MEDICAL GRAND ROUNDS
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"EXTRINSIC ALLERGIC PNEUMONIAS"

DE MORBIS ARTIFICUM

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DIATRIBA 1713

Diseases of Sifters and Measurers of Grain

All kinds of grain and in particular, wheat, whether they are stored in pits and trenches as in Tuscany, or in granaries and barns with roofs as is done in the whole country on both sides of the Po, always have mixed in with them a very fine dust; not only the dust that they pick up from the threshing-floor, in the threshing, but also another less innocent sort which is shed from the grain itself when it is kept for long. Inasmuch as the seeds of cereals are full of volatile salt, and so much of it that unless they are well dried in the summer sun before stored they become overheated and very soon crumble to dust, it follows that fine particles are continually dropping from the skin with which the grain is coated; besides these there is the residual dust and decay caused by the grubs, borers, and weevils that consume the grain and by other such corn pests and their excrements. Hence, whenever it is necessary to sift wheat and barley or other kinds of grain to be ground in the mill, or to measure it when corn-merchants convey it hither and thither, the men who sift and measure are so plagued by this kind of dust that when the work is finished they heap a thousand curses on their calling. The throat, lungs, and eyes are keenly aware of serious damage; the throat is choked and dried up with dust, the pulmonary passages become coated with a crust formed by dust, and the result is a dry and obstinate cough; the eyes are much inflamed and wattery; and almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach old age; in fact they are very liable to lapse into orthopnoea and finally dropsy. The dust moreover is so irritating thai it excites intense itching over the whole body, of the sort that is sometimes observed in nettlerash.

INTRODUCTION

It is readily apparent that the lungs are at considerable risk from inhaled allergens, and of course asthma is a well recognized consequence. Less well-known is the response in the non-atopic person to a variety of inhaled antigens, now generally recognized as the Extrinsic Allergic Pneumonias'.

The immune responses of the human organism have been classified by Gell and Coombs as is shown in Table 1. Such a classification provides a background from which to understand the pathological responses of the lung to inhaled or blood borne antigens, though in many instances the immune response of the lung may not be restricted to that of Type I, III, or IV, but appears as a combination of effects.

Present evidence would ascribe the typical asthmatic response to specific inhaled allergens, in the 10% of the population who are atopic, as a Type I, Reaginic response. Whereas the response underlying the Extrinsic Allergic Pneumonias', examples of which are listed in Table 2, is considered to be of Type 3, due to the induction of precipitating antibodies.

Persons of relatively high inherited atopic status, approximately 10% of the population, tend to develop Type I, asthmatic responses to a number of allergens early in life, with some waning of their response with age. On the other hand persons of low atopic status may, later in life, develop a similar Type One response, but in this instance usually to only one or two allergens.

Type 3, antigen-precipitating antibody complexes leading to an Arthus reaction, tend to occur in 50% of non-atopic persons heavily exposed to a suitable antigen, e.g. mouldy hay. Nevertheless about 10% of patients with Farmer's Lung develop

asthma in the course of their Extrinsic Allergic Pneumonia. Thus, Type I and III responses are not mutually exclusive, and indeed may occur together, as seen in the syndrome of Transient Pulmonary Infiltrates with Peripheral Eosinophilia (Broncho-pulmonary Aspergillosis, Mucoid Impaction?).

Footnotes:

1. Pepys originally proposed the term Extrinsic Allergic Alveolitis, but much more than the alveolar wall in involved.
2. Anaphylaxis: Portier and Richet. 1902, Literally protection 'up' or 'back'. Faulty coinage to express reverse of protection for which anti-phylaxis might be better.
3. Allergy: Von Pirquet. 1906, Changed reactivity.
4. Atopy: Coca. 1922, Greek for strange disease.

