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Anthrax and its treatment with large doses of serum.

by Hermann Czickeli

Münchener medizinische Wochenschrift, 89: 602-604 (1942).

While anthrax heretofore has played a subordinate part in Germany and usually has held greater interest for the industrial hygienist than for the practising physician, it has now moved more into the foreground due to the expansion of the national boundaries and the inclusion in the German sphere of interest of such countries as the Ukraine, other parts of Russia, and parts of the Balkan area.

The number of anthrax cases in Germany was 100-200 annually (in 1925, for example, 173 cases with 34 deaths were reported), and a similarly unimportant role was assigned to anthrax in the neighboring countries, such as Denmark, Switzerland and Holland. In Europe, the most diseased areas were the Balkan states and especially Russia. In Russia, anthrax was endemic and also appeared from time to time in the form of greater epidemics. Thus, for instance, in 1870, 50,000 animals and 529 persons became ill in the province of Novgorod. The official statistics of the Soviet Union list 31,668 cases of human anthrax for the years 1924 and 1925 (cited after Sobernheim); 13,813 in 1926; 10,684 in 1928, and 11,474 in 1929. It may be assumed, however, that the actual number is much larger, since on one hand we are dealing here with statistically reported cases whose number certainly represents only a fraction of the true picture, and on the other hand the Soviets have always tried to hide unfavorable conditions or, if this proved impossible, to veil them at least.

In Yugoslavia, Roumania and Italy, too, pustula maligna is relatively frequent. Thus, according to the statistics of the year 1928, 1086 cases were reported in Yugoslavia, 1182 in Roumania and 1987 in Italy. The corresponding figures for Poland and Czechoslovakia were 81 and 99, respectively.

Anthrax, and especially pustula maligna, occurs primarily in persons who have had dealings with animals infected with or killed by anthrax, or with their skins, hair, bristles, etc. Virchow has included anthrax, glanders, foot-and-mouth disease and actinomycosis under the designation zoonoses. Widal expresses the same concept when he gives the name charbon agricol to cutaneous anthrax.

My experiences with anthrax were derived during my long activities in Roumania, where I saw numerous cases at the hospital for infectious diseases at Craiova. A. Metzulescu was the director at that time, and he had treated 247 cases of cutaneous anthrax there during the years 1922-1935. 186 of these were men, 61 were women. 78 came from cities, the others were rural inhabitants. They were grouped by the following occupations: 130 farmers, 10 butch 8 tanners, 7 clerks, 5 innkeepers, 2 drivers, etc. The women were almost without exception from farms. The ratio of infected men to women may be easily explained by their occupations. Of the 51 cases observed by me, 38 were

already published in A. Metzulescu's paper (Münch. med. Wschr. 1936, Nr. 4, pg. 137), leaving 13 unpublished cases (9 men, 4 women). 11 came from villages and had agricultural occupations, 1 man was a high bank official, 1 woman was the wife of a physician. Since the material originates from the same hospital and has been treated by the same methods, I am including Metzulescu's cases in my considerations.

The course of the disease varies with the different species, according to H. Hetsch. Sheep and goats, important in the dissemination of anthrax in the Balkan countries, almost invariably were affected by the apoplectic form, whereas an acute, febrile course is seen in cattle, in which visible localizations are rare. Later developments include intestinal manifestations with sanguineous diarrhea and hematuria. At times, strong animals die apoplectically with signs of cerebral apoplexy. Ulcers often form in the mouth and the intestinal canal. Anthrax has a similar course in horses. Swine, on the other hand, show local foci of anthrax in the pharynx and larynx. Dogs and cats usually are infected by eating the meat of animals killed by anthrax; they die with the clinical picture of intestinal anthrax.

In most cases, transmission occurs by way of the contaminated hand, possibly also with the aid of a scratching fingernail. It is still not understood why only the mouth, throat, neck, chin and the upper extremities are involved, while the abdomen and legs are rarely affected. Nasal anthrax never seems to occur. Baeckmann has written an informative paper on this subject in the Münch. med. Wschr. 1936, Nr. 4, pg. 134. He gives a detailed account of the problems of anthrax localization.

