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CHRONIC COR PULMONALE

Report of an Expert Committee

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WORLD HEALTH ORGANIZATION

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EXPERT COMMITTEE ON CHRONIC COR PULMONALE

Geneva, 10-15 October 1960

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CHRONIC COR PULMONALE

Report of an Expert Committee

The WHO Expert Committee on Chronic Cor Pulmonale met in Geneva, Switzerland, from 10 to 15 October 1960.

The meeting was opened by Dr P. Dorolle, Deputy Director-General of WHO. Professor Dickinson W. Richards was elected Chairman, Professor L. Werkö, Vice-Chairman, and Professor C. H. Stuart-Harris, Rapporteur.

INTRODUCTION

The attention of the Director-General of the World Health Organization has recently been drawn to the fact that although the lung diseases causing pulmonary heart disease are being studied extensively in many parts of the world, there is little reliable information concerning the incidence of important secondary effects on the pulmonary circulation and right ventricle.

The terms cor pulmonale and pulmonary heart disease can be used synonymously to describe these secondary effects upon the right ventricle, and it seems reasonable to continue to use either of these terms or their equivalents in various languages. These terms are customarily preceded by the word chronic, when it is intended, as in this report, to exclude secondary effects on the right heart arising in the course of a few days or weeks from acute pulmonary disorders.

Since cor pulmonale is the traditional and accepted term in most languages, using either the original Latin or its exact translation, cor pulmonale will be used exclusively in the present report.

Routine mortality statistics compiled according to the *International Classification of Diseases* cannot at present provide information on the frequency of cor pulmonale as this condition is not properly identified there, being allocated to the residual category "434.4 Unspecified disease of heart". Moreover, according to the existing rules the classification stated by the physician on the death certificate would be related to the underlying cause of death and not to the resulting pulmonary heart disease. One therefore has to turn for indications of the frequency of cor pulmonale to the information derived from autopsies and hospital admissions. Here there are large differences in its reported prevalence. In autopsy series

there is, for example, a range of from 0.9% of all cardiac autopsies in Massachusetts to 54% in Arizona, a favourite resort for subjects with respiratory diseases. So far as hospital admissions are concerned, high figures for the incidence of cor pulmonale among hospital admissions for heart failure ranging from 16% to 38% have been reported from places such as Belgrade, Delhi, Prague and Sheffield. In most reported series more than 50% of the cases are attributed to chronic bronchitis, asthma or emphysema, which constitute an ill-defined group of diseases of uncertain etiology. A large number of other diseases are implicated in various proportions.

From the above information, fragmentary though it is, it is fully apparent that chronic cor pulmonale is of clinical significance. It is furthermore evident that for certain areas of the world's population it has now been recognized to be numerically an important cause of chronic disease and death and therefore a matter of serious concern to public health.

That this has remained so long unrecognized is due probably to a number of causes. For many years the diagnosis was not made: the condition was obscured in the accompanying pulmonary manifestations on the one hand, or else it was identified on the other hand as some other form of heart disease. It is only recently that physiological relationships between chronic pulmonary disease and cor pulmonale have been worked out by the clinical physiologists, and still more recently that adequate methods of diagnosis have been established. Physiologists are only now in the process of simplifying these principles and methods of diagnosis so that the physician can add them to his clinical analysis. Furthermore, there has been no agreement among either physiologists, pathologists or clinicians as to terminology, and great difficulty therefore has arisen in communicating findings of mutual interest and importance.

The wide disparities in the reported incidence of the disease in different areas may simply reflect these inconsistencies in the diagnostic terminology and conventions. If, on the other hand, these reports do indicate real variations in disease experience, they may give important clues to those differences in local environment or ways of life which may underlie the geographical distribution of the disease.

This brief statement will be perhaps a sufficient indication of the need for some unifying statement on chronic cor pulmonale.

The objectives of this report are as follows:

- (1) To define chronic cor pulmonale in terms useful for further discussion.
- (2) To provide a tentative classification of diseases which may be the cause of this syndrome.
- (3) To describe in broad terms the pathophysiology of cor pulmonale and to establish criteria for diagnosis.

If these objectives are attained even in part, it is believed that the report will provide a language with which physicians throughout the world can communicate with one another and compare clinical experience and research findings.

It is well known that many contributions of great importance in the pathophysiology of cor pulmonale have been made in recent years. It is not so well known, and insufficiently emphasized, that contributions of equal importance have been made in the description of the clinical picture and the natural history of the major forms of this syndrome. It may be noted that the physiological derangements and the clinical findings have also been correlated.

A clinical-physiological study of this kind permits a recognition of cor pulmonale in life that is useful. It is not always possible to predict from the history, clinical manifestations and diagnostic findings, the amount of right heart hypertrophy in any given case of chronic pulmonary disease, but one can determine with a fair degree of probability whether the patient has or does not have this hypertrophy, or is likely to develop it at some future time. Such clinical recognition is usually sufficient for management of the case.

With these considerations in mind, attention is given in this report to the natural history and clinical course of the major diseases causing chronic cor pulmonale and to the manifestations of this condition itself. There is no question but that further study along these lines is needed, or that the quantitative determination of right ventricular hypertrophy by pathologists requires more study and standardization of methods.

There is another aspect of cor pulmonale in which, by the combined efforts of physiologists and clinicians, great progress has been achieved, and that is in treatment. In fact, skilful and rational therapy, with new methods and new apparatus, has changed what was once a relentlessly fatal state into one that can be strikingly relieved. The course, though marked by severe exacerbations but also by remissions, often gives the patient a useful life in these intervals. The general principles of therapy are therefore briefly presented in the report.

Also, it must still be recognized that chronic cor pulmonale is a serious, protracted, ultimately fatal human experience, occupying frequently a large segment of the sufferer's life. As a sociological entity, every case has its etiological and aggravating environmental factors and its many economic implications. The whole of this category of disease, in areas where it is prevalent, thus constitutes a serious problem in public health and preventive medicine. This aspect of chronic cor pulmonale will be reviewed briefly in this report.

Finally, the report contains suggestions for future research and recommendations.

2. DEFINITION AND CLASSIFICATION OF CHRONIC COR PULMONALE

There are a large number of diseases in which alterations in the pulmonary circulation impose an increased load on the right ventricle which may result in hypertrophy and ultimately failure. These diseases fall into three broad groups according to their primary impact on the lungs :

- (1) Diseases that primarily affect the ventilatory and respiratory function of the lungs.
- (2) Diseases that act directly on the pulmonary vessels.
- (3) Primary cardiac diseases.

These three main groups of conditions are usually quite distinct in their clinical manifestations. In group (1) the symptomatology is dominated by the causative lung disease, and failure of pulmonary function precedes cardiac involvement. In group (2) the symptomatology is diverse, and when cardiac failure supervenes pulmonary function is not usually seriously disturbed. In group (3) the clinical picture is initially determined by the primary cardiovascular disease. Some members of the Committee thought that the term chronic cor pulmonale should include all these conditions, since in all of them the right side of the heart is affected by primary or secondary vascular changes in the lung. The similarity in the vascular changes in the lung and in the clinical picture of some cases of mitral stenosis or congenital heart disease with left-to-right shunt and with those belonging to group (2) was stressed. Nevertheless, it was agreed that the third group should be excluded in order to conform with current cardiological practice.

Definitions of chronic cor pulmonale have been put forward by many authors in clinical, functional or morbid anatomical terms. A clinical definition is considered unsatisfactory, since the chief clinical manifestation is heart failure, which may be long delayed. A functional definition in terms of pulmonary hypertension or raised pulmonary vascular resistance provides an unsatisfactory basis. This is because vascular resistance is difficult to measure and is variable, and hypertension may be evanescent, may only occur on exercise, and may decline in the terminal phase of the disease. The Committee therefore prefers a definition based upon morbid anatomy, for this provides the only characteristic common to all patients at all stages of the disease.

Chronic cor pulmonale is defined as :

“ Hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary

alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease."

