Cave Sickness
A New Disease Entity?

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DURING the past year we had the opportunity to investigate in Arkansas an outbreak of a peculiar pulmonary disease, mention of which appears only once to our knowledge in medical literature. Cain [1] and his coworkers published a report on just such an episode which occurred in the neighboring state of Oklahoma in 1943. Later a personal communication noted another similar instance happening in Mexico.[2]

In none of the investigations including our own, was an etiologic diagnosis established. We have dubbed the condition "cave sickness" because of the feature common to all three outbreaks and have concluded that this is a new or at least inadequately described disease entity.

Our study was conducted on 21 white male patients who represented the greater part of the 25 persons engaged in a treasure hunt in an old abandoned chalk mine in southwestern Arkansas. Excavation was started September 12, 1947. At intervals beginning with the 4th and ending with the 13th day of operations, all of those who had spent any time in the cave became ill in varying degrees of severity. Data in Table 1 give the ages, incubation periods, calculated from patient's first visit to the cave to date of onset, length of exposure, which could not be defined in terms of hours and minutes, and type of disease.

Only individuals who had entered the diggings were involved in the outbreak. Among them the disease took the form of a febrile illness with pulmonary manifestations. Onset was sudden after a short prodrome of coryza and malaise followed by chills and fever.

The rest of the symptom complex was composed of headache, in some cases with retro-orbital pain, nuchal tension, nervous irritability, slight cough, chest pain, weight loss, and certain general complaints.

There was a dearth of physical findings. Aside from increase in temperature and pulse, all signs were confined to the chest where sonorous inspiratory and expiratory rales were heard early in the illness. These later became moist and sticky and disappeared after coughing.

Clinical laboratory studies were not revealing. Chest radiographs were spectacular and in keeping with the prostration of the patients. The report on these is as follows [3]:

"The striking features of all the films evincing marked pulmonary involvement are the uniform distribution of the lesions from top to bottom, their consistent size and shape, the lack of any tendency to confluence, the absence of any pleural reaction, and the freedom from involvement of both the bronchopulmonary and tracheobronchial lymph nodes. It is my opinion that this process was pro-

TABLE 1

Patients According to Age, Incubation Period in Days, Type of Exposure, and Severity of Disease

Patient	*Age*	*Incubation period*	*Length of exposure*	*Type of disease*
H. M.	11	8	short	mild
L. A.	16	?	short	mild
R. F.	16	6	short	mild
J. W. G.	15	6	moderate	mild
J. H.	19	9	short	moderate
H. H.	13	5	short	moderate
C. D.	15	7	short	moderate
H. G.	13	7	short	moderate
R. M.	16	6	short	moderate
R. B.	16	6	prolonged	moderate
R. C.	16	7	moderate	moderate
D. N.	16	7	moderate	moderate
R. C.	13	7	short	moderate
E. H.	18	8	moderate	moderate
O. B.	55	10	moderate	moderate
W. M.	32	13	prolonged	severe
C. B.	36	7	prolonged	severe
M. M.	23	4	prolonged	severe
D. G.	16	11	moderate	severe
K. M.	17	8	prolonged	severe
M. B.	18	7	moderate	severe

duced by a particulate entity which was spread almost entirely by hematogenous dissemination and which occurred in a single shower."

All patients received sulfamerazine and penicillin in therapeutic amounts without noticeable response. The disease was apparently self-limited to 6 or 7 days at which time the men were able to leave their beds although they complained of weakness and a residual dyspnea. These last persist to this writing (February 26, 1948).

The patients suffered in three degrees of severity. We present the record of a patient with the severe type of affection. The moderate and mild cases had lower temperatures and less marked prostration. Length of morbidity and extent of disability in convalescence did not vary in the three classifications.

M. M., 23 year old white planter. This patient worked prolonged periods in the cave. On the 4th day after beginning work there he noted a mild coryza with "stuffed-up" head, dry throat, and feeling of slight malaise. Late in the evening he had a shaking chill during which time his temperature reached 105° F. This was followed by profuse sweating. His temperature remained between 103° F. and 105° F. for 72 hours, despite treatment with oral penicillin, 100,000 units every 3 hours, and a sulfamerazine mixture containing 1 gm. of sulfamerazine and 1 gm. of potassium citrate per teaspoon. Resolution of his fever was by crisis, but for 4 days thereafter the patient had a daily afternoon elevation up to 103° F., accompanied by a shaking chill and followed by sweating.

