LYMPHOGRANULOMA VENEREUM IN THE FEMALE

A CLINICAL STUDY OF NINETY-SIX CONSECUTIVE CASES

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LYMPHOGRANULOMA venereum is a venereal infection of virus origin with a remarkable predilection for lymphatic structures. The disease manifests itself by a primary evanescent genital lesion and subsequently by one or more subacute to chronic secondary localizing lesions. These are inguinal buboes, genital elephantiasis, rectal stricture and warty papillary excrescences or polypoid growths about anus, vulva, urethra and in the rectum and vagina. Ulceration commonly occurs either as a continuation and extension of the primary lesion or as a sequel to lymph stasis. Rectovaginal fistulae and ischiorectal abscesses are occasionally observed. Frequently systemic reactions occur.

Etiology. Lymphogranuloma venereum is due to a filtrable virus, immunologic response to which is shown by the Frei test. This test, when positive, remains so throughout life. It is a venereal disease which affects all races but in America is predominately found in the colored race. In our locality more white males are affected than white females. The highest incidence occurs during the most active period of sex life. The incubation period is inconstant and varies greatly. The primary lesion usually occurs ten to fourteen days after exposure and the adenitis twenty-one to thirty days. In an 11 year old girl with a history of a forced coitus (rape) the bubo appeared one month later. Twelve to forty days and longer may elapse from the time of the primary lesion before a positive Frei test is obtained.

In our series of cases there were ninety-two colored and four white females. Three of the white women, aged 26, 27 and 28 respectively, were married. One husband was tested with Frei antigen and reacted positively. The other white female, aged 20, was unmarried. Salpingitis was a complication in this patient. The colored women ranged in age from 11 to 56, nineteen being 20 or less and thirty-four from 21 to 30.

There is a high incidence to other venereal diseases in this group of patients. Twenty-seven either had active chancroid lesions or were positive to the intradermal chancroid test. Fifty-five either had a positive serologic test for syphilis or had been under treatment for this disease. Lesions of granuloma inguinale (diagnosed by finding Donovan bodies in smear or in tissue section) occurred in seven of this series. Three colored women had all four of the above venereal diseases and may have had gonorrhea in addition, inasmuch as no note of latent gonorrhea was made in this study. A considerable number have had salpingitis and several had been operated upon for this condition.

The time of appearance of the initial lesion according to the months of the year, where it was possible to determine, is recorded as follows:

January	5
February	1
March	3
April	3
May	2
June	1
July	2
August	4
September	4
October	2
November	1
December	2

Clinical Manifestations. Usually within two or three weeks after exposure a primary, often transitory, papule or vesicle may develop. This may quickly heal and the patient rarely connects it with the later manifestations which occur within a few weeks. Fever, joint pains and malaise are frequent systemic reactions accompanying unilateral or bilateral inguinal adenitis. Because this disease attacks the lymph channels and glands there may result localized elephantiasis of the vulvar region, labia and clitoris, or production of nodular tags of tissue about the anus or urethra, leading to the various inguinal, urethral or anal syndromes. Some of these lesions may ulcerate, become secondarily infected and heal with difficulty. The ulcers may excavate, especially when combined with other infections as chancroid, syphilis, fusospirochetosis, or secondary infection by other organisms. All manifestations may occur with or without fever which may be remittent and sometimes chronic.

Types. Genital. This is characterized by blockage of the lymph channels with resulting chronic edema and ultimate ulceration of the skin. There is a tendency to formation of elephantiasis of the labia, especially the labia majora, and of the clitoris. Deep, suppurating subcutaneous abscesses may develop. These may rupture through the skin and cause persistent fistulous tracts. Healing and scar tissue occasionally result in stricture or fistula of the vagina. In this series there were thirty-five ulcerative lesions located as follows: vulva 18: vagina 14; cervix 5; anus 2; buttocks 2. Elephantiasis occurred in twenty-three patients and in the following structures: vulva, either one or both labia majora, 20; clitoris 5. Seven of the above patients had both ulceration and elephantiasis. There was one stricture of the vagina.

