Experimental syphilis: guinea pig model

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SUMMARY Outbred Hartley male guinea pigs (300-400 g) were infected intradermally with various concentrations of Treponema pallidum Nichols strain in the pubic region. The median lethal dose (ID₅₀) was approximately 10⁴. The animals produced lesions visible by darkfield microscopy, treponemal antibodies (IgG only), and histopathological changes in the lymphoid organs. Though less susceptible to T pallidum infection than the rabbit when infected with a sufficient number of organisms, the guinea pig may be a useful model in experimental syphilis.

Introduction

The guinea pig has been known to respond to Treponema pallidum infection since Bertarelli's successful eye infection.¹ Truffi² was successful in infecting the scrotum of guinea pigs, and a number of researchers confirmed Truffi's results.³⁻⁷ Kole and Evers,⁸ who were the first to use the Nichols strain of T pallidum, established the time required to disseminate T pallidum in guinea pigs infected through abraded skin, subcutaneously, or intrathecally. Tani et al⁹ contributed to the guinea pig model by observing that males were more susceptible to infection than females and that younger animals were more susceptible to infection than older animals. Dold and Worms¹⁰ were unable to produce clinical symptoms in guinea pigs infected intradermally but did find that the lymph nodes and testes of these animals were infective. The infectivity (using rabbit testes) could still be shown after three consecutive blind passages of the lymphoid organs into healthy guinea pigs. Other researchers¹¹⁻¹² also reported difficulty in producing symptomatic infection in guinea pigs but did demonstrate the infectivity of various organs, including the brain. After infecting guinea pigs with various strains of T pallidum in multiple sites Turner and Hollander¹³ concluded that the incidence of symptomatic infection varied depending on the strain of T pallidum and the site of infection.

Wicher et al¹⁴ and Lesinski et al¹⁵ infected male guinea pigs with T pallidum Nichols strain (obtained from the Fournier Institute of Paris, France) intravenously, intrathecally, and intradermally. Intravenous injection did not produce symptomatic infection nor were the inguinal lymph nodes infective three months after T pallidum injection. Intrathecally infection did not produce typical orchitis, as seen in infected rabbits, but the testes and inguinal lymph nodes were still infective six months after infection. Intradermal infection in the pubic region produced darkfield-positive lesions in 67% of the animals appearing between 13 and 23 days after infection. Regardless of whether the animal developed lesions the lymph nodes and testes remained infective six months after infection. Wicher and Jakubowskiv⁶ ¹⁷ tried without success to manipulate the immune mechanism of T pallidum-infected guinea pigs by injecting cortisone (7.5 mg/kg body weight) for various lengths of time.

Immune responses of T pallidum-infected guinea pigs have been studied only sporadically. Lesinski et al¹⁸ examined guinea pigs infected intravenously, intrathecally, and intradermally with T pallidum Nichols strain for antibodies using the complement fixation, flocculation, and T pallidum immobilisation (TPI) tests. The tests for cardiolipin antibodies gave equivocal results. Treponemal antibodies started to appear in several animals two to three months after infection, were still present at four to five months, but in the animals infected intravenously and intrathecally they disappeared before the eighth month. In the guinea pigs infected intradermally the treponemal antibodies remained beyond the tenth month after infection.

Wicher et al¹⁹ using a T pallidum strain from the Centers for Disease Control, Atlanta, GA, and housing the animals under more controlled conditions, were unable to find cardiolipin anti-
bodies in intradermally infected guinea pigs by the complement fixation test. Treponemal antibodies were detectable by the fluorescent treponemal antibody-absorbed (FTA-ABS) test in the first month after infection.

To our knowledge the cellular response of infected guinea pigs to T pallidum antigen has not yet been explored. Wicher et al. found that peritoneal exudate cells from T pallidum-infected guinea pigs (obtained four days after injection of oil), when examined by the capillary leucocyte migration method in the presence of Reiter antigen, produced enhanced leucocyte migration, which reached significant values between six and 24 weeks after infection. The leucocyte enhancement-migration factor, the production of which was confirmed by the indirect leucocyte-migration test, was not, however, characterised.

The present study was undertaken to expand the knowledge of the rarely used animal model for syphilis research and to set up immunopathological indices which would be useful in future exploration of inbred strains of guinea pigs for experimental syphilis. Studies of syphilis in genetically defined guinea pigs may have far reaching consequences.

