12-1959

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Brenton M. Hamil
William R. Eyler
John W. Rebuck
Gerald A. LoGrippo

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BRONCHOPULMONARY MYCOSIS:
A 20 YEAR STUDY OF SIBLINGS

BRENTON M. HAMIL, M.D. *1,2

W. R. EYLER, M.D.,** J. W. REBUCK, M.D.,*** AND G. A. LOGRIPPO, M.D.***

Throughout a period of twenty years, records have been accumulated of the acute onset and progress of bronchopulmonary mycosis in four siblings and their mother, with recovery of all the children, supervision of a fatal accident to the mother and the subsequent death of a fifth sibling, possibly due to the presence of the disease.1 The five children had been under school health observation and were in good health prior to the onset of their illness. The sibling who died of what was diagnosed “atypical pneumonia with relapse” in another community at a later date was observed for only a short time following the onset of acute illness in the other four siblings and the mother. He lived in comparable environment, however, and no autopsy was done. The mother was observed for about one year and later was killed accidentally and autopsy was not possible. The four sibling children who were seen from the time of the acute onset of their illness were treated periodically in the hospital and through outpatient service over a period of four years. The treatment used which was considered to be the most effective in the accomplishment of healing was iodides which were used in large doses; potassium iodide by mouth, sodium iodide by vein and ethyl iodide by inhalation.

Both Candida albicans (Monilia Pinoyi) and Aspergillus niger were found repeatedly in all sputa and Candida albicans was grown from material taken from far down the main bronchus by bronchoscope in two patients and Aspergillus niger from the other two. The symptoms and lesions were similar in all and the cause was thought to be a mixed infection in all. Terminal treatment in three patients consisted of autogenous vaccine with Aspergillus niger — (Patient W.C.) and Candida albicans — (Patient P.C.) given in increasing dosage weekly for 50 weeks. This was begun in the third year of the illness, following cessation of Iodide therapy.

The source of the infection was determined likely to be the feathers in new feather beds which the patients slept between at the time of the acute onset of illness. These had been made from chicken feathers bought from a neighbor farmer who had killed his entire flock for market because of an illness which had plagued them. Other sources were possible in their environment but this seemed to be the most likely. Cultures of the fungi were obtained from samples of these feathers together with a variety of other fungi and yeasts. The four patients have been free of pulmonary or general symptoms since this time and have led normal, useful and productive lives. Periodic information has been obtained from all throughout a

Scientific exhibit prepared under the direction of Mr. T. Stebbins, Dept. of Medical Illustration and Mr. J. Kroll, Dept. of Photography, Henry Ford Hospital. Presented at the 108th Annual Meeting, American Medical Association, Atlantic City, June 8-12, 1959 and at the IX International Congress of Paediatrics, Montreal, Canada, July 18-25, 1959.

*Department of Pediatrics.
**Department of Radiology.
***Department of Laboratories.
Figure 1. Scientific Exhibit
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period of 20 years. Three of them have had periodic roentgenograms of the chest annually or more often during this time. There have been no significant illnesses, no symptoms referable to the lungs, all are married and three have two or more normal, healthy children. One patient developed a partial transverse myelitis during the latter part of treatment at which time an organism identified as Candida albicans was obtained from the spinal fluid. No other complication has occurred.

All four patients showed a cross-reaction to application of a variety of fungus antigens early in the subacute course of their illness. Their sera showed a moderately positive agglutination titre to the autogenous Candida albicans (P.C) and autogenous Aspergillus niger (W.C).

The patient who had the greatest extent of lung lesions and who developed partial transverse myelitis during the course of her treatment was ambulatory and had inadequate supervision of therapy for 2 years before satisfactory hospital controlled intensive treatment was started. This is in contrast to the treatment which was received by the three siblings whose controlled therapy began 2 months after the onset of illness. This patient did not have the course of autogenous vaccine desensitization because of the occurrence of her partial transverse myelitis near the termination of drug therapy. Her present hypersensitivity is marked.

