WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE EASTERN MEDITERRANEAN

ORGANISATION MONDIALE DE LA SANTÉ

BUREAU RÉGIONAL DE LA MÉDITERRANÉE ORIENTALE

WHO/FAO SEMINAR ON FOOD HYGIENE, ZOONOSES CONTROL AND VETERINARY PUBLIC HEALTH PRACTICE

Lahore, 29 October - 6 November
Teheran, 7 - 11 November 1964

EM/SEM.VPH/16
20 September 1964

ORIGINAL: ENGLISH

NOTES ON VARIOUS ZOONOSES

by

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I ERYSIPELOID

Erysipeloid is an erysipelas-like infection in man, which is caused by Erysipelothrix insidiosa (rhusiopathiae) a bacterium and is world-wide. It is capable of living as a saprophyte, or at least surviving for months in water, soil, pastures and decaying organic materials; also on fish and in the carcasses of meat animals, even after smoking, pickling or salting. It can also be a pathogen as its name implies, causing disease in domestic and laboratory animals, birds and man. The bacterium, Streptococcus pyogenes Group A of which there are some 40 types, that produces erysipelas in man, does not affect animals and can be readily differentiated from erysipeloid infections in man by clinical signs and laboratory tests.

The most frequently encountered form of the disease in man is the localized cutaneous infection mainly among persons handling swine, turkeys and fish. Veterinarians sometimes infect themselves when they accidentally puncture their fingers or hands while immunizing swine with virulent live culture vaccines, or injure themselves while doing necropsies on swine or turkeys. These infections in man apparently provide a good immunity since reinfections seldom if ever occur.

The incubation period in man is from one to five days. The initial signs at the point of inoculation are redness, swelling and pain. Sometimes the infection spreads to adjacent parts involving the entire hand and other parts of the body. This is accompanied by itching, burning or prickliness. There may be fever as well as swelling and tenderness of the regional lymph nodes and joints. Suppuration does not occur. Most cases are of a moderate nature and recover in two to three weeks, rarely some persist longer.

A diffuse or generalized form of disease occasionally is seen. This usually begins as a localized infection which spreads slowly over the body. Sometimes there are eruptions in distant parts that may be the result of re-entry of the organism, or septicaemia. Fever, regional lymphadenopathy and joint pain accompany the spread. In these cases the patient is depressed and comes to feel that no therapy is of value.

The septicaemic disease is naturally the most serious. All kinds of signs and symptoms are observed depending upon what organs are affected, lymphadenitis, polyarthritis and endocarditis. Skin eruptions usually

are present and are significant in establishing a diagnosis; confirmation of the disease is by recovery of the E. insidiosa from the blood. Laboratory mice and pigeons are quite susceptible and are used to isolate the organism.

Morphologically in smears the bacterium is a slender, gram positive, non-motile, non-sporulating rod, 1 to 2 microns long. On artificial media it is a mixture of short rods and long filaments ranging up to 20 microns in length. The organism is resistant to many disinfectants including alcohol, formaldehyde, hydrogen peroxide and phenol. It is however readily destroyed by caustic soda and strong chlorinating agents. The E. insidiosa is quite sensitive to penicillin, less so to the broad spectrum antibiotics, and is not affected by the sulphonamides. Hence penicillin is the agent of choice in treatment of both man and animals. Since the advent of penicillin the complications that were occasionally seen in man are very rare.

Therapy as practised today consists of large doses of penicillin. Antiserum was formerly used but less so since penicillin has been available and has given such satisfactory results. Antiserum is usually given in 5 to 20 cc, infiltrated around the site of the cutaneous lesion. During and following World War II erysipeloid infections were common in man in Europe. The only therapeutic agent available was antiserum which gave quick relief and aided recovery.

The disease in animals takes various forms - erysipelas, septicaemia, endocarditis, polyarthritis and diarrhoea in birds. In swine a variety of signs and symptoms are seen principally in young animals. It is fairly common in the swine-producing areas of North America, Europe and the USSR. In young pigs the acute septicaemia is most common, and frequently fatal. Onset is not characteristic. Inappetence, depression and a high body temperature up to 108°- 110°F. An increase in pulse and respiratory rate accompanies the fever. A less severe form of the disease is the cutaneous form which is called "diamond skin disease". The temperature is usually high 104°- 108°F., the appetite depressed and sometimes the joints are affected. The skin lesions erupt after 48 - 60 hours. These are light red patches on the chest, ventral and dorsal surfaces, thighs and shoulders. The number and size vary but they are usually quadrangular in shape; however some are rounded. The course of the disease is 8 - 14 days and the

animals usually recover as the eruptions turn dark red and dry up. A chronic form sometimes occurs, and usually causes enlargement of the joints and a painful arthritis. A vegetative endocarditis may develop in animals that have apparently recovered from the acute disease. This is usually recognized on necropsy but cardiac insufficiency results in animals being short of breath, coughing, lassitude, and resting on the sternum and elbows, or even sitting on their haunches instead of lying on their side.

Lambs suffer from a non-suppurative polyarthritis. Calves are affected in a similar manner. Infection usually is the result of a wound or navel infection. These animals do not have a localized infection at the wound site or of the skin.

The disease in turkeys is an acute or subacute septicaemia, with males affected more often. It usually occurs in the fall about the time birds are ready for market. The first signs are dullness, inappetence and diarrhoea. A red purple swelling of the wattles is suggestive but this is also seen in other diseases. The case fatality rate is 30 to 40% in untreated birds. Treatment consists of penicillin I.M. at the rate of 5000 units/lb. On necropsy multiple diffuse haemorrhages are seen in the muscles and in the viscera. Occasionally ducks and geese as well as pigeons (squabs) are affected. E. insidiosa seldom produces disease in chickens.

The mode of infection is not clearly understood although wounds are considered the route of entry of the bacterium. It is difficult to reproduce the natural disease under experimental conditions, which suggests that there is great variability in virulence of the agent, and susceptibility of the experimental animals except for mice and pigeons. As stated earlier the organism is widespread, but it is suspected that virulent strains are sometimes introduced in animal feeds, feed supplements, or in new additions to swine herds. Wild birds may be mechanical carriers. Garbage that is fed to swine may carry the infectious agent in meat scraps or viscera.

With the improved immunizing agents available the disease is being successfully controlled in enzootic areas where some farms have outbreaks year after year. Also the extensive use of penicillin in animal medicine has averted outbreaks, and controlled disease when it has occurred. All this in turn has reduced human exposure and disease. Most human infections are now seen as occupational disease among fish handlers and turkey processors, and even here it is rare as any suspected lesion on the hands is promptly treated with penicillin, and a diagnosis is seldom made.

II GLANDERS

Glanders is a highly communicable disease of horses, mules, donkeys, and less so for cats, dogs and man. The disease is one of the oldest known and was described by ancient Greek and Roman physicians. As early as the 17th century the contagious nature was recognized but this was not proved until 200 years later by two German veterinarians, Loeffler and Schutz. It is seldom reported in any species today except among the equidae. Sporadic cases have been reported in man in southern Europe, Asia and South America. The last observed case in the United States was in 1948 in a person who had travelled extensively. The World Health Organization (Food and Agriculture Organization Year Book, Animal Health, 1962) reports that glanders is present only in Mexico and Brazil in the Americas, and Somalia in Africa. It was not reported in Europe. Asia has a wide distribution, Jordan, Iraq, Iran, Syria and Arabia in the Middle East, Pakistan, India, Burma, Cambodia, Thailand and Indonesia in the south, and China and Mongolia in the north.

The infectious agent is the glanders bacillus, Actinobacillus mallei previously called malleomyces mallei, also known as Pfeifferella mallei in the older literature. From this array of names one can readily understand that there is some degree of confusion as to the proper name of the genus to which the glanders bacillus belongs. The organism varies considerably as to its morphological characteristics. In young cultures the bacteria are long slender rods. As they grow older they change shape (pleomorphism) and vary in size from coccoid elements to long slender filaments. The cells are always gram negative. Spores are not formed; there are no capsules or flagella. The organism is susceptible to drying, heat and chemicals but under favourable conditions can survive up to two or three months.

1. Pathogenicity

The organism is highly pathogenic for horses, mules and donkeys, and can cause disease in cats, dogs, goats and man. Sheep, cattle and swine are highly resistant. Cats and dogs usually acquire the infection from the ingestion of infected horse, donkey or mule meat. Man is sometimes infected when handling diseased animals or working with the organism in the laboratory. When the disease was widespread in the equidae population years ago, veterinarians and their assistants, as well as stable hands and

liverymen were occupationally exposed. Many veterinarians and other exposed persons died of the disease up to the advent of sulphonamides and the antibiotics.

The mode of infection can be by various routes although there is argument as to what route is most frequent. The spread from animals to man is usually by direct contact with diseased animals, their tissues or cultures of the bacteria and the handling of soiled contaminated articles such as harnesses, feed bags and brushes used in grooming horses. The organism is thought to enter the body via wounds or breaks in the skin. The disease is also caused by ingestion;although rare in man,this was considered the most probable means among horses. Feed and water, especially contaminated feed and water troughs were a common source. Airborne infection is possible as has been demonstrated among experimental animals.

2. Clinical Findings

Two forms of the disease are described· a generalized disease, acute or chronic, and a localized form usually characterized by nodules along the surface lymph vessels. The latter form is called farcy.

