Shortness of Breath*

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"Breathing is truly a strange phenomenon of life, caught midway between the conscious and unconscious, and peculiarly sensitive to both" (Richards, 1953).

The sensation of breathlessness is at one and the same time both fascinating and baffling. To the patient breathlessness as a symptom is a translation from the blissful state of unawareness of respiration, in which the healthy among us pass most of our lives, to an existence where the night holds terror or the day becomes one of increasing inability to undertake normal activities. The practising clinicians among us used to use breathlessness much as we did other symptoms, to point towards the diseased organ, but now we seek to render it objective, to measure it, and to establish its significance as evidence of a functional failure of vital organs. The respiratory physiologists are probably the persons most fascinated by breathlessness, but then they regard it as a distraction from the serious problem of the control of respiration, upon whose mechanism they are still disagreed. The trend in respiratory physiology is ever towards a more mathematical expression, and perhaps the ordinary mortals among us may be forgiven for regarding the present atmosphere of their subject as too rarefied for comfort.

Control of Respiration

The act of respiration is singular in that it represents one of the fundamental rhythmic activities of the body persisting even in states of deep unconsciousness while behaving in normal circumstances as a movement under almost complete voluntary control (Dornhorst, 1963). The change from ordinary respiration to the conscious awareness of the need to breathe is expressed as breathlessness both by normal persons and by those with disease. Yet we use the word "dyspnoea" to stress the difficult breathing of states of pathological breathlessness and "hyperventilation" or "hyperpnoea" to describe the altered breathing of the normal person during exercise. How valid this distinction is to-day may be questioned, and any who have watched the face of one who has completed strenuous athletics such as a four-minute mile or has been mountaineering with a heavy load may wish to use the word dyspnoea for the normal sensations under conditions of distress.

Much has recently been published on pulmonary structure and function and on the control of respiration. Symposia in Britain were held by the Ciba Foundation (de Reuck and O'Connor, 1962) and to celebrate the J. S. Haldane Centenary (Cunningham and Lloyd, 1963), while in America the New York Academy of Science devoted a meeting to the subject of the regulation of respiration (Nahas and Fink, 1963). Dornhorst (1963) has described the control of respiration

in the language of modern control-system theory with the respiratory centre as a computer receiving information from the brain, from muscles and tissues via the nerves, and from the blood by chemical stimuli, and calculating from this the demand for ventilation. The effector organ of respiration composed of the respiratory muscles, the chest wall, and lungs responds to the ventilatory urge received from the respiratory centre while feeding-back information to the centre via chemical and nervous stimuli. Somehow or other nervous impulses and chemical relations represented by carbon dioxide and oxygen tension and the pH of the arterial blood are perfectly integrated so that tissue needs and tissue metabolites are equated. It is possible to relate ventilation and the main chemical stimuli from the CO₂ and O₂ alveolar gas tensions and the blood pH in a mathematical formula (Cunningham *et al.*, 1961). In effect, the response to alterations in CO₂ tension, so long regarded as a powerful controller of ventilation, depends upon the level of oxygen tension in the blood and therefore alters when the normal subject breathes air with different oxygen percentage composition (Nielsen and Smith, 1951).

For the normal person, however, exercise provides the greatest stimulus to ventilation, and the interrelation of nervous and chemical factors is then clearly shown. The immediate rise in ventilation from the first moment of exertion (Dejours, 1959) can only be due to nervous impulses, probably from the skeletal muscles, for the blood gases and the pH are then normal. The "slow component" continues the stimulus to ventilation during the later phase of exertion, when chemical changes are found in the blood. Matell's (1963) studies suggest a closer relation between excess ventilation and blood acidity than with gas tensions. Oxygen saturation alters little during exercise, and yet normal subjects given oxygen to breathe exercise better and ventilate less. Under these conditions of exercise during oxygen-breathing the CO₂ tension of the arterial blood rises much more than during exercise while breathing air. The linear relation between ventilation and oxygen uptake found during exercise is, however, a fundamental response of the normal cardio-respiratory systems.

Alteration of the Work of Breathing in the Normal Subject

Exercise, then, is the main circumstance which provokes the sensation of breathlessness normally, and it is also the chief stimulus to dyspnoea in those with pathological conditions of the lungs and heart. Yet its study does not provide the best model for unravelling the mechanism of dyspnoea in diseases in which changes in the mechanical behaviour of the chest or lungs can be demonstrated. An illuminating series of observations have been made by Campbell and his associates at the Middlesex and Postgraduate Medical Schools in London, in which normal subjects were asked to assess their ability to recognize loads of different kinds imposed upon their

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respiration. Campbell *et al.* (1961) first studied the ability of conscious subjects to recognize an increase in elastic resistance imposed by breathing from closed rigid drums of various dimensions. In this way it was found that an increase of the normal elastance of 10–20 cm. H₂O/litre by as little as 2.5 cm. H₂O/l. could be recognized. As this represented an increase of only 10–20% of the elastic load of breathing it is obvious that the pathological conditions of chronic lung disease where there may be an increase of from 25 to 100% above the normal would be readily recognized as an increased load. The resistance to distension of the pathologically rigid lung or thoracic cage must therefore be a potent stimulus to dyspnoea.

