



# Lymphogranuloma Inguinale

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COURTESY OF CITIZENS AID SOCIETY

I. ABSTRACTLYMPHOGRANULOMA INGUINALE  
(Lymphopathia Venerea)

J. W. Tedder

Historical

Lymphogranuloma inguinale is a chronic low grade inflammation of the lymphatic nodes, of venereal origin, resulting in complications of fistulae, esthiomene, or anorectal syndrome in an estimated 50% of infected persons. This clinical picture has been described under a variety of titles since the middle of the 19th Century. How long previous to this time the disease has existed cannot be definitely stated. Coutts interestingly traces reports of a similar condition which was known to the Greeks and Romans as "pannus" or "inguen" and to the Arabs as "al-thun." Incan pottery depicts lesions very much like our present day genito-anorectal syndrome. According to some authors, the disease was common among Negro women in Africa long before the discovery of America.

Synonyms

Durand, Nicoles and Farve, in 1913, and again in 1922, recognized and pointed out the specificity of this disease, and its probable venereal origin and described it as "subacute inguinal lymphogranulomatosis." Previous to this time and subsequently, this entity has been described under a variety of titles, including climatic bubo, tropical bubo, non-venereal bubo, subacute inguinal paroadenitis, the fourth venereal disease, strumous bubo of the groin, non-tuberculous granulomatous lymphadenitis, subacute lymphadenitis, maladie de Nicolas-Farve, hypertrophic bubo, and lymphopathia venereum. This last name, lymphopathia venereum, was suggested by Wolf and Sulzberger in 1932, and much can be said in its favor. The older and better known name has a confusing resemblance to that of other diseases and does not embrace the various extra-inguinal localizations now recognized as being of identical etiology.

Confusing Terms

The relationship of lymphogranuloma inguinale to granuloma inguinale, syphilis tuberculosis, Hodgkin's disease, chancroidal bubo, tularemia, pyogenic infections, and in certain parts of the world, bubonic plague, has been clearly defined. Previously, many cases of this disease have, no doubt, been classified and treated as tuberculosis or syphilis. It is well to further differentiate lymphogranuloma inguinale from granuloma inguinale. Their greatest similarity is in name. The latter disease must be remembered as one of the skin and subcutaneous tissues and the Donovan bodies are found in scrapings from the lesion. Their only relationship is that both are disseminated by venereal contacts.

The term, lymphogranulomatosis, (Hodgkin's disease) is also confused with lymphogranuloma inguinale where their similarity is limited to their names.

Bacteriology and Etiology

The filterable virus thought to be responsible for lymphogranuloma inguinale has been the subject of much study. It has been successfully transmitted to apes, mice, rabbits and other laboratory animals. In the ape, the virus appears to have a special affinity for the central nervous system tissue where it causes an encephalitis. After passage through apes, it has been used to reinoculate human paralytic patients. The fact that the nerve tissue in apes is involved proves that the virus does not limit its actions to the lymphatic tissue. The virus loses its virulence very rapidly in glycerine, but retains it for 22 days in the frozen state.

That the disease is predominately one of venereal origin cannot be doubted. Nichols reported the case of 3 soldiers exposed to the same source, all of whom developed lymphogranuloma inguinale. One of the soldiers was married, and subsequently infected his wife. Cases are known in which the female acts as a host for the virus and can infect exposed partners without developing either clinical

signs of the disease or a positive Frei test.

Hellerstrom reports the case of a young surgeon who in 1904 acquired an infected finger, through a traumatic wound, while operating upon a patient with inguinal adenitis of unknown origin. The axillary nodes later became enlarged and fluctuating. Extirpation was necessary. Years later, in 1927, Hellerstrom did a Frei test on this individual and found it to be strongly positive.

The earliest cases of lymphogranuloma inguinale reported were in two children. The first was a girl of 8 years who developed rectal manifestations. The second was a Negro girl of 10 years who reported to the hospital with an adenitis. While under observation, the Frei test became positive. The child's mother and a boarder in the home had positive Frei tests. The husband's test was negative.

Several extragenital cases have been reported involving the oral cavity with subsequent cervical adenopathy and fistulae. In these cases, after being confronted with positive Frei tests, a history of irregular sex habits were obtained.

Cases reported by Curth, and by Buschke and Curth, had the primary lesion of lymphogranuloma inguinale on the tongue. Later, the cervical glands were enlarged and fistulae developed. The reaction at the site of primary inoculation appears to be greater in these cases than when the primary lesion develops on the penis. Here, the early lesions are comparable with the esthiomene and elephantiasis of the vulvae.