In man the symptoms include fever, swelling and pain at the point of infection, regional lymphadenopathy, nasal and oral ulcers, skin abscesses and pustules, joint inflammation and septicaemia. Bronchopneumonia is usually seen in the terminal stage preceeding death.

The disease in animals is similar to that described for man, although the disease appears to affect the lungs more frequently indicating that airborne infection is the most probable route of entry. The lung lesions may take the form of nodules or a diffuse pneumonia. The nodules are similar to tubercles. Occasionally the primary lesions are seen in the nose and mouth. The lesions in the nasal passages begin as submucosal nodules which ulcerate and discharge a thick purulent exudate that contains thousands of dangerous organisms.

The nodules are also found in other parts of the body, especially the liver and spleen. Nodules frequently form under the skin (farcy). The nodules break down and form craterlike ulcers that discharge a sticky exudate teeming with the glanders bacillus.

3. Diagnosis

Diagnosis is by isolation and identification of the organism as well as by serological tests. Guinea pigs and hamsters are quite susceptible, the rabbit less so. The complement fixation test has proven to be the most accurate of the serological tests. It is usually positive by the third week. The agglutination tests are good in acute cases but less so in chronic infections. The precipitation test is similar to the agglutination test. Those who have worked with them state that a positive agglutination or precipitation is definitely indicative of glanders, but a negative test does not exclude glanders.

In animals, the mallein test is used extensively and is considered quite accurate. The test is similar to the tuberculin test in which an exudate (made from glanders bacilli) is injected under the skin. In horses the mallein is injected into the lower eyelid. If the animal is infected there is a local swelling and a pus forming inflammation of the eye occurs. All equidae moving in between countries are tested by this procedure, the intrapalpebral test.

4. Treatment

Sulphonamides are quite effective in treating the acute disease, and less so in chronic cases. Antibiotics are not considered to be as effective as the sulphonamides. There are no satisfactory immunizing agents.

Prevention in man depends upon the elimination of infected horses, mules and donkeys which are the primary reservoir. With the decline of equidae populations in most countries the disease has disappeared. The eradication has been furthered by the extensive use of the mallein test, which is very specific in the identification of infected animals, which may serve as a reservoir. If this test is applied throughout the world all infected animals could be identified and destroyed.

III MELIOIDOSIS

Melioidosis or pseudo-glanders is a glanderlike disease first described in Burma at the beginning of the century. For many years it was thought to be primarily a disease of rodents, that sporadically was transmitted to man. Up to the last war it was only known in South East Asia, subsequently it was found in northern Australia, Okinawa, Panama, Aruba and more recently Ecuador. The causal agent is a gram negative

bacillus that closely resembles Pseudomonas aeruginosa, named Pseudomonas pseudomallei or Malleomyces pseudomallei. The older literature called it the Bacillus of Whitmore or Malleomyces whitmori.

Pathogenicity

The organism is pathogenic for rodents, cats, dogs, pigs, goats, sheep, horses and man. The acute disease is usually characterized by a small caseous nodule which may coalesce to form large areas of caseation and eventually break down into abscesses, that lead to septicaemia and death in both man and animals in days or at the most a few weeks. The chronic form is characterized by multiple sinuses that affect all parts of the body and the disease may persist for months or years. Inapparent forms are thought to exist in man where the disease is enzootic e.g. South East Asia. On autopsy the organism may be in nodules or abscesses in lymph nodes, the spleen, lungs, liver, joints, nasal cavity and even the spinal cord.

Most of the human infections reported in recent years have been among rural residents, farmers and stock-handlers. The onset is characterized by painful lesions, presumably at the point of entry of the organism, which becomes erythematous and oedematous. Fever and chills follow within a few days. The lymph nodes of the region involved are frequently enlarged and painful. This often leads to a tentative diagnosis of tularaemia or plague. Terminal symptoms in man are severe prostration, delirium and dyspnoea.

Diagnosis of the disease depends on the isolation and identification of the organism rather than on clinical or autopsy findings, or serological tests. The fluorescein-labled antibody test can be used for rapid identification of the organism, and is considered quite accurate. The clinical diagnosis cannot readily be differentiated from glanders or plague.

The transmission of the disease among rodents, its natural reservoir, is said to be by biting insects, fleas and mosquitoes. Rodents are the primary reservoir and from them the disease is transmitted to domestic animals through insects and contaminated food. The infection in man is thought to be the result of trauma or wounds. Airborne infections have been produced experimentally in rodents and farm animals.

The sulphonamides are said to be quite effective in treating melioidosis in the early stages of the disease. Also the antibiotics, aureomycin, chloromycetin and terramycin are reported to be efficacious. The bacterium has the capacity to become streptomycin resistant very quickly.

IV PLAGUE

Plague, the black death of ancient Rome and the middle ages, is said to have killed more human beings than any other pandemic disease during the dark ages. In Europe alone it is estimated that 25,000,000 people died during the 14th century. It continued to be an epidemic disease in central Europe up to the 19th century. The disease is known to have been endemic in Asia and Africa for centuries before the Christian era. It did not appear in the new world until the 19th century although some investigators believe it was enzootic in ground rodents of the western United States long before it was identified.

In man, plague is a severe and often fatal disease. The incubation period is from 2 to 6 days in bubonic plague and 3 to 4 days in pneumonic plague and other forms. It is characterized by toxaemia, high fever, shock, fall in blood pressure, rapid and irregular pulse, restlessness, staggering gait, mental confusion, prostration, delirium and coma. Conjunctival injection is common and haemorrhages may occur. There are two common forms of the disease: bubonic and pneumonic, and two rare forms: septicaemic and a tonsillar form.

Bubonic plague is more frequently seen than pneumonic plague. It affects the lymph nodes, draining the site of the original infection, causing an acute inflammation and painful swelling of them. These swollen lymph nodes are known as buboes. Secondary invasion of the blood often leads to localized infection in other parts of the body, the most important being pneumonia which is frequently terminal and provides another avenue for the spread of the disease. Untreated bubonic plague has a case fatality rate of 30 to 50%. All persons are susceptible but in some individuals the bubonic infection is occasionally no more than a localized infection of short duration. This mild disease is known as pestis minor. Immunity after recovery is temporary and of a relative nature.

Primary septicaemic form, proved by blood smear or culture, is rare. It is a form of bubonic plague in which the buboe is obscure. It is highly fatal.

Primary pneumonic plague is rare today. Formerly localized epidemics occurred, especially among tribes and families closely associated who were taking care of the sick, or visiting the patient, or expressing condolences. Pneumonic plague is usually fatal.

Tonsillar septicaemia plague is likewise rare, and is only seen during outbreaks. The source usually is a human pneumonic plague case. It is frequently fatal as pneumonia and septicaemia are common complications.

Modern antibiotic therapy materially reduces the case fatality rate in all forms of plague, especially bubonic plague.

Diagnosis is by clinical findings when axillary or inguinal lymphodenopathy is encountered along with a history of having been in plague-infested areas. In the United States the western states beyond 100° longitude are enzootic areas where plague bacillus is carried by ground rodents including ground squirrels. The diagnosis is confirmed by the demonstration of the plague bacillus, Pasteurella pestis in fluid by the buboes, blood or sputum.

1. Causal Agents

The P. pestis is a gram negative bipolar ovoid rod and measures about 1.5 x 0.5 microns. It stains readily with ordinary stains, and can be readily demonstrated in tissues or fluids. The organism grows best below body temperature between 25° and 30°C. It does not show any marked resistance to deleterious influences. Its life outside the host is precarious. The bacillus disappears rapidly from soil, water and buried cadavers. It can survive for months in the dried carcasses of small animals in dry climates.

P. pestis is pathogenic for rodents. The disease may be diagnosed by inoculating guinea pigs subcutaneously, or when specimens are grossly contaminated and decomposing, by rubbing the material on the freshly shaven abdomen; the plague bacilli penetrate the minute abrasions while the contaminants do not. The guinea pigs die in 2 to 5 days. Post-mortem findings are characteristic including subcutaneous and general congestion especially the spleen, a granular liver and pleural effusion.

2. Epidemiology

The natural reservoir of plague is wild rodents involving many different species throughout the world. Periodically epizootics affect these populations and result in high mortality. The infection can be transmitted to urban rats in urban areas where overlap with wild rodents occurs. This rarely occurs today except in under-developed areas.

In the United States P. pestis has been isolated from many species of wild rodents, rabbits and other mammals as well as their ectoparasites in 15 western states (130 counties) including Hawaii. During the past 50 years there have been many human cases, all sporadic, including 63 deaths which were attributed to wild animal contact. In recent years some of these cases and deaths have been associated with the handling of wild rabbits in the South West In these instances it is thought that the organism penetrates the skin and eventually causes a buboe.

The classical transmission of plague is by the bite of the rat flea and certain other fleas. The infective fleas are those whose stomachs,oesophagus and proventricules have become blocked by multiplication of the P. pestis at these sites. This prevents the fleas from taking up a blood meal and results in the blood being regurgitated and returned to the host upon which the flea is attempting to feed.

The blood during this process of being drawn into the infected flea becomes contaminated with plague bacillus and they are carried into the host. Fleas may remain infected for weeks but those that are blocked with P. pestis die in a few days of starvation. Fleas may also transmit the disease by mechanical means when their proboscides have been recently contaminated.