Materials and methods

Animals

Albino male Hartley guinea pigs (300-400 g, 6-8 weeks), an outbred strain, were obtained from Buckberg Animal Farm, Tompkins Cove, New York. The animals were housed individually at a controlled temperature of 19-22°C and given antibiotic-free food and water in unlimited amounts. All experimental and control guinea pigs were drawn from the same source.

Bacterial strains

T pallidum (Nichols) was obtained in 1970 from the Centers for Disease Control (CDC) and maintained by intratesticular passage in New Zealand rabbits. Treponema phagedenis biotype Reiter, also obtained from the CDC, was maintained in the spirochetal medium described by Hanson and Cannefax. The organisms were grown for several days at room temperature (20-24°C), centrifuged at 12 000 × g, washed three times with phosphate-buffered saline (PBS), and counted. The organisms were used as suspension for in-vitro lymphocyte transformation tests.

Infection of animals

Inocula of T pallidum (Nichols) were obtained from the testes of infected New Zealand rabbits at the peak of orchitis (9-12 days). The treponemes in the supernatant were enumerated by the method of Morgan and Vryonis as adapted by Magnuson et al. For all experiments the animals were infected intradermally in the pubic region.

Determination of infective dose

Portions (0.25 ml) of the suspension, containing 5 × 10⁶ to 5 × 10⁷ T pallidum, were used to infect 34 guinea pigs. The virulence of the treponemes was examined by duplicate intradermal injections into the clipped backs of rabbits. Infected guinea pigs were examined daily until the lesions appeared and every two days until the lesions disappeared.

Humoral immune response

To study the kinetics of the antibody response 20 guinea pigs were each infected with 5 × 10⁶ organisms. Blood for serum was obtained by cardiac puncture under light ether anaesthesia. Sera were obtained at nine days and at 3, 6, 12, 27, and 52 weeks after infection were examined for antibody content. For cardiolipin antibody the Venereal Disease Research Laboratory (VDRL) and cardiolipin complement-fixation tests were used. For treponemal antibodies the slightly modified FTA-ABS test was used. Commercial T pallidum-coated slides and sorbent (Palomer Chemicals, Carlsbad, CA) were used in a quantitative test in which test sera were diluted with a sorbent. As conjugate, fluorescein-conjugated antisera to guinea pig IgG and IgM were prepared in rabbits in our laboratory. Only the antisera to IgM was rendered class-specific by absorption with insolubilised, electrophoretically pure guinea pig IgG, α₂ protein, and human C3, which cross reacts with guinea pig C3. Globulin fractions of the rabbit antisera were conjugated with fluorescein isothiocyanate by a standard procedure. A positive test result was considered to be a reaction from 4+ to 1+ and the end point titration as the last dilution of a test serum exhibiting 1+ reaction (normal guinea pig sera did not demonstrate ± or 1+ reaction).

Two groups of five animals each served as controls for the specificity of treponemal antibody production. One group received supernatant from a preparation of normal rabbit testes (NRT) that had been processed in the same manner as the infected testes. The second group received T pallidum-free supernatant from infected rabbit testes from which the treponemes had been removed by centrifugation at 48 200 × g for one hour. Sera from the control animals were obtained every three weeks for three months and examined by the FTA-ABS procedure with conjugated antisera to both IgG and IgM.
Experimental syphilis: guinea pig model

ABSORPTION OF SERA OF INFECTED GUINEA PIGS

Sera of four infected guinea pigs with IgG titres by the FTA-ABS test of 80 or 160 were diluted 1/5 with PBS, and 1-ml aliquots were mixed separately with thrice washed, pelleted *T. pallidum* (1 x 10^9 organisms) or 10 mg of lyophilised NRT protein. The mixtures were left overnight at 6°C on a rotator and centrifuged at 48 000 x g for 30 minutes. The absorbed sera were examined by the FTA-ABS test. Some aliquots of sera were absorbed twice.