SUMMARY OF COURSE

Representative Siblings with Variation of Clinical Management

Case: J.C. (F. age 15 years at onset of illness) — Severe "flu" type symptoms 1-20-38 to 2-20-38; fever, chills, general malaise, prostration; relapse March 7, 1938 with continued fever, malaise, sweating, cough with gruel-like, sweetish, blood-streaked sputum, substernal pain and much prostration. Hospitalized 3-23-38 for intensive treatment program. Three siblings and the mother similarly, but less severely ill, and a brother had no symptoms, and chest x-ray negative. He developed atypical pneumonia 20 months later and expired in a relapse in his local hospital, having had same exposure to fungi. Aspergillus niger cultured from the hyperemic friable bronchial mucosa of J.C. and sibling W.C. Candida albicans cultured from white plaques on the bronchial mucosa of P.C. and sibling A.C. These organisms, together with other fungi, were grown from samples of feathers taken from newly made feather beds which were slept between. Mantoux O.T. and P.P.D. continously negative. Early response result of early intensive treatment with iodides. Autogenous vaccine used for attempt at desensitization at end of iodide therapy in this patient and two siblings hospitalized early. 50 weekly injections in gradually increased dosages.

Case: P.C. (F. age 12 years at onset of illness). Onset of symptoms almost simultaneously with three siblings and mother (Jan.-Feb. 1938). Remained ambulatory under potassium iodide medication at home. First hospital adm. 5-10-40 for intensive therapy 28 months after onset. Course of illness more protracted than of siblings who were hospitalized early. Developed partial transverse myelitis, upper lumbar cord (6-14-41). Candida albicans was found in one Sp.F. culture. This fungus was cultured from white plaques in bronchi (1-4-41) [also from bronchi of one sibling (A.C.)] [Aspergillus niger cultured from friable hyperemic mucosa of bronchi of siblings J.C. and W.C.].
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Attempt at desensitization (6-20-41) with autogenous vaccines made from these organisms, consisting of 50 weekly injections in gradually increased dosages given to other three siblings, but not given to this patient. Mantoux O.T. and P.P.D. negative throughout observation for twelve years. Reaction to P.P.D. now positive. Delayed reaction to histoplasmin marked at this time. Protracted more severe course result of late intensive treatment with iodides. More antigen sensitivity possibly due to less heterologous neutralizing antibody because of no vaccine desensitization.

**DIAGNOSIS AND CLINICAL MANAGEMENT**

The following significant factors have been considered to be important in the diagnosis and treatment of these patients. Other drugs were used for short periods but intensive therapy with iodides was the most significant. The only untoward reaction from the massive doses of iodides was the occurrence of symptoms of hyperthyroidism in one patient which soon disappeared when the drug was temporarily stopped.

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1. History of onset.</td>
<td>1. Adequate and prolonged rest.</td>
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<tr>
<td>2. Initial cough.</td>
<td>2. Good diet high in protein and iron.</td>
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<tr>
<td>4. Scant sputa.</td>
<td>10% Sod. Iodide I.V. 100cc daily.</td>
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<td>Ethyl Iodide by inhalation 4cc. q. 2-3 days.</td>
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<td>5. Few or no auscultatory findings.</td>
<td>4. Expectorant as desired.</td>
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<tr>
<td>6. Roentgenographic appearance of lungs.</td>
<td>5. Periodic CBC and Sed. rate to detect exacerbation.</td>
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<tr>
<td>7. Negative tuberculin test.</td>
<td>6. Occupational therapy and other supportive measures.</td>
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<tr>
<td>10. C.F. Serology if suitable material is available.</td>
<td>9. Avoidance of reinfection.</td>
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<td>10. Vaccine therapy at termination of roentgen healing.</td>
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**IMMUNOLOGICAL RESPONSE TO FUNGUS ANTIGENS**

Cytology of Exudate After Application of Antigens

(Skin Window Technique)

