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Prevalence and Pathogenesis of Pneumoconiosis in Coal Workers

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Dust dose and composition do not appear to account wholly for changes in the prevalence of coal workers' pneumoconiosis in Europe. In certain coal pits high progression evidently occurred with relatively low dust exposure or vice versa, whereas progression in relation to dust levels might be variable. Exceptionally high quartz concentrations occur in coal mine dust when pneumoconiosis may progress with unusual rapidity. Under such circumstances lesions resembling silicotic nodules may be found, but with the customarily lower levels of quartz the pathological features assume the form characteristic of coal workers. Morphological changes in relation to dust content of human and animal lungs, as well as cellular behavior, have not accounted completely for the epidemiological findings. Considering all the pathological evidence helps explain the pathogenesis of pneumoconiosis and vagaries of progression. The origin of progressive massive fibrosis cannot be explained simply in terms of dust burden or immunological features, and the role of an infective factor cannot be dismissed. Moreover, lipid secretion by alveolar epithelium introduces a new element that could affect the development of simple and complicated pneumoconiosis. *In vitro*, cytotoxicity appeared to be too variable for predictive purposes, though direct assay of fibrogenicity using the macrophage fibrogenic factor suggested that dust dose was more important than dust composition. Assessing individual susceptibility presents serious obstacles.

Prevalence

Dust Levels

The long-term epidemiological and environmental survey of British collieries carried out under the Pneumoconiosis Field Research (PFR) program of British Coal established conclusively the beneficial effect of dust suppression measures in reducing the prevalence of pneumoconiosis (*1*). Over a period of 22 years, the prevalence of all categories of the disease fell from 8.2% to 1.3% of men X-rayed, although older miners had much higher rates than younger men (Fig. 1), and South Wales continued to display higher levels than other coal fields. Similar changes were evident when category 2 or more simple pneumoconiosis and progressive massive fibrosis (PMF) were considered separately. The importance of measures to suppress dust was emphasized by the demonstration that progression of simple disease among face workers was directly related to colliery mean (coal face) mass concentration of respirable dust (*2*). Where the prescribed standard was met, calculations suggested that, at a mean long-term dust concentration of 4.3 mg/m^3, a man with no initial evidence of disease had a 3.4% chance of developing category 2 simple pneumoconiosis after 35 years of exposure. Furthermore, it was estimated that the prevalence then obtaining should at least be halved during the succeeding 35 years, but overall progression appeared to be greater in men with some evidence of disease at the inception of the program.

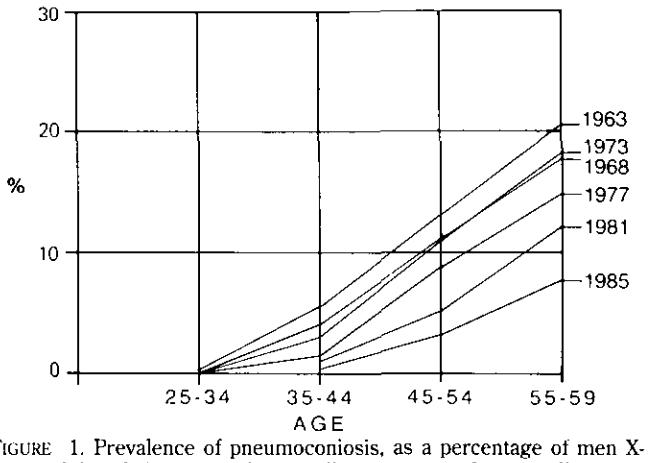

FIGURE 1. Prevalence of pneumoconiosis, as a percentage of men X-rayed, in relation to age for 30 collieries surveyed repeatedly over a period of 22 years. By courtesy of Dr. J. Burns, Director of Medical Service (*1*).

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Subsequent findings from the PFR disclosed that the picture was not uniform across all the coal fields. When dust exposures were calculated for individual members of the populations previously studied, the most significant index of pneumoconiosis hazard remained the overall mass concentration of respirable dust, but at particular collieries substantial variations between observed and expected values of pneumoconiosis progression were found for which the environmental data afforded no explanation (*3*). Further examination revealed 20 collieries in which the progression indices were similar, but the level of radiological change was at variance with the dust level, and in seven pits there was extreme temporal variation in progression indices (*4*). Among eight selected collieries progression was consistent when high progression was set against low dust or low progression set against high dust, but was inconsistent in other pits, where both extremes were observed at different times.

Quartz Concentration

Quartz, a well-known fibrogenic agent, is the component of respirable coal mine dust to which most attention has been devoted. However, a poor correlation was found between radiological evidence and quartz concentration (*2*). Moreover, no generalization could be made about the effect of quartz, as percent progression increased with percent quartz in some collieries and diminished in others to produce an overall negative effect when the quartz concentration did not exceed 7.5%, the limit of the data (*3*). No pattern was discerned between quartz content of mixed dusts and the probability of developing simple pneumoconiosis at quartz levels averaging 5% and rarely exceeding 10%, but some miners showed unusual radiological changes with higher proportions (*5*). A case-control analysis of this exceptional material reaffirmed the absence of an overall effect of quartz and provided support for the unfavorable reaction of some miners to coal mine dust that had a relatively high quartz content (up to the 20% level) (*6*).

