715 (84.0)
Totals	ALL (%)	546 (64.2)	305 (35.8)	851 (100.0)

Table 41. Relationship lung/pleural metastases to dyspnoea status (* $X^2 = 7.677$, df = 1, $p < 0.01$, difference in % dyspnoeic to non-dyspnoeic, with lung/pleural metastases, = 8.0).

Table 40 shows method of diagnosis of lung and pleural metastases in Cohorts 1 and 2. No record of method of diagnosis was kept for Cohort 3, or the first 70 of the 303 patients in Cohort 1. Figures include those whose dyspnoea status was unknown and so vary from table 41, which only includes those of known dyspnoea status.

Table 41 records data as to presence of lung or pleural metastases and their relationship to dyspnoea status. For 11 patients in Cohort 1, 86 patients in Cohort 2B and 20 patients in Cohort 3, no information was obtained as to presence of lung or pleural metastases, or their dyspnoea status, and these were therefore excluded.

4.11 Smoking

Of the 155 patients in Cohort 2A, 35 (22.6%) were still smokers on admission, and 101 (65.2%) had been smokers in the past.

Smoking status	Dyspnoeic (%)	Non-dyspnoeic	All
Smokers now	* 22 (62.9)	13	35
Non-smokers now	49 (40.8)	71	120
Past smokers	** 51 (50.5)	50	101
Past non-smokers	20 (37.0)	34	54
Totals	71 (45.8)	84	155

Table 42. Smoking and dyspnoea. Cohort 2A.
* $X^2 = 4.498$, df = 1, $p < 0.05$
** $X^2 = 2.019$, df = 1, $p > 0.1$, NS

Of the 29 patients with carcinoma of the bronchus, 28 (96.5%) had smoked in the past, and 9 (31.0%) were still smokers on admission.

4.12 Asbestos exposure

Thirty (19.4%) of the 155 patients in Cohort 2A recalled exposure to asbestos dust. Of these, 16 (56.7%) were dyspnoeic ($X^2 = 0.539$, df = 1, $p > 0.1$, NS). All five patients with pleural mesotheliomas remembered exposure to asbestos dust.

4.13 Hyperventilation study

Two groups of patients were studied as to diagnosis of the hyperventilation syndrome (HVS). Group 1 comprised 24 patients from Cohort 2A, who had a hyperventilation provocation test (HVPT) carried out. Group 2 (Cohort 3, the hyperventilation study) comprised 125 consecutive admissions of whom 67 (53.6%) had an HVPT.

Of those in cohort 3 who had an HVPT (N = 67), 32 (47.8%) were male and 35 (52.2%) were female. Of those who did not have an HVPT (N = 58), 30 (51.7%) were male and 28 (48.2%) were female.

The mean age of those tested in cohort 3 was 66.4 years, and of those not tested, 66.3 years.

Dyspnoea status	Cohort	Hyperventilation Provocation Test		Totals
		Positive	Negative	
Dyspnoeic	2A	11 (68.7%)	5	16
	3	12 (29.3%)	29	41
	Both	23 (40.3%)	34	57
Non-dyspnoeic	2A	2 (25.0%)	6	8
	3	2 (7.7%)	24	26
	Both	4 (11.8%)	30	34
Totals	2A	13 (54.2%)	11	24
	3	14 (20.0%)	53	67**
	Both	27 (29.7%)	64	91*

Table 43. Dyspnoea status and HVPT outcome. Cohorts 2A and 3. * $X^2 = 7.055$, df = 1, $p < 0.005$ (one-tailed). Difference in proportions = 28.5% (both cohorts). ** $X^2 = 3.203$, df = 1, $p < 0.05$ (one-tailed). Difference in proportions = 33.1% (Cohort 3).

Because dyspnoea is known to be associated with HVS[10], a one-tailed chi-square test was carried out (see table 43) comparing dyspnoea status with outcome of the HVPT as indicative of HVS, and a statistically significant association shown.

Dyspnoea Status	Sex	Hyperventilation Provocation Test Positive (% of those tested)	Negative	Not done	Totals
Dyspnoeic	M	5 (27.8)	13	13	31
	F	7 (30.4)	16	8	31
	Both	12 (29.3)	29	21	62
Non-Dyspnoeic	M	2 (14.3)	12	12	26
	F	0 (0.0)	12	5	17
	Both	2 (7.7)	24	17	43
Not assessed	M	0	0	5	5
	F	0	0	15	15
	Both	0	0	20	20
All	M	7 (21.9)	25	30	62
	F	7 (20.0)	28	28	63
	Both	14 (20.9)	53	58	125

Table 44. Relationships gender and dyspnoea status to HVPT result. Cohort 3.

Table 44 shows that at least one in five of those tested in Cohort 3 had a positive HVPT. No relationship was shown between gender and a positive HVPT.

	Hyperventilation Provocation Test			
	Positive	Negative	Totals	Difference in mean/median ages (yrs)
Cohort 2A				
Mean Ages (yrs)	60.8	63.0	61.8	2.6
Median Ages (yrs)	59.0	66.0	63.0	7.0*
N	13	11	24	
Cohort 3				
Mean Ages (yrs)	60.9	67.9	66.4	7.0
Median Ages (yrs)	63.0	69.0	67.0	6.0**
N	14	53	67	

Table 45. Mean ages and HVPT results.
* Mann Whitney test: U = 37, p = 0.05
** Mann Whitney test: U = 231.5, p = 0.007

Mean and median ages were lower (table 45) in those with a positive HVPT than in those who were negative. Patients with organic lung disease were more likely to have a positive HVPT than those without (table 46).

Organic lung disease	Hyperventilation Provocation Test Positive	Negative	Totals
Present	18 (43.9%)	23	41
Absent	9 (18.0%)	41	50
Totals	27 (29.7%)	64	91

Table 46. Association organic lung disease and HVPT results. (X^2 = 5.975, df = 1, $p < 0.05$, difference in proportions = 25.9%). Cohort 2A and 3.

Diagnoses of organic lung disease are shown in table 47.

Diagnosis Lung Pathology	Hyperventilation Provocation Test Positive (% of those tested)	Negative	Not done	Totals
Carcinoma Bronchus	9 (40.9)	13	7	29
Lung metastases	9 (50.0)	9	10	28
Pleural effusion	5 (71.4)	2	3	10
COAD	4 (100.0)	0	4	8
Asthma	4 (100.0)	0	1	5
Consolidation	1	2	0	3
Pulmonary embolus	1	0	1	2
LVF	0	1	0	1
Fibrosis	0	1	0	1
Lymphangitis	1	0	0	1
Acute bronchitis	0	0	1	1
Mediastinal node metastases	0	1	0	1
Pathological # ribs	0	1	0	1
All diagnoses	34 (52.3)	31	28	93
No lung disease	9 (18.0)	41	37	87

Table 47. Organic lung disease and HVPT result.
NB: Some patients had more than 1 pathology.
Cohorts 2A and 3.

CCEI Subset	HVS (N = 13) Mean	Median	Interquartile range	Non HVS (N = 11) Mean	Median	Interquartile range	All (N = 24) Mean	Median	Interquartile range	Mann-Whitney Test U	P
A	9.1	11.0	6.0 - 12.5	4.6	5.0	2.0 - 8.0	7.1	6.5	3.0 - 11.0	28.0	0.011 *
P	6.5	6.0	3.5 - 9.5	4.3	4.0	1.0 - 6.0	5.5	4.5	2.2 - 9.0	46.0	0.137 NS
O	8.9	9.0	6.0 - 11.0	7.5	7.0	4.0 - 10.0	8.3	8.0	6.0 - 11.0	53.0	0.280 NS
S	11.5	12.0	10.0 - 14.0	7.3	6.0	4.0 - 10.0	9.5	10.0	6.0 - 13.0	29.0	0.013 *
D	5.6	5.0	4.0 - 7.5	4.2	4.0	2.0 - 6.0	5.0	4.5	3.2 - 6.8	44.0	0.107 NS
H	2.9	2.0	0.5 - 4.0	2.4	2.0	0.0 - 3.0	2.7	2.0	0.0 - 4.0	57.5	0.407 NS

Table 48. Comparison of Crown-Crisp Experiential Index (CCEI) scores with diagnosis of HVS by HVPT. Cohort 2A.

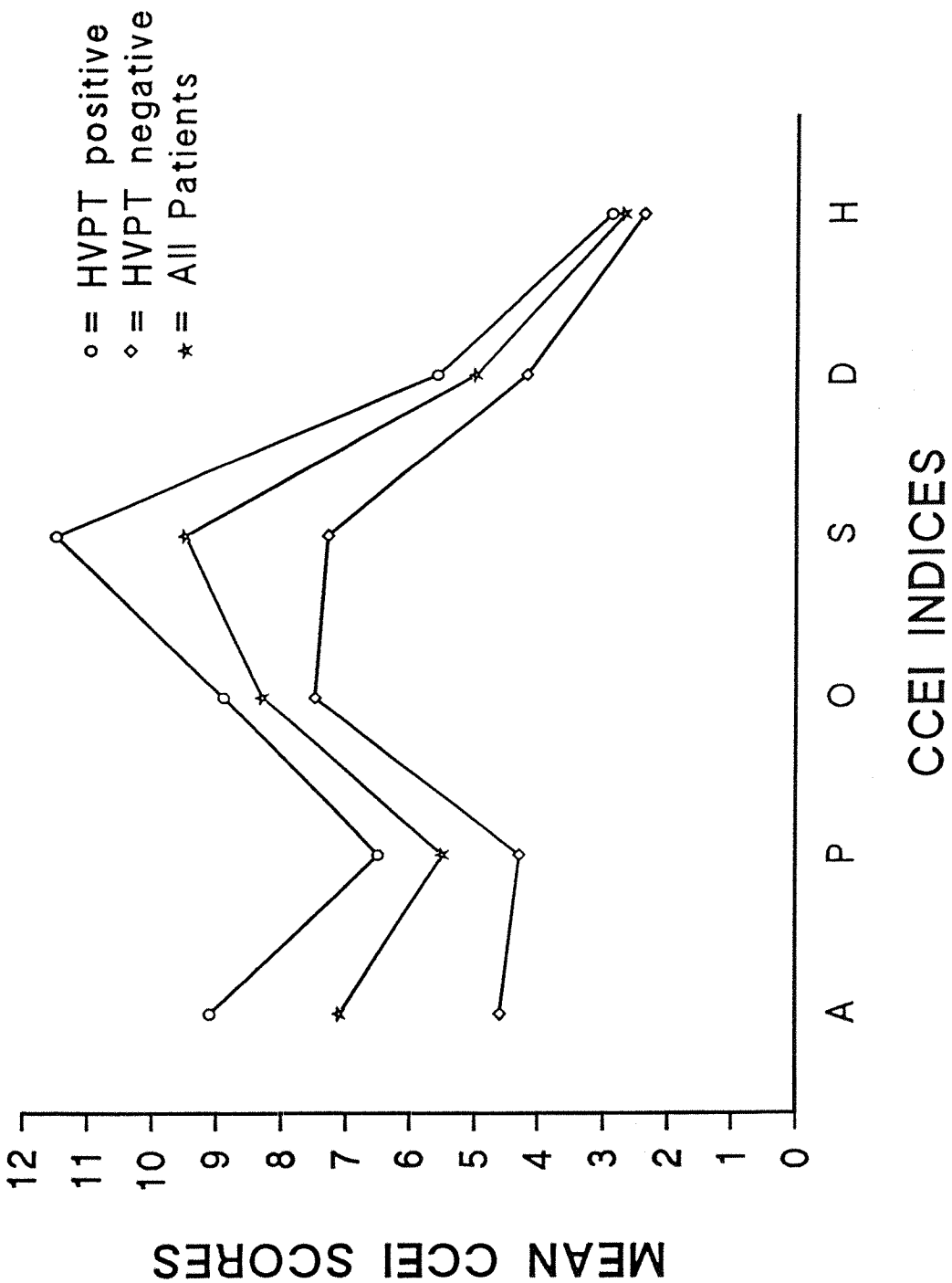


Fig 21. Mean CCEI scores and HVPT result.
Cohort 2A. N = 24

Table 48 and fig 21 show that scores for free-floating anxiety and somatic anxiety were significantly higher statistically in those with HVS as diagnosed by a positive HVPT than those who were negative.

	Mean	Median	Range	SD
Total breaths taken	18.1	20.0	7-20	3.9
Number breaths taken to onset symptoms	14.5	17.0	2-20	5.9

Table 49. HVPT. Number of breaths actually taken. Cohorts 2A and 3.

Number of symptoms per patient	1	2	3	4	7
Patient numbers	12	7	4	3	1

Table 50. Symptom numbers in patients with a positive HVPT. Cohorts 2A and 3. N = 27.

A few patients failed to complete the 20 deep breaths due to weakness, as shown in table 49. Most that were positive volunteered 1 or 2 symptoms (table 50).

Symptoms volunteered (table 51) fell into groups with similar meanings (table 52).

Rank	Symptom	Patient numbers	
1	Light-headed	12	
2	Dizzy	8	
3	Dry mouth or throat	4	
	Faintness	4	
5	Chest pain	3	
6	Chest tightness	2	
	Tiredness	2	
	Pressure in head	2	
9	Couldn't take another breath	)	
	Palpitations	)	
	Tremor hands	)	
	Tremors	)	
	Breathlessness	)	
	Tingling	)	
	Tingling in head	)	
	Fast heart rate	)	
	Burning throat	)	
	Headache	)	
	Back pain	)	1 each
	Facial pain	)	
	Abdominal pain	)	
	Flushing	)	
	Relaxation	)	
	Reduced pain	)	
	Panic	)	
	Feeling hot	)	
	Increased effort with each breath	)	
	Faraway feeling	)	

Table 51. Symptoms reproduced by HVPT. 28 different symptoms in 27 patients recorded 57 times. Cohorts 2A and 3.

Rank	Symptom group	Patient numbers
1	Faintness	17
2	Dizziness	8
3	Sympathomimetic	6
4	Breathlessness	5
	Dry mouth	5
	Alterations in pain level	5
7	Chest pain	3
	Pressure in head	3
9	Tiredness	2
10	Tingling	2
11	Changes in anxiety levels	2

Table 52. Main symptom groups reproduced by HVPT. Cohorts 2A and 3.

CHAPTER 5 DISCUSSION

5.1 Frequency

In this study, dyspnoea occurred in nearly two-thirds of patients on admission to CMH. The lower prevalence in cohort 1 (55.5%) may be due to dyspnoea status being assessed retrospectively from admission notes. The prevalence of dyspnoea in those ineligible for the main study (cohort 2B, 84.6%) was much higher than those entered for this study (cohort 2A, 45.8%) probably because ineligibility often implied iller patients more likely to be dyspnoeic (see p 98).