At the onset the patient complained of severe headaches, retro-orbital pains, and a definite nuchal tension, and exhibited a marked nervous irritability characterized by dramatic response to stimuli. However, on the 4th day of his illness he became lethargic and lapsed into what was described as a semicomatose state lasting about 48 hours, from which he recovered spontaneously.

He also complained of anorexia and slight nausea, and lost 24 pounds during his illness. His illness was self-limited to 7 days, after which time he was able to leave his bed. His appetite improved and his general feeling of malaise disappeared, but during convalescence he was bothered by a definite fatiguability and shortness of breath. Also among his

residuals were numbness and paresthesia along the course of the ulnar nerves in both hands. His past history had been entirely negative except that he had contracted dengue fever while serving on Tinian Island during World War II.

Physical examination revealed a temperature of 103° F., rapid pulse and respirations and very few other positive findings. These were entirely confined to his chest with wheezing inspiratory and expiratory rales early in his illness, which later changed to moist, fine inspiratory rales disappearing after coughing. Laboratory studies revealed 4,190,000 RBC, 8,400 WBC with a normal differential. Widal was positive in 1:80 dilution (patient had typhoid vaccine while in military service). Negative agglutinations for tularemia and Q fever were obtained. His sera failed to protect against the viruses of the psittacosis-lymphopathia group, Saint Louis and western equine encephalitis, and were negative for cold hemagglutinins.[4] Complement-fixation for Histoplasma capsulata was four plus in dilution of 1:2 and one plus in dilution of 1:4 on two successive examinations at a 6 week interval. Coccidioides studies revealed the same results.[5] Peripheral blood examinations for the spirochetes of relapsing fever and the parasites of malaria and toxoplasmosis were negative.[6]

His urine was normal. Respiratory capacity was 3.8 liters. Sputum and throat cultures on blood agar and Saboraud's media revealed a normal flora. Direct smears of this material for tubercle bacilli, eosinophiles or other cellular elements were negative.[6] Spinal fluid was not obtained.

Skin tests with coccidioidin in dilutions of 1:1,000 and 1:100 were negative as were those with histoplasmin at 1:100 and 1:10. Intradermal O. T. in a dilution of 1:1,000 was positive. The report of the radiologist [3] on this patient is as follows:

"Three serial postero-anterior films on this individual have been reviewed. The first is not dated but is presumed to have been taken the latter part of September. The second film was made October 8, 1947, and the third was made November 29, 1947. The first film presents a picture almost identical with an acute miliary tuberculosis. The lung fields are uniformly studded from apex to base with minute, discrete infiltrations measuring 2 mm. in diameter. These shadows suggest that the process is of an exudative nature. There appears to be no tendency for confluence of the lesions, and special attention is called to their individual nature. The lesions appear to occur at the bifurcations of the linear chest markings. There is no apparent pleural reaction and there is no involvement of the bronchopulmonary or tracheobronchial lymph nodes. There is a Ghon tubercle in the left costophrenic angle but this is thought to be unrelated to the present pathological process. The diaphragmatic shadows are regular in contour and sharp in outline. The heart is of apparent normal size and contour, and no bony abnormalities are noted.

"Diagnosis: An acute miliary pneumonitis, apparently of hematogenous dissemination but of unknown etiology.

"The subsequent films show an even clearing of the lung fields by absorption, so that the film of November 29, 1947, is practically normal. There is certainly, however, no evidence of replacement fibrosis in the sites of the individual lesions, nor is there any apparent attempt at calcium deposition. There is insufficient evidence on the film of November 29, 1947, to explain the residual dyspnea complained of by the patient."

The chief symptoms of which the patients complained are tabulated (Table 2).

