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INHALATION ANTHRAX, by E. Fraenkel

One of those acute infectious diseases that every year cost the lives of a small number of persons in pre-war Hamburg, I mean anthrax, has almost completely disappeared during the last two war years and the following three peacetime years. This is explained by the circumstance that cessation of trade between Hamburg and certain extra-European countries, due to the war, closed the sources leading to infection with anthrax. These consist of dried animal hides imported from those countries, including some from anthracic animals. The transport of these hides from the ship to the warehouse leads to infection of persons engaged in this work. The overwhelming majority of the resultant casualties involves external anthrax. However, the dust raised in the storage spaces when the hides are dropped leads to occasional cases of inhalation anthrax (IA) that characterizes so-called rag or wool sorter's disease.

The curve in Fig. 1 gives a good perspective on cases subjected to section because of anthrax in the Eppendorf Hospital. Their grouping by decades is particularly instructive, revealing a great increase in fatal cases of anthrax from decade to decade. In the first decade following the opening of Eppendorf Hospital (1889 to 1898), only 6 cases of anthrax were submitted for autopsy. There were 13 in the second decade (1899-1908) and 20 in six years (1909 to the beginning of the war in 1914). A steep downward curve follows. Three more persons died of anthrax in the two years following 1914, whereas no fatalities were registered during the next five, from 1917 to 1921. The year 1922 brings two, as does 1923. This coincides with the resumption of trade with those countries that again sent dried animal hides to Hamburg.

It is not my intention to impart to the reader my knowledge of human anthrax gained from a large material at Eppendorf Hospital and to discuss its clinical, etiological and pathologic-anatomical relations. I intend to limit myself to certain observations of inhalation anthrax, specifically one case involving the bronchi which, to my knowledge, has not been published heretofore. Generally speaking, we are fairly well informed about the changes taking place in the air passages in inhalation anthrax, especially through Paltauf and Eppinger's studies of so-called rag disease. Thus Paltauf, in 1888 (The Etiology of Rag Disease, Wien. klin. Wochenschr, No. 18 and following) refers to a report by Kundrat and mentions that most cases reveal prominent necrotic lesions in the trachea and the large bronchi, ranging in size from a pinhead to a lentil, the surrounding mucous membrane showing dark erythema and hemorrhagic permeation. Although I have no experience with cases of fatal rag disease, I know of inhalation anthrax of different etiology which frequently reveals lesions somewhat characteristic of anthrax in the mucosa of the trachea, i.e. in the area of bifurcation, which sometimes continue into one or both bronchi.

At this time I shall give a brief description of such a case (Specimen Catalogue No. 2255, Section 30/1906) (Fig. 2). At the point of bifurcation, and only there (the remaining tracheal mucosa being completely unaffected), the mucous membrane shows a strong, dirty erythema on the anterior and right wall of the left bronchus and the dorsal wall of the right bronchus, with fine granulation resembling the surface of a raspberry; in addition, the dorsal wall of the right bronchus is permeated with punctate extravasates.

A slightly different appearance was presented by the trachea of a case seen in 1922 (Section 393/1922). There the mucosa above the bifurcation and in the left bronchus, to a lesser extent in the right bronchus, showed intense erythema tending slightly toward a blue coloration. At about the fifth cartilaginous ring of this bronchus, almost exactly in the center, there is a 3 mm wide, 1½ mm high, whitish eschar. The mucous membrane of the right wall, just below the bifurcation, has a spot of velvety coarseness one-half the size of a small fingernail.

