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CHAPTER 71

Pneumoconioses

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Summary and Conclusions

THE GENERAL TERM "PNEUMONOCONIOSIS" was first suggested by Zenker to describe lung disease due to the inhalation of dust (70) and is currently so used in a shortened form, "pneumoconiosis." The dusts concerned may be of mineral or organic origin (31), and their effects on the lung encompass a wide spectrum of pulmonary pathology, *making it impossible* to generalize about the physiological disturbances of pneumoconiosis. In this chapter an attempt is made to describe the physiological patterns in those pneumoconioses that have a pathological identity. Thus it is necessary to include descriptions of pathology more detailed than usual in such a context, and discussion is focused on those *pneumoconioses* whose effects on lung function have been studied.

THE MINERAL-DUST PNEUMOCONIOSES

1. Pneumoconioses Characterized by the Presence of Much Dust in the Lung, but Little Fibrosis [Welders' Lung, Siderosis, Stannosis (of Tin Miners), Barytosis, Coalworkers' Pneumoconiosis]

It has been suggested that any mineral that is relatively insoluble and not immediately toxic can produce a pneumoconiosis if inhaled in sufficient quantity (31). When the dust is inhaled, only a certain amount is retained (see Chapter 8, this *Handbook*). Retained particles may pass directly into alveolar walls, or may be ingested by alveolar phagocytes which either collect in alveolar walls, or are discharged by the alveolar clearance mechanism to the level of the respiratory bronchiole, where they penetrate the mucosa and collect (36).

The subsequent response of the lung to dust varies greatly both in animals and in man. At one end of the scale certain dusts, of which carbon, tin (86), iron (22, 66 68), and coal dust (43) are examples, can accumulate in considerable amounts in lymphoid tissue without exciting a fibrotic tissue reaction, despite the fact that these accumulations can be dense enough to cause a diffuse nodular pattern on the chest roentgenogram, particularly if the dust is markedly radiopaque; e.g., barium (80) and tin (86). In the case of coal miners, these accumulations may lead to dilatation of the respiratory bronchiole with focal emphysema (43); and this pneumoconiosis, which may progress to massive fibrosis, is the only one in this group that does not always run a benign course.

Recognition of what have been called the "benign pneumoconioses" (all in this group except simple coalworkers' pneumoconiosis) stems from the observed discrepancy between diffuse generalized radiological

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chest disease and apparently normal function indicated by the absence of symptoms, signs, and complications of chest disease (91). One study on 15 welders with radiological disease, though incomplete, does support the clinical conviction that this is not a disabling condition, since vital capacity (VC), exercise ventilation, and maximal ventilation (observed during one minute) were not different from those of control subjects (22). Similarly, in a study on 116 men engaged in processing tin there was no difference in airway resistance and indirect maximal breathing capacity (MBC) of the 26 men in the group with grade 3–4 radiological disease, compared with the men with no radiographic change (30). Indeed, impairment of physiological measurements would not be anticipated from the pathology, except perhaps in mechanical properties, such as tissue resistance, and in the distribution of ventilation with regard to perfusion, particularly during effort, neither of these has been studied.

Simple coalworkers' pneumoconiosis is likewise rarely accompanied by disability except in subjects over 55 years of age. Thus, in the carefully matched studies of Gilson & Hugh-Jones (32) on Welsh coal miners, it is not surprising to find that the lung volumes, resting and exercise ventilation, and MBC in miners with this condition are very little different from values in nonminers of comparable age or in miners with none of the radiological changes of pneumoconiosis. Pulmonary compliance and flow resistance remain within normal limits in most cases (56), and the mass of dust [which may reach 40 g or more (74)] did not affect tissue resistance in one case so studied (61).

Of particular interest, however, is the finding of Gilson & Hugh-Jones (32) that the only measurable effect of simple pneumoconiosis on lung function was a disturbance of gas distribution. Review of their data also reveals that their distribution index of residual inequality (a postdead-space index that allowed for an anatomical dead space equivalent to that in normal subjects) clearly indicated delay in simple pneumoconiosis if compared with the normal state. In contrast, their index of biphasic distribution [which indicates the extent to which the postdead-space washout of the lungs deviates from a single exponential (25)] grouped the men with simple pneumoconiosis much more closely to the normal controls. Thus there was no apparent increase in the percentage of lung making up the poorly ventilated space, there was only a reduction in its tidal volume, whereas the smaller and better-ventilated space may even have increased in size. Overinterpretation of these findings should be avoided,[1] but it is tempting to interpret them as indicating a series-mixing defect, resembling an increased dead space, and to equate this with the dilated respiratory bronchioles in the areas of focal emphysema which are the common pathological finding in this condition (43). One might further speculate that it is not the extent of such an emphysematous change (in terms of percentage of respiring tissue involved) that should be related to the distribution defect, but its strategic situation. If one respiratory bronchiole of the third order supplies 12 alveolar ducts (58), dilatation and distortion of all such bronchioles in a miner's lung involving only about 8 per cent of the respiring tissue might yet be sufficient to impair distribution throughout the lung. Thus even emphysema graded as "slight" [i.e., if less than 25 per cent of respiring tissue is involved (97)] in the autopsy examination of the lungs of these Welsh coal miners (14) may be responsible for such a distribution defect.