Bennett *et al.* (1962) next studied the response of subjects caused to breathe through tubes with a narrowed airway. They found that a normal non-elastic resistance of 1.5–3.4 cm. H₂O/l./sec. required to be increased by up to 25% for subjective detection. How far this falls short of the changes in disease can be seen from the fact that in chronic lung disease the airway resistance may be increased from 100 to 700%. Campbell *et al.* (1963) compared the ability of normal subjects to discriminate between elastic and non-elastic loads to breathing. They found that this was possible, but only with the higher loads and not at the 50% response level. Campbell and Howell (1963) have speculated upon the mechanism of the recognition of the increased load to breathing. As the volume of ventilation is rapidly adjusted to an increased elastic load and inspiratory muscular tension must therefore be increased rapidly, they believe that nervous impulses from the muscle spindles found abundantly in the respiratory muscles are responsible. Similarly, an increase in airway resistance by obstruction causes an immediate increase in expiratory lung volume, thus necessitating greater shortening of the respiratory muscles.

Campbell and Howell (1962, 1963) have used the term “length/tension inappropriateness” to describe the basis for the sensation of breathlessness, which they believe to be neuromuscular in origin. From their experiments and those of others it seems that the Hering-Breuer inspiratory reflex from pulmonary receptors is only feebly developed in adults. Direct signalling from pathologically indistensible lungs via pulmonary nervous pathways is, in their view, not important, though little direct evidence exists to support their own theory that the respiratory muscle spindles are the main sensory structures.

One can afford to leave this controversial subject of mechanism to the giants of the respiratory physiological arena, particularly as Comroe *et al.* (1962) have marshalled their own views and those of others on the mechanism of dyspnoea. Few will dispute that any pathological condition of the lungs, the chest wall, or muscles which results in an increase in the work of breathing or inability to perform the normal work is likely to cause dyspnoea. Difficulty in breathing is thus equated with work, which is a delightful way of avoiding the issue because of the impossibility of measuring work directly. In the meantime Campbell's experiments are valuable, for they mimic the two chief abnormalities in mechanical functioning of the lung produced by disease—increased resistance to distension or restricted ventilation and increased airway resistance or obstruction. Although in any particular pathological condition one or both of these abnormalities are present, it is helpful to consider separately the conditions in which there is restriction of breathing from those with obstruction of the airways, however these may arise.

Clinical Assessment of Breathlessness

Acute and Chronic Dyspnoea

Undoubtedly the thought uppermost in the clinician's mind when his patient complains of shortness of breath is the diagnosis. So great are the diagnostic possibilities that the

approach must be equally broad. However, some useful distinctions can be drawn at the outset that serve to narrow the field of inquiry. One must first draw a sharp distinction between acutely breathless patients with a short history and those with a long history of insidiously developing dyspnoea. Acute breathlessness in a previously healthy person is usually due to some acute infective or mechanical derangement of the chest such as pneumonia, pneumothorax, or pulmonary embolism. The accompanying symptoms—pain in the chest, fever, cough, sputum, and haemoptysis, or the physical signs of consolidation, of pleural friction, or other changes—point clearly to the lesion. Acute breathlessness in both young and old may, however, be the result of congestive cardiac failure due to intrinsic heart disease, such as mitral stenosis, hypertension, or ischaemic heart disease. It is unlikely that the onset of pulmonary congestion and oedema, causing either nocturnal attacks of cardiac asthma or breathlessness by day, will arise without a forewarning in the form of diminished capacity to exercise, so that the cardiac patient falls more properly within the group of those with a long history, though there are exceptions.

Among the chronically breathless patients, however, there are those who are prone to intermittent attacks of dyspnoea with reasonable health in between. Asthma is *par excellence* the example of recurrent acute breathlessness, and though immediate semantic difficulties are encountered in attempting to define the use of the word few would disagree that it is the intermittency of the airway obstruction which is the chief characteristic of this disease. Again, however, as in cardiac cases, acute asthmatic attacks do not often supervene in a previously completely healthy person. Though there is always a first time even for asthma, the history is essentially a chronic one with a fluctuating degree of breathlessness noted on exertion in between attacks. It is this chronic state of disability common in middle-aged and elderly asthmatic patients which causes the confusion between asthma and chronic bronchitis with its accompanying state of obstructed airways and perhaps of emphysema.

