LYMPHOGRANULOMA VENEREUM*

ARTHUR W. GRACE

Professor of Dermatology and Syphilology, Long Island College of Medicine

LYMPHOGRANULOMA venereum is a widespread, contagious, venereal disease of human beings caused by a minute organism. The infective agent enters the body through the skin of the external genitalia without, however, always producing a demonstrable lesion at the portal of entry. It may also enter by way of the mucosa of the anal or rectal canals, and, much less frequently, by extragenital routes. The virus multiplies readily in the lymph nodes draining the affected areas, and probably, also, in the anal and rectal mucosae. It is transmissible to certain laboratory animals. The lesions of lymphogranuloma venereum are inflammatory in nature, subacute or chronic in quality of reaction, and are often marked by the development of multiple small foci of suppuration. Mortality is low. The disease is systemic with local manifestations appearing chiefly in the anorectal, inguinal and genital regions. It is customary, and convenient, to speak of the disease pictures in these areas as the anorectal, inguinal and genital varieties of lymphogranuloma venereum. There is, however, no evidence of the existence of any difference, other than regional, between the disease in the various sites.

Diagnosis of lymphogranuloma venereum is made, at present, by means of a skin test of a high degree of specificity and sensitivity which has been named after its discoverer, Wilhelm Frei.[1] Treatment of the disease with certain members of the sulfonamide series of drugs, notably sulfanilamide and sulfathiazole, has been very successful. The use of these drugs in the treatment of lymphogranuloma venereum has been of the highest value in that, prior to their introduction, there was no adequate remedy for the disease.

HISTORY

The inguinal variety of lymphogranuloma was the first of the manifestations of this disease to be suspected of being a separate clinical

* From the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine, and The New York Hospital and Department of Medicine, Cornell University Medical College.
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entity. John Hunter[2] described, in 1786, a condition in which buboes developed without apparent cause, and were unaffected by mercury. Credit, however, for the earliest definite description belongs to William Wallace[3] who, under the title of "indolent primary syphilitic bubo," gave an accurate description of what would now be regarded as a chronic suppurative case of the inguinal variety of the disease.

H. G. Klotz[4] first called attention to the disease in this country. He reported having seen, in New York City, between the years 1879 and 1889, over 120 cases of a clinical entity which can hardly have been other than the inguinal variety of lymphogranuloma.

Durand, Nicolas and Favre,[5] in 1913, gave the best clinical and pathological study hitherto published of the inguinal disease. They believed, erroneously, that the histological picture of lymphogranuloma resembled that of Hodgkin's disease, or lymphogranulomatosis, and proposed the term lymphogranuloma inguinale for the disease. The clinical and pathological manifestations of lymphogranuloma, however, are not peculiar to the disease and accurate identification was not possible until the introduction of the Frei test in 1925. Study and knowledge of the disease have progressed rapidly following Frei's important discovery.

In 1928, using the recently developed skin test, Frei and Koppel[6] showed that a positive reaction was given by persons presenting inflammatory stricture of the rectum. Experimental proof of the lymphogranulomatous etiology of this condition was established in 1932 by Ravaut, Levaditi, Lambling and Cachera[7] and Laederich, Levaditi, Mamou and Beauchesne[8] who isolated a strain of the virus of lymphogranuloma venereum from inflamed rectal tissue. Mocquot, Levaditi and Reinié,[9] in 1935, isolated from an inflammatory condition of the colon a strain of the virus with which Levaditi, Mollaret and Reinié,[10] in the same year, produced the pathological changes characteristic of lymphogranuloma in the rectum of chimpanzees by direct inoculation into the mucosa.

The etiological agent of lymphogranuloma venereum was shown to be a virus in 1930 by Hellerström and Wassén[11] who inoculated *Macacus rhesus* and *Macacus cynomolgus* monkeys intracerebrally with suspensions of infected human lymph node. Two years later, Levaditi, Ravaut and Schoen[12] reported the transmission of the disease to mice by the intracerebral route. The mouse has since proved to be a very valuable animal in the study of lymphogranuloma. Strains of the virus have