In one colliery, 3.37% of miners experienced radiological progression of simple pneumoconiosis despite low exposure to mixed coal mine dust as compared with matched controls without disease (*7*). The quartz content of this dust was significantly higher in cases (13%) than in controls (8%), compared to a level of about 5% in British collieries as a whole. The higher levels of quartz in this mine were due to incursion into rock strata adjacent to the coal seam. The common radiological features were a nodular appearance, and the cases experienced greater exposure to mixed dust. In 10 British coal mines, the probability of developing radiological category 2/1+ simple pneumoconiosis depended on the mean concentration of dust and duration of exposure, but, among exceptions, one colliery with high ash and quartz in the dust had a prevalence one-fifth of that predicted, another with low ash and quartz had almost twice the prevalence expected, and in a third, the risks were eight- to ninefold greater than average (*8,9*). Moreover, a similar inverse relationship to epidemiological findings existed in comparison with cytotoxicity and the pulmonary reaction. The apparent discrepancies were reemphasized by a low progression colliery having the highest quartz percentage and a high progression colliery having the lowest quartz percentage (*4*). Nevertheless, at its customary low level in mixed dust, there was no evidence that quartz affected the probability of developing simple pneumoconiosis (*8*).

Rank of Coal

Rank increases from lignite through bituminous coal to anthracite and reflects increasing content of fixed carbon with diminishing volatile matter and ash. Early work from the South Wales coal field suggested that rank of coal was a determinant of prevalence, high rank anthracite constituting a greater hazard than low rank bituminous (*10*). This effect was, however, explained by the mass concentration of respirable dust (*2*). High exposure to clay minerals (kaolin and mica) apparently antagonized the hazard from increasing quartz exposure, and the existence of a factor or factors varying between collieries but not reflected in the available environmental data was postulated (*3*). A well-marked connection was demonstrated between a radiological category of at least 1/0 and rank of coal mined; there was a fivefold increase of prevalence in miners who worked in high rank collieries compared to those who worked in low rank collieries (*11*). However, large differences in prevalence were also found between separate areas in the coal field of equal rank, suggesting that factors other than rank, such as dust concentration, were involved.

Other Countries

The epidemiological evidence from Germany, where long-term surveys of coal workers have also been carried out, is consonant with that obtained in Britain. The development of pneumoconiosis generally reflected the cumulative effect of dust exposure, but the relationship varied between collieries at which dissimilar factors might operate (*12*). The risk of contracting the simple disease varied between 2 and 40%, although miners had comparable levels of dust exposure (*13*). Differences in the mineral content of respirable dust did not account for the wide range of prevalences, and the hazard was not affected by quartz content. In fact, a low prevalence of pneumoconiosis sometimes occurred in collieries with higher gravimetric concentrations of quartz, and this led to the proposal that fine dusts possess a specific noxiousness. Pulmonary changes occurred more frequently in German miners of anthracite than in men working with gas or long flame coal, in which the proportions of ash and quartz were highest, but the decisive factor

was attributed to higher concentrations of respirable dust, both total and quartz, in high rank mines (*14*). Similar observations were made in studies of French miners. The prevalence of pneumoconiosis in different mines showed wide disparities, as measured by the time it took for 5% or more of the workers to contract the disease (*15*). The quantity of dust inhaled appeared to play the most important role, but only when the nocivity of the dust was equivalent. Hence, investigators in France, as in Germany, entertained the idea that different coal mine dusts exhibited particular levels of noxiousness. American observations indicated a declining prevalence of disease, both simple and complicated, for which dust control measures partly accounted (*16*), but, so far, anomalies of progression such as those encountered in Europe have not apparently been observed in American miners.

Pathogenesis

Since changes in prevalence are incompletely explained by dust dose and composition, the underlying pathological evidence from human, animal and cellular sources deserves scrutiny to determine whether factors currently overlooked need to be included in the debate on prevalence. A search for pathological indicators might be useful to determine what appears to be the multiple etiology of pneumoconiosis.

Human Responses

Dust Content and Composition. The pathological grading of Welsh miners with simple pneumoconiosis tended to be reflected in both the radiological category from 0 to 3 and the lung dust content, but within each category mean dust values obscured extensive ranges that overlapped considerably, not only in respect of total dust, but also of quartz content (*17*). Quartz content averaged 2.8% of total lung dust, with a range of 0.5 to 10.5%, although the highest level did not lead to a specifically silicotic response, and the proportions of coal and quartz exhibited no constancy. Later analyses included material from other coal fields and separated simple from complicated disease by excising the lesions of massive fibrosis (*18*). Although the concentration of dust in PMF was approximately double that in the rest of the lung affected by simple disease, the dust composition remained similar. No significant difference in quartz percentage was found between simple pneumoconiosis and PMF when high and low dust contents were compared. Further disparities between pathological grade, total dust content, and composition were revealed when miners from South Wales were compared with men working in low rank pits in Cumberland (*19*) and Lancashire (*20*).