History

In my view the differentiation of the various states of chronic breathlessness still begins with the taking of a careful history and the outlining of the mode of evolution of the symptoms. There is nothing esoteric about this, only that it takes time and awareness of the important clues. It is necessary to start in childhood in order to obtain the background of ailments such as whooping-cough, measles, or repeated attacks of pneumonia which may have left a legacy in the form of bronchiectasis. There is also the fact that constitutional conditions of an allergic character often reveal their presence in childhood by infantile eczema or hay-fever. The occurrence of repeated wheezing and breathless attacks during acute respiratory infections in childhood often suggests an abnormality of the bronchial tree, but the after-history in adult life of those who were wheezy in childhood is not clearly known and there is no proof that such wheeziness is the forerunner of chronic bronchitis. Finally, many and often the most intractable cases of asthma declare their presence before puberty, and, though many such children improve in early adult life, most bear some stigma in the form of reduced tolerance to exertion even if they are not subject to incapacitating attacks.

Retrospective history-taking in adults often calls for a feat of memory not to be expected of the average mortal. Probably for this reason, in adults with chronic bronchitis a history of always being prone to a cough from childhood onwards is, in my experience, commoner than one of specific ailments. On such a background, and after an interval of time varying from 10 to 20 years or more, there is written the history of recurrent attacks of disabling cough, sputum, and breathlessness which constitute the characteristics of chronic bronchitis. In other patients there is no preceding childhood illness, but the same

recurrent disability follows a relatively short history of productive cough, perhaps after a cold or an attack of an acute lower respiratory infection. A history of rapid fluctuation of breathlessness suggesting the development of attacks of dyspnoea not necessarily related to exertion should raise once again the query of asthma. It is the essence of chronic bronchitis but not of asthma that the symptoms are worse in winter than in summer and that severity of dyspnoea may bear a relation to environmental alterations, such as of the weather. Whatever the background of previous health, the complaint of dyspnoea should therefore lead to questions concerning its association with cough, sputum, and wheezing, its time of occurrence, and its relation to fog and damp weather or exposure to conditions of work.

The story of insidiously developing dyspnoea experienced only on exertion raises the need for differentiation of cardiac from pulmonary dyspnoea. Associated symptoms of either form of breathlessness usually help, but there are some difficulties. The middle-aged or elderly patient with hypertensive or ischaemic cardiac disease may experience retrosternal pain of an anginal character which may easily be confused with the tightness of the chest found in chronic bronchitis. Often, however, dyspnoea occurs on exertion without accompanying pain, cough, or sputum. As common ailments occur commonly, there may also be a combination of hypertension with chronic bronchitis, and this cannot be sorted out on the history alone.

In conclusion, the history of the breathless patient should include a note concerning personal habits, and particularly of smoking—the number of cigarettes or the amount of tobacco smoked and the duration of the habit. The family history is unlikely to be of definitive importance, particularly because of semantic confusion between asthma and chronic bronchitis.

Occupation

There are so many specific hazards to health of the respiratory tract due to the person's occupation that it is absolutely essential to take a careful history of the latter, including the duration of the various tasks in which the patient has been employed. In addition to the well-known pneumoconioses after exposure to silica in all its forms and minerals such as beryllium, there is the problem of vegetable dusts and the products of fermentation such as of mouldy hay. The history of farmer's lung is often that of an outbreak of acute breathlessness among men engaged in dismantling a particular hayrick, thus suggesting an acute infective episode. In byssinosis due to inhaling cotton dust the dyspnoea is worse on Monday than on other days of the week and it is accompanied by a feeling of tightness of the chest. Some recent work has clearly revealed the presence of a chemical substance possessing constrictor properties for smooth muscle in cotton-dust extracts (Davenport and Paton, 1962). The nature of this substance is still unknown. New industrial processes are constantly arising and the hazard from inhaled chemicals must never be forgotten. Something akin to detective work is often needed, because the exposure which results in illness may not be appreciated either by those employed or by those concerned in management. It must, however, be admitted that the problem of ordinary chronic bronchitis or of emphysema is far greater than that of specific forms of industrial lung disease, and that the occupational factor in bronchitis may be no more than exposure to dust or to fumes.

Physical Accompaniments of Breathlessness

Hitherto dyspnoea has been regarded purely as a symptom, yet there is accompanying evidence, visible on examination, which renders it a physical sign. The patient who enters the

consulting-room and announces his complaint in short sentences of a gasping character is rated dyspnoeic whatever the origin of his breathlessness. Similarly, the patient with severe influenzal pneumonia who cannot find the breath to give a history must and will be classified as dyspnoeic. However, it is still correct to regard dyspnoea as a symptom requiring objective assessment by physical examination, including the use of radiology and physiological methods of study. It is not possible here to categorize all the physical abnormalities which one seeks, particularly when most of them are so well known. Undoubtedly the most important clinical points can be summarized as follows: (1) cyanosis—its degree and presence in the mucosae, including the tongue, as an indication of the oxygen saturation of the arterial blood; (2) the presence of some general condition such as obesity, pregnancy, or anaemia; (3) signs indicative of intrinsic cardiac disease, such as cardiac enlargement, ventricular hypertrophy, valvular lesions, hypertension, ischaemia, or congestive failure; and (4) signs suggesting disease of the thoracic cage, including the chest wall and spine, of the neuromusculature, or of localized or generalized disease of the lung.