TABLE I

NEW CASES OF LYMPHOGRANULOMA VENEREUM AND TOTAL NEW IN- AND OUT-PATIENT ADMISSIONS, NEW YORK HOSPITAL, 1934-40

Year	No. of new cases of L.V.	Total No. of new admissions	Cases of L.V. per 10,000 admissions
1934	26	43419	6.0
1935	23	44123	5.2
1936	31	45977	6.7
1937	35	44484	7.9
1938	35	43411	8.1
1939	28	41895	6.7
1940 (9 months)	34	31447	10.8

been maintained by successive mouse passage over a period of years and the infected brain has provided useful material, both as a source of virus for experimental purposes and for the performance of the Frei test. The etiological agent of lymphogranuloma was undoubtedly first seen by Gay Prieto[13] in 1927 in the form of small cytoplasmic granules in material obtained from infected inguinal nodes. The granules were one micron or less in diameter and appeared frequently in small aggregations. They were also described, and figured, by Findlay[14] who suggested the possibility that they represented the virus. Granules, however, appear sparsely in preparations of animal and human tissue, a fact which made it impossible until recently to procure active suspensions of the virus free from a large proportion of inert material. The work of Rake[15] and his colleagues, who employed the yolk-sac technique of Cox,[16] has now afforded a means of obtaining rich suspensions of granules. Successive passage of lymphogranulomatous material in tissue culture was observed by Sanders[17] to increase the potency of the virus as high as one thousand times.

STATISTICS OF THE FREQUENCY OF OCCURRENCE OF LYMPHOGRANULOMA VENEREUM

Lymphogranuloma has been studied at the New York Hospital for the past eight years, for most of the time in a clinic specially devoted to

TABLE II

DISTRIBUTION, BY VARIETIES, OF 242 CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM IN 218 INDIVIDUALS

Variety	No. of manifestations	Per cent
Anorectal	145	59.9
Inguinal	60	24.8
Genital	28	11.7
Asymptomatic	6	2.5
Miscellaneous*	3	1.1

* Includes one case each of carcinoma of rectum, cystitis, and granulomatous pelvic masses.

the purpose. Close coöperation with all of the departments of the hospital has enabled every case of the disease found in the institution to be examined and treated. Table I shows the number of new cases seen annually since 1934, as well as the ratio of these cases to the total annual in- and out-patient new admissions. It will be seen that the proportion of cases of lymphogranuloma is increasing in the community from which the New York Hospital draws its clientèle. A further analysis of the material has revealed the increase to occur equally among all the varieties of the disease.

The local manifestations of lymphogranuloma constitute the most striking element in the clinical picture and occur, in order of frequency, in the anorectal, inguinal and genital regions. Table II shows that the anorectal is approximately two and one half times as common as the inguinal and about five times as frequent as the genital variety. The most frequently occurring combinations of varieties are the genital and inguinal and, less commonly, the anorectal and inguinal.

A small proportion of individuals give positive Frei reactions without any evidence of an existing, or preceding, infection with lymphogranuloma. Such people are usually detected in the performance of surveys of the incidence of the disease in a community, or during investigation of the contacts of an infected person.

Clinical manifestations of the disease, which do not fall into one of the three main varieties, represent about one per cent of the cases and,

in our material, are composed of, respectively, carcinoma of the rectum, cystitis, and granulomatous pelvic masses.

The Anorectal Variety of Lymphogranuloma Venereum

In conformity with all of the manifestations of the disease, the anorectal variety is acquired chiefly by sexual contact. Evidence which has been presented elsewhere, by the author and Henry,[18] has shown that most cases of this variety, in males, arise by the direct implantation of the virus upon the anal or rectal mucosae, through the practice of sodomy. Infection of the lower bowel has also been acquired, in adults and in children of both sexes, by the use of an enema tip in common with a person suffering from the anorectal variety of the disease. It is clear, therefore, that the mucosa of the lowest portion of the human bowel provides an excellent medium for the growth of the virus of lymphogranuloma venereum. Experimental evidence has shown this to be true for the chimpanzee.[10] The mode of acquisition of the anorectal disease by women has been the subject of much discussion. One school, represented by Bensaude and Lambling[19] in France, is of the opinion that owing to the intimate connection between the vaginal and perirectal tissues, the disease begins in the latter tissues and spreads through the rectal wall into the mucosa. In support, it was claimed that of eighty women with rectal stricture, only twelve showed accompanying active inflammation of the rectal mucosa. These authors said, in effect, that if a case of anorectal lymphogranuloma showed stricture and proctitis, it could be assumed that the disease began in the rectal mucosa. If, however, there were stricture alone, the condition probably began outside the rectal wall and traveled through to the mucosa.