Pneumonic and tonsillar plague are transmitted from person to person by contact with patients with primary pneumonic plague or from patients who develop terminal plague pneumonia.

3. Treatment

Streptomycin, tetracyclines and chloramphenicol used early are highly effective in all forms of plague. Results are good even in pneumonic plague if therapy is begun within 24 hours of onset, but uncertain thereafter. When fever reappears after initial success with streptomycin, the infectious agent may be resistant, or a complication has developed, such as secondary pneumonia due to other bacteria. In these cases other antibiotics are indicated including penicillin, which is not effective against the plague organism but is against streptococcus and pneumococcus.

Streptomycin is the drug of choice and is usually given 1 gm intramuscularly initially, followed by .5 gm every 4 hours until temperature remains normal for 4 or 5 days. Broad spectrum antibiotics are used concurrently beginning with 1 gm parenterally, followed by 2 - 4 gm orally daily. Sulfadiazine is also used beginning with 4 gm initially followed by dosages of 1.5 to 2. gm every 4 hours for 15 to 20 days.

The patient should be watched closely for signs or symptoms of shock and necessary precautions taken. Any suspected case should be reported to the local health authority who will consult with the state and federal authorities. International regulations require that any case be reported to the World Health Organization.

Any suspected patient should be hospitalized. Ordinary aseptic precautions should suffice for patients with bubonic plague. Strict isolation is essential for primary pneumonic plague or patients developing plague pneumonia. Discharges of the patient should be considered dangerous and properly disinfected before being disposed. Terminal disinfection is necessary when patients die. The bodies should be handled with strict aseptic precautions.

Quarantine and surveillance of contacts and premises are put into effect by state and local health authorities when indicated. Investigation of contacts and sources of infection are carried out by the health authorities. Rat control is important in urban areas as well as suburban and rural zones. In sylvatic plague it is necessary to survey the area so as to delineate the infected zones before control operations can be instituted.

Immunization with live avirulent plague vaccine is said to be of value in endemic areas. Killed vaccines are less useful because of the necessity of administering repeated injections.

Plague is disappearing from many areas of the world where formerly it was a problem. Good housing, rat control insecticides, and improved hygiene have all contributed to this successful campaign. Maybe with continued effort it can be eradicated from many countries and eventually continents. The effort would be well worth-while.

V TETANUS

Tetanus or lockjaw is one of the oldest clinical entities recorded by physicians. It has been described in man and animals for thousands of years. It is an acute disease induced by the toxin of the tetanus bacillus, Clostridium tetani, growing anaerobically at the site of injury. The incubation period is variable, usually 7 - 10 days and longer. It has been reported as brief as 2 days and upwards to 35 days. It is characterized by painful muscle contractions, primarily of the voluntary muscles of the head, neck and trunk which explains the pathognomic appearance of the patient. The person affected is frequently unable to speak and his facial expression is one of fear - pleading for relief. He is helpless yet conscious to suffer the violent muscular seizures which may involve any striated muscle - usually those of the upper body. Opisthotonus with rigid anterior bowing of the abdomen, marked nuchal rigidity, and trimus are pathognomic signs. There is also an appearance of marked increase of salivation because the patient cannot readily swallow. Death may occur at the peak of any of the muscular contractions. These painful contractions may last from a few seconds to several minutes depending on the severity of the disease. Nearly 75% of all deaths are due to respiratory failure.

1. Causal Agent

The diagnosis of tetanus is based on clinical signs and symptoms. In a study of 91 clinically diagnosed cases in Minnesota a few years ago, the investigators recovered the organism in only 28% of the cases. Tetanus is caused by a gram positive spore forming bacillus that is commonly found in soil, street dust, animal and human faeces. The source of contamination is the intestinal canal of domestic animals, especially the horse, and also man, dogs, rats and even birds. The isolation of Cl. tetani from soil and intestinal excretions varies considerably, indicating that the organism is not a normal inhabitant. Cl. tetani are highly resistant and when protected from light and heat remain viable for years. Some strains resist steaming at 100°C. for 40 to 60 minutes. 5% phenol is said to destroy tetanus spores in 10 to 12 hours; the addition of one-half percent hydrochloric acid reduces the time to 2 hours.

2. Pathogenicity

Infection in man and all animals is the result of wound contamination e.g. dirty wounds containing foreign material, particularly soil, animal and human faeces. The organism multiplies at the site of entry and does not migrate. The toxin is thought to be carried to the central nervous system via the peripheral nerves by absorption, and that it passes through the nerves centripetally until it reaches the motor cells of the anterior horn of the cord, at which time general symptoms of tetanus appear. The question of animal bites and the possibility of tetanus infection is of concern to all physicians. The biting animal does not normally have Cl. tetanus in its mouth or saliva, but contaminates its mouth by its feeding habits and anal licking. It is well known that the tetanus spore will live and multiply in dead or anaerobic tissues. The tetanus spore does not germinate in living tissues probably because of the presence of too much oxygen. It is known that tetanus spores washed free from toxin do not ordinarily produce tetanus when injected into animals but are taken up by phagocytes and destroyed. Strangely, it has been shown that the injection of washed tetanus spores in a dilute solution of calcium chloride produced tetanus, and that infections regularly occurred in animals receiving inoculated washed spores in areas of the skin in which calcium chloride solution had been injected.

The tetanus organism also enters the body in burned areas. Sometimes trivial or unnoticed wounds provide the entry. Tetanus neonatorum usually occurs through infection of the unhealed umbilicus. The disease may also be a complication of surgery, especially in amputations where infected or necrotic tissues are favourable sites for the multiplication of the organism.

There is no evidence that the disease can be caused by the ingestion or inhalation of the tetanus bacillus.

3. Occurrence

The disease is world-wide, in all climates, and affects all age groups although tetanus neonatorum is seen more frequently in the tropical areas. In the United States less than 500 cases

are reported. Most of these are among adults and with good medical care more than half recover. There is no reason for tetanus to occur in any country where there are public health services inasmuch as the present-day tetanus immunizations are among the most effective prophylactic disease control measures known. Tetanus toxoid was developed over 40 years ago and can be manufactured in volume at little cost.

Animal tetanus infections are most frequent in herbivorous animals especially the horse. Infections in horses are frequently the result of nail wounds in the foot. In cattle it may be a puerperal infection after calving, or it may follow castration, dehorning and nose ringing of bulls. In swine it usually is seen as a complication of castration wound infections. Carnivorous animals are seldom affected and birds never have the disease even though the tetanus bacillus is occasionally found in their intestinal tract. The occurrence of naturally acquired disease seems to correspond with the susceptibility of the animal to tetanus toxin. The amount of toxin per gram of body weight to kill a dog is about 600 times greater than that needed to kill a horse*, and to kill a chicken requires 350,000 times as much. The brain tissue of chickens and birds seems to have no affinity for the toxin. The brain tissue of all susceptible animals possesses the power of uniting with tetanus toxin in vitro and thereby neutralizing it.

4. Immunity

Natural immunity occurs in some species such as birds that are naturally resistant to infection. The species have no antibodies in their tissues and the brain tissue does not combine with the toxin. Natural occurring neutralizing antibodies are found in the blood of cattle and lesser amounts in sheep and goat blood. These animals are relatively resistant to the disease.

Active immunity follows the administration of tetanus toxoid (anatoxin). This was first used in horses by the French veterinarians Ramon and Lemetayer of the Pasteur Institute. Horses so immunized are resistant to tetanus for at least one year and if they are exposed at a later date a booster dose will stimulate an increase in antibodies.

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* Man and horse are considered to be equally susceptible to tetanus toxin.

The agent of choice in the prevention of tetanus in man is the toxoid. During the past war millions of men received the toxoid, usually three doses given 2 to 3 weeks apart, which proved very successful in preventing tetanus. Today tetanus toxoid is given to all children in combination with diphtheria toxoid and pertussis vaccine, and booster doses given every 4 to 5 years. Adults who have not previously been immunized should receive two initial doses of toxoid not less than 4 weeks apart followed by a reinforcing dose 8 to 12 months later; and thereafter in the absence of injury at intervals of 5 years. In case of injury a booster dose of toxoid should be given.

5. Treatment

There are a number of factors to consider when a person has an injury in which steps should be taken to prevent tetanus:

(1) The patient who was previously immunized against tetanus should receive a booster or reinforcing dose of 0.5 ml fluid of tetanus toxoid at the time of injury or as soon as possible thereafter. Toxoid has a great advantage over passive or temporary immunization with tetanus antitoxin, and prevents any risk of horse serum reactions, which are not uncommon. Naturally the wound should be cleaned and dead tissue excised. Antibiotic therapy is recommended and is very effective against the vegetative form of the tetanus bacillus if they can reach the foci of infection.

(2) The patient who has had no previous immunization against tetanus must of necessity receive passive or temporary immunization provided they are not sensitive to horse serum. The injection of tetanus antitoxin varies considerably. Public health authorities recommend 3000 to 5000 units of tetanus antitoxin provided the patient is seen on the day of injury and there are no compound fractures, gunshot wounds or other wounds not readily described. If delay is greater or complications exist, the recommended dose is 6000 to 10,000 units or higher.

