Papers and Originals

Respiratory Failure*

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Under the terms of the Goulstonian Trust of 1632 this lecture should be read "between Michaelmas and Easter, on three days together, both forenoon and afternoon, on some dead body if possibly it can be procured, which shall then and there be dissected for the diseases treated of. . . ." The Harveian Librarian has suggested to me that this marathon clinico-pathological conference was both compressed into a short time and held at this season so that the maximum information could be obtained from the body before it became too decomposed for further examination to be profitable or tolerable. The Goulstonian Lectures replaced the annual cold-weather dissections, and were regarded as a duty rather than as an honour for the four youngest Fellows. The first lecture was to have been on diseases of the nether belly, but "whether this enjoyable function took place is not recorded" (Clark, 1964). The censors have wisely reduced the ordeal from three days to one hour, and also, by tradition, the conditions of which the lecturer treats have rather changed their nature, so that the concept of a disease based upon morbid anatomy and demonstrable only at necropsy has become inessential—thus in recent years lecturers have reviewed body-fluid depletion, the uraemias, and medical education.

In respiration the break with tradition occurred as early as 1736, when Benjamin Hoadley gave three lectures on the organs of respiration, the first and second of which are minor classics in the history of respiratory physiology. In the appendix to the published lectures, where a reference to the necropsy might be expected, there is instead a description of an elegant mechanical model of the chest and lungs (Hoadley, 1740).

These precedents are a comfort, because I also am going to deal with a subject whose frame of reference is not that of structure. Respiratory failure should be diagnosed and can to a large extent be managed without reference to an anatomical lesion. Although attempting a broad survey of the subject, I shall, as is usual, concentrate on those aspects in which my colleagues and I have taken particular interest.

Definition

The function of the respiratory system is to secure gas exchange between blood and ambient air so that the arterial blood gas pressures are kept within certain limits. Therefore respiratory failure may be defined as impairment of this function of such degree that the arterial blood gas pressures depart from these limits.

Criteria

There may be a gradation through various degrees of impairment of function from "normality" to "failure," and there can also be degrees of failure. But, having decided to take the state of the blood gas pressures as the defining characteristic,

the degree and circumstances of the departure from normal seem to me to be matters of convenience. Thus, although the most generally useful criteria may be based upon normal values at rest and at sea-level, the definition could be applied to exercise or altitude. In preparing this lecture I have used the following criteria: respiratory failure is present in a subject at rest breathing air at sea-level if, because of impaired respiratory function, the arterial blood Po_2 is below 60 mm. Hg or the PCO_2 is above 49 mm. Hg. These values are somewhat beyond the usual normal limits, but they seem to me to be clinically useful.

The only condition other than respiratory failure in which blood PCO_2 is raised is non-respiratory or metabolic alkalosis. It is even arguable that, if we avoid the teleological interpretation of the increased PCO_2 as "compensatory," the hypercapnia of non-respiratory alkalosis is a form of respiratory failure. The only condition other than respiratory failure causing the arterial blood Po_2 to be reduced is right-to-left cardiovascular shunting.

Other Definitions

In relating respiratory failure to the state of the arterial blood gas pressures I have chosen what I believe is the most useful but not the only possible defining characteristic, and some would prefer a broader definition. There is an understandable tendency to apply the term, for example, to a patient with status asthmaticus or emphysema who is incapacitated by breathlessness but whose blood gases are often little disturbed. Such an attitude leads some to apply this or a similar term to any patient whose activities are limited in any way by his breathing. While respecting the humanity behind this usage, I think it is sentimental and leads to a debasement of the term, making it too wide to have any discriminative value. It becomes confused with breathlessness, from which respiratory failure can and should be distinguished.

Although breathing is such an obvious manifestation of life and inadequacy of breathing such a common manifestation of disease that respiratory failure and similar terms abound in the medical literature, the term has acquired useful meaning only in the last fifty years with the elucidation of respiratory physiology. Even now formal definitions of the term are rare and the intended meaning must usually be induced from the context in which it is used. Meakins and Davies (1925), Moncrieff (1935), Arnott (1960), and Bates and Christie (1964) obviously intend a meaning similar to that used here. The leading American pioneers (Baldwin *et al.*, 1948) do not use the term but recognize the most severe degree of "pulmonary insufficiency" as that associated with abnormalities of the blood

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gases, and this usage is common in North America (Cherniack and Cherniack, 1961). "Manifest respiratory insufficiency" is used by the leading Swiss school (Rossier *et al.*, 1960) to describe patients with arterial desaturation at rest, a usage that seems to have been adopted in Germany (Heilmeyer, 1960). Leading Dutch (Sluiter *et al.*, 1964), French (Sadoul and Lacoste, personal communication), and Swedish (Birath, personal communication) authorities observe definitions almost identical with that put forward here.

Relation of Respiratory Failure to Breathlessness

Respiratory failure, as defined above, is essentially a functional concept. The main symptom related to respiration is breathlessness. Some simple relationship between them might therefore be expected, such that patients in respiratory failure are breathless or vice versa. But in fact the relation of the state of the blood gases to breathlessness is by no means simple. This is not the occasion to go into the physiology of the sensation of breathlessness (Campbell and Howell, 1963a), but it must be recognized that many breathless people have normal blood gases, and, conversely, many patients whose blood gases are abnormal are not breathless. The blood gases are normal in a healthy subject during vigorous exercise; they are often little disturbed in many patients with status asthmaticus, or, as the late Sir Francis Fraser described in the Goulstonian Lectures of 1927, in dyspnoea of cardiac origin; they are also often little disturbed in breathless paralysed patients who are adequately ventilated, and who, of course, are not performing any respiratory work. On the other hand, patients with "primary" alveolar hypoventilation are little distressed by their breathing, although the PCO_2 and PO_2 of their blood are very abnormal.

Holding the breath is a simple experiment which dissociates the state of the blood gases from respiratory distress—although I would not insist that the sensation is the same as other forms of dyspnoea. Hold your breath as long as you can; when you "give in" and take a breath the relief is immediate—although the gas pressures in the blood perfusing the chemoreceptors and the brain do not improve for several seconds. The experiment can be kept almost as simple and made more elegant if the breath is taken from a bag of gas with the same PCO_2 and PO_2 as the alveolar air. Despite the fact that the blood gases are not improved by breathing this "foul air," the relief of distress is such that the breath can be held for a further period (Fowler, 1954).

Fig. 1 is a simple block diagram similar to that of Dornhorst (1963) which indicates how this separation of the sensation of breathlessness from the state of the blood gases may be explained. The respiratory chemostat issues a demand for ventilation dependent upon the state of the blood gases (other stimuli to ventilation are also important but not immediately relevant). This demand is fed into those complicated mechanisms in the brain and spinal cord which control voluntary muscles, and

which are labelled "Motor Nervous System." Their operation ultimately results in a demand for shortening being sent to the inspiratory muscles. These shorten, the act of breathing occurs, and ventilation results. The act of breathing produces non-chemical nervous feedback, giving information about the movements of the chest; ventilation produces chemical feedback by altering the blood gases.

