BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 21 1953

# THE DEFINITION AND ASSESSMENT OF RESPIRATORY FUNCTION*

BY

K. W. DONALD, D.S.C., M.D., F.R.C.P.
*(Reader in Medicine in the University of Birmingham)*

## PART I

Many clinicians who specialize in diseases of the lungs will declare quite honestly that they understand little if anything about lung function. There are good reasons for this. The constant presentation of special tests, some simple and some very complicated, dealing with one particular aspect of lung function, as a general clinical test of great value has made the clinician justifiably sceptical. The great gap between modern knowledge of respiratory function and what is taught to the students in their most receptive years is unfortunate. In the hurly-burly of respiratory research few pause to consider and agree upon what gains have been made and what may be of real practical value. On the other hand, it is surprising that chest physicians and surgeons, who spend many years perfecting their skill and increasing their knowledge, are reluctant to devote a year or so to the study of respiratory physiology. Without such a training in early professional life it is hardly possible to develop an informed curiosity concerning the problems of respiratory function.

The new era of thoracic surgery has come as an abrupt challenge in this field. Lung resection and collapse can be life-saving measures, but there is always the problem of whether the remaining lung will support a tolerable existence. Operations are frequently contemplated on a background of disease, and thus, although the lung that will remain may have impaired function, some attempt must be made to assess this function so that the feasibility and safety of the operation can be reasonably foretold.

The function of the lungs is to maintain normal and nearly constant oxygen and carbon dioxide tensions and content in the arterial blood in all physiological circumstances, without causing any undue sensation of ventilatory discomfort or adverse effect on the heart or any other organ. This constancy of the arterial blood gases in all degrees of activity and oxygen usage is maintained only by the efficient transfer of gas between the alveolar air and the blood passing through the alveolar capillaries. Such a transfer demands the intimate bringing together of blood and gas and the maintenance of an adequate gas-tension gradient between them. It is the function of ventilation that maintains and freshens the alveolar gases despite the constant interchange of oxygen and carbon dioxide with the venous blood. This ventilation must not only be adequate in total quantity but must be efficiently distributed to all alveoli through which blood is flowing. Similarly, the venous blood from the right heart must be efficiently distributed to all ventilated alveoli. In this way an enormous blood–gas interface is created. Any lack of correlation between the ventilation and circulation of the lungs, in the form of ventilation of unperfused alveoli or perfusion of underventilated alveoli, will mean wasted ventilatory effort or imperfect oxygenation of blood, and will cause a reduction in the effective blood–gas interface. Finally, there must be no undue interference with the diffusion of gases through the structures present between the alveolar gases and the blood.

### VENTILATION

The purpose of lung ventilation is to refresh the lung alveoli constantly with atmospheric air so that adequate oxygen diffuses into, and carbon dioxide diffuses from, the blood as it passes through them. The act of ventilation is unconscious, and, although a healthy person may be transiently aware of his respiration, it causes him no discomfort or embarrassment. The only important factor causing changes in the volumes ventilated in everyday life is the degree of body activity. If normal subjects exercise very violently, or subjects with lung disease increase their activity unduly, then they will complain of "shortness of breath" or dyspnoea. In the past this sensation has been attributed to many factors such as excess carbon dioxide, anoxaemia, and increased hydrogen-ion concentration, and their effect upon the central nervous system. In recent years increasing evidence has accumulated that dyspnoea is no more than ventilatory discomfort, when the volumes ventilated are excessive for the ventilatory capacity present. Dyspnoea can thus be caused by very large ventilatory volumes in the presence of a normal ventilatory capacity, or by very moderate ventilatory volumes in the presence of a severely impaired ventilatory capacity.

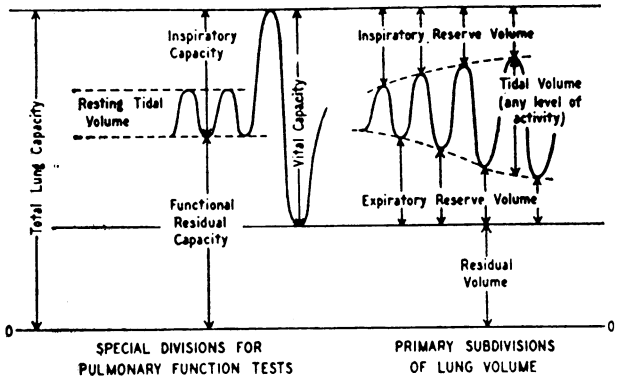
#### Lung Volumes

The lung volumes—the boundaries, as it were, within which ventilation takes place—have for many years been regarded as one of the most important quantitative measurements in the assessment of lung function. There

*Adapted from lectures given in the "Science and Medicine" series, Postgraduate Federation (London University), 1950–1.

is no doubt that undue emphasis has been laid upon this aspect. The study of lung volumes alone in various lung diseases can be particularly misleading if the observers assume that changes in the lung volumes are closely correlated with total lung function or the severity of a particular disease.

The terminology employed in the study of lung volumes has been so diverse that unnecessary confusion has arisen. Christie (1932) made excellent suggestions to standardize the nomenclature, and his terminology has been almost universally accepted. Recently, however, a further standardization has been put forward by a large group of interested workers (Pappenheimer *et al.*, 1950), and their suggestions are a further advance (see Diagram). The primary subdivisions of lung volume are




Subdivisions of the lung volume (after Pappenheimer *et al.*, 1950). All gas volumes corrected to body temperature, pressure, and saturated with water vapour (B.T.P.S.).

shown on the right, and apply to all levels of respiratory effort and contain no overlapping volumes. On the left are the terms used when the patient is studied at rest. It will be noted that the expression "air" to denote a volume is carefully avoided. All gas volumes should be corrected and stated at body temperature, pressure, and saturated with water vapour (B.T.P.S.), as the vital phenomena occur within the chest and not within the spirometer.

The vital capacity is, by Hutchinson's (1846) original definition, the volume of gas that can be expelled by a maximal expiration following a maximal inspiration. It can be measured by expiring into any gas-volume-measuring apparatus that affords no appreciable resistance and is of sufficient accuracy. In the closed circuits usually employed, when a tracing is obtained, high percentages of oxygen are used. Accurate volumetric tracings while breathing air or any other mixtures of gases can be obtained by the box-bag technique (Donald and Christie, 1949). In a series of observations on four normal subjects by this method I could find no significant change in vital capacity when breathing oxygen, air, 12% oxygen and nitrogen, or 5% carbon dioxide in air. When determining the vital capacity several trials are carried out. If successive measurements show a large increase, owing to better understanding and effort, then the procedure should be continued until nearly constant values are obtained. According to definition, the maximal value observed is recorded as the vital capacity.

