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DIFFUSE INTERSTITIAL PULMONARY SYNDROMES

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During the past two years three of the du Pont Company Textile Department Plants each yielded several cases of diffuse interstitial pulmonary disease. Since these syndromes occurred in comparatively young employees (all under 50), a special study of these cases, of the prevalence of comparable lesions in other employees, plus a review of the general problem of diffuse interstitial pulmonary disease has been initiated. The present paper reviews preliminary data garnered to date.

The main interest naturally centers in those cases in which pulmonary biopsies or resections were performed. Drs. Savage, Dickerson and Weaver have contributed twelve specimens. Their salient features have been summarized in Table 1. In addition, Dr. Savage collected lung tissue slides prepared from 100 deceased, non-company employees on whom autopsies had been performed during the past several years at Waynesboro General Hospital. These cases serve as controls for the Waynesboro area. The slides from the twelve cases were also reviewed by Wilmington pathologists, staff members of the Johns Hopkins University and the Armed Forces Institute of Pathology. In addition, these slides were compared with eight pulmonary biopsy preparations recovered from personnel of the Textile Division of another company in which comparable clinical syndromes have been detected. Dr. Sidney Pell has also reviewed the prevalence rates of chronic bronchitis in the Textile Divisions of the du Pont Company as compared with the overall incidence of this disorder in Company personnel (Table 2). Further biostatistical analyses and clinical studies are in progress or are contemplated.

Histopathology

The lesions present in the twelve biopsy specimens reflect a wide range of lung changes. There is, however, a pattern of histologic features common to all.

The primary components of the reaction are represented by cases 1, 2, 3, 5 and 11. In these instances the following are present: (a) proteinaceous exudation into alveolar spaces, (b) selective release of cells into alveolar spaces, (c) infiltration of alveolar walls by phagocytes, many of which contain inclusion bodies, (d) perivascular and peribronchial accumulation of cells, (3) extensive injury and secondary repair of the bronchiolar mucosa, (f) retarded interstitial fibrosis, (g) atrophic and confluent emphysema.

Secondary lesions discovered in this group are represented in cases 4, 6, 7, 8, 9, 10, and 12. These include: (a) extension of the atrophic emphysema and bronchiolar lesions to create pneumatoceles, cysts and vanishing lung complexes, (b) superimposed pleural effusion and hemothorax, (c) granuloma formation, (d) proliferation of bronchial epithelium with formation of bronchial adenoma and obstructive bronchiectasis. While the latter group of lesions may be causally related to the interstitial reactions, they may also be mere incidental findings.

Traces of the proteinaceous exudate are present in the alveolar spaces in the majority of cases. In its most fully developed form this exudate fills and distends alveolar spaces. Much of it is probably derived from the blood since many erythrocytes are present within the exudate in some areas. Its brightly eosinophilic character apparently reflects its high fibrin content. At various points crystals, morphologically identical with cholesterol plates, are present. In some areas the exudate is being resorbed by histiocytes. Some of these exudate-laden cells are seen to be penetrating into the alveolar walls. In several of the alveoli an inspissated residuum of the exudate forms a thin dense layer over the septal surfaces. This residuum resisted decolorization by alcohol and acid when the Ziehl-Neelsen stain was applied in one case.

The specific cells found in the alveoli vary according to the age and severity of the reaction. In areas where little or no exudate exists, the dominant cell is the plasma cell. For the most part these cells possess abundant opaque cytoplasm without inclusion bodies. Histiocytes are more prevalent where there is exudate and apparently serve a phagocytic function. In terms of morphological criteria these cells are histiocytes, but it is also likely that they are desquamated alveolar septal cells. Their cytoplasm contains spherical eosinophilic inclusions, fine vacuoles, large spherical nonstaining bodies or vacuoles, glycoproteins, oil or fat droplets, nonpolarizing acicular crystals, hematin pigment and opaque particles. The most impressive inclusion bodies are the oil or fat droplets. In some of the alveoli the histiocytes have fused to form multinucleated syncytia or giant cells. In one instance these syncytia completely fill the alveolar spaces and contain multiple vacuoles in which small, spherical, clustered particles occur. These elements are too large to be Histoplasma capsulatum but the tissue is being further investigated to exclude the possibility that these bodies may represent fungal spores, e.g. Cryptococcus neoformans or Coccidioides imitis. Bacteriological stains have proved negative in all other cases.