W. Koch has tabulated 1077 cases (cited after H. Hetsch); of these, 490 cases affected the face and head, 370 the upper extremities, 45 the throat and neck, 35 the trunk and 26 the lower members. Of Metzulescu's and my cases, 145 had anthrax pustules on the face, 36 on the arms, 31 on the throat, 19 on the hands, etc. None on the nose.

In the event transmission of germs should take place by means of scratching, the legs of barefooted persons ought to be particularly involved, according to Baeckmann, since they are especially exposed to insect bites, as well as the nose, which is frequently rubbed. Again, considering the dissemination of scabies, anthrax pustules ought to be a frequent occurrence on the abdominal skin or on the flexure of the groin. This, however, is not the case.

Whether Baeckmann's explanation to the effect that, in the main, those parts become involved which are frequently washed and de-oiled, is appropriate, may remain unresolved. In his opinion, the nose is protected because the nasal skin possesses many sebaceous glands which continuously grease the skin. At any rate, I remember seeing very dirty shepherds who came down with anthrax pustules in spite of their layer of dirt and grease. The legs of barefooted persons are also washed quite frequently, and yet they are seldom involved.

In England, as later in other countries, infections were observed which were due to shaving brushes produced from Chinese horse hair. Whether the

brush alone is sufficient, or a tiny cut with the razor is required, is still debatable. Graf has recommended a full beard for exposed persons. It is true, however, that parts of the face not touched by the brush, such as the eye lids, the forehead and the neck, also are attacked.

In one case I was obliged to blame transmission on a massaging brush. The 60-year-old wife of a physician was staying at a spa with a rheumatic affection. Baths were prescribed, in which a brush was utilized. A pustula maligna developed on the right breast -- allegedly following a scratch wound inflicted by the brush --, yielding to appropriate treatment after 8 days.

Gadflies seldom take part in the transmission of anthrax, otherwise the incidence of the pustule would be much higher in summer than in winter. This is not the case. Racowitza reports 292 fatalities from anthrax in Roumania during 1933. Of these, 170 fall on the five months from November to March, in which flies are rare or absent, and only 122 on the seven months from April to October, in which flies are abundant. The largest aggregates of fatal cases are found in January (52), February (42) and December (30), i.e. during months in which there are no flies at all.

This mode of infection must nevertheless be taken into consideration in rare cases. Thus I saw a 47-year-old bank official with an anthrax pustule on the neck. He had never had any dealings with animals, pelts, etc. He claimed to have been severely bitten by a large fly. The anthrax pustule developed at the same site.

According to Zulzer, the incubation time of cutaneous anthrax extends from several hours to 2-3 days, rarely longer. A small, red papule develops, then, 12-14 hours later, a small vesicle filled with serous or blood-colored fluid with a hard base. A black scab is formed, usually as a result of scratching, capable of reaching a diameter of 1-2 cm. The surrounding tissue is reddened and swollen, frequently doughy. The edema may cover large expanses. The insignificant pain accompanying this process is noteworthy, allowing differential diagnosis against carbuncles. Strong tumescence of the lymph glands and erythema of the lymph vessels appear in severe cases. In favorable cases the scab loosens in 6-8 days and the wound becomes well granulated. If the carbuncle is situated at a point where loose connective tissue is present, as in the region of the eyes and the mouth, severe edema often appears (oedema charbonneux or charbon blanc). This anthrax edema, previously called the "erysipelateous form," is due to anatomical conditions.

It is noted concerning fever, that light cases may progress almost apyretically. In 81 of our cases the temperature returned to the norm within 2 days, in the others it lasted up to 7 days.

Pulmonary anthrax is extremely rare in Roumania. Metzulescu has seen only 1 case in 35 years.

Intestinal anthrax has never been seen at Craiova. I have been informed of a small epidemic by a colleague, which, to my knowledge, has not been published. In late summer a few years ago, a choleroïd disease struck a

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military camp at the Black Sea port of Konstanza. The possibility of a cholera importation was indicated by the active maritime traffic to and from the Orient. News of the disease leaked out and caused a panic among the summer guests, who departed in large numbers. In part of the patients the disease resembled dysentery. Bacteriologic tests and post mortem section revealed intestinal anthrax. The infection had been due to the ingestion of fried (not raw) meat from an anthrax-infected sheep. According to my colleague, all persons partaking of the meat became ill and died. Fourteen soldiers were said to be involved.