The anticipated consequences of uneven distribution of the sort documented by Gilson & Hugh-Jones (32) have been demonstrated in Belgian coal miners by Brasseur (10); namely, decreased alveolar ventilation with increased alveolo-arterial O_2 differences, demonstrable at rest and exaggerated under the stress of exercise. Furthermore these changes are detectable at a relatively early stage of nodular disease, become progressively more marked as the radiological picture advances, and considerably antedate the appearance of symptoms and disability. Indeed these clinical manifestations do not appear to develop until there is an associated fall in ventilatory volumes [as reflected in maximal ventilatory volume (MVV)], which usually coincides with the progression of the disease to the conglomerate form discussed in the next section.

2. Pneumoconioses Characterized by the Presence of Much Dust in the Lung and Massive Localized Fibrosis (Progressive Massive Fibrosis of Coal Miners, Conglomerate Silicosis)

Mineral-dust pneumoconiosis may progress to conglomerate lesions of dense massive fibrosis. These usually start in the midlung fields bilaterally, and may progress to large conglomerate masses of fibrous tissue that replace the air-filled lung. This progression may occur years after exposure to dust ceases. In coal workers' pneumoconiosis the development of this

[1] The technique used, an open-circuit wash-in followed through two logarithm cycles, overlooks certain types of regional inequalities (78). However, the point of interest is comparison with data on normal subjects using the same technique

complication is more frequent, the more advanced the simple pneumoconiosis (15). Why this complication develops is not known; but most evidence suggests that it results from an added tuberculous infection (15). In classical silicosis nontuberculous infections also have been incriminated (96). Lobar or diffuse emphysema also may develop after progressive massive fibrosis.

Disability usually accompanies the onset of progressive massive fibrosis in coal miners (10, 32). The concomitant changes in physiological measurements include a reduction in lung volume due to a reduction in vital capacity. The ratio of residual volume to total lung capacity (RV/TLC) thus increases. There is further inequality of ventilation (suggesting both increased dead space and regional inequalities), but the disturbance is not usually of the same severe degree seen in nonindustrial emphysema (32). Increase in alveolo-arterial O_2 differences with minor degrees of arterial desaturation, particularly on effort, may be seen (10, 72); reduction of this difference by intermittent positive-pressure breathing on air suggests that the desaturation is the result of inadequate ventilation to areas of well-perfused lung (73). Percentage removal of carbon monoxide during the breathing of low concentrations of this gas is not much reduced even in severe complicated coalworkers' pneumoconiosis (32); but the examination of this value in relation to volume of gas breathed (i.e., direct measurement of pulmonary diffusing capacity) is necessary to establish the absence of significant diffusion defects in this condition. The available evidence, however, suggests that this parameter is not much reduced (10, 72), and that the most important mechanism accounting for the increased alveolo-arterial difference is ventilation-perfusion imbalance. Such imbalance might follow pathological encroachment on the pulmonary vascular bed (89) or might be the consequence of disturbance of adaptive mechanisms that maintain the balance in normal lungs.

Mechanical properties of the lung are less affected than might be anticipated by the presence of progressive massive fibrosis. Thus, despite the fairly consistent reduction of MBC in this condition (32, 56), flow resistance during quiet inspiration and expiration (as reflected in the nonelastic work of breathing) frequently remains within normal limits (56). In such instances the mechanism by which MBC is reduced might be limitation of maximal flow rates due to reduction of functioning lung volume (26), a possibility that could not be examined directly, as there are no reports of flow resistance and lung volumes on the same subjects. However, reduction of the available lung tissue might be inferred from reduction in lung compliance,[2] which has been reported in progressive massive fibrosis, more frequently in the older miners than younger men (56). Though the observations were restricted to dynamic compliance, it is reasonable to deduce that static compliance values are probably similarly affected, since distribution factors are unlikely to be important in the presence of normal or near-normal values for flow resistance (79). Thus there is nothing in the available evidence to conflict with the hypothesis that reduction of ventilated lung volume due to its replacement by fibrous masses may be a frequent mechanism for disability in progressive massive fibrosis, perhaps as common as associated generalized emphysema; and indeed such an explanation is most easily equated with the pathology.

3. Pneumoconioses Characterized by the Presence of Little Dust in the Lung; Generalized Nodular Fibrosis (Classical Silicosis of Hard-Rock Miners)

Dust containing free silica, one of the most frequently occurring constituents of the biosphere, is almost unique in its capacity to evoke a fibrous-tissue response in animal tissue, whether amphibian or mammalian (53). The reaction appears to start with alteration of the macrophages by the dust (53). A fibroblastic reaction follows, peribronchiolar (96) or perivascular, or both (104), ultimately leading to the development of the fibrous silicotic nodule characterized by layers of whorled connective tissue arranged concentrically, like an onion bulb. High concentrations of finer silica dust are probably responsible for producing a more diffuse type of fibrosis (31, 53, 101). Small amounts of silica in the presence of inert dusts produce a mixed-dust fibrosis (66) in which the arrangement of the reticulin and collagen is linear and radial, resulting in a nodule whose outline is irregular and stellate.

Under experimental conditions, animals can be exposed to controlled amounts of dust of known chemical composition and size distribution. However, the hazards to which man is exposed in mining or industrial enterprises are seldom pure dusts, but usually comprise mixed materials varying considerably in chemical composition and in size distribution. It is generally true, however, that the greater the amount of free silica in the dust hazard, the more severe the fibrosis. Thus between the extremes of, for instance, simple pneumoconiosis of coal miners, in which the

[2] When equivalent ventilatory volume is accommodated in fewer lung units, the distending pressure must be greater (69).

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lungs contain much dust (perhaps 80 g) but little fibrosis (74), and classical silicosis, in which the lungs contain little dust (perhaps 10 g) and extensive fibrosis (74), there is a wide range of pathological change in which dust content and degree of fibrosis in the lung vary in amount and degree. Emphysema develops in a small proportion of cases.