If in such cases the peculiar location and the strictly focal character of the lesions with its hemorrhagic or hemorrhagic-necrotic inflammation leads the expert to suspect an anthrax infection, it is soon confirmed by concomitant hemorrhagic inflammation of lymph nodes in the mediastinum, in the bifurcation and in the hilus of one or both lungs, as well as by usually present at times, quite massive serous or serous-hemorrhagic exudates in the pleural spaces. The lungs are not necessarily involved in such cases, and this is one of the reasons why the condition should be called inhalation anthrax and not pulmonary anthrax. To this finding, typical of IA, permitting the diagnosis of anthrax by itself, is naturally added the demonstration of pathogens by means of a simple streak preparation from the hemorrhagic lymph nodes. Oddly enough the best-known textbooks of bacteriology and the pertinent manual of infectious diseases by Jochmann do not mention the occurrence of such foci in the trachea and bronchi. With a reference to Eppinger, Jochmann states on p. 908 that pulmonary anthrax frequently manifests itself "already on the nasal mucosa in the form of hemorrhagic infiltrates and pustular forms", and that "the laryngeal mucosa shows similar lesions in addition to being intensely erythematous". Sobernheim differentiates IA (Kolle-Wassermann, Vol. III, p. 651) by the appearance of remarkable changes in the region of the entire respiratory tract which, starting with sanguineous-spotty infiltration of the nasal mucosa, lead in the form of edematous swelling and bleeding via the larynx and trachea into the lungs. The description does not indicate whether the author was thinking of a continued affection of the air passage mucosa from the nose down, or whether he favors intermittent attachment of the pathogen found in every case of IA. In my opinion neither is correct, since the findings are quite irregular and present a wholly different appearance at times, as I shall demonstrate later. Friedberger and Pfeiffer's Textbook of Microbiology, 1919 (p. 423) fails to list any of the anatomical changes demonstrable in IA. The authors limit themselves to the remark that "pulmonary anthrax is nearly always a fatal disease that is caused by the inhalation of anthracic material, is known as rag disease and is observed among rag sorters and wool workers". Finally, I should like to refer to Graber, Rubner and Ficker's Manual of Hygiene (1913, p. 146-47) which also ignores the anatomical changes of the respiratory apparatus in "pulmonary anthrax", as it is called by the authors. In order to mention a pathologist who excells in the field of bacteriology, reference is made also to F. von Baumgarten who devotes a short passage to IA in his Manual of Pathogenic Microorganisms (p. 866), without, however, treating the anatomical findings in the respiratory organs. He merely reiterates Eppinger's viewpoint, whose studies of rag disease led him to conclude that the spore-containing material is brought by the air stream directly into the alveoli where bacterial growth causes inflammatory processes in the lungs and secondary infection of the blood. Baumgartner categorically rejects this concept of Eppinger, since it lacks experimental support. He does not exclude the possibility that "the

portal of entry is located in the mucosa of the upper air passages and that the anthracic affection of the lungs has a hematogenic origin". One can readily agree with the first part of Baumgarten's opinion, and the findings listed by me in this paper as well as the indicated description of Sobernheim should be understood in this sense. The situation is different with respect to the second part of Baumgarten's hypothesis, which I should like to contrast with another, more likely theory according to which the anthrax bacillus settles in the upper air passages - preferably in the area of bifurcation, particularly at the tip and the neighboring regions of both bronchi (*) - from where it reaches the lungs by aspiration and leads, possibly without involving the latter, to those characteristic, severe, hemorrhagic inflammations of the regional lymph nodes. If animal tests have been unable so far to duplicate these symptoms in the air passages of animals, this only proves, in my opinion, that the test conditions have been incorrect. Future research should uncover these. Among human beings, the findings in those cases where the focal involvement of the trachea resembles that described by me are so unequivocal that another concept seems very unlikely. I should like to support my hypothesis with a case published by Risel in Vol. 42 of the Zeitscher, F. H. (p. 381), also involving IA whose genesis was traced to a portal of entry "in the left main bronchus, about 2 cm below the bifurcation, in the form of a hemp-seed-sized, dark red spot". Risel presents a precise description of the focus, considered by him to be a "small, undeveloped anthrax pustule" and explains by means of an illustration (Fig. 1 on Plate 5) that the Tun. propr. in the region of the missing epithelial layer is covered by a continuous cover consisting of dense aggregates of anthrax bacilli. With respect to the entry of bacilli into the lungs, Risel assumes (l. c. page 392) that "their invasion has proceeded along the same path as established by Eppinger and Paltauf in earlier cases of human pulmonary anthrax (rag disease) and confirmed by later investigations, namely via the lymphatics". I cannot agree with Risel's concept on the basis of his detailed histological descriptions and Fig. I and II included in his work, the last of which also dipicts a small bronchus filled with dense, leukocytic exudate and containing bacilli; I maintain that the pathogens had reached a number of small bronchi by aspiration from the primary focus in the left bronchus (rightly considered as the portal of entry), had been aspirated further into the alveoli and had traveled from there via the lymphatics into the intestinal tissue and the regional lymph nodes. This assumption is strengthened also by the histological findings in the tracheobronchial focus already described (Catalogue No. 2255). The invasion of pathogens (Fig. 3) between the cells of the partially still unimpaired, multi-layer epithelium and their subsequent penetration into the Strat. prop. of the mucous membrane, densely packed with leukocytes, was established. Elsewhere the epithelium was missing (Fig. 4). The mucous membrane seems to have eroded here, and its area on the surface is infiltrated by leukocytes and numerous bacilli (Fig. 5). Is it too far-fetched to assume that free bacilli reach the deeper air passages with the air stream and may lead simultaneously to the characteristic, hemorrhagic lesions in the pulmonary parenchyma and, by dissemination via the lymphatics, to infection of the regional, mediastinal, peritracheal and hilar lymph nodes? When this filter is overcome, they may flood the fluid mass and cause metastases, including