The search by physical methods of examination is not only for evidence of disordered anatomy but also for an explanation for the breathlessness. Patients in the early stage of exertional dyspnoea, due, for instance, to anaemia, may show little evidence other than their symptom. But the cyanosed patient, and the man whose chest is grossly deformed or is held rigidly in an inspiratory position with little movement except that in a vertical plane, declare objectively that their dyspnoea is real. To recall an earlier remark, the main functional abnormalities of the mechanism of breathing are restriction of pulmonary distension and obstruction to the airways. The latter is evidenced clinically by a wheeze, by use of the accessory muscles of inspiration, by a prolonged expiratory phase, and by inability to expel a jet of air through the open mouth as shown by the match-test. Restricted breathing is more difficult to discern clinically, but, though there is apparently free inspiration and expiration, exercise is soon accompanied by hyperventilation, with obvious evidence of excessive use of the respiratory muscles.

So long as the excessive work imposed by mechanical deformity of the chest wall or lung can be accomplished there will be little evidence of an objective character to indicate the functional disturbance. In order to distinguish between dyspnoea caused by such restriction and that caused by obstruction it is necessary to pursue physiological investigations.

Investigation of Pulmonary Function

The investigation of pulmonary function in the breathless patient does not so much help in the differentiation of various pathological conditions as it assists in defining the prognosis and guiding the treatment. Respiratory failure whether it is due to the bellows, the alveoli, or the pulmonary capillaries, causes in its earliest stages the premature experience of shortness of breath on exertion. One must therefore look at the functioning of the whole respiratory apparatus for the explanation of this symptom in chest disease. Now, although it is possible to separate this functioning into the traditional divisions of ventilation, diffusion, and the pulmonary circulation, it is often forgotten that tests of these measure the overall function of the lungs rather than that of separate portions. Inevitably, therefore, a discrepancy occurs between breathlessness arising from localized disorders of the lung and abnormalities demonstrated by standard tests. Fortunately it is the diffuse pulmonary diseases which are of chief numerical importance, and in these the questions that can be posed and answered are initially four in number: (1) Is there evidence of airway obstruction? (2) Is there restriction of ventilation in the absence of obstruction? (3) Is the pulmonary gas exchange normal or abnormal at rest or on exercise? (4) Is there alveolar hypoventilation?

Airway Obstruction

Airway obstruction is probably the commonest disorder of lung function and yet one in which knowledge concerning the precise mechanism is still incompletely known. It is typified by asthma, chronic bronchitis, and emphysema. Reversibility of the obstruction can be complete as in asthma, partial as in chronic bronchitis, and unobtainable in emphysema. Simple spirometric measurements of the vital capacity (V.C.) and the ratio to this of the forced expiratory volume in one second (F.E.V.₁) readily reveal obstruction of the airways. Both are reduced in amount, but the ratio of F.E.V.₁/V.C. falls even more (Table I). The F.E.V.₁ is chiefly used in Britain because of

TABLE I.—*Disturbances of Ventilation*

Measurement	Obstruction (e.g., Chronic Bronchitis)
Vital capacity	Diminished
F.E.V. ₁	Large decrease
F.E.V. ₁ /V.C.	<75%
Inhaled bronchodilator on F.E.V. ₁ ..	Increase
Total lung volume	Increased
Functional residual capacity	>45%
R.V./T.L.V.	
Gas-mixing	Impaired (slow and fast space)

its reproducibility with minimal need for patient co-operation, its possible use even in severely disabled persons, its ease of repetition after inhalation of bronchodilator drugs, and its relation to the maximum breathing capacity (M.B.C.). Direct measurement of the M.B.C. has, I believe, been largely given up, though it is probably still useful in field survey work. The maximum mid-expiratory flow-rate (Bates *et al.*, 1962) and the flow-volume loop (Branscomb, 1962) have also been advocated. If the F.E.V.₁/V.C. ratio does not give a clear-cut answer, the size of the lung compartments, of the functional residual capacity (R.C.), and of the ratio of the residual volume (R.V.) to the total lung capacity (T.L.C.) may help. One must warn against the view that a high R.V. or a high ratio of R.V. to T.L.C. means emphysema. It is true that it occurs in increase of the size of the air-spaces beyond the terminal bronchioles, but it also occurs in obstructed airways. Defects in gas-mixing within the lung may also arise either from airway obstruction or from emphysema.