If a respiratory tracing is taken over a period the two components of the vital capacity, the inspiratory capacity (O.T. complemental air) and the expiratory reserve volume (O.T. reserve air) can also be determined. This subdivision affords some difficulty even in normal subjects. There is a tendency to alter and vary the "respiratory level" (which can be precisely described by the volume of air in the chest at the end of quiet expiration) during such breathing gymnastics. Further, subjects with respiratory disability are even more prone to such alterations. The temporary increase of oxygen uptake resulting from a deep inspiration (Armitage and Arnott, 1949) also makes the analysis of the record more difficult.

The vital capacity alone is not of great value in assessing respiratory disability. A patient with greatly reduced vital capacities may have remarkably good ventilatory function, and vice versa. The two subdivisions of vital capacity have also been overinterpreted.

It was thought that the determination of the residual volume (that volume of gas remaining in the lungs after a maximal expiration) by various indirect methods would give far more meaning to lung-volume measurements, particularly as this would allow the total lung capacity to be studied. Thus the residual volume and the total capacity would give the minimal and maximal lung volumes. The residual volume could be considered not only absolutely but also as a percentage of the total lung volume. Christie (1932) has reviewed 47 methods of determining the residual volume.

*Open-circuit Method.*—The so-called "open-circuit" of Darling *et al.* (1940) is used extensively in America. When a subject breathes oxygen the total amount of nitrogen in the expired gas will be a simple function of the volume of gas in the lungs and the change in the lung nitrogen concentration. The expired gas is collected in a large spirometer (Tissot) for seven minutes. The patient is then switched out of the oxygen circuit and told to exhale maximally, an alveolar sample being taken with an evacuated gas-sampling tube. There are many valid criticisms of this method: poor washing-out of underventilated areas of lung, no tracing is available, and direct alveolar samples (end of maximal expiration) are unreliable in many lung diseases.

*Closed-circuit Method.*—This method of determining the residual volumes, which is used extensively in this country and Europe, employs a closed circuit and a physiologically inactive gas. Its principle is that the degree of dilution of a known quantity of inert gas is a simple function of the combined volumes of the lungs and the spirometer circuit. In 1800 Humphry Davy used hydrogen for this purpose. Van Slyke and Binger (1923) measured the residual volume by first determining the functional residual capacity during quiet normal breathing. Christie (1932) improved this technique and used the nitrogen present in the lungs at the time of turning the patient into the circuit as his indicator gas. Herrald and McMichael (1939) introduced the important modification of running oxygen into the circuit so as to keep the spirometer tracing level. This procedure ensured a constant spirometric and circuit volume despite oxygen uptake. They also employed a katharometer, which, by measuring the changing thermal conductivity of the gas, indicated the completion of mixing in the circuit and lungs. McMichael (1939), by reintroducing hydrogen as the indicator gas, with its high thermal conductivity, was able to use the katharometer not only to determine the rate and completion of mixing, but also the final concentration of hydrogen. Meneely and Kaltreider (1941) introduced the use of helium as the indicator gas. It has all the advantages of hydrogen without the risk of explosion, and it has been almost universally adopted for this purpose. These workers also pointed out that the rate of mixing of helium in the lungs, while measuring the residual air, was greatly retarded in emphysema.

The present methods of determining lung volumes are undoubtedly satisfactory, and the results obtained are certainly not far from the actual volumes being measured. Lung-volume studies of the same patients by the open- and closed-circuit methods have shown a remarkable agreement despite the faults of the simpler method (Gilson and Hugh-Jones, 1949). Many excellent studies of the lung volumes in various types of pulmonary disease are available. The stage has now been reached where it is more important to consider the value and meaning of lung-volume determinations than to attempt to improve their accuracy. It is also important that the values and ranges of variation of the lung volumes in normal persons at various ages should be more carefully determined.

The upper "normal" limit of the residual volume of the lungs, when expressed as a percentage of the total capacity, is usually considered to be from 20 to 30%, increasing slightly with age. However, in recent years more and more instances have been reported of healthy persons, particularly those over 50 years of age without any history of lung

disease or dyspnoea, with a residual volume of well over 40% of their total lung capacity (Greifenstein *et al.*, 1952). This is in no way surprising to anyone who has attempted to measure biological phenomena, but it has not deterred an appreciable number of workers from assessing the degree of severity of such diseases as pulmonary emphysema by this figure alone.

### Pulmonary Emphysema

The old clinical observations that the lungs cannot empty adequately and that the respiratory level is much raised in this disease are in general confirmed. Stating this in terms of lung volumes, the residual volume and functional residual capacity are increased. However, the relationship of this increase to the degree of disability is very variable indeed. Baldwin *et al.* (1949b), in their extensive study of emphysema, divided the patients into four different groups, the severity of the disease being judged by the degree of arterial blood desaturation at rest and with exercise, by the presence or absence of carbon dioxide retention, and, finally, by the development of right heart failure. Although they found that most of these patients had a pronounced increase of residual volume (both absolutely and in relation to total capacity) the mean figure of the residual volume percentage of total capacity was in the region of 50 in all groups, despite the fact that these groups represented from moderate to very severe emphysema. Further, some of the most disabled patients had almost normal residual-volume/total-capacity ratios, and some patients in the earliest group, who did not even show arterial blood desaturation on brisk exercise, had some of the highest residual volumes. It has been my own experience and that of many other workers that, although the residual volume is usually greatly raised in emphysema, the relation of this rise to respiratory function, as judged by exercise tolerance and other tests, is most variable and unreliable.

Baldwin *et al.* also found, as many others have reported since, that there was very poor correlation between the vital capacity and ventilatory capacity (as measured by voluntary hyperventilation). Further, although the total capacity is increased in some cases of emphysema, this is by no means invariable, and most patients with this disease have a total capacity within the normal range. It follows, speaking generally, that if the total capacity, which is the combined residual volume and vital capacity, is not greatly altered in this disease then the size of the residual volume cannot be expected to correlate any better with function than the vital capacity.

### Pulmonary Fibrosis

In diseases in which there is generalized pulmonary fibrosis the interpretation of lung volume data becomes even more difficult. Pulmonary fibrosis can occur without any significant degree of emphysema. In most of these patients all the various subdivisions of the total capacity are reduced proportionately and both the vital capacity and the residual volume are abnormally small.