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* Oddly enough, Eppinger does not mention such localization in his monograph on rag disease.

metastases to the brain. If they remain limited to the respiratory tract, the possibility of a gastro-intestinal infection is given by swallowing of bronchial secretion reaching the pharynx through expectoration.

On the other hand, simultaneous intrusion of infectious material into the air and digestive passages may cause the affection of the latter directly, without the agency of infective sputum, as seen recently in a case of clear clinical pulmonary anthrax (Sect. 985/1924). The patient, admitted with the symptoms of asthenic pneumonia, presented a very severe clinical picture out of proportion to the weakly pronounced pulmonary findings, leading to the early suspicion that a special type of infection was involved. Culture of the frankly sanguineous sputum yielded anthrax bacilli, confirming the diagnosis of pulmonary anthrax. Oddly enough the patient's principal complaint in the anamnesis and during the brief stay at the hospital involved the stomach, and section disclosed a large anthracic focus in that organ. In addition, there were two similar, smaller ones in the upper jejunum. It is conceivable that the pathogen, invading the digestive tract and the respiratory apparatus simultaneously, had first formed the large focus in the stomach and the concomitant symptoms, and had later affected the lungs. Although the morbid process of the latter organ had developed last, it had caused the patient's death under a complex of symptoms characteristic for this form of anthrax. The mode of infection cannot be established with certainty in this case. The patient had been unloading dried hides from abroad six months ago. Since the assumption of such a prolonged latency of anthrax bacilli invading the organism at that time is highly improbable, the only remaining possibility indicates that material containing spores had adhered to his clothing and had entered the organism via the respiratory and digestive passages by an unfortunate accident just prior to the appearance of the acute morbid signs.

It is not possible in all cases of IA, even in those where hemorrhagic foci have formed in the lungs, to demonstrate signs of bacterial growth in the form of small hemorrhagic-necrotic spots in the larger air passages. This still leaves the objection that smaller foci, possibly localized in bronchi of the second or third order, remain undetected and besides, the absence of such primary infectious points invokes a categoric demand for examination of the nasal cavity which is readily accomplished with the aid of Marke's section. I should mention that the formation of these foci, considered by me to be virtually characteristic of anthrax, is not absolutely necessary. It seems sufficient to find inflammatory, hemorrhagic erythema strictly limited to the point of bifurcation and its transition to the main bronchi, as I observed in a 28-year-old man who succumbed to IA (Catalogue No. 5432, Section 593/22). In addition to a dirty brown-red coloration of the tracheal mucosa near the bifurcation, the mucous membrane of the right main bronchus revealed one extravasate half the size of a small fingernail and several others of pinhead-size. Simultaneous presence of hemorrhagic lymph nodes led to a tentative diagnosis of anthrax just from this phase of section, being confirmed when examination of the cranial cavity revealed hemorrhagic inflammation of the soft meninges in addition to numerous punctate and slightly larger extravasations in the cerebral substance. The last link in the chain of evidence was furnished by culture of pure anthrax bacilli from the meninges, spleen and vertebral marrow.