There is strong evidence to suggest that respiratory distress is not caused directly by chemical stimulation. Howell and I believe that the sensation or sensations are due to "inappropriateness" at one stage or another in the nervous chain of command leading to the act of breathing. Thus, distress may be experienced if the neurochemical demand for breathing is inappropriate to the apparent needs, as at altitude, if the neuromuscular effort of breathing is inappropriate to the breathing that is achieved, as in asthma, or if the neural effort is inappropriate to the muscular act that is achieved, as in muscular paralysis. We suggest that the relations listed above are being continuously sensed unconsciously (as indicated in Fig. 1)—indeed, the adjustment of breathing requires that they must be. Should there be more than a certain degree of inappropriateness it reaches consciousness, and should the inappropriateness be excessive it causes distress (Campbell and Howell, 1963b). These ideas and the term "inappropriateness" may seem strange, but they follow logically if ventilation, including the act of breathing, is thought of as being regulated by a series of controls analogous to amplifiers. If the "gain" required of these amplifiers departs from the normal or expected range then a state of "inappropriateness" is created.

Whether or not these suggestions improve our understanding of breathlessness, in the present context the important fact is that, despite the presence of "inappropriateness" and the implicit stress imposed on one or another of the nervous controls, the whole system has so much reserve that it will usually operate sufficiently well to prevent the blood gases becoming abnormal. On the other hand, there are conditions discussed later in which chemical responsiveness is impaired and dyspnoea is slight. We would explain this absence of breathlessness as a reflection of the lack of demand or "drive," which therefore does not call for excessive or "inappropriate" gain at any of the "amplifiers."

Types of Respiratory Failure

The definition could lead to a classification of respiratory failure into two types: one causing hypoxaemia and the other causing hypercapnia. But in practice, if air is breathed, an increase in alveolar and arterial PCO_2 inevitably causes some reduction in alveolar and arterial PO_2 , and usually by the nature of their diseases patients with arterial CO_2 pressures over 49 mm. Hg have arterial O_2 pressures of less than 60 mm. Hg. So a more useful classification is that given below, in which two types are characterized by the presence or absence of hypercapnia; each type is further subdivided according to the physiological process or processes at fault.

Types of Respiratory Failure

Hypoxaemia with Hypercapnia, which may be due to:

- Inadequate ventilation
- Inadequate neural drive or muscular power
- Inadequate pulmonary or thoracic mechanics
- Ventilation: perfusion imbalance, particularly reduced perfusion of ventilated lung—"increased physiological dead space"

Hypoxaemia without Hypercapnia, which may be due to:

- Inadequate O_2 transfer
- Inadequate alveolar-capillary membrane
- Inadequate pulmonary capillary bed
- Ventilation: perfusion imbalance, particularly reduced ventilation of perfused lung—"increased shunt-like effect"

FIG. 1.—Organization of breathing. In this simple model the organization of breathing is represented as two control systems, one within the other. The outer one maintains the long-term stability of the blood gases and in fact depends for its operation on information about them, notably the arterial PCO_2 ("chemical feedback"). The inner system attends to the performance of each breath and depends upon proprioceptive information ("nervous feedback").

Hypoxaemia with Hypercapnia

This variety is sometimes called "ventilatory failure" because it is intuitively obvious that inadequate ventilation must cause both the alveolar PO_2 to be low and the alveolar PCO_2 to be high. But we must recognize that in many conditions of combined hypoxaemia and hypercapnia the inadequate gas exchange is largely due to a disturbance of ventilation: perfusion relationships; in parts of the lung with a reduced blood-flow, ventilation accomplishes little removal of CO_2 or uptake of O_2 . This is commonly called the "dead-space-like effect" of unequal ventilation: perfusion relationships. Although in theory hypercapnia could be caused solely by an extreme imbalance between ventilation and perfusion, in practice it occurs only if ventilatory capacity is limited. Otherwise total ventilation can be increased sufficiently to maintain an adequate alveolar ventilation despite the increased physiological dead space. So, provided these qualifications are remembered, ventilatory failure is an acceptable term for this type of respiratory failure.

Hypoxaemia without Hypercapnia

The exchange of gases between the alveolar air and the pulmonary capillary blood may be unduly hindered if the membrane is thickened or reduced in area. The uptake of O_2 is more severely affected than the elimination of CO_2 because, being less soluble, O_2 diffuses much less readily. Exchange may also be hindered if the volume of the capillary bed is too small to permit the diffusion of gases through the red cell and the various chemical reactions within the red cells to reach equilibrium in the time available. Oxygen is again at a disadvantage compared with CO_2 because it accomplishes these processes more slowly.

This type of respiratory failure has been called "alveolar-respiratory failure" (Baldwin *et al.*, 1948), or "alveolar-capillary block," because there appears to be a "block" or increased pressure drop for O_2 between the alveolar air and the pulmonary capillary—and hence systemic arterial—blood. But we must recognize that in many conditions the major cause of the defective oxygen uptake is again a disturbance of ventilation: perfusion relationships; in parts of the lung with a reduced ventilation the blood-flow accomplishes little O_2 uptake or CO_2 removal. This blood has a big "shunt-like" effect on the arterial oxygenation, but, although in principle it should cause hypercapnia, in practice it has little effect on the PCO_2 of the arterial blood, first because the PCO_2 of the "shunted" venous blood is little greater than that of the arterial blood, and, secondly, because the slight hypercapnia which might result is readily abolished by a very slight increase in total ventilation.

In all these situations we must maintain the clarity of the underlying concepts while recognizing that our techniques cannot completely disentangle them. Many approaches and techniques are available, and may be needed according to the difficulty of the particular problem and the sophistication desired of the solution. Perhaps the most important difficulty facing the clinical physiologist is the identification of "alveolar air." Intuitively it can fairly readily be appreciated that the gaseous composition of the air in each alveolus depends upon the relative amounts of air and blood which the alveolus receives. The more air the alveolus receives the less carbon dioxide and the more oxygen there will be in the alveolus, and the more venous blood the alveolus receives the more carbon dioxide and the less oxygen there will be. Alveoli vary very considerably in what are nowadays called their "ventilation: perfusion ratios," and before we pursue this topic very far, particularly when we depart from normal conditions, we find ourselves asking the question, "Is it possible to define the alveolar air composition?" Limitation of time forces me to resist the temptation to explore and explain this subject any further and to refer those who feel the need for a fuller account to the

excellent reviews by Rahn and Farhi (1961, 1964), and West (1963).

I think the best approach available at present for clinical purposes is to adopt the concept of "ideal" alveolar air introduced by Riley and Cournand (1949), and to accept that an adequate approximation to the measurement of this ideal state is to take the arterial PCO_2 as being equal to alveolar PCO_2 ; the alveolar pressure of oxygen and the other alveolar gases can then be calculated. With this approach, parts of the lung which have a ventilation: perfusion ratio above average ("more air than blood") are quantified as an apparent increase in physiological dead space, and those with a ventilation: perfusion ratio lower than the average ("more blood than air") are quantified as an apparent increase in the shunt-like or venous-admixture component of the systemic blood-flow. Provided the limitations of the assumptions are respected, this approach is never misleading in analysing the functional disturbances in patients. Moreover, the analysis is integrative in the manner developed by Barcroft (1934), enabling assessment of the relative contributions of different processes to the performance of the whole.

