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CHRONIC GLANDERS*

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HUMAN glanders is a rare disease. Robins[1] (1905), in a very excellent monograph on this subject, succeeded in collecting reports of 153 cases up to that time. Luhrs[2] (1921) believes that only 50 cases of glanders occurred in Germany during the war. Sobol[3] (1933) states that in the Ukraine, where the frequency of glanders in horses is very high, it is a very rare disease in man. In the district about Constantinople it is said that 90 per cent of horses give a positive mallein reaction, yet human glanders is rare there.

Glanders is a specific, infective and contagious disease, occurring in most parts of the world, and caused by *B. mallei*. It affects, chiefly, the horse, mule and ass, and is communicable to man. It may be contracted by inhalation, ingestion, or by direct inoculation of the organism into the skin or mucous membrane. When it leads to a systemic disease, frequently associated with nasal ulcers, and involvement of the lungs, it is known as "glanders"; when the lesions are limited to the skin, it is known as "farcy". Both are manifestations of the same disease. Both types of the disease may co-exist in the same individual, and may be acute or chronic.

Since 1906, there have been some 48 reports of glanders in the literature, which I have been able to trace. A few notes on some of these may be given.

Hoffmann's[4] case of chronic glanders developed the disease as a result of contact with a human case. The infection developed in the elbow, with purulent exudation in the joint. The patient then developed ulcers of the gums, followed by involvement of the soft palate, the posterior pharyngeal wall and the fauces. Extension to the upper lip, with ulceration, occurred. Strauss' inoculation test was positive, and Hoffmann obtained, by means of a modified Wassermann reaction, a positive complement fixation with an antigen of *B. mallei*.

Dudgeon, Symonds and Wilkin[5] reported the case of a man who developed an abscess in the lower end of the right humerus, followed during the next four months by many more abscesses over the body. There was no evidence of nasal discharge, nor was contact with horses established. *B. mallei* were demonstrated only after repeated passages through guinea pigs. There was a negative complement fixation reaction on the first occasion, but a strong reaction was obtained two months later, and a high titre agglutination. He stresses the value of complement fixation and agglutination reactions.

Fischer[6] reports a case of nasal glanders successfully treated with auto-vaccine. The initial onset was influenzal, followed by ulcers (furunculoid in type) on the legs and nose, associated with deafness. In three years, the nose had been destroyed, and there was much scarring of the upper lip. Diagnosis was established on: (*a*) complement fixation test positive; (*b*) glanders bacilli found in the tissues; (*c*) positive guinea pig inoculation with Strauss' reaction; (*d*) ophthalmic mallein test positive. Twelve injections of auto-vaccine were given, with a gradual increase of the dose every three to four days. Fever reactions were present. The ophthalmic mallein test was negative after completion of treatment. Recurrence followed within two months, with unstated results.

Januschke[7] reported the case of a man whose infection began with fever, bronchitis and infiltrations in the subcutaneous tissues of the leg. Foci developed in other areas. Guinea pig inoculations were positive for glanders. The agglutination test was positive in a dilution of 1-100, and the complement fixation test was negative during the formative stage, whereas later, during the healing stage, the agglutination test had an entirely normal value, and the complement fixation was positive. This fact has been noted in horses, namely, that the formation of agglutinin and amboceptor do not go hand in hand.

Watson[8] reports a series of three cases, which occurred in an epidemic in Manitoba in 1922. Many horses were affected with the disease. His first case showed five or six discharging sinuses in the right leg. The *B. mallei* was isolated from the pus. Following injection of anti-mallein serum in one month all

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discharge had ceased, and the sinuses had completely healed. The total duration of the disease had been one year. The complement fixation test was strongly positive. A recurrence developed in two months, with abscesses in the elbow and head. The doctor in attendance on the case developed an infection of the index finger, as a result of contact. *B. mallei* were identified. Serum treatment was instituted and cure resulted within two months. It is to be noted that where the disease had been diagnosed early and antimallein serum used the results were excellent.

Rateau[9] states that glanders may be classically considered as follows: (*a*) Acute farcy with violent general symptoms resembling typhoid; (*b*) acute primary glanders beginning with a picture like acute articular rheumatism; (*c*) chronic farcy, sometimes isolated, sometimes associated with glanders; (*d*) chronic glanders following chronic farcy or chronic primary glanders.

Mendelson[10] states that the disease may remain latent for long periods and he believed that it would be advisable to keep patients under observation for many years, stimulating their resistance by the use of vaccine and proper hygienic methods.