Inguinal Adenitis and Buboes. Possibly due to the difference in lymph drainage, this is less common in the female than in the male. Nevertheless it occurs quite frequently, producing unilateral or bilateral adenitis with definite tendency to focal softening and subsequent drainage through multiple fistulous tracts. Twenty-nine of these patients had buboes and four had a history of buboes. The location of the bubo or buboes was about equally divided among the three possibilities, right, left and bilateral. In two patients with buboes in whom both the Frei and chancroid tests were positive, the Ducrey bacillus was isolated from the aspirated pus in pure cultures.

Anorectal Syndrome. This may be a subacute proctitis with redness, swelling and discharge from the mucosa. It may be chronic with resultant benign fusiform stricture of the rectum as though a rubber band of varying width were tightly wrapped around the rectal mucosa. This stricture, although it may be narrow longitudinally, is usually fusiform and regular in outline. It begins almost abruptly from a few centimeters to 8 to 10 cm. above the anus and extends upward a variable distance, sometimes to a length of 10 cm. In the early cases the constriction readily admits a finger but in the later ones hardly a knitting needle. While it is not strictly elastic, moderate dilatation is possible in the early stage. All patients with rectal strictures not due to trauma of hemorrhoidectomy, have had a positive Frei test. In addition to the stricture there is a definite tendency for verrucous tags of epithelium to develop at the anal orifice. Rectal strictures occur commonly in the female, possibly because of the relationship of the posterior vaginal wall to the rectum. This condition occurred in twenty-two

patients, i.e., about 23 per cent of the cases. In eleven patients it was uncomplicated. It was associated with elephantiasis

unnecessary. Anal tags were present in eight cases.