TABLE 1
CLASSIFICATION OF IMMUNE MECHANISMS

	Type I Immediate	Type II Cytotoxic	Type III Intermediate	Type IV Delayed
Reaction	Allergen and non-precipitating antibody (Reagin IGE 7.9S)	Cell or cell bound antigen	Antigen and precipitating antibody (7.S)	Delayed hypersensitivity
Clinical	Asthma	Hemolytic disease, Goodpasture's	Farmer's lung, P.I.E.	Tuberculosis, Sarcoidosis
Pathology	Bronchoconstriction, plugs, mucosal edema eosinophilic infiltration	Cell damage	Epithelioid infiltration ± granulomata	Granuloma with epithelioid cells (Caseation)
Aerocontaminants	Pollen, etc.	———	Actinomycetes thermophilic, Aspergilli, etc.	Mycobacteria, Fungi, Beryllium
Mechanism	Allergen:IGE complexes fix to tissue, release of SRS, Histamine, Kinins, Acetyl-choline	Antibody on cell antigen ± complement	AG:AB complex mediate tissue damage ± complement	Transfer factor complement?
Tests	Immediate prick, passive transfer (P-K), not affected by steroids	Rh tests, etc.	Arthus (6-24 hrs.) Precipitins, prevented by steroids	Delayed (48-72 hrs.) passive transfer by cells
Site	Bronchiolar with obstruction	RBC Lysis, etc.	Peripheral airway, restriction, D_L reduced	Interstitial

TABLE 2

EXTRINSIC ALLERGIC PNEUMONIAS

FARMER'S LUNG. Air conditioners, etc.
BAGASSE WORKER'S LUNG. Bible printer's lung.
BEFEUCHTERUNGSANLAGEFIEBER. Rural cotton mattress workers.
MOULDY VEGETABLE MATERIAL, corn, tobacco, sisal, mushroom compost, etc.
THATCHED ROOFS (New Guinea). Black fat tobacco.
MAPLE BARK DISEASE. SEQUOISIS. SUBEROSIS.
MALTWORKERS, Molasses fermentation (massive exposure to Aspergilli, Candida, etc.).
Paprika cleaners. Tamarind size. Cheeseworker's lung.
Grain weevil. Enzyme detergents. Smallpox handler's lung.
BIRD FANCIER'S LUNG. HEN LITTER.
PITUITARY SNUFF.
COFFEE WORKERS. FURRIERS.

Panters, Lungers, and Fog Fever of Cattle.
Broken Wind and Heaves in Horses.

TABLE 3

EXTRINSIC ALLERGIC PNEUMONIAS

Disease	Dust Exposure	Antigen Source
Farmer's Lung Fog Fever, Cattle	Mouldy Hay	Micropolyspora faeni Thermoactinomyces vulgaris
Bagasse Worker's Lung Mushroom Picker's Lung Maple Bark Disease	Mouldy Sugar Cane Mushroom Dust Mouldy Maple Bark Dust	Thermoactinomyces ? " " ? " " ? Cryptostroma Corticale
Cheese Worker's Lung	Mouldy Cheese	?
Bird Breeder's Lung	Pigeon, Parakeet, Turkey, Hen Droppings	Proteins of Serum and Droppings
Pituitary Snuff Lung	Porcine and Bovine Post: Pituitary Powder	Serum and Pituitary Proteins
Sequiosis	'Mouldy' Red Wood Dust	Graphium. Pullalaria
Suberosis	Oak Bark, Cork Dust	Not Known
Smallpox Handler's Lung	Smallpox Scabs	Not Known
Bible Printer's Lung, etc.	'Mouldy' Paper	Not Known
Wheat Weevil Disease	Wheat Flour Weevils	Sitophilus granarius
Enzyme 'Detergents'	Detergent Powder	Alcalase. Enzyme from B. Subtilis

FARMER'S LUNG

> 'Pulmonary Disease due to the inhalation of the dust of mouldy hay or other vegetable produce characterized by symptoms and signs attributable to a reaction in the peripheral part of the broncho-pulmonary system and giving rise to a defect in gas exchange.'
>
> Ministry of Pensions and National Insurance, 1964.

