An Epidemic of Inhalation Anthrax, the First in the Twentieth Century*

I. Clinical Features

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DURING a ten-week period in 1957, five cases of inhalation anthrax occurred among the employees of an industrial plant in Manchester, New Hampshire, in association with four cases of cutaneous anthrax. Four of the five patients with inhalation anthrax died, one recovered.

During the nineteenth century inhalation anthrax, popularly called "wool-sorters' disease," occurred frequently in workers handling animal hairs, wools or hides, and approximately 200 cases were reported before 1900 [*1–3*]. In the Bradford district of England, for example, where the animal hair industry was concentrated, Spear [*1*] reported twenty-three cases of the disease occurring between November 1879 and September 1880. Since 1900, however, only twenty-one sporadic cases and no epidemics have been reported in the world literature [*4*], a fact which some have attributed to better ventilation of factories [*5*].

In view of the unusual opportunity to study this disease afforded by the epidemic, an effort was made to collect the clinical data retrospectively. Epidemiologic studies are reported in another paper [*6*]. The presently described outbreak demonstrates that inhalation anthrax may still be a hazard to workers handling goat hair, and that the disease still is a fulminating one most often terminating fatally.

CASE REPORTS

The greater part of this information was obtained from hospital records and from interviews with the physicians and families of the patients. The summaries of the autopsies are derived from a report by Albrink, Brooks, Biron and Kopel [*7*]; we are most grateful to them for permission to use their data.

Strains of Bacillus anthracis recovered from the patients were examined for macroscopic appearance after eighteen hours' growth on 5 per cent human blood agar plates incubated at 37°c.; for microscopic appearance of a gram-stained preparation; for lysis by B. anthracis gamma bacteriophage [*8*]; and for pathogenicity in white mice. The strains recovered appeared from these tests to be typical of B. anthracis.

Inhalation Anthrax

Patient T. T. (No. 1),† a sixty year old white man, had worked at the mill since 1941, most recently as a noil remover in the combing department. He was in good health, except for an asymptomatic non-toxic nodular goiter present for twenty-five years.

On Tuesday morning, August 27, 1957, backache and headache developed, and the patient left his job at noon. That afternoon the family physician visited him at home and found an oral temperature of 102°F., pulse 100, and blood pressure 110/70 mm. Hg. A few rhonchi were noted on auscultation of the chest. The diagnostic impression was influenza, for which aspirin and codeine tablets were prescribed.

† The numbers in parentheses at the head of each case report correspond to the chronologic order of the onsets of illness, given in Table 1, and serve to identify the cases in the discussion of their epidemiology [*6*].

* From the New Hampshire State Department of Health and the Communicable Disease Center, Public Health Service, Atlanta, Georgia, U. S. Department of Health, Education, and Welfare. This work was supported by a contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Maryland.