### Differential Diagnosis

In the differential diagnosis of lymphogranuloma inguinale, the history of the temporary presence of a small innocuous-appearing lesion on the glans penis 3 to 10 days subsequent to sexual contacts, and followed by an inguinal adenitis, in from 10 to 30 days should immediately excite one's suspicions to the diagnosis of this disease.

Other diseases that must be considered in every case of inguinal adenopathy are - syphilis, chancroid, granuloma inguinale, tuberculosis, Hodgkin's disease, tularemia and pyogenic infections. In the case of syphilis, either the chancre or signs of its past existence can be located, the nodes are sharply defined, hard and painless, and rarely suppurate unless complicated by other infections. The dark field examination and repeated Wassermann test are the deciding factor. Granuloma inguinale, as stated before, is a skin and subcutaneous disease of venereal origin. Chancroids and their accompanying gland changes are probably the most difficult to differentiate from lymphogranuloma inguinale. It must be remembered that the primary lesion is on the penis, and the glands are secondary in chancroids, while this is not true in lymphogranuloma inguinale. The type of suppuration occurring in the lymph glands also differentiates the two diseases. In the acute painful adenopathy associated with chancroids, there is typically a massive suppuration, while in lymphogranuloma inguinale the nodes are less acutely inflamed and less painful and there are multiple foci of suppuration. The bacillus Ducrey can be found in smears of the chancroid, and later there is a positive Ito-Reenstierna reaction. (Unfortunately, neither the material for this test nor Delmoc's vaccine for the treatment of chancroid can be obtained in the United States because of existing import laws.) Tuberculosis and Hodgkin's disease are usually of a more generalized distribution and if sections are made, should offer little diagnostic difficulty. Tularemia and pyogenic lymphopathies reveal their point of origin to the careful examiner.

### Frei Test

The greatest individual aids towards the correct diagnosis of the disease entity now recognized and diagnosed as lymphogranuloma inguinale are: (1) its recognition as a specific disease of venereal origin, and (2) the discovery by W. Frei of a specific diagnostic test.

The material for the preparation of the Frei antigen is obtained from the

suppurating glandular tissue of a known case of lymphogranuloma inguinale. This material must be obtained under aseptic conditions and it is preferable that the subject has not had any other venereal disease. The material may be obtained by aspiration or incision. Following its collection in sterile containers, it is placed in the sterilizer at 60°C for 2 hours the first day, and for 1 hour the second day. Following sterilization, control cultures are made and if no growth occurs, the material is diluted with from 5 to 10 parts of sterile normal saline, depending upon its thickness. The antigen is then placed in sterile ampules for future use. The virulence and specificity of the newly prepared antigen should be tested upon a known case of lymphogranuloma inguinale and upon a control. The patient from whom the antigen was made cannot be used for this test of specificity. The technic of the Frei test consists of the intracutaneous injection of 0.1 cc. of the antigen. The reading is made in from 36 to 72 hours. If positive, there will be an elevated erythema several millimeters in diameter. In strongly positive individuals, small areas of necrosis may occur.

Frei antigen prepared as outlined above, and kept sterile, may retain its potency for as long as 6 months or a year, but one must continuously test its virulence upon known cases and its sterility by cultural methods. The first Frei antigen prepared here in 1933 from a case in the Minneapolis General Hospital was successfully used for over one year. Due to contamination, its further use was discontinued.

Frei antigen prepared from the brains of mice infected with the virus of lymphogranuloma inguinale were found to be unsuitable for routine diagnosis by Strauss and Howard. They found that the brain emulsion from non-infected mice gave a reaction that is indistinguishable from a true positive test. The nature of this reaction is unknown. This perhaps can account for several unaccountable reactions we have seen here after using the commercially prepared antigen.

### Evaluation of Laboratory Tests

By the judicious use of Frei antigen, the diagnosis of lymphogranuloma inguinale can be satisfactorily made. It must be realized that the limitations of the Frei test are the same as those of other biologic tests, that is the presence of a positive Frei test does not always classify the disease under observation because of the fact that a previously acquired infection could account for the positive reaction.

It is well to remember that the very early case of lymphogranuloma inguinale will not give a positive Frei test. It is believed by some authorities that the test does not become positive until the glands have increased in size and become fused to the skin. A more probable explanation is that the test becomes positive only after the patient's allergic mechanism has been stimulated.