The diagnosis of cutaneous anthrax is not difficult, if this possibility is considered, or if the patient's occupation suggests contact with cattle, pelts, bristles, etc. It is true that there have been human cases that had nothing whatever to do with animals or their products. Furuncles and carbuncles may initially start with a small vesicle; dissemination is much faster, however, in the case of pustula maligna. The anthrax pustule causes little or no pain. The patient is bothered only by a feeling of tension and by itching. Some cases may suggest erysipelas, but differentiation is not difficult. In doubtful cases the diagnosis of an anthrax infection is established by means of microscopic examination of smears, by animal tests with white mice or guinea pigs, or by blood culture. The blood culture is positive only in severe septic cases, however.

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Becker examined 39 anthrax patients with the aid of blood cultures; 9 of them showed a positive culture, and all 9 succumbed to the disease. Ghinzburg had 9 cases with septicemic conditions among 120 cases; 5 of these died. Ghinzburg noted an increase in leukocytes to 12,000-13,000, even 25,000, following injection of serum in those cases where the serum had a favorable effect. In unfavorable cases, on the other hand, the number of leukocytes did not rise after serum instillation.

The prognosis depends on the mode of treatment.

While mortality in Italy, according to Sclavo, amounted to 24.16%, it sank to 6.7% after the introduction of serum treatment. Page reports from England that mortality had formerly amounted to 26.56%; it had decreased to 7.4% following the acceptance of serum treatment. The death rate in the hospitals of Bucharest now is set at 6.8%, the figure which is also given by Ghinzburg for his cases. Metzulescu reports that 19.5% of 48 cases treated at Craiova between 1900 and 1921 had died, while 4.8% of 248 cases had a fatal outcome between 1921 and 1925. Of 13 of my own cases, 1 died. Baekmann assumes a mortality of 10-15%, other authors report mortality rates up to 44%.

With respect to the localization of pustules, eruptions on the lip and at the throat are prognostically more unfavorable than sites on other parts of the body.

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Prophylaxis can be carried out only through the control of anthrax among domestic animals, especially through immunization. The cadavers of dead animals must be burned, or, if this is not possible, buried deeply and covered with chloride of lime. Sanitation of infected pastures is well nigh impossible,

since anthrax spores possess a tremendous resistance and cannot be killed with the means available to us. According to E. Fraenkel, there are cultures whose spores may stay in 5% carbolic acid solution for 2-3 days, and others that endure 40 days without losing their viability. Some anthrax cultures resist flowing steam for 25-30 minutes. This resistance explains the impossibility of disinfecting contaminated pastures.

A considerable portion of the anthrax cases admitted to the infectious wards of the hospital at Craiova came from the same locale, a large community.

Investigations about the reason for the prominence of this location led to the discovery that a severe anthrax epizootic had afflicted the sheep flocks of this community during the world war, claiming many animals. The cadavers were only superficially buried on the communal pastures. As this region becomes flooded in spring, the infection spread to other pastures. Numerous attempts at disinfection undertaken in the meantime have proved futile. This epizootic was one of the causes of the steep increase in anthrax morbidity, which rose from 48 cases in 21 years prior to the world war to 261 cases within 15 years after the world war. At one time, 16 cases of cutaneous anthrax were diagnosed on a single farm.

Due to the lack of personal experience, I cannot evaluate the reliability of the thermo-precipitation test after Ascoli in the determination of infected animal products. Martos has proved by way of the micrurgical method that 1 anthrax bacillus suffices, under certain conditions, to cause the animal's death.

Concerning the therapy of cutaneous anthrax, all authors agree on one point, namely, that pustula maligna should not be managed surgically. Most investigators also advise against burning, cauterization, etc.

Best results were achieved by the immobilization of the affected member, dressing with aluminum acetate solution, alcohol, iodine solution, etc.

Recker has introduced salvarsan therapy into the treatment of anthrax and has obtained good results. This method of treatment is also praised by other authors. I have no personal experience with salvarsan.