The diseases that may cause chronic pulmonary heart disease are listed in Table 1, classified into broad etiological groups.

TABLE 1. CLASSIFICATION OF CHRONIC COR PULMONALE
ACCORDING TO CAUSATIVE DISEASES¹

1. *Diseases primarily affecting air passages of the lung and the alveoli*
 - 1.1 Chronic bronchitis with generalized airways obstruction with or without emphysema *
 - 1.2 Bronchial asthma *
 - 1.3 Emphysema without bronchitis or asthma *
 - 1.4 Pulmonary fibrosis, with or without emphysema, due to :
 - (a) Tuberculosis *
 - (b) Pneumoconiosis *
 - (c) Bronchiectasis *
 - (d) Other pulmonary infections
 - (e) Radiation
 - (f) Muco-viscidosis *
 - 1.5 Pulmonary granulomata and infiltrations
 - (a) Sarcoidosis *
 - (b) Chronic diffuse interstitial fibrosis *
 - (c) Berylliosis *
 - (d) Eosinophilic granuloma or histiocytosis *
 - (e) Malignant infiltration
 - (f) Scleroderma
 - (g) Disseminated lupus erythematosus
 - (h) Dermatomyositis
 - (i) Alveolar microlithiasis
 - 1.6 Pulmonary resection *
 - 1.7 Congenital cystic disease of the lungs
 - 1.8 High-altitude hypoxia
2. *Diseases primarily affecting the movements of the thoracic cage*
 - 2.1 Kyphoscoliosis and other thoracic deformities *
 - 2.2 Thoracoplasty *
 - 2.3 Pleural fibrosis *
 - 2.4 Chronic neuromuscular weakness—e.g., poliomyelitis
 - 2.5 Obesity with alveolar hypoventilation
 - 2.6 Idiopathic alveolar hypoventilation

¹ Conditions marked * are those which might receive two fourth-digit sub-divisions "with" and "without" chronic pulmonary heart disease in the next revision of the *International Classification of Diseases*. Syphilitic arteritis, rheumatic arteritis (without rheumatic heart disease), primary pulmonary haemosiderosis and ankylostomiasis do not seem to the Committee to be sufficiently well documented causes of chronic pulmonary heart disease to merit inclusion in the list of causes despite their occurrence in the literature.

3. *Diseases primarily affecting the pulmonary vasculature*3.1 *Primary affections of the arterial wall*

- (a) Primary pulmonary hypertension
- (b) Polyarteritis nodosa *
- (c) Other arteritis

3.2 *Thrombotic disorders*

- (a) Primary pulmonary thrombosis *
- (b) Sickle cell anaemia *

3.3 *Embolism*

- (a) Embolism from thrombosis outside the lungs *
- (b) Schistosomiasis (bilharziasis) *
- (c) Malignant embolism
- (d) Other embolism

3.4 Pressure on main pulmonary arteries and veins by mediastinal tumours, aneurysm, granuloma or fibrosis.

If mortality statistics are to provide information on chronic cor pulmonale it is necessary that it should receive an identifying number in the next revision of the detailed list of the *International Classification of Diseases* and that provision should be made for indicating its etiology. This could be done in two ways:

(a) By providing a new three-digit title for cor pulmonale and providing further fourth-digit sub-divisions under this title according to etiology. A suggested list of fourth-digit sub-divisions, suitable for this provision, is given in Table 2.

TABLE 2. SUGGESTED LIST OF MAIN CAUSES OF
CHRONIC COR PULMONALE FOR INTERNATIONAL CLASSIFICATION
OF DISEASES

0. Chronic bronchitis with or without emphysema
1. Generalized obstructive lung disease (without mention of emphysema) or asthma
2. Emphysema without mention of bronchitis
3. Pneumoconiosis and other occupational diseases of the lung
4. Parasitic diseases affecting the lung
5. Other diseases of the lung or pleura
6. Chest deformities, congenital or acquired
7. Thrombo-embolic diseases
8. Other diseases of blood or blood vessels
9. Unspecified cause

(b) By providing two fourth-digit sub-divisions, "with pulmonary heart disease" and "without pulmonary heart disease" under those existing etiological categories which are of sufficient importance to warrant such

sub-division. These categories are marked with an asterisk in Table 1 (see page 7).

Provision (b) appears preferable since it would conform better with present practice of codification and would permit a more precise identification of the association of pulmonary heart disease with the disorders that may be complicated by it.

3. PHYSIOLOGICAL DERANGEMENTS IN CHRONIC COR PULMONALE

The physiological disturbances in this group of diseases comprise those related to the respiratory function (gaseous exchange) and those connected with the haemodynamics of the pulmonary circulation. Though individual diseases can be classified broadly according to the predominant physiological disturbances, it must be recognized that these frequently overlap and are present to a variable extent at different stages of the diseases.

3.1 Disturbances in the respiratory function

The alterations in respiratory function which can be recognized are four in number :

- 3.1.1 *Obstructive ventilatory impairment*—Impairment due to obstruction to airflow somewhere within the tracheobronchial tree.
- 3.1.2 *Restrictive ventilatory impairment*—Impairment due to reduction of ventilatory capacity without obstruction to air-flow.
- 3.1.3 *Impairment in pulmonary gas diffusion*—Disturbance in gaseous interchange between alveoli and pulmonary capillary blood due to anatomical or functional alterations.
- 3.1.4 *Reduction in the ventilation-perfusion ratio*—This implies that some of the blood traversing the lungs passes through areas of diminished or absent ventilation or through arteriovenous pulmonary shunts.

The final effect of these functional alterations is seen by reference to the arterial blood and to the respective tensions therein of oxygen and carbon dioxide. The interactions in the various alterations in function may best be seen by reference to the following examples :

In chronic bronchitis with emphysema the main disturbance is that of obstructed ventilation but this may be accompanied by various degrees

of impairment of the pulmonary gas diffusion and by reduction in the ventilation-perfusion ratio. In severe pulmonary fibrosis the main disturbance is one of restricted ventilation but this may be accompanied by reduction in pulmonary gas diffusion and in the ventilation-perfusion ratio.

3.2 Disturbances in the haemodynamics of the pulmonary circulation

The pulmonary vascular resistance to which pulmonary blood pressure and blood flow are related determines the work of the right ventricle. The hypertrophy of the right ventricle found in chronic cor pulmonale arises from increased work due to changes in the haemodynamics of the pulmonary circulation in disease. These include the disturbance in pressure/flow relationships during exercise as compared with those found in normal persons. Increased pulmonary vascular resistance may be found in conjunction with :

- 3.2.1 Obstruction to the pulmonary vessels—as, for instance, in thrombosis, embolism, obliterative changes arising in the vessel wall, or as a result of pressure from outside the wall.
- 3.2.2 Reduction in size of the pulmonary capillary bed as in lung resection or emphysema.
- 3.2.3 “ Functional ” alterations involving the calibre of the pulmonary vessels and affecting the relationship between the capacity of the vascular bed and the blood-flow or volume.

The various factors that may produce an increase in the pulmonary vascular resistance may interact in various degrees according to the primary disease. “ Functional ” alterations appear to be frequently related to hypoxaemic states which may accompany disturbances in the respiratory function listed above. The importance of other factors such as carbon dioxide tension, nervous stimuli, hormones and alterations in the blood flow, including shunts, and blood itself remains to be established. The effect of hypoxaemia on the myocardial metabolism also requires further study.

In most cases, however, a variety of mechanisms make simultaneous contributions to the pulmonary hypertension. In emphysema, for example, there are various combinations of loss of pulmonary vasculature, compression of capillaries by increased intra-alveolar pressure, vasoconstriction secondary to hypoxaemia and hypercapnia, hypervolaemia, polycythaemia and increased cardiac output. Further, the relative importance of these different mechanisms may be modified by inter-current disease, particularly during an acute attack of bronchitis which may accentuate alveolar hypoventilation, increasing the effects of hypoxaemia and hypercapnia. Thus

it is seen that disturbances in the respiratory function and in the pulmonary vascular resistance occur in one and the same disease. It is, however, possible to indicate the broad relationships between the various disease processes classified in Table 1 and the functional disturbances as follows :

(1) Diseases primarily affecting air passages of the lung and the alveoli

(2) Diseases primarily affecting the movements of the thoracic cage

In both these groups alterations in respiratory function and in the pulmonary vascular resistance co-exist.