Early cases of lymphogranuloma inguinale have a tendency to cause a false positive Wassermann reaction. Many cases have been treated as syphilis on the basis of these tests. If there is no evidence of a chancre, Wassermann tests should be repeated several times before treatment is started.

Several investigators have found that the serum of early cases of lymphogranuloma inguinale when injected intracutaneously into a known case gives a positive test, but this could not be repeated by other workers.

Once the Frei test becomes positive, it remains so for life, providing, of course, that the patient's allergic status is not disturbed by infection or lowered resistance. In such cases, a known positive Frei test may become negative.

### Clinical Course and Incidence

The clinical course of lymphogranuloma inguinale begins with the initial lesion, usually on the glans penis or in the urethra in the male, and on the external

or internal genitalia in the female. The primary lesion may be anyone of four types, as described by Phylactos:

1. Herpetic type
2. Ulcerative type
3. Nodular type
4. A specific urethritis

All of these lesions may be transitory and pass unnoticed by the infected individual.

Within from 5 to 30 days after exposure, the patient becomes aware of a gradual enlargement of the inguinal nodes. His attention may be directed to this condition by the limitation of motion of the lower extremity rather than by pain.

In the male, the inguinal adenopathy is accounted for by the fact that the inguinal nodes and the deep iliac nodes drain the genital regions. The female genitalia drain directly to the lymph plexuses about the rectum, with the exception of the clitoris and external vulvae that drain to the inguinal nodes. This accounts for the difference in the clinical picture presented by the male and female and explains the former belief that males were more frequently infected than females.

Following the development of lymphadenopathy or associated with its occurrence, the patient may have an elevation of temperature associated with malaise, anorexia and headache. The lymph nodes gradually become matted together and painful as they increase in size and fuse with the overlying skin. After this fusion occurs, the skin assumes a reddish-violet hue described by Phylactos as the "adenite violette" and considered to be very diagnostic. As the tension on the skin increases, it becomes shiny, and many areas of necrosis develop in the underlying glands. Perforation occurs and multiple fistulae are formed. This process may be repeated as other glands become involved.

In the female, the draining lymph glands about the rectum develop an inflammation that spreads to the rectal walls by way of the lymph channels. Following

this, these vessels become thrombosed and result in inflammatory changes followed by scar tissue formation with narrowing of the rectal lumen. These changes occur for the greater part in the lower 6 cm. of the rectum and rarely extend higher than 10 cm. Occasional cases have been reported by Hevaditi and Revant in which the rectum of homosexual males have been involved.

Seneque concludes that there are 4 types of lymphogranulomatous strictures of the rectum.

1. A pure stricture limited to the rectum.
2. A rectal stricture with elephantiasis of the external parts.
3. Rectal stricture complicated by fistulae, and formally classified as tuberculosis, even when Koch bacillus was not found.
4. Rectal strictures with pelvic cellulitis.

These types, therefore, include anorectal syphiloma with stricture of Fournier and esthiomene. (Chronic ulcer of vulva with elephantiasis.)

Associated with these glandular changes, which may become generalized, are constitutional signs and symptoms that range from polyarthritis to various types of skin eruptions such as, erythema multiforme or erythema nodosum.

The course of the disease may be very prolonged or the patient may be able to overcome the infection with the aid of supportive measures in a short time. These extremes are well-exemplified by two patients that we have observed.

## II. CASE REPORTS

A white male, age 32, unmarried, had observed an inguinal adenopathy following numerous sexual exposures. The glands continued to enlarge and become more painful until he was obliged to report to the hospital for care.

At the time of the first examination,

there was no sign of penile scar. There was a bilateral inguinal adenopathy with numerous fluctuating points on the right side beneath a very tense and bluish skin. Temperature 101° F. Leucocyte count 12,400. Wassermann test negative, Kahn test negative. No foci of infection or generalized disease could be held accountable for the lymphadenopathy. Frei antigen of proven value was obtained and the result of the test was a strongly positive reaction.

Under conservative treatment and strict bed rest, the suppurating glands were drained. Potassium and antimony tartrate was given intravenously biweekly in increasing dosage. The patient became very comfortable and began to gain weight. The glands decreased in size and 11 weeks after admission he was discharged as an arrested case.

Nine months later this same patient returned to the hospital with a recurrence of the same physical findings except that the glands of the left side were necrotic. The recurrence had developed following exposure and lowered resistance. The condition did not respond readily this time to symptomatic treatment. He was given a course of four diathermy treatments and was unable to leave the hospital 14 weeks after admission.