Urethral Syndrome. In some cases there

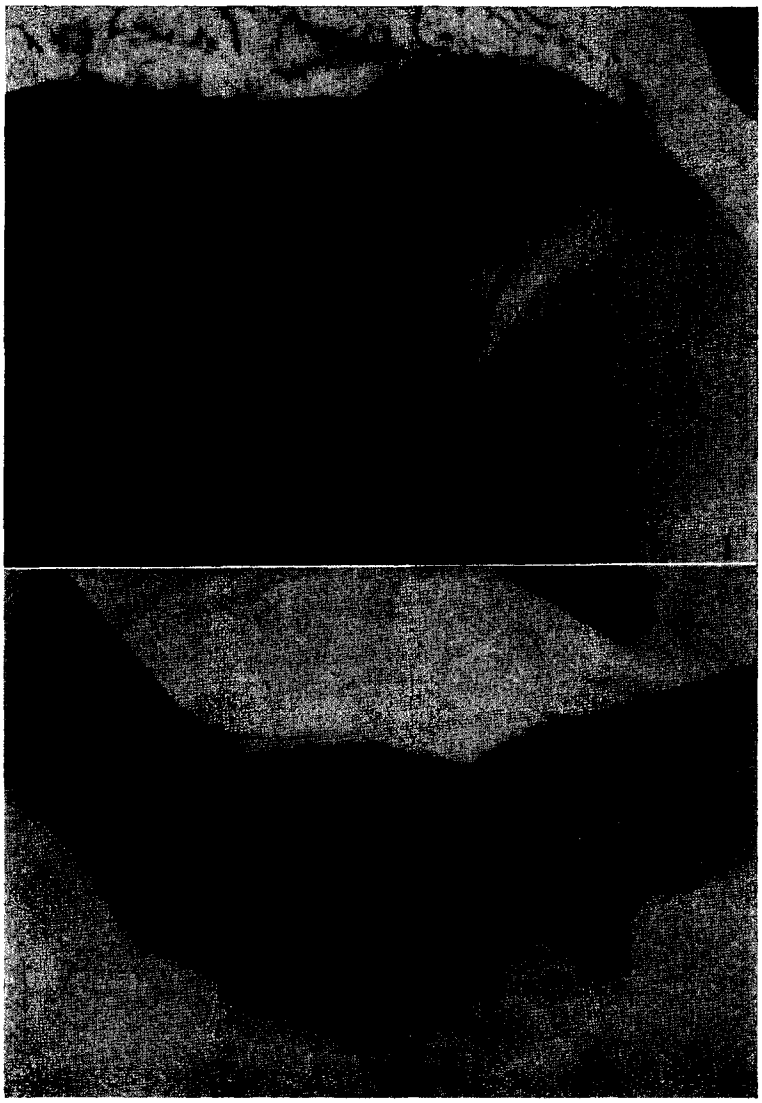

Fig. 1. Lymphogranuloma venereum—inguinal syndrome. Note the typical multinodular type of bubo.

Fig. 2. Lymphogranuloma venereum—genital syndrome. Note the elephantiasis of the vulva.

of the vulva in one patient; with vulvar ulceration in one; with urethral syndrome in one; with history of bubo in three; with previous colostomy in three; and with carcinoma of the anus in one. In the last two years the strictures have been gently dilated once a week with the gloved fingers. Colostomies have thus far been

is a tendency to development of papillary elevations of mucosa about the urethral meatus with inclination to loss of sphincter action. The accompanying symptoms, which are often intractable, are dysuria, frequency, and later incontinence, and in this series it was noted that there was a tendency to ulceration about the meatus.

We have never observed a urethral stricture in any of our patients. Six patients presented the urethral syndrome; all were complicated except one. Most of them were in association with vulvar lesions and one with rectal stricture.

Diagnosis. In the earliest manifestation of the initial lesion a nigrosine or dark-field study is necessary to eliminate syphilis. A smear study should be made for Ducrey bacilli to differentiate, if possible, chancroidal infection. The adenitis and bubo must be distinguished from those of chancroid, syphilis, gonorrhea (rare) and from the early inguinal lesion of granuloma inguinale (venereum) as well as from inguinal tumors, herniae, hydroceles, etc. The vulvar lesions may be simulated by granuloma inguinale, chancroidal infection, syphilitic lesions, tuberculous ulcers, or by epithelioma. In the tropics it is also necessary to differentiate the elephantiasis from that due to filaria Bancrofti. The urethral syndrome may be initiated by a urethral discharge which may be mistaken for that due to gonorrhea. The rectal stricture must be distinguished from that due to malignancy or to trauma of operative procedures. The anal tags may simulate hemorrhoids.

Consequently it is almost essential to inaugurate a diagnostic routine for all of these cases somewhat as follows: serologic blood test for syphilis; Frei intradermal test for lymphogranuloma venereum; intradermal bacillary antigen tests for chancroid. These skin tests should be read at forty-eight hours and the central papules or area of induration should be 7 mm. in diameter with a halo of erythemata of 14 mm. in diameter for a positive reaction. Smears of ulcers should be studied for Donovan bodies, Ducrey bacilli, fusospirochetes, and other secondary invaders. A biopsy of ulcerated tissue should be sectioned and stained for tubercle bacilli, carcinoma or Donovan bodies.

Therapy. Chemotherapy has been disappointing, as has been the experience in other virus diseases. Anything which increases general resistance is indicated. This should include improved general health by good food, rest and vitamins, active treatment of complications as syphilis, granuloma inguinale, gonorrhea, chancroid and especially secondary invaders of ulcerations. Active immunity seems to be enhanced in many cases and in some remarkably by repeated Frei intradermal tests or repeated subcutaneous injections of Frei antigen. In one case of rectal stricture in a white female the use of transfusions from the husband who was a Frei positive with a previous history of infection gave marked temporary relief. It may be that passive immunity holds great possibilities.