(3) For the individual who has signs of tetanus they have recommended a single large dose totaling 50,000 to 100,000 units of tetanus antitoxin intravenously and intramuscularly. Some physicians recommend that 10,000 units be infiltrated around the injury.

Bovine tetanus antitoxin is available for the individual who is sensitive to horse serum. More recently human tetanus antitoxin

(immune globulin) has become available. This human tetanus antitoxin which is hyper-immune gamma globulin, is derived from the serum of persons who have been hyper-immunized against tetanus.

Human tetanus antitoxin has a number of advantages over equine or bovine tetanus antitoxin, including the obvious fact that there is no need to inquire or test for sensitivity. (Properly prepared, human immune globulins do not, as far as is known, transmit serum hepatitis).

(1) Human tetanus antitoxin does not cause any allergic or anaphylactic manifestations that are associated with horse or bovine antitoxin.

(2) Human tetanus antitoxin gives protective levels of circulating antibodies for much longer periods of time at much lower dosage than does equine or bovine antitoxin. The currently recommended dose is 500 units intramuscularly following injury, although more recently the Massachusetts Public Health Laboratories have demonstrated that 250 units is adequate when given at time of injury. The 500 unit dose as well as the 250 unit dose both give protective antibody level for 3 to 4 weeks.

(3) Human tetanus antitoxin given at the time of injury will not interfere with the primary immune response to the tetanus toxoid given at the same time in another site and may actually enhance it. Thus, when the second dose of tetanus toxoid is given in 4 to 6 weeks, continuous protection will be provided as the antibody produced by the toxoid replaces the slowly disappearing passive antibodies.

The increasing availability of human tetanus antitoxin, will eventually replace the use of equine or bovine antitoxin and the attendant risks of anaphylaxis and serum sickness.

The availability of human tetanus antitoxin should not decrease the efforts toward active immunization of all persons with toxoid prior to injury, or the initiation of active immunization with toxoid at the time of injury.

There is no reason that any human being should suffer the agonies of tetanus today. With proper immunization with tetanus toxoid in childhood and boosters or reinforcing doses every 4 to 5 years until adulthood, and occasional doses thereafter, the population could be protected against tetanus throughout their lives.

VI ANIMAL INFLUENZA

The term 'influenza' has been used to describe acute respiratory diseases in animals almost as long as the word has been used to describe human illness. The first mention of equine influenza in the English literature was in 1688. The disease is reported to have begun and ended its course within a few months. During the pandemic of human influenza between 1728-1733 there were many reports of coincident disease in man and horses. Similar reports followed in the 18th and 19th century The last epizootic of horse influenza that affected the nation was that of 1872-1873, when traffic in New York, Boston and Washington D.C. came to a halt because there were no healthy animals to draw the horse carts, drays and delivery wagons. As the horse population declined from a high of 20,000,000 in 1910 to less than 3,000,000 in 1962, the disease called influenza declined and only occurred sporadically.

In 1948 veterinary virologists demonstrated a virus that was thought to be the cause of equine influenza. This virus was not related to the influenza A or other groups that cause human disease, nor does it cause disease in any other species than the horse.

A new form of equine influenza was reported by Swedish investigators in 1955. In 1956 this infection spread through central and eastern Europe. Later, it appeared in western Europe and by 1960 it was identified as the cause of 'flu outbreaks among horses in the United States. The aetiological agent, a myxovirus that is related to the group A influenza group was isolated in Czechoslovakia in 1956. Although this agent belongs to the type A influenza virus groups, it does not affect man, including those who handle diseased horses or the virus in the laboratory. It is described as A1/equine/Prague/56.

A recent report from the United States indicates that horses are also susceptible to an influenza type A2/equine/Miami/63. Horses develop a fever 103°-105°F, dry cough, general malaise and loss of appetite of varying degree under natural conditions and when experimentally exposed. There is no evidence to indicate that horse influenza strains may be the source of viral respiratory infections for man.

1. Swine influenza

Swine influenza is an acute respiratory disease which is frequently seen in the late summer, fall and winter and is caused by a group A influenza virus. The onset is sudden and the attack rate high. Virus pneumonia of pigs is very similar and cannot be differentiated clinically. Swine influenza or hog flu was first recognized in September 1918 in Iowa when the pandemic of human influenza was rampant. Most veterinary epidemiologists are of the opinion that swine 'flu was contracted from man originally in 1918 Surprisingly, the disease in swine has persisted with hardly any variations for almost a half century How the infection persists is not understood Shope has demonstrated that the virus can be found in lung-worms of swine, and that it is passed out in the ova, which in turn are ingested by earthworms where the virus remains, until the earthworms are ingested by swine. Then the lung-worm larvae leave the earthworm, and complete their biological cycle by migration to the lungs where the lung-worm reaches maturity. The swine influenza virus causes a mild respiratory infection experimentally, but if a bacterium, hemophilus suis is introduced, about 50 per cent will develop a clinical disease, from which both the virus and bacteria can be recovered. The immunity in swine is of short duration. Animals may contract the disease several times during their comparatively short lives. Medical investigators find swine influenza an interesting problem for study because the virus may be a residual of the great pandemic of 1918. Practically all of the human population born before 1918 are said to carry antibodies against this virus. Whereas those born afterwards show a continuous decline of these antibodies. Some investigators speculate that when the swine influenza antibodies disappear in the human population at the close of this century this disease could become a public health problem. If that should occur, an effective vaccine could be made to protect the human population. As far as can be determined, there is little evidence today that swine influenza causes disease in man, although it may cause infection which can be recognized by the antibody titre in human sera.

2. Avian influenza

A severe sinusitis has been seen in 1956 in ducks in Czechoslovakia from which a group A influenza virus has been recovered. The disease had a high attack rate, affecting 40 per cent of the ducks on the farm where it appeared, with an equally high case fatality rate. Fortunately, the disease is not transmissible to man.

Another group A influenza virus has been isolated from young ducks in England in 1942. This infection was only seen in England and apparently died out after its brief appearance. No human infection was attributed to this agent.

Fowl plague is an acute, highly fatal disease of chickens which was first recognized about 1880. The disease was never a problem in the United States, although it was present for a short period in the 1920's. The virus of fowl plague is closely related to the group A influenza agents, and some authorities believe it should be considered a species. Human infection is practically unknown, although the virus has been recovered from a veterinary investigator, who was seeking the disease in the field. In this case it is thought that the virus was able to establish itself in man as the patient was suffering from infectious hepatitis concurrently.

3. Other animal infections

Occasionally reports are received of influenza in dogs, cats, cattle and sheep. Epidemiologically, none of these infections are of concern to the public health. Feline influenza is correctly described as feline pneumonitis and is caused by a large virus belonging to the Bedsonia group (psithicosis-lymphogranuloma). It is not transmissible to man. Dog influenza is a misnomer for canine distemper, a viral disease which causes pneumonia, enteritis and encephalitis. It likewise does not affect man.

Bovine influenza was described in Japan in 1889, and until 1953 the etiology was unknown. At that time American investigators demonstrated that a disease called bovine encephalitis was due to a Bedsonia group agent. Shortly thereafter, Japanese veterinarians

reported that bovine influenza was due to the same agent. Additional viruses have also been associated with respiratory diseases in cattle which are described as para-influenza viruses. Type 3 para-influenza found in cattle appears to be closely related to a similar agent found in children that have upper respiratory infections. There is no evidence that animals are a reservoir.

Sheep are known to be susceptible to group A influenza viruses, but there are no epidemiological data to indicate that they have a role in maintaining any influenza viruses in nature.

4 Summary

There is considerable data evidence that some animals are susceptible to human group A influenza virus, namely swine, horses and sheep but there is no epidemiological data to indicate they are a source of infection for man except swine. The swine 'flu virus apparently can produce an antibody response in man, and possibly a mild disease that is seldom recognized as such.

The World Health Organization inaugurated a world-wide surveillance of influenza in 1956 when Asian 'flu appeared. Some of the expert advisers to WHO believe that there may be an extra-human reservoir of influenza virus in nature, possibly in mammals either domestic or sylvatic, or in birds. The evidence at hand does not support this, but it is of sufficient interest to world health that this possibility should be explored thoroughly.

VII THE ANIMAL POXES

The pox diseases in both man and animals are characterized by the formation of pustules on the skin, with or without generalized illness They occur in all domestic animals except dogs and cats; namely cattle (cowpox), swine, sheep, goats, horses, camels, buffaloes, rabbits and mice. Birds are also subject to pox infections, which are immunologically different from the animal pox. Turkeys, chickens, pheasants, pigeons, canaries and many wild birds are not infrequently infected with the avian pox viruses. Some medical historians believe that all of the pox diseases originate from a basic virus, which in time have changed with their adaptation to various hosts.

The pox viruses are fairly large being of the order of 150 to 200 millimicrons in diametre. These viruses usually only invade epithelial tissues, where they form inclusion bodies, which in turn contain the smaller elementary bodies that are the virus.

Man can be successfully infected with the cowpox virus, and cattle are susceptible to the smallpox virus. Immunologically, these two viruses are very closely related to each other, and also to the horsepox virus. Man is not known to be affected by the other pox viruses which cause disease in sheep, swine, camel, buffalo and goats, or those affecting birds. A pox disease is occasionally seen in monkeys and other primates which is difficult to diagnose, but has been described as either monkey-pox or chicken-pox (human origin). The former agent is immunologically related to the vaccinia virus.