This definition of Farmer's Lung clearly separates the condition from that of asthma, 'intermittent increase in airways resistance reversible spontaneously or by therapy', yet is broad enough to allow the inclusion of Bagasse Worker's Lung, or any similar response.

Farmer's Lung is the staple commodity of the Extrinsic Allergic Pneumonias, being the oldest, the most common, and the one from which most of our understanding has grown.

The disease results from repeated exposure to the dust of mouldy hay (oats, corn, barley, beet pulp, etc., but not to soybean or peanuts). Only about 50% of those heavily exposed become affected.

CLINICAL FEATURES

After a variable period of exposure to the dust of mouldy hay, commonly 6 - 10 weeks, re-exposure is followed 4 - 6 hours later by symptoms.

Thirty-five percent of cases present with this delayed sudden onset of malaise, anorexia, shivering, non-productive cough, and shortness of breath. Examination reveals fever, tachypnoea, and possibly scattered inspiratory rales. After a few days the symptoms resolve pending further re-exposure.

Forty-nine percent present with a less typical insidious onset of progressive weak-

ness and shortness of breath, that may suggest some other interstitial process.

Nine percent commence with an insidious onset, and with repeated re-exposures, develop more typical acute attacks.

Ten percent give a history of acute or insidious onset, to be followed later by attacks of asthma on further exposures.

After years of exposure, the patient may present, even after a considerable lapse of time, with a picture indistinguishable from diffuse interstitial fibrosis.

RADIOLOGIC FINDINGS

The changes are usually bilateral, but may not be symmetrical. Diffuse infiltrates, varying in size from millet seed (miliary) to large coalescent densities may be seen, or alternatively, areas of 'alveolar' consolidation and atelectasis. Hilar lymphadenopathy is not a feature. Resolution may take weeks or months.

Sub-acute cases with insidious onset may have a normal radiograph, and chronic cases, a picture of diffuse interstitial fibrosis. Only in the acute phase does the radiograph correlate with the clinical state.

PATHOLOGY

The acute response is a nodular and diffuse non-caseating interstitial granulomatous pneumonitis, with areas of atelectasis and soft enlargement of the mediastinal glands. The bronchi may show some mucoid material but are not hyperemic.

The nodules reveal proliferating Type 2 alveolar epithelioid cells, with lymphocytes, mononuclear, and multinucleate foreign body and Langhans type giant cells. The alveolar walls and septae are thickened and edematous, with vasculitis of the capillaries and small vessels. Occasional bronchioles may show damage and obstruction. Brown,

doubly refractile, PAS positive material may be seen in the tissue or in alveolar macrophages.

As the disease progresses, the features of interstitial 'sarcoid' like granulomata are replaced by those of interstitial fibrosis and pulmonary hypertension.

PHYSIOLOGY

The definition of the disease states that there is a defect in gas exchange, and thus in the acute stage there will be tachypnoea, hypoxemia with respiratory alkalosis, and a decrease in the diffusing capacity with increased arterial desaturation on exercise. The hypoxemia may be severe and life-threatening, and lead to pulmonary vasoconstriction and right heart failure. Few studies are available of lung volumes, compliance, and resistance in the acute phase, though mechanically there is predominantly a restrictive defect.

Lung function studies may return to normal after one or two attacks, but with repeated episodes the changes become less and less reversible, and with progressive interstitial fibrosis an obstructive ventilatory defect becomes superimposed.

IMMUNOLOGY

The attacks are induced by the inhalation of mouldy hay, which may often contain greater than 10^9 actinomycete spores per gram. Pepys and others were able to show that following exposure, the subjects' serum developed precipitating antibodies to extracts of mouldy hay, and that the antigen in mouldy hay arose from Thermophilic actinomycetes.