IMMUNISATION WITH LIPIDS

Twenty-eight control guinea pigs were divided into six groups of four or five animals each and immunised with lipid-carrier or carrier preparations as follows: groups 1 and 2 received the lipid content of an alcoholic extract of normal guinea pig kidney mixed with porcine serum (group 1) or with PBS (group 2) prepared according to the procedure of Sachs et al.; group 3 received diluted porcine serum alone; and groups 4 and 5 received VDRL antigen that had been evaporated and resuspended in PBS (group 4) or 0.1% methylated bovine serum (group 5) to give each animal approximately 60 μg of cardiolipin in 0.2 ml of suspension. Bovine serum albumin was esterified by using absolute methyl alcohol and 12 mol/l HCl according to the method of Mandell and Hershey. The preparations were given intravenously in a series of 15 injections, one every four days. Group 6 received purified cardiolipin incorporated into Freund’s complete adjuvant. Each guinea pig received three intramuscular injections, each containing approximately 300 μg of cardiolipin, 10 days apart. For each group sera were obtained 10 days after the last injection and examined for antibody to cardiolipin in the same manner as sera from infected animals.

DIRECT PLAQUE ASSAY

The ability of *T. pallidum*-infected guinea pigs to respond to sheep red blood cells (SRBC), a T-dependent antigen, was determined by the direct plaque assay of Jerne et al. Thirty-six animals infected with 1 x 10^7 *T. pallidum* were killed in groups at two-week intervals for 12 weeks. Seven days before each killing four infected and two normal control animals were injected intraperitoneally with 0.5 ml of washed SRBC (1 x 10^9). Spleens of the killed animals were aseptically removed and examined by the plaque assay in quintuplicate. To distinguish between IgG and IgM plaque-forming cells the slides were incubated for one hour with 0.2 mmol/l 2-mercaptoethanol before treatment with complement.

CELL RESPONSE TO MITOGENS AND ANTIGEN

Splenic lymphocytes of infected and control animals were used for the standard assay of in-vitro lymphocyte transformation in the presence of optimal concentrations of concanavalin (Con A, 12-5 μg/culture; Sigma Chemical Corporation, St Louis, MO), phytohaemagglutinin (PHA, 2-5 μg/culture; Wellcome Reagents Ltd, Beckenham, England), or a suspension of 3 x 10^5 to 3 x 10^6 *T. phagedenis* biotype Reiter. The test was done in triplicate samples using 2 x 10^5 cells in 0.2 ml and reagents in 10 μl volume. The samples were incubated (37°C, CO₂) for three days for mitogens and five days for antigen. Six hours before harvest each culture was pulsed with 0.4 μCi of [3H]Tdr, harvested, washed (MASH II) and the incorporation of [3H]Tdr determined in liquid scintillation counter (Mark II). Results were expressed as a difference of counts per minute (acpm) obtained by subtracting the cpm of non-stimulated cultures from the cpm of stimulated cultures. The stimulation index was also calculated and the results analysed.

HISTOPATHOLOGY

Inguinal lymph nodes and spleens from infected (5 x 10^9 organisms) and control guinea pigs were obtained in the second week of infection and at two-week intervals for 12 weeks. The organs were placed in 10% buffered formalin immediately after necropsy. Sections were prepared and stained with haematoxylin and eosin for histology and by the Warthin-Starry method for detection of treponemes.

Results

INFECTIVE DOSE

The number of demonstrable lesions, their severity, and their time of development varied with the infective dose. Lesions started to appear as early as day 6 after infection in guinea pigs infected with 5 x 10^7 organisms but not until day 42 in animals infected with 5 x 10^6 organisms (table I). The median infective dose (ID₅₀) for these outbred guinea pigs was approximately 10⁵ *T. pallidum*.

<table>
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<th>Infective dose*</th>
<th>No of animals</th>
<th>Infected</th>
<th>With lesions</th>
<th>% Infected</th>
<th>Onset of lesions (days)</th>
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<td>8</td>
<td>6</td>
<td>75</td>
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<td>8</td>
<td>6</td>
<td>75</td>
<td>17-30</td>
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<tr>
<td>5 x 10⁴</td>
<td>10</td>
<td>2</td>
<td>20</td>
<td>42</td>
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*Virulence of infective doses was determined by intradermal injections into shaved rabbits.*
FIG 1  (a) Darkfield-positive lesion (developing nine days after infection in the pubic region of a T pallidum-infected (5 × 10⁶) guinea pig) showing formation of centralised necrosis; (b) healing lesion covered with scales decreasing in size.