Overall, percentage prevalence figures are probably under-estimates because in 117 of the 968 patients (12.1%) no assessment of dyspnoea could be made since they were too ill, unconscious or confused and it is this group which is most likely to be dyspnoeic.

These figures are higher than in most other studies (see table 1, p 20) despite the results of these other studies being for incidence *throughout* the terminal period. The difference may be due to improved methods of data collection. The only other study to measure prevalence[22] showed a figure of 64% in patients whose survival was on average 7 days from measurement, which agrees more closely with the present investigation.

Thus dyspnoea is very common and underdiagnosed in advanced cancer.

5.2 Sex

Although past studies suggest that dyspnoea is commoner in men than woman (see Table 5, p 23) perhaps because lung cancer is more frequent in men, this difference did not reach statistical significance in this study. (Table 16, p 115).

5.3. Age

Even though older people would be more likely to have chronic respiratory problems, such as COAD (and hence be dyspnoeic), than younger people, age was not found to be related to dyspnoea status; this is in agreement with Reuben and Mor[22].

Since cancer tends to be a disease of old age, there will be a narrow spectrum of ages where cancer occurs commonly, and relatively few outliers. Hence, larger numbers would need to be studied to detect subtle differences.

5.4 Socio-economic status (SES)

This was not found to affect dyspnoea status, (see table 17, p 117. Classes 3,4 and 5 might be expected to contain groups more likely to be exposed to materials potentially toxic to the lung, such as coal dust, asbestos, or textiles, leading to dyspnoea. The absence of association may reflect the relatively small number studied so that minor differences do not show up. Further, there is no coal mining in the Southampton and Portsmouth areas.

5.5 Race

Only 1 patient out of 155 in the main study (Cohort 2A) was not white. The numbers were too small for statistical analysis. However, these figures do not reflect the racial mix nationwide where about 3.5% are black[82].

It has been shown that ethnic minorities may be under-represented in hospices[188]. Differences in age, disease distribution, cultural attitudes and language may explain this discrepancy[189].

5.6 Abode

No difference in frequency of dyspnoea was found comparing urban with rural dwellers (see table 18, p 118). Urban dwellers are more likely to have poor housing conditions and to be exposed to toxic materials such as coal dust and asbestos. They would therefore be expected to be more commonly dyspnoeic. Improvements in housing conditions and safety standards in industry may be the reasons no difference was found.

Patients who had lived abroad (N = 36) were statistically less likely to be dyspnoeic (27.7%) than those who had not (N = 119, % dyspnoeic = 51.3) (see Table 19, p 118). Most (25/36, 69.4%) lived in tropical and sub-tropical countries. Possible reasons for this "protective" effect might be:

1. No cold winters
2. Lack of atmospheric pollution
3. Less likely to be in jobs with a risk of lung toxicity.
4. The figures may be a statistical artefact.

5.7 Survival

This was clearly shorter in dyspnoeic patients than those not dyspnoeic (see pp 119-126 and fig 12); similarly, survival was obviously inversely proportional to severity of dyspnoea (see table 21 and fig 14) so much so that median survival (Cohort 1) in non-dyspnoeic patients was 21 days, and in those with severe dyspnoea, (that is level 3 on a scale of 0-3) was 3 days. When patients, therefore, feel that they might die of breathlessness, their fears may be well-founded.

Mean survival was however longer in Cohort 2A reflecting the fact that iller patients likely to die sooner were not eligible to enter this group.

It seems then that advancing organic pathology, particularly lung disease, is a common and often fatal concomitant of increasing dyspnoea. However, surprisingly, survival was not found to be related to the presence of carcinoma of the lung or of lung metastases (see pp 125-126 and table 23). Other pathology, such as pneumonia and COAD, may therefore play a part. Further, although figs 19 and 20 show a link between anxiety, as measured by the CCEI, and dyspnoea, it appears that the major trigger for dyspnoea is organic, with resulting anxiety, rather than anxiety alone.

It is important to note also that overall, median survival was much shorter than mean survival (see tables 20 and 21, pp 120-121), because most patients were already very ill and would die within a fortnight of admission, but there were a few patients who survived much longer.

Since Cohort 2A was not a random sample, it would be less likely that any link was shown between measures of dyspnoea and survival. In table 22, p 125, this is confirmed, apart from a relatively weak negative correlation using the Dyspnoea Quality-Quantity Score (DQQS). This suggests that the DQQS may be the best dyspnoea measure, and it is sufficiently sensitive to detect differences in dyspnoea despite the biased population and the fact that the components used to calculate the DQQS, namely the VASMe 24 and TSS (see p 103) did not themselves correlate with survival. The various dyspnoea measures will be considered in more detail on p 164.

Survival was not found to be significantly related to the primary site of the five commonest cancers in Cohort 1 (table 23, p 126) even though, at first sight, patients with carcinoma of the prostate seemed to survive longer (median = 45.0 days) than the whole sample (median = 14.0

days). The numbers involved were small and it would therefore need a very strong association for a statistical link to be shown.

5.8 Measurement of dyspnoea

This presents the researcher with problems because dyspnoea is subjective, a sensation, like pain, and hence only the patient can say what it feels like. The difficulties include:

1. What past experiences has the patient had of dyspnoea? A patient who has suffered from recurrent dyspnoea from, for example, COAD, will know better just how bad dyspnoea can become than another patient, previously healthy, with relatively mild dyspnoea from early lung metastases.

2. As with pain, there may be different types of dyspnoea from difference pathologies (see p 46).

3. The patient may not have a wide enough vocabulary to describe the difference types of dyspnoea. They may also find it easier to use phrases or sentences, which are harder to put into measurable terms, than single words[51].

4. Interpretation can lead to ambiguities. A "tight chest" may mean dyspnoea to one patient and pain to another.

5. The patient may wish to please the doctor and so bias his reporting of his dyspnoea.

6. Dyspnoea involves both a quantity (how difficult is it to breathe?) and quality (how unpleasant does it feel?). How, then, is it possible to know if the patient is referring to one or other or both of these modalities?

7. The doctor or nurse looking after a dyspnoeic patient may equate the degree of abnormality of respiratory signs (such as frequency or depth of respiration) with the degree of dyspnoea and, as has been discussed (p 16) this is not always so.

A number of different approaches have been tried (see p 61). The ideal measure would be simple, quick, reproducible, reliable, sensitive and specific. For research purposes a more complex measure which takes longer to apply can be justified if it improves accuracy of measurement.

Measures which involve exercise (such as the various respiratory stimulation tests) were excluded because of the frailty of the patient population in question. Voice change measures are not suitable for reasons given on p 68.

This leaves visual analogue scales (VAS) and numeric, verbal or activity scales. The author decided to test each of these to see how useful they would be in clinical practice and how they compared with one another. The VAS was used as the standard by which to compare the other measures, for reasons given on p 62. Use of the VAS to measure dyspnoea only at the time the scale was presented to the patient was excluded for the following reasons:

1. Some patients were only dyspnoeic on exertion and so would always mark the scale at zero.

2. It was difficult to ensure that patients had always had a period of rest before completing the scale. Recent previous exertion such as having just had a bath would affect the level of dyspnoea.

Hence, three variants were used:

1. VASMe 24 - measuring the average level of dyspnoea over the last 24 hours.

2. VASMax 52 - measuring, on admission, the worst level of dyspnoea over the last week.

3. VASMe 7 - the average level of dyspnoea over the last week since the VASMe 24 was measured.

The VASMe 24 has been validated by Lunt et al[26]. The VASMax 52 and VASMe 7 have not, to the author's knowledge, been used before. They were included because dyspnoea levels over the previous 24 hours might be much worse or better than the previous week depending on advancing pathology or successful treatment. In this way a fuller assessment was obtained.

Administration of the VAS was simple and patients did not find any problems in using it.

A numeric-verbal combined scale the Dyspnoea Word Scale or DWS (see appendix 7.4, Dyspnoea Questionnaire 1) was also tested as it would provide a rapid bedside method of assessing dyspnoea in day to day practice and it was important to see whether there would be a significant loss of sensitivity by using a 5 point scale as opposed to the continuous VAS.

Because of the drawback that all the scales so far mentioned are only quantitative and do not take account of qualitative differences, a new measure, the Dyspnoea

Assessment Questionnaire (DAQ) was developed using the McGill-Melzack Pain Questionnaire (MMPQ)[97] as a model (see pp 65-66, 99-103 and appendices 7.1 and 7.2).

Since patients were not usually able to describe their dyspnoea with single words or short phrases, an initial word list had to be collected from doctors (see p 99 and appendix 7.1). That 164 words were collected emphasises the complexity of studying dyspnoea and suggests that as with pain, different descriptors of dyspnoea may be allied with different pathologies. Even a brief study of the words reveals a rich vocabulary of often subtle qualitative differences, whereas there are few words that are purely quantitative.

It was essential to reduce this large number of words to a manageable size for a questionnaire without significantly affecting sensitivity. Further it was important only to include words which most respondents felt were valid. Hence 85% agreement was chosen as a cut off point which met both the above criteria.

It became apparent that there were many ways possible of scoring completed questionnaires (see p 101), some being similar to the MMPQ, some not. By analysing these scores and comparing them with VAS scores from the same patient, the optimum scoring methods were obtained.

Turning to the results of the different ways of scoring dyspnoea, the method used in Cohort 1 (retrospective notes review), although quick and simple, was likely to miss some dyspnoeic patients and with only 3 levels of dyspnoea, lacked sensitivity. It was also based only on the doctor's perception, not the patient's view. However it did show that severe dyspnoea was common.

The fact that mean time dyspnoeic (196.1 days, table 24, p 128) was far longer than the median suggests skewness by a few patients with long term respiratory problems such as

COAD. The median time (26 days) is surprisingly short, suggesting that respiratory problems tend to develop late in the advance of incurable cancer.

Changes in dyspnoea over time were studied (p 129). Only small numbers could be followed up due to most patients dying within three weeks. Table 26 seems to suggest little change in mean dyspnoea scores of 15 patients reviewed. However, when individual scores were analysed, 9 of the 15 improved and 6 worsened. The mean reduction in VAS of those improving (27.3%) suggests significant success in therapy for nearly two-thirds of patients. For patients whose dyspnoea increased, it may be that scores would have been worse without treatment. The sample is too small to attach to much weight to these conclusions, although they do suggest that dyspnoea is less well controlled than pain where good analgesia can be achieved in over 90% of patients[201].

Considering the DAQ (table 28, p 132; and appendix 7.1), words most popular with patients revealed surprising trends - "uncomfortable" and "variable" seemed at first sight less likely top choices than say "breathless" which is only ranked thirteenth. However, when the best word analysis (table 30, p 134) was assessed, "short of breath" came out first. Some words which seemed obvious choices such as "winded" or "choking" scored very low.

A possible reason for these findings is that the number of words in each category of the DAQ varies (see appendix 7.1). For example in category 4, "uncomfortable" is the only word and so was either chosen or that category left blank. However, in category 9, there are 5 words to choose from - "short of breath", "puffed", "out of breath", "winded" and "breathless" - and so each word in that category had much less chance of being picked. This was borne out by the fact that of the 7 single word categories, 6 were in the top 14 words chosen.

When *categories* were studied (table 29, p 133), the rankings obtained made more sense, the most popular being category 9 (air quantity) with categories 10 (respiratory effort, ranked 4th) and 3 (constrictive pressure, ranked 5th) not far behind.

When all the different ways studied of measuring dyspnoea were compared with the VASMe 24 as the standard (table 31, p 135), highly significant correlations were obtained for all measures except the Dyspnoea Exertion Score (DES). This may be because patients in the trial were often very restricted in their mobility and rapidly deteriorating. Hence their judgements about the level of exertion needed for dyspnoea to occur may have been inaccurate.

Another possibility was that patients did not only take account of activity limitation when assessing how much of a problem dyspnoea was to them, but also of how difficult and how unpleasant their breathing was. Further, patients who lived within the limits of their restriction of activity by dyspnoea may not therefore have seen dyspnoea as much of a problem.

Contrariwise the bar chart (fig 18, p 139) of DES scores also demonstrated that though the scoring system was deliberately weighted towards dyspnoea developing even with little exertion (see p 103), the distribution was still skewed to the right. Thus dyspnoea in these patients was very disabling in terms of activity limitation.

The DAQ was therefore validated in the following ways:

1. Words were only used in the DAQ if there was 85% or more agreement that they were valid descriptors of dyspnoea (appendix 7.1).

2. Only one word ("strangling") was never picked by patients presented with the DAQ (table 28, p 132). Hence the DAQ words were ones the patients found they could use.

3. Good correlation was found betwen the VASMe 24 and all of the DAQ measures.

4. The single "best word" scores (table 30, p 134) also correlated well with the VASMe 24 showing that the method of developing severity scores for each word (appendix 7.1) has validity.

How did the different DAQ scoring methods compare with one another?

The Number of Words Chosen Score (NWCS) was a measure of the variety of different respiratory sensations that the patient equated with breathlessness.

The Total Severity Score (TSS) would be expected to be the best method as the scores were developed from subject's assessments rather than mathematical models such as the Total Class Scores (TCS) or Total Interval Scores (TIS). However, inspection of the scores used in the TSS (see appendix 7.1) show them to be weighted towards the higher end of the 0-5 scale, with few words scoring below 2.5. The TCS and TIS had a wider range. Despite this, scoring methods for all 3 showed similar levels of correlation with the VASMe 24.

The "average" scoring methods (see p 101) were developed to take account of patients who chose high scoring words in each category, implying severe dyspnoea, but chose few categories, so their overall scores were low. The advantage gained in reducing bias in this way was negated by the fact that the process of averaging caused high and low scores in each category to cancel each other out and so reduce sensitivity.

The SBW (Score Best Word) had the same potential bias in weighting of scores as the TSS. Further, it lacked the ability of the TSS to take account of a wide variety of sensations.

Did the DAQ assess dyspnoea status as well as or better than the VASMe 24? Table 24, p 128 shows that mean scores as a percentage of maximum possible scores for the TSS, TCS and TIS were all lower than the VASMe 24. Hence, more people scored higher on the VASMe 24, but for a minority the reverse was true. So, neither score was better, they measured different things - the VASMe 24 being chiefly quantitative and the DAQ mainly qualitative, particularly describing emotional distress - but with considerable overlap.

The VASMe 24 would be expected to change rapidly with changes of dyspnoea, even over minutes, whereas the DAQ would alter more slowly since qualitative factors do not link so closely to time. It is possible too that in certain conditions the VASMe 24 might increase and the DAQ decrease. For example morphine might reduce the subjective distress of dyspnoea but have no effect on the effort needed to breathe.

For research purposes, both would be needed to provide the most complete measure of dyspnoea and can to this end be combined as the Dyspnoea Quality-Quantity Score (DQQS) [p 103] using the TSS as the best DAQ scoring method.