Airway obstruction is commonly accompanied by an increase in airway resistance. This can be measured and separated from mechanical defects in breathing caused by an increase in tissue resistance by the use of the body plethysmograph (DuBois *et al.*, 1956). Indeed, measurement of airway resistance and its alteration in response to inhaled substances is now a delicate and elegant research tool. To digress for a moment, the work of McDermott *et al.* (1964) on the effect on the airway resistance of smoking a single cigarette seems to promise an objective method of confirming the existence of a functional abnormality of the bronchial tree in the earliest stage of chronic bronchitis. In groups of men aged between 35 and 60 the airway resistance and thoracic gas volume were measured by the body plethysmograph before and after smoking a cigarette or before and after a control period. Twenty-eight men had a history of coughing up sputum daily for at least three months of the year, and 32 failed to reach this level of symptoms or denied the production of sputum altogether. F.E.V.₁ of the bronchitic persons was 2.9 l. and that for the normals was 3.3 l. The mean airway resistance of the normals of 0.91 cm. H₂O/l./sec. was increased by +0.09 by smoking, and that of the subjects with bronchitic symptoms was 1.16 cm. H₂O/l./sec. and increased by +0.4 after smoking. Some of the bronchitic subjects showed remarkable increases in resistance, but their response from day to day was also more variable than that of the normal persons. A wider study of this technique applied to several hundred men is now in progress. The work is, however, striking confirmation of the altered response of the airways of those with chronic bronchitis to inhaled substances which has

been so much stressed by workers in France and the Netherlands (Orie and Sluiter, 1961).

Restricted Ventilation

The clearest instances of restriction of ventilation due respectively to disease of the thoracic cage and of the lung are kyphoscoliosis and pulmonary fibrosis. In pure instances of either disease the airways are not obstructed, the gas-mixing is normal, but the small total lung volumes and proportionately reduced vital capacity, forced expiratory volume, and the residual volume tell a story that contrasts well with obstruction (Table II). Unfortunately pathological processes occur in mixtures as well as in a pure form, and patients with either of these disorders may also develop bronchitis with airway obstruction. This occurred in about half of a series of patients with kyphoscoliosis investigated in 1958 in Sheffield (Hanley *et al.*, 1958). Nevertheless, the functional problem in kyphoscoliosis largely arises from the mechanical problem of the deformed chest which causes a great increase in the work of

TABLE II.—*Disturbances of Ventilation*

Measurement	Restriction (e.g., Pulmonary Fibrosis)
Vital capacity	Large decrease
F.E.V. ₁	Normal—diminished
F.E.V. ₁ /V.C.	75% or more
Inhaled bronchodilator on F.E.V. ₁ ..	Unchanged
Total lung volume	Decreased
Functional residual capacity	40% or less
R.V./T.L.V.	
Gas-mixing	Normal

breathing consequent upon diminished compliance of the chest wall (increased elastic resistance). Bergofsky *et al.* (1959) also showed that the non-elastic resistance was normal. Caro and DuBois (1961) have shown that the excess rigidity of the thoracic cage in kyphoscoliosis is a late development, the elastic resistance being normal in children with scoliosis. The factor of a stiff chest in other conditions has yet to be extensively explored, and recent work by Cherniack and Hodson (1963) indicates its importance in ordinary cases of chronic bronchitis and emphysema in which the lung compliance may be normal but the chest wall compliance is greatly reduced. The double handicap of increased airway resistance and of increased resistance of the thoracic cage to distension probably is responsible for the crippling effect of chronic bronchitis and emphysema.

In pulmonary fibrosis there may also be a complicating bronchitis, seen particularly in sarcoidosis and the pneumoconiosis of coal-workers. On the other hand, the diffuse interstitial fibrosis of the Hamman-Rich variety may be free from disease of the airways.

The pursuit of the mechanics of respiration, which alone can give actual measurements of the resistance to breathing, may thus provide the necessary clues to the factors concerned in dyspnoea. In addition to the use of the body plethysmograph, measurements of intra-oesophageal pressure in relation to tidal volumes and rates of air-flow are required. The matter is essentially one for research rather than for clinical usage.

Pulmonary Gas Exchange and the Arterial Blood Gases

Although it is easy to understand the dyspnoea of those with obstructed or restricted ventilation in terms of disordered mechanism, it is more difficult to understand the effect of alteration in the gas exchange in the lungs. Hypoxia which develops only on exercise and which is unaccompanied by a change in the CO₂ tension or arterial blood acidity may be unconnected with disorders hitherto mentioned (Table III). Thus it occurs in shunts in congenital heart disease and arteriovenous

anastomoses in the lung or elsewhere. But a similar hypoxia with normal CO_2 may result from a shunting of blood through unventilated areas of the lung as is known to occur in diseases such as emphysema and chronic bronchitis, or it may result from a disturbance of gaseous diffusion through a thickened alveolar lining. CO_2 , which is twenty times as diffusible as oxygen, passes freely; oxygen transfer is inhibited by such alveolar changes. A state of impaired diffusion was the usual

TABLE III.—*Blood-gas Changes*

O_2 Saturation	CO_2 Tension	Condition
96%	38–40 mm. Hg	Normal
96%	30–35 " "	Hyperventilation (e.g., mitral stenosis)
<90%	38 or less mm. Hg	Alveolar-capillary block; shunting
<90%	<45 mm. Hg	Alveolar hypoventilation (e.g., anoxic cor pulmonale)

explanation given for the syndrome of alveolar-capillary block which occurs in pulmonary fibrosis or granulomatosis. Finley *et al.* (1962) have, however, put forward the view that even in such cases the cause of the hypoxia is a disturbance of the ventilation/perfusion ratio much as in airway obstruction.

