ANTHRAX

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Anthrax is an acute infectious disease, primarily of herbivorous animals, caused by the *bacillus anthracis*. It can be transmitted from these animals to man, when it takes two forms: external, the malignant pustule or malignant oedema; internal, pulmonary or intestinal. The disease has been known from antiquity, the name being derived from the Latin *anthrax*, a carbuncle.

Aetiology

The *bacillus anthracis*, owing to its large size, was the first bacterium to be identified. It was designated by Cohn in 1875, and finally proved to be the cause by Koch in 1877. It is a non-motile gram-positive rod of 7 to 10 μ in length and 1.2 μ in width, with square sharply-cut ends. In the tissues of man and animals it possesses a capsule, and outside the body it forms oval spores which are resistant to heat, standing boiling for some minutes, and resistant to such chemical disinfectants as mercuric chloride. These spores are, however, susceptible to oxidizing agents such as potassium permanganate.

The organism grows on agar in characteristic long chains, and its identity can be proved by mouse inoculation, when it produces haemorrhagic exudates and septicaemia.

Epidemiology

The disease can occur in all mammals, though it primarily affects herbivores and small rodents. However, elephants are also very susceptible. Amongst these animals infection is spread by the alimentary tract by ingestion and not by direct contact. Pastures contaminated by nasal and anal discharges in warm, moist climates allow growth of the organisms outside the body. Other animals feeding on this pasture may then be infected. In colder climates artificial foodstuffs may cause the spread. The disease in animals is a septicaemia which may present as an acute, sudden, fatal illness, or less rapidly with intestinal symptoms. The economic problem is considerable all over the world, domestic cattle, sheep and goats being seriously affected even in Europe.

Human infections are derived from contact with animals or their products. They have been divided into 'agricultural anthrax' and 'industrial anthrax.' Agricultural anthrax occurs in farmers, herdsmen and those who come into close contact with animals, for example in butchers skinning the carcasses or even in those using hides as sleeping mats. It may be of the cutaneous type from direct infection of the skin, or of the intestinal type resulting from eating animals which have died of anthrax, a not uncommon practice in primitive communities. Industrial anthrax, on the other hand, occurs as a result of handling hides and skins, or in dealing with wool, animal hair, or bristles. It may again be of the cutaneous type or inhalation may result in pulmonary disease. Cases of cutaneous anthrax have resulted from the use of infected shaving brushes.

The incidence of the agricultural type is, of course, related to the incidence of the disease in animals. This is heavier in primitive areas than in civilized countries, where stringent veterinary control has reduced the incidence to small proportions. There is generally a seasonal variation depending on temperature and humidity.

On the other hand, industrial anthrax has no such seasonal variation, the only factors affecting its incidence being the source of the animal material and the degree of industrial hygiene. Thus hides from Central Asia were notoriously liable to be infected, while improvements in ventilation, the use of respirators, and general hygienic measures have reduced the incidence of pulmonary disease from above to below that of cutaneous.

Prevention

This may be considered under two headings: (a) Prevention of the disease in animals; (b) prevention of the spread of the disease from animals to man.

(a) This is, of course, a veterinary problem. Stringent rules with regard to notification of deaths of animals from anthrax, and also as to the disposal of the carcasses are an important feature,

Spores are not formed until the body fluids or exudates reach the exterior. Therefore no post-mortem examinations should be done, and the carcase buried at once in a deep pit with quicklime. Oxidizing disinfectants such as permanganate should be used liberally wherever the animal had been resting. In some countries prophylactic vaccination of stock using heat-killed vaccines has proved of value.

(b) Industrial anthrax can be lessened by careful hygiene, ventilation and protective clothing. The pneumonic wool-sorters' disease has been markedly decreased by the automatic processing of wool by alkaline baths and formaldehyde. Unfortunately no satisfactory process has yet been developed for hides.

Morbid Anatomy

In the cutaneous disease there is an acute inflammation with an extreme tissue oedema, but little polymorphonuclear infiltration. Necrosis follows. The appearances are not particularly specific nor are they of diagnostic value. In internal anthrax the pathology is that of a septicaemia. There is lividity and discoloration of the tissues and staining of the intima of the aorta and large vessels. Serous exudates occur, particularly in the pleural and pericardial spaces. Haemorrhages, both petechial and gross, are found in the lungs, pericardium and intestines. The liver, kidneys and lungs are congested. The spleen is large and tending to be diffuent. Most marked is the gelatinous oedema containing bacilli which may be found in the subserous tissues, the bronchial submucosa and retroperitoneally.

Clinical Description and Symptomatology

Cutaneous anthrax. The malignant pustule is the usual form. This is usually seen at a late stage of its development, but where workers are 'anthrax conscious' it may be seen at the earliest stage.