The ideal alveolar air approach makes use of the fact that arterial PCO_2 is more representative of alveolar PCO_2 than arterial PO_2 is representative of alveolar PO_2 . Nitrogen is even better because, being an inert gas, there is no arteriovenous N_2 difference, and therefore "true" shunts have no effect on arterial PN_2 . The recent development of practicable methods for the measurement of PN_2 in addition to PO_2 and PCO_2 has thus provided a very subtle approach to the analysis of the processes of gas exchange (Rahn and Farhi, 1961, 1964; Farhi, 1964).

Causes of Respiratory Failure

Respiratory failure may result from lesions or disorders at any of the following sites: brain, spinal cord, motor neurone, neuromuscular junction, respiratory muscles, thoracic cage, pulmonary circulation, lung, airway. These are the sites we would examine were the ancient traditions of this lecture still observed. I see little profit in supplying a full list of what might be found, and prefer to spend the time available describing those physiological features of clinical importance in respiratory failure due to lesions at these sites.

Brain

Respiratory failure due to damage to the brain might conventionally be explained quite briefly by attributing it to failure of the "respiratory centre." But this is a sterile approach belonging to a passing era in neurophysiology, and I doubt if there will be much more profit in thinking of the structural matrix of respiratory control as residing in one "centre" (or in two or three). Perhaps I am attacking men of straw, but whether or not these remarks have any point I am sure that clinically it is both possible and important to distinguish failure of respiratory drive from failure of the respiratory act. Were their fundamental significance more certain one might go further and invent a classification like those of the disorders of speech and willed movement. Were patients examined with the possibility in mind, failure of drive or failure of transmission of the drive to the motor nervous system might be found to be more common than paralysis. Here are some examples of admittedly uncommon conditions in which the distinction seems to me unequivocal.

1. The term "primary alveolar hypoventilation" has been applied to patients with a normal or near-normal ventilatory capacity who do not breathe enough. This syndrome overlaps with the "Pickwickian" syndrome, which was so-named by Burwell *et al.* (1956) because of the resemblance of the patients to the fat boy in "The Pickwick Papers." Superficially it is tempting to describe and explain these patients as follows: they eat too much, become obese and cannot breathe; they

therefore develop hypoxaemia, which in turn causes polycythaemia, pulmonary hypertension, heart failure, and oedema; the hypoxia and hypercapnia also cause drowsiness. But this story does not bear critical examination (Gilbert *et al.*, 1961). Although hypoventilation may sometimes be due to gross obesity which mechanically restricts the breathing, in many patients with alveolar hypoventilation the obesity is mild and may be absent (Richter *et al.*, 1957; Rodman *et al.*, 1962; McNicol and Pride, 1965). Conversely, gross obesity (over 30 stone; 190 kg.) is compatible with a normal blood PCO_2 (Said, 1960; Cullen and Formel, 1962; Billiet *et al.*, 1964). Furthermore, the polycythaemia and mental changes may be disproportionate to the hypoxaemia and hypercapnia (Alexander *et al.*, 1962).

This condition of "primary" hypoventilation must have several causes. In some patients the disorders of regulation of breathing, causing underventilation and periodic breathing; of consciousness, causing somnolence; of red-cell formation, causing polycythaemia; and of the regulation of weight, causing obesity, may all represent collateral functional disturbances due to damage of the higher levels of the autonomic nervous system, probably anatomically very high in the brain-stem reticular formation. It may be significant that one of our patients and those described by Garlind and Linderholm (1958) and Cohn and Kuida (1962) had had encephalitis.

2. Turning to the lower end of the brain, we have recently seen two patients with the Arnold-Chiari malformation in whom profound hypoventilation was present despite relatively well-preserved ventilatory capacity (Rowlands and Pallis, in preparation). Rodman *et al.* (1962) describe the case of a patient with cervical syringomyelia who probably had the same disorder.

These are two examples of the phenomenon of failure to breathe in response to a high blood PCO_2 . It is therefore tempting to call the state "chemostat failure," making use of the term "chemostat" (Grodins *et al.*, 1954) to emphasize that this is a functional concept which does not necessarily imply that the fault lies in the chemoreceptors; it may lie in their central connexions. Nor should it be thought that loss of responsiveness is confined to CO_2 . Bainton *et al.* (1965) have shown that there is a loss of response to hypoxia in chronic mountain-sickness. Loss of response to hypoxia is very unlikely to be recognized at sea-level, because in all those clinical situations in which it may occur the inadequate ventilatory response can apparently be attributed to failure to respond to CO_2 .

Returning briefly to the original requirements of the Goulstonian Lecture, I must point out that anatomical examination provides little clarification in many of these conditions because the relation of structure to function in the brain-stem reticular formation is to-day viewed with less confidence than a few decades ago (Brodal, 1957).

Spinal Cord, Motor Neurone, Neuromuscular Junction, and Respiratory Muscles

We now leave the complexities of respiratory control and the brain-stem reticular formation. Damage at the sites we turn to seems by contrast easy to understand: weakening of the act of breathing may cause underventilation. But there are physiological subtleties of clinical importance.

First, the functional reserve of the respiratory muscles is very great and may not normally be measurable by tests such as the vital capacity. Considerable weakness may be present, but undetected by these tests. Such weakness may be suspected when other actions involving the use of the respiratory muscles are weakened or when other muscles supplied by the same spinal segments or nerves are weak (Campbell, 1958, p. 100).

Secondly, patients with developing muscle-weakness are often very breathless even when ventilation, as judged by the blood gases, is adequate. The explanation for this distress may lie in the need

for excessive drive in the motor nervous system, which is of course embarrassed in all these conditions, as suggested above.

Thirdly, breathing in patients with lesions at these sites must not be judged satisfactory because ventilation is adequate in volume. It is becoming increasingly clear that a healthy mechanical state of the lungs, particularly the patency of the terminal units, depends upon occasional deep breaths to counteract the natural tendency of parts of the lung to close (Mead and Collier, 1959; Ferris and Pollard, 1960). (The lungs overcome the structural problem of providing a large surface area in a small volume by keeping the size of the terminal units as small as possible. The problem of overcoming the contractile force of such small bubbles is largely solved by providing a lining fluid of low surface tension. Even so, the small airways and air spaces in many parts of the lung are unstable, tend to close, and require periodic inflations to maintain their patency and restore the surfactant lining.)

Fourthly, in the absence of these inflations parts of the lung cease to be ventilated but may continue to be perfused so that hypoxaemia may occur in the presence of a normal PCO_2 . This tendency of parts of the lung to close is probably aggravated if the nitrogen in the air, which is only slowly absorbed by the blood, is replaced by a gas which is rapidly absorbed, such as oxygen (Bendixen *et al.*, 1963; Farhi, 1964).