Since there was good correlation between VASMe 24 and STSS (the Short Total Severity Score) this method could be used as a quick bed-side assessment of dyspnoea; this was not however tested prospectively in this study.

VAS scores from patients (VASMe 24), doctors (VASMe D) and nurses (VASMe N) correlated well together (table 31, p 135) but scatterplots (figs 15-17, pp 136-138) show that there were sometimes marked differences. This, together with the fact that doctors and nurses were more likely to score a patient as dyspnoeic than the patients themselves, but more likely to assign lower scores than patients did, (table 24, p 128) showed the importance of finding out from the patient how they viewed their breathing. Possible reasons for these variations were:

1. The doctor or nurse was going more on objective respiratory indices such as respiratory frequency or depth, than on asking patients for their subjective assessment.

2. They took more account of restriction of activity by respiratory problems than the patient did.

3. They may have included historical factors, that is dyspnoea when the patient first presented, which may not have applied at the time of carrying out the VAS.

4. They were using their own subjective assessment of how they would feel if they were in the patient's place, and so going on their own life experience. To one person, being wheezy may have no great significance whereas to another it may signal fear of asphyxiation.

Of the 68 patients who were breathless on admission, 16 (23.5%) marked their VASMax 52 as lower than their VASMe 24 (p 127) when by definition it should have been the same or higher because it was the *worst* level of dyspnoea over the last week. This suggested either that the VAS had a high margin of error, which has not be shown to be the case[88,90], or that patients were not understanding instructions properly and putting a figure for average level of dyspnoea over the last week instead. In an estimated 3 cases, patients were mistakenly asked

for the average level of dyspnoea over the last week, but this was only discovered later, and the figures could not be rectified. For all these reasons, the VASMax 52 results should be treated with caution.

5.9 Psychological Status

The Crown-Crisp Experiential Index (CCEI) was chosen to assess psychological status in cohort 2A because it measures several indices and is quick and simple to administer (see appendix 7.3).

Considering all the patients in this cohort, all indices were raised apart from hysteria, (see table 33, p 143 and figs 19-20, pp 141-142). Somatic anxiety scores were particularly high, which might be expected as physiological symptoms of anxiety overlap considerably with symptoms due to advanced cancer (eg nausea or anorexia). This then provides evidence of the distress that patients are experiencing related to their advanced cancer.

When dyspnoeic patients were considered, all indices apart from depression and hysteria were raised in comparison with non-dyspnoeic patients, though only the 3 anxiety scores (free-floating, phobic and somatic) were significantly higher at the 5% probability level (table 34, p 144). Although depression is known to be related to dyspnoea[35], this was not demonstrated in this study.

Levels of dyspnoea as measured by the DAQ, which takes account of the emotional qualities of dyspnoea, showed a correlation with somatic anxiety and hysteria scores (table 35, p 144). These 2 CCEI scores reflect *expression* of feelings which might therefore be expected to link with dyspnoea of emotional origin. The hysteria scale is thought to measure both hysteria and extraversion[85] and the latter would also fit with this hypothesis.

The other CCEI scores (free-floating anxiety, phobic anxiety, obsessionality and depression) reflect more internal psychological states and so would not be expected to link with emotional dyspnoea to such an extent.

These figures were however from a biased sample, since only patients fit enough to be studied were included in this cohort (2A). Further, figures for comparison of the DAQ scores with CCEI were only for dyspnoeic patients and this may have disguised any links.

Although psychological status may affect prognosis in cancer[106], it was not shown to be related in this study to survival in Cohort 2A, but since iller dying patients tended to be excluded from this part of the project, this is not unexpected.

Further, Spiegel's[106] study only showed significant survival differences in terms of months and years, whereas the time-scale for most of the patients studied here was in days and weeks.

5.10 Site of Primary Cancer

Table 37, p 146 shows that, in general, patients with lung tumours, or cancers likely to metastasise to the lungs (breast, oesophagus, kidney, pleural mesotheliomas), were more often dyspnoeic, whereas those with cancers less likely to metastasise to the lungs were less often dyspnoeic. This was corroborated on statistical analysis of the relationship of the 9 most frequent malignancies with dyspnoea ($p < 0.01$).

Did severity of dyspnoea vary with different primary sites? At first sight, when all patients were considered it seemed that those with carcinomas of bronchus and breast and those with pleural mesotheliomas were more

severely dyspnoeic (see table 38, p 147). When however only dyspnoeic patients were studied, the mean VASMe 24 differences were less marked, as would be expected since non-dyspnoeic patients skewed the results. So, whether, for example, lung metastases came from carcinoma of the breast or colon, would be immaterial to the severity of dyspnoea experienced.

Most carcinomas were diagnosed histologically (table 39, p 148) although the rate was lower in Cohort 2B (those ineligible for the main study) possibly because medical records were not always immediately available on admission and ineligible patients were not followed up.

Lung and pleural metastases

These were mostly diagnosed on chest x-ray (table 40, p 148). There was a higher diagnostic rate in Cohort 2A reflecting the more detailed investigations of these patients and suggesting that these metastases are underdiagnosed in palliative medicine. This was, however, not a failure, but reflected the fact that investigations were only carried out if they affected the patient's terminal care. It would be reasonable to assume, for example, that patients with pleural effusions have lung metastases unless proven otherwise, even if none had been previously reported. As might be expected, patients with lung or pleural metastases were more likely to be dyspnoeic than those not (table 41, p 149).

5.11 Smoking

Table 42 (p 150) demonstrates that present smokers were significantly more likely to be dyspnoeic than present non-smokers (but this did not apply when comparing *past* smokers with past non-smokers). This may have been due to any one of the various diseases related to smoking, such as lung cancer or COAD, or to a combination of these factors in an individual patient.

The figure of 65.2% of admissions having been smokers at some time reflected the past higher levels of smoking in the population[190]. At present, about 35% of the population smoke[190]. Yet again, the close link of smoking with carcinoma of the bronchus (96.5% having been smokers at some time in this study) was all too clearly demonstrated.

5.12 Asbestos exposure

Nearly 20% of patients in the main study, Cohort 2A, recalled exposure to asbestos dust, probably reflecting the high numbers working in the docks in Southampton and Portsmouth. The high prevalence of mesotheliomas in this study (5/155, 3.2%) is similarly explained.

5.13 Hyperventilation Study

In the main study, Cohort 2A, an HVPT was performed on patients within criteria detailed on p 107. As very few were eligible, the criteria were progressively relaxed until near the end of the study, all patients were tested. Hence this group was neither consecutive nor randomised, severely limiting any statistical conclusions. However, since 13 of the 24 tested (54.2%) were positive, it was clearly very important to study this in more depth, as HVS

has not before been reported as a cause of dyspnoea in advanced cancer. Hence a third cohort was investigated (p 151).

Even in this group, only 67 of the 125 consecutive admissions studied were eligible to have an HVPT carried out. However, figures on p 151 show that, despite this, no significant bias was found in gender distribution or in mean ages between those eligible and those not, which added weight to any statistical conclusions drawn.

In the following discussion, for simplicity, a positive HVPT is taken to imply HVS; the diagnostic limitations of the HVPT are discussed further on p 179.

Results (table 44, p 152) did not show any association between HVS and gender. Not surprisingly however, dyspnoea did show a link with HVS (table 43, p 151). This association was still present, though less strongly, when only the patients in Cohort 3 were studied. This difference was because selection of patients for HVPT in Cohort 2A was biased towards those who were thought to have HVS (54.2% positive HVPT) as opposed to the unselected sample in Cohort 3 (20.9% positive HVPT).

Mean ages in both cohorts were lower in those with HVS. There was no obvious reason which would explain this, though the questionable supposition that older people are more accepting of death and so less anxious would fit with this finding. In a general medical setting Lum[36] found the highest age incidences in women aged 30-39 years and in men aged 50-59 years; he suggested this reflected times of maximum stress. Hardonk and Beumer[75] also comment on HVS being commoner in younger people and suggest either that trigger levels of PCO_2 are higher in older people, or that lung and thoracic cage changes make hyperventilation more difficult.

Patients with organic lung disease were significantly more likely to have HVS (43.9%) than those without (18%) (table 46, p 153), which is the reverse of general medical practice[10]. It would seem then that the sequence of events was that organic lung disease (OLD) caused dyspnoea leading to anxiety and hence HVS, rather than another non-organic trigger causing anxiety, leading to HVS and hence dyspnoea (see fig 4, p 34). The important clinical implication of this is that it may wrongly be assumed that in a patient with OLD, all of their dyspnoea is due to this, whereas in fact HVS may also be present. If this is not recognised, therapeutic success may be suboptimal. Having said this, table 46, p 153 shows that there were many patients with OLD who were not shown to have HVS.

It is likely that some patients had undiagnosed OLD. This subset of the "OLD absent" group would have been expected to have a higher frequency of dyspnoea than those in the group who genuinely did not have OLD. This implied a higher rate of positive HVPT's in the "OLD absent" group than would have been the case in those actually without OLD. Hence the real association of HVS and OLD may be stronger than was found in this project.

The numbers studied were too small to ascertain whether a particular diagnosis such as carcinoma of the bronchus was associated with HVS (table 47, p 154).

The high figures found for frequency of HVS reflect the findings in studies on HVS in general medicine showing it to be common and under-diagnosed[36].

Table 48, p 155 shows that CCEI scores for free-floating and somatic anxiety were significantly higher in patients with HVS in Cohort 2A than in those not so diagnosed, which bears out similar findings in the general medical setting[36]. Further, the above-mentioned scores were even higher in patients with a positive HVPT than in those simply shown to be dyspnoeic (see table 34, p 144; table

48, p 155; figs 19, 20 and 21). Somatic anxiety scores are however difficult to interpret since many of the symptoms developed, such as shortness of breath or anorexia, may also be cancer-related.

Most patients were able to complete the 20 deep breaths needed for the HVPT (table 49, p 157). It was a clinical impression that some patients with low FEV_1 were too weak effectively to take 20 *deep* breaths and hence some who would have been positive might have been missed. It was possible too that in those who were able to carry out the test properly there were some who may have become positive if they had hyperventilated longer since most who developed symptoms did so towards the end of the 20 deep breaths (table 49). The time taken to carry out the HVPT was not formally measured, but was usually less than about 2 minutes. Lum[36] points out that most patients develop symptoms within 3 minutes, but a few take much longer, up to 30 minutes in one case.

The symptoms volunteered (table 50, p 157) were similar to those described in other studies[36,75] (table 7, p 50) with light-headedness and dizziness the most common both as individual symptoms and as headings for groups of symptoms (see table 51, p 158). Other symptoms characteristic of HVS were volunteered - these included difficulties with breathing, tingling, palpitations and tight chest. Further symptoms such as back pain or relaxation were not characteristic. However, none of the symptoms were specific to HVS and so diagnosis rested on their *reproduction* by hyperventilation. The process of hyperventilation may itself have caused symptoms other than through hypocapnoea. Thus dry mouth might have been related to mouth breathing; tiredness might have been related to a weak, frail patient rapidly becoming exhausted; back pain might have been induced in patients with rib or spinal metastases by the extra thoracic movements needed to hyperventilate. Hence diagnosis of

HVS by the HVPT must take the above into account. In practice, however, the author found that these confounding factors were usually obvious and readily allowed for.

One patient with sub-acute obstruction developed colic during the HVPT. This may have been due to mesenteric artery vasospasm from hypocapnoea causing bowel ischaemia and so stimulating peristalsis and colic.

Other tests such as blood gases or spirography (see p 55) could help to make diagnosis of HVS more certain but may be impractical and unkind in frail dying patients. Further, other studies[9,50,75] have shown good correlation between te HVPT and the above mentioned tests, suggesting that despite theoretical limitations in sensitivity and specificity it is adequate alone in the diagnosis of HVS - other tests could then be reserved for doubtful cases. Some patients with a normal PCO_2 may still develop symptoms, particularly related to dyspnoea, suggesting that cortical mechanisms also play a part (see p 29).

The great majority of patients only volunteered one or two symptoms (see table 50, p 157), though one patient mentioned 7. It is possible that if hyperventilation had been continued longer, further symptoms would have been evoked.

In conclusion then, this study suggests that HVS is common in advanced cancer and readily diagnosed by the HVPT. A further study using blood gas analysis and spirography would provide additional support to these findings.

This has important therapeutic implications which will be discussed further on p 182.

5.14 Problems of research in patients with advanced cancer

The study described was designed to be easy and non-taxing to the patient, requiring only completion of questionnaires and some simple investigations. Despite this, only 28.7% (N = 155/540) were eligible for the main trial (Cohort 2A) and many more dropped out at follow-up. This emphasises how ill the patients in question were and this is further borne out by the figures on p 121 (table 21), showing a median survival of only 11 days in Cohort 1.

What then were the reasons for ineligibility? This was not formally studied, but the following occurred:

1. Confusion
2. Drowsiness impairing concentration
3. Deafness
4. Moribund and unconscious
5. Refused for unspecified reasons
6. Too weak to participate
7. Staff felt the patient was not well enough
8. Impaired vision
9. Expressive or receptive dysphasia
10. Severity of symptoms such as pain or vomiting precluding taking part in the trial till symptom control was achieved.

At follow-up of eligible patients, reasons for dropping out included:

1. Condition deteriorated
2. Refused because did not want to repeat the questionnaires or tests.
3. Died

Hence research in this group of patients was difficult. Despite this, however, worthwhile results can be and were obtained, and must be if improvements in symptom control are to result, particularly because dyspnoea is less successfully relieved than pain at present (p 96).

5.15 Clinical implications for the physician

The results presented have a number of consequences for clinical practice.

1. Dyspnoea is more common in advanced cancer than previous studies suggest. So doctors may sometimes be missing the diagnosis. Possible reasons for this include: patients with chronic respiratory problems having become used to their breathing problems and so playing them down; or the bedbound patient not being dyspnoeic at the time of enquiry, but becoming so later on exertion; or another symptom such as pain over-shadowing dyspnoea. Emphasis of the need for a detailed respiratory history is therefore required.

2. Estimation of prognosis in the dying patient is difficult[12]. The demonstration that severity of dyspnoea is related to survival provides the doctor with a little more knowledge on which to base estimates of prognosis when so asked by the patient or family.

3. A number of ways of measuring dyspnoea were tested. Use of a simple word or numeric scale, or of a visual analogue scale, is adequate for bedside evaluation. A new measure, the dyspnoea assessment questionnaire (DAQ) provides a research tool for fuller assessment of dyspnoea to include qualitative as well as quantitative aspects.

4. The link shown between dyspnoea and anxiety highlights the need to treat the emotional distress of dyspnoea as well as its physical aspects for optimum symptom control.