Balogh[11] emphasizes the difficulties found in post-mortem diagnosis of glanders, acute, subacute and chronic. He did autopsies on seven cadavers. Diagnosis was made before death in three of the cases. In the other four clinicians had diagnosed a variola vera, sepsis of unknown origin, a tuberculosis with chronic suppuration due to hyphomycetes, and a pulmonary phthisis, and later sepsis due to the tubercle bacillus.

Post-mortem diagnosis by section staining is possible in cases of chronic glanders (according to general experience) only because the patients usually die of new and fresh exacerbations of the disease. The acute changes in the lungs, in the early days of the disease, are likely to become modified and lead the clinician to make a diagnosis of pulmonary tuberculosis. In the fourth case, Balogh did not have his suspicions of glanders raised by the usual microscopic picture of odd lobulated, desquamative, necrotic, bronchial pneumonia, or by articular suppuration, but by the acute exacerbations of the original skin lesions. His assumption was fully confirmed by bacteriological findings. In chronic cases one can count on a progressive, severe necrotic inflammation of the trachea, the main bronchus and several branches.

Contact with horses is, as a rule, necessary for the occurrence of glanders in human beings. It is, therefore, commonly an occupational disease—a point of aid in diagnosis. Robins[1] listed the occupations in which it occurred as groom, soldier, coachman, horse trainer, pathologist, physician and butcher. Inquiry as to nasal discharge, submaxillary enlargements and abscesses in the necks of horses should be made. In man the virus may make an entry through an abrasion of the skin, frequently followed by lymphangitis and then nodules along the course of the lymphatic vessel or in other parts of the body. Glandular enlargements may, but only rarely, break down. The mucous membranes, particularly of the nose, but also of the mouth and genital tract, may frequently become involved. The conjunctiva of the eye has been the point of entry in some cases. In some other cases the site of entry may not be found, and the disease may start as an acute infection, simulating respiratory disease, typhoid or rheumatic fevers.

Acute and chronic glanders vary in the intensity of the process. Acute glanders is practically always fatal; a small percentage of cases of chronic glanders occasionally ends in recovery, although the disease may be long drawn out, over years. Chronic glanders is characterized frequently by periods of acute exacerbations of the process. Where the disease makes its entry through the skin, the primary lesion is a vesiculo-pustule. Where the disease is acute, severe inflammation, with œdema and necrosis, occurs, associated with prostration, pyæmia and death. Generalized eruptions in the skin may occur, of the pustular and crusted types, along with abscess and ulcer formation, which may coincide with pyæmic phenomena. Where the disease tends to be chronic the signs of chronic inflammation are shown locally in marked infiltration, which goes on to abscess formation and ulcers, with, frequently, a tendency to fibrous tissue formation. Great destruction of tissue usually results, as the outcome of ulcerative lesions. Metastatic foci develop commonly in other parts of the body, particularly in the subcutaneous and intramuscular tissues. A common localization is in the muscles of the calf of the leg. Inflammatory processes in the nose tend to invade the fauces and throat, and much destruction results to both soft and bony tissues. Where the joints are involved the picture tends to be, at first, that of acute rheumatic fever, but the involved joints tend to become purulent. The lungs may be involved, primarily or secondarily, in a bronchiolitic process, or with numerous consolidations simulating tuberculosis, or as pneumonic areas. Foci may develop, where generalization supervenes, in the spleen and liver. Abscesses have been noted in the brain, causing signs of meningitis. The gastro-intestinal tract is rarely involved, but the organism has been found in a case of gastric ulceration. In a long standing case, amyloid disease of the viscera may occur.

Robins states that there is no essential difference between chronic and acute glanders, except in the severity of the process. It has been frequently attested to in the literature that the virulence of the organism is exceedingly

variable. Relative inactivity is common in chronic glanders, and the disease may remain localized, but it is frequently associated with periods of exacerbation and extension. This would seem to be a commonly characteristic phenomenon in glanders. It is further pointed out that periods of latency are not unusual, lasting over a period of some years. The disease simulates tuberculosis and syphilis in this regard. The incubation period in acute glanders is commonly 5 to 6 days, but in the chronic forms it may be many weeks.

B. mallei should be sought for in the discharges from open lesions. It may be demonstrated easily in acute glanders and in the acute clinical exacerbations of chronic glanders. In chronic glanders, where the disease is more or less stationary, it is exceedingly difficult to demonstrate the organism. Sometimes the *B. mallei* has been demonstrated in tissue sections, but this is difficult. Cultures should be made on glycerine agar and potato, and inoculation of pus should be made intra-peritoneally into male guinea pigs. The characteristic Strauss' reaction should be looked for. The organism may be so feeble that two or three passages through guinea pigs are necessary to raise its virulence. Certain other organisms, notably those of the brucella group, may also give the Strauss' reaction.