Even if some authors, like Pella, Kraus, Baeckmann and others, have assumed a sceptical attitude towards the efficacy of anthrax serum, the number of favorable cases observed by different physicians on both sides of the ocean is so great that no doubts can be entertained any longer about the effectiveness of the serum. It is understood that a good serum must be available. Efficacy fluctuates strongly, depending on the method of production and the strains utilized. The serum was first dispensed extensively in Italy by Sclavo and in South America by Mendez, and was then generally accepted into therapy on the basis of the favorable results.

In Roumania, we use the anthrax serum of the Roumanian State Serum Institute, obtained from horses immunized with anthrax strains of diverse origin, i.e. from diseased persons, horses, cattle, sheep and swine, by intravenous injection of increasing doses.

The dosage varies considerably with different authors.

Romberg writes that repeated injections of 20-40 ccm serum are indicated; according to Struempell, experience is still inadequate with respect to humans, although cures have been achieved in animals. W. Schulz recommends serum in doses of 20-40 ccm intramuscularly and intravenously. H. Hatsch: "The dosage must naturally be geared to the quality of the serum and the severity of the disease. At least 30-40 ccm must be injected, in severe cases 50-60 ccm. The injection may be repeated for several days, depending on the circumstances. Aside from subcutaneous injections and local instillation around the carbuncles, intramuscular and intravenous injections are recommended. The latter, of which some authors even dispense doses of 100-150 ccm all at once, seems to be the most efficacious." Staehelin recommends 100-150 ccm Sobernheim serum intravenously.

Although I did not obtain important improvements in the result of treatment by increasing the quantity of dispensed serum in the management of diphtheria and epidemic meningitis, significant improvement in the curative effect was noted in connection with the instillation of high doses of serum in the case of anthrax and tetanus (Czickeli, *Münch. med. Wschr.* 1942, Nr. 7, p. 144).

In comparison to quantities listed by above authors, the doses introduced by Metzulescu, and continued by me, were enormous. The serum was dispensed intramuscularly and subcutaneously, in very severe cases also intravenously. This method of treatment was introduced at Craiova following the publication of Penna's papers in 1921 at Buenos Aires. Initially and true to the original method, the serum was always injected intravenously, but since 1923 the serum is dispensed in this manner only in severe cases with high fever, strong edema, etc.; otherwise intramuscularly and subcutaneously. The injections are made in doses of 100-200 ccm in the morning and evening. The criterion for the required quantity of serum consisted of observations of the pulse, fever and edema. The largest amount of serum dispensed was 1020 ccm; usually 400-500 ccm sufficed. In addition, the diseased part was immobilized and dressings with 1.0 iodine, 10.0 potassium iodide to 1,000.0 water, were applied.

Serum sickness appeared in about one-third of the cases, but more severe grades were seen in only four. Aside from the itching caused by urticaria, the tension and fever, there were no injurious after-effects. Treatment with calcium, adrenaline and dressings followed the usual procedure.

The effect of the serum manifested itself in the subjective condition as well as in local findings, reduction of edema, pulse and fever. Frequently the edemas receded after 24-36 hours. The fever showed irregular curves, sometime abating soon after the instillation of serum, sometimes continuing to rise, in order to return to the norm after 6-7 days. The conditions for successful serum therapy consist of its timely utilization and the availability of an effective serum. If the resistance of the organism is already severely lowered owing to the flooding of the blood with anthrax bacilli, the use of serum comes too late. Thus, 8 of the 13 fatal cases were admitted in a moribund state and died a few hours to 18 hours after admission. Of the treated cases, 224 had 1 pustule, 24 had 2, 7 had 3, 1 had 4, 3 had 5, 1 had 6 and 1 had 12 pustules.

Summary

261 cases of cutaneous anthrax are reported, which were treated with large doses of serum -- 100-200 ccm twice daily subcutaneously and intramuscularly, intravenously in severe cases. 13 died = 5%. Cauterization, formation of eschars, etc., were not performed. Local treatment consists of immobilization and dressing with diluted Lugol's solution. The serum has been furnished by the Roumanian State Serum Institute.

Following the introduction of treatment with large doses of serum, the mortality rate of cutaneous anthrax has decreased to one-fourth the previous rate.