It is possible also for inhalation and external anthrax to coexist, as shown by preparation 2255. Unfortunately the pertinent anamnesis is missing. However, I have indicated on the specimen container that the patient had been marked by high-grade cyanosis during his lifetime. In addition to the described, very characteristic tracheo-bronchial disease focus, the autopsy had disclosed bilateral hydrothorax which adequately explains the patient's high-grade cyanosis. The patient's death was due to severe IA, independent of the pustule localized at the throat. The interpretation of such cases offers no difficulties. The spore-containing material reaches the outer covering through the fingers and is introduced simultaneously into the respiratory apparatus with the air stream. It would be incorrect to assume a lymphogenic or hematogenic etiology for lesions found in the airways in such cases. Entry of pathogens between the cells of the epithelial coat, observed by me in this particular case, excludes such an assumption.

Just as the anthrax pathogen is able to attack the organism directly at two points to cause cutaneous and inhalation anthrax, or inhalation and gastro-intestinal anthrax, this observation indicates further that the causative agent may become established at two different locations within the respiratory apparatus and induce dissimilar changes. I should like to recount one such case here, involving a laborer, 35 years old, who was admitted in a moribund condition. (Catalogue No. 3310, Section 414/1910). Aside from conspicuous cyanosis, hemorrhagic pleural effusions, and two hemorrhagic nodes (one in the ileum, near the valve, and one ½ inch higher, near the airways), the autopsy disclosed the following (Fig. 6): The mucosa at the tip of bifurcation and extending into the right bronchus is in a state of severe hemorrhagic inflammation. Near the center of the affected zone there is a small necrotic focus that exposes the cartilaginous ring underneath. At the division of the main bronchus and the branch leading to the lower lobe the mucosa is covered with shreds of fibrous pseudomembranes, some in a floating state. Along the trachea there is a chain of hazelnut-sized, coarse lymph glands with dark red sectional surfaces. Lymph glands of the pulmonary hilus are up to a small fist in size, coarse, and resemble bluish-red marble upon section. There is a particularly large lymph gland in the bifurcation, forcibly separating the bronchi. The lungs have a soft consistency; they are limp and free of foci. Pure cultures of anthrax bacilli were grown from the heart blood, spleen and hilus glands, as well as from the unchanged brain.

The anamnesis failed to establish the source of infection. The patient was said to have coughed for some time and to have been seriously ill for only two days. He was admitted on 26 February 1910 at 7 p.m. and died at two o'clock the next afternoon. Although there are regrettable uncertainties about the mode of infection, this case undoubtedly involves classic inhalation anthrax. Observation made during the short clinical course support this assumption. Severe dyspnea and cyanosis was noted during admission, as well as a strongly accelerated pulse in an afebrile patient. These are, precisely the symptoms that might almost be considered pathognomic for IA. The rapidly developing pleural effusions leading to quick reduction of the respiratory surface explain the manifestations with respect to the respiratory organs. To this are added the high pulse frequency and the relatively insignificant findings involving the lungs, which are usually out of proportion to the severity of disease. For the experienced observer, such cases point to suspected pulmonary anthrax, or

more correctly, inhalation. The indicated puncture will almost invariably reveal an effusion in one or both pleural spaces, frequently with hemorrhagic signs, which normally shows anthrax bacilli on stained smear preparations, confirmed within the next few hours by culture. We have made it standard procedure at Eppendorf to carry out lumbar puncture in all cases of anthrax and to examine the liquor bacteriologically. This frequently enables us to establish involvement of the meninges at an early date. Blood cultures are started as a matter of routine. Important clues are obtained thereby to the prognostic evaluation of individual cases.