It is thought that silica produces its effects by acting on the lung phagocytes (38, 75), but the mechanism whereby it affects these phagocytes is unknown. Neither a mechanical nor a simple solubility theory is adequate to explain the disease (75); inactivation of specific cell enzyme systems cannot be conclusively incriminated (75); the effect of polysilicic acid on co[illegible]n precursors may be important (45); and the demonstration of increased gamma globulin in cases of silicosis has led to the view that silica may act as a nonspecific antigen (75), and that immunological mechanisms are significant. A point of contrast between this type of nodular disease and the diffuse fibroses has been emphasized by Nagelschmidt (74). He noted that in classical silicosis, fibrosis and dust content (of the ashed lung at autopsy) increase concomitantly, whereas in the pneumoconioses characterized by diffuse fibrosis, the more advanced the fibrosis, the lower the dust content of the lung at autopsy. This suggested to him that in some way the continued presence in the lung of insoluble silica dust causes the nodular disease of classical silicosis, and any acceptable theory of the disease should be compatible with these findings.

The only consistently abnormal finding in the nodular stages of coalworkers' pneumoconiosis (a disease characterized by much dust in the lung with little fibrosis discussed under section 1 above) is an increased alveolo-arterial O_2 difference, most other measurements remaining within normal limits. In contrast, in classical silicosis in the nodular stage other measurable compromise of function usually can be shown (8), and increases in alveolo-arterial differences must by analogy to coalworkers' pneumoconiosis (10) also exist, although as yet they have not been systemically studied.

However, in a small but significant proportion of cases [reported as 15 (8) to 18 per cent (90) in different series] these other function measurements (which include VC, MVV, lung volumes, compliance, and airway resistance but not alveolo-arterial O_2 differences, which as indicated above have not been studied) may appear normal.

One can reconcile such normal values with the presence of dust foci consisting of no more than reticulin fibrils holding in place the dust-laden phagocytes (as in simple coalworkers' pneumoconiosis), but it is harder to speculate how the lung can be studded with fibrous tissue nodules of silicosis without having such measurements compromised.

There are several possible reasons for this anomaly. The failure may lie in insensitivity of techniques or of interpretation. Sensitivity of techniques is discussed elsewhere in this volume (see Chapter 53). In connection with the interpretation, the common practice of relating observed values to the predicted normal values deserves comment. The standard error of estimate for such predictions usually exceeds 10 per cent,[3] so that although such parameters may be 20 per cent below predicted values (i.e., within the normal range of twice the standard deviation) after exposure to a dust hazard, there could in fact have been a decrease of 40 per cent from pre-exposure levels of 20 per cent above the predicted value. Annual studies of exposed subjects commencing before the period of exposure and continuing during exposure may at some future date reveal function defects of this order.

Alternatively, the lungs in silicosis may be the site of two pathological processes with opposite effect on, for instance, the volume of the areas they affect namely, fibrosis with its characteristic restriction of functional residual capacity and residual volume but preservation of the tests of airflow (3, 110, 114), and emphysema with the opposite effects of hyperinflation and decreased airway conductance (4, 106). Measurements of these particular parameters might thus appear near normal, although other parameters, such as gas distribution, exercise ventilation, ventilation-perfusion ratios, and arterial gas tensions, might be measurably affected. Such cases have been documented.[4]

Allowing that insensitivity of technique and interpretation might account for some of the normal measurements in a proportion of cases of silicosis, there are still others in which the lungs indeed appear to accommodate the nodules of fibrous tissue with very minimal compromise of function, even in parameters such as compliance[5] (8) and tissue resistance (61). The situation of the nodules and preservation of intervening tissue may provide the explanation

[3] For subdivisions of lung volume, ventilatory tests, gas distribution, diffusing capacity, and resting and exercise ventilation at a standardized external work load (34, 54, 76).

[4] Case IV, described by Wright & Filley (110), had normal lung volumes and exercise capacity. Lung rinsing, maximal breathing capacity, and arterial P_{O_2} on effort were reduced.

[5] Dynamic compliance only has been reported (8), not the more sensitive parameter of static compliance from FRC to VC (60).

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Dayman (personal communication) has suggested an analogy to a fishnet, in which knots (or fibrous *nodules*) *at the points of crossing of the mesh might* affect function minimally, in contrast to knots in the intervening strands, which might be expected to impair expansion and distribution.

When function measurements eventually become disturbed by the presence of silicosis, the function pattern may suggest obstructive airway disease or *restriction of lungs* (see Chapter 63) or a mixture of these patterns (87), variations that probably correlate with the predominant underlying pathology. Thus, though cases of silicosis are commonly used to exemplify the physiological effects of *pulmonary fibrosis* (3, 48, 110, 114), they are also cited as examples of emphysema (4) when they appear to be indistinguishable *on the basis of function* from cases in which there is no associated dust disease in the lung. From the roentgenogram it may not be possible to predict whether the function pattern will suggest restrictive or obstructive disease, a mixture of these pathologies, or whether it will be within normal limits (see table 1). The majority of cases exhibit a mixed-function pattern, and perhaps this is why results for a randomly selected group of cases (including the three individual results of table 1) show only minimal changes (8). Disability to the patient (in terms of dyspnea on exertion) has been shown to correlate with an increase in the ratio of exercise ventilation to maximal voluntary ventilation,[6] and is due to both an increase in the *former* value (8, 50, 88) and a reduction in the latter value (8, 88).