However, if the vital capacity is reduced but the residual volume is still normal then the latter will represent an abnormally large percentage of total capacity. In the absence of knowledge of how pulmonary fibrosis may affect the filling and emptying of the lungs it is difficult, if not impossible, to assess the degree of emphysema in such patients on this evidence alone. The diagnosis of emphysema in pulmonary fibrosis is of great importance, as it is most desirable to be able to assess in what ways pulmonary fibrosis causes respiratory disability, apart from concomitant or secondary emphysema. Increase of the absolute residual volume over the normal range is usually thought to be good evidence of emphysema, but the assessment of emphysema in the presence of lung fibrosis is exceedingly difficult.

If the disease process is unilateral or different in each lung—that is, collapse or fibrosis with contralateral lung distension—the lung-volume measurements, as obtained by external spirometry, are impossible to interpret. Even if the lung volumes of the separate lungs are obtained by bronchial catheterization, one cannot be certain whether the changes demonstrated are due to actual emphysema or fibrosis or to mechanical events in the chest such as mediastinal shift and collapse. Again, it should be emphasized that it is unwise to regard the various subdivisions of lung volume as a permanent expression of morphological or pathological changes. There can be great changes in the respiratory level (as measured by the functional residual capacity) and the residual volume in the same patient in relatively short periods of time. Exacerbations of bronchospasm and bronchitis will cause considerable but reversible increase of the functional residual capacity and residual volume.

Finally, it can be stated that, although the lung volumes are useful data and represent one of the first attempts to measure disturbances of lung function, they are of very limited value alone, and in our present state of knowledge they can be grossly overinterpreted.

### Ventilatory Capacity (Maximum Breathing Capacity)

The lung-volume measurements are entirely spatial and have no relation to time. Thus the vital capacity is a measure of the maximum filling and emptying of lungs, but provides no information whatsoever concerning the speed and efficiency of this filling and emptying during increased ventilation. The ventilatory capacity depends more upon this speed and efficiency than upon the absolute size of the range of movements. The voluntary maximum breathing capacity first introduced by Hermannsen (1933) is of great value in the assessment of ventilatory function. The maximum breathing capacity (M.B.C.) is defined as the maximum volume of air that can be breathed in unit time. It is usually measured for 15 seconds and then converted to litres a minute. It should be emphasized that the ventilatory volumes obtained by maximum voluntary hyperventilation, although a most useful measure of the efficiency of the bellows action of the lungs, far exceed those obtained during the heaviest possible exercise or by maximum respiratory stimulation by increased tensions of carbon dioxide. If the true ventilatory capacity were defined as the maximum volume that can be ventilated in unit time without undue discomfort, then it is usually about half the maximum breathing capacity. The maintenance of a high ventilatory capacity requires good neuromuscular co-ordination (which is rarely affected), even and adequate application of negative pressure to the lung surfaces, a normally patent tracheobronchial tree, normal elasticity and rebound of the lung tissue, and movable components of the chest wall. It is manifest that a large number of important factors are being assessed simultaneously. The prediction formulae of the maximum breathing capacity employ the age and body size (Baldwin *et al.*, 1948) or age alone (Wright *et al.*, 1949). There is a large reduction of maximum breathing capacity as the age increases.

There are two commonly used methods of determining the maximum breathing capacity. In the first and more informative method an ordinary Benedict type spirometer is employed. It is important that the resistance is kept to a minimum, and wide non-corrugated tubing should be employed: 1½-in. (3.8-cm.) tubing is adequate; the use of very wide tubing introduces new errors. The inertia and natural frequency of the system will cause inaccuracies, but if the bell is reasonably light it has been shown (D'Silva and Mendel, 1950) that reliable results can be obtained up to respiratory frequencies of 110 a minute. Other workers measure the maximum breathing capacity with non-return valves each side of the mouthpiece and collect the expired air in a Douglas bag or a Tissot spirometer. It is important that the valves used should have a reasonably low resistance even at very high rates of air flow. This method is particularly useful when dealing with a "mixed" population of tuberculous and non-tuberculous patients. Only the mouthpiece and valves need be cleaned and sterilized, as there is no rebreathing.

In this test the subject is usually told to breathe as deeply and as rapidly as possible. These instructions are self-contradictory, but many authors state that the compromise reached by the patient is his best ventilatory state. There is as yet no proof

of this, and there is in fact good evidence (Bernstein *et al.*, 1952) that unless a respiratory rate of 70 a minute or over is reached low values will be obtained. Emphasis on speed and dictating the rhythm imparts a sense of urgency and need for maximum effort. The personality and power of exhortion of the observer is important, and this factor is another cause of the varying figures obtained in different laboratories. It would be more satisfactory if a standard apparatus and technique could be agreed upon by all workers in the field, but at present this does not seem to be possible. There may be some risk in pulmonary tuberculosis and other chronic infections, such as bronchiectasis, that this highly unnatural and relatively violent respiration will cause aspiration of actively infected material into healthy lung tissue. Although several workers have mentioned this hazard, only to dismiss it, common sense would suggest that the procedure is not without danger. In such instances I have satisfied myself with asking the patient to take a few rapid and forced respirations, using a high-velocity tracing. The ventilatory rate for each breath is measured in litres a minute, and the highest recorded is noted. The comparison of such results with the maximum breathing capacity measured by the usual method in less ill patients has been most satisfactory.

Gaubatz (1938), Tiffeneau and Pinelli (1948), Gaensler (1951), and Kennedy and Stock (1952) have measured the volume of gas expired in standard time during a single forced expiration after filling the lungs. Gaensler employs a spirometer with an automatic timing device so that the volume expired in a fixed time can be measured without a tracing. This is a great advantage in routine clinical work. He has shown an excellent correlation between this "timed capacity" ($\frac{3}{4}$ second) and the maximum breathing capacity.

How is the maximum breathing capacity affected in pulmonary emphysema? It is in this disease, in which the ventilatory capacity is most impaired, that the test is most valuable. It is much more simple than those used to determine the residual volume, and assesses the disability which is the main cause of the patient's dyspnoea and discomfort. One important disadvantage of this method should be mentioned. Bronchospasm, including bronchiolar obstruction due to oedema or secretion, will greatly reduce the maximum breathing capacity, and thus its value as a measure of true emphysema and permanent lung damage is greatly reduced in just those cases in which emphysema threatens and needs to be assessed.

