

## SERUM IMMUNOGLOBULIN LEVELS IN COAL WORKERS' PNEUMOCONIOSIS

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**Abstract**—Sera from 155 U.S. coal miners whose chest radiographs represented varied types of simple, rheumatoid (Caplan's syndrome) or complicated coal workers' pneumoconioses (CWP) were examined for levels of immunoglobulins IgA, IgM, IgG, IgD and proteins C3 and  $\alpha$ -1 antitrypsin as measured by radial immunodiffusion. Concentrations of C3,  $\alpha$ -1 antitrypsin, IgA and IgG were significantly higher ( $P < 0.05$ ) in sera from anthracite than in sera from bituminous miners with complicated pneumoconiosis (progressive massive fibrosis). Few differences in serum immunoglobulin and protein concentrations were noted among other subtypes of CWP. When subtypes were combined within each pneumoconiosis category and compared to normal (control) values, serum levels of C3,  $\alpha$ -1 antitrypsin, IgA and IgG were significantly higher than control values for Caplan's syndrome, for simple (with the exception of  $\alpha$ -1 antitrypsin) and for complicated pneumoconioses. The percentage of miners with elevated serum protein levels was not significantly different between bronchitic and non-bronchitic miners for all categories of pneumoconiosis. The selective stimulation of components of the immunoglobulin system by coal dust and by other occupationally-related agents is discussed.

### INTRODUCTION

THE VARIETY of immunologic responses noted in association with certain types of occupational mineral pneumoconiosis and pulmonary diseases suggests that immunologic mechanisms may be involved in some aspects of pathogenesis. Rheumatoid and antinuclear factors have been detected in sera of both human and experimental silicosis, asbestosis, coal workers' pneumoconiosis (CWP), and unexplained pulmonary fibrosis (CAPLAN, 1953; TOMASI *et al.*, 1962; SCHROEDER *et al.*, 1962; ESBER and BURRELL, 1967; NAGAYA *et al.*, 1969; TURNER-WARWICK and PARKES, 1970; LIPPMANN *et al.*, 1973; SOUTAR *et al.*, 1974). A correlation has been established between such soluble mediators as migration-inhibitory factor (HENDERSON *et al.*, 1972), lymphocytotoxin (MARX and BURRELL, 1973), blastogenic factor (HANIFIN *et al.*, 1970; DEODHAR *et al.*, 1973) and skin sensitivity in sensitized animals or in patients with berylliosis. That certain pneumoconioses may be auto-immune disorders has been suggested by the appearance of antinuclear antibodies in relation to the extent of fibrosis in subjects with silicosis and asbestosis (KANG *et al.*, 1973). In the case of CWP and silicosis, the demonstration of lung antibodies, serum and secretory IgA elevations, the detection of globulin in pulmonary nodules and depressed cell function but enhanced T cell responsiveness are additional evidence redolent of immunologic involvement (VIGLIANI and PERNIS, 1963; ESBER and BURRELL, 1967; MILLER and ZARKOWER, 1974; BURRELL, 1977).

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In workers whose occupations resulted in their exposure to particulates of either asbestos (EL-SEWEFY *et al.*, 1971a; KAGAN *et al.*, 1977), beryllium (RESNICK *et al.*, 1970), cement (EL-SEWEFY *et al.*, 1971b), coal (LEWIS *et al.*, 1971; VIDAL *et al.*, 1971) or silica (HAGADORN and BURRELL, 1968) abnormal variations in serum proteins and immunoglobulins have been reported which may be indicative of a disorder in immunologic profiles. Hyperglobulinemia and hyperproteinemia with significant elevations of either one or more of the serum immunoglobulin fractions, IgA, IgM, IgG, were common findings. The availability of sera from 155 U.S. coal miners, who had participated in an earlier serological survey (LIPPMANN *et al.*, 1973) and whose chest radiographs represented varied types of coal workers' pneumoconiosis (CWP), prompted us to re-examine globulin fraction concentrations of these sera.

This report describes an attempt to determine whether there is an association among the relative concentrations of serum immunoglobulins (IgA, IgM, IgG, IgD) and selected serum proteins with the type of simple, rheumatoid, or complicated coal workers' pneumoconiosis.