Thoracic Cage

The respiratory effects of lesions of the rib cage or pleura are on the whole easy to understand. Their main subtleties are similar to those mentioned in the preceding section, but one further important principle must be emphasized. Firmness and mechanical uniformity are of paramount importance; in their absence the contractile force of the respiratory muscles cannot be properly applied to the surface of the lungs. Thus the rigid symmetrical rib cage of ankylosing spondylitis seldom causes respiratory failure (Travis *et al.*, 1960; Zorab, 1962; Miller and Sproule, 1964), whereas the distorted cage of kyphoscoliosis often does (Hanley *et al.*, 1958; Bergofsky *et al.*, 1959), and so does the crushed or stove-in chest. In passing, the trend of opinion seems to be that artificial ventilation by intermittent positive pressure (which is a form of internal splinting) will probably prove much more important than mechanical splinting in the management of chest injuries (Griffiths, 1960; Windsor and Dwyer, 1961; d'Abreu, 1964). Furthermore, surgical procedures have not been shown to benefit respiratory function in the common chronic lesions of the rib cage, such as funnel deformities (Fink *et al.*, 1961; van Buchem and Nieveen, 1963) or kyphoscoliosis (Gucker, 1962).

Pulmonary Circulation

In experimental studies of isolated lungs reduction of blood-flow and of pulmonary arterial pressure may stop the perfusion of parts of the lungs; the ventilation of these parts then becomes "dead space" (West and Jones, 1965). In the intact animal experimental reduction of pulmonary blood-flow has additional effects which summate to cause both hypoxic and stagnant hypoxaemia, and, if total ventilation is limited, hypercapnia (Freeman and Nunn, 1963). If, as commonly happens in clinical practice, pulmonary function is further compromised by venous congestion the situation becomes even more complicated, and it is not surprising that hypoxaemia due to disturbed ventilation:perfusion relationships is being increasingly recognized in cardiac and circulatory disorders. Hypoxaemia after haemorrhage has often been reported (Freeman and Nunn, 1963). Recent studies of patients with myocardial infarction causing hypotension or left ventricular failure have shown increased physiological dead space (Higgs, unpublished observations), an increased alveolar-arterial PO_2 difference, and hypoxaemia; the arterial PCO_2 is usually normal or low (MacKenzie *et al.*, 1964; McNicol *et al.*, 1964; Higgs, unpublished). In many patients the rise in arterial PO_2 when

breathing 100% O₂ is incomplete, which suggests that some of the blood-flow is through vessels inaccessible to gas exchange; these may be in unventilated lung.

In pulmonary embolism hypoxaemia is uncommon, although an increased alveolar-arterial PO₂ difference is usual. The physiological dead space is often increased and the arterial PCO₂ is characteristically low (Wilhelmsen *et al.*, 1963; Jones and Goodwin, 1965).

The abnormalities of gas exchange found in many patients with disorders of the pulmonary circulation resemble those found in many chronic diffuse pulmonary infiltrations. This similarity emphasizes that the same functional disturbances may result from very different causes, a fact which must be faced so often in medicine when trying to draw conclusions about structure from studies of function.

Lungs : Syndrome of "Alveolar-capillary Block"

A pattern of disordered function found in many diffuse pulmonary infiltrations is characterized by the following features: absence of airway obstruction; increased dead-space ventilation, and often increased alveolar ventilation; defective CO uptake; an increased alveolar-arterial PO₂ difference and reduced arterial oxygenation, particularly during exercise; the lungs are also usually stiff (uncompliant). I have used its vogue-name, but in inverted commas. I do not like it, because it perpetuates a naive view of the processes of pulmonary gas exchange. For more than half a century the diffusion of O₂ through the alveolar-capillary membrane has been a topic of interest, and, at times, of controversy (Douglas, 1954). Were the alveolar-capillary membrane to be thickened or reduced in area difficulty in O₂ uptake but not difficulty with CO₂ output might be expected, because CO₂ is so much more diffusible. When methods of measuring blood gas pressures and "diffusing capacity" were applied to diffuse pulmonary conditions the patients were found to have low blood PO₂, normal or low blood PCO₂, and low diffusing capacity.

The simple concept of a "diffusion barrier" seemed to be supported, and the term "alveolar-capillary block" appeared (Austrian *et al.*, 1951). To be fair to the pioneers in this field, they did not suggest that the physiological disturbance was due simply to a diffusely thickened alveolar-capillary membrane, and the term alveolar-capillary block has the merit of focusing attention on the anatomical site of the lesion which unquestionably hinders exchange of gases. But so great is the "diffusing capacity" of the lung that even in these patients the wide alveolar-arterial PO₂ difference and hypoxaemia are chiefly due to disturbance of ventilation: perfusion ratios rather than to failure of alveolar and blood PO₂ to reach equilibrium within individual pulmonary capillaries. The term has, however, proved attractive, and it has been helped by the reintroduction of CO as a substitute for O₂ in the measurement of "diffusing capacity." Two points must be remembered: first, the methods usually employed for estimating the "diffusing capacity" are affected by so many other processes that many think the term should be replaced; "transfer factor" has been suggested (Cotes, 1963). Secondly, hypoxaemia due to defective pulmonary gas exchange is usually due to disturbance of ventilation: blood-flow relationships and rarely if ever due to loss of diffusing capacity as originally—and rigorously—conceived (Finley *et al.*, 1962; Hamer, 1964).

Lungs and Airways : Conditions Associated with Diffuse Obstruction of the Airways

I have left these to the end because, although disorders of the lung and airways are the most common cause of respiratory failure, they are also functionally the most complicated.

In recent years it has become increasingly clear that the terms asthma, chronic bronchitis, and emphysema as com-

monly used conceal quite a variety of disorders, and do not contribute to the progress of understanding (Scadding, 1963). An important step in improving the situation has been the recognition that the cardinal feature from the physiological and clinical standpoints in the patients to whom the terms are applied is airways obstruction, and we now tend to make this the first diagnosis. This diagnosis has the great merit that it can be made by methods applicable during life. "Reversible airways obstruction" is at present the best definition of asthma (Ciba, 1959), although it should be improved when we know more about the mechanisms of airway obstruction.

Dr. Fletcher and his colleagues at the Postgraduate School (Fletcher *et al.*, 1963) have been studying patients with chronic irreversible airways obstruction to try to distinguish recognizable subgroups, and within the past few years they have fairly convincingly separated two extremes which are apparently recognizable also on the other side of the Atlantic (Fletcher *et al.*, 1964; Burrows *et al.*, 1964; Mitchell *et al.*, 1964; Briscoe and Nash, 1965). First (Type A or B), patients in whom there is usually good radiological evidence of emphysema. The other features of these patients are: a history in which incapacitating breathlessness is more prominent than cough; reduced pulmonary CO uptake as measured by the single-breath method; they develop respiratory failure, enlargement of the heart, and oedema only as terminal events. The second extreme group (Type B) consists of people whose x-ray films do not show evidence of emphysema, who usually have a long history of cough and sputum, in whom breathlessness is not so incapacitating, who have less severely reduced CO uptake, whose hearts enlarge, and who become oedematous, often years before death. They usually die after a long period of chronic respiratory failure with hypercapnia, punctuated by acute exacerbations with the syndrome commonly called cor pulmonale.