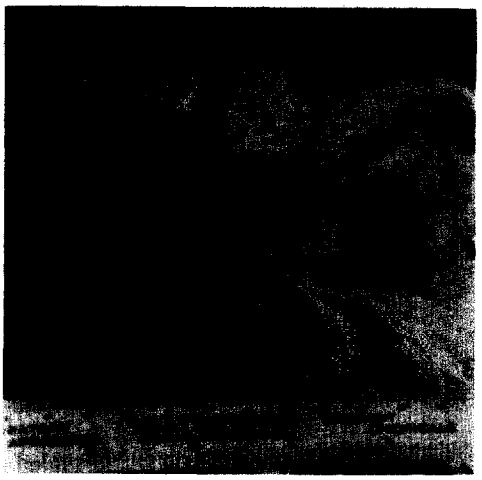

Fig. 3. Lymphogranuloma venereum—rectal syndrome. Arrow points to the stricture of the rectum. This patient developed an epithelioma at the anal margin.

More recently intravenous injections of small amounts (0.05 to 0.3 c.c.) of Frei antigen have been employed in therapy, but its value over subcutaneous injections has not as yet been evaluated. Excellent results have been obtained with the use of sulfanilamide.* It is of value only in draining buboes, sinus tracts, ulcerations, etc., by its probable action on secondary con-

* Sulfanilamide used in this study was provided by the Department of Medical Research of the Winthrop Chemical Company, Inc., in the form of Prontylin—5 gr. tablets.

taminants. Ulcers frequently heal, proctitis and rectal leucorrhea abates and drainage from sinuses ceases. However, it does not seem to have any definite effect on the secondary lesions per se, such as the rectal stricture, chronic elephantiasis, or growths and papillary excrescenses about the genitalia.

FIG. 4. Lymphogranuloma venereum—genitourinary syndrome. Note the papillary excrescences about the urethral orifice. This patient also has vulvar elephantiasis.

Fluctuant buboes should be aspirated as often as necessary but should not be incised because intractable ulceration may result. Furthermore, the sterilized pus is of value in preparation of Frei antigen. This should be standardized with known antigen. Ulcerations are best treated by cleanliness and elimination of secondary invaders by weak antiseptic and oxidizing solutions. Fusospirochetosis is well managed by a mixture of arsphenamine 4½ per cent in equal parts of glycerine and cod liver oil. This may be applied directly or as a saturated dressing and is more comfortable if a 1 or 2 per cent solution of a local analgesic is added. As an alternative, a creamy paste of cod liver oil-zinc peroxide mixture may be used. It is less expensive and is quite efficacious.

Rectal strictures are probably best dilated gently once a week. Neglect of this form of therapy on the part of the patient or physician will in the great number of cases ultimately lead to colostomy for relief of an advanced stage of stricture. Since we have inaugurated active treatment of the stricture by repeated dilatation we have not had to perform any colostomies. In the case of elephantiasis and polypoid growths the patient may be greatly benefited by surgical removal of redundant tissue by partial or complete vulvectomy or clitorectomy.

SUMMARY

1. Ninety-six consecutive cases of lymphogranuloma venereum in the female are

analyzed and are found to fall into four overlapping groups, i.e., genital, inguinal, anorectal, urethral syndromes.