FIG 2  T pallidum in a skin lesion of an infected guinea pig. Characteristic treponemes are evident at the epidermodermal junction. Warthin-Starry stain (× 1000).
FIG 3  Histopathology of skin lesions in an infected guinea pig (a) showing degeneration and necrosis of the epidermis (× 40); and (b) (magnified area marked on (a)) showing histiocytic and lymphocytic infiltrate (× 1000).
Each lesion first appeared as a barely discernible erythematous area 2-3 mm in diameter and progressed to a definite induration, similar to a chancre in man, with centralised necrosis (fig 1). The diameters of the lesions reached a maximum of 1.5 cm in animals infected with $5 \times 10^7$ or $5 \times 10^6$ organisms but only 1.0 cm in those infected with $5 \times 10^4$ organisms; animals infected with $5 \times 10^4$ organisms showed only erythema and induration of 4 mm after six weeks.

Exudates from lesions contained motile treponemes, as shown by dark field microscopy. When tissue sections from the lesions were stained by the Warthin-Starry method (fig 2) treponemes could be seen in all layers of the skin, but the largest concentration was at the epidermodermal junction. Histologically the lesions were characterised (figs 3 and 4) by degeneration and necrosis of the epidermis with considerable mononuclear cell infiltration. The dermis showed pronounced histiocytic, lymphocytic, and polymorphonuclear infiltration, and the inflammatory reaction extended deep into the fatty subcutaneous layer.

**HUMORAL IMMUNE RESPONSE**

No IgM-antitreponemal antibodies were detected, but IgG antibodies started to appear as early as nine days after infection (two animals). By 12 weeks after infection all 15 surviving animals (five had died during cardiac bleeding) showed IgG antibodies by the FTA-ABS test. Sera of control guinea pigs that had been injected with NRT or *T. pallidum*-free supernatant showed no antibody activity when examined by the FTA-ABS test periodically for three months after injection.

Sera from nine animals of the infected group were chosen for titration of treponemal antibody (table II). There was a slow but steady rise in titre up to one year after infection. These titres were, however, much lower than those found in sera of infected

**FIG 4** Histopathology of skin lesions in an infected guinea pig showing infiltration of the fatty subcutaneous layer (x 40).
rabbits or man. Sera of four infected guinea pigs were absorbed with *T. pallidum* or NRT. *T. pallidum* lowered the titres from 160 to 80 or from 80 to 20; NRT had no effect. The decrease of titre after absorption with *T. pallidum* may be indicative of specificity of the antibodies for *T. pallidum*.

No antibodies to cardiolipin were detected in sera of infected guinea pigs examined by the VDRL or complement fixation tests. Guinea pigs immunised repeatedly with various lipid preparations also failed to produce antibodies to cardiolipin detectable by these tests. Antibodies with specificity for the carrier serum protein (porcine) were shown by double-diffusion gel precipitation in sera of all guinea pigs receiving the protein.

**PRODUCTION OF IgM ANTIBODIES TO SRBC**

Both infected and control animals showed wide variations in response to SRBC, but the infected animals responded as well as the controls. Reduction of the number of plaques after treatment with 2-mercaptoethanol suggested that most of the antibodies causing the complement-mediated plaques were IgM.

**CELLULAR RESPONSE**

Spleen lymphocytes of both infected and control animals responded well to mitogens. Infected group: Con A, Δcpm 44 482-66 541; PHA, 41 044-57 145; controls: Con A, Δcpm 15 167-107 310; PHA, 9397-86 580. No proliferative response of splenic lymphocytes to various concentrations of *T. phagedenis* biotype Reiter was observed in either group of animals.

**HISTOLOGY**

Infection of guinea pigs with *T. pallidum* resulted in activation of the germinal centres in the cortex of the lymph nodes. Hyperplastic and hypertrophic changes in these centres gradually increased and reached a maximum at about six weeks after infection (fig 5). At eight weeks follicular activity started to decrease, but it was still apparent 18 months after infection. Most of the early changes were in the follicles, which contain predominantly B cells; with time the T-cell areas of the cortex and medulla became more prominent.