In the PFR program the quantity of dust extracted was least in macules and greatest in PMF of maximum size, but between other pathological groups clear differences were not observed (*21*). Coal retention appeared greatest for high rank cases. Miners of low rank coal evidently retained most ash, including quartz, but rank differences could not always be explained. When individual types of lung lesions were analyzed, the mean dust levels rose between simple and complicated disease, but the variation factor in dust content for a particular form of lesion was great and even extreme (*22*). Percentage composition between pathological grades from the same rank corresponded (*23*). Smaller particle size may favor alveolar deposition of ash, but hardly accounts for the range of pathological changes or for the lower prevalence of disease in low rank collieries whose respirable dust contains most ash.

Emphysema. A characteristic though not universal component of simple dust lesions is localized emphysema. Precise distinction of such localized emphysema from other morphological forms encountered in the lungs of coal workers, or in the general population, depends on three-dimensional microanatomy (*24*). The focus of this discussion is on features that may affect radiological assessment of the prevalence and progression of simple pneumoconiosis.

Although proximal acinar emphysema attributable to the accumulation of coal mine dust cannot be read as such on radiographs, its existence apparently led to a marked degree of overreading of coniotic changes (*25*). Small rounded opacities of p-type were associated with more circumscribed emphysema than larger opacities (*26,27*), although irregular shadows exhibited a greater degree of emphysema, as well as a larger decrement in forced expiratory volume (FEV_1) or gas transfer, than rounded ones (*27,28*). Radiological category of simple pneumoconiosis was less important than the occurrence of accompanying emphysema in reflecting ventilatory impairment (*29*). Moreover, emphysema of unspecified type, as judged by the naked eye, existed in approximately 60% of cases with small rounded opacities, but about 90% of men were affected when the opacities were small and irregular (*30*). These findings re-emphasized the inability of X-rays to identify consistently the presence of emphysema whether dust related or not, quite apart from its severity.

Morphologically, proximal acinar emphysema may occur in relation to small accumulations of dust, but the disparity puzzled some workers (*21*). A satisfactory explanation had, however, been provided by the observation of an inverse relationship between the persistence of smooth muscle in coal foci around respiratory bronchioles and the presence and degree of related emphysema (*31*). Loss or immobilization of smooth muscle by dust accumulation may be expected to impair or eliminate expiratory shortening and narrowing of respiratory bronchioles and so contribute to the development of the peculiar circumscribed form of emphysema. Individual variation in the amount of smooth muscle naturally present would affect the readiness with which dust emphysema forms. Recent findings support a complex relationship

between radiological features and underlying pathological changes (*32*).

Progressive Massive Fibrosis. The attack rate of progressive massive fibrosis (PMF) in Welsh miners was determined by the average radiological category of simple pneumoconiosis. Control of the development of PMF depended on preventing miners reaching category 2 (*33*). A PFR analysis confirmed the increase of attack rate of PMF with increasing background of simple pneumoconiosis and indicated that the rate was unduly high in South Wales but unduly low in Scotland (*34*). The magnitude of respirable dust exposure was a major contributor to the incidence of PMF, but wide variations in susceptibility were detected, and there was no evidence that quartz exposure was involved. However, half the cases of PMF occurred in men with category 0 or 1, and, hence, prevention of categories 2 and 3 would solve only half the problem (*35*). Furthermore, those men who developed PMF on the basis of category 0 appeared to have had high cumulative exposures to dust, and a preradiological form of pneumoconiosis was therefore considered to exist. This phenomenon accounted at least in part for the difference in PMF attack rate between Scotland and South Wales. The 20-fold range of risk among collieries in the PFR was only partly explicable by high risks at pits with a high proportion of carbon in the coal (*36*). Although the incidence of PMF was in general unrelated to the magnitude of the previous exposure, its incidence in men with no simple pneumoconiosis was directly related, but the quartz content did not warrant special measures of control. A later PFR analysis (*37*) attributed the central factor in the development of PMF to cumulative exposure to respirable dust, which determined the category of simple pneumoconiosis, but irrespective of the latter, older men were at greater risk of attack.

The total dust factor alone fails to explain the genesis of PMF, as some victims of simple pneumoconiosis had as much dust in their lungs as did victims of complicated disease (*38*). The overlap was also apparent in later material, so much so that for a particular dust burden lungs displayed widely divergent pathological features (*21,22*). Morphologically, simple pneumoconiosis exhibits a symmetrical distribution of numerous small, discrete lesions, but PMF occurs asymmetrically, often as a single large lesion, in sites favored by chronic tuberculosis. Severe simple disease is not invariably the seat of one or more massive lesions, but massive lesions may occur in men with a minor degree of dust accumulation.