Dr. N. L. Jones (1964) has made some observations of pulmonary gas exchange during exercise which seems to explain the anomaly that the blood gases of the patient of Type B were worse at rest despite better CO uptake at rest. He found that the alveolar to arterial oxygen pressure difference does not increase in the patients of Type B during exercise, whereas it does increase in the patients of Type A. This observation accords with studies carried out by Briscoe and Nash (1965), suggesting that the patients of Type B have a large volume of very poorly ventilated but well-perfused lung. As there is a large amount of blood flowing through this very poorly ventilated volume of lung it produces desaturation in a similar manner to that produced by frankly shunted blood. A slight improvement in the ventilation of this volume of the lung can greatly improve the saturation of the blood. This is what appears to happen during exercise—that is, the ratio of ventilation to perfusion in this "poorly ventilated" space increases. In the patient of Type A, on the other hand, whose gas-exchange surface may be severely limited, the demands of oxygen uptake are greater than the lung can achieve without widening the oxygen-pressure difference between the alveolar air and the pulmonary capillary blood. This widening difference in the lung is reflected in a widening difference between the alveolar air and the arterial blood, and ultimately in severe hypoxaemia if the exercise is sufficiently heavy.

Most patients with chronic irreversible airways obstruction show features of both types, and the diagnosis of the type is not to be regarded as an end in itself but as a step on the road to better understanding both of the individual patient and of the general problem.

Diagnosis of Respiratory Failure

If our definition is observed, the diagnosis of respiratory failure requires the demonstration of hypoxaemia or hyper-

capnia and the demonstration that it is due to inadequacy of respiration rather than to other causes.

Hypoxaemia

Before discussing the diagnosis of hypoxaemia I would like to digress briefly on the distinction which I think should be made between hypoxaemia and *damaging* hypoxaemia (Fig. 2). Although the supply of O_2 available to the tissues is always reduced in hypoxaemia, there is in fact little evidence that this reduction causes damage of even the most sensitive tissues until the arterial saturation falls to about 50% or the arterial PO_2 falls to about 30 mm. Hg (Fig. 2). An arterial PO_2 below 20 mm. Hg seems to be insupportable (Campbell, 1965). In hypoxaemia the brink of disaster is very sheer—quite different from hypercapnia.

FIG. 2.—Oxygen dissociation curve. The O_2 dissociation curve relates the saturation of the haemoglobin to the partial pressure of oxygen (PO_2) in the blood. In a normal subject at sea-level the arterial PO_2 is 90–110 mm. Hg and saturation 95–98%. In this lecture I have taken the knee or shoulder of the curve (PO_2 60 mm. Hg, saturation 90%) as the threshold of hypoxaemia. Cyanosis cannot be detected reliably until the saturation falls to 70–75%. Although hypoxia even of slight degree has effects on the respiration, circulation, and bone-marrow, they are essentially adaptive; unless there is some complicating factor, damage occurs only at a PO_2 of 30–40 mm. Hg (saturation about 50%). An arterial PO_2 below 20 mm. Hg seems to be insupportable (Refsum, 1962; Campbell, 1965). Note that a fall of PO_2 of over 40 mm. Hg is required to produce “reliable” cyanosis; a further fall of only 20 mm. Hg may be fatal. (The curve has been given a “shift to the right” in its lower part because there is usually an acidemia in respiratory failure.)

The effects of hypoxia are protean and non-specific; the only pathognomonic sign of arterial hypoxaemia is “central” cyanosis—that is, a blue colour of the mucous membranes where the blood-flow is high and stagnant hypoxaemia is unlikely. Unfortunately cyanosis is an unreliable sign which even under the best conditions can be recognized confidently only when the saturation is less than 75% (Comroe and Botelho, 1947; Medd *et al.*, 1959), implying a PO_2 below 50 mm. Hg—only 20 mm. Hg above the level at which hypoxic damage to various organs begins to appear. Giving O_2 to breathe may help to confirm or exclude cyanosis due to hypoxaemia, because the arterial hypoxaemia of respiratory failure is very readily abolished by even modest enrichment of the inspired O_2 concentration. Therefore the colour of the mucous membranes should be re-examined after the patient has breathed 100% (or even 30%) O_2 for half a minute or so. Should a doubtful bluish tinge disappear (or even a pink colour become more pink), then the diagnosis of arterial hypoxaemia due to respiratory failure is supported. Conversely, should the colour not change, then the cyanosis is probably not due to arterial hypoxaemia of respiratory origin.

Hypercapnia

I believe that, although hypercapnia is less dangerous than hypoxaemia, paradoxically the diagnosis of hypercapnia is much more important. Unfortunately the clinical diagnosis is very difficult; for unless the PCO_2 is either grossly raised or accompanied by a considerable acidemia, hypercapnia produces few and non-specific symptoms or signs. Recently some of our house-physicians (Gross, Godfrey, Hargreaves, and Winter-ton, unpublished) have extended Gross and Hamilton's (1963) earlier studies with an evaluation of the incidence and observer-error of physical signs of hypercapnia and acidemia. The only manifestation regularly present in hypercapnia was some disturbance of consciousness (drowsiness proceeding to narcosis). Some old friends such as papilloedema and extensor plantar responses were found to be uncommon, and there was often disagreement between observers about their presence or absence. In essence I agree with Christie (1964) that the “diagnosis of CO_2 retention . . . is a matter of knowledge and of laboratory technique rather than clinical acumen.” I quarrel with the term “laboratory” because our house-staff measure PCO_2 in the ward or the side-room, using a simple rebreathing method (Campbell and Howell, 1962). Some people have difficulty with this method, but success requires only a little understanding and motivation—our house-physicians rapidly acquire both.

Differentiation from Other Causes of High PCO_2 or Low PO_2

Differentiation of the hypercapnia of respiratory failure from the secondary hypercapnia of a non-respiratory (metabolic) alkalosis is usually possible on clinical grounds, but occasionally an estimation of the H^+ activity of the blood is required and can be achieved either by measuring the pH or by measuring both the PCO_2 and the bicarbonate concentration of the blood. It may still be difficult to differentiate between the two conditions, and they often coexist, as, for example, in a patient with respiratory failure who becomes depleted of chloride or potassium (Refsum, 1962; Kassirer *et al.*, 1965). Occasionally proof that hypercapnia is due to respiratory failure requires other measurements of respiratory function, but the chief value of such measurements is not in establishing the diagnosis but in assessing the severity of impairment of function.