The characteristic changes in the alveolar septa include: epithelial proliferation, infiltration by cells, belated fibrosis, capillary distension or collapse according to whether cellular infiltration is far advanced or not, presence of inclusion bodies, rupture of the septa. The epithelization is sporadic and continuous epithelial sheets have formed in only one case. The infiltrating cells are plasmacytes, histiocytes and, in one case, eosinophilic polymorphonuclear leukocytes. Plasma cells predominate and resemble those found within the alveolar spaces. In one case some of these cells are filled with minute spherical eosinophilic granules. The histiocytes are smaller than those of the alveoli. They display eosinophilic inclusion bodies in one instance. In a large proportion of cases these cells are filled with small or large vacuoles. That these vacuoles represent fat or oil is suggested by a positive reaction to Sudan IV in one representative case. In addition to these intracellular droplets, a number of spherical bodies, not obviously lying within macrophages, are present. In one case these bodies displayed a negative reaction to the periodic acid Schiff reagent. On this basis these bodies may represent oxidized lipid. Fibrocytes are not prevalent, but a few could be identified in the areas where vacuolated phagocytes are congregated most densely. Here delicate strands of collagen support the phagocytes. Eosinophils noted in one case have infiltrated the alveolar walls as solid cords.

The extent of the mural infiltration varies considerably. In most areas the alveolar septa are thickened to twice or thrice their normal caliber and the blood capillaries wind over or around the collections of cells without apparent occlusion. In other areas the cellular involvement is more extensive. Not only are the alveolar septa transformed into cellular cords measuring 20 to 40 times the normal caliber of the septa, but the capillaries have become obliterated or deeply buried within these cell collections. At the same time the alveolar spaces have become encroached upon and in the more advanced cases are completely occluded, transforming extensive portions of the pulmonary parenchyma into solidly cellular areas.

The alternative response to cellular infiltration of the alveolar septa is by rupture. In this manner several adjacent alveolar spaces have become confluent. This atrophic emphysema is regionally emphasized so that fairly large intrapulmonary spaces have resulted.

In three cases large multilocular cysts or pneumatoceles have formed. Since these space lesions occur in lungs in which atrophic emphysema of the foregoing type is also present, it is necessary to consider whether the cystic lesions and the emphysema are

part of the same basic process. In one case (No. 6) the cyst has a cuboidal epithelial lining similar to that of the bronchioles. In the other two instances such an epithelium is lacking. Granulomata with vacuolated cells occur in parts of the cyst wall or the trabeculae. The lung parenchyma has not been compressed so that these cysts do not represent expanding spaces which have encroached upon other portions of the lung. It seems rather that these spaces represent portions of lung from which alveolar septa and terminal respiratory passages and blood vessels have been withdrawn without ensuing atelectasis. This is characteristic of one of the forms of the vanishing lung syndrome.

While the pleura has remained relatively free from involvement in most instances, two of the cases presented as spontaneous pneumothorax with pleural effusion in one and hemothorax in the other. There is nothing specific about these lesions. In one case, however, the subpleural lung tissue displayed mural infiltration by vacuolated cells of a type similar to those present in other granulomata from this group of cases.

Granulomatous lesions developed in several specimens. It is not clear whether granulomatosis is an end result of local evolution of the lesions, or whether it is an independent reaction. The most elementary granulomata are represented in Case 5. In this case the granulomata are paravascular and parabronchiolar and are a composite of intramural and intra-alveolar cells. In some granulomata lipophages with abundant pale cytoplasm form a prominent component. In other unit lesions multinucleated giant cells are present. These cells are of the Langerhans type with a central collection of amorphous matter yielding negative reactions for the Ziehl-Neelsen and periodic acid Schiff tests. The predominating cells are plasmacytes and histiocytes. Several of these cells contain inclusion bodies, e.g. eosinophil granules in the case of the plasma cells and vacuoles and erythroid bodies in the case of the histiocytes.

