ANIMAL MODEL OF HUMAN DISEASE

Syphilis in the Syrian Hamster

A Model of Human Venereal and Congenital Syphilis

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Biologic Features

Syphilis can present in at least two forms in man: 1) the venereal form, well-known for its various primary, secondary, and tertiary manifestations, as well as congenital transmission, and 2) the nonvenereal form, also called endemic syphilis or bejel, a treponematosis that usually has its onset in childhood and is transmitted from child to child by close skin-to-skin contact and possibly by fomites such as communal drinking vessels. It is only infrequently transmitted by sexual contact. It is not known to produce later (tertiary) cardiovascular or central nervous system manifestations, as venereal syphilis does, and congenital transmission has not been documented.[1] The etiologic agent in both diseases is *Treponema pallidum*, but it is thought that different subspecies induce each disease.

LSH Syrian hamsters infected with *T pallidum* subspecies *endemicum* (Bosnia A strain), the etiologic agent of endemic syphilis (bejel), develop an infection that is in many respects similar to human venereal syphilis. Experimental studies with this model have been published.[2-8] The *T pallidum* subspecies *endemicum* Bosnia A strain was originally isolated from a penile ulcer of a 35-year-old male patient from Bosnia, Yugoslavia.[2] This strain was obtained from Dr. Paul Hardy, Jr., John Hopkins University, and is maintained by passage in LSH hamsters. Viable treponemes are obtained from the supernatant of lymph node suspensions and injected intradermally in the inguinal regions.[3-8] Primary lesions appear about 3 weeks later at the site of inoculation and consist initially of erythematous papules. The indurated areas enlarge, and at 4 weeks, the skin overlying the induration becomes ulcerated (Figure 1A). The ulcerations continue to expand until the sixth to eighth week. Thereafter, they begin to heal slowly; and at 16–20 weeks after the inoculation, either these primary lesions are completely healed or only minor crusted lesions remain. At approximately 24 weeks after infection, perioral ulcers spontaneously develop which become increasingly severe (Figure 1B). An erythematous rash is seen in the paws and anterior truncal region. At this point the lesions at the site of injection are completely cleared in almost all animals, and the perioral lesions and the erythematous rash are regarded as secondary manifestations of the disease. Most animals die 28–32 weeks after inoculation, probably because of malnutrition, because these animals do not eat after the perioral lesions become severe.

Approximately 12% of the animals survive this period, with healing of the perioral lesions. The gross pathologic features include enlarged lymph nodes (inguinal, axillary, intraabdominal and intrathoracic) and thymic atrophy (present since the first week of