The state of hypoxia with hypercapnia accompanied by an elevated CO_2 tension in the arterial blood is, however, much commoner than hypoxia alone in patients with chest disease, and this is the result of alveolar hypoventilation. There are two phenomena requiring explanation. First, the failure of the body to get rid of its excessive load of CO_2 in the blood; and, secondly, the effect upon ventilation of breathing oxygen. The lack of response to CO_2 in the blood, or when given to patients with hypoxia and hypercapnia, is still not fully explained. It is obvious that the fault lies partly in the respiratory centre, for the state resembles that seen in profound anaesthesia; also, treatment of the patient with stimulants such as amphetamine is beneficial. One view, therefore, is that the respiratory centre has become unresponsive and is narcotized by the hypoxia so that it permits a rising CO_2 tension. This view ignores the fact that in normal persons hypoxia makes the respiratory centre more sensitive to CO_2 . The other view is that so much CO_2 is produced by the excessive use of the respiratory muscles in states of severe mechanical limitation of breathing that further hyperventilation is impossible. This is the view that it has become "too costly to breathe."

I should like to draw attention instead to the work of Penman (1962a, 1962b), who showed that the acid-base balance is most important in such patients with hypoxia and hypercapnia in determining the ventilatory response. Everyone knows that oxygen rapidly relieves the distress of patients with alveolar hypoventilation. It does so by depressing the respiration, but the CO_2 tension rises still higher and the patient may become comatose. Hypoxia disappears and a usual explanation of this depression of respiration is that the anoxic stimulus has been abolished. But Penman (1962a) showed that the ventilatory response to oxygen depended on the pH of the arterial blood. If this was below 7.35 the response was normal, if above then oxygen-breathing depressed respiration. Penman (1962b) further showed that when oxygen was given the blood lactate, already raised much above normal, fell. The production of lactate, which is the most important of the fixed acids in the body, is related to cell metabolism, and its level could well be vital to the disordered respiratory centre.

One cannot end these comments on alveolar hypoventilation without making the point that this is the terminal common end-result of many different processes. Chronic cor pulmonale due to the airway obstruction of chronic bronchitis, asthma, or emphysema, to kyphoscoliosis, profound obesity, or even the terminal respiratory failure of neuromuscular disorders, is thus characterized by both anoxia and hypercapnia. That variety of cor pulmonale due to obstructive pulmonary arterial disease or to pulmonary fibrosis is also accompanied by anoxia, but the CO_2 tension is not raised until the terminal phase of illness.

Whatever the explanation of the alveolar hypoventilatory state it is important to realize that it can be reversed only if the primary disease process is reversible. Unfortunately this is rarely possible. The recognition depends upon measurement of the arterial blood gases, which, in my view, is a necessity in the investigation of patients with cardiopulmonary disease. The help afforded by bedside estimation of the Pco_2 is also of great value, and Campbell and Howell's (1959) rebreathing technique can be recommended. I have said nothing about the pulmonary diffusing capacity, but its measurement is important only when it is combined with other methods. By itself it probably adds little to the clinical assessment of pulmonary dysfunction.

Dyspnoea in Heart Disease

When one turns to consider the problem of the dyspnoea of heart disease, ignorance and perplexity are greater than knowledge. Here is one of the basic symptoms of cardiac disease occurring long before any evidence of heart failure exists and often constituting the only complaint. One would surely expect in this day of great advances in understanding of the circulation that investigations would have revealed the mechanism of cardiac dyspnoea. Unfortunately this is not so. Christie (1938), reviewing the subject of dyspnoea, wrote: "Cardiac dyspnoea is largely if not wholly due to the increased rigidity of the lung which follows pulmonary congestion. This pulmonary rigidity causes reflex dyspnoea through stimulation of the vagal nerve endings in the lung." He added that there was no evidence that biochemical changes in the pH of the respiratory centre or anoxaemia were concerned.

Since then a large amount of information has accrued on the state of the pulmonary circulation in heart disease and the effect of this upon the functioning of the lung. The measurement of the pulmonary blood-pressure has brought about the recognition of increase in the pressure of the pulmonary veins and capillaries in cases of pulmonary congestion secondary to disease of the left side of the heart. Other forms of pulmonary hypertension due to obstruction of the pulmonary vascular bed or to pre-capillary narrowing of the pulmonary vasculature in chronic lung disease have also been found. Christie's hypothesis of an increased rigidity of the lung in pulmonary congestion was based on his early work with Meakins (Christie and Meakins, 1934) on the disturbed pulmonary mechanics in heart disease. The pulmonary compliance has been measured many times since then and it has been found to be reduced, for instance in mitral stenosis, thus causing an increase in the work of breathing. The air-passages of the lung have mostly been exonerated, at least in the early stages of heart disease, for the maximum breathing capacity and vital capacity are little if at all reduced. Therefore the glib interpretation of cardiac dyspnoea as a consequence of disturbance in the pulmonary circulation causing rigidity of the lungs has come to be accepted.