Examination of our material on this subject reveals that of sixty-seven women with stricture, no less than sixty-two, or 92.5 per cent, had an accompanying proctitis. By Bensaude and Lambling's own criterion, therefore, practically all anorectal infection with lymphogranuloma in women begins upon the mucosal surface and not outside the bowel wall. I am of the opinion that, in women, the virus, deposited during the sexual act by the infected partner, is enabled through the moisture of the parts to find its way to the anorectal mucosa and there to flourish, as in the case of the male. I am prepared to concede to Bensaude and Lambling the existence of some cases of anorectal lymphogranuloma which begin in the outer coat of the bowel. The clinical

TABLE III

ANALYSIS OF 145 CLINICAL MANIFESTATIONS OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Number	Per Cent
Stricture with proctitis	107	73.8
Stricture without proctitis	7	4.8
Proctitis without stricture	14	9.7
Esthiomène with stricture and proctitis	3	2 0
Fistula-in-ano	8	5.4
Perirectal abscess	2	1.4
Scarring of perianal tissues	1	0.7
Rectovaginal fistula	1	0.7
Elephantiasis of female genitalia with stricture	1	0.7
Elephantiasis of male genitalia with stricture and proctitis	1	0.7

TABLE IV

RACE AND SEX DISTRIBUTION OF 128 CASES OF THE ANORECTAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	Total cases	Per cent			
		White male	White female	Black male	Black female
Stricture with proctitis	107	38 3	15.0	3.7	43.0
Stricture without proctitis	7	28.6	14.3	0.0	57.1
Proctitis without stricture	14	71.4	7.1	21.5	0.0

condition in such cases is probably stricture without proctitis, of which we have only seen seven cases, two in men and five in women.

The clinical manifestations which are included in the anorectal variety of lymphogranuloma are chiefly the three entities of stricture with proctitis, stricture without proctitis and proctitis without stricture. These comprise over 88 per cent of the variety. The frequency of their distribution by race and sex is shown in Table IV where the comparatively high proportion of cases in white males should be noted.

I believe that proctitis without stricture represents the earliest objective sign of anorectal lymphogranuloma, and that, untreated, the great majority of such cases proceed to the development of stricture while the proctitis is still active. Of fourteen cases of proctitis without stricture I have only observed one to heal spontaneously, and that in a white man. Thirteen of the fourteen individuals were male homosexuals who adopted the passive role. Consideration of the history of their infection indicated that an average period of six weeks elapsed between infection of the rectal mucosa and the development of symptoms.

It should be the endeavor of all persons interested in the study of lymphogranuloma venereum to detect cases of the anorectal variety in the "proctitis without stricture" stage. Complete and rapid cure can then be obtained in over 75 per cent of cases. It is more difficult to heal a proctitis after the development of stricture. Little more than one-tenth of our cases of proctitis were observed before stricture had developed.

The earliest symptom of proctitis is the passage of blood and pus per anum. This is a direct consequence of the replacement of a portion of the anorectal mucosa by granulation tissue. Untreated, the granulomatous process extends deeper into the bowel wall, beginning usually at the posterior aspect and ultimately encircles the lumen. In the majority of cases, the replacement of granulation tissue by fibrous tissue begins to be evident, as a narrowing of the anal or rectal canals, less than three months after the onset of proctitis. In untreated cases, narrowing is slowly progressive.

I have only been able to observe closely three untreated persons during progression from early infection to complete closure of the bowel. In two of these the gamut of the disease was run in six, and in the third, in seven years. The number of cases, however, in which colostomy is required for relief of obstruction is relatively few, only nineteen persons out of a total of 128, or 14.8 per cent, having had to submit to this operation.

A question may be raised at this point as to the proportion of cases of stricture with proctitis, stricture without proctitis and proctitis without stricture which are lymphogranulomatous in origin. The question is answered in Table V in which it is assumed that clinical conditions may be regarded as lymphogranulomatous when the Frei reaction is positive, and non-lymphogranulomatous when it is negative. Accordingly,

TABLE V

THE FREI REACTION IN CERTAIN CLINICAL CONDITIONS

Clinical condition	Number of Cases			Per cent Frei-positive
	Frei-positive	Frei-negative	Total	
Stricture with proctitis	107	3	110	97.3
Stricture without proctitis	7	3	10	70.0
Proctitis without stricture	14	8	22	63.6
Fistula-in-ano	8	17	25	32.0
Perirectal abscess	2	8	10	20.0
Ulcerative colitis	0	29	29	0.0
Regional ileitis	0	3	3	0.0

97 per cent of cases of stricture with proctitis, 70 per cent of cases of stricture without proctitis and 63 per cent of cases of proctitis without stricture are due to the virus of lymphogranuloma.