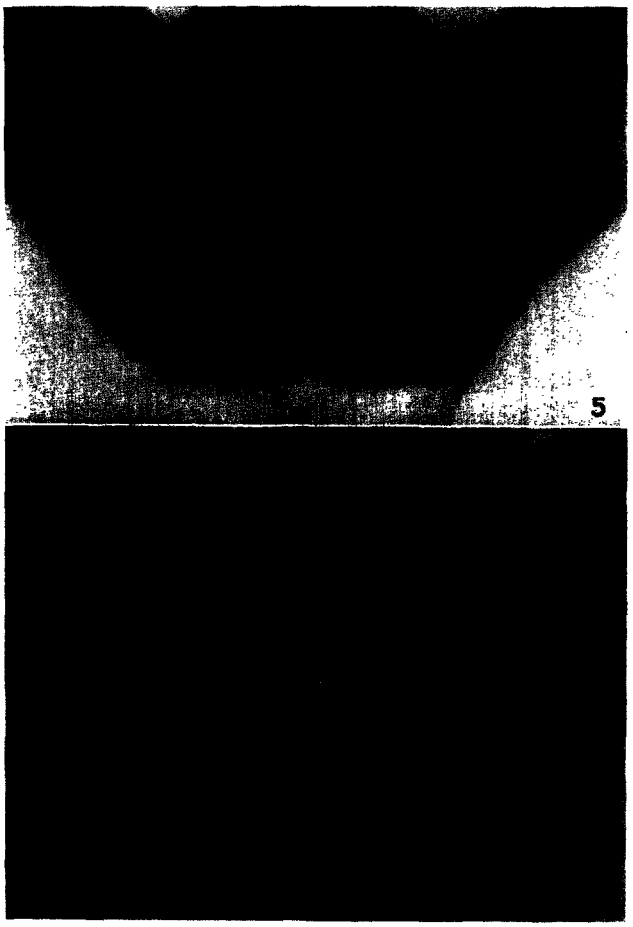

FIG. 5. Lymphogranuloma venereum—inguinal genito-anal syndrome. Note the left inguinal bubo, the multiple draining sinuses and swelling of the left vulva, and the sinus on the inner fold of the left buttocks draining an ischiorectal abscess.

FIG. 6. Lymphogranuloma venereum—genito-anorectal syndrome. Note the elephantiasis of the clitoris and labia, the anal growths. This patient also has a rectal stricture.

2. Various therapeutic measures are recommended. A specific has as yet not been found. Sulfanilamide has proved a valuable adjunct to therapy. It is of value in checking the rectal leucorrhea that is so often attendant upon rectal stricture, as an aid in the healing of ulcerations, and in permitting drainage from ischiorectal abscesses, sinus tracts and draining buboes to cease. However, thus far but little effect has been observed on the secondary lesions per se, such as rectal stricture, elephantiasic vulvae, or papillary excrescences and growths about the genitalia.

ADDENDUM

Since submission of this paper for publication, we have studied forty-nine new female cases of lymphogranuloma venereum. The distribution of the lesions, the clinical course and symptomatology are much the same as those already described in this analysis. In one patient 5 years of age, bilateral buboes followed attempted rape. Two colored women had

abscesses in the rectovaginal space which were associated with rectal disease. Further observations on sixteen cases treated with sulfanilamide bear out our earlier findings. It is a valuable adjunct to the therapeutic armamentarium. We cannot, however, share the enthusiasm expressed in some recent reports, particularly that of Gjuric (*München. med Wchnschr.*, 85: 335, 1938). We are in agreement with the conservative report of Shaffer and Arnold (*Arch. Dermat. & Syph.*, 87: 7305, 198).

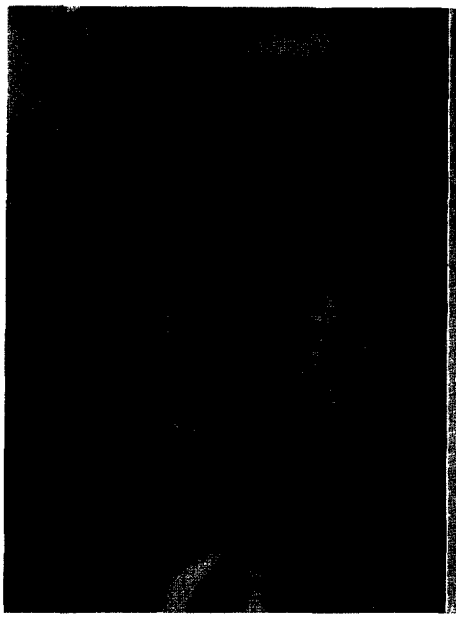

FIG. 7. Lymphogranuloma venereum—genital syndrome. Note the elephantiasis of vulva, clitoris, the pendulous polypoid mass (right lower vulva), and the papillary excrescences.