Abundant proliferation of the bronchial epithelium has occurred in Case No. 7. This has occluded the bronchus at one point where an adenomatoid lesion is present. In the surrounding lung, interstitial pulmonary infiltration by vacuolated macrophages furnishes a clue that this process may be related to that present in other cases from this series. It is also possible that the adenomatoid lesion represents an unrelated finding.

In Case No. 8 numerous minute apparently encapsulated bodies are present within the giant syncytia. In this instance some peripheral fibrosis has occurred around each unit lesion. These structures are being further investigated for they resemble fungal elements but may also represent lipid particles. In three additional cases the

predominating cell is a vacuolated histiocyte supported by a network of fibrocytes and collagen bundles. The latter lesions are indistinguishable from the oleogranulomata associated with inhaled mineral oil droplets.

Clinical Aspects

Symptomatically these cases share certain characteristics, not only with one another but also with syndromes in plant personnel who were not subjected to lung biopsy.

In a number of instances the chronic phase of the syndrome was preceded by single or repetitive respiratory tract infections diagnosed as "sinusitis", "frequent colds", "virus pneumonitis", "influenza", "bronchitis" or "pleurisy". In other instances the onset was insidious without prodromal symptoms. The subacute or chronic phase, extending over months to years, was often ushered in by asthma-like episodes with paroxysmal dyspnoea as a main symptom. These attacks sometimes were associated with febrile phases, with or without productive coughing. In some cases antibiotic therapy and antihistaminics alleviated the distressful symptoms; in others, cortisone had a significantly favorable influence.

Almost all patients experienced spontaneous remissions. In several employees symptoms abated as soon as the persons concerned were assigned to a new work area. In other instances the converse was obvious, i.e., the patients underwent relapses, or symptoms were aggravated shortly after in-plant work was resumed. No job-relatedness of symptoms was obstrusively evident in a further group.

Laboratory tests were on the whole inconclusive except for their negativeness. Evidence of sensitization to biological or chemical agents was conspicuously lacking.

Pulmonary function studies were carried out preoperatively in four subjects in whom biopsy confirmation was later effected. Comparable studies were also instituted in other men not subject to biopsy. The feature common to all these cases was mixing, dilution and diffusion defects. Mild polycythemia was present in some instances. No electrocardiographic defects were discoverdd.

Radiographically no clues were elicited concerning the diffuse lesions. Major complications were, of course, detected (e.g. focal granuloma, pneumatocele, bronchial obstruction). The basic process being at the alveolar level it is understandable that so little was revealed by conventional x-ray techniques.

Environmental Studies

Careful surveys of the plant environments failed to identify a specific hazard. While the pulmonary symtoms occurred mainly in long-service personnel, there was not any clear-cut identification of the clinical cases with particular occupations. The only air-borne components which entered into the plant environments transiently, before being drawn into the air-conditioning system, appeared to be acetone, fiber finishes, lubricating oils and fragments of textile products or containers. Acetone can apparently be excluded since cases occurred in both acetone using and nonacetone areas Very little evidence of dissemination of textile or container particles was found. This leaves as possible pathogens only the mists, smokes and vapors created through the impingement of lubricating oils or fiber finishes on fast moving, often heated textile fibers. However, many of the men most heavily exposed to these agents showed the least pulmonary involvement.

Nothing comparable has been found in persons from the geographic areas where the textile plants are located who are not employed in these plants. The 100 randomly selected autopsy specimens which served as controls were all negative. These observations suggest that the cause may be industrial rather than biological.

Differential Diagnosis

Interstitial pulmonary infiltration has been reported with increasing frequency during the past three decades. It is not possible to review this problem fully in this presentation but the classification given in Table 3 may indicate the wide scope of conditions from which the present series of cases have to be differentiated before a new syndrome may be proposed.

A biological etiology is still held high on the list of possibilities, even though the process has manifested itself primarily in plant personnel. Even though the process appears to be occupation related, the possibility of augmentation or facilitation of injury by air-borne industrial agents by preceding or through concommittant bacterial, viral, mycotic or parasitic invasions of the lung must be further explored. Recovery of micro-organisms was unfortunately not attempted at the time the biopsy samples were taken. In Case No. 7 an acid-fast bacillus was identified in the sputum on one occasion, but the histological appearance of the lung tissue did not favor a diagnosis of tuberculosis. Skin reactions for tuberculosis, histoplasmosis, coccidioidomycosis proved negative in other cases. Further study should be made of bacterial and fungal agents in the textile plants since it is possible that micro-organisms may insidiously proliferate on textiles or in chemical solutions.