Arterial desaturation is not usually present in the diffuse nodular stage of silicosis either at rest (8, 89) or on mild exertion [about 50 w or 300 kg-m *per min* (8)], although it is likely that there is an increase in alveolo-arterial O_2 differences at this stage of the disease. At *heavier exercise loads* (150 w), however, a considerable proportion of cases show desaturation (89), and would presumably also show greater alveolo-arterial O_2 differences. Collateral evidence has led to the conclusion that this fall in saturation is usually the result of inequalities of ventilation with regard to perfusion, either due primarily to uneven distribution of inspired air or *to restriction of the pulmonary capillary bed by* the pathological process (72, 90). Disturbances of the ventilation-perfusion balance in the lung may also account for the reduction in diffusing capacity; this has been demonstrated by means of the single-breath CO technique in the eight subjects with silicosis

[6] Variously referred to as the "dyspneic index" (32) or the "pulmonary reserve" (50).

TABLE 1. *Pulmonary Function Studies on Three South African Gold Miners**

	Case 1 Normal	Case 2 Restrictive	Case 3 Hyperinflated
Age, years	53	54	53
Height, cm	173	169	173
Surface area, m^2	1.78	1.81	1.88
Subdivisions of lung volume			
VC, % predicted	110	83	65
RV, % predicted	100	79	162
TLC, % predicted	108	82	95
FRC, % predicted	108	79	130
FRC/TLC, %	56	52	58
RV/TLC, %	34	33	73
Mixing index, liters/liters FRC (normal limit, 4.86)	3.79	5.27	5.23
% Arterial O_2 saturation, by oximeter			
At rest	95	94	98
At work, 300 kg-m/min	94	94	94
Ventilation liters/min			
At rest	12.7	15.8	11.7
At work, 300 kg-m/min	30.0	35.3	33.9
MVV liters/min, % predicted	146	100	52
Mechanics			
Cdyn (10-25)†	.298	.090	.091
Cdyn (30-40)	.227	.103	.071
Flow resistance (exp.) cm H_2O/liters per sec	4.10	4.47	7.32

* With apparently identical radiological pictures of generalized nodular silicosis. For details of techniques, prediction values, etc., see Becklake *et al.* (8).

† Cdyn = dynamic compliance in liters/cm H_2O at 10-25 *or 30-40 breaths per min.*

reported to date in the literature (16, 51). More severe restriction in diffusing capacity has been found in a small proportion of cases (18 out of 90) in which the pathological process was predominantly a diffuse *chronic interstitial fibrosis* in association with the nodular disease (27); and these cases, probably resulting from heavier exposure to very finely divided dust, are more correctly classified into the next group to be considered, namely, pneumoconioses characterized by diffuse pulmonary fibrosis.

Classical silicosis, like simple coalworkers' pneumoconiosis, *may progress to conglomerate* disease, but there has been little systematic documentation of the consequent effects on pulmonary function. Because symptoms are usually present in the discrete nodular stage of the disease, the progression of the disease cannot be pinpointed to their onset as in the case of simple coalworkers' pneumoconiosis, and it is probable that

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there is not much difference between the effects of diffuse nodular and conglomerate disease on function (87) until the latter reaches an advanced stage.

4. Pneumoconioses Characterized by Diffuse Pulmonary Fibrosis

ASBESTOSIS. In contrast to the relatively insoluble dusts that produce the nodular pneumoconioses, those causing diffuse fibrosis appear to act via certain slowly dissolving constituents released into surrounding body fluids (74).

In the case of asbestos, the size of the dust particles[7] has been held responsible for their tendency to remain in the alveoli. It has been suggested that the initial reaction to the particles is fluid exudation, recurring with each fresh dust exposure (59). As the result of the inflammatory reaction they excite, the particles become covered with a smooth protein film that later becomes impregnated with iron; and the particles are then transformed into the characteristic golden-brown asbestos body (6). In this form they may apparently be inert for considerable periods of time (5) and indeed are considered by some to remain permanently so. Few seem to reach the lymphatic system and lymphoid deposits, fewer still reach the hilar lymph nodes (59), and their presence in the pleura is unknown (42, 103). This is somewhat surprising in view of the fact that the pleural reaction in asbestosis is usually severe, varying from pleural adhesions (sometimes the only pathological change) to dense adhesive fibrous pleurisy and even malignant changes in the form of mesothelioma (103) in some kinds of exposure. In the course of time (often years later) reaction in the lung tissue starts, ascribed by some to disruption of the asbestos body, a process that may be accelerated by pulmonary infections and cardiac failure (7). The fibrosis, which may start in a peribronchiolar situation (102) and subsequently spread to obliterate many of the air spaces by collagen, may even result in the replacement of the bulk of functioning lung tissue by cystic spaces lined by flattened epithelium, a change referred to as "honeycomb" lung (42). Bronchiectasis may be associated with the more advanced stages of the disease (42, 57) and has been suggested as the determinant of the two prominent clinical features, namely, clubbing of the fingers and basal crepitations (57). Emphysema, if present, is not usually of a marked degree, and appears to be more of an incidental occurrence (42).

In asbestosis function changes are of the pattern

[7] Particles up to 100 μ have been seen in the terminal respiratory units (65).