Irrespective of size, dust composition in PMF was similar to that in the rest of the lung, although the concentration of dust was approximately doubled; in particular the quartz percentage in small or large massive lesions was no higher than in the remainder of the lung and varied between 1 and 10% (*18*). From the lungs of certain coal workers with PMF no quartz could be recovered (*39*). The PFR material corresponded and indicated that some cases had very low concentrations of quartz or none (*22,40*), whereas a few cases exhibiting lesions with silicotic features had high or low levels of quartz (*21*). A parallel situation was observed in hematite workers, in whom the quartz content did not differ between simple and complicated disease (*41*), which apart from color resemble the changes seen in coal workers. Further evidence against the quartz hypothesis came from cases of massive fibrosis, indistinguishable pathologically from the changes in coal workers, who had been exposed to purified carbon and from whose lungs quartz was not isolated or only isolated in traces (*42,43*). Moreover, massive fibrosis was encountered in a man exposed to nepheline, a feldspar devoid of free silica, where the lesions resembled those seen in coal workers in all but color but from which no free silica was recovered (*44*). It thus seems justifiable to conclude that this component of the dust does not play a specific or overriding role in the genesis of massive fibrosis in coal workers.

Caplan's recognition of the eponymous syndrome (*45*) gave impetus to implication of the immune system in the coniotic response. Epidemiological studies established the association between rheumatoid arthritis and a special form of radiological appearance in the lungs of coal workers (*46*), rheumatoid and orthodox pneumoconiosis being distinguished pathologically (*47*). The serum titer of rheumatoid factor (RF) was highest in Caplan's syndrome and some cases of PMF, in which lesions the factor was frequently localized by immunohistology (*48*). Subsequent surveys of coal workers both in Britain and the U.S. detected RF and antinuclear antibodies (ANA) in the sera of a variable proportion, often a minority, of cases with PMF (*49–51*).

Elevation of I_gG and I_gA levels occurred in simple and complicated disease but was subject to unexplained variations, and humoral competence was unaffected (*52,53*). Antibody levels possessed no predictive value in the genesis of massive fibrosis (*54*). A parallel existed in respect to sandblasters' silicosis, in which high levels of ANA, RF and serum immunoglobulins were unrelated to the stage of disease, radiological progression, or decrement of lung function (*55*). Since T- and B-lymphocyte levels were not related to category of pneumoconiosis (*56*), a special reactivity on the part of individual miners to the presence of dust or infection seems unlikely. Moreover, a role for histocompatibility antigens in determining simple or complicated disease may be discounted (*57–59*). The inescapable conclusion is that a primary pathogenetic role cannot be attributed to the immunological factor, since the phenomena are inconstant, often affecting a minority of men, and depend on preexisting lesions with a fibrotic component. The occurrence of I_gG and I_gA in massive lesions along with fibrinogen and fibronectin (*60,61*) suggests exudation. The development of ANA may well reflect the rate of macrophage demise, to which infection (*vide infra*) could exert an additive response.

How then may the attack rate of PMF be explained? Dust alone by mass or composition is insufficient in view of the distinct pathological features of simple and complicated disease, and collapse of lung tissue has been invoked. Apart from lack of a causal lesion, calculation suggested that the volume of normal lung which a massive lesion might have occupied would require the whole lung section to be larger than in fact it was (*18*). If collapse is excluded, consolidation by a chronic inflammatory or reactive process is the alternative, and the question of its causation arises. Prevailing fashion decries tuberculosis as an etiological element, partly because disparities transpired between exogenous or endogenous tuberculous infection and the attack rates of PMF (*33*), but largely because recovery of bacilli using a laryngeal swab during life was possible in only 1.1% of cases of massive fibrosis (*62*).

From characteristically closed lesions discharge of organisms would not, however, be expected. In hospitalized cases tubercle bacilli were identified by biological and cultural means in the sputum of 7.7% (*63*); cultures from the bronchus prior to necropsy dissection yielded positive results in 28% of cases with massive lesions (*64*). The strongest evidence in favor of a tuberculous etiology derives from James' detailed analysis of massive lesions from 245 Welsh coal workers (*65*). Relying on bacteriological (culture and guinea pig inoculation) and histological findings, 40% were found to be positive; broken down by age, 88% of lesions from men younger than 40 proved positive, but 29% of men of 60 or older were positive. The pattern was confirmed when tubercle bacilli were recovered from 35% of 118 such lesions with pathological evidence in 28% (*64*). The PFR program afforded no bacteriological results, as all the lung specimens were fixed on receipt. James' findings suggested that tuberculosis was involved in the initiation of massive fibrosis and that with advancing age the infection tended to die out. Epidemiological observations afforded a parallel in that the rate of progression of PMF diminished with increasing age (*66*). Tuberculin sensitivity among inhabitants of the Ruhr, both miners and nonminers, was held to indicate a high morbidity rate for tuberculosis among miners (*67,68*). Apart from evidence of tuberculosis, the histological appearances of massive lesions are similar in younger and older men. The occurrence of deeply situated tuberculous foci argues against infection after establishment of the lesions, whether airborne or hematogenous, since they are poorly vascularized even to the point of ischemic necrosis, and an internal source has not been identified for such a mechanism. The morphology of PMF bears some resemblance to fibroid phthisis, a lesion no longer seen in the general population of developed countries. The decline in incidence of respiratory tuberculosis over recent decades in England and Wales (*69*) and other countries is no doubt shared by coal workers and may well contribute to the decreasing prevalence of PMF. The evidence pointing to an infective factor in the genesis of PMF is too strong to be discounted, and no organism other than *Mycobacterium tuberculosis* has been incriminated in man, although IV infection with *M. kansasii* of guinea pigs previously exposed to inhalation of pure coal led to massive lesions with increased collagen content whereas alone coal had little effect and infection regressed (*70*). Interpretations of the genesis of massive fibrosis that neglect the infective element while emphasizing dust or other factors fail to give a balanced perspective. To distinguish cases of PMF postmortem as a large lesion without or with neighboring fibrotic nodules or as a group of fused small nodules (*71*), thereby implying a separate origin, becomes unnecessary once a tuberculous component is admitted.