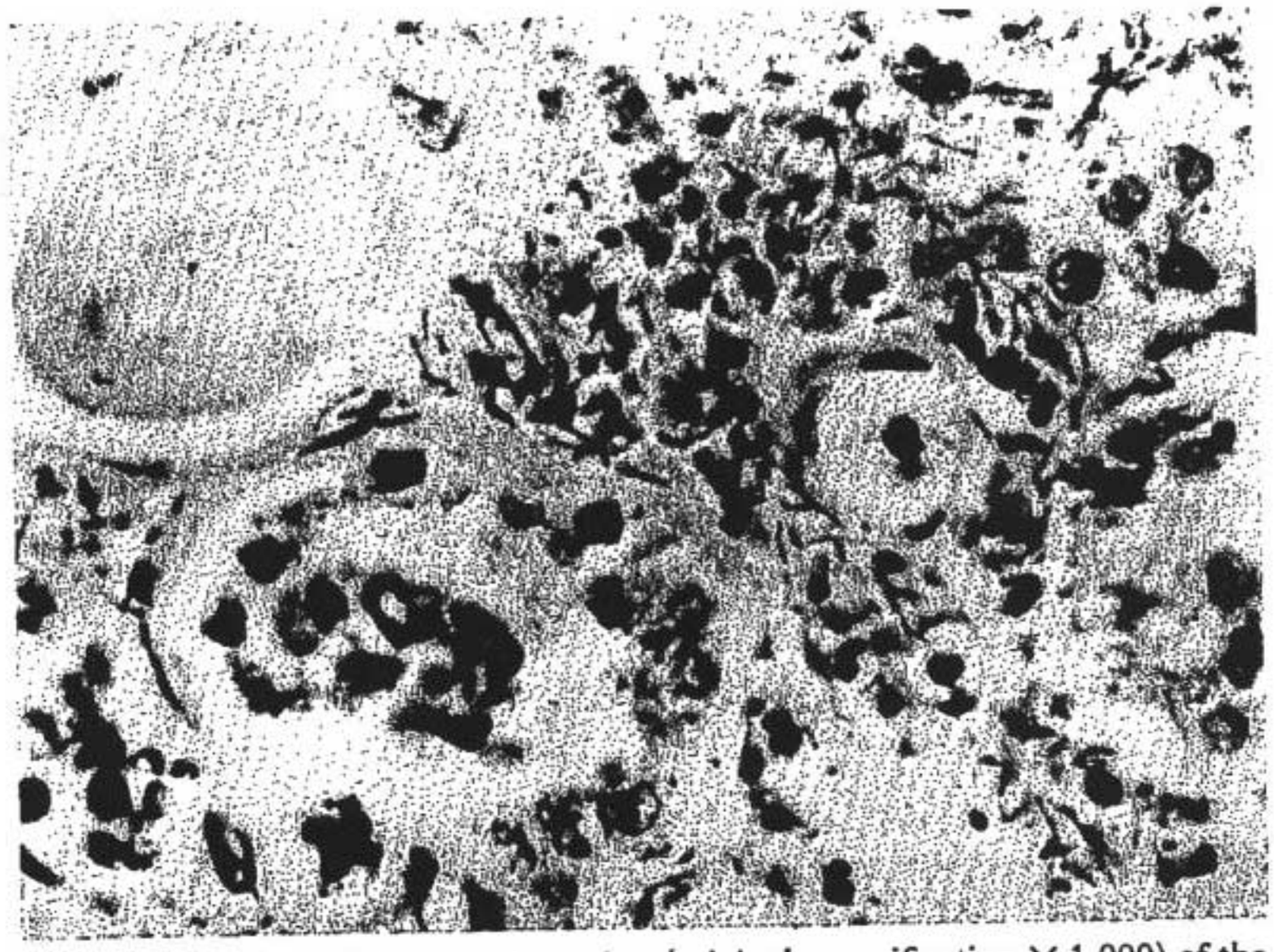

FIG. 1. Patient T. T. Microscopic section (original magnification × 1,000) of the thyroid gland showing many anthrax bacilli in the hemorrhagic interstitial tissue. (Courtesy of Dr. W. Albrink.)

On August 28 the patient's oral temperature was 100°F., and except for a persistent cough he was improved. However, he stayed home from work and on the following day, August 29, his neck suddenly became considerably swollen in the area of the goiter. During the day the swelling did not appear to discomfort the patient, who ate normally and was ambulatory. In the evening, however, the patient's condition suddenly worsened. The swelling spread from his neck to his chest. Perspiration was so profuse that five changes of bed clothing were required. The physician was summoned again at 11:00 P.M. and on noting that the patient was afebrile with an irregular pulse and cold, clammy, tremulous hands, administered 5 drops of Lugol's iodine solution. During the next four hours the patient fainted twice. He was admitted to the Elliot Hospital at 4:45 A.M., August 30. During positioning for an emergency x-ray film of the chest such severe respiratory stridor developed that the film could not be made and tracheostomy was considered. After being placed in an oxygen tent, the patient was less dyspneic. His temperature was 102°F., blood pressure 100/60 mm. Hg, apical pulse 92, and respirations 24. On auscultation of the chest moist basilar rales were heard bilaterally. Digitalis and Demerol® were given, and his breathing improved further. However, at 6:00 A.M. he refused a bedpan and walked to the lavatory, where he suddenly became extremely cyanotic, collapsed, and died.

At autopsy the entire mediastinum was occupied by a hemorrhagic edema infiltrating all soft tissues. Scattered throughout this edematous mass were enlarged, hemorrhagic lymph nodes. The parenchyma of the lungs showed a slight increase in consistency which was due to congestion and edema rather than pneumonitis. The trachea was deviated to the right by the swollen lymph nodes and by the left lobe of the thyroid gland, which was enlarged by extensive hemorrhage. Bilateral pleural effusion and splenomegaly were present. The cerebrospinal fluid was clear and colorless.

Gram-positive bacilli were seen in sections of mediastinal lymph nodes, thyroid (Fig. 1) and spleen, and cultures yielded pure growth of B. anthracis.

Patient A. L. (No. 8), a thirty-three year old white man, began working at the mill on August 26, 1957, as a noil remover in the combing department. In his medical history were two hospital admissions: the first for anxiety state with gastric somatization; the second (December 1955) for early hepatic cirrhosis.

The present illness began on October 30, with chills, fever, cough, malaise and generalized muscular aches. He stayed at his job through October 31, but that evening he remained at home and was seen by his physician. Physical examination revealed a temperature of 104°F., slight rhinorrhea, and a non-productive cough. The posterior pharynx was moderately reddened, and occasional wheezes were heard on auscultation of the chest. Profuse sweating was the most striking physical finding.

The physician diagnosed Asian influenza and left the patient 8 to 10 tablets (200,000 units) of oral penicillin. It is uncertain how many tablets were actually taken.

On November 2, the patient appeared improved; his throat was only slightly sore, and he perspired less. That night he slept well, but the following day a sud-

den change took place. Marked diaphoresis recurred, and he had difficulty swallowing saliva. He complained of tightness in the chest, and regurgitation followed attempts to take liquids. The family physician arrived at 1:00 P.M. and found the patient lying motionless in bed, oriented but uncooperative, with his jaws clamped tightly. Dyspnea was not observed, but rhonchi were heard bilaterally over the upper lobes. At 2:00 P.M. the patient became agitated, began to rub his legs, and complained of inability to breathe. Dyspnea increased and cyanosis became evident.