The mallein reaction is specific in horses, and its specificity has been carefully worked out. On the other hand, Topley and Wilson[12] state that in man the mallein test has been used in so few cases that it is difficult to gauge its value. Robins, in his monograph, reports a number of cases where the mallein test was negative in the presence of proved glanders. A few cases in the other literature are also reported as negative. This may possibly be due to the very low pathogenicity of certain strains of the organism, inasmuch as the virulence of the organism is exceedingly variable. A positive mallein reaction is not an urticarial, erythematous lesion, but a marked cellular and inflammatory response, characterized by a local erythematous swelling with œdema and infiltration lasting forty-eight hours, and associated with a systemic reaction and fever.

Topley and Wilson state that the complement fixation test is the most reliable laboratory test. According to Reinhardt (1919), there are faulty positives in 4 per cent of healthy horses, and faulty negatives in 2 per cent of glandered horses. Watson[8] found complement fixation specific in a high titre in three proved cases. He has observed the reaction in a small number of normal human sera. A further series of controls in both healthy human sera, and also in other human pathological sera, is being investigated. Topley and Wilson state, apparently referring to horses, that the best combination for proof of the disease is the complement fixation test and the conjunctival mallein reaction.

The agglutination test is also used, but its value is more doubtful. A precipitin reaction is thought not to be trustworthy enough for practical purposes.

CASE REPORT

A man, aged 59, who has always resided in North America, a butcher by trade, following discharge from the army in 1919 developed inflammatory lesions in the scrotum. These gradually enlarged, were painful, broke down, and discharged purulent material. Within a year the inner and upper parts of the thighs and buttocks became involved. There was no history of febrile disturbance. In 1923 an exacerbation occurred and lesions developed in the right axilla. In 1925 the left axilla became involved. It is characteristic of the process in this man that the discharge and associated pain varied greatly from time to time, but there had been no tendency for the lesions to recede. The man was admitted to hospital on June 1, 1934, for investigation, about fifteen years after the onset of the disease.

Condition on admission.—The patient was well nourished and healthy. His weight was well maintained. There was no adenopathy. There was a linear scar in the right axilla, where a focus was successfully removed surgically in 1925. In the groin, involving the scrotum, inner and posterior upper thirds of both thighs and perianal portion of the buttocks, there was a curious combination comprised of a semi-keloidal, semi-inflammatory process, through which numerous oblique and vertical sinuses were to be seen. Some of the orifices of these sinuses were dilated, and others were contracted by thickened scar tissue. The left axilla was similarly involved (see figures). The inflammatory processes in these areas were more marked at the periphery of the lesions, whereas scarring occurred in the central parts. No glands were to be seen and no bony involvement was present. Careful medical examination revealed no organic disturbance. The urinalysis was normal, and no anæmia was present. The white blood count, on different occasions, showed 15,000 white cells, with a relative increase of polymorphonuclear leucocytes. A sugar tolerance test showed a delayed assimilation. The cardiac, respiratory and abdominal organs revealed normal findings, and there was no organic nervous disease. Nose and throat examination was negative, and there was no history of nasal discharge.

Microscopic examination of pus and scrapings from the walls of the sinuses showed no fungus or yeast organisms. Thorough bacteriological investigation showed many staphylococci, along with a non-pathological diphtheroid, *B. mallei* was not grown. Numerous injections of pus and crushed-up curettings were made into the peritoneal cavities of guinea pigs. All were negative for *B. mallei* and any other pathogenic organism. Repeated passages were made in guinea pigs, without any gross or microscopic evidence of disease.

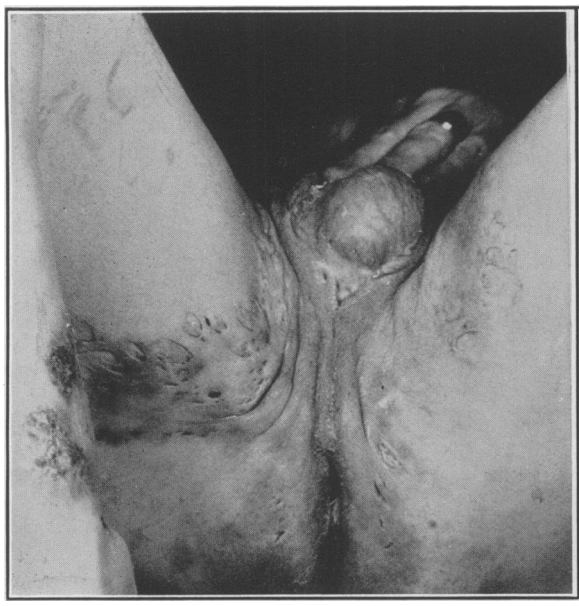

Fig. 1.—Extensive, chronic, inflammatory lesions, with sinus formation and scarring about the scrotum, thighs and buttocks.