It must nevertheless be emphasized that there are difficulties in this view. First of all, experimental studies in animals (Borst *et al.*, 1957; Hughes *et al.*, 1958) have shown that one can vary the pulmonary blood-flow and pressures within wide limits without producing a comparable change in pulmonary compliance. In cases of mitral stenosis in man, White *et al.* (1958) found an inverse relation between the pulmonary capillary (wedge) pressure and the lung compliance. Saxton *et al.* (1956), however, found little correlation between vascular pressures and compliance and Donald (1959) has commented that the effects of exercise or of valvotomy in mitral stenosis also fail to indicate a direct relation between these variables. Moreover, as McIlroy (1959) has stressed, the fall in pulmonary capillary pressure after valvotomy is accompanied by simultaneous improvement in cardiac output. Reduction in dyspnoea brought about by valvotomy may therefore be the end-result of several changes. All this is not intended to be a denial of the importance of pulmonary mechanics in the dyspnoea of

heart disease so well described by Arnott (1963), but rather to emphasize gaps in our knowledge.

The simple facts are that cardiac patients exhibit a disturbance of ventilation in that they breathe excessively at rest and on exercise show a rapid increase in ventilation out of proportion to the increased uptake of oxygen. They maintain a normal arterial-oxygen tension while washing-out CO_2 and thus exhibit a PCO_2 below normal, which contrasts greatly with the state of affairs in chronic disease of the airways. The best analogy to the patient with cardiac dyspnoea on mild exertion is that of the normal person at the extreme limit of exertion when ventilation rises more steeply than oxygen uptake. As the basic mechanism for the dyspnoea of exercise is still *sub judice* it is probably wise to maintain an open mind about that of cardiac disease.

Mechanical obstruction to the pulmonary circulation is also a complex matter, as Halmagyi and Colebatch (1961) showed by their experimental work in sheep. Embolism, which induces a steep fall in pulmonary compliance, naturally enough causes an increase in the pulmonary vascular resistance. But the Sydney workers found a simultaneous rise in airway resistance reversible by isoprenaline, which also caused a fall in vascular resistance. One is not accustomed to considering the airways in relation to pulmonary embolism, but it is now obvious that they cannot be neglected. Similarly the rise in the low pulmonary compliance found in patients with cor pulmonale due to chronic lung disease during recovery from heart failure may have a dual explanation (Hammond, 1957, 1961). The pulmonary blood-pressure has been demonstrated to fall in these patients as oedema and venous congestion disappear (Whitaker, 1954), but obviously the airway obstruction also diminishes. It would be fair to end these remarks on the problem of dyspnoea in heart disease by pointing to the existence of airway disease secondary to disease of the left heart. The wheeze of cardiac asthma and the repeated attacks of bronchitis in mitral stenosis are both evidence of airway alterations even though they are late phenomena. Meanwhile, Campbell and Howell's doctrine of length-tension inappropriateness of the respiratory muscles as the basis for dyspnoea applies to increased demand as well as to increased resistance to ventilation and thus to heart as well as lung disease.

Dyspnoea in Pregnancy, Anaemia, and Thyrotoxicosis

There remain to be considered conditions in which the heart and lungs are structurally normal and yet in which dyspnoea is experienced on exercise to a degree short of that needed to induce it in normal persons. Thus dyspnoea may occur in early pregnancy, and Cugell *et al.* (1953) showed that the pulmonary mechanics were then normal. Both these authors and Bader *et al.* (1959) showed a high resting ventilation in pregnant women with a steeper rise in ventilation than that in the oxygen uptake on exercise. Both anaemia and thyrotoxicosis are accompanied by changes in the functioning of the circulation, the so-called hyperkinetic state. Yet dyspnoea may be experienced at a stage of the disease in which oxygen transport is certainly normal and the lungs are normal. Bishop *et al.* (1955) demonstrated a steeper rise in the ventilation on exercise in both diseases than in normal persons, and Sproule *et al.* (1960) confirmed this in anaemic patients. Curiously enough, the latter authors did not think that their patients were more dyspnoeic than normal persons during exertion, yet it is a common clinical observation that anaemic persons do complain of breathlessness. The effect of slight degrees of anaemia in cardiac patients is also impressive, though this may be due to an effect upon muscular contraction.

Stein *et al.* (1961) studied the pulmonary mechanics and ventilation in patients with hyperthyroidism. They noted a decrease in pulmonary compliance and a diminished muscular respiratory effort against resistance, but there was also increased ventilation on effort in excess of the oxygen uptake. They

thought that rapid shallow breathing causing increased dead-space ventilation might underlie this lack of normal relation between ventilation and oxygen consumption.