TABLE 4

ORDER 5	FAMILY 3	GENUS
ACTINOMYCETALES	STREPTOMYCETACEAE	1. STREPTOMYCES (4 thermophilic) 2. MICROMONOSPORA 3. THERMOACTINOMYCES (50-60 °C)

Further extraction and purification lead to the isolation of a more or less specific antigen from a Thermoactinomyces, Micropolyspora faeni. (Previous taxon: Thermospora polyspora). Additional antigens reacting with some sera could be obtained from Thermoactinomyces (Micromonospora) vulgaris and Streptomyces violaceus.

Hay with a moisture content of more than 30% rapidly acquires numerous bacteria, actinomycetes, and fungi. Self-heating occurs, along with a rise in pH and of soluble and volatile nitrogen, encouraging the abundant growth of thermophilic actinomycetes, mainly M. faeni. The hay crumbles to dust, which if shaken liberates up to 1.600 million spores per cubic metre of air!

F.L.H. antigen prepared from M. faeni gives positive precipitation reactions with sera of Farmer's Lung cases, by double diffusion on agar gel, or by immunoelectrophoresis, in about 90% of cases. The antigen gives a negative immediate Prick test, but a positive Type III delayed Arthus skin reaction, and by the aerial route will reproduce the symptoms of Farmer's Lung after a characteristic 4 - 6 hour interval. After withdrawal from exposure the antibody level falls, and 'bands' or 'arcs' decrease or disappear. Ten percent of cases do not demonstrate precipitating antibodies to F.L.H. antigen, and 12 - 15% of exposed, but uninvolved Farmers, may give weak positive tests.

TABLE 5
IMMUNOELECTROPHORESIS TEST - MOULDY HAY (PEPYS)

	Numbers of Subjects	Positive Percentage	Grade of Reaction Percentage		
			1.	2.	3.
Normal	28	18	7	4	7
Other Lung Disease	94	17	11	5	1
Farmer's Lung	205	87	10	31	42
Other Vegetable Dusts	16	50	31	0	19

The steps in the development of the disease, which in essence will be similar for other examples of Extrinsic Allergic Pneumonia, is summarized as follows:

(1) Development of 7S precipitating serum antibodies, induced by the inhalation of a specific antigen.

(2) In this instance the antigen, probably a glycopeptide, is formed by thermophilic actinomycetes, usually M. faeni, growing abundantly under the suitable conditions of wet, moulding, self-heating hay.

(3) After an incubation period allowing the production of precipitating antibodies, further exposure provides an antigen excess leading to a brisk intermediate Type III Arthus reaction in the presence of beta. I.C. complement, at the terminal bronchiolar-alveolar level.

(4) Certain of the morphologic changes, e.g. epithelioid granuloma, suggest that the tissue response may in part be mediated by a Type 4, or delayed hypersensitivity reaction, though antigen:antibody complexes are known to be capable of inducing similar changes.

(5) Subjects of low atopic status, about 10%, may later develop an additional Type I, or immediate response, and thus present clinically with a dual response, i.e. asthma followed by the more common delayed symptoms of malaise, shortness of breath, etc.

PROGNOSIS

Death in acute attack is rare, but about 10% die within six years of diagnosis. Following withdrawal from exposure, 70% of survivors become asymptomatic, and 30% remain dyspnoeic. An unknown percentage of the asymptomatic group will have objective evidence of impairment of ventilatory function or of gas exchange.

PREVENTION

(1) Avoidance of mouldy material.

(2) Masks: If efficient are uncomfortable.

(3) Ensiling crop after drying or wilting.

(4) Spray bales with 2% propionic acid, an inexpensive fungicide.

THERAPY

(1) Removal from exposure.

(2) Oxygen, inhalation therapy, and physical therapy.

(3) Steroids induce immediate subjective improvement, but no evidence yet for long-term objective benefit.

(4) No specific indication for antibiotics.