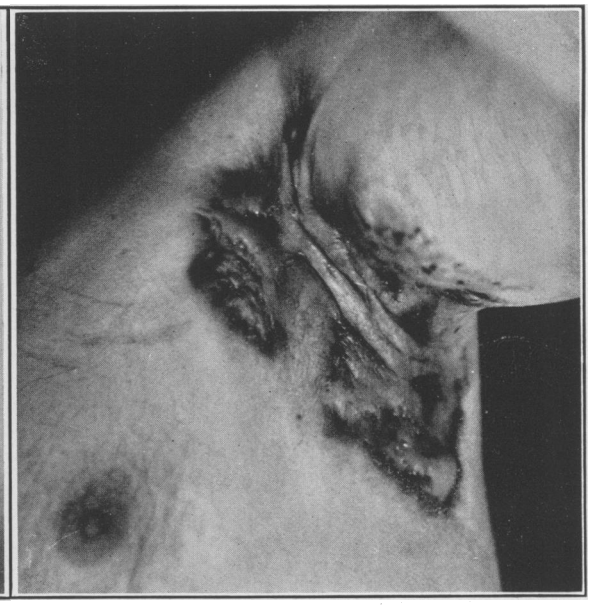

Fig. 2.—Chronic granulomatous lesion, with keloidal scarring and sinus formation in the left axilla.

The blood Wassermann reaction was negative at this time. During his stay in hospital, a daily rise of one to two degrees of fever was present.

Two c.c. of mallein injected subcutaneously gave a violent local and general reaction, with fever which lasted 48 hours. This dose was excessively large. Later doses of 0.2, 0.1, and 0.5 c.c. were injected intra-dermally. Each test showed a marked local reaction, with an accompanying rise in temperature of 102 to 103° F., associated with a feeling of pain and tension in the lesions. At the site of each injection an area of erythema developed within 24 hours, with œdema and infiltration, associated with swelling of the arm. This acute phase lasted over 48 hours. The nodular, inflammatory zone at the site of injection lasted for one month. One of these lesions (0.1 c.c. mallein) was excised after 7 days. The histological report of this lesion was as follows:—

"The mid-part of the corium shows an area of necrosis, without definite borders, containing polymorphs, red blood cells and debris. In addition, there are focal areas in the lower corium about dilated and proliferated blood vessels, where there is also intense cellular reaction, consisting of epithelioid, polymorphonuclear and lymphocytic cells. There is intense œdema and exudation of more or less degree throughout the section, with secondary acanthosis and hyperkeratosis."

Auto-inoculation of pus from a sinus to an area on the chest was done. A focal reaction resulted, with erythema, infiltration and crusting, which disappeared in ten days.

Lymphogranuloma inguinale was excluded by means of the Frei test. This was completely negative on two occasions. Control tests on three cases of lymphogranuloma inguinale, using this antigen, were positive. A portion of tissue was removed from the margin of a lesion for histological report, which is as follows.

"In the central portion of the section there is a small ulcer where the epithelium is replaced by hæmorrhagic, necrotic, granulation tissue. The epidermis shows marked hypertrophy at the margins. Beneath the granulation tissue is an intense, inflammatory cell mass, made up of lymphocytes and plasma cells, with numerous polymorphonuclear cells towards the centre of the lesion. Some hæmorrhage is seen in the central area. Beneath and on either side of, this area the corium is formed by fairly dense fibrous tissue, which extends into the subcutaneous tissue. There is a fairly marked vascular dilatation through the section."

Specimens of blood were sent to Dr. E. A. Watson, Chief Pathologist to the Animal Diseases Research Institute of Canada. A complement fixation test for glanders was strongly positive (4-plus). It is well known that previous mallein tests may give rise to antibodies in the bloodstream, and thus provoke a positive complement fixation and agglutination test. It has been shown by Brocq-Rousseau, Forgeot and Urbain that the antibodies disappear and the serum returns to normal in 45 days in horses. The test, therefore, was repeated at the end of three months, when it was again found to be strongly positive (4-plus). At this time, the patient was readmitted for further investigation. We were unable to demonstrate the presence of the *B. mallei*, in spite of repeated attempts during his second admission.