5. The hyperventilation syndrome (HVS) has not previously been described as a cause of dyspnoea in advanced cancer, nor that it may coincide with organic lung disease so that both are factors in giving rise to dyspnoea. HVS is treatable (see p 92). The therapies are simple but may be time consuming because repeated sessions of say relaxation exercises or breathing retraining may be needed. These can however lead to marked improvement in dyspnoea. For example, relaxation exercises carried out at Countess Mountbatten House for dyspnoeic patients showed reductions in VAS scores in the order of 60 mm on a scale of 100 mm (personal observation). Increased recognition of HVS should therefore lead to improved control of dyspnoea.

5.16 Results of hypotheses tested (p 13)

1. Dyspnoea is a common and major problem in advanced cancer - confirmed.

2. Patients, doctors and nurses do not always agree as to presence and degree of dyspnoea - confirmed.

3. Words employed by patients to describe their dyspnoea may be used to provide a score of its severity - confirmed.

4. The comprehensiveness of measurement of dyspnoea may be increased by taking into account qualitative as well as quantitative factors - confirmed.

5. HVS is a common and under-recognised cause of dyspnoea in advanced cancer - confirmed.

6. Anxiety and depression levels are higher in dyspnoeic than non-dyspnoeic patients - confirmed for anxiety; refuted for depression.

7. Dyspnoea is at present less effectively relieved than pain - confirmed.

CHAPTER 6 SUMMARY AND CONCLUSIONS

1. Dyspnoea in advanced cancer has been little studied compared with pain.

2. The literature on dyspnoea in advanced cancer up to the beginning of 1992 is therefore reviewed.

3. A study was carried out of the epidemiology, measurement and some causes of dyspnoea in advanced cancer with special reference to psychological status and the hyperventilation syndrome (HVS).

4. Nine hundred and sixty-eight patients with advanced cancer at Countess Mountbatten House, Southampton, were investigated over 835 days. These were divided into 3 Cohorts - (1) preliminary study, (2) main study and (3) hyperventilation study. The main study Cohort was divided into those eligible (2A) and ineligible (2B) (see p 97). The special problems of research in patients with advanced cancer are discussed on p 181.

5. Data were collected from the clinical notes, by questionnaires and by investigations (see appendices 7.1 - 7.6).

6. Dyspnoea was measured in 4 ways - the Dyspnoea Word Scale (DWS), various forms of visual analogue scale (the VASMe 24, 7, D, N and VASMax 52) and 2 new scales, the Dyspnoea Exertion Scale (DES) and the Dyspnoea Assessment Questionnaire (DAQ) (see pp 98-105 and appendices 7.1 and 7.4).

7. The DAQ comprises 43 words, each with a pre-assigned score, in 16 classes. Several scoring methods were used. Patients were asked to choose a word from each class best describing their dyspnoea, and overall scores were thus obtained (pp 99-103).

8. The DAQ was validated (p 169 and table 31, p 135).

9. Dyspnoea occurred in 64.4% of all admission (p 113). 11.4% were severely dyspnoeic on a scale of 0-3 (table 21, p 121).

10. Of patients with a survival of less than one day, 82.1% were dyspnoeic (table 27, p 131).

11. No link between age, gender or socio-economic status and dyspnoea was found (pp 114-117).

12. Patients who had lived abroad were less likely to be dyspnoeic than those who had not. This finding is of doubtful significance (p 118).

13. Dyspnoeic patients had a shorter survival than the non-dyspnoeic (fig 12, p 122).

14. Severity of dyspnoea was inversely proportional to length of survival (table 21, p 121; fig 14, p 124).

15. Length of survival was not found to be related to primary site of cancer or presence of lung metastases (pp 125-126).

16. The median time that patients were dyspnoeic before admission was 26 days. No correlation between the duration of dyspnoea and severity was found (table 24, p 128).

17. Dyspnoeic patients in this study received the same treatment as all other patients admitted to CMH. Of 15 patients whose change of dyspnoea was studied over time, 9 (60%) improved, with a mean reduction in VAS scores of 27.3%, and 6 (40%) worsened (p 129).

18. In comparison with the VASMe 24 (the mean level of dyspnoea over the last 24 hours) all the other types of VAS scoring (VASMe N, D and VASMax 52 - see pp 105-108) correlated well, as did the DWS and all the DAQ measures derived. However, the DES did not show a correlation (table 31, p 135).

19. Of the various scoring methods developed from the DAQ, the Total Severity Score (TSS) and Total Interval Score (TIS) correlated best with the VASMe 24 (table 31, p 135).

20. It is suggested that VAS scores measure predominantly quantitative aspects of dyspnoea whereas the DAQ measures mainly qualitative aspects, although the 2 scales overlap considerably (p 171).

21. An overall measure combining the TSS and VASMe 24, the Dyspnoea Quality-Quantity Score (DQQS) was derived to provide the most complete evaluation of dyspnoea status (p 103).

22. A short form of the TSS (the STSS) was derived by using only the 14 most popular words that patients chose (table 28, p 132) to calculate each patient's severity score from words they had already chosen in completing the DAQ (p 103). The STSS correlated well with the VASMe 24 (table 31, p 135) and could be used as a quick bedside method of measuring dyspnoea. It needs to be tested prospectively.

23. The main use of the DAQ is considered to be a research tool to improve the accuracy of measurement of dyspnoea (p 171).

24. The Crown-Crisp Experiential Index (CCEI) as a measure of psychological distress showed raised mean free-floating, phobic and somatic anxiety scores and

raised mean obsessionality and depression scores in patients admitted to CMH. Hysteria scores were not raised (table 33, p 143).

25. For dyspnoeic patients, the 3 anxiety scores (free-floating, phobic and somatic) were significantly higher statistically than for non-dyspnoeic patients (table 34, p 144).

26. Patients with primary or secondary lung carcinomas or pleural metastases were more likely to be dyspnoeic than those not (table 37, p 146; table 41, p 149).

27. Patients with tumours likely to metastasise to lung (oesophagus, breast, kidney, pleural mesothelioma) also had high dyspnoea rates (table 37, p 146).

28. Smokers were more often dyspnoeic than non-smokers (table 42, p 150).

29. There was a high rate of asbestos exposure (19.4%) and of mesotheliomas (3.2%) in the main study, perhaps related to high numbers working in local docks (p 150).

30. The Hyperventilation Provocation Test (HVPT), used in this study to diagnose the hyperventilation syndrome (HVS), was positive in 20.9% of patients tested in Cohort 3 (table 44, p 152), suggesting HVS may be common in advanced cancer.

31. The sensitivity of the HVPT would have been reduced in those patients too weak to take adequate deep breaths. Its specificity was limited where symptoms could have originated either from HVS or the cancer itself (p 179).

32. HVS patients were more likely to be dyspnoeic than those not so diagnosed (table 43, p 151).

33. Mean age was lower in those with positive HVS than those not so diagnosed (table 45, p 153).

34. HVS was more common in those with organic lung disease than those without (table 46, p 153).

35. CCEI anxiety scores were higher in those with HVS than those with dyspnoea (figs 19, 20 and 21 on pp 141, 142 and 156).

36. CCEI anxiety scores were higher in those with HVS than those not so diagnosed (table 48, p 155).

37. Despite theoretical limitations in the sensitivity and specificity of the HVPT, it is suggested that this is a suitable method for diagnosing HVS in advanced cancer (pp 58 and 180).

38. HVS has not previously been described in advanced cancer. It is treatable. Its increased recognition should lead to improved control of dyspnoea (p 183).

CHAPTER 7 APPENDICES

7.1 APPENDIX 1 - Development of the Dyspnoea Assessment Questionnaire (DAQ) and Dyspnoea Exertion Score (DES).

DYSPNOEA RESEARCH PROJECT

COUNTESS MOUNTBATTEN HOUSE

DESCRIPTIONS OF DYSPNOEA LIST

NAME OF PARTICIPANT: DATE COMPLETED:

Part of this research project involves obtaining descriptions of dyspnoea from patients here. Since patients may have difficulty in finding words to describe their dyspnoea they will be presented with a classified list. In order to do this I would like to ask you to write down below all the words you can think of to describe dyspnoea.

Please think in the widest terms e.g. quantitative and qualitative and so on. Please use only single words and avoid even short phrases. Hyphenated words are acceptable. Please go over the page if necessary. When you have done this please return the completed form as soon as possible to:

Dr. Louis Heyse-Moore, Countess Mountbatten House, Moorgreen Hospital, Botley Road, Southampton SO3 3JB Tel Southampton (0703) 477414.

When all the forms return, I will then classify the words used, and I would like then to ask you on another form which I will send to you to signify whether you agree or not with the classification, and if not, which classification you would make for that word.

Please contact me if you have any queries.

- - - - - // - - - - -

INITIAL WORD LIST

- Aching
- Agitating
- Agonising
- Air Hunger
- Airless
- Anguishing
- Asphyxiating
- Asthmatic
- (Audible)
- Awful

- Bad
- Binding
- Bloated
- Blowing
- (Blown)
- (Blurring)
- Breathless
- Broken-winded
- Bronchitic
- Bubbling
- Bursting
- (Bushed)

- (Catching)
- Chesty
- Choking
- Clamping
- Claustrophobic
- Cold
- Compressing
- Congested
- Constricting
- Contorting
- Coughing
- Cramping
- Crushing

- Dangerous
- (Dark)
- Depressing
- (Deep)
- Desperate
- Difficult
- Disabling
- Distorting
- Distressing
- Dizziness
- Doom-laden
- Dragging
- Drawing
- Dreadful
- Drowning
- Dry
- Dull
- Dying

- Effort
- Emptiness
- Exhausting
- Expiring
- Extreme

- Faintness
- Fatiguing
- Fearful
- Flattening
- Frightening
- (Frightful)

- Gagging
- Gasping
- (Grasping)
- Gripping
- Gruelling
- Gulping
- Gurgling

- Handicapping
- Harsh
- Heaving
- Heavy
- Hissing
- Hoarse
- Horrible
- Hot

- Immobilising
- Intolerable

- Killing

- Lethal
- Light-headed
- (Lonely)
- (Loud)

- (Mewling)
- Mild
- Miserable
- Moaning
- Moderate
- Muffled
- Murderous
- (Musical)

- Nauseating
- Noisy
- Numbing

- Out of breath
- Overwhelming

- Painful
- Panic
- Panting
- Pressing
- (Pressure)
- Puffed
- Pulling
- Punishing
- Punctured

- Racking
- Rasping
- Rattling
- Raucous
- Raw
- Resisting
- Restricting
- Rough

- Scaring
- Severe
- Shallow
- (Short)
- Short of breath
- (Short-winded)
- Shut in
- (Sibilant)
- Sickening
- Sighing
- (Snuffly)
- Spent
- Spluttering
- (Squeaking)
- Squeezing
- Stertorous
- Stifling
- Straining
- Strangling
- Strident

- Suffocating
- Suppressing
- Sweaty

- Terrible
- Terrifying
- Thick
- Thirst
- Throttling
- Tight
- Tingling
- Tiring
- Torturing
- Trapped
- Tugging
- Twisting

- Unbearable
- Uncomfortable
- Unending

- Variable
- Vice-like
- (Viscous)

- Weak
- Wheezy
- Winded
- (Worse)
- Worrying
- Wretched

- Yawning

Words in brackets rejected (see p 99)

DYSPNOEA DESCRIPTION LIST

CLASSIFICATION SYSTEM

1. QUANTITATIVE	1.1. Intensity
	1.2. Temporal
2. SENSORY	2.1. Constrictive pressure
	2.2. Traction pressure
	2.3. Expansion pressure
	2.4. Torsion pressure
	2.5. Pain
	2.6. Fluidity
	2.7. Nausea
	2.8. Neurological
	2.9. Sound quantity
	2.10. Dry sound
	2.11. Wet sound
	2.12. Energy
	2.13. Thermal
	2.14. Air quantity
	2.15. Dullness
3. MOTOR	3.1. Respiratory effort
	3.2. Loss of power
4. AFFECTIVE	4.1. Fear
	4.2. Depression
	4.3, Claustrophobia
	4.4. Dread
	4.5. Punishment
5. MORTALITY	5.1. Loss of life
	5.2. Suffocation
	5.3. Illness

Southampton and South West
Hampshire Health Authority

Countess Mountbatten House
Moorgreen Hospital

BOTLEY ROAD
WEST END
SOUTHAMPTON SO3 3JB

Telephone:
Southampton (0703) 477414

Ref: LHM/RMN.

20th March 1987

Dear

I am in the process of carrying out a research project on the problems of dyspnoea in advanced cancer. As part of this project, I want to find out whether there is a link between words patients use to describe their dyspnoea and their diagnosis. I also want to develop a better way of measuring dyspnoea. To do this, I will present patients with a classified list of words describing dyspnoea. From their choices of words, I can see if there are correlations between words and diagnosis. Further, by assigning a number on a scale of severity of 0-5 for each word chosen, a measure of the level of dyspnoea can also be obtained.

I have gathered a list of words describing dyspnoea and have classified them. I now need to validate the words and their classification and to obtain a scale of severity number for each; I am therefore circulating a questionnaire to a number of doctors working in terminal care.

May I ask therefore if you would be prepared to complete the enclosed questionnaire? Enclosed with it are an instruction sheet and stamped, addressed envelope. Please could you also pass on photocopies of the questionnaire to other doctors in your unit and ask if they, too, would be prepared to participate?

Please let me know if you have any queries.

Yours sincerely,

LOUIS HEYSE-MOORE
SENIOR LECTURER and
HON. CONSULTANT PHYSICIAN.

Southampton and South West
Hampshire Health Authority

Countess Mountbatten House
Moorgreen Hospital

BOTLEY ROAD
WEST END
SOUTHAMPTON SO3 3JB

Telephone:
Southampton (0703) 477414

Ref: LHM/RMN.

20th March 1987

Dear

Thank you very much for sending back to me the list of words describing dyspnoea. I have now collated all the word lists I have received and, after initial pruning, have classified them.

The purpose of this study is to be able to present a classified list of words to patients who are dyspnoeic and from their choices of words see if there is a correlation between certain words (or classes) and diagnoses. Further, by assigning a number on a severity scale of 0-5 for each word, a new more inclusive measure of the severity of dyspnoea can be made.

The next part of the study is, therefore, validation of the words and classes, and assignment of a number as a measure of severity. To do this, I am sending you the classified list of words in the form of question sheets, and an instruction sheet and S.A.E. I would be grateful if you could complete the question sheets and return them to me as soon as possible.

Please let me know if you have any queries.

Thank you for your help.

Yours sincerely,

LOUIS HEYSE-MOORE
SENIOR LECTURER and
HON. CONSULTANT PHYSICIAN.

DYSPNOEA DESCRIPTIONS LIST - INSTRUCTIONS FOR QUESTIONNAIRE

NAME: DATE COMPLETED:

Column D contains a list of words describing dyspnoea.