TABLE 2

Symptoms, with Number and Percentage of Patients Exhibiting Each

Symptom	*Number of patients*	*Per cent of patients*
Fever	20	95
Headache	20	95
Coryza	19	94.7
Cough	17	81
Chill	14	67
Sputum	13	62
Nausea	13	62
Sweating	10	47
Vomiting	9	43
Chest pain	8	38
Nuchal tension	8	38
Nervous irritability	6	30
Retro-orbital pain	3	14
Coma	1	5
Neurological disturbance	1	5

In the severe cases the initial temperature reached 103° F. to 105° F. It persisted at a relatively high level for 48 to 72 hours, and dropped by crisis to normal or nearly normal. Subsequent daily afternoon elevations to 101° F. to 103° F. for 3 or 4 days occurred. In the moderate to mild cases the fever was of a lower degree and less typical in its course.

Headache was the presenting complaint in nearly all patients seen. This headache was severe, generalized, and persistent. Temporary relief was obtained from patent remedies and codeine. Several patients developed a post-orbital pain in association.

Coryza with a "stuffed-up" head, dry throat, and occasional rhinorrhea was a very common prodromal sign. Two patients complained that their palates felt "corrugated." None admitted or mentioned sore throats.

The cough was of a hacking type, productive of very little sputum. At the time they were seen only 2 patients were producing enough sputum for examination.

About half the patients had a definite rigor, the others merely a chilly sensation. In those who had the true shaking chills, sweating followed, soaking bed clothing and linens. In all cases the first chill followed within 12 hours of onset of their malaise.

In 7 patients the chest pain was of a sharp constricting type noticeable on deep inspiration at a point under the lower part of the sternum. Another patient stated that his was a sharp, stabbing, pleuritic pain over the left lower anterior ribs which forced him to breathe shallowly for the 3 to 4 days it lasted.

The complaint referrable to the patients' necks was not definite pain or rigidity, but what they described as a tense feeling which did not prevent but rather discouraged movement of the neck and turning of the head.

The nervous irritability was characterized by striking response to the stimulation of noise, touch, and shaking of the bed by involuntary movements of their extremities. One patient became irrational and lethargic and remained semicomatose for about 48 hours. This same patient complained of numbness and paresthesia of both hands along the distribution of the ulnar nerve. This numbness was not confirmed neurologically.

Malaise was complained of generally as was anorexia. Nausea and vomiting followed medication with sulfa and oral penicillin in some patients. No urinary or bowel disturbances occurred.

DIFFERENTIAL DIAGNOSIS

Our differential diagnosis in this outbreak was an extensive one. It ran the gamut of disease entities from the usually suspected to the more exotic and bizarre (Table 3).

TABLE 3

Differential Diagnoses Considered

I. Inhalation of Irritants
   - A. Gases
   - B. Dusts—Pneumonoconioses

II. Pulmonary Infections
   - A. Bacterial
     1. Lobar pneumonia, pneumococcal
     2. Tularemia pneumonia
     3. Bronchopneumonia
     4. Interstitial pneumonia, acute
     5. Bronchiolitis, acute
     6. Acute disseminated hematogenous tuberculosis
   - B. Viral
     1. Primary atypical pneumonia
     2. Influenza
     3. Psittacosis (ornithosis)
   - C. Rickettsial—Q fever
   - D. Fungal
     1. Coccidiodomycosis
     2. Histoplasmosis
     3. Bronchopulmonary moniliasis
   - E. Protozoal—toxoplasmosis

III. Malaria

IV. Dengue fever

V. Relapsing fever

It was the belief of the people of the town that gas inhalation was the basis of the victims' difficulties. Some of the radiologists who viewed the plates felt that the picture could conceivably fit such a diagnosis. Analysis of samples of air from the cave, which consisted of a series of small rooms connected by small apertures, failed to reveal any noxious gases or organic irritants.[7] Two guinea pigs left in the cave for a prolonged period remained perfectly well. We also scouted the possibility of the condition arising from the inhalation of an irritant dust of the material from the cave substance. The rock in the cave analyzed as typical limestone[7] (Table 4).