Differentiation of the hypoxaemia of respiratory failure from that of right-to-left cardiovascular shunting is usually possible on clinical grounds, including observation of the effect of breathing 30% and 100% O_2 on the colour of the mucous membranes. Sometimes measurement of the arterial blood PO_2 while the patient breathes 100% O_2 is required; in respiratory failure the arterial PO_2 rises by several hundred mm. Hg when 100% O_2 is breathed, and, unless there are completely unventilated parts of the lung through which there is “frank shunting,” it may reach 600 mm. Hg.

Value of Blood Gas Measurements

Within the past five years methods of measuring the blood gases have become technically fairly easy (I say *fairly* easy because they are still by no means foolproof), and since “complete” blood gas analysers are being widely sold perhaps some remarks based upon ten years' experience may not come amiss. For the first five years I had only Riley's microtonometric or “bubble” method (Riley *et al.*, 1957). This is “touchy,” and the whole procedure requires nearly an hour; I was the only person in the hospital trained to do it. Nothing so concentrates the mind on the value of an investigation to the management of a patient in one's care as knowing that one has then and there to spend a trying hour in the middle of the day's work or late at night doing it oneself. To be brief, this

experience taught me never to grudge time spent measuring PCO_2 , but that I rarely needed the PO_2 and very seldom changed the treatment after learning it (Campbell, 1961).

Arterial Oxygen Pressure or Saturation.—In respiratory medicine the measurement of arterial PO_2 is of more value than the measurement of arterial saturation. It is, however, short-sighted to make the measurement in isolation with the simple aim of diagnosing hypoxaemia. Measurements of arterial PO_2 are really informative only when related to the alveolar PO_2 , and therefore must be made together with the arterial PCO_2 . This enables the alveolar-arterial PO_2 difference to be determined. These procedures are useful in evaluating respiratory function in the relatively stable conditions of chronic disease. I believe they are of less value and are certainly inessential in acute situations for the following reasons (Campbell, 1965). First, it is both easier and safer to give oxygen to a patient who may be hypoxic than to make a measurement of arterial oxygenation, which at best can only cause oxygen to be withheld because serious hypoxia has not developed—yet. Secondly, arterial oxygenation is related to respiratory function in a very non-linear manner; it may change greatly and rapidly with minor changes in clinical condition, and vice versa. Thirdly, the demonstration of arterial hypoxaemia does not reveal whether the cause is inadequate ventilation or defective alveolar-capillary gas exchange; hypoxaemia due to both these mechanisms is corrected by oxygen administration, but inadequate ventilation may be more difficult to treat.

Blood PCO_2 .—It used to be academic and impractical to extol the clinical value of measurements of the blood PCO_2 , but Astrup (1959) and Severinghaus (1959) have now made the measurement of PCO_2 in blood relatively easy, and the rebreathing method can be used without any blood at all. There are six reasons why knowledge of the blood PCO_2 is valuable:

1. A very high PCO_2 is toxic. I put this reason first because it is the simplest to understand and the least important. Toxic levels of PCO_2 are uncommon, and in fact can occur only when the inspired air is enriched with O_2 . For reasons given below, the highest PCO_2 possible while breathing air is about 90 mm. Hg. This degree of hypercapnia is not dangerous of itself. When the

PCO_2 rises above 100 mm. Hg the patient becomes drowsy and the small respiratory excursions allow the lungs to deteriorate. But this degree of hypercapnia is still not dangerous of itself. In fact I am not sure what is the tolerable limit of hypercapnia (or of the associated acidemia). Provided the inspired oxygen concentration is adequate it seems possible to survive a PCO_2 of 150–200 mm. Hg and a (H^+) of 100–150 nanoNormal (pH 7.0–6.82). Observations in anaesthetized animals in the interesting state of “supercarbina” suggest that there is almost no limit to the biological tolerance to PCO_2 . Dogs at a PCO_2 of 600 mm. Hg and a (H^+) of 400 nN (pH 6.4) breathe spontaneously, and their hearts seem to function very well (Graham *et al.*, 1959; J. F. Nunn, personal communication).

2. Once a patient develops chronic hypercapnia the regulation of ventilation tends to become defective and the PCO_2 tends to become unstable. Such patients may develop severe CO_2 retention when given sedatives or O_2 ill-advisedly. I wish in passing to voice my doubt that there are any safe sedatives for these patients.

3. Patients with respiratory disease become oedematous only if their PCO_2 is raised, or perhaps the converse statement is more accurate: such patients rarely become oedematous while the PCO_2 of their blood is normal unless they develop some complication such as pulmonary artery thrombosis (Hamilton and Gross, 1963). This knowledge may help in the differential diagnosis of chronic heart failure. The explanation for this fact is uncertain, but it casts doubt upon the usual hypotheses offered for the cause of oedema in “cor pulmonale” (Campbell and Short, 1960).

I have just given three empirical reasons for finding measurements of PCO_2 valuable; the other three are fundamental and can be expressed mathematically. In giving these equations I do not wish to imply that the clinician need often solve them explicitly, but they should be at the back of his mind, and he should be prepared to solve them approximately to see if the solutions might be helpful or important; if so, further action can be taken.

4. The arterial PCO_2 reveals the adequacy of alveolar ventilation:

$$\text{Arterial } \text{PCO}_2 = \frac{\text{CO}_2 \text{ production}}{\text{Alveolar ventilation}} \times 0.86^1 \quad (\text{Eqn. 1})$$

$$\frac{\text{Metabolic rate}}{\text{Effective breathing}}$$

Thus the PCO_2 is the criterion of the adequacy of alveolar ventilation and the best index of progress in a patient with inadequate ventilation.

5. PCO_2 is the respiratory parameter of the acid:base equation of which Eqn. 2 is in Henderson's form and Eqn. 3 is in Hasselbalch's form.

$$(\text{H}^+) = 24 \frac{\text{PCO}_2 \text{ mm. Hg}}{[\text{HCO}_3^-] \text{ (milliNormal)}} \quad (\text{Eqn. 2})$$

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2} \quad (\text{Eqn. 3})$$

If PCO_2 is known and one of the other two variables is also known the acid:base composition of the blood is fully described. This use of PCO_2 is obviously relevant to the acidosis of respiratory failure, but is also valuable in the elucidation of other acid:base disturbances.

6. The PCO_2 enables the alveolar PO_2 to be calculated, using the alveolar-air equation or the $\text{CO}_2:\text{O}_2$ diagram of Rahn and Fenn (1955) (Fig. 3).

$$\text{Alveolar } \text{PO}_2 = \text{Inspired } \text{PO}_2 - \frac{\text{Arterial } \text{PCO}_2}{\text{Resp. Quotient}} \quad (\text{Eqn. 4})$$

The alveolar-air equation, of which the above is a simplified version, sufficiently accurate for most clinical purposes, is based upon the fact that, of the four gases in the alveolar air, water vapour is at a pressure fixed by body temperature; N_2 is not exchanged; and O_2 and CO_2 are reciprocally related by the ratio in which they are exchanged during metabolism—the respiratory exchange ratio or respiratory quotient (normally about 0.8).