The admitting physician at the Manchester Veterans' Administration Hospital found the patient to be *in extremis:* delirious, extremely dyspneic, cyanotic and exhibiting marked diaphoresis. On auscultation of the chest many moist rales and wheezes were heard. The possibility of a laryngeal obstruction was considered and a clear airway was seen on direct laryngoscopy; the mucosa was red and injected, but no edema was noted. Morphine, atropine, oxygen, aminophylline, lanatoside C and norepinephrine were administered, and 150 cc. of blood were removed by venesection, all without effect. The patient died at 3:30 P.M.

At autopsy the mediastinum, the mediastinal lymph nodes and the lungs were infiltrated by hemorrhage and edema, and there was bilateral pleural effusion. Several areas of necrosis, hemorrhage and edema were noted in the ileum, but the mesenteric lymph nodes were not enlarged. The brain was covered by a diffuse hemorrhagic leptomeningitis. Microscopically, many gram-positive bacilli were seen in the lungs, meninges, liver, kidney and spleen, and B. anthracis was cultured from the lung, brain and heart's blood. Staphylococcus aureus (phage type 6/47/53/54/77/VA4) and non-hemolytic streptococci were also found in the lung and blood cultures.

Patient A. J. (No. 2), a forty-nine year old white man, had worked at the mill as a card-fixer since June 1956. He had no history of serious illness. In early August 1957 a dry cough developed which he attributed to an increase in the amount of dust in the carding room.

On September 1, 1957, the patient's cough worsened and he became febrile. During the next few days he complained of discomfort in his chest and of anorexia, but continued to work. After attending church on the morning of September 5, he returned home apparently well, but shortly thereafter he was found lying in bed mumbling unintelligibly. His oral temperature was 103°F. A physician was called, who diagnosed a severe cold, possibly bronchitis. An intramuscular injection of 800,000 units of aqueous procaine penicillin and 1 gm. of dihydrostreptomycin was given. At 4:00 P.M. his wife was unable to awaken the patient. At 6:00 P.M. he had a temperature of 104°F. and was incontinent of feces. The patient was unconscious on admission to St. Joseph's Hospital in Nashua, New Hampshire, with a temperature o 105°F., rapid and shallow respirations, and rale audible over both lungs. A lumbar puncture revealed bloody cerebrospinal fluid; a diagnosis of cerebra hemorrhage was made on that basis. At midnight or September 5, another injection of 800,000 units o penicillin and 1 gm. of dihydrostreptomycin wa given. He died at 6:00 A.M. on September 6 withou regaining consciousness.

At autopsy a diffuse hemorrhagic leptomeningiti with an exudate containing large numbers of polymorphonuclear leukocytes and gram-positive bacilli, morphologically resembling B. anthracis, was found. No culture was made from the brain, but on staining the bacilli reacted strongly with fluorescent antibody prepared against capsular substance of known B. anthracis organisms [*10*]. There were small foci of soft consolidation about the hila of both lungs, which microscopically revealed congestion, edema and some hemorrhage into the alveoli and the walls of the bronchioles. The mediastinal lymph nodes were edematous, and there was a left-sided pleural effusion.

Patient E. C. (No. 3), a sixty-five year old white woman, had been employed at the mill since 1946 as a bobbin cleaner in the weaving department. Aside from an asymptomatic non-toxic nodular goiter the past medical history was negative.

She complained of malaise on September 2, 1957. On the following day she was fatigued but went to work, and on September 4 a mild pain in the chest and a cough developed. She visited the company dispensary on September 5 where an oral temperature of 99°F., a pulse of 92 and a respiratory rate of 24 were noted. The next day she complained of upper abdominal pain for which she consulted her family physician; his impression was possible cholecystitis.

On admission to the Elliot Hospital in Manchester the patient's oral temperature was 95.6°F., pulse 100, respiratory rate 24 and blood pressure 110/90 mm. Hg. The white blood cell count was 16,400 per cu. mm., with a differential of 76 per cent neutrophils, 11 per cent band forms, 9 per cent lymphocytes and 4 per cent monocytes.

On the following morning, while in the radiology department for a cholecystogram, the patient became acutely ill with marked dyspnea and stridor. She was seen by a medical consultant who noted a thready pulse, a frequent, tight, brassy cough without production of sputum, marked stridor (like a child with the croup), and profuse diaphoresis. She was afebrile and had a blood pressure of 90/0 mm. Hg. There was dullness to percussion over the base of the left lung; coarse basilar rales were heard bilaterally. No distention of jugular veins or edema of the ankles was noted. An electrocardiogram showed small QRS complexes and T wave inversion without alteration of the S-T segments.

A portable x-ray film of the chest showed medias-

FIG. 2. Patient E. C. Roentgenogram taken approximately twenty-two hours before death. Mediastinal enlargement, bilateral pleural effusion and perihilar streaking extending to the periphery are seen.

tinal enlargement and perihilar streaking extending to the periphery of the lungs. (Fig. 2.) The base of the lungs were obscured by pleural effusion, and interlobar effusion was present in the fissure of the middle lobe of the right lung. The cholecystogram taken previously did not demonstrate an abnormality.