A study of the ventilatory capacity before and after the inhalation of such "antispasmodics" as adrenaline can be carried out in order to assess the separate effect of bronchospasm. However, this is only a crude method, as such a procedure never raises the figure to that obtained if and when the bronchospasm remits naturally.

In patients with generalized pulmonary fibrosis and without emphysema, as judged clinically, radiologically, and by normal or reduced residual volumes, the ventilatory capacity is not greatly impaired. The mean of the maximum breathing capacity in a series of 39 such patients was 78% of the mean of a large group of normal subjects (Baldwin *et al.*, 1949a). Yet the vital capacity of many of these patients was greatly diminished. The decrease of the range of the lung bellows seemed to be compensated by increased efficiency and speed of movement. However, despite their relatively unimpaired ventilatory capacity, many of these patients were dyspnoeic on moderate exertion.

### Ventilatory Capacity and Dyspnoea

Cournand and Richards (1941), in order to study the relationships between ventilatory demands and ventilatory capacity, employed a standard step-test of thirty 20-cm. steps in one minute and measured the minute-ventilation during this time and for five consecutive minutes afterwards during recovery. This gave the minute-ventilation during a standard exercise and also allowed the study of the various ventilatory volumes associated with various degrees of dyspnoea. They studied a large group of patients suffering from pulmonary tuberculosis with varying degrees of disease, fibrosis, and collapse. After the step-test 68 patients experienced dyspnoea. During the last minute of dyspnoea the mean minute-ventilatory volume, when expressed as a percentage of the patient's maximum breathing capacity, was 37%. In the minute following relief from dyspnoea the mean ventilation was 29% of the maximum breathing capacity. They emphasized that there was considerable variation in different individuals.

In a later study of patients with generalized pulmonary fibrosis (Baldwin *et al.*, 1949a) a remarkably similar relationship was found. They also reported that the mean minute-ventilation of those with moderate dyspnoea was 49% of the maximum breathing capacity, and with very severe dyspnoea 69%. It was clearly shown that the cause of the dyspnoea in these patients with pulmonary fibrosis was partly the loss of ventilatory capacity and partly the abnormally large volumes ventilated on exercise.

When patients with severe emphysema and very limited ventilatory capacity, as measured by the maximum breathing capacity, were studied many signalled that they were relieved of dyspnoea when the minute-volume fell to 50–60% of the maximum breathing capacity (Baldwin *et al.*, 1949). It has been suggested that the emphysematous patient is grateful for small mercies and regards what, to him, is only moderate ventilatory discomfort as tolerable and not constituting shortness of breath. In any case there is no doubt that these relationships are no longer valid in patients with extremely impaired ventilatory capacities.

Cournand and Richards (1941) termed the unused percentage of the maximum breathing capacity the "breathing reserve" and related this figure to the various degrees of dyspnoea. This term can be criticized, as a large amount of this so-called reserve can never be used. Even a normal subject ventilating 50–60% of his maximum breathing capacity after very violent exertion is uncomfortably dyspnoeic. It cannot be overemphasized that the maximum breathing capacity is only an arbitrary measure of the bellows action of the lungs and does not represent the maximum volume that can be ventilated by that person in response to natural physiological stimuli.

Other workers state the ventilation in any given state as a fraction of the maximum breathing capacity, and call this the "dyspnoea index" (Wright, 1944). It is simpler to state the actual ventilation under any given condition as a percentage of the maximum breathing capacity. This is self-explanatory and avoids the false inference of infallibility associated with the word "index." The term "dyspnoeic index" has been employed (Hugh-Jones and Lambert, 1952) to describe the percentage of the maximum breathing capacity ventilated during a step-test when standard work is performed. The height or the number of steps in unit time are adjusted to standardize the work done with different body weights. The standardization of the amount of work done is of value when studying the ventilatory responses in patients whose weights vary greatly or in the study of ventilatory behaviour in different groups of patients. However, it is undesirable to convert this well-established method of measuring ventilatory discomfort in various degrees of activity into a rigid "index of dyspnoea." The careful elimination of the effect of body weight in assessing dyspnoea in real people with different body weights is also unfortunate. These variable body weights will cause varying ventilation and resultant dyspnoea during any standard activity (walking, stair-climbing, etc.).

It is still not known why a person should be extremely uncomfortable when his physiological demands—for example, exercise—cause him to ventilate about half of the air he can shift at rest, and without distress, by voluntary hyperventilation. There is great need for a more precise study of the ventilatory mechanisms during exercise causing dyspnoea in normal subjects and in those with various lung diseases. The level at which these patients breathe, the range and speed of their respiration, and the movement of the diaphragm and ribs during shortness of breath would not only be of fundamental interest but would bring important knowledge that could be applied to the various collapse and surgical procedures causing reduction of the ventilatory capacity.

### Ventilatory Volumes

These can easily be determined by collecting the expired air during various activities. A Douglas bag can be carried by the observer if the patient is walking or going upstairs, and the volume of gas expired during a fixed period be measured by passing the gas collected through a flowmeter or into a Tissot spirometer. Walking on a treadmill or a simple step-test will allow the expired gases to be collected and measured with greater ease, and a gas-meter type of recorder can be used. The disadvantage of the step-test is that the patient is usually not in a stable state, nor can the data be easily related to everyday activities. Many workers take the opportunity of carrying out arterial blood studies during these exercise tests.

Remarkably different ventilatory volumes are obtained in different patients. Many will ventilate only 10 litres a minute while walking at moderate speed, whereas patients are encountered who ventilate as much as 50 litres a minute. The demands on the ventilatory capacity will obviously be very different in two such patients, and, although they may have the same ventilatory capacity, the latter patient will obviously become dyspnoeic with a far less degree of exertion.

Passing from these empirical determinations of ventilatory volumes, let us briefly consider some of the factors that influence the amount of ventilation in various diseases.

In the normal subject about one-quarter to one-third of the inspired air does not pass beyond the passages lined by mucosa (the so-called anatomical dead space) where no significant gas exchange with blood takes place. In many lung diseases this "dead space effect" is greatly increased by the ventilation of unperfused lung tissue, and thus an abnormally large proportion of inspired air takes no part in the removal of carbon dioxide and the oxygenation of blood. This will render larger ventilatory volumes necessary for a fixed task, and this added demand can be ill afforded in the face of reduced ventilatory capacity. In certain lung diseases the changes in the elasticity and physical properties of the lung tissue in certain areas of lung may result in overventilation of the more healthy areas, and this overventilation is also wasteful and will have the same effect as increased dead space.