Some instances of Fog Fever in cattle, and rare instances of the heaves in horses have been associated with serum precipitating antibodies to F.L.H. antigen.

BAGASSE WORKER'S LUNG

Bagasse is the residue left over after sugar cane is pulped. It has a variety of applications in the construction industries, card-board and paper manufacturing, oil drilling, as a manure, and as a development source for a single cell protein.

Repeated exposure to the dust of mouldy bagasse results in a disease clinically similar to Farmer's Lung, though possibly of greater severity with more permanent effects.

In 1964 an outbreak in a local 'asphalt expansion joint boarding' plant resulted in severe disease in 7 of 15 exposed personnel.

The mouldy bagasse at 60°C grew three thermophilic actinomycetes, one still unidentified, and the other two being M. faeni and Thermoactinomyces (Micromonospora) vulgaris.

Full serological studies were undertaken against a number of antigen extracts of the clean and mouldy bagasse, the organisms isolated, and against F.L.H. antigen. Serial samples of patients' sera, exposed unaffected personnel, and of controls were examined here, and also by Dr. Pepys in London. No specific results were obtained in either laboratory, and disappointingly at this time it is true to say that the presence of precipitins in bagasse workers is of no clinical significance.

TABLE 6

AGAR GEL STUDIES

Serum from:	Antigens						
	Coca Extract Bagasse		Farmer's Lung Hay Antigen	Aspergillus Niger	White	Yellow	Beige
	Moldy	Clean					
7 patients	7	4	5	7	0	0	0
17 unaffected personnel	17	5	7	16	—	—	—
7 control subjects	4	0	—	4	0	1	1
3 subjects with farmer's lung	Not done	—	3	—	0	2	1

TABLE 7

DOUBLE DIFFUSION GEL PRECIPITIN TESTS:
INHABITANTS OF DALLAS (U.S.A.), PUERTO RICO, JAMAICA, AND U.K.

Test Extract	Sera									
	Dallas, U.S.A.				Puerto Rico Bagassosis Patients		Jamaica Unaffected Bagasse Workers		U.K. Normal Unexposed Controls	
	Bagassosis Patients		Unaffected Bagasse Workers							
	No.[1]	%	No.	%	No.	%	No.	%	No.	%
Puerto Rican	4/7	57	4/6	67	NT	NT	5/17	29	30/50	60
Trinidadian	1/7	14	0/6	0	0/14	0	1/17	6	0/50	0
Dallas Mouldy	1/7	14	1/6	17	NT	NT	0/17	0	3/50	6
Dallas Clean	1/7	14	1/6	17	NT	NT	0/17	0	0/50	0
Jamaican (a)	NT	NT	NT	NT	2/14	14	1/17	6	0/50	0

[1]No. Number of positive reactions/number of sera tested
NT Not Tested

Hearn and Holford-Strevens

Salvaggio and co-workers in New Orleans have claimed more specific results with extracts of T. vulgaris harvested from mouldy bagasse, but once again controls also reacted, and the antigen gives negative results with sera of cases from Trinidad, and rather variable results against sera of our seven cases. (Personal communication, Dr. V. Holford-Strevens.)

Finally electron microscopy studies on lung biopsies from two of our cases allowed the observation of sequential changes of the Type 2 alveolar cell to a characteristic laminated epithelioid cell.

PIGEON BREEDER, BIRD FANCIER'S LUNG

A similar syndrome may result from the inhalation of bird dust and droppings, and is to be distinguished from asthma occurring in some atopic subjects, following exposure to birds. Birds incriminated to date include Parakeets (Budgerigars), Pigeons, Hens, and Turkeys. The antigen involved is of animal origin, and affected persons carry precipitating antibodies in their serum to extracts of either the bird feathers, droppings, sera, or egg white. The antigens from these sources are not identical, but there may be reactions of partial identity between similar extracts from different species of bird. Exposed, unaffected persons may show weak reactions.