Mammalian pox is a rare disease in the United States and Europe, and no measures are taken to control it. Occasionally true cowpox may occur but usually it is self-limiting. Sometimes the vaccinia virus will spread from recently vaccinated persons to milch cows, and they in turn will carry back to persons who may have an eczema or weeping lesion. Persons newly vaccinated should not handle milch cows until a scab or immune response has appeared. When smallpox was present in the United States cowpox was quite common, which leads one to suggest that cowpox is a modified form of smallpox. Likewise, horsepox can spread to cattle and man when the opportunity arises. It is also suspected that newly vaccinated persons may infect horses with vaccinia virus, causing vesicles around the muzzle, lips and throat.

Another form of pox disease seen in the United States today is pseudo cowpox, which is not related to the true cowpox. This virus causes a condition in man called milkers nodules. These nodules usually appear on the hands and forearms, regardless whether the person has been vaccinated with vaccinia virus. The disease is spread among cows by the milker's hands or contamination of the milking machines. Non-lactating animals and bulls rarely become involved.

The milker's lesions are usually a single nodule, but there are some cases described where as many as forty nodules were seen on one hand The lesions begin as papules, five to seven days after exposure. They gradually enlarge into firm elastic, purplish, smooth hemispheres, varying in size up to 2 centimetres. They are relatively painless but do itch. When fully developed they have a dimple on the top, but do not break down with pus formation. They are highly vascular. After maturity, the granulation tissue that makes up the mass of the nodule gradually becomes absorbed, the lesion slowly flattens and disappears in six to eight weeks. Sometimes there may be a slight swelling of the axillary lymph node

The disease is rather common in cattle, but relatively rare in man, indicating that man is relatively resistant except under unusual circumstances

Swinepox is unusual in that two different viruses may cause the disease. One is a vaccinia-like virus seen only in the Old World. Pigs can be immunized against this disease with vaccinia. Presumably man could be infected with this swine birus, but there are no reports to that effect in the literature. The other swinepox-like virus is not related to the vaccinia group. This agent is seen in the United States but does not affect any other species, including man. This latter agent is transmitted by the hog louse (Hematopinus suis). It is also believed that other biting insects can carry the virus. The disease usually disappears as soon as cold weather eliminates the insects.

Sheep-pox is a very serious economic problem in Africa and Asia, and formerly in Europe. It is believed that sheep-pox is the first disease in which variolization was practiced in which shepherds used a thorn to carry a small inoculum from animal to animal when the disease appeared. Sheep-pox is much like smallpox in man, causing a generalized eruption of the skin, and similar lesions on the mucous membrane of the pharynx and trachia, as well as the alimentary tract. Haemorrhagic inflammation of the respiratory tract and digestive tract also occurs. Pneumonia is a frequent complication. The mortality varies from five to fifty per cent and higher.

Vaccination against the disease is commonly practised in enzootic areas. Fully virulent lymph from skin vesicles is injected interdermally into the skin or rubbed into a scarified area. Fortunately, man is not susceptible to sheep-pox or any of the goat-pox infections.

Goat-pox is a moderate disease and does not cause haemorrhagic lesions. The mortality is much less than sheep-pox.

Buffalo-pox has only been reported in southern Asia, where it is seen among work animals. It may also affect cattle, which have confluent lesions covering the body, similar to that seen in the buffalo. It apparently is not transmissible to man.

Camel-pox is confined to Africa and the Middle East. It is usually observed in the young animals. Vaccinia is said to protect the young camels. There are no reports of its transmission to man or other species.

Mouse-pox or ectromelia is a highly infectious, often fatal, disease of laboratory mice. In nature, it persists as a chronic asymptomatic infection with low mortality. It does not affect other species. Vaccination in the foot pad with commercial vaccinia vaccine will provide good protection against ectromelia.

Rabbit-pox is an acute generalized disease of laboratory rabbits, characterized by skin rash, fever, nasal and conjunctival discharges. Mortality is quite high. The disease has not been observed in wild rabbits, which raises questions as to its origin. The causal virus is a member of the vaccinia group. Rabbit pox can be controlled by the use of vaccinia vaccine. Animals so inoculated are immune.

The fowl-pox that affects chickens, turkeys, canaries, pheasants and wild birds is caused by a virus that is immunologically different from the mammalian pox group. The disease causes tumor like lesions. It is spread by insect bites, injuries and inhalation. Spread by direct contact is slow. There are no carriers among recovered birds. The virus can survive for long periods in scabs. Mortality is generally low except for canary pox. None of the avian pox viruses affect man or mammalian species.

VIII CONTAGIOUS ECTHYMA

Contagious ecthyma, or sore mouth, is an infectious dermatitis of sheep and goats affecting primarily the lips of young animals. It is seen in all parts of the world where sheep and goats are raised, usually in the summer and early fall. The nature of the lesions warrant its inclusion in pox diseases that affect man and animals

The disease is caused by a virus which causes vesicles and pustules on the skin of the lips and sometimes the nose and eyes. These vesicles rapidly change to pustules and finally thick scabs. The virus is highly resistant to dessication and is reported to survive for years in scabs that have been held at a moderate temperature. It has been demonstrated that viable virus will survive in scabs that fall off from recovered animals. These scabs contaminate the soil and cause infection in new-born animals the following year. Contagious ecthyma seldom causes mortality except when complications occur due to secondary invasion by the necrosis bacillus (Spherophorus necrophocus), or parasitic infestation by the screw-worm (Cochliomyia Americana) larva. It is not uncommon for ewes, suckling infected lambs, to develop lesions on their udders.

Field studies in Texas revealed some years ago that lambs and kids which recovered from this disease were solidly immune thereafter. Later, experiments demonstrated that it was possible to immunize them successfully with a technique similar to that used for vaccinating man against smallpox. The vaccine consists of fully virulent material contained in the dried scabs, which is ground and suspended in glycerol and saline solution. This is applied with a stiff bristled brush to a superficially scratched area. A pustular lesion develops at the site of the inoculation. This becomes covered with a scab later, which falls off after several weeks.

The disease in man* is an occupational problem among shepherds, veterinarians and others who may handle sick animals, or the viable vaccine. The lesions begin as abrasions. They consist of rather large

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*Known as Orf in Australia

vesicles that may be multiple in structure. The surrounding skin becomes inflamed and swollen, and may be quite painful. The patient may have some fever and there may be a moderate swelling of the axillary lymph nodes when the hands or arms are involved. Occasionally there may be lesions on the face or genitalia which may be quite proliferative and distressing. Secondary infections are frequent and healing is often rather slow. Naturally, such complications result in incapicitation.

Diagnosis in man is usually based on history of occupation and exposure to infected animals, handling of vaccine, or self-inoculation. Confirmation of the diagnosis is established by transmitting the virus from man to a susceptible lamb or kid. Complement fixation test may be a value in the diagnosis.

Treatment is non-specific, except for antibiotic to eliminate secondary bacterial infections, and analgesics to relieve discomfort. It is thought that an individual who has had the disease, or been exposed, is usually resistant to further infection.

IX COLORADO TICK FEVER

Colorado tick fever appears to be a widespread disease of small animals in western United States where the infection is spread by the bite of the wood tick (Dermacentor andersoni) and other ticks in this area. It is thought that squirrels, rabbits and porcupines as well as other rodents constitute the reservoir in nature. Experimentally various laboratory animals including mice, hamsters, cotton rats as well as opossums develop viraemia. Domestic animals do not appear to be susceptible.

The disease occurs in the western states and adjacent areas of Canada during the peak of the tick season. It was first described in 1930 although it is thought to have been widespread for a hundred years or more. In 1944 the virus, a small one of ten millimicrons, was first isolated in Colorado. Since then it has been recovered from New Mexico to British Columbia.

In man, the disease is an acute febrile disease of a biphasic nature with an erythematous rash. The infection begins with clearly defined onset: chilly sensations and severe body pains. The disease is

characteristically mild but can be severe in children, with signs of encephalitis. Diagnosis is based on a history of exposure to ticks, a biphasic temperature curve and a leukopaenia

Laboratory confirmation is by the isolation of the virus from the blood. Serological tests are of little value as the antibodies form slowly and may not be evident for two or three weeks. Second attacks are unknown indicating that a good immunity results from the disease.

There is no specific therapy. Prevention of disease is the avoidance of the tick infested areas, and the immediate removal of any ticks attached to the body. Suitable clothing impregnated with tick repellants is recommended. There are no satisfactory vaccines available.

Tick paralysis

Tick paralysis does not resemble the tick-borne fevers in any way. It is caused by a neurotoxin produced by the female tick during feeding. Most cases in man and animals are seen in the spring and early summer. The disease is described as a flaccid, afebrile, ascending motor paralysis. It has been recognized in North America, Australia, South Africa and Europe. In North America the disease is found in north-western United States and the adjoining regions of Canada. The wood tick (Dermacentor andersoni) is the principal cause of the paralysis in this area. Tick paralysis has occasionally been diagnosed in some of the eastern and southern states, where it is caused by the dog tick (Dermacentor variabilis), Lone Star tick (Amblyomma americanum) and the Gulf Coast tick (Amblyomma maculatum).