Secondly, there is the influence of changes in the partial pressure of carbon dioxide in the alveoli and body fluids, which are compensated and perpetuated by similar changes in body base. If the partial pressure of carbon dioxide is lowered by intermittent but repeated hyperventilation on exercise the respiratory centre will become more sensitive to a fixed amount of carbon dioxide produced on exercise, as the resulting increase in H-ion concentration will be greater than normal owing to the decreased buffering effect. These increased ventilatory volumes are necessary to remove a standard amount of carbon dioxide, as the alveolar gas is now relatively poorer in carbon dioxide content. In a number of cases of pulmonary fibrosis, pathological infiltration of lung, and heart failure, the carbon dioxide in the alveoli and blood is much reduced and there is little doubt that this factor is partly responsible for the hyperventilation encountered in these diseases.

If, as in severe emphysema, there is a lag of carbon dioxide excretion on each occasion when the patient exercises, owing to ventilatory disability, there will be a tendency for the partial pressure of carbon dioxide to rise, and if this is increasingly buffered then carbon dioxide retention (compensated gaseous acidosis) occurs. It must be emphasized that the gradient of this gas across the alveolar membrane between blood and alveolar air is unaltered, the partial pressure of carbon dioxide being raised throughout the lungs and body. In such cases the respiratory stimulation by a fixed amount of carbon dioxide is diminished, as the increased buffering will cause less increase in H-ion concentration. It can be shown that there is significantly less ventilation on exercise in this group of emphysematous patients as compared with those without high blood and alveolar carbon dioxide tensions. It has also been suggested that the respiratory centre becomes less sensitive to carbon dioxide and H-ion changes in these cases.

Thirdly, the added anoxic stimulus to respiration is important in certain diseases. Although it is generally known and taught that anoxaemia at rest causes a definite but not very pronounced increase of ventilation, it is less often appreciated that anoxaemia associated with exercise causes a most dramatic increase of ventilation. The increased ventilation caused by anoxaemia at rest washes out carbon dioxide and also reduces the H-ion concentration in the body. Thus two of the normal stimuli to respiration are reduced and the effect of anoxic stimulation is mainly counteracted. If, however, the patient is exercising, and the body carbon dioxide and H-ion concentrations are maintained or increased despite the increased ventilation, then the anoxaemic stimulus becomes more fully apparent (Gray, 1950). This mechanism is particularly important in diseases in which oxygen transfer is inadequate but the ventilatory capacity is but little impaired, as such patients are capable of marked temporary activity, causing abrupt anoxaemia. Good examples of this are certain types of pulmonary infiltration causing difficulty in oxygen transfer across the alveolar membrane (Austrian *et al.*, 1951; Donald *et al.*, 1952). Such patients become anoxaemic and dyspnoeic despite a relatively unimpaired ventilatory capacity. Their dyspnoea is due to the enormous ventilatory volumes that occur with exercise.

Another instructive example is seen in patients with large intracardiac shunts and pulmonary stenosis. On exercising these patients are unable to increase the pulmonary blood flow and oxygen uptake to any appreciable extent, and extreme anoxaemia ensues. Despite their relatively normal lungs and ventilatory capacity they become extremely dyspnoeic owing to their enormous ventilatory volumes—that is, 50–60 litres a minute walking slowly. The low carbon dioxide tension in the body will also contribute to this extreme hyperpnoea.

It is often stated that the Hering–Brauer reflex, causing inspiratory inhibition with a certain degree of lung distension, is increased in activity in many pulmonary diseases, particularly in pulmonary fibrosis. If overactive this reflex causes more frequent and shallow respiration. It is not yet proved that overactivity of this reflex can cause increased total ventilation. There is good evidence that the inhibition of inspiration occurs earlier than normally in the pulmonary congestion of cardiac origin, causing more frequent and shallow respirations, although it is still doubtful whether this is the cause of increased ventilation (Christie, 1932). With regard to the Hering–Brauer reflex being increased by pathological processes or fibrosis in lung disease, this is still only a hypothesis, and no good definitive evidence has yet been forwarded to substantiate it.

### Intrapulmonary Gas-mixing

Efficient gas exchange is to a large extent dependent upon the efficient distribution of inspired air to all alveolar spaces. Overventilation of one part of the lung cannot compensate for poor oxygenation in underventilated lung. The haemoglobin is saturated to all intents and purposes by adequate ventilation, and further ventilation will add but little oxygen to the blood perfusing that area. If the tidal air that passes the relatively rigid anatomical dead space is almost equally distributed to all alveoli, as we have good reason to believe is the case in the healthy lung, then it is certain that normal lung will be a remarkably efficient mixer of inhaled gases. Further, if the rate of mixing of inhaled gases is studied, then this will be a useful measure of the efficiency of gas distribution in the lungs. A number of factors that will influence the speed at which an inhaled foreign gas will be mixed throughout the lung spaces can be predicted on first principles—for example, the tidal volume, the size of the rigid anatomical dead space, the functional residual volume, and the rate of respiration (Darling *et al.*, 1944; Birath, 1944).

Cournand *et al.* (1941) measured the alveolar nitrogen after seven minutes' quiet oxygen breathing during the determination

of the residual volume. They showed that this was abnormally high in emphysema and attributed this to the inefficient ventilation of many alveoli and air spaces.

Birath (1944) compared the actual mixing curves obtained by serial sampling while breathing a hydrogen mixture with theoretical curves calculated with all the known variables, and assuming mixing to be perfect. Any retardation of mixing, no matter what the cause, was expressed as being due to a certain-sized rigid space between the mouth and properly ventilated lung. If this figure was greater than the accepted size of the normal anatomical dead space, then the excess figure expressed the mixing deficiencies of the lung. This method is unsatisfactory, as the anatomical dead space cannot be accurately measured or foretold even in normal subjects. Other workers (Boothby *et al.*, 1948; Carlson *et al.*, 1948; Fowler and Comroe, 1948) have carried out continuous recordings of the nitrogen washed out and alveolar nitrogen concentration (end of tidal air samples), while breathing oxygen, by means of the Lilly-Hervey nitrogen meter.