In view of the readiness with which the virus produces lesions in the lower bowel, our material was further studied to determine the extent to which the Frei reaction is positive in acute and chronic ulcerative colitis and in regional ileitis. No positive reaction was obtained in twenty-nine persons with ulcerative colitis or in three with regional ileitis. It may, therefore, be assumed that the virus of lymphogranuloma venereum does not often play a demonstrable part in the etiology of these two conditions. Our results with ulcerative colitis are in keeping with the experience of Rodaniche, Kirsner and Palmer[20] who reported that thirty-two of thirty-four patients with chronic ulcerative colitis had negative Frei reactions and showed no evidence of neutralizing antibodies in their sera against the virus of lymphogranuloma venereum. In regard to the two Frei-positive persons in their series, consideration was given to the possibility that the virus, although not directly responsible for the bowel ulceration, might have paved the way for other necrotizing agents to become established, as Frei originally suggested.

The remaining clinical manifestations of the anorectal variety of lymphogranuloma are shown in Table III. With the possible exception of esthiomène, which can be closely mimicked by granuloma venereum

TABLE VI

CLINICAL MANIFESTATIONS OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No. of cases	Per cent
Suppurative adenitis, unilateral	34	56.7
Suppurative adenitis, bilateral	9	15.0
Non-suppurative adenitis, unilateral	14	23.3
Non-suppurative adenitis, bilateral	3	5.0

and which may occur without rectal involvement, the seven lowest entities in the table are by no means strictly of lymphogranulomatous origin. Further consideration of Table V shows that only about one-third of the cases of fistula-in-ano, and approximately one-fifth of those of perirectal abscess, are due to the virus of lymphogranuloma.

A word should be said about esthiomène, a term which, in the original Greek, meant eating or eroding. The disease is peculiar to women and the original description given by Huguier[21] in 1849 is applicable today. He said, "This chronic malady is characterized by a leaden or violaceous tint of the parts. Deformity, ulceration and destruction may occur with concomitant hypertrophy and infiltration of such a nature that the orifices and canals which open into the vulvoanal region can be at the same time ulcerated, enlarged and strictured."

THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

The inguinal variety results from the deposition of the virus within the territory drained by the inguinal and femoral nodes. The actual site of invasion of the tissue—the primary lesion—is not often demonstrable. In sixty cases of this variety in our material, it was present in fourteen, or 23.3 per cent.

The virus is lymphotropic and produces clinical manifestations in the affected nodes 7 to 21 days after the infecting coitus. The nodes enlarge, sometimes to a considerable size, are painful, and the overlying skin is of a dusky red or purplish tint. In Table VI are shown the clinical manifestations of the inguinal variety in our material. In about four-fifths of the cases the disease is unilateral and in the remaining one-fifth,

TABLE VII

RACE AND SEX DISTRIBUTION OF 60 CASES OF THE INGUINAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Race and Sex	No. of cases	Per cent
White male	39	65.0
White female	2	3.3
Black male	15	25.0
Black female	4	6.7

bilateral. Frank pus appears in the nodes in approximately three-quarters of the infected persons and, in the absence of treatment, breaks through the overlying skin. The sinus thus formed may persist for months constantly draining seropurulent material. Many of the non-suppurative cases heal spontaneously.

The most striking element in the architecture of the diseased node is the presence of a large number of small foci of suppuration which are termed stellate abscesses.

The inguinal variety of lymphogranuloma venereum occurs rarely in women. In our series of sixty cases only six, or 10 per cent, were found in women (Table VII).