(3) Diseases primarily affecting the pulmonary vasculature.

In this group the disturbance in the pulmonary vascular resistance predominates over and precedes any ultimate disturbance in respiratory function.

4. CLINICAL RECOGNITION OF CHRONIC COR PULMONALE

Recognition of chronic cor pulmonale rests upon the demonstration of right ventricular hypertrophy in the presence of the diseases listed in Table 1. In some of these diverse clinical conditions, the abnormal signs indicative of right ventricular hypertrophy may be readily apparent during life. In other conditions, right ventricular hypertrophy may be unrecognisable in life though demonstrable at autopsy.

The anatomical diagnosis of right ventricular hypertrophy has been considered by the Committee, but it is suggested that further observations using standardized techniques are desirable. For this reason no recommendations concerning this aspect of the problem have been formulated, but current practices are referred to in the Annex (see page 34). Similarly, the anatomical diagnosis of the various lung diseases, and particularly of the common condition of emphysema, requires further study by standardized techniques such as those mentioned in the Annex (see page 34).

The clinical manifestations and criteria of diagnosis on which the clinical recognition of cor pulmonale in life depends are reviewed in the following sections, which deal in order with :

Diagnostic indications of right ventricular hypertrophy in pulmonary diseases (section 4.1); definition and diagnosis of pulmonary diseases with special reference to chronic bronchitis and emphysema (section 4.2); the clinical picture of chronic cor pulmonale secondary to pulmonary diseases (section 4.3); chronic cor pulmonale secondary to vascular diseases (section 4.4).

4.1 Diagnostic indications of right ventricular hypertrophy in pulmonary diseases

4.1.1 Clinical findings

There are no symptoms specifically related to the presence of right ventricular hypertrophy. The cardiac signs are often concealed by distension of the overlying lung, but may include a systolic thrust. This is indeed the only physical sign directly related to right ventricular hypertrophy. Its exact position varies, being sometimes to the left of the sternum, sometimes over the sternum itself and sometimes in the epigastrium. Other physical signs, including a loud pulmonary second sound, a gallop rhythm and jugular venous pulsation are related either to the severity of the pulmonary hypertension or to right heart failure.

4.1.2 Radiological findings

There may be no observable cardiac abnormality in the chest radiograph. The heart may be small even in the presence of right ventricular hypertrophy. Enlargement of the right ventricle indicative of dilatation and not necessarily of hypertrophy may be seen in the lateral, though invisible in the postero-anterior (P.A.) position. Enlargement in the transverse diameter of the heart in the P.A. film is indicative of dilatation and not necessarily of hypertrophy. An alteration in contour of the pulmonary conus with filling-in of the normal concavity or actual convexity seen particularly in the right oblique position may be a manifestation of hypertrophy of the outflow tract of the right ventricle.

Changes in the size of the main pulmonary arteries or of their branches are related to altered haemodynamics of the pulmonary circulation rather than to hypertrophy of the ventricle. Dilatation of the stem and main branches of the pulmonary artery, and a contrast between the enlarged hilar and the diminished peripheral vascular shadows are common radiological findings in pulmonary hypertension. In this respect they may indicate indirectly the existence of right ventricular hypertrophy.

4.1.3 Electrocardiographic findings

It must be appreciated that there may be no alterations in the electrocardiogram in cases of chronic cor pulmonale in spite of the presence at autopsy of right ventricular hypertrophy. There are, however, many observed deviations from the normal electrocardiogram, some of which are related to changes in the position of the heart and others of temporary phases of illness. Amongst all these deviations the changes usually accepted

as those indicative of right ventricular hypertrophy appear and remain in a proportion of cases and therefore constitute important criteria in life.

The presence of a qR pattern with delayed R wave in VI (onset of intrinsicoid deflection more than 0.03 second) is not commonly seen in cor pulmonale, but, if present, may by itself be considered to be highly suggestive of right ventricular hypertrophy. It is often better observed in V3R and V4R which should thus be recorded in patients in whom right ventricular hypertrophy is suspected. In the absence of a qR pattern a combination of at least two of the following changes must be present for these alterations to be indicative of right ventricular hypertrophy :

- (1) Alteration in the ratio R/S in the left chest leads with R/S less than 1 in V5.
- (2) Predominant S wave in standard lead I.
- (3) Presence of an incomplete right bundle branch block with QRS less than 0.12 second.

The significance of a P pulmonale in which the P wave in lead II is 2.5 mm or more in height, though considered to be suggestive of hypertrophy of the right atrium and seen in some patients with cor pulmonale, cannot be regarded as diagnostic of cardiac involvement. Right axis deviation of an extreme degree (110° or more) accompanies extreme rotation of the cardiac axis and so may be found in association with right ventricular hypertrophy. Inversion of the T wave in the precordial leads VI to V4 or in leads II and III may also occur, but may be transitory. A combination of one or more of these alterations in the P or T waves or the QRS complex, together with those mentioned in relation to right ventricular hypertrophy, reinforces the indication of cardiac disease.

4.1.4 *Haemodynamic findings*

The most accurate method of defining the altered state of the pulmonary circulation in cor pulmonale is that of cardiac catheterization which permits measurement of blood flow and pressures. Although the demonstration of pulmonary hypertension does not necessarily imply right ventricular hypertrophy, its presence implies strain upon the right ventricle, and persistent hypertension will certainly cause hypertrophy. Catheterization is needed, however, for diagnostic purposes in only very few patients. When performed, both cardiac output and pressure measurements should be made and it is important that the patient should be in a steady state. The technique requires standardization, and catheterization should be performed only by well-trained and well-equipped observers.

The following are regarded as the upper limits of normal values with the reference point ¹ 10 cm above the level of the back in the supine position :

	<i>Systolic</i> <i>mm Hg</i>	<i>Diastolic</i> <i>mm Hg</i>	<i>Mean</i> <i>mm Hg</i>
Right atrium	—	—	6
Right ventricle	25	6	—
Pulmonary artery	25	12	15
Pulmonary arteriolar wedge pressure	—	—	9

The total pulmonary resistance lies between 150 and 300 dynes sec. cm⁻⁵

Pulmonary hypertension is usually considered to be present when the mean pressure in the pulmonary artery exceeds 25 mm Hg at rest. In many instances of pulmonary heart disease this value will not be exceeded at rest. The effects of exercise on the pulmonary artery pressure, though considerable in the presence of pulmonary heart disease, will depend on the amount of work and on the stage of disease. Actual values for the normal mean pressures on exercise are not quoted because of lack of standardization of available figures.

* * *

The clinical, radiological, electrocardiographic and haemodynamic findings should be considered together, since the diagnosis of right ventricular hypertrophy becomes increasingly probable with increase in the number and severity of abnormalities demonstrated. It is not possible at present to state any simple definitive criteria which would command general acceptance.

4.2 Definition and diagnosis of pulmonary diseases with special reference to chronic bronchitis and emphysema

4.2.1 Introduction

In most of the diseases listed in Table 1, section 1 (see page 7), the diagnosis is made by established methods which need no elaboration, but some comment is necessary on the definition and diagnosis of emphysema and related conditions (Table 1, sections 1.1 to 1.3) which in all published series are the commonest causes of chronic cor pulmonale.

4.2.2 Definition of emphysema

The word emphysema is at present used to describe a variety of morbid states of the lung which differ widely in their pathology and clinical effects.

¹ A more customary reference point 5 cm below the sternal angle is also used with approximately the same normal values. This is not recommended.