Sheep, dogs and man appear to be particularly susceptible to the neurotoxin; one tick being able to cause the paralysis. In one instance observed at a state university veterinary hospital, a 2,000 pound bull was paralyzed and after a diligent search, one lone tick was found on the neck just behind the head. There are reports from Wyoming, Montana and British Columbia where large numbers of cattle and sheep have been heavily infected with considerable loss.

The paralysis can be produced experimentally in guinea pigs, hamsters and marmots. Symptoms are gradual with the first signs being incoordination in the hind limbs. Reflexes disappear but sensation is present. The paralysis ascends slowly for two to three days until the victim is immobilized. Further advance results in respiratory failure and death. No lesions aside from the tick bite can be seen in these experimental animals nor in naturally infested animals or man.

The diagnosis of the disease in animals, as well as man, is based on the appearance of the signs described and the presence of ticks. Usually the female ticks must have been attached and feeding for six to seven days before signs of paralysis appear. This allows animals to travel to areas where ticks may not be present. Man usually has such an experience. In livestock the ticks usually attach themselves to the head, whereas in man they may be found in any part of the body.

Prevention consists of the avoidance of tick infested fields during the tick season. People entering known infested areas should wear close fitting garments that have been impregnated with available mosquito repellents. Persons should examine themselves nightly and their clothing daily before dressing.

Therapy is the removal of the offending tick. Within minutes after the removal of the offending tick, that is secreting the neurotoxin, the patient dramatically improves. Within twenty-four hours they will be up and around with no residual signs of paralysis. The most unfortunate experience is to find a tick attached to the deceased victim.

X ENCEPHALOMYOCARDITIS

Encephalomyocardis, or EMC, is a virus disease found in many parts of the world, in a wide range of animals including primates, mongooses, squirrels, rodents and swine. It has also been recovered from mosquitoes in Africa. The disease usually occurs only in warm climates except those cases caused by laboratory accidents. In the United States the natural occurring disease has been mainly reported in the southern states. There it is commonly found in rats and swine, and on a few occasions in squirrels. Rodents do not seem to have any obvious disease signs, whereas

swine become quite ill - suffering from depression, loss of appetite, fever and in some instances cardiac failure and encephalitis. The disease has become so common in some areas that veterinarians can now diagnose it from the clinical signs. The disease in squirrels causes encephalitis signs which are confused with rabies.

The aetiological agent is a small virus of less than thirty millimicrons. It is quite stable and apparently can survive in rodent and swine faeces for some time under moderate conditions. The natural transmission among rodents and swine is believed to be by the ingestion of food or water contaminated with animal droppings and urine. The role of squirrels as a reservoir of virus is unknown. Other small animals found in enzootic areas and examined for signs of EMC were uniformly negative.

The clinical features of the disease in man vary from a mild febrile "three-day fever" to a severe encephalitis from which the patient recovers within a week with no recognizable sequellae. A febrile disease with lymphocytic pleocytosis and some CNS involvement is the most frequent form in those human cases which have been well studied. Myocarditis, fortunately, is not one of the symptoms observed in man. Severe headache, nuchal rigidity, photophobia, vomiting and delirium have been seen by some observers. Other cases described include such findings as high fever reaching 104°F and persisting for two or three days accompanied by pharyngitis, stiff neck, and hyperactive deep reflexes. The only notable laboratory finding has been the pleocytosis of from 50 to 500 cells, principally lymphocytes in the spinal fluid. All of the patients recovered with no relapses or sequellae There are no reported fatalities.

The diagnosis of EMC in man depends on the isolation and identification of the virus, and the demonstration of specific antibodies. The symptoms and signs of disease in man are not sufficiently diagnostic to differentiate it from other febrile neurologic infections.

Treatment is symptomatic and supporative.

XI VESICULAR DISEASES

Vesicular diseases of animals are most serious infections that attack cattle, sheep, goats, swine and to a lesser degree horses, mules and donkeys. They may also affect a wide variety of cloven hoofed wild animals. The vesicular diseases are acute, highly contagious and characterized by a short immunity following an attack, hence the same disease may recur. The pox diseases which have been described previously differ in that the lesions begin as papules and change to pustules; also they have an enduring immunity and seldom recur in the same animals.

1. Foot and mouth disease

Foot and mouth disease occurs in most of the cattle raising areas of the world, except Australia, New Zealand and North America. The disease is exceedingly contagious and can be controlled only by complete eradication. The United States has had ten invasions of the disease in the past century. Each has been stamped out. The last outbreak was in 1929, thirty-four years ago. More recently there were epizootics in Canada (1951-1952) and Mexico (1946-1952) which caused considerable concern in the United States.

Foot and mouth disease is the most feared disease of cattle the world over. Periodically, the disease sweeps across Europe from south to north, or east to west in great panzootics. Eastern Europe has had an unusually severe panzootic this past year. In these areas the disease never completely disappears but remains active in small infected zones, from which it spreads when new susceptibles appear. The importance of foot and mouth disease lies not so much in its case fatality rate but in the morbidity losses, loss of flesh, milk, abortion and even sterility.

The disease in cattle is characterized by depression, fever and the appearance of vesicles on the mucous membranes of the mouth and the skin of the muzzle, around the feet and on the teats. They may also extend into the trachea, oesophagus and rumen. The aetiological agent is one of the smallest viruses in nature, being less than twenty-five millimicrons in diameter and spherical in shape. It is very resistant to freezing and thawing, and will survive in the cold for long periods. It appears

to be quite sensitive to heat, although recent experiments have demonstrated that some particles, probably the incomplete virus, can live for many hours at temperatures much above that of pasteurization. There are at least seven different immunological types of foot and mouth disease virus, three of which are described as European types A, O, C; three South African types 1, 2, 3; and one Asian type. Some of these also have subtypes, or variants, which make immunization even more difficult.

The most serious aspect of the foot and mouth disease is the carrier phase in animals that recover from the disease. Sometimes sporadic cases occur months after the original outbreaks have run their course. Even though it is difficult to demonstrate the virus, all evidence at hand indicates that the virus persisted in some recovered animals. The virus may also survive outside the animals in darkdamp areas for long periods. Hence thorough physical cleaning is necessary. It is also known that the virus may be shipped to distant parts of the world in infected meat. For this reason no fresh meat can enter the United States from known enzootic areas, South America, Asia, Africa and Europe. The recent epizootic (1960) in England began with swine fed on cooked garbage in which the virus was able to survive. The last outbreak in the United States (1924 and 1929) began in swine fed on garbage that contained meat scraps that originated in Asia and South America. As a result of these experiences, ships or aeroplanes coming from countries where foot and mouth disease exists are not allowed to land garbage in any of our ports.

The disease in man is quite rare although there are occasional cases reported. Only this year three cases were reported in German laboratory workers and another in a butcher. There have been no recognized cases of human infection in the United States since the 1914 outbreak, nor were there any during the Mexican and Canadian outbreaks a decade ago.

The symptoms in man are fever, a sense of heat and dryness in the mouth, vomiting and the development of small vesicles on the lips, tongue and cheeks, as well as on the hands and arms. The course of the disease is short and no serious complications or death has been reported in substantiated cases. Confirmation of the foot and mouth disease is by the isolation of the virus from the vesicles.

2. Vesicular stomatitis

Vesicular stomatitis occurs naturally among horses, cattle and swine. The disease may also occur in feral swine, raccoons and deer. Experimental infections have been produced in sheep, ferrets, hamsters and chinchillas. The disease is very similar to foot and mouth disease with vesicles in the mouth and occasionally on the feet, although they are not nearly as severe. The great danger of disease is its similarity to foot and mouth disease from which it must be properly differentiated when it appears in cattle or swine. Inasmuch as foot and mouth disease does not effect horses, vesicular stomatitis in horses is of little concern.

The virus is much larger than the foot and mouth disease virus, being sixty to ninety millimicrons in size. It appears to be more resistant than the foot and mouth disease virus to chemical agents and heat. It can survive 64°C for up to thirty minutes. The disease occurs sporadically in the United States and Canada during the summer months, and disappears after the first killing frost. In Mexico and tropical America it occurs the year round, although more frequently during the dry periods.

The disease has been reported in man, especially among veterinarians, laboratory workers and animal handlers. The virus has been recovered from the lesions of some persons. The disease is generally mild and influenza like, although some cases have been quite severe. The disease has a sudden onset with fever, chills, malaise and muscle soreness. Stomatitis and tonsillitis are seen in some cases. A few show a diphasic fever curve with a second peak about five days after the first. Some patients have prolonged weakness and malaise although most recover in a week or two. The demonstration of neutralizing antibodies in the patients' serum is confirmatory. In south-eastern United States many persons have neutralizing antibodies but do not recall having had the disease, which would indicate that it may affect man much more frequently than it had been previously suspected.

3. Vesicular exanthema

Vesicular exanthema occurs naturally only in swine. All other experimental animals, except hamsters, horses and dogs, are refractory to the infections. Man is also completely resistant even though attempts have been made to produce infection experimentally. There are at least seven serological types of the virus, all immunologically distinct. The virus is a very small one being between fourteen and twenty-two millimicrons. It can survive for long periods in infected tissues without loss of virulence.