Experimental observations conform with the idea that coal dust, in contrast to silica, may restrict the extent and progression of tuberculous infection. Quartz and Bacille Calmette-Guerin stimulated functional activity of the mononuclear phagocytic system (*72*), but coal dust, having a lower toxicity than quartz, is less likely to overtax the macrophage response and hence permit more effective cellular resistance to tuberculosis and impair its progression. Guinea pigs infected by tubercle bacilli of low virulence combined with the administration of coal (*73,74*) or hematite dust (*75*) led to more extensive fibrosis than bacilli or dust alone. As fibrosis became more severe, the infection died out (*73*), supporting the interpretation that tuberculosis is involved in the origin of PMF and not just a late phenomenon. Lesions resembling massive fibrosis followed treatment of guinea pigs with anthracite mine dust or kaolin combined with other mycobacteria, though separately each component was much less harmful (*76*).

A recent proposition envisages PMF as a secondary development to severe dust-induced changed in hilar lymph nodes as a consequence of ulceration through the walls of adjacent main bronchi or pulmonary arteries with peripheral dissemination of activated dust-laden cells (*77*). Erosions of the kind described are well recognized and may lead to massive pulmonary thrombosis, but it is surprising that many of their cases with the most severely affected nodes (i. e., breaching the bronchus or artery) escaped development of PMF. To attribute the inception of PMF many years earlier to a lesion revealed terminally seems unjustified, and the hypothesis does not account for the occurrence of PMF in the presence of minimal (category 0) simple pneumoconiosis. The application of the term "activated" to dust-laden phagocytes hardly accords with its proper connotation as immunologically specific enhanced antimicrobial behavior or antitumor cytotoxicity of macrophages (*78*). Moreover, the evidence favoring an infective factor in the genesis of PMF cannot be so summarily dismissed. The conventional view that this lesion is primarily of pulmonary origin is more firmly based.

Animal Responses

Fibrosis. The focus of attention remains the means by which the fibrogenic activity of quartz is affected by other constituents of coal mine dust. For this purpose, airborne samples, fractions, and artificial mixtures with quartz, all in the respirable-size range, have been administered by injection or inhalation. Given intratracheally to rats, coal itself induced little fibrosis and admixed silicates revealed no uniformity of response. Stone dusts produced widely different reactions, some strongly and others weakly fibrogenic, as were isolated fractions (*79*). Variation in the degree of fibrosis occurred in similarly treated rats with high proportions of quartz in the lung dust (*80*). Inhaled mixtures of anthracite and quartz in proportions ranging from 5 to 40% led to distinct fibrosis, assessed histologically and biochemically, only when the quartz level reached 20%, and became severe at 40% (*81*). Exposure of rats to coal mine dusts from the same seam, but possessing wide natural variations of quartz content (7–25%), led to more profuse nodular changes after medium and high than low quartz contents; all lesions remained highly cellular, but the fibrotic component was relatively minor in degree, and mean collagen levels differed little between groups (*82*). In similarly treated individual animals the dust burden and pathological changes differed considerably, and a fibrogenic role for small amounts of quartz, customary in coal mine dusts, was not apparent.

Clay minerals, natural to coal mine dusts, inhibited the pulmonary response to quartz (*83*), the moderating action being thought to depend on coating of quartz particles by dissolution of other unidentified mineral matter present in coal mine dust and whose protective effect may vary according to source and be temporary (*84,85*). Aluminum, an element of clay, or its soluble compounds were able to modify the action of silica prophylactically or therapeutically either by surface coating, or, more likely, by substitution of aluminum for silicon ions in the silica lattice, an effect which was apparent experimentally with coal-quartz mixtures but not with pure coal (*86–89*).