The use of a single word for a multiplicity of disorders results in misunderstanding between investigators, which retards advance in knowledge of a group of common and often seriously disabling diseases. Cases are not infrequently seen in which the diagnosis of emphysema has been made during life, on clinical and functional grounds, but in which, at post-mortem, there is no anatomical emphysema, or in which the emphysema is localized, leaving large areas of the lung unaffected. Cases are also seen with anatomical emphysema at autopsy in which clinical or physiological evidence of emphysema during life has been lacking. Indeed, it is still impossible to correlate anatomical emphysema—which may occur in a variety of forms—with any single characteristic clinical, radiological or functional syndrome.

A definition of *emphysema in anatomical terms* is therefore proposed as follows :

Emphysema is a condition of the lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole, with destructive changes in their walls.

4.2.3 Definition of chronic bronchitis

Although it would be desirable to define chronic bronchitis in anatomical terms, the Committee do not consider this possible at present. A definition in clinical terms is therefore proposed as follows :

Chronic bronchitis is a chronic or recurrent increase above the normal in the volume of bronchial mucous secretion, sufficient to cause expectoration when this is not due to localized broncho-pulmonary disease. The words chronic or recurrent may be further defined as present on most days during at least three months in each of two successive years.

4.2.4 Definition of generalized airways obstruction

Airways obstruction may occur with or without chronic bronchitis in two main forms :

Intermittent or reversible airways obstruction : asthma :

Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease.

Persistent or irreversible generalized airways obstruction :

Irreversible or persistent airways obstruction refers to the condition of subjects with widespread narrowing of the bronchial airways, which has been present for more than one year and which is unaffected by bronchodilator drugs.

Comment

It is important to note that most cases of persistent airways obstruction also have some degree of reversible obstruction or asthma. The term "generalized airways obstruction" is accurately descriptive and its use in diagnosis would encourage the conscious consideration of the degree to which it is reversible, or irreversible, and when irreversible, the separation of those cases with evidence of destructive emphysema from those without such evidence.

*4.2.5 Clinical diagnosis**Symptoms*

The main symptoms of this group of diseases are productive cough, exertional dyspnoea of abnormal severity, and wheezing. A history of previous lung diseases is also of interest, since it may be of etiological importance.

Physical signs

The physical signs of these diseases when they are severe enough to cause chronic cor pulmonale do not at present enable any distinction to be made between reversible and persistent airways obstruction or between patients with and without emphysema as defined.

Severe airways obstruction is evidenced by laboured breathing with use of accessory muscles, an expanded chest with limited respiratory excursion, hyper-resonance, wheezing expiration and often faint breath sounds. In the presence of hypoxaemia and hypercapnia there may be a characteristic jerky tremor and mental confusion. Cyanosis is prominent chiefly in cases with polycythaemia.

Radiological diagnosis

Although anatomical emphysema of at least moderate severity may be present without any radiological abnormality, there are a number of radiological signs which strongly suggest its presence. These are :

- (a) Localized transradiancy with wide spacing of pulmonary vessels or with hairlines indicating the walls of bullae. Generalized transradiancy is a sign of emphysema only if technique is scrupulously standardized.
- (b) A flat diaphragm lying below the level of the seventh rib anteriorly with a movement of 2 cm or less between full inspiration and expiration.
- (c) An increase in the retrosternal space seen in a lateral radiograph.
- (d) A decrease of peripheral vascular shadows. Selective angiography can demonstrate these changes more precisely.

4.2.6 *Functional diagnosis*

The main disturbances of respiratory function that may lead to cor pulmonale are listed in section 3. They can be diagnosed by three main groups of tests :

- (a) tests of ventilatory function and lung volume determination ;
- (b) tests of alveolar-capillary gas exchange ;
- (c) measurement of arterial blood gases.

When primary lung disease is of sufficient severity to cause cor pulmonale, it is exceedingly rare (if it ever occurs) for one aspect only of pulmonary function to be impaired, so that a full pulmonary function study is always desirable. A complete and detailed account of all the techniques that are available for such studies is not presented, for these may be found in various textbooks and reviews. Only the simpler investigations that may be regarded as the minimum necessary to identify the relevant disorders of pulmonary function are mentioned.

The effects of exercise on the blood gases and on respiratory function are of great interest, and they are of special value in the diagnosis of suspected alveolar-capillary block. The technique requires careful standardization. Such tests are, however, not essential in the investigation of respiratory function in cases of cor pulmonale.

(a) *Tests of ventilatory function and measurement of lung volume*

Various simple methods are available for estimating impairment of ventilatory function. The most widely used method, and one that is both valid and, if correctly performed, relatively free from subject and observer variation, is to measure the maximum volume of air that the subject can exhale after a full inspiration (*i*) forcibly during the first second of expiration ($FEV_{1.0}$)¹ and (*ii*) to full expiration (VC).²

The value of $FEV_{1.0}$ gives an indirect estimate of maximum ventilatory capacity, while the $FEV_{1.0}$ expressed as a percentage of VC indicates whether impairment, if present, is predominantly obstructive or restrictive.

A spirometric tracing of minute volume, forced expiratory and inspiratory vital capacities, and of maximum voluntary ventilation can provide additional valuable information.

There is a wide variety of methods by which the obstructive and restrictive components of ventilatory impairment can be much more accurately estimated than by spirometry, but most of these require relatively elaborate equipment and are not essential for the diagnosis and assessment of impairment sufficient to cause chronic cor pulmonale.

¹ Forced expiratory volume in the first second of expiration.

² Vital capacity.

Measurement of the total lung volume, of the functional residual capacity and of the residual volume may assist in the differentiation of the obstructive and restrictive type of impairment and in the diagnosis of the severity of anatomical emphysema.

In patients with obstructive ventilatory impairment these tests should be repeated after the use of bronchodilator drugs and also after prolonged appropriate treatment, in order to show how much of the airways obstruction is reversible.

(b) Test of alveolar-capillary gas exchange

Alveolar-capillary gas exchange may be studied by estimating pulmonary diffusing capacity, either by steady-state or single-breath carbon monoxide methods. The techniques are complicated and the results difficult to interpret. Most of the essential information can be obtained from measurements of arterial blood gases.

(c) Measurement of arterial blood gases

Oxygen

Hypoxaemia is defined physiologically as arterial oxygen tension (pO_2) decreased below normal limits. In practice, oxygen saturation (derived from oxygen content and capacity) is used to estimate the degree of hypoxaemia.

Determination of pO_2 presents technical difficulties. The development of oxygen electrodes permitting continuous recording of pO_2 may, in the future, provide great advantages with considerable simplification.

Oxygen saturation is still best determined by the manometric method of Van Slyke and Neill. The recent and more convenient method of spectrophotometry can only be recommended for well-trained observers. Oximetry gives only a rough value for the oxygen saturation.

Carbon dioxide

Hypercapnia and hypocapnia are defined respectively as increase and decrease in arterial carbon dioxide tension (pCO_2) beyond normal limits. pCO_2 can be obtained by direct measurement or by calculation from pH and CO_2 content of the blood.

In the absence of any cause of metabolic alkalosis, the CO_2 content of the plasma provides a useful suggestion that there may be elevation of pCO_2 .

4.2.7 Interpretation of alteration in arterial blood gases

There are four main disturbances of pulmonary function which may cause hypoxaemia with or without changes in arterial pCO_2 :

(a) *Reduction of ventilation-perfusion ratio*

If some of the blood traversing the lungs passes through areas of diminished or absent ventilation, it will retain to various degrees its venous composition. When it mixes with blood coming from normally ventilated lung (venous admixture) the ensuing mixture will be hypoxaemic, but increased ventilation of the well-ventilated areas of lung will usually rid the blood of excess CO₂. Thus, reduction of ventilation-perfusion ratios or, in the extreme case, shunts of blood through unventilated areas, produce *hypoxaemia with normocapnia*.