For one to three days after the infection there is a reddened patch on the skin with a flea-bite appearance, which develops into a painless papule. This in turn develops into a vesicle with a dark purple-black centre. This stage is associated with marked itching. In the mildest form the vesicle may dry up and form a scab, with little toxæmia and no surrounding oedema. In the more virulent forms the papular and vesicular stages are associated with toxæmia and fever, while locally there is a spreading oedema of the soft tissues. In the malignant pustule itself the next development is coagulation necrosis at the centre forming a black leathery slough, while around a ring of secondary vesicles form. This is the typical appearance on which a diagnosis can be made

clinically, and is developed in three to four days. Recovery is indicated by the gradual separation of this slough without further extension and by the reduction of the surrounding oedematous infiltration. This is a slow process, the separation of the slough taking at least two weeks, and the healing up of the ulcer by granulation, scarring and epithelialization taking at least as many more. The site of the lesion varies according to the nature of the industry and the protective clothing worn. Hide porters are affected frequently on the face and neck, but in warmer climates where a minimum of clothing is worn almost any part of the arms or trunk can be affected. Oedema is particularly prone to occur when the pustule is on the face or neck.

There is an amazing difference between some cases where a small pimple or ulcer is all that there is to show for the disease, and others where the patients are acutely ill, with high fever to 104, perhaps comatose, and with haemorrhagic oedema extending widely from the site of infection.

Headache, joint pains, nausea and malaise occur in the invasive stage. Fever is nearly always present. A polymorphonuclear leucocytosis is usual.

Malignant anthrax oedema is also described apart from the pustule. Such cases are probably associated with a small primary pustule, but the toxæmia, oedema and invasiveness overshadow the local process.

Internal anthrax. This may be pulmonary, arising from inhaled bacilli in industrial processes, or intestinal from eating infected animals. In both types the symptoms tend to be those of an overwhelming toxæmia due to septicaemia.

In pulmonary anthrax there is an acute onset with fever, headache and tightness in the chest. There is often severe dyspnoea with a rise in the respiration rate to 50 or 60 per minute. The nose and throat show a general ingestion, while the signs in the chest are those of bronchitis. Gradually increasing cough, pain in the chest and signs of pneumonic infiltration are associated with a frothy blood-stained sputum which may contain anthrax bacilli. Collapse and death occur early. Unless the history leads to suspicion, and the blood and sputum are examined microscopically, ante-mortem diagnosis is difficult or impossible.

In gastro-intestinal anthrax there is generally an acute gastro-enteritis at the onset, and the vomit and the stools may be watery and blood-stained. The abdomen is distended and tender due to the accompanying peritonitis. The temperature does not rise very high, but anxiety, restlessness and cyanosis lead on to collapse and death within one to three days. Post-mortem

examination shows haemorrhagic exudates in the bowel wall.

Diagnosis

This is, of course, simplified when the occupation leads to suspicion, and if the cutaneous lesions present the typical appearance. Pathological corroboration, or in doubtful cases distinction between a malignant pustule and a simple coccal lesion, is simple if a microscope is available. A smear of the vesicle fluid, or if the vesicle has already broken down, a smear from the fluid produced as a result of scraping the edge of the lesion, can be stained with Giemsa or similar eosin-methylene blue stain, when the typical long capsulated bacilli can be demonstrated. Gram staining will confirm the nature of the organism. Full bacterial confirmation can be made by the inoculation of peptone agar plates and the production of the long-chained growth, or by animal inoculation in guinea pigs or mice.

In severe cases or in the terminal stages the blood culture is positive for the bacilli.

Prognosis

As a result of more modern methods of treatment the outlook in cutaneous anthrax has improved radically. Whereas at the turn of the century the mortality was of the order of 25 per cent., the introduction of Sclavo's anti-anthrax serum and, later, of first the sulphonamides and then the antibiotics has reduced this to not more than 5 per cent. The results depend to a large extent on the early institution of treatment, as if delay allows the infection to gain the upper hand and toxæmia to go too far, even the most heroic doses of the most powerful antibiotics may come too late.

With internal anthrax opportunities of applying modern treatment have been few and late, and the mortality is still very high; speed in giving the treatment as soon as possible is all-important. It is necessary, too, to stress the variability of the toxæmia. Sometimes the disturbance is profound, in others the illness appears only as a mild superficial sore without general involvement. Serious signs are restlessness, coma or delirium, rapid breathing, or vomiting and diarrhoea. The greatest mortality appears to occur about the fourth day.

Treatment

Surgery. Excision or scraping of the pustule, once practised, need now only be mentioned to be condemned. Any surgery is unnecessary and dangerous.

Anti-anthrax serum. This, the first great step forward in treatment, is probably still of value in

toxic cases. Unfortunately, large amounts such as 100 to 500 c.c. intravenously or intramuscularly are needed, and the resultant reaction may be severe. In addition, the serum is not generally readily available, whereas other effective drugs are; hence it is comparatively seldom used. These difficulties may, however, be overcome in part. The progress in the fractionization and concentration of sera with the use of the gamma globulin fractions should reduce the dose required to manageable proportions, while in England at any rate the Ministry of Health makes the serum available through certain hospitals and centres. If readily available, all severely toxic cases, with high fever or delirium, should receive serum in addition to the further treatment described.

Arsenicals. Novarsenobillon, 0.6 to 0.9 gm. intravenously, is undoubtedly of value, and has been used successfully in South Africa.