Release of aluminum from clays may vary and account for the greater protective effect of illite as opposed to kaolin (*84*). Auger spectroscopy and thermoluminescence of dust from the Ruhr and Saar mines (*90,91*) led to the idea that the biological behavior of dusts depended on the extent to which the surfaces of quartz particles were covered by inorganic material, although the exposure may be submicroscopic and thereby account for disparities between physical and biological findings. The role of quartz nevertheless remained problematic, as the responses of lungs and regional lymph nodes to these injected dusts did not correlate with the mass of dust recovered (*92*). However, the clay minerals muscovite, illite, and kaolin themselves induced appreciable collagen formation (*84*), which may thus counteract any inhibitory effect they exert on quartz. Quartz dilution by other constituents of coal mine dust was disputed on the ground that fibrosis was not suppressed by mixture with inert titanium dioxide (*84*). Intimate and even dispersal is, however, unlikely, as electron microscopically the small particles of TiO_2 occurred in large masses, which sonication was insufficient to disaggregate (unpublished observation). Simple dilution remains a plausible explanation.

Selective concentration of quartz in the regional lymph nodes (*93*) was adapted for quantitative analysis by the mediastinal lymph node test after IP injection (*94*). Histological evaluation correlated weakly if at all with mineral composition, but discriminant analysis based on "quartz typical areas" (*83*) suggested that toxicity to tissues rose with increasing quartz and mineral contents of the coal mine dusts. However, the fibrogenic and cytotoxic potentials of quartz are themselves subject to variation according to source (*84,85,95,96*). The excess of observed over predicted prevalence in the PFR was inversely connected not only to quartz and ash composition but also to cytotoxicity and experimental lung changes. Although the mean extent of mediastinal lymph node reaction suggested some degree of correlation with prevalence, pronounced variations of response characterized individual animals from particular groups (*9*).

Disparity between pneumoconiosis hazard and composition of airborne dust led to the suggestion that, compared to alveolar deposition, sampling might overestimate the ash, including quartz, content for finer dusts and underestimate ash content in coarser dusts (*97*). The coarser fractions of coal mine dusts contained more quartz, ash proportion decreased, and the larger particles were intergrown with coal and other minerals. Size fractions possessing a maximum frequency of 3 to 5 μm in geometric equivalent (i.e., microscopic) diameters were thought to be closest to alveolar deposition (*98*). The coarser fractions of injected coal mine dusts tended to be especially retained in the lung, though for all fractions coal enrichment and mineral depletion were observed, along with preferential migration of smaller particles, notably the mineral and quartz components, to the hilar nodes; clay minerals nevertheless inhibited penetration of quartz (*99*). Fibroblastic activity provoked in lymph nodes, expressed in proportion to the quantity of dust, was maximal for the geometric equivalent range of 6 to 8 μm (*100*). The emphasis on quartz content in the usual low range is not evident in British material, and the lung itself constitutes the ultimate size selector. Particles recovered from humans and from animals after inhalation exposure possessed mean median equivalent spherical diameters of 2.5 μm (*21,101*), whereas in a German coal miner particles lay predominantly in the 2-μm zone (*13*). These results conform with earlier evidence based on physiological measurements and, although the use of radioaerosols and body counting in three normal individuals breathing through the mouth suggested that maximum alveolar deposition occurred with particles of 3 to

4 μm aerodynamic diameter, deposition was confined to the alveolar region up to a size of 2.4 μm (*102*).

Lipidosis. Interpretations of pathogenesis customarily refer to phagocytosis and especially fibrosis, that is, to macrophage and fibroblast behavior, but alveolar epithelium also reacts, secretory type II cells being stimulated from an early stage. Attention was drawn to this component following certain exposures to inhaled quartz, as a consequence of which a state indistinguishable from human alveolar lipo-proteinosis developed (*103,104*), a resemblance that extended to ultrastructural aspects (*105*). Biochemically, the outstanding feature was massive intra-alveolar accumulation of material predominantly composed of lipid and in particular phospholipid, the kinetics of which emphasized greatly augmented type II cell secretion (*106*). Failure of particles to engage with macrophages or isolation of these cells from contact with fibroblasts of the interstitium may be expected to inhibit generation of the macrophage fibrogenic factor (*107,108*). Inhalation by rats of airborne dusts collected from coal mines of various ranks did not implicate unequivocally the rank factor in elimination (*109,110*). Histologically, however, lipid accumulation in alveoli, whereby particles were dispersed in a free state or within distended phagocytes, varied not only with rank but also between animals of the same group, and a consistent pattern failed to emerge. Later accounts also indicated a lipid response to different quartz dusts (*85*), to inhaled coal-quartz mixtures in which mica and illite but not kaolin may be important (*84*), or to natural coal mine dusts with widely differing contents of quartz (*82*).

In humans, lipidosis followed intense exposure to silica-rich dusts (*111*), emphasizing a correspondence with the experimental disease. Minor degrees of this reaction in coal workers may not readily be apparent, but the cellular behavior toward particles could still be affected and, as in rats, represents an individual response. The extent of lipid accumulation in terms of coal dust amount and composition is thus rendered uncertain, so that aggregation and disposal of dust, as well as fibrogenesis, may be unpredictable. The lipid element in the response to airborne particles has escaped recognition as a potential contributor to anomalies of prevalence.