In general the presence of antibody (hypersensitivity reaction) is reflected by the degree of lymphocyte response after application of the antigen to the scarified area. If there is little or no antibody present, as in the coccidioidin test, the exudative response for the first 12 hours is dominated by neutrophils, following which macrophages become the dominant type. In contrast, when there is a high degree of hypersensitivity or in other words a high titre of antibody present, the lymphocytes begin to predominate in the first 12 hours. This is shown in the cytological response for the two pathogens, Candida albicans and Aspergillus niger, and also to a less extent for the histoplasmin reaction. (Fig. 2-9)

*aAll pertinent data and information collected during the course of management of these patients are given in this reference.*
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Figure 2. P. C.: Aspergillus — 10 hours

Figure 3. P. C.: Candida albicans — 10 hours

Figure 4. P. C.: Coccidioidin — 10 hours

Figure 5. P. C.: Histoplasmin — 10 hours

Skin Windows

Figure 6. J. C.: Aspergillus — 10.5 hours

Figure 7. J. C.: Candida albicans — 10.5 hours

Figure 8. J. C.: Coccidioidin — 10.5 hours

Figure 9. J. C.: Histoplasmin — 10.5 hours
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INTRADERMAL HYPERSENSITIVITY
(Commercially Available Antigens)

20 YEARS AGO AT ONSET
Candida Albicans—Immediate reaction purpuric center with pseudopodia. (Pathogen)
Delayed reaction 24-48 hours.
Negative.

Aspergillus—Immediate reaction purpuric center with pseudopodia. (Pathogen)
Delayed reaction 24-48 hours.
Negative.

Coccidioidin—No reaction.
(not found on culture)
(Cross-reaction to various other fungi).

Histoplasmin—Immediate reaction negative.
(not found on culture)
Delayed reaction 24-48 hours.
3 cm with no squamous exfoliation.

PRESENT REACTION
Candida Albicans—Immediate reaction purpuric center with pseudopodia. (Pathogen)
Delayed reaction 24-48 hours extensive erythema with squamous exfoliation.

Aspergillus—Immediate reaction purpuric center with pseudopodia. (Pathogen)
Delayed reaction 24-48 hours extensive erythema with squamous exfoliation.

Coccidioidin—No reaction.
(not found on culture)

Histoplasmin—Immediate reaction negative.
(not found on culture)
Delayed reaction 2 cm. No squamous exfoliation.

CLINICAL INTERPRETATIONS
Histoplasma capsulatum was never cultured from any sputa or aspirated bronchial secretions. Intradermal positive hypersensitivity to Histoplasmin (delayed type reaction) was present early in the disease and is still present to a less degree after 20 years.

Candida albicans and Aspergillus niger were cultured repeatedly from bronchial aspirations. The marked immediate intradermal reactions to antigens of these fungi has changed over the 20 years to show extreme hypersensitivity in an extensive erythematous, exfoliative delayed reaction to these fungus antigens showing that they are unquestionably the pathogens for this disease.

The positive Histoplasmin reaction is significant only of its ubiquitous profusion in nature.5

Serologic results are unreliable with any presently available commercial fungus antigens except Histoplasmin, because of anticomplement materials which they contain. Complement fixation titres increase after intradermal reaction to the antigens and
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therefore true results can be obtained only before intradermal tests are applied. (Fig. 12,13)

![Figure 12. P. C.: Complement fixation titre](image1)

![Figure 13. J. C.: Complement fixation titre](image2)

The tuberculin (Mantoux) reaction with O.T. and P.P.D. has remained negative in one patient throughout the 20 years of observation. That of the other patient whose disease became more advanced before intensive treatment was initiated has converted in recent years without evidence of a demonstrable tuberculosis lesion. Her contacts with tuberculosis patients have been more intimate because of the need of hospital orthopedic care for management of her transverse myelitis.

Adequate iodide therapy, Sat. Sol. K.I. 5cc. to 20cc. daily, 10% Sol. Sod. iodide I.V., 100cc. daily, Ethyl iodide by inhalation 4cc. q. 2-3 days is the proven treatment of choice for a broncho-pulmonary mycosis of this severity. Antibiotic preparations have not proven effective in conditions of this extent.