FIG. 3.—Severity of respiratory failure represented on a carbon dioxide: oxygen diagram. This is a $\text{CO}_2:\text{O}_2$ diagram for a barometric pressure of 760 mm. Hg. The value of 20 mm. Hg (equivalent to a saturation of 30–40%) chosen for the minimum tolerable arterial PO_2 is based upon general experience (Refsum, 1962; Campbell, 1965). The horizontal lines are observed values; the height of the line is the arterial PCO_2 ; the right-hand end is the alveolar PO_2 ; the left-hand end is the arterial PO_2 ; the horizontal length is the alveolar-arterial PO_2 difference. The line N gives average normal values. The other lines are taken from a series of 81 patients with hypercapnia whose arterial blood was examined soon after admission to hospital and before the administration of O_2 . 1 is the state of the patient with the highest PCO_2 (88 mm. Hg); 2 is that of the patient with the lowest arterial PO_2 (19 mm. Hg); 3 is that of the patient with the greatest alveolar-arterial PO_2 difference (57 mm. Hg). (Taken from the data of McNicol and Campbell, 1965.)

¹ 0.86 is a good average value at sea-level for a factor depending chiefly on barometric pressure.

Severity of Respiratory Failure

The reciprocal relationship between alveolar PO_2 and PCO_2 embodied in the alveolar air equation (Eqn. 4) and shown graphically in the $\text{CO}_2\text{:O}_2$ diagram (Fig. 3) has a very important practical implication: when PCO_2 rises the inevitable fall in alveolar PO_2 , by causing hypoxaemia, sets a limit to the tolerable height of arterial PCO_2 . When allowance is made for the difference in PO_2 which is always present between the alveolar air and the arterial blood this ceiling PCO_2 is lower than the level which causes serious toxic effects. Fig. 3 embodies this physiological truism and clinical data (McNicol and Campbell, 1965) to support it. The triangle bounded by the line representing the R.Q. and the vertical dashed line representing a PO_2 of 20 mm. Hg in Fig. 3 defines the possible problems to be faced when a patient with respiratory failure is admitted to hospital breathing air. This triangle delimits the battlefield and the possible disposition of the enemy. If I may anticipate, the best strategy is to draw the enemy to the east by raising the inspired PO_2 while one keeps close contact with his northern flank, prepared to resist any northward wheel but without necessarily attacking this flank.

But what about the acidemia? Predictions based upon the acid:base equation (2 or 3) and the buffer capacity of the body suggest that the (H^+) of the blood cannot or should not rise above 70 nN (pH fall below 7.15). Observation again supports prediction: the highest (H^+) observed in the patients referred to above (McNicol and Campbell, 1965) was 65 nN (pH 7.19), a serious but not dangerous acidemia. It is salutary to read the following passage: "CO₂ excess is unlikely of itself to be of dangerous or even serious significance . . . provisions for the excretion of CO₂ by the lungs are so much more generous than those for the absorption of oxygen that in a person breathing ordinary air any interference with the gas exchange must cause death from anoxia before CO₂ accumulation becomes dangerous" (Peters and Van Slyke, 1931, p. 950).

The fact that the PCO_2 cannot exceed a certain level while a patient in respiratory failure is breathing air has an important corollary: should a patient for any reason develop a PCO_2 over 100 mm. Hg he will inevitably have hypoxaemia of sufficient degree to cause damage unless his inspired gas contains more than the 21% O₂ (150 mm. Hg PO_2) present in air. Interruption of the supply of O₂ for even a few minutes in such a patient may be disastrous. Moreover, the normal defensive responses to hypoxia are usually embarrassed or inactivated by one or another of the things that have happened to him.

Time and Respiratory Failure

The increasing use of methods for measuring the blood gases and acid:base state has shown that many patients in hospital have very severe respiratory acidosis—more severe than Peters and Van Slyke would have suspected. There are a number of reasons for this. First, modern medical, surgical, and anaesthetic procedures can greatly affect the lungs and respiration; secondly, CO₂ unresponsiveness may allow the PCO_2 to rise to narcotic levels if oxygen is administered in an uncontrolled way (Comroe *et al.*, 1950; Westlake *et al.*, 1955); but most important is failure to appreciate the time relations of respiration and the speed with which things can go wrong. Here are three instances: first, provided the inspired air is enriched with O₂, depression of ventilation can cause the PCO_2 to rise to narcotic levels in half to one hour, and acidemia may develop fifty times more rapidly than in the most acute uncontrolled diabetes. Secondly, as stated earlier, lack of an occasional fairly full expansion by a deep breath causes even normal lungs to deteriorate within half an hour both mechanically and probably as gas-exchangers. (The patient in CO₂ narcosis breathes shallowly and does not cough effectively.) Thirdly, the different storage capacity of the body for O₂ and

CO₂ means that a withdrawal of O₂ may lead temporarily to a more intense hypoxia than if O₂ had never been administered at all. These facts prompt my campaign against uncontrolled O₂ therapy, and, worse, intermittent O₂ therapy, a practice resembling that of bringing a drowning man to the surface of the water—occasionally.

Management of Respiratory Failure

Tradition does not encourage nor time permit a detailed discussion of treatment, but having emphasized the physiology underlying other aspects I wish to finish by stating briefly certain principles which are based upon the combination of physiology and clinical experience, and which form a summary of much of this lecture. These remarks will be chiefly concerned with the commonest and most difficult form of acute respiratory failure—that occurring in patients with diffuse airways obstruction.

1. *Assessment and Control are Easier if Measurements are Made.*—The condition can be managed clinically without any physiological measurements just as acute nephritis can be managed without measuring the blood urea, or as diabetic ketosis can be managed without measuring the blood-sugar, or myocardial infarction without measuring the blood-pressure. But assessment and control are better if some physiological measurements are made.

2. *Hypoxia is often Dangerous, Respiratory Acidosis Rarely Is.*—Death from hypoxia sets a limit to the possible severity of respiratory failure while breathing air. Although they may have severe hypoxia, patients cannot enter hospital in very severe respiratory acidosis.

3. *Abolition of Hypoxia is Easier than its Diagnosis.*—Therefore, although pleased to have measurements of arterial oxygenation, I do not feel the need of them.

4. *Underventilation is more Difficult to Treat Than Hypoxaemia.*—Therefore measurement of PCO_2 is much more valuable because it indicates the adequacy of ventilation in relation to metabolic needs (Eqn. 1).

5. *Acidemia is not Usually a Problem.*—Estimates of H^+ activity are required only occasionally if ventilation and oxygenation are controlled and provided no electrolyte abnormalities develop. When an estimate of H^+ activity is desirable it can readily be obtained by relating the bicarbonate concentration of the venous blood to the PCO_2 (Eqn. 2) without necessarily resorting to measurement of blood pH (Campbell, 1962).

6. *Rapid Reduction of PCO_2 is Usually Undesirable.*—The patient—not the PCO_2 —must be treated. The aim is to prevent the PCO_2 from rising, not to lower it, unless it is so high that it has obviously risen recently and excessively as a result of failure of treatment. If properly managed and unless his lungs are too permanently damaged the patient will lower his own PCO_2 . Overenthusiastic restoration of the PCO_2 to "normal" may have unfortunate results (Lancet, 1965).