## METHODS

### *Subjects*

The 155 subjects selected for this study were part of an Inter-agency Study that involved over 9000 working miners. Data made available from limited medical examination consisted of postero-anterior and lateral chest films, spirometry, and the administration of a questionnaire on bronchitis and respiratory symptoms. The subjects selected fulfilled the following requisites: (a) had previous radiographic diagnosis of coal workers' pneumoconiosis (CWP) and (b) resided within 1 day's drive of the Appalachian Laboratory for Occupational Safety and Health, Morgantown, W. Va. This latter criterion meant that the subjects were drawn from West Virginia and Pennsylvania. They consisted of active or former bituminous coal miners. Active or former anthracite miners from eastern Pennsylvania were also included in the selected population.

The control population of 71, consisted of 21 West Virginia underground miners, who had no radiographic evidence of CWP, and 50 West Virginia male adults who were non-miners.

### *Categorization of radiographs*

The chest films of the 155 miners with previously diagnosed coal workers' pneumoconiosis were examined by three readers. They were independently reinterpreted by one observer (W.K.C.M.), who had no knowledge of previous readings or of the subjects' geographical origin. Those films whose features suggested the presence of rheumatoid pneumoconiosis (Caplan's syndrome) were subdivided into (a) those with evidence of classical features of Caplan's syndrome, (b) those whose features were compatible but not classical, and (c) those whose features were unusual for simple coal workers' pneumoconiosis and who had, in addition, one or two features suggesting Caplan's syndrome (CAPLAN, 1953). The criteria used were as follows:

- (1) The presence of at least four rounded opacities between 0.5 and 5 cm in diameter.

- (2) A peripheral location of opacities.
- (3) A background of either category 0 or 1 simple pneumoconiosis.
- (4) The absence of typical progressive massive fibrosis.
- (5) The rapid appearance of opacities.
- (6) The presence of cavitation in the rounded opacity.

Films of subtype (a) met at least the first four criteria; those in subtype (b) had at least the first criterion in association with one other; those in subtype (c) did not meet any of the first three criteria completely (for example, having only two opacities that were centrally situated and that could be infectious granulomata). From these criteria the films of 35 miners were classified in the rheumatoid pneumoconiosis category: of these only 1 had the classical features of subtype (a), 4 were diagnosed subtype (b) and the remaining 29 were in subtype (c) (possible Caplan's syndrome).

The other 121 subjects, who had no features suggesting Caplan's syndrome, were categorized according to the UICC/Cincinnati classification (UICC, 1970). Miners with simple pneumoconiosis were further subdivided by the size of opacities that predominated in the chest radiograph. The smallest opacities (*p*) are those up to 1.5 mm in diameter; (*q*) opacities range from 1.5 to 3 mm, and (*r*) opacities range from 3 mm to 1 cm.

Table 1 shows the age and occupational characteristics of our subjects. The median age and median time spent underground were almost identical between categories, except for the underground miners with a clear chest film who were

TABLE 1. AGE AND OCCUPATIONAL CHARACTERISTICS OF SELECTED COAL MINERS IN PENNSYLVANIA AND WEST VIRGINIA, 1971-1972

Group	Coal type*	Miners	Median age	Median time underground
		<i>no.</i>		<i>years</i>
Caplan's syndrome				
classical	A	1	56	37
compatible	AB	4	56	34
possible	AB	29	54	33
Progressive massive fibrosis				
anthracite	A	23	56	34
bituminous	B	17	53	33
Simple pneumoconiosis opacities†				
<i>p</i>	AB	38	54	31
<i>q</i>	AB	31	55	28
<i>r</i>	AB	12	54	31
subtotal		155	54	32
Control				
normal underground miners	B	21	48	22
non-miners	NA‡	50	40	NA
total		226		

\* Type of coal mined: A = anthracite only; B = bituminous only; AB = either anthracite or bituminous but not both types of coal.

† *p* = up to 1.5 mm; *q* = 1.5-3 mm; *r* = 3 mm-1 cm.

‡ Not applicable.

younger and had spent less time below the surface. Non-mining subjects were also younger. However, for purpose of comparing serum immunoglobulin levels to standard age related values (MADDISON *et al.*, 1975), they were within the same age range as that of miners.