Cellular Responses

Cytotoxicity. The toxicity of respirable coal mine dusts to peritoneal macrophages, judged by the triphenyltetrazolium chloride (TTC) method, could not be correlated simply with the quartz or mineral content, and an unknown factor associated with age or rank of seams was postulated (*13*); the same conclusion was reached in regard to alveolar macrophages (*112*). Mine dusts exhibited no progression of cytotoxicity with quartz levels up to 8% (*113*). It was not therefore feasible to assess pneumoconiosis risk solely in terms of the TTC test.

French experience indicated that *in vitro* procedures failed to coincide with the results of *in vivo* examination and, moreover, the risk of contracting pneumoconiosis did not correspond with an *in vitro-in vivo* synthesis (*15*). Comparison of different techniques employed in four European laboratories to gauge toxicity failed to establish a correlation between dust composition, *in vitro* results, and epidemiology, while *in vivo* procedures fared only a little better, the lymph node reaction seeming to carry promise (*114*). The problem of predicting risk from *in vitro* methods is compounded by the remarkably higher resistance to the toxic effects of coal mine dust and quartz exhibited by human macrophages as compared with those of rodents (*115*).

In an attempt to standardize the target cell, macrophagelike cells derived from a permanent tumor-cell line ($P388D_1$) were employed against respirable dusts from several British collieries, the composition varying markedly between them and also between different samples from the same seam (*116*). For high rank dusts, kaolin and mica contents related better to toxicity than quartz; for low rank dusts these mineral components were not so related. Pneumoconiosis risk and cell tests correlated poorly and, with widely varying toxicity in the presence of similar amounts of quartz, its role remained enigmatic. Relying on the same tumor-cell line, tested against dusts from many European mines, the best index of cytotoxicity appeared to be viability, but the role of quartz was insignificant (*9*). The $P388D_1$ line, however, became unpredictable and has been replaced by freshly harvested alveolar macrophages (G. M. Brown and K. Donaldson, personal communication).

Fibrogenicity. The behavior of macrophages, whether peritoneal or pulmonary, represents only the initial stage of a two-phase process implicated in fibrogenesis by silica. Following treatment *in vitro* with quartz, macrophages released a factor that promoted collagen formation by fibroblasts (*107,108*). The macrophage fibrogenic factor (MMF) was subsequently shown by Kulonen and his colleagues working in Turku to be a low molecular-weight protein which was formed *in vitro* and *in vivo;* since these investigations were summarized (*117*), the Turku investigators have elucidated the amino-acid composition of the factor. Quantitative application of this technique to the question of mine dust fibrogenicity offered a fresh approach by substituting direct assay of collagen formation for indirect reference to deleterious effects on macrophages alone (*118*). After establishing the appropriate conditions, artificial mixtures of coal with different proportions of quartz along with natural mine dusts of respirable size from European producers were employed in the system. Dust composition appeared less important than concentration. The quartz and ash contents bore no apparent relation to fibrogenicity, nor did major noncoal constituents kaolin and mica. Correlations *in vitro* may be improved by adjusting the doses of dust, macrophages,

and fibroblasts, but *in vivo* other factors are evidently concerned, and, of these, the behavior of type II alveolar epithelium, with which inhaled particles rapidly come into contact, has received too little attention.

Comment

Dust concentration and duration of exposure remain major determinants of disease prevalence in coal workers, but within the overall pattern exist anomalies that require explanation. Emphasis on the role of quartz is evident at all levels of inquiry, but without emergence of a consensus. Across the spectrum of rank, as exemplified by the South Wales coal field, the focal aggregates of mine dust, typifying simple pneumoconiosis, excite a comparatively minor degree of fibrosis disposed as a network, which assists retention of particles. Silica-poor dusts evidently lead to a nonspecific though characteristic reaction, but silica-rich dusts stimulate the formation of nodules in which connective tissue predominates and has a distinctively whorled or concentric arrangement. The proportion of quartz in respirable coal mine dust varies considerably among British and German collieries and when greater than 10%, perhaps closer to 20%, the pathological features might be expected to conform more to those of silicosis than coal workers' pneumoconiosis, the simple lesion of which occurs when the quartz percentage is low or undetectable. Difficulties of interpretation arise in mines whose dusts contain intermediate proportions of quartz and then clay minerals may interact, possibly by inhibition of reactive groups on the surfaces of quartz particles or on the contrary by contributing to fibrogenesis themselves. Substitution of aluminum for siliconions in the quartz configuration could modify its effect permanently, though surface covering of atomic thickness by associated minerals or their derivatives might be removed *in vivo*. Dilution of the quartz action by the other particles of airborne dust as readily and more simply explains impairment of cellular reaction with quartz and hence generation of the MFF, although diluent particles may contribute to the simulation of collagen synthesis (*118*).