The second case to be described to show the association of cutaneous lesions was that of a white female, age 23. This patient had been hospitalized for 28 months. There was a history of gradual but continuous loss of weight associated with anorexia, headache and multiple draining fistulae in the inguinal region. There was no history of sexual exposure but the patient admitted having kept company with the opposite sex. The chest plates were negative. Mantoux test negative in various dilutions. Anemia present. Urine normal. Wassermann and Kahn tests negative. Loss of weight, 40 lbs. Frei test positive.

On examination of this girl, in addition to the draining fistulae in the left inguinal region, there were numerous lesions of erythema nodosum extending down the anterior surface of the left leg.

The patient was extremely emaciated and in spite of selected diets and insulin she had not gained weight. Biopsy of the drainage tract did not give specific information. It was decided that she should be given the possible benefit of heat treatments and a course of diathermy treatments was given. The results were gratifying. The patient began to gain weight and after several months was able to leave the hospital in excellent condition.

#### Incidence

Probably a dozen cases of lymphogranuloma inguinale have been observed in the Minneapolis General Hospital and the University of Minnesota Hospitals. These cases have presented a variety of findings. There has been no attempt to do routine Frei tests and in our patients the males have outnumbered the females three to one.

The incidence of lymphogranuloma inguinale has been surprisingly high where routine Frei tests have been done. In the series of 1,010 persons tested by De Wolf and Van Cleve, there were 58 positive reactions. Gray and others in St. Louis made a study of patients in the city hospitals and found that of 790 Frei tests on white and colored patients the incidence of lymphogranuloma inguinale in the white race was 3.4% and in the colored race 40%. The factor of race susceptibility is very striking in this series. Another point emphasized by these workers was the absence of a history of previous infection in 50% of the patients tested.

Goldblatt found that 32% of the prisoners quarantined for venereal diseases in the Cincinnati workhouse gave positive Frei tests when tested with several antigens.

#### Pathology

The general pathological picture of lymphogranuloma inguinale is that of a subacute lymphadenitis. Difficulty is occasionally experienced in differentiating this condition from tuberculosis and syphilis microscopically. In certain

of the cases, however, the microscopic picture is very characteristic. The disease has been diagnosed from a biopsy of the penile lesion before lymphadenopathy occurred.

When the involved glands are removed by surgical excision, there appears to be an enormous amount of peri-glandular exudate that has resulted in the matting together of the lymph nodes. If the nodes are removed early, there is only an inflammatory congestion and a small amount of exudate. On section, the glands can be seen to have numerous individual stellate abscesses of various sizes. The necrotic material is of a whitish-gray color and is very thick.

The histologic picture, as described by Nicolas, appears to be a definite one and he believes it to be specific. There are numerous stellate abscesses with epitheloid foci and giant-cells together with numerous polymorphonuclear and round cells. The inflammation of the glandular epithelial structure is diffuse and causes the normal shape of the glands to be lost. The changes are greatest in the medullary portion of the gland. The gummas are formed of a central degenerated nucleus which is finely granular and surrounded by a wide band of epithelial cells. The leucocytes migrate through the epithelial borders of the gummas and abscesses are formed. These may assume any one of a variety of shapes, depending upon the portion of the gland involved. In their borders, typical giant-cells of large size with numerous nuclei are found. The entire glandular wall may be lost in the larger abscesses. The degenerated portion is made up of many polymorphonuclear cells and large acidophilic mononuclears. Numerous epithelial foci are found throughout the gland and parenchymal tissue that do not have giant-cells. The follicular lesions of the lymph nodes and the type of cellular exudate represent the morphologic characteristics of lymphogranuloma inguinale.

#### Treatment

The large number of suggested therapeutic aids convinces one of their non-

specificity. Treatment may be divided into four groups:

1. Physical
2. Surgical
3. Biologic
4. Chemotherapeutic

The physical agents employed in the treatment of lymphogranuloma inguinale are heavily filtered x-rays, diathermy, ultraviolet light, hot air, and hot baths. Of these methods, our experience has been limited to the use of diathermy and hot baths. The object is to elevate the general body temperature for periods ranging from 15 to 30 minutes daily in the hot bath, and from 4 to 6 hours of continuous temperature elevation weekly by means of diathermy. The latter treatments are given until a course of from 4 to 8 have been completed. Our results from the use of diathermy compare favorably with those from other therapeutic agents, especially in the late cases.