As previously mentioned, Meneely and Kaltreider (1941) showed that the rate of helium mixing in emphysema during lung-volume determinations is much reduced. Bates and Christie (1950) studied this phenomenon with greater thoroughness. They determined and corrected the effect of delayed mixing in the circuit and katharometer lag as well as allowing for the known variables already mentioned. No attempt was made to correct for the anatomical dead-space effect. Gross impairment in mixing was demonstrated in a group of emphysematous subjects. They also showed that there was considerable impairment of mixing, even in normal subjects, with increasing age. One asthmatic subject was studied while in severe bronchospasm and on two occasions during his recovery. The mixing efficiency rose remarkably as his bronchospasm abated. It is apparent that, like lung-volume and ventilatory studies, this test is also at the mercy of bronchospasm and bronchial obstruction, and is therefore not a reliable index of permanent lung damage.

All these methods show that the mixing capacity and inspired gas distribution in various lung diseases are impaired and abnormal. However, this disturbance is only assessed as if the lungs were dry unperfused organs. Such an assessment gives no information concerning the relationship of the alveolar underventilation, which is being indirectly demonstrated, to the blood flowing through the lungs. Fowler and Bateman (1950), who have contributed greatly to the study of mixing deficiencies, now feel that the study of the gases encountered in the lungs while breathing air and the correlation of such studies with arterial blood-gas tensions will yield far more valuable data on the real effects of alveolar underventilation. Although hydrogen and helium are excellent gases to demonstrate mixing deficiencies they are light and highly diffusible gases which behave very differently from the gases present in the lungs during ordinary air-breathing. Rauwerda (1946) has produced a valuable monograph on the subject of intrapulmonary gas-mixing.

### Respiratory Velocities

The physician of the last century who asked a patient with respiratory disease to whistle or blow a candle out was crudely assessing the maximum respiratory velocities. Sensitive and accurate instruments have been evolved to record instantaneous air-flow velocity (Silverman, 1945). The rate of flow is stated in litres a minute, as the actual velocity recorded is a function of the cross-section of the apparatus where the air flow is being measured. The velocity of flow in the air passages and finer bronchioles, under different conditions and in various diseases, is yet to be determined. Although many workers have obtained records in a number of normal and abnormal subjects under different conditions, little of real significance has emerged from its use. However, this approach is relatively new and may yet yield important findings. It is possible that a simple whistle-like instrument to measure the maximum expiratory velocity will become a standard clinical tool.

### Breathing Exercises

Most of us are inclined to believe that breathing exercises are a convenient placebo, and an indirect form of psychotherapy in respiratory conditions where little else can be offered. I would make an exception of post-operative breathing exercises, where the principle of encouraging an early return to full function, in what is usually normal lung, is sound. It must be remembered that these physiotherapy sessions are expensive in personnel, time, and money. It is my belief, although I have no proof, that breathing exercises have no effect whatsoever on emphysema and bronchospasm. Recent studies have shown that physiotherapists and singing teachers have no more control over their diaphragmatic movement than those whom they instruct (Wade, 1951). It is high time that more precise studies of the effect of these procedures on respiratory function were carried out to determine in what type of case, if any, physiotherapy is of value.

### Summary

Summarizing this rapid and imperfect survey of spirometric methods relating to the efficiency of ventilation, I would like to repeat that in the past too much emphasis has been laid on the static aspects of the lung volumes. It is more important to determine the ventilatory capacity of the lungs by such simple tests as those described and then to determine what ventilatory demands will be encountered in conditions that simulate normal activities as closely as possible. The factors that increase these ventilatory demands in various diseases have not been adequately studied. Finally, I would state that if I could have only one figure in a case of emphysema, although I should like many more, I would ask for the maximum breathing capacity.

## THE PULMONARY CIRCULATION

Let us next consider the haemodynamics of the pulmonary circulation, particularly the flow and pressure relationships. The important aspects of the relationships of alveolar circulation to ventilation will be considered separately. It has long been a matter of debate whether the pressure and volume variations in the pulmonary circulation are the passive result of conditions imposed upon it by respiration and the systemic circulation or whether there is active vasometricity of pulmonary vessels. Except for transient differences, the blood flow through the lungs is equal to that through the whole systemic circulation. However, despite this, the pressures in the lesser circulation are of a far lower order than those in the systemic circulation. The short, distensible, and capacious pulmonary arteries, arterioles, and pre-capillaries, and the enormous network of large pulmonary capillaries surrounded by air, allow the whole cardiac output to flow through the pulmonary vascular bed with a pressure head of only one-sixth of that in the systemic circulation.

The introduction of the technique of cardiac catheterization has made it possible to study the pulmonary circulation in both normal and abnormal subjects without any great disturbance of physiological status. Many normal subjects have now been investigated under near basal conditions, and the upper limit of normal pulmonary artery systolic pressure is believed to be 30 mm., of mean pressure 15 mm., and of diastolic pressure 10 mm. Hg. These pressures are measured from the level of the right atrium, and are the mean of the values throughout a full respiratory cycle.

Riley *et al.* (1948) studied the effect of exercise on the pulmonary artery pressures in three normal subjects. Resting studies were carried out with the subjects lying supine and exercise studies while riding a bicycle ergometer in the upright position. It was shown that, even though the oxygen consumption increased sixfold and the cardiac output more than doubled, the pulmonary artery pressure did not alter significantly. The resistance of the pulmonary vascular bed to this increased flow was greatly diminished on exercise, being only a third of the resistance at rest. As a result of this, the work of the right ventricle against pressure was only doubled; whereas that of the left ventricle was trebled. Hickam and Cargill (1947) obtained similar results, although their subjects did not increase their oxygen uptake and cardiac output to the extent of Riley's subjects. Both these groups of workers pointed out that the decrease of pulmonary resistance could not be explained by the passive

dilatation of the vascular bed, but that there must be independent and active widening of the vessels, or the opening up of new channels. Dexter *et al.* (1951) have shown that if normal subjects are exercised in the supine position so that the oxygen consumption exceeds 400 ml. per m.$^2$ of body surface, per minute, then a slight but significant rise of the pulmonary artery pressure occurs. They found that under these conditions the pulmonary resistance showed little alteration during exercise. These different findings may have been due to errors of pressure-recording in the erect position or as yet undemonstrated differences in intrapleural pressures while exercising in the supine and erect positions.

This demonstration that the pulmonary vascular bed is a low-resistance low-pressure system both at rest and with exercise is important. Not only is it advantageous from a purely mechanical aspect, but these properties of the lung vessels will allow considerable restriction of the vascular bed by resection or disease without marked pulmonary hypertension or right ventricular embarrassment.