Splenic changes were not as conspicuous as those in lymph nodes (fig 6). Ten weeks after infection the number of cells in the periarteriolar lymphatic sheath appeared to have increased. At the time extra-medullary haematopoiesis became evident in the red pulp of the spleen.

**Discussion**

The guinea pig has been a neglected model in experimental syphilis. The rabbit, whose susceptibility and humoral immune response are similar to those in early syphilis in man, overshadows the guinea pig as a model. The lack of concordant results on the guinea pig's susceptibility to *T. pallidum* infection and on its immunopathological mechanism also makes the model unattractive. The guinea pig offers some advantages over the rabbit, however, especially the availability of inbred and genetically defined strains, which may be contributory to the exploration of immunity in a *T. pallidum*-infected host.

The susceptibility of the Hartley strain of guinea pigs is far less than that of the rabbit, but our results indicate that the percentage of symptomatic infections may be dose-related especially in view of recent experiments (K Wicher and V Wicher, unpublished observations) in which 100% of symptomatic infection was obtained with 10⁶/ml of *T. pallidum*. The animals' susceptibility may, however, depend on their age and sex.9 Young animals are more susceptible than older ones, and males seem more susceptible than females. Adler et al90 observed that baby guinea pigs were susceptible to infection with *Leptospira interrogans* serovar *pomona* but rapidly became resistant as they matured.

Manipulation of the guinea pig immune system by injecting cortisone will not provide results similar to those observed in *T. pallidum*-infected rabbits. Guinea pigs infected intradermally with *T. pallidum* but given cortisone (7·5 mg/kg body weight) a week before infection and throughout the course of infection responded with a prolonged incubation time, a shorter duration, and less pronounced lesions than animals not receiving cortisone.16

The reasons for the difference in susceptibility to *T. pallidum* infection between the guinea pig and the
FIG 5 Histopathology of the lymph nodes of an infected guinea pig; (a) normal and (b) six weeks after infection ($\times$ 40).
FIG 6  Histopathology of the spleen of an infected guinea pig; (a) normal and (b) after infection (x 40).
rabbit is unknown. Several factors may play a role. Klein et al., using various inbred strains of mice, produced symptomatic lesions regularly only in some strains, indicating dependence on host susceptibility. The genetically controlled resistance could be restored in irradiated mice by transfer of syngeneic spleen cells, suggesting that a radiosensitive lymphoid cell is involved in the outcome of the infection.

Differences in the susceptibility of guinea pig strains to infection with Mycobacterium tuberculosis were shown by Wright and Lewis. They examined the genetic factors and concluded that there might be some inherent resistance in guinea pigs to infection with this organism.

The lower susceptibility of guinea pigs to T. pallidum infection may also be due to the animals' extremely vigorous reaction to rabbit proteins (K Wicher, unpublished observations). The T. pallidum used for infection is extracted from orchitic rabbit tissue and is covered with a variety of rabbit serum proteins, making it a good target for the guinea pig immune system. Most of the organisms may be eliminated before they can coat themselves with guinea pig proteins. Thus a guinea pig-adapted strain of T. pallidum may work in guinea pigs as well as the Nichols strain does in rabbits.

Thus far very little is known about the humoral response of T. pallidum infected guinea pigs. Positive complement fixation results have been observed in the sera of a few animals infected intravenously, intratesticularly, and intradermally; the positive reactions appeared during the fifth month of infection and disappeared after one to three months. Whether this reaction was due to cardiolipin antibodies was not explored, and the results, especially in view of more recent and the present studies, must be considered unexplained. In the earlier work the animals were infected with T. pallidum Nichols from the Fournier Institute. That strain seems to be more virulent than the Nichols strain from the CDC, as it also produced much more severe lesions in rabbits. Furthermore, the animals used in the earlier experiments were raised and kept in a moist colder environment and were fed grass and hay.

In more recent studies conducted with animals obtained from one source, infected with T. pallidum Nichols from the CDC, and kept in more controlled conditions, no cardiolipin antibodies were detected by the complement fixation or VDRL tests for an observation period of six months after infection with 2 x 10^7 T. pallidum. We have now confirmed the lack of cardiolipin antibodies: sera of animals infected for a whole year did not show positive complement fixation or VDRL results.