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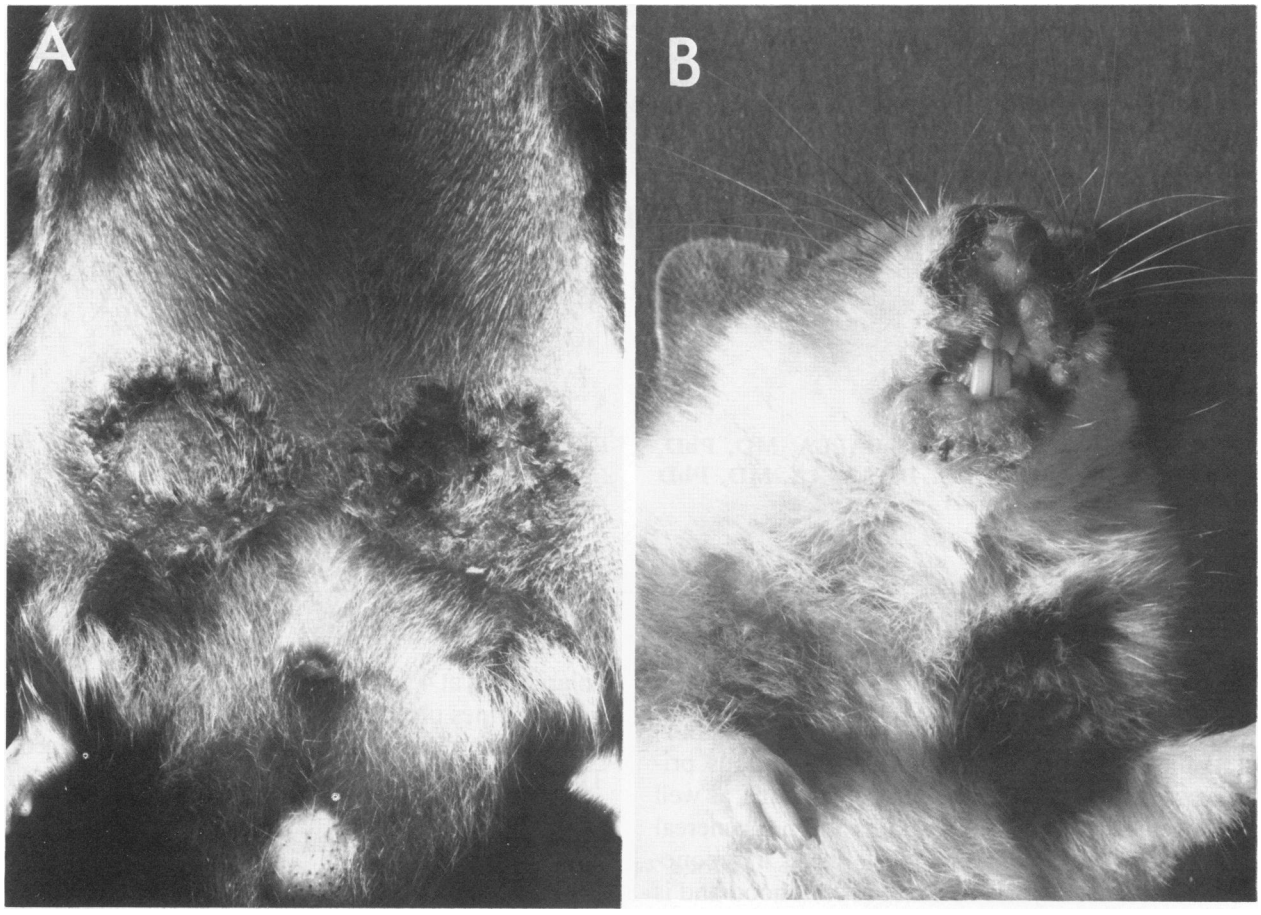

Figure 1—Primary and secondary syphilitic lesions. **A**—Primary cutaneous ulcers with elevated indurated borders. **B**—Secondary perioral ulcers.

infection).[6] Histologically, there is a generalized follicular hyperplasia of lymph nodes (Figure 2) with prominent plasma cell proliferation. The liver shows periportal foci of mononuclear cell infiltrate and diffuse increase of mononuclear cells in the sinusoids. There is an intense polymorphonuclear infiltrate at the base of the perioral ulcers. As demonstrated by darkfield microscopy and by injection into uninfected animals, treponemes are present in the lymph nodes and perioral ulcers.[2,4,7]

Female hamsters infected up to 2 months before or at early stages of pregnancy (up to 4 days) congenitally transmit syphilis. A major proportion of the offspring (>50%) will exhibit rhinitis and radiologic evidence of osteitis and periostitis and will fail to thrive. If sacrificed during the first week after birth, >75% of the offspring will show *T pallidum* in their livers by darkfield microscopy.