Column C is the classification I have made of these words.

INSTRUCTIONS:

1. In COLUMN E, please indicate by a ✓ or x whether you agree or disagree that each word is valid descriptor of dyspnoea.

   By this I mean a word describing the sensation of dyspnoea itself (e.g. breathlessness) but not a word describing an accompanying sensation (e.g. shivering).

2. In COLUMN F, please assign a number on a scale of severity of dyspnoea of 0-5 for each word.

   e.g. If you think that the word "intolerable" is equivalent to 4 on a scale of 0-5, please write 4 in column F opposite intolerable. This is a way of assigning a measure of quantity to a word with a qualitative meaning in the same way that different colours can be assigned a measure of optical density on a black-and-white scale.

   Please assign a number even if you don't think the word is a valid descriptor of dyspnoea.

3. In COLUMN B, please indicate by a ✓ or x whether you agree or disagree with the classification in which the word has been placed.

   Please do this even if you don't think the word is a valid descriptor of dyspnoea.

4. In COLUMN A, if you disagree with the present classification position of a word please write down the classification position you feel would be more appropriate for that word.

   N.B. Don't invent a new classification system; use the present one. If you agree with the present classification position of the word do not write anything in Column A.

   A list containing the classification system only has been included for easy reference.

5. Don't spend long on any one question.

6. When you have finished, please check very carefully that you have answered all the questions.

7. If you have any queries, please contact me:
   Dr. Louis Heyse-Moore,
   Countess Mountbatten House,
   Moorgreen Hospital,
   Botley Road,
   West End,
   Southampton. SO3 3JB Tel: 0703 477414

8. Please return the completed questions in the S.A.E. provided, to me at the above address, within two weeks of receiving it.

THANK YOU FOR YOUR HELP.

DYSPNOEA DESCRIPTION LIST - QUESTIONNAIRE

A	B	C	D	E	F
Revision classification of word	Validity classification ✓ or x	Classification	Words	Validity of word ✓ or x	Scale of severity 0-5
		1 QUANTITATIVE			
		1.1 Intensity	Awful		
			Bad		
			Difficult		
			Extreme		
			Mild		
			Moderate		
			Overwhelming		
			Severe		
			Unbearable		
		1.2 Temporal	Unending		
			Variable		
		2 SENSORY			
		2.1 Constrictive pressure	Binding		
			Clamping		
			Compressing		
			Constricting		
			Cramping		
			Crushing		
			Flattening		
			Gripping		
			Pressing		
			Restricting		
			Squeezing		
			Suppressing		
			Tight		
			Vice-like		
		2.2 Traction pressure	Dragging		
			Drawing		
			Pulling		
			Resisting		
			Tugging		

DYSPNOEA DESCRIPTION LIST - QUESTIONNAIRE

A	B	C	D	E	F
Revision classification of word	Validity classification ✓ or x	Classification	Words	Validity of word ✓ or x	Scale of severity 0-5
		2.3 Torsion pressure	Contorting		
			Distorting		
			Twisting		
		2.4 Expansion pressure	Bloated		
			Bursting		
			Congested		
		2.5 Pain	Aching		
			Agonising		
			Numbing		
			Painful		
			Raw		
			Rough		
			Tingling		
			Uncomfortable		
		2.6 Fluidity	Dry		
			Sweaty		
			Thirsty		
		2.7 Nausea	Gagging		
			Nauseating		
			Sickening		
		2.8 Neurological	Dizziness		
			Faintness		
			Light-headed		
		2.9 Sound Quantity	Muffled		
			Noisy		
			Raucous		

A	B	C	D	E	F
Revision classi-fication of word	Validity classi-fication ✓ or x	Classi-fication	Words	Validity of word ✓ or x	Scale of severity 0-5
		2.10 Dry sound	Hissing		
			Hoarse		
			Moaning		
			Rasping		
			Stertorous		
			Strident		
			Wheezy		
		2.11 Wet sound	Bubbling		
			Gurgling		
			Rattling		
		2.12 Energy	Exhausting		
			Fatiguing		
			Spent		
			Tiring		
		2.13 Thermal	Cold		
			Hot		
		2.14 Air quantity	Air-hunger		
			Airless		
			Breathless		
			Broken-winded		
			Out-of-breath		
			Puffed		
			Punctured		
			Short-of-breath		
			Winded		
		2.15 Dullness	Dull		
			Heavy		
			Thick		

DYSPNOEA DESCRIPTION LIST - QUESTIONNAIRE

A	B	C	D	E	F
Revision classification of word	Validity classification ✓ or x	Classification	Words	Validity of word ✓ or x	Scale of severity 0-5
		3 MOTOR			
		3.1 Respiratory effort	Blowing		
			Coughing		
			Effort		
			Gasping		
			Gulping		
			Heaving		
			Panting		
			Shallow		
			Sighing		
			Spluttering		
			Straining		
			Yawning		
		3.2 Loss of power	Disabling		
			Handicapping		
			Immobilising		
			Weak		
		4 AFFECTIVE			
		4.1 Fear	Frightening		
			Fearful		
			Panic		
			Scaring		
			Terrifying		
			Worrying		
		4.2 Depression	Agitating		
			Anguishing		
			Depressing		
			Distressing		
			Emptiness		
			Intolerable		
			Miserable		
			Wretched		

DYSPNOEA DESCRIPTION LIST - QUESTIONNAIRE

A	B	C	D	E	F
Revision classi-fication of word	Validity classi-fication ✓ or x	Classi-fication	Words	Validity of word ✓ or x	Scale of severity 0-5
		4.3 Claustrophobia	Claustrophobic		
			Shut-in		
			Trapped		
		4.4 Dread	Desperate		
			Doom-laden		
			Dreadful		
			Horrible		
			Terrible		
		4.5 Punishment	Gruelling		
			Harsh		
			Punishing		
			Racking		
			Torturing		
		5 MORTALITY 5.1 Loss of life	Dangerous		
			Dying		
			Expiring		
			Killing		
			Lethal		
			Murderous		
		5.2 Suffocation	Asphyxiating		
			Choking		
			Drowning		
			Stifling		
			Strangling		
			Suffocating		
			Throttling		
		5.3 Illness	Asthmatic		
			Bronchitic		
			Chesty		

ANALYSIS DYSPNOEA WORDS - 33 FORMS RETURNED

CLASS	WORD	WORD CONSIDERED VALID DESCRIPTOR	% VALIDITY
1.1.1	Awful	31	94.0
2	Bad	31	94.0
3	Difficult	27	81.8
4	Extreme	26	78.8
5	Mild	27	81.8
6	Moderate	27	81.8
7	Overwhelming	25	75.8
8	Severe	29	87.9
9	Unbearable	30	91.0
1.2.1	Unending	28	84.8
2	Variable	30	91.0
2.1.1	Binding	18	54.5
2	Clamping	19	57.6
3	Compressing	29	87.9
4	Constricting	31	94.0
5	Cramping	18	54.5
6	Crushing	28	87.8
7	Flattening	16	48.5
8	Gripping	25	75.8
9	Pressing	25	75.8
10	Restricting	31	94.0
11	Squeezing	28	84.8
12	Suppressing	14	42.4
13	Tight	32	97.0
14	Vice-like	26	78.8
2.2.1	Dragging	21	63.6
2	Draining	15	45.4
3	Pulling	19	57.6
4	Resisting	17	51.5
5	Tugging	22	66.7
2.3.1	Contorting	7	21.2
2	Distorting	8	24.2
3	Twisting	14	42.4

CLASS	WORD	WORD CONSIDERED VALID DESCRIPTOR	% VALIDITY
2.4.1	Bloated	22	66.7
2	Bursting	26	78.8
3	Congested	22	66.7
2.5.1	Aching	25	75.8
2	Agonising	28	84.8
3	Numbing	17	51.5
4	Painful	23	69.7
5	Raw	21	63.6
6	Rough	17	51.5
7	Tingling	16	48.5
8	Uncomfortable	31	94.0
2.6.1	Dry	20	60.6
2	Sweaty	14	42.4
3	Thirsty	13	39.4
2.7.1	Gagging	16	48.5
2	Nauseating	22	66.7
3	Sickening	22	66.7
2.8.1	Dizziness	22	66.7
2	Faintness	20	60.6
3	Light-headed	22	66.7
2.9.1	Muffled	17	51.5
2	Noisy	30	91.0
3	Raucous	19	57.6
2.10.1	Hissing	16	48.5
2	Hoarse	22	66.7
3	Moaning	15	45.4
4	Rasping	27	81.8
5	Stertorous	28	84.8
6	Strident	26	78.8
7	Wheezy	33	100.0
2.11.1	Bubbling	29	87.9
2	Gurgling	25	75.8
3	Rattling	31	94.0
2.12.1	Exhausting	31	94.0
2	Fatiguing	31	94.0
3	Spent	20	60.6
4	Tiring	31	94.0

CLASS	WORD	WORD CONSIDERED VALID DESCRIPTOR	% VALIDITY
2.13.1	Cold	16	48.5
2	Hot	17	51.5
2.14.1	Air-hunger	28	84.8
2	Airless	26	78.8
3	Breathless	33	100.0
4	Broken-winded	20	60.6
5	Out of breath	33	100.0
6	Puffed	33	100.0
7	Punctured	13	39.4
8	Short of breath	33	100.0
9	Winded	32	97.0
2.15.1	Dull	17	51.5
2	Heavy	22	66.7
3	Thick	17	51.5
3.1.1	Blowing	25	75.8
2	Coughing	22	66.7
3	Effort	26	78.8
4	Gasping	33	100.0
5	Gulping	24	72.7
6	Heaving	29	87.9
7	Panting	33	100.0
8	Shallow	30	91.0
9	Sighing	27	81.8
10	Spluttering	20	60.6
11	Straining	28	84.8
12	Yawning	17	51.5
3.2.1	Disabling	30	91.0
2	Handicapping	27	81.8
3	Immobilising	28	84.8
4	Weak	23	69.7
4.1.1	Frightening	31	94.0
2	Fearful	30	91.0
3	Panic	31	94.0
4	Scaring	29	87.9
5	Terrifying	30	91.0
6	Worrying	31	94.0

CLASS	WORD	WORD CONSIDERED VALID DESCRIPTOR	% VALIDITY
4.2.1	Agitating	26	78.8
2	Anguishing	24	72.7
3	Depressing	26	78.8
4	Distressing	31	94.0
5	Emptiness	12	36.4
6	Intolerable	29	87.9
7	Miserable	26	78.8
8	Wretched	24	72.7
4.3.1	Claustrophobic	27	81.8
2	Shut-in	28	84.8
3	Trapped	28	84.8
4.4.1	Desperate	27	81.8
2	Doom-laden	15	45.4
3	Dreadful	29	87.9
4	Horrible	27	81.8
5	Terrible	28	84.8
4.5.1	Gruelling	23	69.7
2	Harsh	23	69.7
3	Punishing	23	69.7
4	Racking	25	75.8
5	Torturing	24	72.7
5.1.1	Dangerous	25	75.8
2	Dying	25	75.8
3	Expiring	24	72.7
4	Killing	22	66.7
5	Lethal	21	63.6
6	Murderous	22	66.7
5.2.1	Asphyxiating	32	97.0
2	Choking	32	97.0
3	Drowning	29	87.9
4	Stifling	31	94.0
5	Strangling	31	94.0
6	Suffocating	33	100.0
7	Throttling	28	84.8
5.3.1	Asthmatic	28	84.8
2	Bronchitic	27	81.8
3	Chesty	31	94.0

ANALYSIS DYSPNOEA WORDS

≥ 85% validity words. Each class listed in order of severity.

33 questionnaires analysed. 16 classes. Total 43 words.

CLASS	WORD	WORD AGREED VALID		SEVERITY (0-5)		CLASS AGREED	
		No	%	Total	Mean	No	%
1. Quantitative							
1.1. Intensity	Bad	31	94.0	100	3.03	32	97.0
	Severe	29	87.9	125	3.79	33	100.0
	Awful	31	94.0	127	3.85	33	100.0
	Unbearable	30	91.0	156	4.73	32	97.0
1.2. Temporal	Variable	30	91.0	70	2.12	33	100.0
2. Sensory							
2.1 Constrictive pressure	Restricting	31	94.0	88	2.67	32	97.0
	Tight	32	97.0	96	2.91	33	100.0
	Compressing	29	87.9	99	3.00	33	100.0
	Constricting	31	94.0	102	3.09	33	100.0
2.5 Pain	Uncomfortable	31	94.0	61	1.85	31	94.0
2.9 Sound quantity	Noisy	30	91.0	91	2.76	33	100.0
2.10 Dry sound	Wheezy	33	100.0	99	3.00	32	97.0
2.11 Wet sound	Bubbling	29	87.9	105	3.18	33	100.0
	Rattling	31	94.0	115	3.48	33	100.0
2.12 Energy	Tiring	31	94.0	78	2.36	33	100.0
	Fatiguing	31	94.0	101	3.06	33	100.0
	Exhausting	31	94.0	130	3.94	33	100.0
2.14 Air Quantity	Short of breath	33	100.0	82	2.48	32	97.0
	Puffed	33	100.0	83	2.51	32	97.0
	Out of breath	33	100.0	86	2.61	32	97.0

CLASS	WORD	WORD AGREED VALID		SEVERITY (0-5)		CLASS AGREED	
		No	%	Total	Mean	No	%
2.14 Air Quantity (cont'd)	Winded	32	97.0	93	2.82	33	100.0
	Breathless	33	100.0	100	3.03	33	100.0
3. Motor							
3.1 Respiratory effort	Shallow	30	91.0	78	2.36	31	94.0
	Heaving	29	87.9	106	3.21	32	97.0
	Panting	33	100.0	107	3.24	32	97.0
	Gasping	33	100.0	131	3.97	32	97.0
3.2 Loss of power	Disabling	30	91.0	120	3.64	32	97.0
4. Affective							
4.1 Fear	Worrying	31	94.0	86	2.61	32	97.0
	Scaring	29	87.9	111	3.36	32	97.0
	Fearful	30	91.0	117	3.54	32	97.0
	Frightening	31	94.0	123	3.73	32	97.0
	Terrifying	30	91.0	149	4.51	32	97.0
	Panic	31	94.0	149	4.51	32	97.0
4.2 Depression	Distressing	31	94.0	103	3.12	29	87.9
	Intolerable	29	87.9	146	4.42	29	87.9
4.4 Dread	Dreadful	29	87.9	118	3.58	31	94.0
5. Mortality							
5.2 Suffocation	Stifling	31	94.0	109	3.30	32	97.0
	Strangling	31	94.0	135	4.09	32	97.0
	Choking	32	97.0	136	4.12	32	97.0
	Drowning	29	87.9	138	4.18	31	94.0
	Suffocating	33	100.0	142	4.30	32	97.0
	Asphyxiating	32	97.0	152	4.61	32	97.0
5.3 Illness	Chesty	31	94.0	77	2.33	31	94.0

DYSPNOEA ASSESSMENT QUESTIONNAIRE

NAME: ..... DATE: ..... TRIAL NO: .....