The preferential migration of quartz from lungs to hilar nodes, a phenomenon recognized in both humans and animals, raises a further complication. A twin effect of mine dusts has been postulated (*119*), whereby factor A, which determined particle penetration to the nodes, was unrelated to quartz and not inhibited by polyvinylpyridine-*N*-oxide (PNO), while factor B represented the specific fibrogenic activity, which was dependent on quartz content and responded to PNO. If penetration of quartz to the nodes is affected by other constituents of coal mine dust whose proportions may vary independently, removal of quartz from the lungs may be unpredictable and account for minor changes in the relative proportions of dust to fibrous tissue that may be seen in focal lesions of men working in different coal fields and even between individuals. The extreme ranges of the "quartz typical areas" observed in mediastinal lymph nodes from rats treated IP with diverse European mine dusts and the lack of a clear correlation with lower quartz contents (*9*) raise doubts about this method of assay for fibrogenicity. Moreover, the formation of these numerous discrete groups of epithelioid cells seems to contradict the alleged dispersion of quartz particles in lymph nodes (*92*).

Dust deposition patterns, possibly affected by particle shape, as well as size and density, need to be examined in relation to anatomical segments of the airway. Individual components of inhaled mine dust may settle preferentially on proximal or distal subdivisions of alveolated air passages and so affect aggregation and even retention or elimination. Furthermore, deposition patterns may not be the same once coniotic lesions have been established. The lower quartz contents of the finest fractions of coal mine dust and vice versa (*120*) illustrate the desirability of anatomical study of deposition in relation to particle size and nature.

The occurrence of a lipid component in the pulmonary response to inhaled or injected particles has gradually been acknowledged, but its significance is still neglected. Lipo-proteinosis was observed in rats exposed to dusts of different composition without allowing for its impact on fibrogenesis (*82,84*), which lipid had been shown to inhibit (*103,104*). The inconsistency between *in vitro* and *in vivo* tests of dust noxiousness was connected with the lipid element (*121*), although its attribution to macrophage breakdown probably implies prior ingestion of secretion from type II cells. Their activity may be regarded as a protective response to irritation by particulate matter, animate or inanimate, though whether type II cells react directly or via an intermediary product derived from macrophages is unknown. The relationship between lipidosis and fibrosis remains complex (*122*), but it is not necessary to assume an inverse quantitative correlation of the two processes, as separation of macrophages from particles and their relative isolation in phagosomes may be achieved as effectively by small as by large amounts of lipid. Moreover, the degree of lipid stimulation may depend on the nature and proportion of noncoal components and be reflected in colliery-associated disparities of prevalence. To these interrelationships the role of lipid in systemic recruitment of macrophages (*123*) adds a further facet to problems that may ultimately bear on prevalence.

The lipid factor carries another implication. Radiologically simple pneumoconiosis presents as rounded opacities sometimes combined with irregular ones, the underlying pathological changes consisting of typical coal macules around respiratory bronchioles (*24*) and dust-impregnated interstitial fibrosis (*28*). Although smoking was a suspected cause, the interstitial change has so far defied explanation. If, however, at some periods of a lifetime exposure the inhaled dust was of such a nature as to provoke greater than usual type II

cell secretion, lipid accumulation could readily impair aggregation of particles, whether free or within macrophages, leaving the dust more diffusely distributed to be incorporated into alveolar walls by overgrowth of epithelium. At other times aggregation may be envisaged as proceeding normally and leading to focal lesions. The responses of rats to inhaled coal mine dusts (*110*) give credence to this view, allowing for both focal and diffuse changes, and patchy interstitial fibrosis sometimes followed the lipidosis induced by quartz (*104*). Subsequent degradation of lipid (*106*) might mean that the causative factor in pigmented interstitial fibrosis could no longer be traced at necropsy. In the same way, lipid may contribute to nonoccupational interstitial fibrosis, which sometimes progresses to honeycomb lung and from which coal workers are not exempt (*24*).

In the face of so many obstacles, recourse may be taken to individual susceptibility to account for resistance or vulnerability to inhaled coal dusts. Neither immunological reactivity nor complement of histocompatibility antigens provided a basis for risk assessment in respect of simple or complicated pneumoconiosis. In principle, age and body build might bear on the prevalence of PMF (*124*), although by what means remains obscure; predictions were too prone to error to be of value. Furthermore, difficulties are inherent in gauging susceptibility by case-control or longitudinal studies of working populations exposed to inhaled particles (*125*). Similar considerations apply to animal experiments, whose human application may also be fraught with reservations. The individual factors held to predispose to silicosis (*126*), and which apply equally to disease in coal workers, seem to be related more to environmental influences than to purely personal characteristics.

To resolve the outstanding problems surrounding the prevalence of coal workers' pneumoconiosis demands integration of all the pathological facets; neglect of even one factor obscures the issue. A silicotic type of pulmonary reaction may be expected when the long-term concentration of quartz in the airborne dust is exceptionally high. A specific role for quartz inhaled at the customarily low levels by coal workers is difficult to sustain and sometimes can be excluded. Though counter to much conventional opinion, it would be wise not to underestimate tuberculous infection as an initiator of complicated disease. For simple pneumoconiosis, the lipid component, with its implication for fibrogenesis and the development of PMF, could well be a major contributor to anomalies of prevalence and, lacking evidence of a quantitative correlation, might prove imponderable.

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