A diagnosis of cardiac failure with superimposed pneumonia was made. Administration of digitalis, diuretics and bronchodilators was begun at 3:00 P.M. on September 7, but the patient became progressively more dyspneic and perspired profusely; the blood pressure remained at 90/0 mm. Hg. At midnight her pulse was weak and thready, with a rate of 142; her respiratory rate was 32. One hundred milligrams of cortisone and 400,000 units of aqueous procaine penicillin were given intramuscularly and the same dose of penicillin was repeated at 8:00 A.M. on September 8. After twelve hours of marked dyspnea and cyanosis despite continuous oxygen therapy, the patient died at 10:40 A.M. Permission for a postmortem examination was refused.

Patient L. L. (No. 4), a forty-six year old white man, had been employed at the mill since October 1955 as a card tender. His previous medical history was non-contributory.

The patient felt a slight malaise on September 9, 1957. Three days later, September 12, there was a sudden onset of fever (103°F.), chills, cough, dyspnea and profuse diaphoresis. He was seen at home by one of the authors (M. U.), who gave him an injection of

FIG. 3. Patient L. L. Roentgenogram taken on the fourth day of illness. Consolidation of lower lobe of right lung is evident.

400,000 units of aqueous procaine penicillin and recommended immediate hospitalization.

On admission to the Sacred Heart Hospital in Manchester, he was an acutely ill, slightly cyanotic and dyspneic man who coughed frequently and appeared to be confused. His pulse was 108, respirations 32 and blood pressure 120/80 mm. Hg. His conjunctivas were slightly reddened and his pharynx had a single small ulceration in the left tonsillar area. The tongue was heavily coated. There was dullness to percussion over the base of the right lung and moist expiratory rales were heard over the same area. The hemoglobin was normal, the white blood cell count was 9,900 per cu. mm., with 60 per cent neutrophils, 24 per cent band forms and 16 per cent lymphocytes.

Urinalysis was negative except for 8 to 10 white blood cells per high power field of centrifuged sediment. A sputum specimen cultured shortly after admission yielded a non-hemolytic, coagulase-negative Staph. albus. Subsequent blood cultures were negative. A roentgenogram of the chest taken on September 12 showed a patchy consolidation involving the posterior and middle division of the lower lobe of the right lung. (Fig. 3.)

A combination of 800,000 units of procaine penicillin and 1 gm. of dihydrostreptomycin was administered intramuscularly at 4:00 P.M. and was repeated every twelve hours thereafter. During the evening the patient continued to cough and appeared extremely apprehensive. It was necessary to change his bed linen frequently, due to excessive diaphoresis. A second sputum specimen obtained on September 13, subsequent to two inoculations of penicillin and dihydrostreptomycin, yielded a pure culture of non-hemolytic, coagulase-negative Staph. aureus.

The patient's temperature on September 14 was 101°F.; on September 15 he was afebrile, and by

September 19 he felt almost well. However, roentgenographic examination showed no resolution of the consolidation in the right lung. A repeat white blood cell count September 23 was 15,600 per cu. mm. with 69 per cent polymorphonuclear leukocytes, 10 per cent bands, 17 per cent lymphocytes and 4 per cent monocytes.

A roentgenogram taken on October 1 revealed a moderate amount of pleural fluid in the right thorax without resolution of the consolidation. A thoracentesis was performed and 300 ml. of sterile blood-tinged fluid were removed.

A second thoracentesis on October 4 yielded a small amount of frankly bloody fluid. Papanicolou-stained preparations of both fluids were negative, and Wright-stained preparations showed numerous red blood cells with occasional lymphocytes and polymorphonuclear leukocytes but no bacteria. From the second pleural fluid "Bacillus subtilis" was recovered. The identification was based on a gram stain of the nutrient broth culture. Since the technician believed the organism a contaminant, the slide and culture were discarded without additional identification.

Another roentgenogram taken on October 5 showed early resolution of the consolidation. Bronchoscopy revealed only diffusely hyperemic bronchial mucosa. A second strength PPD skin test was negative.

Roentgenographic examination on October 25 demonstrated more clearing of the opacity in the lower lobe of the right lung. By January 11, 1958, there was only slight x-ray evidence of residual disease in the lower lobe of the right lung. The patient has remained asymptomatic since his discharge and has returned to work.

Serologic studies were performed on serums obtained twenty-seven and sixty-four days after the onset of illness (earlier specimens were not available). A complement fixation test against a crude filtrate of a culture of B. anthracis showed a titer of 1/30 in the first serum and 1/60 in the second. Control serums have not given titers over 1/15 [*9*].

A precipitin test using the agar double diffusion technic [*10*] showed titers of 1/8 in both serums against purified protective antigen from anthrax culture filtrates [*11*]. Titers of 1/8 have been found also in persons immunized by protective antigen: demonstrable titers have not been found in unimmunized persons and those not exposed to anthrax organisms [*12*]. By chance, a serum* obtained from this patient in 1953 was available, which gave no titer against anthrax antigen.