Motley *et al.* (1947) have convincingly demonstrated that a rise in the pulmonary artery pressure is rapidly induced in normal subjects by breathing 10% oxygen for a short period of time (ten minutes). The average rise in mean pulmonary artery pressure in five subjects was from 13 to 22 mm. Hg. This increased pressure could not be attributed to increase in flow, as the cardiac output was but little altered. More recent experiments (Cournand, 1950) show that there is, in fact, some increase of cardiac output under these conditions, but that this increase is of such an order that it could have little effect on the pulmonary artery pressure. The work of Dexter *et al.* makes it necessary to review the accuracy of this statement, but it would seem to be still valid. Drinker (1945) has demonstrated that anoxia can cause altered capillary permeability, oedema, stasis, and perhaps increased resistance. However, the almost immediate reversibility of the rise in pulmonary artery pressure due to anoxia makes this hypothesis unlikely. There is no good evidence of left ventricular failure with back pressure. Wade, Cumming, and I (1951, unpublished observations) have measured the pulmonary "capillary" pressure, a crude transpulmonary measurement of pulmonary venous pressure obtained by occluding a branch of the pulmonary artery with the tip of the cardiac catheter, in several subjects with normal cardio-respiratory systems, while breathing air and 10% oxygen, and no significant change in this pressure was recorded. The only feasible explanation of the rise in pulmonary artery pressure when breathing low tensions of oxygen is that there is active constriction of pulmonary vessels.

Liljestrand and von Euler (1946) demonstrated that moderate anoxia caused pulmonary hypertension in intact cats. They produced good evidence that this rise in pressure was due to the direct action of low oxygen tension upon the tone of the arterioles or pre-capillaries. They did not believe that it was due to nervous influences, increased flow, or increased back pressure. It was suggested that this local anoxic action would result in an exquisite control of alveolar circulation, causing blood to flow to the areas where efficient ventilation and normal oxygen tensions were present.

### Pulmonary Circulation in Lung Disease

As the only reliable method of studying the haemodynamics of the pulmonary circulation in lung disease is by cardiac catheterization, the present knowledge is still very scanty. In one of the earliest studies (Riley *et al.*, 1948) a very heterogeneous collection of lung diseases was investigated. The diagnosis included pulmonary fibrosis, bronchiectasis, emphysema, and silicosis with tuberculosis. Most of these patients were unable to exercise vigorously. Even in these severe, chronic, and disabling respiratory diseases the pulmonary artery pressures were normal or but little raised while at rest, and showed only a moderate rise above normal when the patients exercised. Those who suffered the greatest rise of mean pulmonary artery pressure—that is, 13 to 42, 23 to 42 mm. Hg.—on exercise also showed a significant degree of arterial blood desaturation. However, even those who did not develop arterial hypoxaemia showed some abnormal rise of pressure, and it seemed that the pulmonary vascular bed was no longer capable of accommodating increased flow without some rise in pressure.

### Pulmonary Emphysema

The piecing together of the natural history of pulmonary hypertension and right ventricular hypertrophy and failure in this disease requires ventilatory and arterial blood studies, and cardiac catheterization of a large number of patients over long periods. I am particularly grateful to Drs. Harvey, Ferrer, Richards, and Cournand (1951) for allowing me to use, before publication, some of the results in the largest series yet studied, of which I have some personal knowledge.

The first group studied consisted of mild to moderate cases of emphysema as judged clinically and radiologically. Their residual volumes were increased and the ventilatory capacity greatly impaired. There was no significant degree of arterial blood oxygen desaturation (90% or above) and the standard step-test did not cause any fall in arterial oxygen saturation below this level. None of these patients showed any rise of pulmonary artery pressure or circulatory abnormality while at rest. A few who were exercised showed a moderate increase in pulmonary artery pressure. Such a finding in the absence of arterial hypoxaemia would suggest that the pulmonary vascular bed was unable to accommodate the increased flow with exercise without a rise in pressure. This would further suggest that the pulmonary bed is damaged and restricted in this disease.

In the second group studied the emphysema was more severe, as judged clinically and radiologically and by the increase of residual volume and impairment of ventilatory capacity. All these patients showed considerable arterial blood desaturation on exercise and most of them had carbon dioxide retention (high arterial $pCO_2$). As in the previous group, none had a history suggesting right heart failure. Only moderate pulmonary hypertension was found, the mean pulmonary artery pressure at rest being about 25 mm. Hg. There was no alteration of the size of the heart or of the pulmonary arteries. Electrocardiographic studies, using the criteria of Goldberger (1944), Wilson *et al.* (1947), and Myers *et al.* (1948), showed no evidence of right ventricular hypertrophy. The cardiac output, total blood volume, and haematocrit reading were slightly raised. There are no reports of the effect of exercise in this type of patient, although a few that I have catheterized have shown a considerable rise of pulmonary artery pressure.

Lastly, there is the group of emphysematous patients in congestive heart failure (cor pulmonale). Almost without exception the failure had been precipitated by an acute anoxic episode such as severe bronchitis or pneumonia. All these patients had severe pulmonary hypertension (around 50 mm. Hg mean pressure) and extreme arterial blood oxygen desaturation (50 to 60% saturation). Polycythaemia was pronounced and the total blood volume was increased. These patients had large right ventricles and the electrocardiogram showed marked right ventricular hypertrophy. These electrocardiographic findings are a measure of muscle mass, and one must conclude that hypertrophy had been present for some time. In most of these cases the cardiac output was high or high normal. The few patients who had low cardiac outputs in this state did not recover.

When these patients responded to treatment such as oxygen therapy, antibiotics, aerosol inhalations, and "antispasmodics" to improve ventilatory function, and mersalyl, digitalis, and bleeding to relieve the circulatory embarrassment, and were again studied, a surprising series of findings emerged. The pulmonary artery pressure dropped to very moderate and, in some cases, near normal figures. The respiratory function, as judged by arterial percentage haemoglobin saturation, lung volumes, and ventilatory capacity, was also greatly improved. In fact, after recovery from heart failure these cases were almost indistinguishable from the previous group, who had very mild pulmonary hyper-

tension and no evidence of right heart hypertrophy or insufficiency. A number of patients who had had right-sided heart failure, and had recovered, showed similar findings. The blood volume was significantly raised, and there was of course evidence of right ventricular hypertrophy. This marked fall in pulmonary artery pressure on recovery is probably due to relief of the anoxic vasoconstriction, decrease in the blood volume and viscosity, and the reduction of cardiac output. Thus the old concept that right-sided heart failure in these patients is mainly due to irreversible structural damage to pulmonary vessels can no longer be supported. Prompt and active therapeutic measures are life-saving and cause a dramatic reversal of many of the most adverse factors.