It seems permissible to exclude from this group the endogenous category of interstitial lesions. None of the cases conformed to the other criteria characterizing these syndromes. Thus, there was no bone involvement, no splenic or liver enlargement. None of the patients had been subjected to trauma, so that fat embolism may be excluded. No cardiac or renal lesions were discovered so that we are not dealing with the so-called Schatsky lung syndrome. Allergy will require further exploration, but one of the patients was a hyper-reactor to common antigens.

It seems likely that the cause may be found in the chemically determined group of etiological agents. There is no evidence of any physical forces in the plant environments of the categories listed in Table 3 which could have produced these pulmonary lesions. Attempts have also been made to compare the lesions with the group of syndromes currently classified as of unknown origin. The divergences appear to be greater than the resemblances. Moreover, since Hodgkins disease, sarcoidosis, scleroderma, Hamman-Rich syndrome, alveolar proteinosis or hyaline membrane disease must a priori ultimately be resolved as either biologically or environmentally determined, no useful purpose can be served by exploring resemblances to these conditions further than seems obvious.

Lipid pneumonitis appears to be the condition most strongly suggested by the histological evidence. Further inquiry is in process to exclude jatrogenic oleogranulomatosis. While a clear history of excessive use of nasal or pharyngeal oil instillations could not be elicited, it may be recalled that patients frequently have unreliable memories about such matters. Lipiodol also was used in one case for diagnostic purposes. Though vegetable oils generally cause no permanent pulmonary damage in normal lungs, less is known about their capacity to provoke tissue reactions in abnormal lungs.

Considerable experimental research and human experience has accumulated since Laughlin identified the first case of oleogranulomatosis. Pertinent experimental data culled from the literature on this subject (Refs. 1-21) have been summarized in Table 4. These reveal that the lungs react variably to different kinds of oils. The reactions to most vegetable oils are least significant. This may be due to their low fatty acid content and their rapid hydrolysis or elimination from the lung tissue. Chaulmoogra oil has a high fatty acid content and this correlates with its marked capacity to provoke progressive chronic pneumonitis, pulmonary granulomatosis, focal necrosis, epithelial proliferation, pulmonary fibrosis, bronchila lesions and cellular catarrh. The ricin oleic acid of castor oil causes acute pulmonary inflammatory reactions but no chronic response. In this respect it behaves similarly to croton oil. In the case of peanut oil the arachidic acid is capable of producing acute as well as chronic pulmonary lesions.

The majority of the animal-derived oils are markedly irritating to the lungs, provoking both acute and chronic reactions. Attention may be directed more especially to their propensity to excite giant cell systems and proliferation of alveolar septal cells. In the case of lard there is an additional tendency to pleural reaction.

Mineral oils produce yet a further variety of reactions in which lipophages form a conspicuous feature. No hydrolysis by lung lipases occurs in these cases, but the fine subdivision of the mineral paraffinomata.

Lipid pneumonitis is a well-documented problem in human affairs. Gross pulmonary disease and scores of deaths have been induced by the intrapulmonary introduction of oils of various kind, particularly milk fats, cod-liver oil, croton oil, peanut oil, menthol-camphor and mineral oil. Since oils form an important ingredient of fiber and machine lubricants used in textile plants, it is imperative that first consideration be given to the possibility that at least some of the cases of chronic interstitial pulmonary disease may be sequential to the prolonged inhalation of small amounts of oil. In this connection the inhaled oils could function either as a primary cause or as cofactors. The question of periodic exposures to surges of enhanced exposure, always a possibility in almost any industrial operation, but seldom reflected in average exposure charts, needs to be considered. The adjuvant or synergistic action of oils of different kinds must also be explored. Variations of the formulae for fiber finishes may enhance or retard the pulmonary reaction to inhaled droplets. Such explanations may account for the unequal distribution of case material in the various plants.