Surgically, it has been suggested that the entire glandular adenopathy be removed. The contra-indication to this procedure is the possibility of subsequent lymph stasis of the lower extremity. Nichols, Barthels and Biberstein agree with Frei that partial removal of the involved glands gives good results. This is especially to be recommended in the early cases.

The histologic agents suggested include foreign protein, autohemotherapy and the intracutaneous injections of Frei antigen at regular intervals as recommended by Wein and Perlstein of Chicago.

Chemotherapeutic agents generally used in the treatment of lymphogranuloma inguinale are: 1% antimony and potassium tartrate given biweekly in doses beginning with 5 cc. and increasing gradually to 10 cc. for a period of from 6 to 8 weeks. Potassium iodide by mouth and intravenously. The salts of copper, arsenic and mercury have been used. With the exception of antimony and potassium tartrate, the use of these drugs has been disappointing.

In summarizing the effectiveness of

the variously recommended therapeutic agents, it is very probable that supportive measures, as bed rest and a nourishing diet in connection with the partial extirpation glands in the early cases, of the institution of full drainage in the late cases together with potassium and antimony tartrate offer our most effective therapeutic attack. In the late cases of esthiomene and of anorectal stricture, the results of treatment are routinely poor.

### Impressions

1. Lymphogranuloma inguinale is a chronic, low grade inflammation of the lymphatic nodes of venereal origin, resulting in complications of fistulae, esthiomene, or the anorectal syndrome in an estimated 50% of infected persons.

2. This clinical picture has been described under a variety of titles since the middle of the 19th century. It was probably known before that time.

3. It has also been known for some time that the disease was a specific entity and was probably venereal in origin. Many confusing terms are found in the literature, including conditions with similar names without any other relationship.

4. A filterable virus is thought to be responsible for the disease. The disease has been successfully transmitted to apes, mice, rabbits and other laboratory animals.

5. In the ape, the virus appears to have a special affinity for the central nervous system tissue causing an encephalitis.

6. The disease is mainly one of adult-life although occasional cases are reported in children.

7. The history of a small innocent appearing lesion on the glans penis, 3 to 10 days after sexual relation, followed by inguinal adenitis in from 10 to 30 days, should make one suspicious of lymphogranuloma inguinale.

8. The differential diagnosis should be made from syphilis, chancroid, granuloma inguinale, tuberculosis, Hodgkin's disease, tularemia and pyogenic infections.

9. Frei antigen tests are of great value in making the diagnosis.

10. Be sure the antigen is potent at the time of use.

11. Limitations of the Frei test are identical with those of other biological tests. Early cases of lymphogranuloma inguinale have a tendency to give a negative Frei and a false positive Wassermann reaction.

12. Once a Frei test becomes positive, it remains so for life providing of course that the patient's allergic status is not disturbed by infection or lowered resistance.

13. Through this test, it has been learned that many people have had this disease.

14. In the male, the inguinal adenopathy is accounted for by lymph drainage. In the female, involvement about the rectum is explained on a similar basis.

15. As the disease progresses, the infected lymph nodes mat together and become painful. Fusion with the overlying skin produces an appearance which is highly suggestive of the disease.

16. The rectal involvement may give confusing clinical pictures.

17. The course of the disease may be prolonged or the patient may be able to overcome the infection within a relatively short time.

18. Frei tests done on groups in the population in which the venereal disease ranks high often show a large number of positive tests.

19. The treatment is physical, surgical, biological, and chemotherapeutic.

20. Supportive measures, bed rest and a

nourishing diet with partial extirpation (to avoid lymphastasis) of the nodes in the early cases or full drainage and potassium and antimony tartrate in the late cases are the most effective. In the late cases of anorectal involvement the results are routinely poor.

Note:

Von Haam, E. and D'Aunoy, R., J.A.M.A. 106: 1642, (May 9) 1936, demonstrated the virus in the spinal fluid of human cases. They believe that the disease is a systemic one and suggest that the fever and headache support this idea.

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J.A.M.A. 106: 517 (Feb.15), 1936.

III. LAST WEEK

Date: May 7, 1936

Place: Recreation Room,  
Nurses' Hall

Time: 12:15 to 1:15

Program: Movie: Attention - Suckers.  
Tumors of Jaw  
Introduction of Dr. T. B.  
Cooley by I. McQuarrie

Present: 101

Discussion: Carl Waldron  
L. G. Rigler  
K. W. Stenstrom

IV. MOVIE

Title: Sunny Worthersee

Released by: Austrian State  
Tourist Department.

Gertrude Gunn,  
Record Librarian