Although many cases of severe emphysema are under medical supervision over long periods, it is most unusual for one of these patients to develop a large heart with right ventricular hypertrophy and, finally, failure while under observation. In fact, practically all patients with cor pulmonale due to emphysema are seen for the first time when they are, or have recently been, in heart failure and already have right ventricular hypertrophy. Further, when these patients are studied after recovery a number show a smaller degree of pulmonary distension and a better ventilatory capacity than severely emphysematous patients without cardiac involvement.

I would like to offer a tentative explanation of these facts. If a patient with emphysema suffers from severe ventilatory disability, then this of itself may protect the right ventricle by greatly limiting activity and any resultant pulmonary hypertension due to increased blood flow and, perhaps, severe anoxia. Thus right ventricular hypertrophy and dilatation, which in some ways is the "beginning of the end," does not develop. However, those patients with less ventilatory impairment are not so limited in their activities and are able, without intolerable ventilatory discomfort (dyspnoea), to carry out regularly enough exercise to cause pronounced pulmonary hypertension. Thus right ventricular hypertrophy may develop and any sudden further stress due to infection or added anoxia may cause failure.

Although ventilatory studies help to measure dyspnoea, the most important symptom and disability so far as the patient is concerned, the circulatory aspects of this disease must also be studied, especially when prognosis is being considered. Clinical examination, electrocardiography, and screening make this assessment relatively easy in most cases, without cardiac catheterization, which should be reserved for those who are studying the disease, as well as the patient. Even in cases with moderately good ventilatory function, if there is right ventricular hypertrophy then there is constant danger of heart failure that may be precipitated by one of the almost inevitable respiratory infections that are a feature of this disease. At present there is no general agreement as to whether patients with emphysema should restrict their activities or not. It would be of great use to know whether elaborate and unremitting therapy to improve alveolar ventilation, in an attempt to avoid anoxaemia and pulmonary hypertension, is really worth while. Further work is needed to clarify such problems so that the clinician is better equipped to advise the patient with emphysema.

### Pulmonary Fibrosis

Up to the present pulmonary circulatory studies have been carried out in very few cases of generalized pulmonary fibrosis. Any attempt to assess the disability and prognosis in occupational lung fibrosis must include a thorough study of the effect of the disease upon the pulmonary circulation and the right heart. Electrocardiographic studies are not enough, and the development of pulmonary hypertension, and its relation to exercise, must be determined. In view of the fact that the ventilatory capacity is often not greatly restricted, the safety of encouraging men with pulmonary fibrosis to increase their activity, and even carry out hard physical tasks, should be more carefully considered.

[*Part II, with a list of references, will appear in our next issue.*]

# SYMPATHETIC NERVES AND ECLAMPSIA

BY

**G. W. THEOBALD, M.D., F.R.C.S.Ed., F.R.C.O.G. M.R.C.P.**

*(From St. Luke's Maternity Hospital, Bradford)*

It is the rule, rather than the exception, for a woman who suffers from eclampsia at the end of her first pregnancy to have normal subsequent confinements. The earlier the onset of hypertension and proteinuria during pregnancy the more likely is the patient to suffer the same sequence of events in succeeding pregnancies. The onset of this so-called toxaemic state at or about the 30th week of pregnancy is often associated with an unduly small foetus, which does not appear to grow, and which is prone to die *in utero*, with or without evidence of ante-partum haemorrhage.

These facts are illustrated by the following two case histories; several others could be cited.

*Case I.*—The patient was aged 36 in 1949. *First pregnancy, 1941:* eclampsia at 32nd week; stillborn premature infant. *Second pregnancy, 1944:* eclampsia at 32nd week; S.B. premature infant. *Third pregnancy:* last menstrual period (L.M.P.) March 4, 1949; expected date of delivery (E.D.D.) November 12. On May 26 the blood urea was 20 mg. per 100 ml.; urea concentration, 4.4%; intravenous pyelogram, normal. No abnormal cells discovered in urine. July 5: booked; B.P., 130/80 mm. Hg; urine, N.A.D.; weight 11 st. 6 lb. (72.6 kg.). September 1: 26 weeks pregnant; urine, N.A.D.; B.P., 140/90. From September 1 to October 10 the B.P. varied between 140/90 and 170/120; no proteinuria. October 11: B.P., 180/130; proteinuria; oedema; weight, 13 st. 3 lb. (83.9 kg.). October 19: 32 weeks pregnant; alb.,* 11 parts; oedema; emesis. Caesarean section: male infant, 4 lb. 3 oz. (1.9 kg.), died from pulmonary atelectasis. November 25: B.P., 140/70; urine, N.A.D.; very well.

This patient, influenced largely by her doctor and her husband, refused to have her iliac vessels denervated and asked instead to be sterilized.

*Case II.*—This patient, aged 25, had Raynaud's disease, Bilateral cervical sympathectomy had been successfully carried out in 1950.

*First pregnancy, 1949* (in Sunderland): 30th week. B.P., 166/110; alb., 2–8 parts; oedema of ankles. April 3: spontaneous delivery; stillborn (S.B.) foetus, 3 lb. 2 oz. (1.4 kg.). *Second pregnancy, March, 1950:* an abortion. *Third pregnancy, 1951:* L.M.P., February 27; E.D.D., December 6. May 29: 12–14 weeks pregnant; B.P., 100/64; urine, no protein; weight, 8 st. (50.8 kg.); Hb, 65%. From May 29 to August 17 the B.P. varied between 110/66 and 120/80. August 25: admitted with B.P. of 150/100; no proteinuria. B.P. then varied between 140/90 and 156/90; no symptoms. September 17: sudden appearance of 6 parts of albumin in urine; oedema; B.P. rose to 170/120; weight, 8 st. 5 lb. (53 kg.). September 29: spontaneous breech delivery; S.B. macerated foetus, 2 lb. 6 oz. (1.1 kg.). October 7: B.P., 104/76; trace of albumin in urine. October 9: B.P., 150/110; trace of albumin in urine; recurrence of symptoms of Raynaud's disease.

Such cases are not common, but they demonstrate that women without detectable stigmata of the cardiovascular–renal system may develop recurrent hypertension, proteinuria, oedema, and other symptoms at about the 30th week of pregnancy in spite of the most careful antenatal care.

*Alb.=proteinuria expressed in parts recorded in Esbach's albuminometer.