In human and rabbit syphilis the origin of the cardiolipin that elicits an antircardioplin response is unknown, but cardiolipin may be either host-derived from tissue destruction or present in the T. pallidum itself. The reason for the lack of cardiolipin antibodies in guinea pigs is unknown. Possibly not enough tissue destruction takes place during the infection. The guinea pig is not, however, a good responder to lipids, as shown earlier and confirmed by our experiments.

In earlier experiments treponemal antibodies were detected by the TPI test in guinea pigs infected intravenously, intratesticularly, or intradermally. The antibodies started to appear around the third month of infection, but in the animals infected intravenously and intratesticularly they disappeared around the eighth month. Such a pattern of antibody response is characteristic when heat-killed T. pallidum are injected into rabbits or mice. The TPI antibodies in intradermally infected guinea pigs persisted throughout the studies, which lasted for over 12 months. In other experiments (not designed for kinetics of antibody response) treponemal antibodies (FTA-ABS) were present from the fourth week (sera were not available earlier) until the termination of the experiments at 24 weeks. In present experiments on the kinetics of antibody response, we have established that the treponemal antibodies (FTA-ABS) started to appear as early as nine days after infection and that the titres slowly but steadily increased throughout the 12 months of observation (table II). The activation of the germinal centres in the cortex of the lymph nodes and the persistent changes observed for over 18 months support the findings of prolonged antibody production. The titres, however, remained rather low in comparison to the rabbit or man. In more recent experiments using an inbred guinea pig strain infected with a higher dose of T. pallidum, the titres in some animals exceeded 1 000 (K Wicher and V Wicher, unpublished data), indicating that the treponemal antibody titres may be dose-dependent, genetically determined, or both.

The slow but continuous increase in antibody titres in the present experiments suggests the possibility of a constant source of treponemal antigen. This is supported by the work of earlier investigators, who demonstrated infective treponemes in infected guinea pig organs for almost one year.

The production of IgG treponemal antibody, detectable by the FTA-ABS test seemingly without previous production of IgM antibody, did not follow the normal immunological response. Since relatively few IgG antibodies were produced, as evidenced by the low FTA-ABS titres, possibly a very little IgM was also produced, but the FTA-ABS technique was not sensitive enough to detect it. Also, the initial time
Experimental syphilis: guinea pig model

of sampling (nine days) may have been too late to detect IgM, even though some animals did not yet have visible lesions and most had no detectable IgG antibodies at that time. Watanabe et al. demonstrated the presence of a genetically controlled subclass of T cells which selectively suppresses the B cells responsible for the production of IgE antibodies. In the guinea pig a similar situation may possibly occur which selectively suppresses the production of IgM antibodies during T pallidum infection. Such a suppression would have to be antigen-specific, since the infected guinea pig is able to produce IgM antibody to another T-dependent antigen, SRBC; infected and control animals alike produced antibodies to SRBC in T pallidum-infected rabbits was significantly increased over controls for up to seven weeks after infection. Such enhancement of the IgM response to SRBC was not detected in infected guinea pigs.

The in-vitro cellular response was not well explored. Because guinea pig peripheral blood is not the best source of active lymphocytes, we used splenic lymphocytes. In the past Reiter antigen has been used successfully to examine the cellular response in infected rabbits.40 The lymphocytes of infected guinea pigs responded to mitogens similarly to cells from non-infected control animals but did not respond to Reiter antigen. In recent experiments using nylon-wool-purified peritoneal T lymphocytes from T pallidum-infected inbred guinea pigs the lack of reaction to Reiter antigen was confirmed; the T lymphocytes did react to T pallidum antigen (K. Wicher and V. Wicher, unpublished observations). Evidently the immune response in T pallidum-infected guinea pigs is more specific than in the rabbit or man, which do respond to Reiter antigen. The changes in the T-cell areas of the cortex and medulla in the outbred guinea pigs support the assumption that lymphocytes are activated by the infective agent.

Thus, the guinea pig is less susceptible to T pallidum infection than the rabbit and, when infected with a sufficient number of T pallidum, responds with darkfield-positive lesions, production of treponemal antibody, and histopathological changes in the lymphoid organs. The immune response in the guinea pig may be more specific than in the rabbit or man, since no cardiolipin or cross-reactive antibodies or cellular response to Reiter antigen was detected.

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References