(b) *Generalized alveolar hypoventilation*

An over-all reduction in alveolar ventilation, from whatever cause, produces a numerically equal fall of pO₂ and rise of pCO₂ in the alveoli and hence in the arterial blood, but owing to the different slopes of the dissociation curves of oxygen and carbon dioxide, while the change in arterial carbon dioxide content is relatively large in relation to the change in pCO₂, the change in arterial oxygen content is relatively small. Thus, generalized alveolar hypoventilation produces *hypercapnia with relatively large reduction of oxygen tensions but only slight decrease in oxygen saturation of the arterial blood*. In profound hypoventilation desaturation is also severe.

(c) *Alveolar-capillary block*

Alveolar oxygen exchange may be impaired if there is thickening of the alveolar walls or if the area of contact between alveolar gases and pulmonary capillary blood is reduced; but the exchange of carbon dioxide, which is thirty times more diffusible than oxygen through liquids, remains normal or may be reduced by the hyperventilation. On exercise, the more rapid passage of blood through the lung exacerbates the hypoxaemia. Thus, alveolar-capillary block produces *hypoxaemia, increased or only manifest upon exercise, often with hypocapnia*.

(d) *Breathing of low oxygen tensions*

This, in practice, only occurs at high altitudes. It results in *hypoxaemia with hypocapnia* from increased alveolar ventilation.

4.3 The clinical picture of chronic cor pulmonale secondary to pulmonary diseases

Hitherto this report has been concerned with the definition of the causative diseases and the description of the signs found in the various disorders without reference to individual patients. The recognition of chronic cor pulmonale during life depends, however, very largely on an

appreciation of the evolution of the clinical picture which, though complex, may be described in three typical forms. These are exemplified (1) by gross fibrosis or granulomatosis of the lung; (2) by emphysema associated with hyperventilation; (3) by chronic bronchitis and emphysema, associated with the state of alveolar hypoventilation.

4.3.1 *Hyperventilation in gross pulmonary fibrosis or granulomatosis* (see Table 1, sections 1.4, 1.5: page 7)

The natural history of patients in this group consists of the gradual development of progressive disabling dyspnoea with alveolar hyperventilation. The patient progresses steadily towards a state of severe failure of pulmonary function. Functional changes arise from the restriction of pulmonary ventilation with little or no increase in the functional residual capacity. In the early stages the oxygen saturation of the arterial blood is reduced only on exercise and the blood carbon dioxide tension is normal or even reduced. (Hypoxaemia with normocapnia or hypocapnia: see page 18, section 4.2.6(c).) The signs of right ventricular hypertrophy are recognized relatively easily and pulmonary hypertension, if moderate at rest, is severe on exercise. Cardiac failure, if it ensues, is shown by venous congestion, hepatomegaly and oedema, and it responds relatively poorly to treatment. Cyanosis is now clinically obvious with hypoxaemia at rest, but the arterial CO_2 tension is still normal. Many patients die without prior development of heart failure.

4.3.2 *Emphysema with hyperventilation* (see Table 1, section 1.3: page 7)

Patients in this group have progressively increasing dyspnoea, with or without chronic cough. Ventilatory capacity is diminished with obstruction to expiration and increase in the functional residual capacity. There is usually ample radiological evidence of emphysema. Hyperventilation is persistent, arterial oxygen saturation is normal or slightly diminished, and the arterial CO_2 tension is slightly below normal. These cases continue in this way for many years, sometimes developing extreme ventilatory insufficiency yet with an unchanging pattern of blood gases. Pulmonary arterial pressure is only slightly increased. Only with the onset of a severe acute respiratory infection may the clinical picture suddenly change. Hypoxaemia now becomes severe, pCO_2 increases, and the patient may rapidly develop right heart strain and enlargement with cardiac failure. With adequate treatment of the pulmonary condition the patient usually recovers promptly, evidence of cardiac involvement recedes, and there is a return to the former state. There may be numerous exacerbations of this kind. On the other hand, many patients in this group never develop cardiac complications.

The experiences of different members of the Committee suggest a considerable variation of the incidence of this form of emphysema relative to that of the bronchitis-emphysema group with alveolar hypoventilation described below.

4.3.3 *Alveolar hypoventilation group* (see Table 1, sections 1.1, 1.2 and 2 : page 7)

The natural history may be seen by reference to a typical case of the bronchitis-emphysema group. There is a long phase of illness whose chief features are the symptoms of the pulmonary disease and during which evidences of cardiac involvement are absent. Cough and expectoration may be the only symptoms in the early stages, and these are present particularly during the winter season or in relation to acute respiratory infections.

During the middle stages of the disease the clinical picture is dominated by the progressively disabling character of acute respiratory infections now accompanied by dyspnoea with wheezing respirations. Dyspnoea is also present on exertion in between these acute illnesses and functional impairment with obstruction to ventilation is demonstrable. The functional residual capacity is increased, and the arterial blood shows slight hypoxaemia with normal or slightly raised carbon dioxide tension. There may be no clinical signs of right ventricular hypertrophy, but radiological or electrocardiographic changes suggestive of cardiac involvement are found in a minority of patients. Both the functional disturbances and the cardiac signs are more pronounced during acute exacerbations of illness. Occasionally, extremely severe acute infections are accompanied by deep cyanosis with profound hypoxaemia and hypercapnia.

The third stage of illness, characterized now by the appearance of the signs of congestive cardiac failure, may be ushered in suddenly by an acute respiratory infection leading to severe hypoxaemia and hypercapnia. Occasionally, however, the onset of oedema is insidious and unexplained. In any event, patients with evidence of cardiac failure may later pursue an intermittent and recurrent course with good response to treatment, or else one of persistent venous congestion relatively unresponsive to therapy. The changes in ventilatory function are similar to those found at an earlier stage of illness, but the elevation of the $p\text{CO}_2$ is more profound. The electrocardiogram, however, becomes increasingly abnormal with some reversible and some irreversible alterations (see page 12, section 4.1). Changes in the pulmonary circulation are present, and pulmonary blood pressure is increased particularly during cardiac failure, when also hypoxaemia and hypercapnia are most profound. The heart undergoes dilatation which may be temporary but later is persistent and considerable.

Tricuspid incompetence may be a feature, particularly in chronically decompensated cases where death may ensue without relief of oedema.

On the other hand, therapy may be apparently successful in relieving cardiac failure but the patient may die from respiratory insufficiency. Clinical features particularly present in patients with alveolar hypoventilation and accompanying cardiac failure are severe central (hypoxaemic) cyanosis, mental confusion or disorientation, warm peripheral extremities, jerky twitchings or tremor of the fingers and a raised haematocrit (polycythaemia). These features are in contrast with those found in right heart failure due to hypertensive, ischaemic or rheumatic heart disease. The clinical recognition of cor pulmonale due to the chronic bronchitis-emphysema syndrome becomes increasingly certain during the final phase of illness when cardiac failure has supervened.

The possibility of right heart failure's being due to pulmonary disease with alveolar hypoventilation should always be considered. Chronic cor pulmonale may be associated with ischaemic or hypertensive heart disease which may confuse the picture, and its recognition is essential in order that therapy should be directed to the causative pulmonary condition. An estimation of arterial $p\text{CO}_2$ or at least of plasma bicarbonate will indicate the correct diagnosis.

4.4 Chronic cor pulmonale secondary to vascular diseases

4.4.1 Anatomical alterations

The essential anatomical change is widespread narrowing or occlusion of pulmonary blood vessels, and the essential physiological change is the consequent increase in pulmonary vascular resistance, leading directly to a continuous increase in the work of the right heart. In general, it can be stated that a characteristic feature of this group, in its uncomplicated form, is manifest hypertrophy and enlargement of the right ventricle either preceding or with minimal clinical symptoms.

It is worth while drawing attention also to lesions of the pulmonary vasculature which may be considered to be reactions to changes in the pulmonary circulation, due to extra-pulmonary factors. It seems that the pulmonary vessels have the property of reacting to alterations in the blood pressure, the blood-flow and the chemical composition of the blood. In many instances a reaction of the pulmonary vascular bed similar to that mentioned above results from disease of the left side of the heart or from congenital heart disease.