The Wassermann reaction had been reported as positive on certain occasions during the past 15 years. While in hospital, numerous Wassermann tests were done. There was a remarkable variation in the reports. The tests were usually reported negative, but on some occasions negative reactions became positive within intervals of two days. It was considered that these positive reactions were probably the result of non-specific antibodies present in the blood stream, and not due to syphilis, of which no other evidence was present.

This patient has had a good deal of treatment in the past 15 years. Anti-syphilitic treatment, consisting of arsphenamine injections, was given without any change in the condition. Pot. Iodide in large doses was given, with no obvious results. Ultra-violet and x-ray exposures were of no avail. Total excision of the area in the right axilla had eradicated the disease in that location, and numerous incisions for evacuation had been made in other areas, with only temporary relief. All local treatment of various forms had been used without success. In view of the excellent results obtained by Watson (*loc. cit.*) with anti-mallein serum, it was decided to institute this form of treatment. Over a period of two months the patient was given subcutaneous injections of this serum in doses of 2.5 c.c. to 10 c.c., every three or five days. At the end of a month considerable improvement had taken place in the inflam-

matory zone about the lesions in the axilla, with lessening of the discharge. In some areas the inflammatory process entirely disappeared, with resulting fibrosis. Shortly after, the treatment was discontinued, as the patient left Montreal. In January, 1935, after two months' treatment, when there was clinical improvement, a serological test gave a 2-plus complement fixation with glanders antigen. In April, 1935, following two months' cessation of anti-mallein serum, a complement fixation test showed reversion to 3-plus.

The curability of chronic glanders, according to Robins, has been greatly over-estimated. Gaiger,[13] in a long personal experience over some years, believed that sunshine and fresh air were of primary value in the cure of this disease. Mallein has also been used in a therapeutic sense to stimulate antibody production, with value, apparently, in some cases.

COMMENT

The clinical picture suggests a chronic infection, as lymphogranuloma inguinale, granuloma inguinale, tuberculosis, syphilis, and other mycotic and yeast infections. All these, we believe, were excluded. The diagnosis of glanders was made. The clinical picture of a chronic, purulent infection associated with sinus formation, and with exacerbations at long intervals, would seem to support this diagnosis. The mallein reaction was strongly positive, and this was associated with markedly positive complement fixation. Investigation is continuing as to the specificity of the mallein reaction in man, and also the value of the complement fixation test. These have proved to be specific in horses, but sufficient evidence has not yet accumulated as to the specificity in human individuals. It is of interest to note the serological evidence of improvement due to anti-mallein serum, of which there was some clinical evidence. The chronicity and marked fibrotic element evidently precluded success by this method. The case is reported to draw attention to the clinical and laboratory diagnostic difficulties of this rare disease.

I am indebted to Dr. E. A. Watson, Chief Pathologist to the Animal Diseases Research Institute of Canada, for serological tests and valued advice in the investigation and report.

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A complete bibliography can be obtained on application to the author.

ADDISON'S DISEASE FOLLOWING ADRENAL DENERVATION IN A CASE OF DIABETES MELLITUS.—J. M. Rogoff cites a case in which an attempt had been made to benefit a diabetic patient by denervating the adrenals. Addison's disease developed. The history indicates that this syndrome was superimposed on pre-existing diabetes by surgical intervention with the adrenals. The surgical manipulations apparently resulted in occlusion of blood vessels and degeneration of the adrenal cortex. Of course the coexistence of diabetes may be assumed to have been unfavourable for possible regeneration of the damaged adrenal cortex. The patient was in a subacute condition of adrenal cortical insufficiency when seen May 12. At that time it appeared that he would survive probably not more than about six months. He died October 18. This prognosis was based on the existing evidence of advanced adrenal cortical insufficiency, indicating extensive and progressive degeneration of the glands. The development of ebony coloured small spots in a patient with Addison's disease is associated with irreparable damage to the cortex of the adrenals. The gravity of the condition was indicated further by the repeated exacerbations and by evidence of progressive adrenal degeneration as interpreted from the costolumbar pressure reaction. The presence of this sign in Addison's disease may be interpreted as evidence of active inflammatory or degenerative processes in the gland. The case illustrates the serious danger of attempting adrenal surgery for the correction of various ailments supposedly related with disturbed adrenal function. Such supposed relations are entirely hypothetical and are not supported by tenable evidence. At any rate, the surgical procedures that have been employed should not be expected to be of permanent benefit, since denervation of the gland by section of its nerves is usually followed by regeneration of the nerve supply within a few weeks. Excision of one gland, as has sometimes been attempted, is subject to the same criticism, and is to be deprecated. The very fact that it is alleged to be of benefit in so great a variety of diseases ought to render the practice suspect.—*J. Am. M. Ass.*, 1936, **106:** 279.