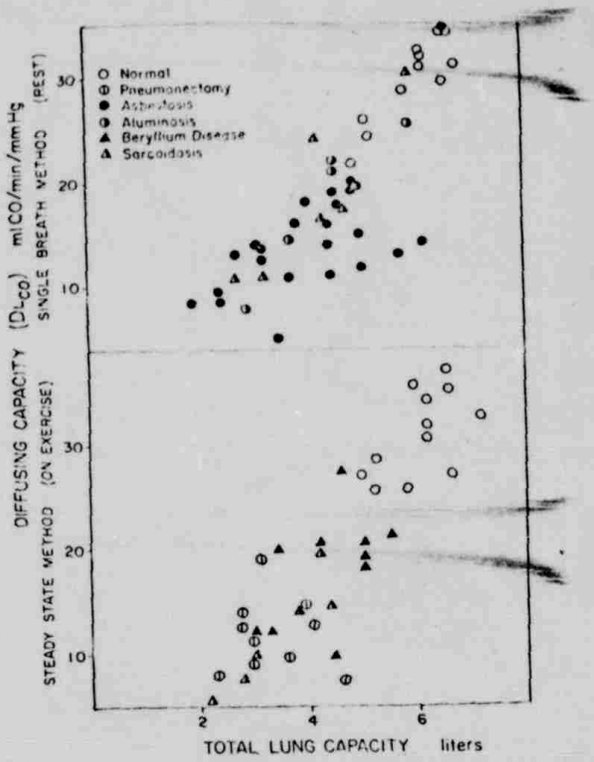


FIG. 1. Relationship between diffusing capacity and total lung capacity in the pneumoconioses associated with diffuse pulmonary fibrosis. All reported cases have been included, provided both diffusing capacity and TLC have been recorded in the subject. The data have been derived as follows. *A*: for the single-breath method at rest, results on normal subjects, chronic beryllium disease, and sarcoidosis from Marks *et al.* (62), on aluminosis from Jordan (49) and Mitchell *et al.* (71), on asbestosis from Thomson *et al.* (98). The data of Williams & Hugh-Jones (107) have been omitted, since their subjects were the same as those of Thomson *et al.* (98). *B*: For the steady-state method on exercise, results on normal subjects, chronic beryllium disease, and sarcoidosis from Cugell *et al.* (16), and for pneumonectomy from McIlroy & Bates (63).

associated with fibrosis (105). Thus there is generalized reduction of lung volume, but in particular of vital capacity, a change ascribed to the severe pleural reaction of asbestosis which limits the range of lung expansion (57, 98, 107, 112). Tests of ventilatory capacity on the whole show moderate preservation, with rare exceptions when the difficulty with expiration seems to be the result of associated emphysema (107), a situation that may be encountered more often in advanced cases (57).

An invariable finding associated with asbestosis, however, is a decrease in the diffusing capacity (2, 57,

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98, 107), and it is of interest that this decrease may be demonstrable before there is definite radiological evidence of the disease (98). This would be in keeping with the suggestion that the earliest reaction to inhaled asbestos particles is an alveolar exudate (3, 59) which one might anticipate would reduce diffusion selectively. Alternatively, the early function changes in this disease, as in coalworkers' pneumoconiosis, might be the result of ventilation perfusion imbalance. As the disease advances, radiological changes become evident, and in one series have been shown to correlate with the reduction in diffusing capacity (107).

Caution must be exercised in ascribing the reduction in diffusing capacity associated with asbestosis exclusively to the increased distance for gas to pass from alveolus to red cell through thickened tissues. Admittedly this explanation is readily compatible with the pathological findings of thickening and separation of the alveolar and capillary walls, and is in keeping with demonstrable changes in the "permeability" of the lungs, the "k" of Marie Krogh (55), recently measured in some subjects with asbestosis by Thomson *et al.* (98). However, a reduction in the surface area for diffusion may be the more important mechanism in some if not most cases (98), a point of view supported by the apparent correlation between reduction in diffusing capacity and in lung volume in cases assembled from various reports in the literature (see fig. 1).

Of all disturbances of function in asbestosis, an increase in the alveolar-arterial oxygen difference appears to be the most consistent (112), occurring even more frequently than the reduction in diffusing capacity to which it was originally ascribed. It now seems probable that other factors contribute to this gradient. One of these is the presence of relatively underventilated but well-perfused areas in the lung, a possibility that was overlooked when intrapulmonary gas distribution was assessed solely on the basis of the end-tidal or alveolar N_2 concentration after seven minutes' pure O_2 breathing (1). Techniques of greater sensitivity, such as continuous measurement of the respiratory quotient (RQ) in expired air (83), have indicated considerable inequalities in ventilation and ventilation-perfusion ratios in asbestosis (83); and these changes undoubtedly contribute in some measure to the arterial desaturation so commonly reported on effort (112), and may indeed be more important than previously thought in cases of alveolo-capillary block due to other causes (24, 44). In contrast, arterial saturation at rest is usually within normal limits, perhaps so maintained by hyperventilation, which is a prominent characteristic of the disease. Arterial CO_2 tensions also are usually within the low normal range (2, 112); lower values, however, may be found in individual cases of marked severity where hyperventilation is particularly striking.

In addition, asbestosis is associated with a marked reduction in pulmonary compliance (57), the result presumably of alteration by fibrosis of the lung's mechanical properties, but probably aggravated too by decrease in the number of functioning lung units (69). Nonelastic work of breathing has been shown to be about twice that of normal breathing at rest (57); the increase might be expected to result from increased tissue flow resistance, although in one case so studied, both airway and tissue flow resistance were at the upper limit of normal (61).

Capacity for work may remain unimpaired despite arterial desaturation (112); when incapacity supervenes, effort tolerance may be diffusion-limited or ventilation-limited (57). In the latter case, the limitation is attributable in very large measure to a rise in the ventilatory requirements of exercise rather than to a fall in the ventilatory capacity, and thus contrasts with the situation in the nodular pneumoconioses, in which the effort tolerance, always ventilation-limited, is restricted primarily by the reduced ventilatory capacity.