7. *Productive Coughing is Vital.*—This not only keeps the larger airways patent, but, by causing deep breaths, also discourages deterioration of the distal parts of the lung. Amateur physiotherapy directed to this every 10 to 15 minutes is of more value than professional attention a few times a day. Dr. J. B. L. Howell (personal communication) believes that the most important single piece of information in deciding against tracheostomy is knowledge that the patient can cough and raise his sputum.

8. *The Critical Phase is from One-half to Four Hours after the Start of O₂ Therapy.*—If progress is satisfactory during this period the more radical forms of treatment, such as pharmacological stimulation, intubation, bronchoscopy, buffer infusions, artificial ventilation, or tracheostomy, are unlikely to be

required. If progress is unsatisfactory this is the time at which steps to institute these measures should be taken; some of them take one or two hours to arrange even in the best-ordered hospitals. Although some of these measures may be required when intensive conservative treatment has failed it may also be that their occasional success represents the salvage of a vessel aground on a reef that better navigation could have avoided.

9. Hypoxia Must be Abolished, Hypoxaemia Need Not be Abolished.—Damaging hypoxia can be abolished by modest relief of hypoxaemia. Modest relief of hypoxaemia is provided by very modest increases in the inspired O_2 concentration (Campbell, 1960a, b). Unless generous facilities are available to deal promptly with an aggravation of underventilation the inspired O_2 concentration should initially not exceed 28% (200 mm. PO_2). The inspired O_2 concentration can be increased hourly if progress is satisfactory. The *essential and primary* aim of oxygen therapy in respiratory failure is to keep arterial oxygenation above the damaging levels of hypoxaemia (Fig. 2). A *desirable but secondary* aim is to keep as far above these levels as possible to guard against further deterioration in the respiration or circulation and to relieve the strain of the adaptive responses (Campbell, 1964, 1965). There can be no compromise over the primary aim. There often must be compromise over the second aim, and the compromise is usually satisfactory.

In severe respiratory failure continuous oxygen therapy is essential. It is particularly important that O_2 should not be withdrawn even if it is thought that the severity of the failure has been due to uncontrolled O_2 administration; other measures must be used to try to rectify the situation while the O_2 is continued.

10. Pulmonary-function Tests Should be Done When the Patient is at His Best—to Set the Target When He is at His Worst.—Perhaps this point should have been the first. When a patient with chronic respiratory disease is admitted to hospital in severe respiratory failure it is sometimes difficult to know how officiously one should strive. The good physician does not wish to inflict a tracheostomy, artificial ventilation, vigorous physiotherapy, and the rest of the paraphernalia on a patient when technical success can only return him to a life of hopeless invalidism. Frequently the history provides sufficient guidance, but often one would like to see objective measurements of respiratory function made during remission to supplement the clinical evidence. Of course, it may be difficult to persuade patients to attend hospitals or clinics when they are well, but many do attend to have repeated chest x-ray examinations which cost more in time and money and are less informative than simple tests of function in following their progress. Moreover, patients who have to be admitted to hospital in relapse can be examined before discharge or at follow-up. Too often these measurements are made only when a patient is in relapse, at a time when it is only too obvious what one is fighting *against*, whereas one wishes to know what one is fighting *for*.

Conclusion

In conclusion I would like to quote the Goulstonian Lecturer of 1943, who recently stated that respiratory failure "is a facet of medicine which is certainly not a passing fad . . . death from respiratory failure can almost always be delayed or prevented, provided that the physician or surgeon is aware of the hazards involved and provided that adequate facilities are available" (Christie, 1964). To encourage discriminating use of these facilities and to encourage those who must practise without them, I would add that a sound grasp of the relevant physiology and a sense of timing enable much to be accomplished and many lives to be saved without drama and without elaborate facilities.

Summary

Respiratory failure may be defined as impairment of respiratory function of such degree that the pressure of CO_2 (PCO_2) in arterial blood rises above normal limits or the pressure of oxygen (PO_2) in arterial blood falls below normal limits.

Respiratory failure should be distinguished from breathlessness. Two types of respiratory failure can be distinguished by the presence or absence of hypercapnia. The causes of these two types are discussed and the importance of disturbed relationships between ventilation and perfusion of the lung is emphasized.

Respiratory failure may result from lesions or disorders of function at any of the following sites: brain; spinal cord; motor neurone; neuromuscular junction; respiratory muscles; thoracic cage; pulmonary circulation; lung; airway. The physiological features of clinical importance are reviewed.

The diagnosis of hypoxaemia and hypercapnia and the value of blood gas measurements are discussed. The particular usefulness of measurements of PCO_2 is emphasized.

So long as the patient breathes air, death from hypoxia sets a limit to the severity of the hypercapnia and acidemia. More severe respiratory failure can develop rapidly if O_2 is breathed, and the lungs may then deteriorate.

Some principles of management of respiratory failure are stated.

I wish to thank all those colleagues and teachers who have contributed both directly and indirectly to the experience and views contained in this lecture.

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Surgery of Carotid Artery Stenosis

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Hunt (1914) first drew attention to carotid artery stenosis and thrombosis as a cause of stroke. Eastcott, Pickering, and Rob (1954) demonstrated that surgical correction of stenosis was possible, with relief of symptoms in one patient. Since then series of patients have been reported by Rob and Wheeler (1957), De Bakey, Crawford, and Fields (1961), and Edwards and Gordon (1962), to mention a few authors.

Atherosclerotic narrowing at the origin of the internal carotid artery is the usual pathological abnormality, and it is remarkable how often the process is limited to this short segment of the vessel. The mechanism by which this may produce the characteristic symptoms of intermittent contralateral stroke or intermittent homolateral blindness has given rise to much speculation and research. Ross Russell (1961) demonstrated emboli in the experimental animal and also in the branches of the ophthalmic artery during attacks in patients. However, anticoagulant therapy does not necessarily relieve the patient's symptoms. Cerebral anoxia secondary to haemodynamic changes originating at the site of the

carotid stenosis has been invoked to explain the symptoms. While the numerous congenital anomalies of the circle of Willis tend to support these theories, cerebral-flow studies (Nylin, 1961) have so far been unable to confirm any overall change in blood-flow during the attacks.

Thrombosis of the internal carotid artery is often the sequel to carotid artery stenosis, and hemiplegic stroke the resultant risk, but stroke does not necessarily result from a complete occlusion. There are several well-documented case reports in which one or both carotid arteries are completely occluded, without symptoms having been experienced by the patient. There are, however, no clinical data to relate the risk of thrombosis to the degree of carotid stenosis, or to the time lapse which may intervene between these events.

The results of surgical correction of stenosis are satisfactory in the early case, and poor in the completed stroke secondary to thrombosis (Rob, 1959; Crawford, De Bakey, and Fields, 1961). The obvious explanation is that the anoxic cortical cell undergoes irreversible change after four minutes and that it is impossible to undertake surgical correction within this time limit.

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