Returning from these clinical remarks to the anatomical findings of the discussed case, the essential result has been found to be: An inflammation accompanied by circumscribed necrosis of a cartilaginous bronchial ring, and a process marked by the formation of fibrinous pseudomembranes which exceeds the hemorrhagic-necrotic region and invades the mucosa of a bronchus of the first order. Proof is offered thereby of the fact that the anthrax bacilli is able to produce genuine fibrinous pseudomembranes, similarly to the diphtheria bacillus and Dipl. Lanc. Generally speaking, this process is very rare; otherwise it would have been discovered by other investigations long ago. I probably owe the observation to the circumstance that I have seen an unusually large number of anthrax cases. I made the first observation of this type nearly a quarter of a century ago and pointed to this property of the anthrax bacillus during subsequent demonstration courses. Pseudomembranes in this position may represent the only change noted in the large air passages. I should like to offer the case of a 34-year-old man as proof thereof. The patient had been working in a warehouse, handling sacks, furs and horse hair. He had stayed home during Pentecost, 3-5 June, without going to bed. He did not feel well, however. On the morning of 5 June he saw a number of persons in the room and under the sofa, and was sent to the hospital because of delirium, where he succumbed in a short time. The condition became clear only during autopsy. There were about 2 liters of sanguineous fluid in both pleural spaces. The lymph nodes of the anterior mediastinum were up to walnut-sized, hemorrhagic, as were the hilus glands on both sides, especially in the vicinity of the left bronchus. The lungs were strongly edematous and free of foci. The aryepiglottic folds were hemorrhagic and slightly swollen. A thick, somewhat rolled fibrinous pseudomembrane on a slightly dirty-grey mucous skin is located in the bronchus that leads to the center of the superior lobe. Histological examination of a piece of membrane after staining according to Weigert's fibrin methods reveals a composition of extremely thin threads of fibrin connected in a delicate network and, in the upper layers, the presence of numerous anthrax bacilli, partly in the form of pseudo-threads (Fig. 7). The contents of cellular elements is very meager, especially in the deeper layers of the membrane. This case also revealed several anthracic foci with partial cicatrization of the mucous membrane in the stomach and jejunum. Again I feel justified in assuming that the digestive tract was infected simultaneously with the air passages, as had been the case with an earlier instance of clinically diagnosed pulmonary anthrax subsequently confirmed by section. We do not know the prerequisites for the formation of fibrinous pseudo-membranes on the mucosa of the airways, a very unusual and rare process attributable to the invasion by anthrax bacilli. In this type of disorder, the regional lymph nodes again react with strong, nearly always hemorrhagic swelling, accompanied by serous or serous-hemorrhagic effusions of variable volume into the pleural spaces. This condition

does not only belong to the appearance of pulmonary anthrax "kat exochen", but occurs upon every settlement of anthrax bacilli in the larger air passages, provided it causes a somewhat more intense inflammation of their mucosa. Especially upon localization of the disease in the area of tracheal bifurcation and the neighboring regions of the main bronchi, a preferred point of attack according to the material discussed here.

At times, the appearance of IA may be completely masked by manifestations of the central nervous system. Raye has observed such a case and presented it to the Biological Department of the Medical Association on 24 February 1914. The 59-year-old patient had been carrying sacks 8 days before exitus. He went to work on 17 February, but complained of malaise, nausea, and weakness in the legs during the day. He had risen on 18 February in spite of nausea and headache. Stupor set in during the afternoon; in the evening the patient became comatose, the pulse was arrhythmic. A lumbar tap carried out at 10 p.m. yielded greyish-white, cloudy liquor. The patient died at 1:45 a.m. The lumbar punctate contained leukocytes and massive rods identified as anthrax bacilli. The upper strata of the fluid contained only bacilli and isolated erythrocytes. Section revealed 150 cc of a fluid resembling meat infusion in each pleural space. The lymph nodes in the pulmonary hilus and at the bifurcation show pronounced swelling and hemorrhagic properties. The lungs are also hemorrhagic-edematous and show pneumonic infiltration over a walnut-sized patch of the right inferior lobe. There is a pseudo-membrane that adheres rather closely to the mucosa at a circumscribed site in the main bronchus leading to the right inferior lobe. The soft meninges are partly marked by hemorrhagic infiltration, partly by gelatinous edema and yellowish coloration. Bacteriological testing of the blood and the liquor yielded pure cultures of anthrax bacilli.

There should be no doubt in this case about the involvement of IA. The meat infusion-like pleural effusion, the strongly hemorrhagic swelling of the hilus lymph nodes, the hemorrhagic-pneumonic focus in the right inferior lobe may be considered pathognomonic for this type of anthrax disease. Similarly, the discovery of a small pseudo-membrane adhering quite tenaciously to the inferior lobe bronchus seems to justify the designation of this point as the primary pathogenic colony. However, the ususually early involvement of the soft meninges caused the picture to be dominated by meningeal manifestations. These also explain the rapid course of this case.