ALUMINOSIS (INCLUDING SHAVER'S DISEASE). Another inorganic dust associated with generalized fibrosis is that of aluminum. In many circumstances this dust is inert as far as the lung is concerned (18, 32); however, it has been held responsible, at least in part, for the diffuse pulmonary fibrosis that may develop in workers engaged in the processing of bauxite for the manufacture of corundum (93). The fibrosis develops after a relatively short period, usually measurable in months rather than years of exposure to the fumes from the fusion furnaces (84). Study of the fumes shows them to consist mainly of particles beyond the resolving power of the microscope (few are as large as 1 μ), and chemical analysis shows them to be rich in aluminum and amorphous silica, of which a proportion is probably free (81). Retention of fine particles of this size is high (41); and it has been suggested that, because of their deep penetration and high retention rate, they concentrate in alveolar spaces, where they are responsible for the development of a diffuse rather than a nodular fibrosis.

The earliest pathological change is thought to be septal edema, followed by infiltration with inflam-

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matory cells in alveolar walls (113). This is followed by a rapidly sclerosing process involving pulmonary septa and probably interfering with dust elimination. Obliterative endarteritis is common. The end result is a diffuse interstitial fibrosis without nodules, but with pleural thickening. Emphysematous bullae both in the fibrosed areas and subpleurally are common; the latter presumably account for the frequent complication of spontaneous pneumothorax, though it is not clear from the pathology why bullae in this condition should be more prone to rupture than emphysematous bullae found in association with all the other varieties of industrial and nonindustrial fibrosis (113).

The similarity of this disease to that reported in workers exposed to fine aluminum powder (35, 49, 71) makes it reasonable to assume that when exposure to aluminum dust of fine-particle size (chiefly under 5 μ) occurs, diffuse pulmonary fibrosis may develop.

Aluminosis is an uncommon disease, and reports of function studies done on only five cases were encountered (49, 71). In one with minimal radiological change, function was normal (lung volumes, maximal ventilatory capacity, timed vital capacity, maximal flow rates, and diffusing capacity). In two there was moderate reduction in the tests mentioned, and in two severe volume restriction and airway obstruction. Reduction in measured diffusing capacity, which was substantial in two cases, could reasonably be ascribed to a reduction of ventilated lung volume (see fig. 1), although of course, as in asbestosis, a "membrane block" cannot be excluded from consideration.

CHRONIC BERYLLIUM DISEASE OF THE LUNG. Beryllium disease of the lung in its chronic form is also associated with a diffuse pulmonary fibrosis. The condition, however, is more correctly classed as a manifestation of a systemic poisoning by beryllium compounds than as a pneumoconiosis (38). Its inclusion here is perhaps justifiable, since the toxin most frequently enters the body via the lungs as an inhaled dust. In the chronic form symptoms may follow exposure or may be delayed for as long as 10 years (39). The earliest pathological lesion is a loose collection of cells surrounded by lymphocytes (100). As the lesion increases in size and age, giant cells appear, often containing inclusion bodies, and giving the appearance of a noncaseating granuloma, frequently indistinguishable from the granuloma of sarcoidosis (19, 108). The granulomata, which are found in septal, subpleural, peribronchial, and perivascular tissue, may progress to hyalinization. Besides these "eye-catching" granulomata, there is a generalized cellular infiltration of alveolar walls (19) which may go on to diffuse interstitial fibrosis (108). Differentiation of chronic beryllium disease from sarcoidosis may be very difficult both on clinical (39) and pathological grounds (108) and can probably be made with certainty only by the demonstration of the element beryllium in tissues or the body fluids (39).

Function changes of chronic beryllium disease are very similar to those of sarcoidosis, the condition that it so closely resembles pathologically. A study of both diseases done in one laboratory (28) recorded almost identical mean values and ranges for a wide selection of function measurements. Thus it presents the features of pulmonary restriction (Chapter 63, this volume), with some decrease in vital capacity, but with preservation of, or only slight increase in, residual volume, and minor delay in N_2 clearance (28). Maximal voluntary ventilation is likewise well maintained (28).

As in other pneumoconioses characterized by the presence of diffuse fibrosis, a most consistent feature of chronic beryllium disease is an increase in the alveolar-arterial O_2 difference (28), associated frequently though not invariably with a reduction of measured diffusing capacity. Though hyperventilation at rest and on exercise usually maintains the alveolar P_{CO_2} within normal limits, minor degrees of arterial desaturation are usual, and on exercise this value appears to decrease *pari passu* with decreases in diffusing capacity. As in asbestosis caution must be exercised in ascribing the change in diffusing capacity solely to an increased distance for diffusion through structures pathologically thickened, particularly in view of the demonstration of normal membrane permeability in a single case so studied (11). Reduction of this measurement could result from a decrease in diffusing area due to replacement of functioning lung by the granulomatous process, a possibility supported by the apparently concomitant fall in total lung capacity and diffusing capacity in patients with this disease, as well as in sarcoidosis, which it so closely resembles pathologically (19, 108) (see fig. 1, in which are graphed data assembled from reports in the literature). Furthermore, the rise in diffusing capacity on effort, proportional to the rise in metabolic activity [in one group varying from 0.8 to 1.7 liters O_2 per min (28)] argues in favor of the unaffected lung tissue's maintaining the capacity to enlarge the capillary bed, an attribute that might not be preserved if the membrane were diffusely thickened when the diffusing capacity at rest or on very light exercise may be the maximal.