#### *Serum protein determinations*

Serum specimens were collected either at the mine portal or at the man's home. Each serum was divided into 0.5 ml quantities and stored at  $-20^{\circ}\text{C}$ . The remainder of a serum specimen when thawed for testing was not refrozen and used in subsequent tests. Control sera were handled and stored in a similar fashion. Radial immunodiffusion plates (Helena Laboratories, Beaumont, Texas) were used to quantitate concentrations of the following serum proteins:  $\alpha$ -1 antitrypsin, complement component (C3), and IgA, IgM, IgG and IgD immunoglobulins. Human serum protein standards and control serum samples were assayed concurrently with test serum samples. Concentrations of serum proteins were expressed as mg/dl. Because protein concentrations in serum samples from control normal underground miners and non-miners were in close agreement, these values were combined and served as the control group. Serum protein and immunoglobulin values of the control group were within the ranges designated by the manufacturer and World Health Organization standards (MADDISON *et al.*, 1975).

#### *Statistical analysis*

Each protein type was tested separately and differences in serum protein concentrations were analysed among individual subtypes comprising a radiograph type, among the three radiograph types, and the control group. Multi- and two-way type comparisons were made using the Kruskal-Wallis and Mann-Whitney procedures, respectively (CONOVER, 1971). Probability of a Type I error was set at 0.05.

### RESULTS

Neither sera from miners with the different types of small opacity seen in simple pneumoconiosis (*p*, *q*, *r*) nor from miners with Caplan's syndrome (classical (a), compatible (b), possible (c)) showed significantly different mean levels of immunoglobulins (IgA, IgM, IgG, IgD) or other serum proteins ( $\alpha$ -1 antitrypsin, C3) among the subtypes within each disease category. However, significant differences ( $P < 0.05$ ) were noted in mean serum immunoglobulin and protein concentrations between anthracite and bituminous miners in the category of progressive massive fibrosis (Table 2). Serum concentrations of IgA, IgG,  $\alpha$ -1 antitrypsin, and C3 were higher in anthracite miners as compared to those of bituminous miners.

Serum globulin fractions and protein values of the subtypes were combined within each of the three pneumoconioses and each category was then compared to control values and to each other (Table 3). Results show that sera from miners with simple pneumoconiosis had significantly higher mean concentrations of IgA, IgG, and C3 than the controls. Whereas IgM and  $\alpha$ -1 antitrypsin levels were not significantly higher, IgD levels, however, were lower than controls. Sera from the simple pneumoconiosis category had C3 levels that were higher than those noted in the progressive massive fibrosis category. Statistically, it was indeterminable whether the levels of

TABLE 2. SERUM IMMUNOGLOBULIN AND PROTEIN CONCENTRATIONS IN ANTHRACITE AND BITUMINOUS COAL MINERS WITH PROGRESSIVE MASSIVE FIBROSIS (PMF)

Category	Serum proteins (Mean value $\pm$ SD, mg/dl)					
	IgA	IgM	IgG	IgD	antitrypsin	C3
Anthracite	311 $\pm$ 147*	179 $\pm$ 98	1390 $\pm$ 384*	10 $\pm$ 7	362 $\pm$ 102*	134 $\pm$ 35*
No. tested	23	23	23	16	23	23
Bituminous	211 $\pm$ 98	155 $\pm$ 62	1159 $\pm$ 238	10 $\pm$ 7	256 $\pm$ 91	101 $\pm$ 26
No. tested	17	17	17	12	17	17

\* Significantly higher than bituminous mean values at  $P < 0.05$ .

C3 noted for Caplan's syndrome were similar to those values for simple or complicated pneumoconiosis. Both sera from miners with Caplan's syndrome and progressive massive fibrosis had higher mean concentrations of proteins than control sera with the exception of IgM and IgD. Mean serum levels of IgM were not significantly higher than control serum levels; however, levels of IgD were significantly lower than controls.