Finally, the patient's serum prevented anticapsular fluorescent labeled antibody from reacting with anthrax organisms: the inhibition titer was 1/80 in the first serum and 1/40 in the second. Seven control serums were negative [*13*].

* Kindly provided by Dr. E. S. Murray, Harvard School of Public Health.

Cutaneous Anthrax

Patient H. T. (No. 6), a thirty-five year old white man, had been employed at the mill since 1950 as a card feeder. On October 10, 1957, the patient noticed a pimple on his forehead, unassociated with pain or pruritus. Oxytetracycline ointment was applied to the lesion by the mill nurse. On the following day a ring of erythema surrounded the dark center of the lesion; the patient was afebrile but complained of headache. The company physician diagnosed cutaneous anthrax, and prescribed tetracycline (250 mg. every six hours). A culture taken on this day was negative for B. anthracis. On October 14 a black eschar 1 cm. in diameter with slightly raised edges was noted within the lesion. Granulation tissue slowly filled in the anthrax lesion and the patient made an uneventful recovery.

Patient R. P. (No. 7), a fifty year old white woman, had worked as a weaver at the mill since January 1956 and had always been in good health. On October 15, 1957, she noted a pimple on her right wrist which itched and burned but was painless. By October 17 the pimple appeared to contain pus. The patient was seen at the company dispensary October 18, where a diagnosis of cutaneous anthrax was made. Benzathine penicillin (1,200,000 units), oral penicillin and local oxytetracycline ointment were prescribed. A culture of the lesion was positive for B. anthracis. By October 23 the lesion was approximately 1 cm. in diameter, with a tan-red central area surrounded by a slightly elevated, pink ring of vesicular tissue. Subsequently the patient made an uneventful recovery and lost no working days due to the illness.

Patient V. K. (No. 5), a sixty-four year old white woman, had been employed at the mill since 1950 as a weaver and had always been in good health. On October 8, 1957, the patient noticed a small pimple on the first phalanx of the fifth finger of the right hand. The lesion was pruritic but not painful. The pimple gradually became larger and by October 14 the entire finger was swollen. On that day a clinical diagnosis of cutaneous anthrax was made at the company dispensary. A culture of the lesion yielded B. anthracis. Antibiotic therapy was instituted in the form of 1,200,000 units of benzathine penicillin administered intramuscularly and local oxytetracycline ointment. Despite treatment the patient's hand was red and swollen on October 15. Within several days, however, the finger and hand returned to normal size and the eschar slowly disappeared.

Patient C. S. (No. 9), a healthy sixty-one year old man, had worked at the mill since August 16, 1957, most recently as a card tender. On November 5 the patient noted a small pimple on his chest approximately 2 inches below the sternal notch. He did not

report to the company dispensary until November 11, at which time a 2 by 1 cm. black eschar with surrounding erythema was noted. The culture obtained on this date was negative for B. anthracis. The patient received 1,200,000 units of benzathine penicillin and local oxytetracycline ointment, and made an uneventful recovery.

COMMENTS

Two patients (T. T. and A. L.) had bacteriologically and pathologically proved inhalation anthrax. In the third patient (A. J.), bacteria were found in histologic sections which morphologically and antigenically resembled B. anthracis. The negative postmortem blood culture in this patient may have been the result of antibiotic treatment which had been given before death.

The evidence for the diagnosis of inhalation anthrax in patient E. C. is clinical and epidemiologic. The course of her illness and the roentgenographic appearance of her thorax were consistent with the disease. Epidemiologically, the fact that the fatal illness occurred at the same time and was accompanied by the same symptoms as proved cases of the disease bolsters the diagnosis of inhalation anthrax.

The case of patient L. L. is of unusual interest because of the rarity of recovery from inhalation anthrax [*14,15*]. His clinical course was similar to those of the proved cases, with one notable difference: apparent localization of disease to one lobe of the lung rather than diffuse involvement. The increase in parenchymal infiltration shown on x-ray examination concomitant with complete amelioration of symptoms is reminiscent of the cutaneous anthrax lesion, which progresses in its typical evolution despite sterilization by antibiotics.

The possible significance of the recovery of "B. subtilis" from the pleural fluid of this patient need hardly be pointed out. Failure to isolate anthrax bacilli from the blood or sputum of the patient would weigh against the diagnosis but for the fact that the cultures were taken after penicillin had been given. The staphylococci which were recovered from the blood and sputum cultures were coagulase-negative. It is possible that these organisms were secondary invaders in an anthrax infection (see patient A. L.).

The time and place of infection constitute epidemiologic evidence for the diagnosis of inhalation anthrax inasmuch as the patient worked in the card-comb room, as did most of the epidemic patients.