Conclusion

While a tentative inference is that we are dealing here with a new industrial syndrome, the matter is by no means resolved by an inquiry as limited as the present. Much more research is required.

First, there must be precise studies of the actual exposures of plant personnel to oil droplets, mists, vapors, smokes, gases and fumes, with analysis of the physical and chemical aspects. These observations must be focused on typical locations where prolonged human exposures are likely. Studies should also follow the selective rate of fall out of components along the paths of air circulation in the plants. Particular attention should be paid to centers of exposures to multiple types of ingredients or potential surges.

Next, the clinical study of plant personnel should be methodically and assiduously pursued. There must be a starting point

for each case at which the process is spontaneously reversible. This physiological state is likely only to be identified by systematic pulmonary function studies. It is unlikely that periodic x-rays will identify these processes early enough. Regular sputum determinations for oil droplets may furnish clues.

Further inquiry into the extra curricular activities of plant personnel seems necessary. Many workmen have an overabundance of energy and engage in hobbies or moonlighting tasks which may be far more hazardous than anything they are likely to experience at their official jobs.

More information should be gathered about the prevalence rates of pulmonary syndromes in the geographic regions where the textile plants are located. This study should include review of clinical as well as autopsy findings.

Last, but not least, comes experimental study of the problem. If there is an injurious component in the working environments of the textile operatives, this point may be clarified by exposing animals to simulated or actual environments. Ideally, such an experiment should include animals subjected to prior or concurrent biological stresses.

We would have had the answer to this problem if two things had been possible. First, it seems illogical that any new industrial operation should be initiated without prior exploration of the theoretical hazards likely to be encountered. The next best thing would be if experimental controls can be introduced as soon as the plants are in operation and whenever technical innovations are likely to introduce new varieties of human exposure.

The second piece of missing information is a complete picture of the background of pulmonary pathology of Company employees. The du Pont Company has pioneered one of the best preventive medical departments in this country and incomparable clinical records are available. Very little is, however, on file about the pathology of the du Pont employee or ex-employee. This information is scattered among scores of hospital and university departments. What we need is a central collecting office to which illustrative biopsy or pathology specimens can be routed. This should be an automatic process. Thus, each company physician could help build the museum or archives on the pathology of du Pont employees by securing data on each case which comes to his attention, whether or not a medico-legal or industrial problem is involved. This material can then be studied systematically. When such information is available, identification of the pathogenesis and etiology of syndromes such as the one described in this review will be greatly facilitated.

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TABLES

1. Pulmonary Lesions in Textile Employees
2. Incidence of Bronchitis
3. Chronic Interstitial Pulmonary Lesions
4. Pulmonary Reactions to Oil

TABLE 1

PULMONARY LESIONS IN TEXTILE EMPLOYEES

Lung Biopsies

Case	Plant	Race	Sex	Main Biopsy Findings
1	A	White	Female	Interstitial infiltration and eosinophilia.
2	A	Negro	Male	Interstitial infiltration and exudation.
3	A	White	Male	Interstitial infiltration and emphysema.
4	A	White	Male	Pneumatocele and oleogranulomatosis.
5	B	White	Male	Interstitial infiltration and oleogranulomatosis.
6	B	White	Male	Pneumatocele and oleogranulomatosis.
7	C	Negro	Male	Bronchial adenoma and oleogranulomatosis.
8	C	White	Male	Granulomatosis and interstitial infiltration.
9	C	White	Male	Vanishing lung and interstitial infiltration.
10	C	White	Male	Alveolar proteinosis.
11	C	White	Male	Spontaneous pneumo- and hemothorax.
12	C	White	Male	Spontaneous pneumothorax, pleural effusion and interstitial infiltration.