The disease was first observed in California in 1932 where it was thought to be foot and mouth disease. Later it was demonstrated to be a new disease, unknown to exist anywhere else in the world. For many years it was only seen in California among garbage fed hogs, or among those in contact with them. In 1952 vesicular exanthema spread across the United States in a matter of months, just twenty years after it was first recognized. A national eradication campaign was initiated and the disease was eliminated by 1956, and has never reappeared in the United States or any other place in the world. A truly remarkable feat. The biological eradication of a disease.

XII LISTERIOSIS

Listeriosis is usually an acute meningitis with or without septicaemia in man and animals. Less frequently a septicaemia occurs without any involvement of the central nervous system. Occasionally the bacterium, Listeria monocytogenes, is the cause of localized abscesses, pustular or papular cutaneous lesions and abortion.

L. monocytogenes (formerly Listerella monocytogenes) is a small Gram positive, non-spore forming, extremely resistant diphtheroid rod. Coccoid elements are commonly found. The bacteria are widespread in nature but are difficult to isolate from blood and various tissues. Growth that resembles streptococci occurs on most ordinary laboratory media.

Diagnosis is possible only by the isolation on blood agar plates and subsequent identification of L. monocytogenes. The presence of small Gram positive rods in stained smears of meconium is presumptive diagnosis in neonates. Stained spinal fluid smears showing intra- or

extra-cellular Gram positive bacilli along with an increased number of mononuclear cells is highly suggestive in meningitis. In other tissues, such as blood, vaginal discharge, amniotic fluids, placenta, pus, the presence of Gram positive rods is not of diagnostic significance inasmuch as saprophytic diphtheroids may be seen frequently in these tissues as contaminants. Serologic tests with the patient's sera are of little or no practical value.

The clinical signs and symptoms range from those of meningitis, septicaemia, localized abscesses, cutaneous lesions, conjunctivitis to an infectious mononucleosis-like disease or a mild influenza.

In meningitis the onset is usually sudden. There is fever, intense headache, nausea, vomiting and signs of meningeal irritation. In the newborn there may be a petechial rash. Delirium and coma often appear early, and some cases actually begin with collapse and shock. These acute cases are usually complicated by septicaemia.

In less severe septicaemias, many different symptoms are encountered, ranging from the more acute to mild or benign cases. If the patient is pregnant the infection may invade the uterus and lead to abortion, stillborn children, or newborn who may have a septicaemia or meningitis in the neonatal period. The mother in these cases is seldom affected.

The mortality in all severe forms of the disease is high in spite of modern chemotherapy, ranging from 70 per cent in premature babies to 40 per cent in neonates. Mortality in adults may be as high as 50 per cent.

Differentiation of listeriosis from infectious mononucleosis and toxoplasmosis is difficult especially when eye lesions are paramount. In these cases positive laboratory findings for abnormal lymphocytes, liver flocculation and serum enzymes are pertinent in infectious mononucleosis. Likewise, in the diagnosis of toxoplasmosis, certain laboratory tests, e.g., methylene blue dye, complement fixation, haemagglutination and FA, being positive are significant.

The occurrence of listeriosis has no specific pattern and is generally said to be sporadic. There are no reported epidemics involving more than a few individuals. There are no obvious seasonal patterns. The highest incidence is among low income or slum dwellers

in urban areas, where most of the cases occur in the newborn. Most of the adult cases occur after the age of forty and are sometimes secondary to primary disorders of other aetiology. The incidence of human infection is unknown but more than 100 cases are said to occur annually in the United States. Inapparent infections are thought to be widespread in all age groups and only cause complications in pregnant women.

The incubation period is unknown but is estimated to be from four to twenty-one days. It is not known when the foetus becomes infected after the occurrence of disease in the mother but it is thought to take place shortly afterwards.

There is no evidence that the disease is communicable from person to person except from the mother to the foetus. Mothers of infected infants may shed the L. monocytogenes for seven to ten days after delivery in vaginal discharges and urine. These contaminated discharges can cause papular lesions on the hands and arms. The mode of transmission is generally unknown except for those mentioned above.

The reservoir and sources of infection for man are thought to be healthy carriers among domesticated and feral animals, fowl and man. The bacteria are frequently found in silage on farms where cattle outbreaks have occurred. The organism is sometimes recovered from sewage and water. Epidemiological investigations have not turned up any definitive sources of human infection except for newborn which are infected in utero. Infections beyond the third week of life are thought to be extra-maternal in origin. Few human cases can be traced to direct contact with infected animals or animal products. Some authorities (M.L. Gray) thought that the human carrier rate may be higher than suspected, and that active infection is incited by physical or physiological stress (pregnancy).

The disease in animals, listeriosis or listerella, as it was called when first described in gerbilles (an African rodent) in 1927, is a world-wide infection in rodents, rabbits, chickens, sheep and cattle.

In the gerbille the disease is described as being plague-like. Rabbits when infected experimentally have a marked mononuclear leukocytosis, focal necrosis of the liver, necrotic areas in the myocardium and extensive involvement of the meninges. Similar lesions

are found in the guinea pig and rodents. The natural disease in the gerbille (Tiger River disease) presented similar lesions. When the organism was instilled in the eyes of rabbits it caused conjunctivitis as well as abortion. The addition of L. monocytogenes to the drinking water will cause abortion in pregnant does and sometimes death. Non-pregnant and male rabbits are not noticeably affected.

Sheep are quite susceptible. The most characteristic sign is circling, due to the meninges irritation, which gives rise to the name "circling disease". Cattle likewise suffer from an encephalitis. Affected sheep and cattle show signs of depression, weakness, incoordination, fever, walking in circles, pushing against objects, progressive paralysis and death within two to three days.

Swine are known to be susceptible; the symptoms are vague, suggestive of brain irritation and disturbances of consciousness. Baby pigs which are infected suffer from diarrhoea, weakness and stiffness.

Horses in which the disease was confirmed have nervous symptoms consisting of paralysis of the jaw and throat muscle, as well as incoordinated gait. The organism was isolated from the liver and musculature.

Foxes in which the disease was recently described were thought to have been rabid and when no Negri bodies or evidence of rabies virus was found, were then examined for other causes of encephalitis which caused the irrational behaviour. L. monocytogenes was isolated from five of twenty (25 per cent) fox brains so examined.

Chickens and birds are susceptible. The most common lesions (necrotic myocarditis) are emaciation and general weakness. The lesions are oedematous tissue, fluid in the body cavities and the pericardial sac, and focal necrosis of the liver. No brain lesions were described.

Control

The immunity of listeriosis in man and animals is not understood. Immunity, if it does exist, is difficult to measure. There are no satisfactory serological methods and animal experiments are equivocal. There is also the problem of different agglutinating groups, of which

there are five types. Type I is a rodent type (rabbits and gerbilles), and is found in man. Type II is a ruminant type found in sheep and cattle and occasionally in man in Europe. Type III is rare in the United States. Type IV (a) and (b) are the most frequently isolated from man and animals in the United States.

Vaccination experiments in sheep and cattle have not been encouraging. Some vaccinates resist challenge but others develop acute or chronic disease. Animal health authorities point out that even if immunization procedures were effective, the sporadic nature of listeriosis in farm animals is such that vaccination would not be practical, except in the face of an epizootic. There is likewise no need for human immunization in the light of the sporadic incidence recorded to date.

Chemotherapy has been practised in animals since the disease was described twenty-five years ago. The sulpha drugs were used successfully until the broad spectrum antibiotics became available. Today these drugs are used in combination or separately, although the antibiotics are recommended. To be successful, treatment should begin early before the animals are prostrate or have signs of encephalitis.

Human treatment has followed a similar regime since the disease was first recognized. The tetracycline antibiotics are the preferred drugs for human therapy. Authorities in the field recommend that they be given immediately in suspected cases and for sufficiently long periods to prevent relapses. In some cases the disease has appeared in adults who have been receiving steroids for other causes. Naturally, steroid therapy should be halted and massive doses of tetracycline antibiotics administered.

Preventive measures include health education of pregnant women to avoid contact with contaminated materials or infected animals on farms where the disease is endemic. Likewise, farmers, ranchers, and veterinarians should exercise proper precautions in handling aborted materials.

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ISOLATION OF LISTERIA MONOCYTOGENES FROM FOXES SUSPECTED OF HAVING RABIES*

I SUMMARY

Twenty fox brains submitted for rabies examination because the foxes had signs of encephalitis were examined for Listeria monocytogenes. After repeated culturing, 5 of these specimens were found to be infected. Brain tissue from only 2 of 4 infected foxes caused death in mice after intracerebral inoculation.

Until 1960, numerous cases of animal rabies were diagnosed in Georgia each year. Foxes were frequently found to be infected and, for the seventeen years from 1945 to 1962, accounted for 25% of the 5,647 laboratory-confirmed cases of rabies[10]. The incidence of fox rabies declined during the late 1950's, and during 1961 no infected foxes were found. Two cases of rabies in foxes were diagnosed in 1962 and three in 1963.

Beginning late in 1962, the number of foxes submitted to the Georgia Department of Public Health for rabies examination increased. These foxes were usually suspected of being rabid because of their unusual behaviour. They had been observed biting cattle, entering houses, attacking dogs, having "fits", running in circles, pawing at their head, or lingering close to human habitats. Although such signs suggested encephalitis, tissues from these foxes were negative to rabies diagnostic tests.