Some of the words below may describe your breathlessness over the last 24 hours. Please look at each group of words in turn and tick one word from each group which best describes your breathlessness. If none of the words in a group fits, leave out that category and move on to the next one.

1. Bad ☐
   Severe ☐
   Awful ☐
   Unbearable ☐

2. Variable ☐

3. Restricting ☐
   Tight ☐
   Compressing ☐
   Constricting ☐

4. Uncomfortable ☐

5. Noisy ☐

6. Wheezy ☐

7. Bubbling ☐
   Rattling ☐

8. Tiring ☐
   Fatiguing ☐
   Exhausting ☐

9. Short of breath ☐
   Puffed ☐
   Out of breath ☐
   Winded ☐
   Breathless ☐

10. Shallow ☐
    Heaving ☐
    Panting ☐
    Gasping ☐

11. Disabling ☐

12. Worrying ☐
    Scaring ☐
    Fearful ☐
    Frightening ☐
    Terrifying ☐
    Panic ☐

13. Distressing ☐
    Intolerable ☐

14. Dreadful ☐

15. Stifling ☐
    Strangling ☐
    Choking ☐
    Drowning ☐
    Suffocating ☐
    Asphyxiating ☐

16. Chesty ☐

_____ // _____

Which of all the above words best describes your breathlessness?

....

DAQ SEVERITY SCORING (SS)

Category	Word	SS	Category	Word	SS
1.	Bad	3.03	11.	Disabling	3.64
	Severe	3.79			
	Awful	3.85	12.	Worrying	2.61
	Unbearable	4.73		Scaring	3.36
				Fearful	3.54
2.	Variable	2.12		Frightening	3.73
				Terrifying	4.51
3.	Restricting	2.67		Panic	4.51
	Tight	2.91			
	Compressing	3.00	13.	Distressing	3.12
	Constricting	3.09		Intolerable	4.42
4.	Uncomfortable	1.85	14.	Dreadful	3.58
5.	Noisy	2.76	15.	Stifling	3.30
				Strangling	4.09
6.	Wheezy	3.00		Choking	4.12
				Drowning	4.18
7.	Bubbling	3.18		Suffocating	4.30
	Rattling	3.48		Asphyxiating	4.61
8.	Tiring	2.36	16.	Chesty	2.33
	Fatiguing	3.06			
	Exhausting	3.94			
9.	Short of breath	2.48			
	Puffed	2.51			
	Out of breath	2.61			
	Winded	2.82		Maximum possible score	
	Breathless	3.03		= 55.06	
10.	Shallow	2.36			
	Heaving	3.21			
	Panting	3.24			
	Gasping	3.97			

DAQ CLASS SCORING (CS)

Category	Word	CS	Category	Word	CS
1.	Bad	1	11.	Disabling	1
	Severe	2			
	Awful	3	12.	Worrying	1
	Unbearable	4		Scaring	2
				Fearful	3
2.	Variable	1		Frightening	4
				Terrifying	5
3.	Restricting	1		Panic	6
	Tight	2			
	Compressing	3	13.	Distressing	1
	Constricting	4		Intolerable	2
4.	Uncomfortable	1	14.	Dreadful	1
5.	Noisy	1	15.	Stifling	1
				Strangling	2
6.	Wheezy	1		Choking	3
				Drowning	4
7.	Bubbling	1		Suffocating	5
	Rattling	2		Asphyxiating	6
8.	Tiring	1	16.	Chesty	1
	Fatiguing	2			
	Exhausting	3			
9.	Short of breath	1			
	Puffed	2			
	Out of breath	3			
	Winded	4		Maximum possible score	
	Breathless	5		= 43	
10.	Shallow	1			
	Heaving	2			
	Panting	3			
	Gasping	4			

DAQ INTERVAL SCORING (IS)

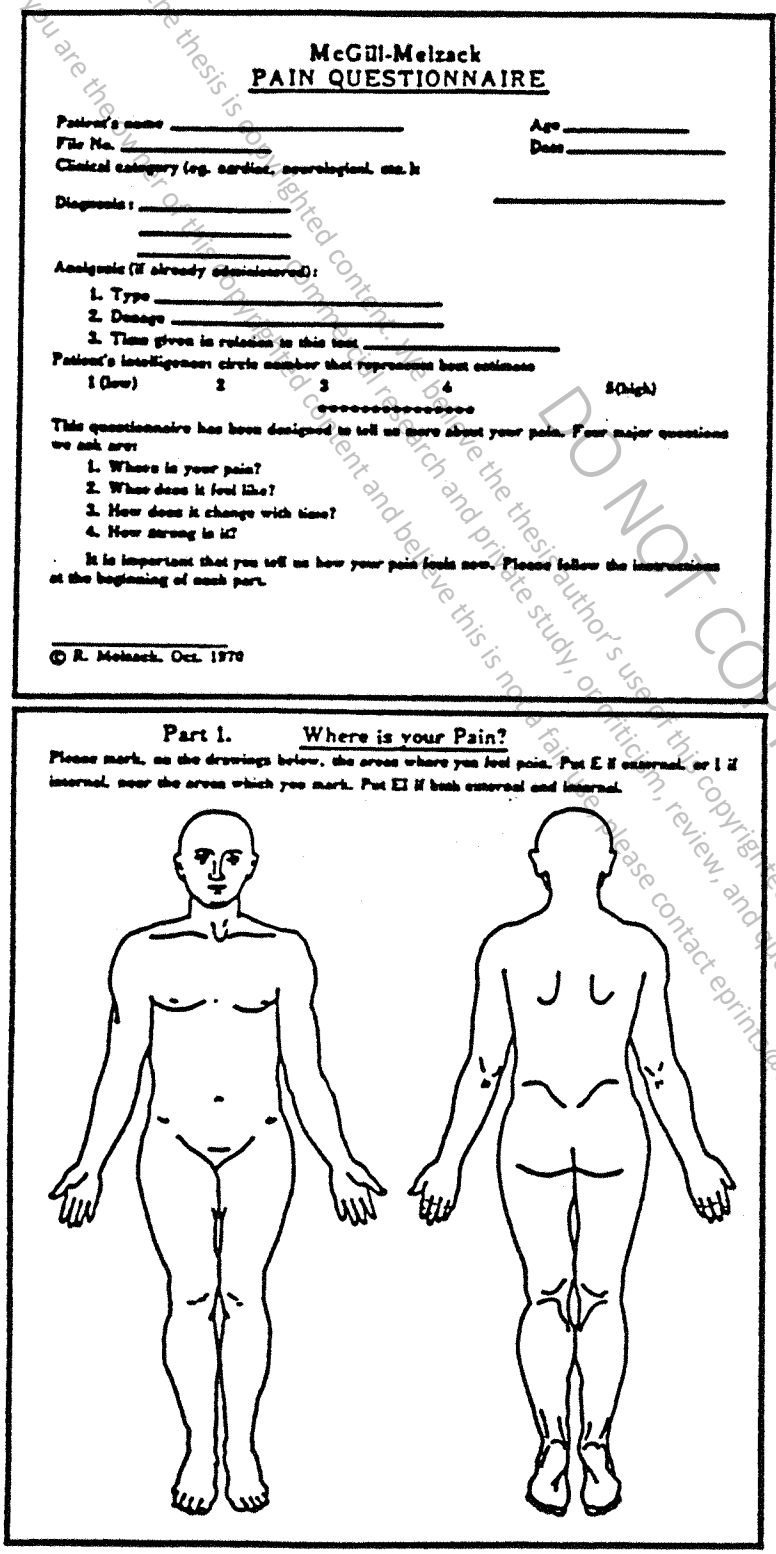
Category	Word	IS	Category	Word	IS
1.	Bad	1.00	11.	Disabling	2.50
	Severe	2.00			
	Awful	3.00	12.	Worrying	0.71
	Unbearable	4.00		Scaring	1.43
				Fearful	2.14
2.	Variable	2.50		Frightening	2.86
				Terrifying	3.57
3.	Restricting	1.00		Panic	4.28
	Tight	2.00			
	Compressing	3.00	13.	Distressing	1.67
	Constricting	4.00		Intolerable	3.33
4.	Uncomfortable	2.50	14.	Dreadful	2.50
5.	Noisy	2.50	15.	Stifling	0.71
				Strangling	1.43
6.	Wheezy	2.50		Choking	2.14
				Drowning	2.86
7.	Bubbling	1.67		Suffocating	3.57
	Rattling	3.33		Asphyxiating	4.28
8.	Tiring	1.25	16.	Chesty	2.50
	Fatiguing	2.50			
	Exhausting	3.75			
9.	Short of breath	0.83			
	Puffed	1.67			
	Out of breath	2.50			
	Winded	3.33		Maximum possible score	
	Breathless	4.17		= 52.64	
10.	Shallow	1.00			
	Heaving	2.00			
	Panting	3.00			
	Gasping	4.00			

DYSPNOEA EXERTION SCALE (DES)

Which is the furthest statement down the list that applies to you?

Statement	Scoring (NB patient does not see the scoring
I am able to walk at my own pace on the level without getting breathless over any distance	0
I become breathless if I walk more than 100 yards on the level at my own pace	1
I become breathless if I walk around the house or on the ward on the level at my own pace	2
I become breathless if I move around in bed or get out of bed	3
I become breathless on talking	4
I am breathless at rest	5

7.2 APPENDIX 2 - The McGill-Melzack pain questionnaires



McGill-Melzack
PAIN QUESTIONNAIRE

Patient's name _____ Age _____
File No. _____ Date _____
Clinical category (eg. cardiac, neurological, etc.):
Diagnosis: _____
_____
_____
Analgesic (if already administered):
1. Type _____
2. Dosage _____
3. Time given in relation to this test _____
Patient's intelligence: circle number that represents best estimate
1 (low) 2 3 4 5 (high)

This questionnaire has been designed to tell us more about your pain. Four major questions we ask are:
1. Where is your pain?
2. What does it feel like?
3. How does it change with time?
4. How strong is it?

It is important that you tell us how your pain feels now. Please follow the instructions at the beginning of each part.

© R. Melzack, Oct. 1970

Part 1. Where is your Pain?

Please mark, on the drawings below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.

McGill Pain Questionnaire.

Part 2. What Does Your Pain Feel Like?

Some of the words below describe your present pain. Circle ONLY those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category—the one that applies best.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	**6**	**7**	**8**
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	**10**	**11**	**12**
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	**14**	**15**	**16**
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	**18**	**19**	**20**
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part 3. How Does Your Pain Change With Time?

1. Which word or words would you use to describe the pattern of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2. What kind of things relieve your pain?

3. What kind of things increase your pain?

Part 4. How Strong Is Your Pain?

People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? ________
2. Which word describes it at its worst? ________
3. Which word describes it when it is least? ________
4. Which word describes the worst toothache you ever had? ________
5. Which word describes the worst headache you ever had? ________
6. Which word describes the worst stomach-ache you ever had? ________

2.

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN ——— WORST POSSIBLE PAIN

P P I

0 NO PAIN _____
1 MILD _____
2 DISCOMFORTING _____
3 DISTRESSING _____
4 HORRIBLE _____
5 EXCRUCIATING _____

Fig. 1. The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1–11 represent the sensory dimension of pain experience and 12–15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue (VAS) are also included to provide overall intensity scores.

7.3 APPENDIX 3 - Main study data collection - initial forms

EXPLANATION OF PROJECT - TO GO WITH CONSENT FORM

The purpose of this project is to discover how much of a problem breathlessness is in people admitted to Countess Mountbatten House, what the cause of the breathlessness is, and to look at ways of measuring breathlessness. Records will also be kept of treatment given during admission here.

We would like to ask you if you would be prepared to take part in this project. It would mean the following:

* Completing some questionnaires with the help of the Research Assistant or Doctor.

* Carrying out some simple breathing tests.

* A visit once a week by the Research Assistant or Doctor to check how your breathing is getting on.

* If breathlessness is not a problem to you, then a phone call once a week to your home to check how the breathing is getting on.

* A chest x-ray may be needed.

* Providing a urine sample for testing.

All information gained will be treated completely confidentially.

This study will not adversely affect the treatment you are having here. It may actually help by making us more aware of any problems and hence providing better treatment.

You can of course withdraw from the study at any time if you so wish.

CONSENT FORM

TITLE OF TRIAL: **DYSPNOEA RESEARCH PROJECT**

I, ..., understand the aim of this study.
It has been explained to me by .....
and the following points were included:

The purpose and length of this study.
What I am being asked to do.
The possible side-effects of any treatment given.

I also understand that I may withdraw from the study at any time if I wish to do so.

Signed: .....

Date: .....

DYSPNOEA RESEARCH PROJECT - DEMOGRAPHIC DATA

NAME: ..... TRIAL NO: .....

DATE COMPLETED: ..... BY: .....

D.O.B: ..... AGE: ..... SEX: ..... STATUS: .....

ADDRESS:

.....

.....

.....

.....

TEL. NO: .....

G.P: ..... G.P. TEL. NO: .....

C.M.H. CONSULTANT: .....

MAIN OCCUPATION: .....

LIVED ABROAD (SPECIFY): ..... RACE: .....

SMOKING (Present) Yes No

SMOKING (Past) Yes No

ASBESTOS EXPOSURE (ie dusty atmosphere) Yes

None known

MAIN PLACE OF ABODE: Country/village

Town/city

Other (specify)

DATE ADMISSION: / ..... / ..... / ..... / ..... / ..... /

DATE DISCHARGED: / ..... / ..... / ..... / ..... / ..... /

DATE DIED: .....

PLACE DIED: .....

RESEARCHER DATA SHEET - CASENOTES

PATIENT'S NAME: ..... TRIAL NO: .....

1. SITE(S) PRIMARY TUMOUR
   .....
   .....

   HISTOLOGY
   .....
   .....

2. LUNG / PLEURAL METS
   L, P or L/P
   .....
   .....

   HOW DIAGNOSED
   CXR = X, Histology = H, Visual = V, Sputum cytology = SC, Pleural cytology = PC
   .....
   .....

3. SITE(S) OTHER METS
   .....
   .....

   HOW DIAGNOSED
   .....
   .....

4. Cough and sputum continuously for 3 months or more per year for 2 or more years

   Yes ☐ Date: .....
   No ☐

5. Reversible airways obstruction on spirometry

   Yes ☐ Date: .....
   No ☐

6. E.C.G. Date: .....

   M.I. or ischaemia Yes ☐
   No ☐

   Other findings: .....
   .....