THE GENITAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Table VIII shows the frequency of occurrence in our material of the entities which comprise this condition. Primary lesions constituted 50 per cent of the genital manifestations. Satellite adenopathy was not always a concomitant of the primary lesion nor was such adenopathy always purulent. The common type of primary lesion is an oval vesicle on a slightly larger, non-indurated, erythematous base. It measures in the neighborhood of 6 millimeters in the longer diameter which is usually placed at right angles to the long axis of the penis. It does not produce subjective symptoms and is commonly found on the shaft or glans near the coronal sulcus. Primary lesions of the vesicular type generally disappear within 2 weeks without leaving a trace of their presence. Ulcerated primary lesions occur rarely, and when they do a concomitant chancroidal or syphilitic infection is sometimes found. Primary le-

TABLE VIII

CLINICAL MANIFESTATIONS OF 28 CASES OF THE GENITAL VARIETY OF LYMPHOGRANULOMA VENEREUM

Clinical manifestation	No. of cases	Per cent
Primary lesion with adenitis	10	35.7
Primary lesion without adenitis	4	14.3
Esthiomène with and without rectal involvement	6	21.4
Elephantiasis of penis	5	17.8
Elephantiasis of labium majus	1	3.6
Abscess of vaginal wall	1	3.6
Periurethral abscess	1	3.6

sions of lymphogranuloma are infrequent in women, two only having been observed in our material, one on the labium majus and the other on a perianal tab.

Esthiomène is the second in order of frequency of the genital lesions and has already been described. Elephantiasis of the male and female genitalia produced by the virus is indistinguishable clinically from that due to any of the other known causes of the condition. Elephantiasis of the penis may be produced by the lymphogranulomatous process itself or may follow extirpation of bilaterally involved nodes. Of five cases in our series, three were the sequel of radical surgery and two arose spontaneously.

PARINAUD'S CONJUNCTIVITIS

Curth[22] recently reported the case of an individual who developed, in May 1932, a painless conjunctivitis of the right eye following perverted intercourse. The right preauricular and submaxillary nodes became swollen and tender. Treatment with ineffectual remedies was continued until 1933 when vision was lost in the affected eye. The condition was untreated for the next 5 years during which there was slow progression of the lesion. In November 1938, the right eye showed swelling and inflammation of both lids with considerable edema, especially of the lower lid, and some purulent conjunctival discharge. There was marked destruction of the inner surface of the lids. The right globe

TABLE IX

CLINICAL CONDITION OF 11 PERSONS FROM WHOM SEMEN WAS OBTAINED FOR TESTING FOR LYMPHOGRANULOMA VENEREUM

Case	Nature and duration of clinical condition
1	Active proctitis, 13 months
2	Active proctitis, 3¼ years
3	Active proctitis, 4 years
4	Active proctitis, 4½ years
5	Active proctitis, 6 years
6	Unhealed suppurative groin nodes, 10 days
7	Healing non-suppurative groin nodes, 3 weeks
8	Suppurative groin nodes, healed, 4 weeks
9	Suppurative groin nodes, healed, 16 months
10	Suppurative groin nodes, healed, 22 months
11	Unhealed primary penile lesion, 14 days

was intensely injected. The cornea was opaque. There was no longer enlargement of any of the lymph nodes. Experimental work by Curth and his colleagues established the lymphogranulomatous etiology of the conjunctivitis, thereby confirming the original observation of Levaditi, Bollack, Basch and Desvignes,[23] in 1936.

ASYMPTOMATIC CASES OF LYMPHOGRANULOMA VENEREUM

This group comprised three white men and three white women in all of whom there was neither existing evidence, nor past history, of infection with the virus. All, however, gave a positive Frei reaction. The marital partners of two men and one woman presented active lesions in the inguinal nodes, the anorectal mucosa and bladder wall respectively. Examination of the contacts of the other three persons was not possible.

Consideration of the group of asymptomatic cases leads to the question as to whether reservoirs of the virus exist other than in the discharges from the bowel and from the infected nodes. An attempt was made by the author to answer this query in 1935 by the examination of specimens of semen from eleven individuals who presented active or healed manifestations of lymphogranuloma. The nature of the lesions

which were presented by the group is shown in Table IX. The existence of virus in the semen was sought by diluting the material with an equal volume of physiologic saline, inactivating by heat, as in the preparation of Frei antigen, and injecting 0.1 cc. intradermally into lymphogranulomatous subjects. In the presence of inactivated virus, positive Frei reactions would have followed this procedure. In no instance, however, was such a reaction obtained. It was therefore concluded that the virus of lymphogranuloma venereum is not present in measurable quantity in the semen and that infection is probably not transmitted by this secretion. The apparent lack of infectivity of semen suggests that lymphogranulomatous proctitis following sodomy arises from an open primary lesion in the active partner, or from an infection of his bladder mucosa.