Serologic evidence of infection can be demonstrated by indirect immunofluorescence in both the congenital (anti-treponeme-specific IgM) and the adult models (IgG).[9]

We believe that in hamsters, the Bosnia A strain of treponemes causes a disease that resembles the human venereal type of syphilis more than it resembles human endemic syphilis, because in this model there is congenital transmission and, because in both the human venereal syphilis and the hamster model the stages of the disease are clear-cut (ie, primary and secondary syphilitic lesions do not overlap). This difference in biologic properties of the same strain in different host species is not surprising in view of the evidence that DNA sequencing experiments indicate that various virulent noncultivable treponemes are genetically indistinguishable, with subspecies Nichols and *endemicum* (KKJ) homologous by DNA/DNA homology studies.[10]

Infected Syrian hamsters differ from both endemic and venereal syphilis in the mode of transmission. In uninfected animals of the same sex that are left in the same cage with infected animals for 6–8 weeks and then separated syphilis does not develop for periods of observation of up to 8 months. Therefore, the transmission by direct contact and fomites seems unlikely.

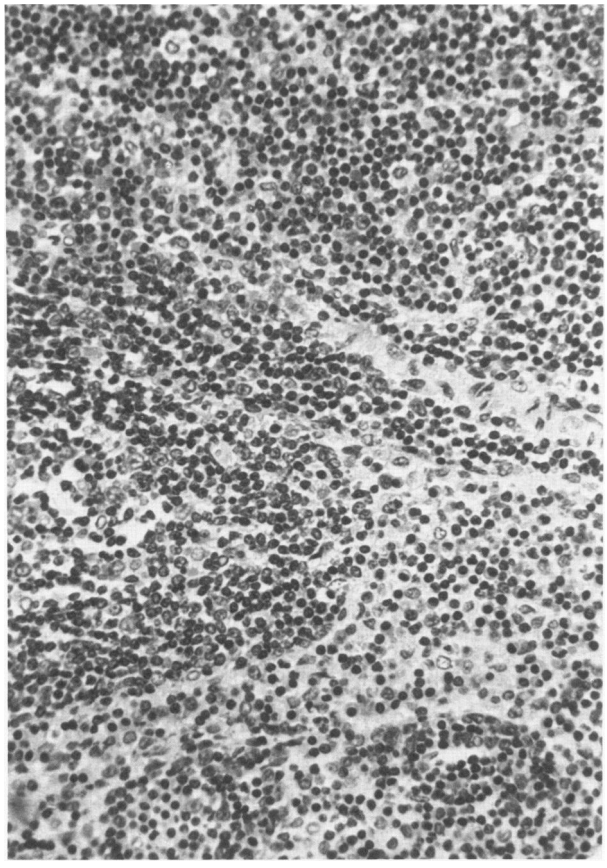

Figure 2—Axillary lymph node section shows increased numbers of immunoblasts and plasma cells at the confluence of three adjacent germinal centers.

The possibility of venereal transmission seems also unlikely, but this hypothesis has not been thoroughly studied.

Gummatous lesions have not been documented in hamsters, possibly because the few animals that survive the secondary phase have not undergone observation for very prolonged periods of time.

Usefulness of the Model

As compared with the other animal models of syphilis,[11-13] the Syrian hamsters are the only experimental animals that have been shown to reproduce the primary and the secondary phases of the disease and transplacental transmission of the disease by syphilitic female hamsters. Syrian hamsters infected with *T pallidum* have been used in the study of macrophage function,[5,8] B-cell responses of uninfected animals to both helper T-cell independent and dependent antigens,[7] passive transfer of immunity by immunoglobulins[3] and T cells,[4] resistance by cross-immunity,[5] and effects of cyclophosphamide and irradiation on T-cell subset function.[14]

Potential uses of this model include mechanisms of specific immune response, antibiotic therapy, vaccination, and prevention of congenital transmission.

Availability

Inbred LSh/Ss Lak Strain Syrian hamsters can be purchased from Charles River Breeding Laboratories (Wilmington, Mass). *T pallidum* Bosnia A strain-infected hamsters can be obtained from Dr. Bagasra. *T pallidum* Bosnia A strain can be obtained from either Dr. Bagasra or Dr. Paul Hardy, Jr.

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