7. V.Q. Scan Date: .....

   Results: .....
   .....
   .....

8. CXR: DATE LAST CXR: .....

REPORT: .....
.....
.....
.....

	Yes	No
PULMONARY OEDEMA	☐	☐
UPPER LOBE DIVERSION	☐	☐
KERLEY B LINES	☐	☐
CARDIOMEGALY	☐	☐
PRIMARY TUMOUR	☐	☐
SECONDARY TUMOUR	☐	☐
CONSOLIDATION	☐	☐
EFFUSION	☐	☐

9. OTHER PATHOLOGY

TYPE	DIAGNOSIS	HOW DIAGNOSED
CARDIO-VASCULAR DISEASE		
RESPIRATORY DISEASE		
NEURO MUSCULAR DISEASE		
PSYCHIATRIC ILLNESS		

TREATMENT RECORD

NAME: .... TRIAL NO: ....

ADMISSION DATE: ....

DRUG	DOSAGE BEFORE ADMISSION	DOSE RANGE DURING ADMISSION	DISCHARGE DOSAGE

TYPE	DATE CARRIED OUT

RESEARCHER DATA SHEET - INVESTIGATIONS AT C.M.H.

NAME: ..... TRIAL NO: .....

1. CXR: DATE: .....

REPORT: .....

.....

.....

.....

	YES	NO
PULMONARY OEDEMA	☐	☐
UPPER LOBE DIVERSION	☐	☐
KERLEY B LINES	☐	☐
CARDIOMEGALY	☐	☐
PRIMARY TUMOUR	☐	☐
SECONDARY TUMOUR	☐	☐
CONSOLIDATION	☐	☐
EFFUSION	☐	☐

2. SPIROMETRY DATE: ..... TIME: .....

TEST	PRE-SALBUTAMOL	POST-SALBUTAMOL
FEV_1	.....	.....
FVC	.....	.....
FEV_1/FVC %	.....	.....

3. BLOODS

TEST	DATE	RESULT
HB	.....	.....
HCO_3	.....	.....
UREA	.....	.....

OTHER BLOOD RESULTS: .....

.....

4. HYPERVENTILATION TEST DATE: .....

RESULT: .....POS/NEG

5. C.C.E.I. SCORE

ANXIETY: .....

PHOBIA: .....

OBSESSION: .....

SOMATIC: .....

DEPRESSION: .....

HYSTERIA: .....

6. AUTOPSY RESULT

	YES	NO
LUNG PRIMARY	☐	☐
PLEURAL PRIMARY	☐	☐
LUNG METASTASES	☐	☐
PLEURAL METASTASES	☐	☐
TUMOUR EMBOLI ON LUNG SECTION	☐	☐

HISTOLOGY .....

OTHER FINDINGS: .....

.....

.....

.....

.....

.....

.....

.....

7. OTHER INVESTIGATIONS: .....

.....

.....

.....

.....

.....

.....

Resting pulse rate ..... B.P.M. Date: .....

Resting Respiratory Frequency ..... Breaths/min Date: .....

Temperature ..... °C Date: .....

Urine: - Date: .....

pH

Ketones yes ☐ no ☐

Sugar yes ☐ no ☐

DYSPNOEA TRIAL

NURSE'S QUESTIONNAIRE - TO BE COMPLETED ON ADMISSION

PATIENT'S NAME: ..... DATE: .....

NURSE: .....

Please mark on this scale your impression of the average level of breathlessness the patient has experienced over the last 24 hours.

Not at all breathless ——————————————— Extreme breathlessness

(NB VAS not to scale in this copy)

DOCTOR'S QUESTIONNAIRE - TO BE COMPLETED ON ADMISSION

PATIENT'S NAME: ..... DATE: .....

DOCTOR: .....

	Yes	No
1. Does this patient have any problems with breathlessness?	☐	☐
2. Has there been cough + sputum continuously for 3 or more months in a year for two consecutive years?	☐	☐
3. Is there a cough with purulent sputum?	☐	☐
4. Is there any wheezing?	☐	☐
5. Are there any of the following?		
(a) Raised J.V.P.	☐	☐
(b) Dependent oedema	☐	☐
(c) Basal respiratory crackles	☐	☐
(d) Rhonchi	☐	☐
(e) Stridor	☐	☐
6. Is the hyperventilation syndrome a possible diagnosis in this patient?	☐	☐

7. Please specify any other abnormal respiratory findings:

(NB VAS not to scale in this copy)

8. Please mark on this scale your impression of the average level of breathlessness the patient has experienced over last 24 hours?

Not at all breathless ——————————————— Extreme Breathlessness

PLEASE ENSURE THAT THE FOLLOWING ARE ARRANGED:

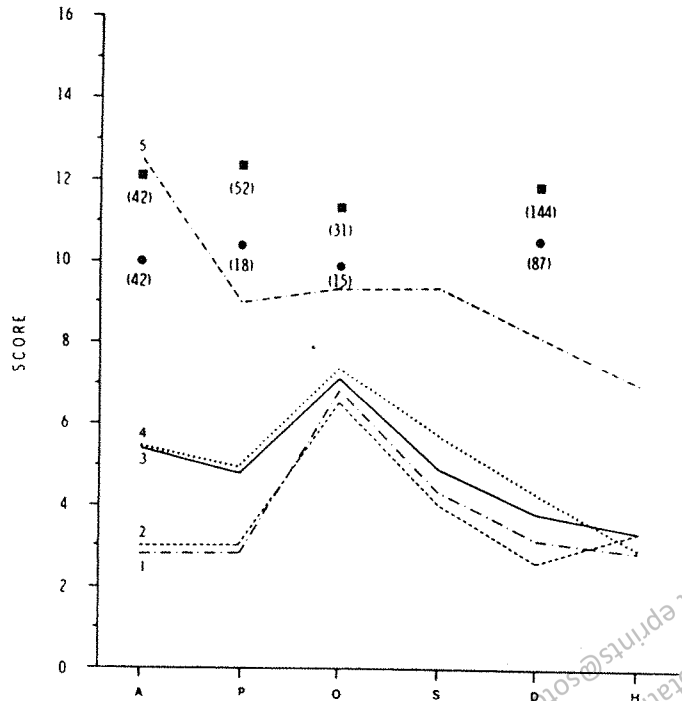
F.B.C. + ELECTROLYTES

CXR (IF NOT WITHIN LAST WEEK, AND CLINICALLY INDICATED)

For office use only

A ..... O ..... D .....

P ..... S ..... H .....



Refer to Figure 1 in the Manual (p. 10) for profile data

Fourth impression 1985

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CROWN-CRISP EXPERIENTIAL INDEX

SURNAME ..... AGE .....

FIRST NAME(S) .....

TODAY'S DATE ..... SEX .....

Instructions

The questions overleaf are concerned with the way you feel or act. They are all simple. Please *tick* the answer that applies to you. Don't spend long on any one question.

Hodder and Stoughton

Crown-Crisp Experiential Index — Template

1. Do you often feel upset for no obvious reason? *Yes* 2 *No* 0 — A
2. Do you have an unreasonable fear of being in enclosed spaces such as shops, lifts, etc? *Often* 2 *Sometimes* 1 *Never* 0 — P
3. Do people ever say you are too conscientious? *No* 0 *Yes* 2 — O
4. Are you troubled by dizzyness or shortness of breath? *Never* 0 *Often* 2 *Sometimes* 1 — S
5. Can you think as quickly as you used to? *Yes* 0 *No* 2 — D
6. Are your opinions easily influenced? *Yes* 2 *No* 0 — H
7. Have you felt as though you might faint? *Frequently* 2 *Occasionally* 1 *Never* 0 — A
8. Do you find yourself worrying about getting some incurable illness? *Never* 0 *Sometimes* 1 *Often* 2 — P
9. Do you think that 'cleanliness is next to godliness'? *No* 0 *Yes* 2 — O
10. Do you often feel sick or have indigestion? *Yes* 2 *No* 0 — S
11. Do you feel that life is too much effort? *At times* 1 *Often* 2 *Never* 0 — D
12. Have you, at any time in your life, enjoyed acting? *Yes* 2 *No* 0 — H
13. Do you feel uneasy and restless? *Frequently* 2 *Sometimes* 1 *Never* 0 — A
14. Do you feel more relaxed indoors? *Definitely* 2 *Sometimes* 1 *Not particularly* 0 — P
15. Do you find that silly or unreasonable thoughts keep recurring in your mind? *Frequently* 2 *Sometimes* 1 *Never* 0 — O
16. Do you sometimes feel tingling or pricking sensations in your body, arms or legs? *Rarely* 1 *Frequently* 2 *Never* 0 — S
17. Do you regret much of your past behaviour? *Yes* 2 *No* 0 — D
18. Are you normally an excessively emotional person? *Yes* 2 *No* 0 — H
19. Do you sometimes feel really panicky? *No* 0 *Yes* 2 — A
20. Do you feel uneasy travelling on buses or the Underground even if they are not crowded? *Very* 2 *A little* 1 *Not at all* 0 — P
21. Are you happiest when you are working? *Yes* 2 *No* 0 — O
22. Has your appetite got less recently? *No* 0 *Yes* 2 — S
23. Do you wake unusually early in the morning? *Yes* 2 *No* 0 — D
24. Do you enjoy being the centre of attention? *No* 0 *Yes* 2 — H

CCEI Template ***page one***

Crown-Crisp Experiential Index — Template

25. Would you say you were a worrying person? *Very* 2 *Fairly* 1 *Not at all* 0 — A
26. Do you dislike going out alone? *Yes* 2 *No* 0 — P
27. Are you a perfectionist? *No* 0 *Yes* 2 — O
28. Do you feel unduly tired and exhausted? *Often* 2 *Sometimes* 1 *Never* 0 — S
29. Do you experience long periods of sadness? *Never* 0 *Often* 2 *Sometimes* 1 — D
30. Do you find that you take advantage of circumstances for your own ends? *Never* 0 *Sometimes* 1 *Often* 2 — H
31. Do you often feel 'strung-up' inside? *Yes* 2 *No* 0 — A
32. Do you worry unduly when relatives are late coming home? *No* 0 *Yes* 2 — P
33. Do you have to check things you do to an unnecessary extent? *Yes* 2 *No* 0 — O
34. Can you get off to sleep alright at the moment? *No* 2 *Yes* 0 — S
35. Do you have to make a special effort to face up to a crisis or difficulty? *Very much so* 2 *Sometimes* 1 *Not more than anyone else* 0 — D
36. Do you often spend a lot of money on clothes? *Yes* 2 *No* 0 — H
37. Have you ever had the feeling you were 'going to pieces'? *Yes* 2 *No* 0 — A
38. Are you scared of heights? *Very* 2 *Fairly* 1 *Not at all* 0 — P
39. Does it irritate you if your normal routine is disturbed? *Greatly* 2 *A little* 1 *Not at all* 0 — O
40. Do you often suffer from excessive sweating or fluttering of the heart? *No* 0 *Yes* 2 — S
41. Do you find yourself needing to cry? *Frequently* 2 *Sometimes* 1 *Never* 0 — D
42. Do you enjoy dramatic situations? *Yes* 2 *No* 0 — H
43. Do you have bad dreams which upset you when you wake up? *Never* 0 *Sometimes* 1 *Frequently* 2 — A
44. Do you feel panicky in crowds? *Always* 2 *Sometimes* 1 *Never* 0 — P
45. Do you find yourself worrying unreasonably about things that do not really matter? *Never* 0 *Frequently* 2 *Sometimes* 1 — O
46. Has your sexual interest altered? *Less* 2 *The same or greater* 0 — S
47. Have you lost your ability to feel sympathy for other people? *No* 0 *Yes* 2 — D
48. Do you sometimes find yourself posing or pretending? *Yes* 2 *No* 0 — H

PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

CCEI Template ***page two***

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7.4 APPENDIX 4 - Main study data collection - dyspnoea forms

For the Dyspnoea Assessment Questionnaire (DAQ) please see p 209.

DYSPNOEA QUESTIONNAIRE 1

QUANTITATIVE AND QUALITATIVE ASPECTS

NAME: ..... TRIAL NO: .....

INTERVIEWER: ..... DATE COMPLETED: .....

1. (a) Please mark on this scale (presented) the average level of breathlessness you have experienced over the last 24 hours. ..... mm

(b) Please mark on this scale (presented) the worst level of breathlessness you have experienced over the last week. ..... mm

2. Which of these words applies best for your breathlessness over the last 24 hours. (present card or read if poor vision)

0	None	☐
1	Mild	☐
2	Moderate	☐
3	Severe	☐
4	Very severe	☐
5	Extreme	☐

3. Which is the furthest statement down this list that applies for you? (present card, or read)

I am able to walk at my own pace on the level without getting breathless over any distance. ☐

I become breathless if I walk more than 100 yards on the level at my own pace. ☐

I become breathless if I walk around the house or on the ward on the level at my own pace. ☐

I become breathless if I move around in bed or get out of bed. ☐

I become breathless on talking. ☐

I am breathless at rest. ☐

/continued...

4. Overall, how long has breathlessness been troublesome to you?

.....

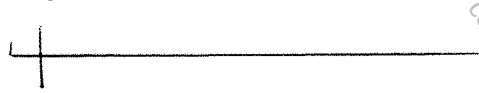
V.A.S. INSTRUCTIONS TO PATIENT

1. We are interested in finding out how breathless you have felt over the last 24 hours. By breathless we mean "shortness of breath", "not getting enough air" - the sort of feeling you may have experienced if rushing to catch a bus or climbing a flight of stairs quickly.

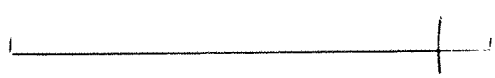
   (Wait for the patient to confirm he understands. If not, try more examples, repeating the above if needed - it is crucial he understands which sensation you are interested in especially as other sensations felt during exercise such as fatigue, aching legs, headache, palpitations etc may get indicated if you are not specific. It may help to tell the patient you are not interested in these other sensations but want to concentrate on his breathlessness.)

2. Explanation of V.A.S.
   This scale allows you to tell us how breathless you have felt on average over the last 24 yours. It is continuous and its two extremes are defined as "not at all breathless" and "as breathless as I could possibly feel". The former is easy to imagine: "not at all" means zero, or none at all. The other end is harder to imagine: "as breathless as I could possibly feel" means the most your breathlessness could ever be - think back to the most breathless you have ever felt in your life: was that the most breathless you could possibly feel or could it have been even worse?

   The scale between these two allows you to show us how breathless you feel. For example:



   This would tell us that you feel a little bit breathless, not very much but more than none at all.



   This would mean you felt very breathless - really very bad but it could still get a little worse.

   This would mean you feel about halfway from none to the worst.

/continued...