The higher elevations in serum protein levels described for the different categories of CWP may have been influenced by the occurrence of bronchitis or other respiratory function impairment in miners. In Table 4, alongside each category of CWP, the number of bronchitics and nonbronchitics are listed with % of those showing elevations of serum protein levels and decreased ratios of forced expiratory volume in 1 s divided by forced vital capacity ( $FEV_1/FVC$ ). The data show that in all categories of pneumoconiosis the percentage of miners with elevated serum protein levels was not significantly different between bronchitic and nonbronchitic miners. In both these latter conditions, however, the percentage of miners with elevated serum protein levels was significantly higher in anthracite than in bituminous miners with progressive massive fibrosis. The percentage of miners with decreased  $FEV_1/FVC$  ratios did not differ significantly between bronchitic and nonbronchitic miners but appeared to vary with the severity of pneumoconiosis. There was no clear association between elevated serum protein levels and decreased  $FEV_1/FVC$  ratios with respect to the different CWP categories with the possible exception of progressive massive fibrosis (anthracite) for which both were maximal. However, this variance may be related to the extent of disease present.

#### DISCUSSION

Most differences in serum immunoglobulins and protein concentrations described in this study were between the types of CWP (simple, complicated, Caplan's syndrome) and normal (control) values. There were few significant differences in serum globulin levels noted among subtypes of CWP. There was a semblance of similarity between some of our findings and results from an earlier study (LIPPMANN *et al.*, 1973) in which these same sera were tested for the prevalence of antinuclear antibodies (ANA). When ANA were found in miners with CWP, these antibodies were associated predominantly with IgG and were also unrelated to any particular subtype ( $p$ ,  $q$ ,  $r$ ) of simple pneumoconiosis. The prevalence of ANA was also significantly higher in anthracite (55%) than in bituminous miners (21%) with progressive massive fibrosis.

TABLE 3. SERUM IMMUNOGLOBULIN AND PROTEIN CONCENTRATIONS IN COMBINED CATEGORIES OF COAL WORKERS' PNEUMOCONIOSIS

Category	Serum Proteins (Mean $\pm$ SD, mg/dl)					
	IgA	IgM	IgG	IgD	$\alpha$ -1 antitrypsin	C3
Simple ( <i>p, q, r</i> )	275 $\pm$ 128*	189 $\pm$ 114	1376 $\pm$ 293*	13 $\pm$ 15*	281 $\pm$ 106	142 $\pm$ 34*†
No. tested	81	81	81	52	81	81
Caplan's syndrome (classical, compatible, possible)	227 $\pm$ 110*	174 $\pm$ 103	1327 $\pm$ 285*	7 $\pm$ 6*	311 $\pm$ 85*	128 $\pm$ 35*
No. tested	34	34	34	19	34	34
Progressive massive fibrosis (anthracite, bituminous)	268 $\pm$ 136*	169 $\pm$ 84	1292 $\pm$ 346*	10 $\pm$ 7*	317 $\pm$ 110*	120 $\pm$ 35*
No. tested	40	40	40	28	40	40
Control	192 $\pm$ 107	121 $\pm$ 55	1093 $\pm$ 184	14 $\pm$ 5	253 $\pm$ 69	99 $\pm$ 19
No. tested	71	70	70	67	71	71

\* Significantly different at  $P < 0.05$  from that of control.

† Significantly different at  $P < 0.05$  from that of PMF.

TABLE 4. OCCURRENCE OF BRONCHITIS IN SELECTED MINERS WITH COAL WORKERS' PNEUMOCONIOSIS IN RELATION TO SERUM PROTEIN LEVELS, AND  $FEV_{1}/FVC$  RATIOS

Categories	No.	Elevated serum protein levels*		Decreased $FEV_{1}/FVC$ ratios†		
		No.	%	No.	%	
Caplan's syndrome (classical, compatible, possible)	bronchitics‡	7	5	71.4	1	14.2
	nonbronchitics	27	21	77.7	5	18.5
Simple pneumoconiosis ( <i>p, q, r</i> )	bronchitics	22	17	77.2	1	4.5
	nonbronchitics	59	47	79.6	5	8.4
Progressive massive fibrosis (anthracite)	bronchitics	11	10	90.9	4	36.3
	nonbronchitics	12	10	83.3	4	33.3
Progressive massive fibrosis (bituminous)	bronchitics	4	1	25.0	1	25.0
	nonbronchitics	13	3	23.0	4	30.7

\* Elevations of 2 or more serum protein levels (IgA, M, G, D; C3 or  $\alpha$ -1 antitrypsin above normal range  $\pm$ SD.