Complement fixation, agar precipitin and indirect fluorescent antibody tests all showed the presence of antibodies to B. anthracis in convalescent serums. At least two separate antigens were involved: the anthrax protective antigen in the complement fixation and agar precipitin tests, and the capsular antigen in the fluorescent antibody inhibition test. Recent serologic studies [*12*] indicate that antibodies detectable by the agar diffusion precipitin inhibition test are found in a significant percentage of persons who are in continual contact with anthrax spores, but who give no history of illness. Although previous inapparent infection may explain the presence of anthrax antibodies in the serum of patient L. L., the occurrence of a pulmonary illness justifies the tentative conclusion that this was a case of inhalation anthrax.

The symptoms, signs and course of the four cases of cutaneous anthrax were typical of the disease [*16,17*]. All the patients incurred their lesions on exposed body surfaces. Antibiotic treatment, although it sterilized the lesions, did not alter the progression to eschar formation.

Symptoms and Signs of Inhalation Anthrax. A characteristic clinical picture of inhalation anthrax can be derived from the literature [*1–5*]. The course of disease is typically in two stages, as seen in Figure 4. The initial stage is marked by the insidious onset of a mild fever, malaise, fatigue, myalgia, non-productive cough, and frequently a sensation of precordial oppression. There are few objective findings aside from fever. Rhonchi may be heard on auscultation of the lungs. This initial stage typically lasts for several days. Slight improvement in the clinical condition of the patient may be seen towards the end of the first stage.

The second stage of the disease develops suddenly with acute dyspnea and subsequent cyanosis. The patient appears moribund, with accelerated pulse and respiration. The body temperature, although usually elevated to 102°F. or more, may be subnormal because of shock. Stridor occurs commonly, perhaps as a result of partial extrinsic obstruction of the trachea by enlarged mediastinal nodes. Profuse diaphoresis is a frequent sign, and subcutaneous edema of the chest and neck may be present. On examination of the chest, moist crepitant rales and signs of pleural effusion are observed. Although the spleen is usually enlarged at autopsy, clinical