If you have not felt breathless over the last 24 hours, make a mark at the zero point. But if you have felt breathless make a mark at a position which shows how breathless you feel.

(confirm the patient understands. Repeat if necessary. If they query breathlessness on exertion, this scale is to test breathlessness which is more than normal exertional breathlessness).

Visual analogue scale for dyspnoea

DYSPNOEA QUESTIONNAIRE 2

CAUSES

NAME: ..... TRIAL NO: .....

INTERVIEWER: ..... DATE: .....

1. In which position, if any, is your breathlessness worse?

Lying down ☐
Sitting up ☐
On side ☐
No difference ☐

2. Is it harder for you to breathe in or to breathe out?

In ☐
Out ☐
No difference ☐

3. What effect does alcohol or sedatives have on your breathlessness?

Better ☐
Worse ☐
No difference ☐

4. What effect does being in a crowded room have on your breathlessness?

Better ☐
Worse ☐
No difference ☐

5. What, if anything, makes your breathlessness better?

.....

.....

6. What, if anything, makes your breathlessness worse?

.....

.....

7. Do you suffer from the following symptoms?

	Yes	No
Tight chest	☐	☐
Chest pain	☐	☐
Dizziness	☐	☐
Light-headedness	☐	☐
Pins and needles	☐	☐
Feeling hot and sweaty	☐	☐
Palpitations	☐	☐
Anxiety	☐	☐

8. Are there any other symptoms that you associate with your breathlessness?

.....

.....

9. i) Do you find your breathlessness varies considerably from time to time for no particular reason? Yes ☐ No ☐

ii) Are you sometimes short of breath at rest and sometimes not? Yes ☐ No ☐

10. Do you find that when you exert yourself sometimes you get breathless and sometimes you don't? Yes ☐ No ☐

11. Is your breathlessness worse at night? Yes ☐ No ☐

12. (a) Does your chest feel tight when you wake up in the morning? Yes ☐ No ☐

(b) If so, for how long? .....

13. Do you develop breathing difficulties when in a smoky room, in traffic fumes, or going from a warm to a cold room?

Yes ☐ No ☐

14. Does anyone in your family have problems with breathlessness?

Yes ☐ No ☐

Relationship	Diagnosis

HYPERVENTILATION TEST - INSTRUCTIONS

SUBJECTS

1. Dyspnoeic patients admitted to C.M.H.
2. FEV_1 > 1 litre on spirometry
3. Suspected of having the Hyperventilation Syndrome, either from the Doctor's questionnaire or from perusal of the completed research questionnaire by L.H.M.

TEST

1. Subject seated comfortably and breathing quietly at rest.
2. Test explained as follows to subject:
   "This is a simple breathing test for finding out the cause of your breathlessness. All you will be asked to do is to take 20 deep breaths like this.....(demonstrate with say 3 or 4 deep breaths at about 1 breath/sec) ..... Breathe in and out as deeply as you can. During the test you may or may not feel some sensations or symptoms. Please indicate straight away by raising your hand the moment you feel any changes, but continue taking deep breaths till you've finished. At the end of 20 deep breaths you will be asked what you feel. Please feel free to stop before the end of the test if you find the symptoms unpleasant."

3. Record after how many breaths the subject raises his/her hand.

4. At the end of the test, ask the subject to describe the sensations/symptoms (s)he experienced if any and note these.

5. Ask if (s)he has had these before in association with breathlessness.

6. If (s)he says there were no symptoms, enquire if (s)he experienced dizziness or light-headedness.

7. If test is positive, inform doctor in charge.

HYPERVENTILATION TEST - RESULTS

NAME: ..... TRIAL NO: .....

DATE AND TIME OF TEST: ..... BY: .....

Number breaths taken to onset symptoms: .....
(ie when hand raised)

(If test aborted) - Number of breaths taken .....

Sensations/symptoms experienced:

.....
.....
.....
.....
.....
.....
.....
.....

Were these sensations/symptoms previously experienced in association with breathlessness?

Yes ☐ No ☐

If the subject denied symptoms, ask if (s)he experienced dizziness or light-headedness?

Yes ☐ No ☐

IF TEST IS POSITIVE, INFORM DOCTOR IN CHARGE.

7.5 APPENDIX 5 - Main study data collection - weekly review forms

DYSPNOEA TRIAL

NAME: ..... TRIAL NO: .....

Please ask at 2nd and subsequent interviews of breathless patients eligible for trial.

Has your breathlessness over the last week:

Improved ☐

Stayed the same ☐

Worsened ☐

DYSPNOEA TRIAL - AUTOPSIES

INFORMATION FOR DOCTORS

This is to let you know that:

.....

Has been entered as eligible for the dyspnoea trial. Should this person die during his or her admission to Countess Mountbatten House, I would be grateful if you could ask permission for an autopsy.

Thank you.

Louis Heyse-Moore.

HMR 104A (Code 90-617)..... HOSPITAL

POST MORTEM DECLARATION FORM

I do not object to a post mortem examination being carried out on the body of .....
and I am not aware that he/she had expressed objection or that another relative objects.

I understand that this examination is carried out:

to verify the cause of death and to study the effects of treatment, which may involve the retention of tissue for laboratory study.

SIGNED

RELATIONSHIP TO DECEASED

WITNESSED BY

Affix Label Here and complete remaining information

Full Names	Unit No.
Date of Birth	
Ward	Consultant

Southampton and South West Hampshire Health District

CLINICAL INFORMATION FOR PATHOLOGIST PERFORMING A POST MORTEM

Date of Admission

Date and Time of Death

Clinical Diagnosis

Short summary of terminal illness and mode of death:
(continue overleaf if necessary)

Special examination required and questions to be answered:

Does the patient have any evidence of contagious disease such as hepatitis or TB? YES/NO

If YES, specify.....

Death certificate issued YES/NO/NOT AVAILABLE

Coroner informed YES/NO

Signature..... Date.....

(NAME - BLOCK LETTERS) Bleep No. .....

This form must be completed by the houseman or registrar for all patients dying in hospital on whom a post mortem is to be performed. It is intended to guide the pathologist about to make the examination, and to indicate the special features requiring investigation.

77/586

7.6 APPENDIX 6 - Hyperventilation Study - forms.

I N F O R M A T I O N A N D I N S T R U C T I O N

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

1. Patients admitted to Countess Mountbatten House.
2. Patients with advanced cancer.
3. Patients of either sex aged 18 or over.
4. Patients willing to give written consent.

EXCLUSION CRITERIA

1. Patients too ill to take part.
2. Confused patients.
3. Patients with expressive or receptive dysphasia.

1. Subject seated comfortably and breathing quietly at rest.

2. Test explained as follows to subject:

   "This is a simple test for diagnosing breathing problems. All you will be asked to do is to take 20 deep breaths like this.....(demonstrate with say 3 or 4 deep breaths at about 1 breath/sec) ..... Breathe in and out as deeply as you can. During the test you may or may not feel some sensations or symptoms. Please indicate straight away by raising your hand the moment you feel any changes, but continue taking deep breaths till you have finished. At the end of 20 deep breaths, you will be asked what you feel. Please feel free to stop before the end of the test if you find the symptoms unpleasant."

3. Record after how many breaths the subject raises his/her hand.

4. At the end of the test, ask the subject to describe the sensations/symptoms (s)he experienced if any and note these.

5. Ask if (s)he has had these before in association with breathlessness.

6. If (s)he says there were no symptoms, enquire if (s)he experienced dizziness or light-headedness.

NAME:

TRIAL NUMBER:

DATE ADMISSION:

BASELINE DATA

DOB: AGE: SEX:

DIAGNOSIS:

KNOWN LUNG METASTASES: T ☐ F ☐

OTHER KNOWN LUNG PATHOLOGY (SPECIFY)

DYSPNOEA (please ask - "Do you have any problem with breathlessness?")

T ☐ F ☐

ELIGIBLE? (see instructions) T ☐ F ☐

If eligible, proceed to page 3. Explain test to patient and obtain consent.

If not eligible, please return forms to Dr Heyse-Moore

TEST RESULTS

DATE OF TEST: ..... BY: .....

Number breaths taken to onset symptom:.....
(ie when hand raised)

(If test aborted) - Number of breaths taken: .....

Sensations/symptoms experienced:

.....

.....

.....

.....

.....

.....

.....

.....

Were these sensations/symptoms previously experienced in association with breathlessness? YES ☐ NO ☐

If the subject denied symptoms, ask if (s)he experienced dizziness or light-headedness? YES ☐ NO ☐

WHEN COMPLETED, PLEASE RETURN FORMS TO DR HEYSE-MOORE.

Please leave this section blank

RESULT HVT POS ☐ NEG ☐

7.7 APPENDIX 7 - Causes of dyspnoea in advanced cancer

APPENDIX 7

CAUSES OF DYSPNOEA IN ADVANCED CANCER

1. **Increased ventilatory demand**
   - 1.1 Fever
     - 1.1.1. Sepsis
     - 1.1.2. Tumour induced
   - 1.2 Exercise
   - 1.3 Anxiety
   - 1.4 Anaemia
     - 1.4.1. Nutritional deficiencies
     - 1.4.2. Bone marrow suppression (chemotherapy or marrow infiltration by tumour)
     - 1.4.3. Uraemia
     - 1.4.4. Anaemia of malignancy
     - 1.4.5. Haemorrhage (clotting defects or erosion of arteries by tumour)
   - 1.5 Thyrotoxicosis (from TSH producing tumours)
   - 1.6 Delirium (from brain metastases)

2. **Decreased ventilatory capacity**
   - 2.1 Ventilation-perfusion mismatch
     - 2.1.1. Chronic obstructive airways disease
     - 2.1.2. Pulmonary emboli
     - 2.1.3. Pneumonia
     - 2.1.4. Asthma
     - 2.1.5. Pulmonary fibrosis
     - 2.1.6. Pulmonary hypertension
     - 2.1.7. Lymphangitis carcinomatosa
   - 2.2 Airways obstruction
     - 2.2.1. Extramural pressure

/ continued ...

2.2. Airways obstruction (cont'd)

2.2.1.1. Cervical, paratracheal, mediastinal lymph node metastases

2.2.1.2. Primary tumours of the oesophagus, thyroid, thymus, spine or nerves.

2.2.2. Mural

2.2.2.1. Tumours of the respiratory tract (bronchus, trachea, larynx, pharynx or nose)

2.2.2.2. Recurrent laryngeal nerve palsy and vocal cord paralysis

2.2.2.3. Asthma

2.2.2.4. Laryngeal oedema from SVC obstruction

2.2.3. Luminal

2.2.3.1. Transudation from congestive cardiac failure

2.2.3.2. Mucus and pus

2.2.3.3. Blood

2.2.3.4. Inhaled vomit or food from oesophageal tumours causing overflow or a tracheo-oesophageal fistula

2.3. Increased lung stiffness

2.3.1. Pulmonary oedema (eg lymphangitis carcinomatosa

2.3.2. Pulmonary fibrosis (eg asbestosis)

2.3.3. Lung tumours if large or multiple

2.3.4. Asthma

2.3.5. COAD

2.4. Loss of elastic lung recoil

2.4.1. Emphysema

2.5. Painful chest lesions

2.5.1. Pleurisy

2.5.2. Fractured ribs / continued ...

2.6. Loss of functioning lung tissue

2.6.1. Collapsed lung

2.6.1.1. Pleural effusion

2.6.1.2. Bronchial obstruction

2.6.1.3. Pneumothorax

2.6.1.4. A large tumour compressing lung

2.6.2. Abnormal lung

2.6.2.1. Pneumonia

2.6.2.2. Oedema (eg CCF)

2.6.2.3. Radiation pneumonitis

2.6.2.4. Chemotherapy-induced interstitial pneumonitis (eg from bleomycia)

2.6.3 Extensive lung resection

2.6.4. Pulmonary infarction

2.6.5. Pulmonary hypertension

2.7. Respiratory mechanics dysfunction

2.7.1. Skeletal (eg kyphoscoliosis from spinal metastatic collapse)

2.7.2. Respiratory muscle nervous control

2.7.2.1. Paraplegia affecting intercostal muscles

2.7.2.2. Phrenic nerve palsy

2.7.2.3. Neuromyopathies and myasthenia (Eaton-Lambert syndrome)

2.7.3. Respiratory muscle dysfunction

2.7.3.1. Diaphragmatic pressure (eg ascites)

2.7.3.2. Cachexia and muscle weakness

2.7.3.3. Metabolic and endocrine disturbances such as hypokalaemia, hyponatraemia, hypercalcaemia, hypoadrenalism or hypomagnesaemia

2.7.3.4. Carcinomatous myopathy and myositis

2.7.3.5. Steroid myopathy

/ continued ...

APPENDIX 7 - CAUSES OF DYSPNOEA IN ADVANCED CANCER (cont'd)

3. **Neural stimulation**
   - 3.1. Peripheral (J receptors)
     - 3.1.1. Lymphangitis carcinomatosa
     - 3.1.2. Pneumonia
     - 3.1.3. Oedema
     - 3.1.4. Inhalation of vomit
   - 3.2. Central (Respiratory Centre)
     - 3.2.1. Metabolic
       - 3.2.1.1. Uraemia
       - 3.2.1.2. Ketoacidosis from diabetes or starvation
       - 3.2.1.3. Type B lactic acidosis from leukaemias and lymphomas
     - 3.2.2. Intracranial lesions
       - 3.2.2.1. Infections
       - 3.2.2.2. Raised intra-cranial pressure
       - 3.2.2.3. Stroke
       - 3.2.2.4. Tumour compressing respiratory centre

4. **Psychogenic**
   - 4.1. Anxiety
   - 4.2 Depression
   - 4.3 Hysteria
   - 4.4. Obsessional personality

7.8 APPENDIX 8 - Summary of treatment of dyspnoea.

The following published papers were included in the bound thesis. These have not been digitised due to copyright restrictions, but the links are provided.

APPENDIX 8

SUMMARY OF TREATMENT OF DYSPNOEA

1. Palliative drugs

a) Antibiotics
b) Glucocorticosteroids
c) Cytotoxics and Hormones

2. Symptomatic drugs

a) Opioids
b) Psychotropics
c) Atropinics
d) Muscle relaxants
e) Local anaesthetic inhalation
f) Oxygen and helium
g) Prostaglandin inhibitors
h) Beta-adrenergic blockade
i) Relief of other symptoms
j) Doxapram
k) Aminophylline
l) Progesterone

3. Palliative Procedures

a) Radiotherapy
b) Laser therapy
c) Stents
d) Pleural taps
e) Pleurectomy
f) Paracentesis
g) Drainage pericardial effusions
h) Drainage of pneumothoraces
i) Blood transfusions
j) Physiotherapy
k) Psychological therapies

4. Symptomatic Procedures

a) Cold air
b) Acupuncture
c) Oral high-frequency oscillations (OHFO)

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