The Systemic Manifestations of Lymphogranuloma Venereum

The chief systemic manifestation of lymphogranuloma venereum is the hypersensitivity of the skin as a whole to the intradermal injection of suspensions of the inactivated virus. In the case of the inguinal variety of the disease, this develops at about the same time as the enlargement of the nodes and, in the anorectal variety, approximately one month after the appearance of the anal discharge.

Lymphogranuloma venereum may present a clinical picture of acute or chronic febrile illness in which local manifestations are present only in minor degree or may be entirely absent. Harrop[24] and his colleagues have recently reported such cases in workers in the virus, two of whom apparently acquired the infection through the respiratory passages. In one instance the sole localizing manifestation was a moderately enlarged supraclavicular node. In the other there were a greatly swollen uvula, non-suppurative cervical adenitis and recurrent bouts of pyrexia of moderate degree. A third person showed only malaise, fleeting muscular pains, and mild fever.

The inguinal variety of lymphogranuloma is usually ushered in with fever of short duration. Chills and joint pains may be present. The patient is seldom more than mildly ill.

Constitutional manifestations rarely accompany the onset of the anorectal variety. As the disease progresses, however, the individual presents the picture of chronic illness. Loss of weight appears most commonly and is accompanied by anorexia, insomnia and nervousness.

Symptoms of intestinal obstruction are much less frequent than the narrowing of the rectal lumen would lead one to expect. After the disease has persisted for several years, arthritis develops in about 10 per cent of the cases. The joints most commonly affected in our series were the wrists, fingers, elbows, ankles and knees in descending order of frequency. There is hydrops of the affected joint and erythema of the overlying skin. Aspirated synovial fluid is bacteriologically sterile and does not contain the virus. Joint destruction does not occur and full function is ultimately restored. Untreated arthritis waxes and wanes over a period of years and is sometimes of sufficient severity to require bed rest.

A systemic effect of lymphogranuloma reported by Gutman[25] is hyperproteinemia due to a large increase in serum globulin. It was found that, of seventy-two lymphogranulomatous persons in all stages of the disease, two-thirds had total serum proteins in excess of 8.0 per cent, the upper limit of normal; and approximately four-fifths had serum globulins in excess of 3.5 per cent. Marked hyperproteinemia occurred particularly in persons with chronic complications, notably in those with rectal stricture. Of forty-two such individuals over 80 per cent showed hyperproteinemia with values up to 11.4 per cent. Repeated determinations, made over periods of almost 2 years, indicated that the elevated serum protein values tend to persist for indefinite periods at an approximately constant level. The significance of hyperproteinemia in lymphogranuloma is as yet unknown.

The Virus of Lymphogranuloma Venereum

The etiological agent of lymphogranuloma is a virus which is filterable through Berkefeld V or Chamberland L 3 candles. It is transmissible to monkeys, mice, guinea pigs, cats, dogs and to certain rodents such as the field vole, the spermophile and the striped ground squirrel. The virus can be observed microscopically in the form of cytoplasmic granules in the lesions of lymphogranuloma venereum of man, in the brains of infected monkeys, in the brains and lungs of infected mice, in experimental buboes in guinea pigs, and in the chorioallantoic membrane and yolk sac of the developing chick embryo. The dimensions of the virus, as shown by filtration through graded collodion membranes, are similar to those of the vaccinia virus, namely 0.125 to 0.175 micron.

The pathogenicity of strains of the virus for experimental animals is

low and little increase in virulence follows successive passage in them and in the chorioallantoic membrane of the chick.

The action of the virus can be inhibited by the use of sulfanilamide, sulfapyridine, sulfathiazole, [26, 27] and by other sulfonamide compounds.[27]

The Diagnosis of Lymphogranuloma Venereum

Owing to the lack of specificity of the histological lesions, accurate diagnosis of the disease is impossible by microscopic methods. None of the clinical manifestations are peculiar to lymphogranuloma, the most pathognomonic lesion being stricture with proctitis of which we have shown that 97 per cent of all cases are lymphogranulomatous (Table V). Detection of the virus in lesions requires highly trained personnel, considerable laboratory equipment, much time, and cannot always be carried out even in known cases of lymphogranuloma.