Mice inoculated with brain suspensions from these foxes occasionally died within two to five days. Such early deaths are not caused by rabies virus but may be caused by an overwhelming bacterial infection. Since the bacterium most commonly causing encephalitis in domestic animals is L. monocytogenes, it was decided to examine the brains of rabies-suspect foxes for Listeria in addition to the usual rabies diagnostic tests.

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Listeriosis is a disease found in man and numerous animal species in all parts of the world. In spite of its ubiquitousness, the origin and mode of transmission of listeric infections remain obscure. One investigator[5] reviewed 539 bacteriologically confirmed cases of listeric infection in man in the United States which occurred between 1933 and 1963. Although this has been considered a rare disease in man, 304 of these 539 cases were reported during the past four years. Cases have been reported from 42 of the 50 states, with infants and older adults most commonly affected. Of the 450 cases in which the course of the disease was known, 35% ended fatally.

In sheep and cattle, the most commonly infected domestic animals, encephalitis is a frequent manifestation of the disease. Other forms of listeriosis including abortion, pneumonia, septicaemia, and myocarditis have been found in sheep, cattle, goats, swine, horses and poultry. Only a few cases have been confirmed in dogs and cats [11].

A number of species of wild animals have been found infected with L. monocytogenes; most commonly, these are rodents or lagomorphs[11]. The role they play in the epizootiology of this disease is not known. In the United States, this organism has been recovered from three feral animals: 2 skunks[2,9] and a raccoon[4]. Commercially raised foxes[3] and ferrets[8] have also been found infected. In addition, the isolation of L. monocytogenes from foxes in Germany, the Netherlands, Sweden and Canada has been reported[11]. Infected foxes have also been found in Russia[7]. The only published report on the examination of rabies specimens for evidence of listeric infection is one in which it was reported that of 258 brains cultured, one, a fox brain positive for rabies, contained L. monocytogenes[1].

II MATERIALS AND METHODS

Histories of foxes submitted for rabies examination from late January to late May 1963, were studied. In those cases where the fox had signs of unusual behaviour suggestive of encephalitis, brain tissue was examined for L. monocytogenes.

The examination consisted of 1) direct culture of fox brain tissue, and 2) inoculation of mice with fox brain tissue suspensions. In instances where the mice died within five days after inoculation, pooled mouse brain tissues were cultured.

For direct cultures, 10% suspensions of fox brain tissue were prepared in sterile distilled water by grinding with alundum. Four white Swiss mice, four to eight weeks old, were each inoculated intracerebrally with 0.03 ml of a similar suspension. Brains of mice dying within five days after inoculation were removed for culturing. With sterile distilled water as a diluent, the mouse brains were prepared in a manner similar to the original tissue. Both fox and mouse tissue suspensions were held at 4°C. for approximately three months and recultured at 10- at 14-day intervals during this holding period.

Thin smears of the tissue suspensions were gram stained and examined to determine presence of gross numbers of bacteria as an indicator of optimum quantity of inoculum. Tryptose agar plates were streaked with one or more loopfuls. After 24, 48 and 72 hours' incubation, the cultures were inspected grossly with the transmitted light of a daylight argon lamp* and microscopically with an oblique method of illumination(6). When gram-stained smears of suspicious colonies revealed small gram-positive diphtheroid-like bacilli, pure culture studies were made on single colonies.

The following biochemical and physiologic tests were performed: carbohydrate fermentation tests, using 1.0% solutions of glucose, mannitol, maltose, lactose, sucrose and xylose in trypticase broth base; urease; Christensen's urea agar; indole, using 2.0% tryptone broth; nitrate reduction, using peptone broth with 0.2% potassium nitrate; citrate utilization; Simmons' citrate agar; methyl red test, using Difco MR-VP broth; and litmus milk reaction, using Difco litmus milk. The final readings were made after 72 hours at 37°C. Motility was tested with overnight broth cultures held at 25°C.

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* Dazor Lamp, Model 2324, Dazor Manufacturing Company, St. Louis, Mo.

III RESULTS

Seven isolations were made which had characteristics typical of L. monocytogenes. Original fox brain tissue yielded five isolates after varying periods of refrigeration, whereas mouse brain material yielded two, both on primary isolation attempts before refrigeration.

Gram stains on all cultures revealed moderately short, slender gram-positive bacilli, with no spores and very little pleomorphism. Biochemical patterns were fairly uniform, with only minor variation. Glucose and maltose were acidified without gas production. Mannitol, lactose and sucrose were unchanged after 72 hours incubation. Acid was produced in xylose by two of the cultures but not by the remaining five. Tests for indole and urease production, nitrate reduction and citrate utilization were negative The methyl red test was uniformly positive in 48 hours. After 72 hours, the litmus milk contained the typical acid without coagulation-zoning phenomenon in the lower three-fourths of the milk column, with the narrow alkaline zone near the top of the column There was tumbling motility in varying degrees in each of the isolates.

Of the five isolations from foxes which represented three serotypes of L. monocytogenes, two were type 1, two were type 4b and one was type 4a. Brain tissue from seventeen foxes was inoculated into mice. Mice in five of the seventeen inoculation groups died within five days. The deaths of mice in only two of these five groups was caused by Listeria. Brain tissue from two foxes (L48 and L49) found to contain L. monocytogenes by cultural methods, failed to cause the death of any mice.

A total of twenty foxes (from fifteen Georgia counties located in various parts of the state) were examined for L monocytogenes (Table 1). Of these five were found to harbour Listeria. Each of the infected foxes came from different counties representing widely separated parts of the state.

TABLE 1

Results of Testing Georgia Foxes for Listeria monocytogenes

(January to May, 1963)

Fox (No.)	County of origin	Culture results		Mortality*
		Fox brain	Mouse brain	
L1	Hall	+ (Type 1)	+ (Type 1)	4/4
L2	Crawford	-	...	0/4
L3	Houston	-	...	0/4
L5	Towns	-	...	0/4
L8	Gordon	-	...	ND
L9	Morgan	-	...	ND
L10	Haralson	+ (Type 1)	...	ND
L30	Jones	+ (Type 4b)	+ (Type 4b)	2/4
L39	Bacon	-	-	1/4
L40	Laurens	-	-	0/4
L41	Laurens	-	-	0/4
L42	Laurens	-	.	0/4
L43	Haralson	-	. .	4/4
L44	Gwinnett	-	. .	1/4
L46	Grawford	-	...	0/4
L47	Laurens	-	...	0/4
L48	Clinch	+ (Type 4b)	...	0/4
L49	Clayton	+ (Type 4a)	...	0/4
L50	Jasper	-	...	0/4
L51	Candler	-	...	0/4

*Numerator equals number of mice that died and denominator the number inoculated.

ND = Not done.

IV DISCUSSION

It was fortunate that mice inoculated with brain tissue from the first fox, to test for rabies virus, died on the third and fourth postinoculation

days These early deaths caused us to suspect listeric infection and led to our first isolation of L. monocytogenes. Subsequent results indicate that Listeria will not always kill mice similarly inoculated, as it did in this first instance, and only from this first fox brain was Listeria isolated on the initial culture attempt. Without this combination of results, additional Listeria isolations might not have been undertaken.

The initial recovery of Listeria from a fox was not unexpected, since it had been isolated from wild animals previously. What was unforeseen was the recovery of this organism from 25% of the twenty foxes tested. Since in all of these foxes there were signs of unusual behaviour suggestive of encephalitis and additional sick and dead foxes were observed in the areas from which they came, it appears that L. monocytogenes may be a relatively common pathogen in the fox. Because the mode of transmission of this organism is unknown, the epizootiologic significance of its occurrence in foxes is obscure. For this very reason, however, further studies on the role of feral animals in the epizootiology of listeriosis should be considered.

The five isolations represent three of the five currently recognized L. monocytogenes serotypes. Types 1 and 4b are the most common types found in the United States[5,11]. The third serotype represented was 4a which is seldom encountered. Because it is necessary to refrigerate and continuously reculture tissues suspected of harbouring L. monocytogenes, extensive studies are not readily undertaken. It has been found that following this procedure for as long as six months may lead to the recovery of Listeria from apparently negative tissues[6]. In this study, ninety days of refrigeration was required to obtain one of the type 4b isolates from tissue from one fox (L30). Listeria was isolated from one specimen on the first (unrefrigerated) subculture from fox L1, whereas 26 days, 5 days and 19 days of refrigeration respectively had transpired before isolations were made from the three others (L10, L48, L49). Positive cultures were obtained from the mouse brain tissues on the first attempt (Table 2). If sufficient laboratories become involved

in studies requiring this tedious process, a new and less laborious diagnostic test for listeric infections may be found. Perhaps the most promising technique being investigated is the use of fluorescent-labelled antibody.

TABLE 2

Refrigeration Period of Brain Tissue Before Listeria monocytogenes was isolated by Cultural Methods

Fox (No.)	Listeria serotype	Fox brain	Mouse brain
L-1	1	+/0*	+/0
L-10	1	+/26 days	Mice not inoculated
L-30	4b	+/90 days	+/0
L-48	4b	+/5 days	No deaths
L-49	4a	+/19 days	No deaths

*Numerator (+) indicates that Listeria was isolated; denominator is the number of days of refrigeration before Listeria was isolated by culture.

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