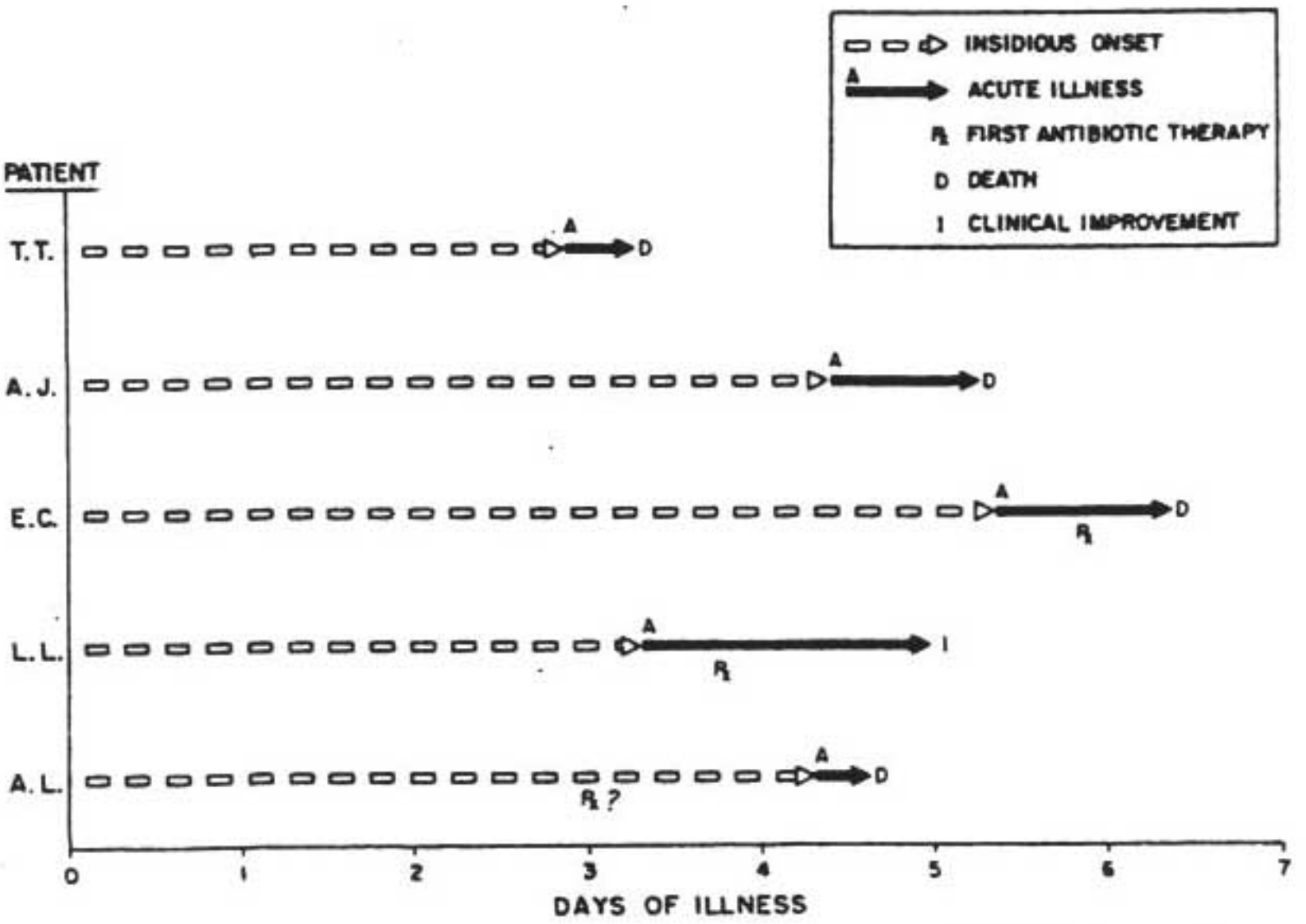

FIG. 4. Diagrammatic representation of the two stages of inhalation anthrax exemplified by the Manchester patients: insidious onset (– – →) and acute toxemia (A →). The occurrence of first antibiotic treatment (Rx), death (D) or improvement (I) are shown in temporal relationship to these stages.

reports rarely mention its palpability. Consciousness typically is maintained until death, but should meningeal involvement occur, there will be disorientation, coma and meningismus. Trismus is a characteristic sign of anthrax meningitis [*18*].

The average duration of the acute stage is less than twenty-four hours, at the end of which death usually occurs. It is interesting that inhalation anthrax also causes sudden death in such diverse species as the cow [*19*], the guinea pig [*20*] and the chimpanzee [*21*].

The identity of the clinical courses of the Manchester patients with the typical one cited is indicated in Table I.

TABLE I
CLINICAL CHARACTERISTICS OF CASES OF INHALATION ANTHRAX

Characteristic	Patient				
	T. T.	A. L.	A. J.	E. C.	L. L.
Stage of insidious onset:					
Duration (days)	3	4	4	5	3
Fever	+	++	+	0(?)	+
Malaise	++	++	+	++	++
Cough	+	+	+	+	+
Precordial oppression	0	+	+	+	0
Stage of acute toxicity:					
Duration (hr.)	10	7	18	25	*
Dyspnea	++	++	+	++	++
Fever	+	+	++	+	++
Stridor	++	++	0	++	0
Diaphoresis	+	++	0	+	++
Pleural effusion	++	+	+	+	+
Disorientation	0	++	++	0	+
Trismus	0	+	0	0	0

NOTE: + = Characteristic present.
++ = Characteristic present in severe form.
0 = Characteristic absent.
* Patient recovered gradually.

Pathogenesis. The pathogenesis of inhalation anthrax in animals has been studied extensively in recent years. Ross [*22*] has shown that the spores of B. anthracis are ingested as inert particles by macrophages in the alveoli. The spore-bearing macrophages migrate through the alveolar membrane into the lymphatics, and are carried to the hilar lymph nodes. According to Barnes [*23*], only 0.1 per cent of the spores of a virulent strain reach the nodes of guinea pigs in a viable state. Here germination of the spore may take place, followed by multiplication of the vegetative form. Multiplication of the bacillus is accompanied by hemorrhage and edema of the lymph nodes and surrounding mediastinal connective tissue. Inhalation anthrax is not primarily a pneumonic disease; parenchymatous infiltration of the lungs if present is usually the result of secondary infection by other bacteria. The pleural effusion which occurs is caused perhaps by lymphatic obstruction [*3,24*].

Eventually, bacilli gain access to the blood stream via the lymphatics [*25*] with a resulting septicemia and subsequent involvement of the meninges, spleen and intestines. The lepto-

meninges are frequently diffusely hemorrhagic, and contain neutrophils and anthrax bacilli. The spleen as a rule is enlarged and teeming with organisms. Necrotic ulcerations in the small intestine are sometimes found as a result of bacterial multiplication in the lymphoid tissue of the intestinal wall. The work of Smith, Keppie and associates [*20,26,27*] has shown that in guinea pigs death from anthrax is caused by the release into the blood plasma of a specific toxin. Once a sufficient level of toxin has been attained, death almost invariably follows, despite sterilization of the animal by antibiotics. In guinea pigs the toxin produces shock due to the loss of blood volume from internal hemorrhage and from edema of the thoracic structures. The bacterial capsule, composed of glutamyl polypeptide, participates in the course of the infection by acting as an antiphagocytic substance [*28*].

The pathologic findings in the three autopsied Manchester cases are summarized in Table II. No common pathologically demonstrable entities have been discovered which increase the susceptibility of persons to inhalation anthrax. Two of the Manchester patients had nontoxic nodular goiters and one had early hepatic cirrhosis, but no single disease was common to all the patients aside from anthrax.

Diagnosis. The premortem diagnosis of inhalation anthrax is difficult. The first stage is often mistaken for influenza or bronchitis, and the second stage resembles cardiac failure or cerebrovascular accident. Viewed as a whole, however, the clinical course is characteristic of the disease. The diagnosis should be strongly considered in a person who has had recent contact with infected materials, and who suddenly becomes severely dyspneic or comatose following several days of mild febrile illness. All goat hair, wool or hides imported from the Middle or Far East should be presumed to contain the anthrax bacillus, a presumption which is at least 50 per cent correct [*29*]. Laboratory workers in contact with the organism also are at risk.