A small proportion of patients only[1] show the com-

[1] Two out of twenty-nine, or 7 per cent, in one series (28).

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plicating features of emphysema as reflected by reduction of ventilatory tests and increase in residual volume. This contrasts with the higher incidence of airway obstructive changes in subjects with chronic beryllium lung disease reported between 1951 and 1955 (11, 23, 111), and has been interpreted as an indication of a changing pattern in an intoxication whose severer forms were seen after a shorter time delay, and whose milder forms, developing after a longer latent period, are only now being recognized. Thus earlier cases were frequently complicated by cor pulmonale, and generally deteriorated rapidly, with a mortality rate of 20 to 100 per cent (28). Nowadays, however, the occurrence of long remissions is recognized, and cases in which the only evidence of the intoxication is radiological lung change have been followed for several years (39).

ORGANIC-DUST PNEUMOCONIOSES

In contrast to the specific nature of the pathological changes found in the lung parenchyma with the inorganic-dust pneumoconioses, those occurring in the organic-dust pneumoconioses are nonspecific and more frequently affect the airways. They range from conditions resembling allergic asthma [such as the disease among weavers following the inhalation of size made from tamarind seed (99)] to diseases like byssinosis (a disease of workers exposed to cotton-mill dust, flax, and hemp) in which the mechanism by which symptoms are produced, though poorly understood, is probably bronchial edema and spasm, but which differs considerably from allergic conditions.

Byssinosis

The pathological features of byssinosis (as yet reported in few cases only) are entirely nonspecific. Some bronchitis and emphysema (35) are generally present and are indistinguishable from the nonindustrial varieties of these diseases. "Byssinosis bodies," or dust particles surrounded by an envelope similar to that seen in asbestos bodies, have been reported in histological sections of some cases only (35) and have not to date been systematically looked for in the sputa of subjects with the typical clinical syndrome. Despite the absence of radiological signs of dust deposition, microscopic examination does reveal an excess of dust in the lungs of byssinosis subjects. The dust, usually not present in any quantity, is apparently carbonaceous, as it is black and collects in foci in which reticulin and an occasional collagen fibril can be seen (92). Thickening of interalveolar walls from edema and cell infiltration, though reported in animals exposed to cotton-mill dust (82), has not been reported in man.

The symptoms of byssinosis are, however, so characteristic as to constitute the basis of diagnosis in a subject with suitable exposure. For example, grade 1 byssinosis can be diagnosed in a millworker who, sometimes soon after, but frequently after some 10 years or more in the industry, complains of chest tightness and dyspnea coming on after the week-end break and passing off some hours later, without troubling him again during the working week. In time symptoms are noticed on the second day as well as the first after the break (grade 2), and they may eventually become persistent (92). Prevalence of byssinosis frequently exceeds 50 per cent (20, 85) of the population at risk, and following its original documentation in the Lancashire millworkers (92) has now been described among millworkers elsewhere in Europe, as well as in India, Egypt (20), and North America (109).

Changes in function parallel the symptoms remarkably closely (64, 92). Thus, in grade 1 of the disease, indirect MBC shows a progressive fall throughout the eight working hours of Monday with only partial recovery overnight, whereas values are lower for the rest of the week but fall less during the hours of exposure (64). In grade 2 initial values for indirect MBC are lower (92) and they fall as much or more on other days as during the working hours of Monday (64); in addition airway resistance shows significant increases during exposure (64). Though the fall of indirect MBC during the working day is not great around 10 per cent (64) the subject may be more aware of it because indirect MBC is lower in millworkers than in persons never so exposed.

There is some evidence that the changes in function already mentioned occur when exposure is to dusts of unrestricted particle size (including particles of 7 μ and over). When the exposure is to fine mill dust[9] or aerosols of mill dust, inequality of alveolar ventilation (10) becomes demonstrable (though not at a level of statistical significance) in addition to the effects on indirect MBC, although airway resistance changes are less marked (65). These observations have led to the tentative suggestion that coarse dust acts on larger airways, producing spasm, and is responsible for the symptom of tightness in the chest; whereas fine dust, despite its low retention rate (41), penetrates more deeply, affecting the smaller airways and hence gas

[9] Particle size 7 μ or less (65).

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distribution (83). Function changes of a similar nature but usually of a less marked degree may be seen in exposed workers without byssinosis (65) and in control subjects exposed to mill dust (10); however, there is no daily fluctuation in ventilatory tests in affected subjects after their removal from this dusty atmosphere (65).

Although there is little doubt that byssinosis is the result of exposure to cotton-mill dust (64), the mechanism by which it acts is not yet understood. The sometimes long exposure before symptoms develop, the high incidence among exposed workers, and the lack of appropriate skin reactions distinguish byssinosis from allergic asthma due to an antigen-antibody reaction (92). Direct release of histamine by the dust could account for the symptoms, but has been shown to occur to only a slight degree under experimental conditions (9, 17, 77). Two other pharmacological effects of the dust, smooth-muscle contraction and increase in cell permeability (17, 77), could explain the symptoms bronchoconstriction from local absorption; and associated bronchial edema, due to a change in cell permeability, which might explain the slow recovery at the end of the day. Epinephrine aerosol (which could relieve both bronchospasm and edema) has been shown to reverse almost completely the results of exposure on indirect MBC in subjects with established byssinosis, an effect as readily demonstrated on a Monday as on a Friday (64).