TABLE 4

Analysis of Rock from Cave

Component	*Per cent*
Magnesium	0.23
Loss on Ignition	38.46
Calcium	60.40
Aluminum and Iron Oxide	0.04
Total Silicates	0.09
	99.22

The content of silicates was less than 0.1 per cent. No arsenic, zinc, beryllium, or other heavy metals were present. We did not examine for the presence of radioactivity.

Among the bacterial infections, lobar pneumonia of the pneumococcal type and tularemic pneumonia were fairly well eliminated by negative bacteriology, agglutination tests, and x-ray picture.

The radiographic picture was regarded by some as consistent with a diagnosis of a bronchopneumonia, an interstitial pneumonia, or an acute bronchiolitis. We were not able to establish a bacterial agent as a cause of any of these. It was suggested that an organism which we do not usually consider pathogenic was at fault. We found a distinct inconsistency in the flora of the sputa and throats of the patients so that it was not possible to implicate any inhabitants. The blood cultures done were negative.

The diagnosis of acute lymphohematogenous tuberculosis has been readily dismissed in spite of the roentgenograms by the conduct of the disease. No acid-fast organisms were obtained from the sputa by direct smear or culture. Only 3 patients had positive tuberculin tests.

Primary atypical pneumonia, influenza, and psittacosis (ornithosis) were considered. The first did not fulfil the x-ray picture of our cases. Studies for cold hemagglutinins were negative. The absence of cross-infection seemed to militate against the diagnosis of influenza as did the peculiar restriction of the disease to the cave workers. No psittacine or columbidian birds were found in or about the cave to indicate the possibility of ornithosis. Protection tests against ornithosis-lymphopathia virus were negative.

Q fever was likewise considered. None of the patients had skin lesions and they all denied having ticks on their clothes or bodies. No ticks were found in or around the cave although undoubtedly there were some on the cattle in the vicinity. Agglutinations were negative.

With the coöperation of many persons and agencies, we were able to do fungus studies. Sputum and throat swabs grown on Saboraud's medium were negative. Repeated skin tests with histoplasmin and coccidioidin down to dilutions of 1:10 and 1:100 respectively were also negative. No material was available for skin testing against Candida albicans.

Complement-fixation for coccidioidomycosis and histoplasmosis was no more revealing than the above case.

Peripheral blood studies for malaria and toxoplasma parasites were negative. No spirochetes of relapsing fever were found in blood or urine. We were unable to obtain complement-fixation for this disease.

No rash was present and other clinical features of this outbreak did not fit the pattern of dengue fever. We were unable to obtain serum protection tests. No *Aedes aegypti* mosquitoes were found although culicines and anophelines were present.

It is evident from the foregoing that we were unable to establish an etiological diagnosis in this outbreak. Our work-up was extensive and we have persisted in following these patients with serial x-ray films. Radiographs have gradually cleared. As previously stated, in all instances the patients still complain of dyspnea on exertion and marked fatiguability. All have, however, returned to their work and studies.

SUMMARY AND CONCLUSIONS

We present here a report of 21 cases of a febrile illness with pulmonary manifestations and a peculiar x-ray film. An extensive differential diagnosis was considered without a definite etiology being established after extremely careful comprehensive study. Reference is made to the only other known outbreak of a similar nature which is recorded in the literature. We conclude from this that we have investigated a new or, at least, a previously inadequately described disease entity.

REFERENCES

1. Cain, James C., Col. M.C., A.U.S., Bevins, Ed. J., Maj. M.C., A.U.S., Downing, John E., Lt. Col. M.C., A.U.S. An Unusual Pulmonary Disease. *Arch. Int. Med.*, 79:626 (June), 1947.

2. Amberson, J. Burns, M.D., Chief of Chest Service, Bellevue Hospital, New York City, A Personal Communication.

3. Curtis, A. C., M.D., Director, Division of Tuberculosis Control, Arkansas State Board of Health.

4. Virus Branch, Laboratory Division, Communicable Disease Center, U. S. Public Health Service.

5. Smith, C. E., M.D., Consultant, Epidemiological Survey, Army Epidemiological Board, Stanford University School of Medicine.

6. State Hygienic Laboratory, Arkansas State Board of Health.

7. Division of Industrial Hygiene, Arkansas State Board of Health.