B. anthracis has been cultured from the blood, cerebrospinal fluid and sputum of patients with inhalation anthrax before death [*14,18,30,31*]. In view of the characteristic appearance of the anthrax bacillus, gram-stained smears of blood, sputum and cerebrospinal fluid should be prepared [*17,30,32*]. Demonstration of mediastinal widening by roentgenography is highly suggestive of inhalation anthrax, in the presence of other signs and a history of exposure.

TABLE II
PATHOLOGIC FINDINGS IN AUTOPSY CASES

Pathologic Characteristic	Patient		
	T. T.	A. L.	A. J.
Edema of chest wall	++	+	0
Hemorrhagic mediastinitis	++	++	0
Mediastinal lymphadenitis	++	++	+
Pleural effusion	++	+	+
Intestinal lesions	0	+	0
Mesenteric lymphadenitis	0	0	0
Splenomegaly	++	0	+
Hemorrhagic meningitis	0	++	++
B. anthracis cultured from tissues	Yes	Yes	No
Gram-positive bacilli seen in tissues	Yes	Yes	Yes

NOTE: 0 = Characteristic not present.
+ = Characteristic present.
++ = Characteristic present in severe form.

It should be noted, however, that several cases have occurred in which no contact with materials containing anthrax spores was discovered [*33,34*]. These patients are thought to have been infected by stray spores from nearby plants handling animal hairs or hides. Infection by contagion has not been reported in human inhalation anthrax [*1*].

Prognosis and Treatment. During the nineteenth century in the textile mills of England, 20 per cent of patients with inhalation anthrax were said to recover spontaneously [*1*]. Only two of the approximately nineteen recovered cases which have been reported in detail, however, had cultural evidence for the diagnosis [*14,15*]. Asymptomatic B. anthracis bacteremia has been observed in chimpanzees [*21*], and in the light of serologic evidence suggesting that inapparent or mild forms of anthrax occur in man [*12*], spontaneous recovery may not be as unlikely as the dearth of case reports would suggest. The recovery of patient L. L. thus may have been unrelated to treatment, particularly in view of the fact that two of the other patients (A. J. and E. C.) also received parenteral antibiotics. On the other hand, the development of meningitis in one, and the delay in beginning antibacterial treatment of the other patient may account for the failure of antibiotics in these cases.

In any event, the use of antibiotics seems clearly indicated in other suspected cases of inhalation anthrax. In workers exposed to anthrax spores, lower respiratory or influenzal illnesses should be suspected of being the first stage of anthrax infection. Although appropriate cultures should be taken first, antibiotic treatment should be given without waiting for the results. This precaution seems justified by the severity of the disease, and by experiments in which eradication of B. anthracis infections in guinea pigs did not prevent a fatal outcome once the stage of toxemia and severe symptoms had developed [*27*].

On the basis of limited numbers of animal experiments, penicillin can be expected to cure inhalation anthrax if given before the onset of toxemia [*23,35*]. It is of interest to note that Keppie et al. [*20*] reported inability to stop anthrax bacteremia in guinea pigs by means of tetracyclines or chloramphenicol, in contrast to success with streptomycin (penicillin was too toxic for the guinea pig). Although the anthrax organism is sensitive *in vitro* to all common antibiotics except polymyxin B [*17,36*], until more complete *in vivo* studies are reported, penicillin or penicillin and streptomycin are the drugs of choice because of their bactericidal properties. Only moderate doses of antibiotics presumably are necessary, since the organism is sensitive *in vitro* to 0.03 units per ml. of penicillin and 1.25 μg. per ml. of streptomycin [*36*].

Anthrax hyperimmune serum made in horses was used with apparent success before the advent of antibiotics in the treatment of systemic anthrax secondary to cutaneous lesions [*37*]. In view of the importance of toxemia to the outcome of the experimental disease, the use of antitoxin seems logically indicated in human inhalation anthrax. Unfortunately, antiserum is no longer available commercially in the United States.

During the severe stage of the disease, measures for the support of any patient in shock should be undertaken.

SUMMARY

Five cases of inhalation anthrax and four cases of cutaneous anthrax are presented. Three inhalation and two cutaneous cases were proved by culture or microscopic demonstration of the anthrax bacillus, and the others were clinically consistent with the diagnosis. These cases constituted an epidemic, for they all occurred within a ten-week period at a goat hair processing mill.

The illnesses of the patients with inhalation anthrax began insidiously with mild fever, fatigue and malaise lasting several days. This mild initial phase was terminated by the sudden development of dyspnea, cyanosis and, in two cases, disorientation and coma. Four patients died within twenty-five hours of the onset of severe symptoms.

The principal lesions found by pathologic examination of three patients were hemorrhagic mediastinitis and lymphadenitis, pleural effusion, acute splenitis and, in two cases, hemorrhagic meningitis.

The pathogenesis, symptoms, diagnosis and treatment of inhalation anthrax are discussed.

Physicians should consider this disease when faced with an acute febrile illness in a person occupationally exposed to anthrax spores.

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