Bagassosis

Exposure to the dust of bagasse (the residue of sugar cane from which the sugar has been extracted) may in certain circumstances result in an acute febrile chest illness, associated with dyspnea and cough, from which the patient usually recovers completely (47, 94). The pathology of acute bagassosis[10] is an acute bronchiolitis; in addition certain dust spicules that rotate polarized light are seen to be embedded in interstitial tissue which may show a fibrous reaction; foamy cells filling alveolar spaces have been noted (94). It has been suggested that fungi in the sugar-cane fiber are responsible for the bronchiolitis and that the fiber itself evokes the interstitial tissue reaction, a view for which there is some suggestive experimental evidence (29).

The question as to whether there are chronic forms of bagassosis is unanswered. Autopsy on one case that ran a protracted course over four years (47) revealed extensive pulmonary fibrosis, bronchiectasis, and emphysema; whereas in another case radiological changes suggesting fibrosis persisted, although the patient was asymptomatic.

During the febrile phase of bagassosis (and presumably when the bronchiolitis is acute and prominent) vital capacity has been recorded as considerably reduced in four cases (13, 94) and arterial oxygen saturation low (91 per cent) in the two so studied (13). This finding was probably secondary to inadequate ventilation to perfused areas, since it was associated with evidence of airway obstruction (reduced timed vital capacities), was corrected by O_2 breathing, and reverted to normal on recovery (13).

Chronic Lung Disease in Sisal Workers

An unusual type of apical fibrosis with bronchiectasis has been found in a percentage of workers in a Uganda factory processing sisal (93). This may be an example of another form of bronchial pathology resulting from the inhalation of organic dust, and is perhaps comparable to the apical fibrosis cavitation and bronchiectasis of workers in the Hungarian pepper industry (46) and to the one reported case of fibrosis and bronchiectasis in a worker exposed to bagasse (47).

Although no acute effects of exposure to sisal dust comparable to the effect of cotton-mill dust in subjects with byssinosis have been demonstrated (33), operatives in sisal factories do have an increase in chest complaints and a reduction in MBC (measured over one minute) compared with control subjects with no such exposure[11] (93). This may be an example of bronchitis due to an organic dust. In addition reductions in VC and MBC were found in the four subjects who had apical fibrosis and bronchiectasis.

SUMMARY AND CONCLUSION

The pneumoconioses are a group of lung diseases due to the inhalation of dust, mineral or organic, in which the pathological manifestations vary considerably according to the kind of dust inhaled.

Among the *pneumoconioses due to inorganic dusts*, four general varieties can be distinguished with their corresponding physiological patterns.

1) *Those characterized by much dust in the lung but with*

[10] Based on two lung biopsies and one autopsy (94).

[11] Values in this control group were lower than those reported in healthy African male subjects by Gray (37), using an analysis of the forced vital-capacity record, a difference probably due to technique.

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little fibrosis. In this group function is subjectively normal; in addition, most objective measurements of *pulmonary function* (e.g., lung volumes, ventilatory tests, and mechanics) are also probably within normal limits. However, in coalworkers' pneumoconiosis (the most extensively studied disease in this group) a distribution defect of a series type (resembling an enlarged dead space) is found, which may be consequent to focal emphysema, a characteristic feature of the *pathology*. Associated with this is an increase in alveolo-arterial O_2 difference, becoming progressively more marked as the degree of nodulation increases in size and extent, and probably due to the imbalance of ventilation with respect to perfusion. Changes of this sort thus represent the first detectable compromise of function in this disease and, as indicated above, antedate the *perception of symptoms and detection of* effort limitation.

2) *Those characterized by much dust in the lung and with large localized areas of fibrosis*. The striking example (and best-documented one) in this group is the progressive massive fibrosis of coal workers. Disability is almost always present, and though in some instances the *mechanism by which it is produced is consistent* with associated generalized emphysema, in other cases replacement of functioning lung tissue (presumably by the fibrous tissue masses) is undoubtedly the predominant mechanism.

3) *Those characterized by little dust in the lung but with diffuse nodular fibrosis*. In this group, about 20 per cent of the subjects have no symptoms and no objective abnormalities of pulmonary function, unless, by analogy to coalworkers' pneumoconiosis, there is an increase in alveolo-arterial O_2 difference, a parameter that has not yet been systematically studied in this disease. Of the remaining 80 per cent who are disabled some have the function changes of fibrosis without significant effect on diffusion, some have the function changes of emphysema, and *in some* the pattern is mixed.

4) *Those characterized by the presence of little dust in the lung but with diffuse interstitial fibrosis*. In this group disability is invariable. Besides severe restriction of lung volume, there is a marked increase of alveolo-arterial O_2 difference. Inequalities in the ventilation-perfusion ratios of the lung may contribute to this difference, as well as to the reduction in the measured diffusing capacity to which the difference is usually ascribed. Other factors contributing to the lowered diffusing capacity include a reduction in diffusion area due to replacement of lung tissue by the pathological process (as in chronic beryllium disease of the lung), whereas changes in membrane permeability consequent to its direct involvement by the pathological process have been shown in some cases of asbestosis.

In contrast, *the pneumoconioses due to organic dusts* do not have specific radiological or pathological features. Diagnosis in byssinosis, the best-documented example in this group, is on the basis of symptoms that are closely paralleled by physiological changes, consistent with airway narrowing.

Thus in general it may be said that the physiological changes in the different pneumoconioses correspond to what might be anticipated on the basis of the known pathology. However, speculation about the pulmonary function in the individual case is so liable to be inaccurate that it cannot justifiably replace direct measurement in every case.

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