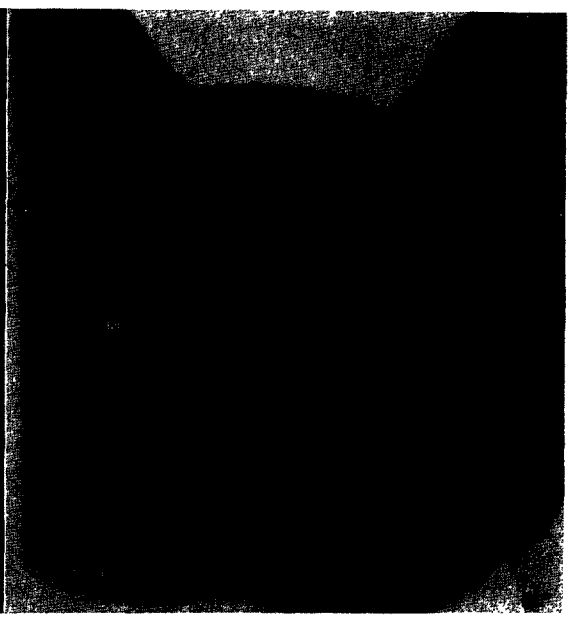

FIG. 8. Lymphogranuloma venereum—genito-anal syndrome. Note the elephantiasis vulvae and the perineal ulceration and growths.

REFERENCES

FREI, WILHELM. The reaction for lymphogranuloma inguinale. *Klin. Wchnschr.*, 11: 512, 1932.

SULZBERGER, MARION B., and WISE, FRED. Lymphopathia venereum. *J. A. M. A.*, 99: 1407, 1932.

DEWOLF, H. F., and VAN CLEVE, K. V. *J. A. M. A.*, 99: 1065–1071, 1932.

WIEN, M. S., and PERLSTEIN, M. O. *Arch. Dermat. & Syph.*, 28: 42, 1933.

COLE, H. N. Lymphogranuloma, the fourth venereal disease and its relation to stricture of the rectum. *J. A. M. A.*, 101: 1069, 1933.

GRACE, A. W., and SUSKIND, F. H. *J. A. M. A.*, 107: 1359, 1936.

STRAUSS, MAURICE J., and HOWARD, MARION E. L. The Frei test for lymphogranuloma inguinale. Experiences with antigens made from mouse brain. *J. A. M. A.*, 106: 517, 1936.

GRAY, LAMAN A. Lymphopathia venereum. "Lymphogranuloma inguinale" of the female urethra. *Surg. Gynec. & Obst.*, 62: 745, 1936.

GREENBLATT, R. B., and WRIGHT, J. C. The significance of fusospirillosis in genital lesions. *Am. J. Syph., Gon. & Ven. Dis.*, 20: 654, 1936.

PREHN, D. T. *Arch. Dermat. & Syph.*, 35: 231, 1937.

DIENST, R. B., and SANDERSON, E. S. Use of nigrosine to demonstrate treponema pallidum in syphilitic lesions. *Am. J. Pub. Health*, 26: 910, 1937.

GREENBLATT, R. B., SYDENSTRICKER, V. P., and PUND, E. R. The fourth and fifth venereal diseases. *J. M. A. Georgia*, vol. 26, Jan., 1937.

ANDERSON, O. L., and HARMOS, OSCAR. Lymphopathia venereum: treatment with diluted Frei antigen intradermally and observations on diagnosis. *Surgery*, 3: 41 (Jan.) 1938.

GREENBLATT, R. B., and SANDERSON, E. S. The intradermal charncroid bacillary antigen test as an aid in the differential diagnosis of the venereal bubo. *Am. J. Surg.*, 61: 384, 1938.