TABLE 2

INCIDENCE OF BRONCHITIS

- Textile Plants -

Plant	Rate/1000/1957 Wageroll Employees	
	Male	Female
A	14.5	17.2
B	5.3	17.4
C	5.4	18.0
D	6.1	18.2
E	4.8	14.0
F	6.1	15.1
Company	7.2	15.8

TABLE 3

CHRONIC INTERSTITIAL PULMONARY LESIONS

Etiological Classification

Group	Order	Genus
BIOLOGICAL	Exogenous	Bacterial Viral Rickettsial Fungal Mycobacterial Parasitic
	Endogenous	Reticulo-endotheliosés Eosinophilic granulomatosis Edemic Metastatic Allergic
ENVIRON-MENTAL	Chemical	Pneumonitis and granulomatosis Emphysema and Bronchitis Pneumoconioses Jatrogenic
	Physical	Radiational Sonic Traumatic Blast Decompression Cold Heat Dessication Drowning
UNKNOWN	Unknown	Hodgkins granuloma Scleroderma pulmonalis Psammomatosis Sarcoidosis Hamman-Rich syndrome Alveolar Proteinosis Cystic pancreatitis Hyaline membrane syndrome

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TABLE 4

PULMONARY REACTIONS TO OIL

(References 1 to 21)

Type of Oil	Species	Lethality %	Pneumonitis	Focal Necrosis	Oleogranulomatosis	Cellular Catarrh	Lipophages	Giant Cell Syncytia	Epithelization	Acid Fast Membrane	Fibrosis	Pleural Involvement	Bronchial Lesions	Lymph Node Involvement	Human Disease	Footnotes
Corn Oil	M	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lipiodol	D	80	++	-	-	-	-	-	-	-	-	-	+	+	+	+
Iodipin	R	0	-	+	-	+	-	-	-	-	-	-	-	-	-	-
Olive Oil	R	0	-	-	-	+	-	-	-	-	-	-	-	-	?	-
Chaulmoogra Oil	R	66	+++	++	+++	++	-	++	+++	-	+++	-	+++	-	-	xx
Croton Oil	R	100	++++	-	-	-	-	-	-	-	-	-	-	-	-	-
Castor Oil	R	0	+++	-	-	-	-	-	-	-	-	-	-	-	-	-
Peanut Oil	R	?	+++	-	++	-	-	-	-	-	-	-	+++	-	xx	(++++ ·/·
Cod Liver Oil	R	10	-	+++	++++	++	-	++++	+++	+++	++++	-	-	-	++++	·/·
	M	0	++	-	-	++	-	-	-	-	-	-	-	-	-	-
Halibut Oil	R	0	+++	-	-	-	-	-	-	-	-	-	-	-	-	-
	M	0	+++	-	-	-	-	-	-	+++	-	-	-	-	-	-
Milk Fat	R	0	-	-	++	-	-	++	+++	-	++	-	-	-	++++	
Rabbit Fat	R	0	-	-	++	-	-	+	++	-	++	-	-	-	-	xxx
Lard	R	84	++++	+++	+++	-	-	+++	++++	-	+++	+++	++	+	-	-
Egg Yolk	R	0	+++	-	+++	+++	+	++	-	-	-	-	-	-	++	?
Lecithin	R	0	+++	-	+++	+++	+++	++	-	-	-	-	-	-	-	-

TABLE 4 (Cont'd.)

PULMONARY REACTIONS TO OIL
(References 1 to 21)

Type of Oil	Species	Lethality %	Pneumonitis	Focal Necrosis	Oleogranulomatosis	Cellular Catarrh	Lipophages	Giant Cell Syncytia	Epithelization	Acid Fast Membrane	Fibrosis	Pleural Involvement	Bronchial Lesions	Lymph Node Involvement	Human Disease	Footnotes
Menthol Oil	R	100	+++	-	++	+++	++	++	-	-	+++	-	+	-	++++	·/·
Camphor Oil	R	0	-	-	++	-	-	+++	-	-	-	-	-	±	-	-
Mineral Oil	R	16	+++	-	+++	-	+++	+	++++	-	-	-	-	-	++++	·/·
	G	100	-	-	++++	++	+++	+	++++	-	++	-	-	-	-	-

D = Dog
R = Rabbit
M = Monkey
G = Guinea Pig

\+ = Slight reaction
++ = Moderate reaction
+++ = Marked reaction
++++ = Extreme reaction

x = In the presence of obstructive lesions favoring retention of oil.
xx = High fatty acid content.

x = Destroys elastic tissue causing emphysema.
xx = Arachidic bronchitic first described 40 years ago.
xxx = Causes local adipose tissue around blood vessels and bronchi.
? = Probably a factor in some cases of human disease.
·/· = Death caused in human subjects.