Sulphonamides. These drugs have also been found to be of use. Sulphathiazole or sulphadiazine, 1 gm. four-hourly, or sulphamezathine, 1 gm. six-hourly, should be given after a loading dose of 2 to 3 gm.

Antibiotics. When it was found that the anthrax bacillus was sensitive to penicillin *in vitro*, this drug was tried out clinically. The results have been very good.

The present position appears to be that the ideal treatment is a combination of sulphonamide in the dosage mentioned above with soluble penicillin in moderately heavy dosage, such as 100,000 units four-hourly. In highly toxic cases an initial dose of concentrated anti-anthrax serum, if available, could also be given. It is possible that the sulphonamide is not necessary, but further experience with controlled series is needed to be sure. The penicillin dosage may be varied according to the severity of the case, mild infections receiving only half this amount, or one injection of 300,000 units of water-soluble procaine penicillin fortified with 100,000 units of soluble in the 24 hours. On the other hand, in a severe case it appears that rapid attainment of high blood penicillin levels is desirable, and $\frac{1}{2}$ to 1 mega unit four-hourly should be used. This treatment should be continued until the temperature is down, signs of toxæmia gone, and the pustule no longer extending or oedematous—that is, for a period of five days to a week. Continuation beyond this point does not aid the ulcer in healing and does not seem to be of any value.

Of the newer antibiotics it is probable that both chloramphenicol and aureomycin may be effective and, indeed, there are favourable reports of the latter in the American literature. Up till now, however, their cost and restricted availability has prevented their use on any scale. It is doubtful

if they will present any substantial advantage over penicillin.

Local and non-specific therapy. In cutaneous anthrax local treatment is comparatively unimportant, and good results are obtained with an occlusive dressing using a mild antiseptic ointment. Rest is, of course, important, with light splinting if necessary.

Healing of the malignant pustule is a slow process. It may take two to three weeks for the slough to separate and to leave a clean floor to the ulcer when, of course, the time of healing depends on the size.

Usually about another two weeks are needed but healing is sufficiently certain to make skin grafting unnecessary.

ANNOTATION

The Treatment of Hyperthyroidism

There are now three methods of treatment for cases of hyperthyroidism—*thyroidectomy*, *thiouracil* and *radioactive iodine*. Crile and McCullagh in a valuable article (*Ann. Surg.*, 1951, **134**, 18) assess the results they have obtained with these methods.

In 540 consecutive cases operated on by the technique now used by them—a radical subtotal thyroidectomy of the Lahey type, with demonstration of both recurrent laryngeal nerves and parathyroids—there were no deaths and only two persistent unilateral recurrent nerve palsies. The late results, five to ten years after operation, are interesting although the follow-up was unfortunately only 50 per cent. complete. Following the older operation in which varying amounts of thyroid tissue were used to preserve the recurrent laryngeal nerves, the incidence of recurrent and residual hyperthyroidism in Graves' disease was 15 per cent. and in toxic nodular goitre was nil. Following the more radical technique now employed the incidence of recurrence in both types of disease was only 2 per cent. Post-operative hypothyroidism requiring treatment was found, with the older operation, in 4.5 per cent. and with the present operation in 21 per cent. of cases of Graves' disease subjected to operation. This complication did not occur in secondary toxic goitre.

Propyl thiouracil, dealt with in the second part of the paper, in doses of 300 to 400 mgm. per day was effective in 96 per cent. of the patients so treated. The use of this drug is advocated both as a definitive treatment and as a pre-operative measure. Mortality is practically unknown, only one case of fatal agranulocytosis being recorded in the literature. Toxic effects were found in 2.5 per cent. of the patients but in only half of these were

they sufficiently severe to require cessation of treatment. Frequent blood counts were considered unnecessary provided patients understood that they should report fever, rash or sore throat at once.

The indications for definitive thiouracil treatment given by the authors are: (1) For patients with Graves' disease who have small goitres. (2) In all patients with a short life expectancy or who are (and remain) poor surgical risks. Of 147 patients treated with propyl thiouracil 70 had long-term remissions after withdrawal of the drug, 18 were never adequately controlled and the remainder had a recurrence of hyperthyroidism after an interval. It is considered that if a recurrence is delayed for four months the remission will be prolonged. Remission in Graves' disease was twice as frequent as in toxic nodular goitre.

The last section of the paper deals with radioactive iodine (I^{131}); 337 patients were treated with I^{131} , of whom 109 had completed treatment from between two months and two years before the report. No death was attributable to treatment and there was no morbidity. In both types of disease the hyperthyroidism was controlled, more rapidly in Graves' disease than in nodular goitre. In Graves' disease eight of 73 cases required treatment for hypothyroidism; complication was not seen in toxic nodular goitre. Recurrence in the short period of the follow-up was seen in only one case (of Graves' disease). The advantages of treatment with radioactive iodine are therefore considerable, but in view of the unknown late radiation hazards caution is advised by the authors until a long follow-up period has elapsed, and its present use restricted largely to older patients.

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