4.4.2 Clinical picture

The general picture of severe pulmonary hypertension, such as is seen in cor pulmonale due to schistosomiasis, is first described, and this is followed by special comments on other examples.

4.4.2.1 *Symptomatology and physical signs*

The disease is generally symptomless for several months or years. Syncope and oppressive dyspnoea on exertion occur later on when the right ventricle fails to increase its output on effort owing to the increased vascular resistance. Sudden and temporary loss of vision and loss of consciousness may follow severe effort. Anginal pains are rare and haemoptysis is not a common symptom. Cyanosis is absent in uncomplicated cases and if it occurs it is peripheral in type (absence of hypoxaemia). Patients in congestive heart failure may show cyanosis. Cardiac arrhythmias are rare and the blood pressure is on the low side of the normal.

4.4.2.2 *Physical signs*

The clinical recognition of this type of chronic cor pulmonale is not difficult since the cardiac signs are not concealed by distension of the overlying lungs, and signs of right ventricular enlargement and dilatation of the main pulmonary artery can thus be easily elicited. A systolic thrust over the lower part of the sternum or to the left of it or in the epigastrium is frequently felt; sometimes a diastolic shock and a systolic thrill may be felt over the pulmonary area. Dullness to the left of the sternum in the second and third spaces and a flat note on percussion over the lower part of the sternum are frequent findings. On auscultation, a loud second sound in the pulmonary area with a pulmonary systolic ejection click suggests pulmonary hypertension. Occasionally harsh systolic and diastolic murmurs are heard over the pulmonary area. Hypoxaemia occurs only in the late stages of evolution of the disease.

4.4.2.3 *Radiological findings*

Dilatation of the pulmonary conus, the pulmonary artery and its branches will be seen, and in advanced cases they may reach a size larger than that met with in other types. Enlargement of the right ventricle is seen. The lungs show a clear periphery with prominent hilar shadows. Selective angiography may be of value in these cases; it shows the dilated tortuous arteries ending abruptly.

4.4.2.4 *Electrocardiographic findings*

The ECG may be normal in the early stages, especially in schistosomiasis; later on, evidences of right ventricular hypertrophy appear. In advanced cases the ECG changes are extreme.

4.4.2.5 *Physiological changes*

The pulmonary artery pressure at rest and the cardiac output are within normal limits in early stages of the disease, but the pulmonary

artery pressure increases on exercise. In advanced cases there is a diminution in cardiac output and the pressure in the pulmonary artery attains very high levels even during rest.

It is a feature of patients in the pulmonary schistosomiasis group that the pulmonary function is not necessarily disturbed. Secondary alterations of the air passages may, however, occur as a result of inflammatory changes, and then impairment of ventilation appears.

Certain additional features deserve mention in regard to particular diseases :

(a) Thrombo-embolism of the pulmonary arteries

This usually originates in peripheral venous thrombosis. The clinical course is variable, some cases developing within a few days or weeks (acute cor pulmonale) whereas chronic cases with recurrent thromboembolism progress gradually for years. The symptomatology also varies, and depends largely upon the presence and size of associated pulmonary infarction. With multiple infarcts pulmonary symptoms and physiological disturbances often predominate, at least in the middle stages of the disease. Severe dyspnoea and tachypnoea occur. The arterial blood shows unsaturation with oxygen, but normal or slightly lowered carbon dioxide tension. Physiologically the alterations in pulmonary function may simulate those of alveolar-capillary block. Patients with multiple small embolisms but no infarcts may be difficult to differentiate from those with primary pulmonary hypertension. In the final stages cor pulmonale becomes severe with terminal intractable heart failure. The pulmonary arterial pressure is very high, and the cardiac output is reduced.

(b) Multiple embolization of the lungs by neoplastic cells

This arises from a tumour elsewhere and is characterized chiefly by the rapid course of the disease. There is a rapidly progressive development of cor pulmonale.

(c) Primary pulmonary hypertension

This is considered to be an example of a primary lesion of the pulmonary arterial wall. The existence of this disease is still denied by some authorities, but a few cases have been recognized which have pursued a rapid clinical course with characteristic physiological findings, yet in which at autopsy almost no anatomical changes are found. This suggests that at least in some cases a physiological increase in vascular resistance precedes anatomical changes. Clinically the disease is more often seen in young women than in men, and pursues a course that follows closely the general description already given above. Only minor alteration occurs in the respiratory function. Some pathologists believe that this condition is not a primary disease but is due to multiple embolism.

(d) *Pulmonary vascular lesions occurring in situ, secondary to generalized systemic diseases*

In such diseases as polyarteritis or systemic lupus erythematosus, involvement of the pulmonary vascular bed may be such as to cause some right ventricular hypertrophy but this is not usually a serious part of the disease. The thrombosis *in situ* in the pulmonary vessels in sickle cell anaemia which may induce cor pulmonale is usually a late and often terminal event.

5. TREATMENT

5.1 Principles of treatment of pulmonary diseases that may cause cor pulmonale

Since the treatment of many of the diseases listed in Table 1 is either well established or largely ineffective, and the appropriate treatment for some of the rare conditions is still a matter for debate, the Committee considered only the treatment of chronic bronchitis and generalized airways obstruction.

5.1.1 *Avoidance of bronchial irritants*

All patients with chronic bronchitis should be persuaded to stop smoking, to avoid exposure to smoke and to take special precautions during fog. A change of occupation is indicated if there is clear evidence that some particular dust or fume to which a patient is exposed exacerbates his symptoms, and if the patient is employed out-of-doors in a smoky environment.

5.1.2 *Treatment of infection*

Since exacerbations of bronchial infection are nearly always the precipitating cause of cardiac failure in these patients, their prompt and effective treatment is of the greatest importance. The correct antibiotic must be chosen and given in adequate doses by the best route of administration.

5.1.3 *Improvement of ventilation*

(a) *Bronchodilators* should be given in full dosage at frequent intervals.

(b) *Corticosteroids*. These drugs are effective in a proportion of cases of generalized airways obstruction, but it is difficult to forecast which patients are likely to respond. In general, those with persistent infection seldom respond, while those with an asthmatic type of history or with marked sputum eosinophilia are the most amenable to therapy.

(c) *Control of excessive bronchial secretion.* In patients with excessive sputum, postural drainage may be of great value. In severely ill patients with ineffective cough it may be necessary to aspirate sputum by a tracheal catheter. When this is necessary it is usually advisable to perform a tracheostomy.

(d) *Oxygen therapy, respiratory stimulants and assisted respiration.* Oxygen should be administered to all hypoxaemic cases of generalized obstructive lung disease. In some patients, relief of hypoxaemia decreases the ventilation and hypercapnia increases to dangerous levels, thus producing mental confusion and even coma. When this happens ventilation may be increased by large doses of respiratory stimulants.

When these drugs fail, tracheostomy followed by artificial ventilation by means of positive pressure or tank respirators should be instituted and continued until the patient is once more able to maintain adequate ventilation without assistance.

(e) *Sedatives.* Morphine and other respiratory depressants should never be prescribed in cases of generalized obstructive lung disease. Only the mildest hypnotics are safe in cases of ventilatory failure.

5.2 Principles of treatment of cardiac failure in cor pulmonale

In general, the treatment of right ventricular failure does not differ essentially from that of other kinds of heart failure.

6. PREVENTION

6.1 Prevention of causative pulmonary conditions

A review of the diseases underlying chronic cor pulmonale listed in Table 1 will make it clear that in some instances the primary cause may be prevented, while in others the evolution of cardiac complications may be delayed by effective treatment. Where the primary disorder is due to specific infections such as tuberculosis or schistosomiasis, the well-known methods of disease prevention are appropriate. In the pneumoconioses, measures designed to reduce dust exposure at work will be similarly effective. The major source of chronic cor pulmonale, however, is believed to be the group of pulmonary disorders in which no single specific factor can be discerned, such as chronic bronchitis, emphysema, asthma and bronchiectasis. The uncertainty of the factors, personal or environmental, which determine the development of these disorders limits the immediate prospect for effective prevention. On the other hand, recent studies in several

fields of medicine have suggested the relevance of various aspects of the working or living environment and of certain personal characteristics and habits.