Cytology of the exudate after application of antigens by the skin window technique and its proper interpretation according to the cellular type response may serve to indicate the significance of pathogen-antigens in the absence of suitable material for dependable serologic testing. 3,4

REONTGENOGRAPHIC INTERPRETATION

Roentgenograms show "soft" parenchymal densities from the apices to the bases of the lungs in the acute phase of the disease with progressive changes in healing by condensation into sharply defined nodules. There is progressive calcification of the nodules with a continued stable appearance to the present. The delay in starting controlled intensive treatment for sibling P.C. seems to have permitted progress of the lesions for 2 years. (Figures 14-29)

DISCUSSION

It is believed that the patients were hypersensitive to histoplasmin at the time they became ill because of the prevalence of such hypersensitivity in the general area where they were raised.* Their initial illness is thought to have been "La Grippe" which was epidemic in the community at the time. This illness altered the condition

*Whitehouse et al° report a skin testing program conducted among school children in the general area where the patients reported here were raised. Chest films were negative in 75% of histoplasmin positive and tuberculin negative school children. There were 9073 children tested and 90% of them had acquired a positive histoplasmin skin reaction by the age of 14 years. This high incidence helps to clarify the findings of a delayed-type hypersensitivity to histoplasmin in these patients.
Figure 14. P. C.: 5-28-38. Multiple patches of pneumonitis up to 8 mm. in size are diffusely distributed through the lungs. Lymph nodes are enlarged in the roots and mediastinum.

Figure 15. P. C.: 8-27-38. No change. (No intensive therapy)

Figure 16. P. C.: 7-16-40. Lesions have increased in size and number; some are more sharply defined. (Intensive therapy has been underway only 2 months.)

Figure 17. P. C.: 2-25-42. All lesions have decreased in size — upper lobe lesions are starting to calcify.
Figure 18. P. C.: 9-10-43. Both parenchymal lesions and nodes have decreased in size. Upper lobe lesions are 50% calcified, but lower lesions are not.

Figure 19. P. C.: 4-26-47. Calcification and resolution progress. Paratracheal nodes are still enlarged.

Figure 20. P. C.: 6-23-49. Lower lobe lesions show central calcification.

Figure 21. P. C.: 11-26-58. High voltage films: the lesions are all calcified and stable. Minimal node enlargement persists.
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Figure 22. J. C.: 4-6-38. Diffuse, uniform distribution of 2-15 mm. patches of density with "soft" borders. Nodes in the mediastinum and lung roots are enlarged.

Figure 23. J. C.: 3-25-39. Lymph nodes remain enlarged, but parenchymal lesions have become smaller and more sharply defined.

Figure 24. J. C.: 8-15-40. Parenchymal lesions have further decreased in size and are beginning to show central calcification. Lymph nodes are smaller except for one right paratracheal node which has enlarged considerably.

Figure 25. J. C.: 4-30-41. Further decrease in size — more central calcification. Nodes are smaller, but still apparent in the lung roots. Large paratracheal node is unchanged.
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Figure 26. J. C.: 6-6-42. The lesions are at least 50% calcified. The nodes have regressed except the large paratracheal node.

Figure 27. J. C.: 2-26-44. Lesions are almost entirely calcified.

Figure 28. J. C.: 4-23-49. Lesions are completely calcified and stable. Single paratracheal node persists.