Thus it seems that in all these conditions where abnormal experience of breathlessness appears to be unexplained there is a demonstrable abnormality in ventilation. Also, in all three, restoration of a state of normality of the persons concerned causes once more a return to normal exercise tolerance. The emphasis must be upon the control of respiration in the normal and the origin of breathlessness on exercise.

Summary

This paper reviews our knowledge of the nature and causes of breathlessness and discusses its assessment and investigation.

The control of respiration by the respiratory centre involves a calculation of the ventilatory demand through nervous and chemical stimuli and knowledge of its achievement by the ventilatory effector mechanism. It remains unconscious unless the muscular effort required is disproportionate to the volume of ventilation achieved. Experimental work on the loading of respiration is described because of its bearing on the mechanism of the sensation of breathlessness in pathological conditions of the lung.

The clinical assessment of dyspnoea by history and physical examination is detailed with reference to the most useful diagnostic points. Physiological tests are required to distinguish between the two chief mechanical abnormalities of pulmonary function in chest disease. Obstructed ventilation, as in asthma or chronic bronchitis, is thus contrasted with the findings in restricted ventilation produced by fibrosis of the lung or deformity of the chest such as kyphoscoliosis. Measurements of the gases of the arterial blood are required for the detection of alveolar hypoventilation which follows extensive derangement of pulmonary function and involves the respiratory centre itself.

In contrast to knowledge of the mechanism of dyspnoea in chest disease, that occurring in heart disease, anaemia, and pregnancy remains largely unexplained. The simple explanation that the compliance of the lung is reduced by pulmonary hypertension or pulmonary oedema in mitral stenosis or left heart failure is regarded as inadequate. Analogy is drawn between the hyperventilation of patients with heart disease or anaemia and that of normal subjects at the limit of exertion, when oxygen uptake increases less than the volume of ventilation.

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Systemic Embolism and Anticoagulant Prophylaxis in Rheumatic Heart Disease

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It has been estimated that a history of systemic embolism is likely to be obtained in 9 to 14% of patients suffering from rheumatic heart disease, and that the embolism is cerebral in about 60%, peripheral in 30%, and visceral in 10% of the cases (Wood, 1954, 1956). As arterial embolism can be a serious complication of rheumatic heart disease and can occur occasionally in patients who have little or no cardiac disability, the long-term management of rheumatic heart disease must take into account the risks of initial and recurrent embolism. In the present study an attempt is made to assess this risk over a longer period in medically and surgically treated cases of rheumatic heart disease and to examine the present position of anticoagulant prophylaxis.

Material

A total of 1,017 patients with acute rheumatic fever with or without cardiac involvement or with chronic rheumatic heart disease have been personally studied between 1942 and 1962. Patients with a history of acute rheumatic manifestations who at the time of writing had no conclusive evidence of valvular lesion, and those with established valvular disease followed for less than one year, have not been considered for the present analysis. Thus 754 patients (656 females, 98 males) with established rheumatic cardiovalvular disease followed for a total period of 5,833 patient-years form the basis of the present observations. The ages of the patients when first seen ranged from 8 to 73 years. The predominant valvular lesion was mitral stenosis in 90%, mitral incompetence in 6.5%, aortic incompetence in 2.5%, and aortic stenosis in 1% of the cases.

All embolic episodes included in this analysis occurred during the said period of observation. So far as one could ascertain from the history, only four embolic episodes occurred prior to our first examination of the patients. Emboli found at post-mortem examination only and not diagnosed clinic-

ally were also excluded from the analysis, and so were emboli occurring in the presence of bacterial endocarditis.

Clinical Observation

Systemic embolism occurred in 72 patients; 14 of them had more than one embolus; the total number of embolic episodes amounted to 89. The incidence and site of emboli in relation to the cardiac rhythm are summarized in Table I.

TABLE I.—Systemic Embolism in Rheumatic Heart Disease. Incidence and Site of Emboli in Relation to Cardiac Rhythm

Cardiac Rhythm	No. of Patients	Period of Observation (Patient-Years)	Embolic Group					Total
			No. of Patients	Limb	Cerebral	Visceral	Aortic-iliac	
Sinus	663	4,749	25	4	27	1	0	32
Atrial fibrillation	219	1,084	49	17	36	3	1	57
Total	754*	5,833	72†	21	63	4	1	89

* 128 patients included in both groups.

† 2 patients included in both groups.

In the embolic group there were 57 females and 15 males. The ages of the patients at the time of the first embolic episode ranged from 17 to 63 years (see Chart). The highest incidence was encountered in the fifth decade.

All patients in the embolic group had mitral-valve disease, pure or predominant mitral stenosis being present in 65 patients, and predominant mitral incompetence in 7. Haemodynamically significant aortic incompetence was present in three patients and aortic stenosis in one patient. Two patients had significant tricuspid stenosis as well. All patients had moderate to great cardiac enlargement (cardiothoracic ratio >55%).

There were 17 embolic recurrences in 14 patients during a period of 214 patient-years. Of the recurrences, 40% occurred within one month and 66% within 12 months of the

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