Mortality analyses have emphasized the gross excess in mortality from these disorders in men in middle life compared with women of the same age; and morbidity surveys of people of both sexes doing the same job suggest that this male excess is not due to any difference in occupational exposure or effort. Indeed, more detailed studies of personal habits and respiratory disability indicate that this sex disparity may be largely explained by differences in cigarette consumption. Prospective studies of men divided according to their smoking habits have confirmed that heavy smoking is associated with a high death rate from these chronic lung disorders.

The large differences in death rates between different parts of the same country cannot be attributed to differences in smoking habits, although some of the international disparities may be thus explained. The urban-rural gradient in mortality and morbidity, the concentration of high rates in industrial areas, and the time relationships between fog and exacerbations of chronic bronchitis have strongly suggested the part played by air pollution in the initiation or aggravation of these diseases. Other urban circumstances such as the increased exposure to infection in crowded communities may be important, but there is little firm evidence on this point.

One of the most striking features of the distribution of chronic bronchitis in the United Kingdom is the marked social class gradient for the death rate, which among unskilled workers is five times the rate prevailing in the professional and managerial classes. This gradient also appears among the wives of the men, divided according to their husbands' occupation. The high death rate among the less skilled workers and their wives is thus probably due more to some factor in the domestic environment which they share than to any specific occupational risk to which the man alone is exposed. The nature of these domestic or social factors is unknown, although infection, made more frequent by overcrowding and more serious by inadequate care or low standards of home heating and ventilation, may be important.

Studies of the natural history of chronic bronchitis have suggested that repeated respiratory infections, beginning quite early in life, are a feature in the development of persistent generalized obstructive lung disease. Support for this concept comes from the demonstration in field enquiries of a significant relationship between recurrent infections and impairment of ventilatory capacity, and from the observations of pathologists who attribute the common centrilobular form of emphysema to antecedent bronchiolitis (see page 35). On the other hand, a proportion of patients with emphysema appear to develop this disease without any previous bronchial infection. However this may be, there is good reason

to suspect that such infection plays a major role in the pathogenesis and evolution of this disease in many patients.

Although, as already noted, there is some evidence that many patients developing chronic bronchitis show a predisposition to repeated respiratory illness early in life, little is known of the factors determining individual susceptibility to such respiratory diseases.

The studies reported above were conducted mainly in industrialized countries in temperate climates. Although within these countries there is some evidence of an association between falling temperature and respiratory disorder, climatic factors cannot explain the major regional and international differences reported in the frequency of the serious forms of these diseases. Further, the relationships found, for example, between urban conditions and chronic bronchitis mortality, may not be identical in different climatic conditions. It seems likely, however, that the evidence of such relationships already accumulated allows certain generally applicable preventive measures to be proposed.

6.1.1 *Cigarette smoking*

The association noted between cigarette smoking and bronchitis makes even more urgent the need for a campaign to control the modern pandemic of cigarette smoking. Since there is reason to believe that the risks of malignant, inflammatory or degenerative pulmonary disease are less in pipe and cigar smokers, efforts to discourage cigarette smoking or to substitute these alternative methods of smoking would be worthwhile. Health education may be most usefully concentrated, however, on dissuading children and adolescents from taking up smoking.

6.1.2 *Atmospheric conditions*

Programmes for the study and control of all forms of air pollution are to be strongly encouraged, and in areas where industrialization is proceeding the avoidance of air pollution by careful siting of factories and disposal of their effluents is of prime importance to the public health. While evidence incriminating air pollution has been produced, the components responsible for the aggravation of chronic respiratory disease have not been clearly identified. Until more is known about this subject it cannot be assumed that the cleaning of air by the removal of particulate matter is the only public health action required.

6.1.3 *Infection*

Experience of the effect of repeated infections on the progress of this disease suggests that all measures designed to prevent respiratory infections

and their complications should be considered. Modern methods of domestic heating and ventilation will reduce the risks presented either by chilling or by cross infection due to overcrowding in the only warm room in the home.

6.1.4 *Working conditions*

In general, the same comments apply to the conditions of work. In addition, however, there are the specific hazards of a dusty environment. As already noted, many of these have already been recognized and dust suppression measures introduced. There remains the need for continuing scrutiny of respiratory morbidity according to occupation in order to detect previously unsuspected sources of bronchial irritation in chemical and other industries.

6.2 **Prevention of cardiac failure in cor pulmonale**

The prevention of cardiac complications of pulmonary disease is primarily a question of treating the causative condition. Methods directed more specifically to the cardiovascular system may, however, reduce the right ventricular work and delay cardiac failure.

6.2.1 *Rest*

Physical rest appears to be one of the best means of reducing right ventricular overload and its therapeutic value in the prevention of threatened cardiac failure in chronic pulmonary disease has not been sufficiently emphasized. Prolonged rest is indicated whenever the cardiac condition deteriorates in patients with pulmonary disease. In earlier stages of the disease adoption of a job that does not involve heavy exertion may be of prophylactic value. It is important, however, to remember that complete inactivity is to be deprecated.

6.2.2 *Anticoagulants*

These drugs have a wide range of usefulness, not only in pulmonary embolism but also in other forms of pulmonary hypertension and in particular those due to primary vascular diseases which are frequently accompanied by secondary thrombosis. They are indicated when there is evidence of peripheral venous thrombosis.

6.2.3 *Venesection*

In patients with a raised haematocrit and blood volume, venesection may be of value.

7. SUGGESTIONS FOR RESEARCH, AND RECOMMENDATIONS

Without attempting to formulate detailed proposals for particular research projects, the Committee wishes to indicate quite broadly the kinds of research most urgently needed to fill the large gaps in present understanding of the geographical distribution, etiology and pathophysiology of cor pulmonale.

7.1 Studies of incidence of chronic cor pulmonale and its antecedent conditions

In the words of a report to the 12th World Health Assembly¹ "contrasting experience is one of the most fruitful stimuli to new thought". Major differences in disease prevalence between two similar populations may be attributable to differences in their respective exposure to environmental agents against which preventive measures may be taken.

The value of international comparisons in mortality from cor pulmonale and its associated diseases would be enhanced by the provision of a suitable category in the revised International Classification of Diseases and by measures to increase the use of consistent diagnostic standards by physicians certifying the underlying cause of death. Such measures are unlikely to be effective in the near future, and alternative methods of comparing the incidence of chronic cor pulmonale in different areas are required.

The selective nature of admissions to teaching and other hospitals usually makes admission data from single hospitals a poor index of the local incidence of the disease. On the other hand, complete censuses of admissions for heart failure of clearly defined clinical types from a number of complete administrative areas may allow soundly based comparisons to be made. As an addition to such studies of hospital admissions, special prevalence surveys in defined populations are clearly needed. Data on respiratory diseases and their cardiac complications may be collected in the course of other field surveys. Although surveys of random samples of the whole population of an area may be ideal, the practical advantages of surveying similar occupational groups in different countries should not be ignored.

International surveys which include the collection of data on habits such as smoking and on respiratory symptoms will allow the confirmation of general relationships between them which are common to all countries and the discovery of any modifying effects of the local environment. More epidemiological research is also needed on the effects of different types of air pollution in countries or areas where different forms of fuel

¹ *Off. Rec. Wld Hlth Org.*, 1959, **95**, 504

and of power production are used. The study of the minor respiratory illnesses in contrasting types of home environment in different countries should be encouraged.