Figure 29. J. C.: 11-26-58. High voltage technique film; Lesions are unchanged.
of the bronchial mucosa sufficiently to the acid state to permit the feather-born fungi capable of pathogenicity for humans to grow in the lung tissues where they were seeded. This may have been more easily facilitated by their possible histoplasma hypersensitivity. Delayed-type hypersensitivity to the pathogen-antigens developed during the effective treatment with adequate doses of iodides. The progress of its development was a slow process, and some immediate-type reaction is still present although the delayed type reaction to the pathogen-antigens is marked.* This and the lymphocytic cytologic response to the application of these antigens in the skin windows gives support to the opinions expressed by Pappenheimer et al and supported by Good et al that the delayed-type hypersensitivity reaction of tuberculin-type is dependent upon a two-stage process. The response for immediate phagocytosis is demonstrated in the skin window cytologic reaction for the other antigens used in these tests. The importance of the lymphocytic response to the pathogen-antigens is as hypothesized by Braunsteiner et al if qualified according to work by Eisen et al. Rebuck et al showed by the "skin-window" technique that lymphocytes may migrate into inflamed areas, hypertrophy and form larger mononuclear cells and even giant cells. Braunsteiner et al confirmed this and found in addition that these derivatives of lymphocytes may then transfer delayed allergy in a highly specific way. Thus a close functional unity beyond morphologic features seems established. Five patients who had recovered from ulceroglandular tularemia and who showed marked skin sensitivity of delayed-type to Tularin had "skin-windows" applied. After 30-40 hours the coverslips showed an almost exclusive mononuclear round-cell, epithelioid cell and occasional giant cell in the accumulated exudate. This was scraped and washed off the coverslips with saline and 10-20 million cells from pooled subjects were injected subcutaneously into tularin-negative recipients. The recipients after this injection showed delayed-type hypersensitivity to tularin. The hypothesis derived from these results is stated as follows:

"Certain substances penetrate the organism, specific antagonistic substances are formed in the lymphatic system and fixed on circulating lymphocytes. The chemical nature of these substances is not as yet clear, but there is a fundamental difference from circulating antibodies. Circulating lymphocytes then reach inflamed areas and become mononuclear, epithelioid or even giant cells and help to build up a granulation tissue which contains extremely high amounts of specific antagonistic substances. Thus infection may be localized. Lymphocytic granulomatous reactions of this type seem to play a major role in a variety of chronic infectious diseases, such as tuberculosis, brucellosis, tularemia and others, but intervene probably in all bacterial, fungal and also viral infections.

"Cellular defense mechanisms may, therefore, include three independent, but coordinated systems: immediate non-specific phagocytosis by granulocytes and later by monocytes, cell-bound antagonistic substances carried by lymphocytes and derivated cells, and circulating antibodies elaborated by plasma cells."

*Martin explains the occurrence of a negative delayed-type skin response in a patient with severe Candidiasis and also a negative complement fixation test although an immediate-type wheal reaction occurred from the intracutaneous injection of hyperimmune anti-C. albicans serum. He suggests the interpretation that the inhibition of hypersensitivity may be due to an excess of soluble antigen in the tissues.
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This hypothesis is further clarified if one enlightens it with the results of work by Eisen et al, Pappenheimer et al and Good et al and other observations previously referred to in this paper.

Rebuck and LoGrippo found that subjects inoculated with inactivated poliomyelitis virus antigens (Types I, II and III) responded to the “window” application with an exudate heavily laden with lymphocytes. Non-vaccinated subjects with a low neutralizing antibody titer produced an exudate which contained very few lymphocytes. The lymphocyte response could be correlated with the neutralizing antibody titer in those tested. In unvaccinated persons the exudative response to 0.02 ml of poliomyelitis virus-inactivated vaccine (prototype III) was dominated by neutrophiles for the first 12 hours and then macrophages became the dominant cell type. At no time up to 24 hours were there more than a few lymphocytes. In contrast a polio III vaccinated individual with 1:256 neutralizing antibody titer, showed a large number of lymphocytes about 9 hours after “window” application of the vaccine. The lymphocytes began to hypertrophy at 12 hours but continued to dominate the cytological picture until the 24th hour.

Eisen et al attempted to clarify some of the confusion that exists in the explanation of the significance of a delayed-type hypersensitivity response. He explains that this reaction does not seem to be dependent upon serum antibody but upon antibody substances associated with cells. Pappenheimer and associates assume that antigen is retained by cells to “alter specifically gamma globulin synthesis.”

Iodides meet the criteria which have been emphasized as requirements for fungicidal or fungistatic agents. They must so alter through changes in metabolic and physiologic requirements for growth and reproduction of the cellular components of the fungus that it becomes non-pathogenic; but in doing so must not be toxic or cause damage to the tissue cells of the host. These requirements seem to have been met in these patients. The disease has been arrested and they show no evidence of toxic ill effects from the treatment.

REFERENCES