In Bird Fancier's Lung, as opposed to Farmer's Lung, the following differences exist:

(1) The history of exposure is often much longer than usual, and may be many years.

(2) Constant contact with parakeets may lead to the development of insidious fibrosis and stiff lungs.

Footnote: Syndrome (syn - together, drom - running).

(3) Histologically there may be large numbers of foamy histiocytes.

Some workers have shown cross-reactivity between the sera from these various conditions and heterologous antigens.

TABLE 8

ANTIGENS

Serum	No.	M. Vulgaris	Mouldy Hay	C. Corticale	Pigeon Guano
B.W.L.	3	3/3	3/3	3/3	3/3
F.L.	2	—	2/2	2/2	2/2
Maple	1	—	—	1/1	—
Pigeon	4	2/4	2/4	4/4	4/4
Control	5	—	—	—	—

Barboriak, et al., Proc. Soc. Exp. Biol. Med., 1967, 125, 991.

Thus this 'fluttering amongst the dovecotes' is by no means entirely settled.

PITUITARY SNUFF LUNG

The use of a powdered preparation of either bovine or porcine posterior pituitary gland, taken as a snuff sniffed up the nose, enjoyed a certain vogue in the treatment of mild to moderate diabetes insipidus. It was effective, and avoided the need for daily injections of pitressin tannate. Now, with the advent of lysine-vasopressin, the use of such pituitary 'snuff' will come to an end.

However, of some interest are the reports of four patients who developed asthma and extrinsic allergic pneumonia following varying periods of such therapy. This implies a dual Type 1 and 3 reaction, confirmed by an immediate skin test response, and the

presence of circulating precipitating antibodies to the pituitary preparation used, bovine or porcine, with some cross-reactivity to the other preparation.

Of even greater interest was the demonstration in these patients' serum, of precipitating antibodies to homologous, human pituitary glands.

FINALE

These conditions, among the more common of the Extrinsic Allergic Pneumonias, illustrate the extent and potential of the lungs' response to a variety of antigens. Tables 2 and 3 list most of the associations capable of inducing such a syndrome, and the causative 'antigen' if it has been determined. The list is incomplete, and new sources are being documented annually. Therefore, when investigating any unusual lung disease, it is important to inquire carefully into all possible sources of allergens, at work, at home, and at leisure.

In conclusion, two other conditions should be mentioned briefly, to assure their distinction.

(1) Byssinosis:

Despite some evidence of serum antibodies to cotton extracts, it is more likely that the airway response is mediated by the chemically induced release of histamine.

(2) Broncho-Pulmonary Aspergillosis:
(Transient Pulmonary Infiltrates with Eosinophilia, and possible 'Mucoid Impaction'.)

This syndrome in Britain has been identified in mild (atopic) asthmatics as being due, usually, to a dual response of the airway to Aspergillus fumigatus, with a good response to steroids.

'Mucoid impaction', clinically very similar, may on occasions have a similar etiology, but in this country may also be related to other mechanisms, or other fungi.

TABLE 9

ASPERGILLOSIS

1. Mycetomata: No bronchial hypersensitivity. Serum precipitins present.

2. Asthma: Due to hypersensitivity to Aspergillus. No precipitins, immediate skin reaction of reaginic type.

3. Asthmatics with pulmonary infiltrates and eosinophilia:
   Show precipitins and immediate skin reaction.

   Asthmatics with precipitins:
   82% had infiltrates and eosinophilia.

   Asthmatics without precipitins:
   30% had infiltrates and eosinophilia.

4. Extrinsic Allergic Pneumonia:
   Massive challenge, i.e. Maltworker's Lung

EPILOGUE

'If seven maids with seven mops
  Swept it for half a year,
Do you suppose,' the Walrus said
  'That they could get it clear?'
'I doubt it,' said the Carpenter,
  And shed a bitter tear.

Carroll, L. 1832 - 1898.

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