† Forced expiratory volume in 1 s/forced vital capacity ratio <65%.

‡ Diagnosed by daily cough and production of sputum for at least 3 months a year.

In part, our findings concur with reports of elevated serum IgA concentrations in coal miners with simple or complicated pneumoconiosis (LEWIS *et al.*, 1971) as well as those with silicosis complicated by progressive massive fibrosis (HAGADORN and BURRELL, 1968). VIDAL *et al.* (1971) reported that the gammaglobulin percentage was higher than normal in coal miners, but on estimation by a weight method, the immunoglobulin fractions, IgA, IgM, IgG, did not show any relative modifications. BENEDEK *et al.* (1976) found no evidence of abnormal levels of serum immunoglobulins (IgA, IgM, IgG, IgE) in U.S. bituminous miners with rheumatoid arthritis nor any correlation with severity of pneumoconiosis. The control values employed in the study were that of men with rheumatoid arthritis who had no history of occupational exposure to silica. Whether the techniques employed to measure immunoglobulin fractions, rank of coal, type of controls and values assigned thereto, or other unrecognized factors could account for some of the differences between our findings and those reported in the aforementioned studies cannot be presently ascertained.

C3, the principal component of the complement series, was measured in its inactive form  $\beta_1$  A-globulin. Both C3 and  $\alpha$ -1 antitrypsin serum levels of miners with Caplan's syndrome or progressive massive fibrosis were higher than the control group. In the category of simple pneumoconiosis the  $\alpha$ -1 antitrypsin concentration was comparable to normal levels, but the C3 level was both significantly higher than control and progressive massive fibrosis groups. Increased  $\alpha$ -1 antitrypsin levels have been noted in acute and chronic inflammatory diseases (KUEPPERS, 1973) and C3 elevations have been associated with the activation of inflammatory response in acute disorders (COOPER *et al.*, 1971).

Bronchitis is defined here, in the industrial context, to denote a condition characterized by cough and sputum for at least 3 months a year with or without airways obstruction (MORGAN, 1978). In this study the effects of long-continued inhalation of dust and smoking on resultant bronchitis could not be distinguished. The evidence indicates that elevated serum protein levels noted in this study were not related to the presence of bronchitis in miners. For all categories of pneumoconiosis, the percentage of miners with elevated serum protein levels was not significantly different between bronchitic and nonbronchitic miners. In both these latter groups, also, the percentage of miners that smoked was not markedly different from the other. The current status of knowledge on industrial bronchitis and pneumoconiosis in relation to dust particle size and total dust exposure has been reviewed by MORGAN (1978). Because cumulative dust exposure measurements were not started in the United States until 1970, there are no data available to estimate the dust experience of the selected coal miners in this study.

Immunoglobulin systems may easily be stimulated by antigenic contact via the respiratory tissues (BURRELL, 1977). Higher than normal levels of IgG in beryllium workers (RESNICK *et al.*, 1970) IgA, IgM, IgG in asbestos cement workers (EL-SEWEFY *et al.*, 1971a, b), and IgA, IgM, IgG in workers with parenchymal asbestosis but not in those with pleural plaques have been reported (KAGAN *et al.*, 1977). Increased concentrations of serum  $\beta$ - and  $\alpha$ -globulins also have been reported for metallic selenium and  $\alpha$ -globulin concentrations for tungsten diselenide and lead in relation to occupational exposures (BRAKHNOVA, 1975). In pulmonary disorders not related to mineral dust exposure, IgA and IgG levels in serum of patients with farmer's lung disease were significantly higher than those of normal individuals (ROBERTS *et al.*,

1973). However, occupational exposure of workers to nitrogen dioxide resulted, in most cases, in elevated levels of serum IgA and IgM but decreases in serum IgG concentrations (KOSMIDER *et al.*, 1973). Studies by PERNIS and PARONETTO (1962) have indicated that silica may act as an adjuvant to antibody formation. The varied silica content of coal *per se* or indigenous components associated with different coal mining dusts, as well as the length of exposure time to dust, may be factors responsible for induction of and subsequent elevations of serum immunoglobulins and proteins in CWP. From the observations described, it appears plausible that a diversity of occupation-associated agents or dusts, therefore, by contact with respiratory tissues, may selectively stimulate components of immunoglobulin systems.

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