In all such comparative studies the need for the standardization of diagnostic procedures and measures—for example, of air pollution, or home, school and work environment—is self-evident. It is in this context that WHO could be most helpful by circulating descriptions of standard methods, arranging for the exchange of observers in field survey work, and in general providing co-ordinating machinery.

7.2 Research in clinical and allied subjects

It is abundantly clear from the summary of physiological derangements in the development of chronic cor pulmonale (see section 3) that there is uncertainty about almost all the functional mechanisms in this condition and especially about their precise *modus operandi* and inter-relationships.

Among the various specific problems, those which most urgently need clarification are the relative importance of haemodynamic, physico-chemical and nervous factors in controlling the pulmonary circulation and the mechanisms by which the vascular resistance increases. The effects of chronic cor pulmonale on the left ventricle should also receive more attention.

Further clarification of these problems is essential for the better guidance of prevention and treatment of the circulatory complications of lung diseases. One of the essential requirements for this clarification is wider standardization of technical procedures and collection of data from all available sources concerning the normal limits by sex and age of the relevant variables.

It is necessary to establish the relative significance of the various electrocardiographic abnormalities by correlating their presence with haemodynamic and pathological investigations in larger series than those already studied. This might permit the application of statistical methods to determine their relative discriminatory value.

It is also important to establish the validity of the radiological signs of right ventricular hypertrophy and of emphysema.

The exact techniques of measurement of right ventricular hypertrophy and of emphysema by anatomical means are not yet generally agreed. Their precision should be increased, perhaps by the standardization of procedures along the lines of those referred to in the Annex (see page 34).

New physical and biochemical methods for the study of pulmonary and vascular pathology are being developed. Their use should be encouraged in relation to cardio-pulmonary diseases.

The relationship between all these techniques with pulmonary function studied during life constitutes an essential field of research.

In respect of therapy, the necessity for applying the established techniques of controlled clinical trials to the assessment of therapeutic methods in chronic cardio-pulmonary disease requires emphasis.

7.3 Recommendations

7.3.1 *Training of investigators*

(a) *Clinical investigators*

Young investigators who have the ability to work in the field of physiological research should be given full opportunities to learn all the necessary techniques—pulmonary, cardiological and pharmacological. It is particularly important that cardiologists should receive training in pulmonary function techniques and that respiratory physiologists should be trained in the techniques of haemodynamics so that widely competent teams capable of appreciating cardio-respiratory relationships may be built up.

(b) *Pathologists*

Pathologists should receive training in the technique and significance of pulmonary function tests, and clinical investigators should devote more effort to ensuring that proper pathological studies are carried out on autopsy on patients who have been studied as completely as possible in life. Correlated clinico-pathological studies should not be confined to fatal or even to advanced cases; information is needed concerning the earlier stages of the diseases at which irreversible pathological changes develop in the pulmonary arterioles and in the architecture of the lung.

(c) *Epidemiologists*

The Committee was informed of a proposal to organize a training course for epidemiologists in cardiovascular diseases and recommends that training in respiratory epidemiological techniques should be included in these courses. Clinical investigators should be encouraged to develop a greater interest in the pre-clinical stages of disease in the general population and to help in the development of simple, accurate diagnostic techniques suitable for epidemiological studies, especially those capable of detecting slight deviations from normal lung function.

7.3.2 *Meetings of experts*

The Committee strongly supported the suggestion that WHO, in conjunction with other agencies, might arrange small international meetings of expert investigators in order to discuss specific problems in cardio-respiratory diseases. At such meetings (an upper limit of 20 participants is suggested), in addition to the valuable exchange of ideas that would

result, recommendations concerning the detailed technique of established experimental procedures and diagnostic criteria might be drawn up.

7.3.3 *Dissemination of information*

To achieve their full value, the conclusions of the meetings of experts which the Committee has recommended must be widely distributed not only by written reports but also by appropriate use of standard illustrations, radiographs and films.

Where standardized techniques exist they should be brought to the attention of all those who might use them. For instance, a standardized questionnaire of symptoms of chronic respiratory diseases, in particular bronchitis, has been developed for epidemiological study by a committee of the British Medical Research Council and has been successfully used in at least five different countries. WHO might help with the dissemination of such information.

7.3.4 *Postgraduate education*

Postgraduate education of surgeons, physicians and pathologists in the use of modern techniques of cardio-pulmonary function and in the diagnosis and management of patients with cardio-pulmonary diseases is undoubtedly needed. This is necessary if sufferers from these diseases are to receive prompt benefit of recent advances of knowledge.

7.3.5 *The Committee believes that WHO as an international organization with world health as its concern is particularly well placed :*

- (a) to encourage, sponsor and co-ordinate those aspects of research for which an international approach is needed, e.g., field surveys where comparative studies in different parts of the world are essential ;*
 - (b) to promote the use of comparable nomenclature, classification and diagnostic criteria and methodology in general ;*
 - (c) to convene meetings of an international nature ;*
 - (d) to encourage training in research requirements.*
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Annex

**SOME PRESENT PRACTICES
CONCERNING ANATOMICAL CRITERIA FOR RIGHT
VENTRICULAR HYPERTROPHY AND FOR EMPHYSEMA**1. *Right ventricular hypertrophy*

The diagnosis of right ventricular hypertrophy at autopsy is often based upon a simple measurement of the thickness of the right ventricular wall. In the adult, any excess over 5 mm in thickness of the right ventricular wall in the outflow tract is generally regarded as indicating hypertrophy. A simple determination of thickness of the right ventricle itself is, however, insufficient, for it is difficult to make allowance for the effects of cardiac dilatation or for the effect of debilitating disease in which the heart mass as a whole may be reduced.

It is therefore preferable to use the more exact method of dissecting the right and left ventricles apart, and weighing them independently, according to the technique first used by Müller (1883)¹ and later described by Herrmann & Wilson². A value lower than 1.5 of the ratio, left ventricle/right ventricle, indicates right ventricular hypertrophy.

The technique described by Fulton, Hutchinson & Morgan Jones³ has been found by certain pathologists to be more satisfactory than previous methods. In this technique the free wall of each ventricle is separated from the septum and weighed individually. The criterion for right ventricular hypertrophy based on this technique "is when the free wall of the right ventricle weighs 80 grams or more. In isolated right ventricular hypertrophy the ratio $\frac{\text{left ventricle} + \text{septum}}{\text{right ventricle}}$ is always less than 2:1. If left ventricular hypertrophy is also present the ratio may be within normal limits or even raised."

2. *Emphysema*

There is no recognized standard procedure for the recognition and estimation of emphysema in the lungs at autopsy. It is important to

¹ Müller, W. (1883) *Die Massenverhältnisse des menschlichen Herzens*, Hamburg u. Leipzig

² Herrmann, G. R. & Wilson, F. N. (1922) Ventricular hypertrophy. A comparison of electrocardiographic and post-mortem observations. *Heart*, 9, 91

³ Fulton, R. M., Hutchinson, E. C. & Jones, A. M. (1952) Ventricular weight in cardiac hypertrophy. *Brit. Heart J.*, 14, 413

realize that emphysema can be diagnosed and classified consistently only on preparations from lungs distended and fixed before they are cut. The type of emphysema requires careful description, and the classification put forward by a British group of investigators¹ is useful in that it distinguishes between simple dilatation and destructive changes. Changes selectively affecting the respiratory bronchioles (centrilobular emphysema), those affecting the whole acinus (panacinar emphysema) and those that are otherwise or irregularly distributed, are also distinguished. Illustrations are also given of suggested grades of severity. This appears to be the first attempt that has been made to provide a method of achieving uniformity in the classification and grading of emphysema. The quantitative method proposed by Sweet et al.² is an alternative technique.

¹ Ciba Foundation (1959) Terminology, definitions and classification of chronic pulmonary emphysema and related conditions. *Thorax*, **14**, 286

² Sweet, H. C., Wyatt, J. P. & Kinsella, P. W. (1960) Correlation of lung macrosections with pulmonary function in emphysema. *Amer. J. Med.*, **29**, 277