Since the autopsy was carried out in private practice, the nasal cavity and its accessory sinuses could not be examined. For this reason I must dispense with discussion of a possible connection between lesions in the nasal cavity, pointing to invasion by anthrax bacilli, and the described hemorrhagic-inflammatory process in the soft meninges, as Risel has done in Case 2 of his paper cited above. The last of my cases discussed here differs from Risel's in the absence of IA with lesions in the larger air passages and in the lungs. Besides, I do not hesitate to assume a hematogenic etiology for the hemorrhagic inflammation of the soft meninges which accompanies a number of anthrax infections, just as in the case of suppurative meningitides that we observe as complications of pneumonias and other acute infectious diseases or, independent of these, in epidemic cerebrospinal meningitis. However, this does not exclude the possibility of genesis by the path described by Risel, via the perineural

lymph sheaths of olfactory nerve branches. At any rate, this path may be considered only for those cases where signs of a primary invasion of anthrax bacilli are present in the nasal region.

In my opinion, the results obtained from the material discussed above may be grouped under the following conclusions: It is recommended to speak exclusively of IA when a disease process is involved which is caused by the entry of anthrax bacilli from the air passages, and not of pulmonary anthrax, since the lungs are affected only in part of the cases. Thus every case of pulmonary anthrax represents IA, but every case of IA does not necessarily involve pulmonary anthrax. In cases diagnosed as IA, there are hemorrhagic or hemorrhagic-necrotic foci in the trachea, variable in size and at times reaching down to a cartilaginous ring, with apparent preference for the bifurcation and the neighboring sector of the main bronchi. Suitable microscopic preparations reveal the invasion of anthrax bacilli between the epithelia of the tracheobronchial mucosa, sloughing of epithelia and formation of mucosal erosion whose region is occupied by anthrax bacilli mixed with leukocytes. Pulmonary foci of anthrax may be formed by aspiration of free anthrax bacilli into the deeper airways, as far as the alveoli, without lymphogenic dissemination of bacilli. Even processes limited to the tracheo-bronchial mucosa usually cause pronounced hemorrhagic swelling of the regional lymph nodes, the mediastinal, hilus and bifurcation lymph nodes, as well as accumulation of variable amounts of serous-hemorrhagic effusions in the pleural spaces. The resultant clinical signs are identical with those of pure pulmonary anthrax, consisting of high-grade cyanosis, strongly accelerated and diminished pulse, pronounced feebleness, occasional high temperature. A number of IA cases are complicated by morbid foci in the digestive tract. The latter may be infected by swallowing of hemorrhagic sputum, especially upon involvement of the lungs, or by simultaneous entry of spore-containing material into the digestive apparatus. Similarly, pathogens implicated in the genesis of IA may also cause an anthracic lesion on the skin. Finally, IA may lead to early infection of the soft meninges by hematogenous route, characterized by the finding of hemorrhagic meningitis which completely masks the complex of symptoms typical of IA. The prognosis of IA, even upon recognition, is extremely poor.

Fig. 1. Curve of fatal cases of anthrax observed at Eppendorf Hospital from 1889 to 1923.

Fig. 2. Anthracic focus on the carina of the tracheal bifurcation. Section 30/06, Collection 2255.

Fig. 3. Bronchus with bacilli invading the epithelium and situated in the mucosa proper. Section 30/06, Collection 2255.

Fig. 4. Upper right: preserved epithelium; Left: absent epithelium. Section 30/06, Collection 2255.

Fig. 5. Bronchus with disintegrating surface epithelium and anthrax bacilli invading the mucous membrane. Section 30/06, Collection 2255.

Fig. 6. Inhalation anthrax; small necrotic focus in the right bronchus just below the carina of tracheal bifurcation, hyperamic zone in the proximity, reaching into the trachea. Large hemorrhagic lymph node in the bifurcation. Catalogue 3310, Section 414/1910.

Fig. 7. Fibrinous pseudo-membrane and anthrax bacilli.