The cutaneous test discovered by Frei has proved to be highly specific and has been, until now, the sole means of accurate diagnosis. The test depends upon the fact that the skin of persons who have, or have had, lymphogranuloma is hypersensitive to the injection of the inactivated virus of the disease. Such hypersensitivity usually persists throughout the life of the individual. In one instance only, a laboratory infection in a worker, has the development and disappearance of this increased cutaneous reactivity been reported.[24]

The test is performed by the intradermal inoculation of an emulsion containing the inactivated virus. The inoculum is known as Frei antigen and the resulting reaction as the Frei reaction. Frei reactions are read at the end of 48 or 72 hours after the performance of the test. The positive reaction appears as an erythematous area, the central portion of which is more indurated and may take the form of a papule, papulovesicle or papulo-pustule according to the intensity of the reaction. The size of the erythematous area is of no diagnostic significance. Exact measurement, however, must be made of the dimensions of the papule when the test is read. The reading is positive when the diameter of the papule is not less than 6 or 7 millimeters, the figure depending upon whether the antigen has been prepared from human or chick, or mouse material. About three-quarters of all positive Frei reactions show a papule whose diameter ranges from 7 to 10 millimeters; the remainder give reactions larger than 10 millimeters. The original Frei antigen was prepared from bacteriologically sterile pus obtained from an unbroken

lymphogranulomatous bubo. The pus was diluted with approximately five times its volume of physiologic saline and the contained virus inactivated by heating at 60° C for two hours on one day and for one hour on the next. This material, now called human Frei antigen, is still used but is unsatisfactory for the following reasons: (1) it is difficult to be certain that the products of noxious agents other than the virus of lymphogranuloma are not present; (2) the supply of suitable pus is very limited; (3) the content of virus (and probably the virulence) varies considerably among different samples of pus; and (4) control material is unavailable.

It was in order to provide an unlimited supply of antigen, free from the disadvantages of human material, that mouse brain antigen was introduced by the author and Suskind[28] in 1934. This material is approximately an 8 per cent suspension, in physiologic saline, of mouse brain infected with a passage strain of the virus and inactivated in the same manner as in the preparation of human antigen. Mouse brain material has none of the drawbacks of human antigen and is a valuable diagnostic agent. It is not, however, a perfect product. In over three-quarters of the tests, mouse brain control gives non-specific reactions which are, nevertheless, distinguishable from positive reactions.

The ideal antigen would appear to be an inactivated emulsion of the granules of the virus. Such material has now been provided by Rake[15] following the growth of the virus in the yolk-sac of the developing chick embryo. The new antigen and control are practically water clear, and have been designated lygranum antigen and lygranum control respectively. Tests of lygranum antigen[29] indicate that it is at least the equal of mouse brain antigen in sensitivity and specificity.

Lygranum control is superior to mouse brain control in producing non-specific reactions in only 6 per cent of persons as compared with 78 per cent in the case of mouse material. Such non-specific reactions are readily distinguished from positive reactions.

It was stated above that the Frei cutaneous test was, until now, the sole means of accurate diagnosis of lymphogranuloma. Within the past 2 months Rake[30] and his colleagues have employed lygranum antigen in a complement-fixation test. The results obtained with the new test have been most striking. In well over 90 per cent of sera there was complete agreement between the results of the cutaneous and complement-fixation tests.[31] My own impression is that the new test is at least

the equal of the Frei test in specificity and sensitivity. It has already established a special place in those instances where the cutaneous reaction is doubtful or negative, in the presence of clinical manifestations which could be regarded as lymphogranulomatous. The new test may also permit of a more delicate appraisal of the progress of the disease than is possible now when reliance must be placed entirely upon symptomatic change. It may not replace the cutaneous test for routine work in the field, for reasons of convenience of performance, but I believe that it will come to be regarded as the final court of appeal in determining the lymphogranulomatous status of a clinical condition.

The Treatment of Lymphogranuloma Venereum

Prior to 1938 treatment was carried on in our clinic by a variety of methods. These included injection of Frei antigen or antimony compounds such as tartar emetic or fuadin; aspiration, excision or incision and drainage of buboes; performance of colostomy with or without resection of the rectum; dilatation of rectal strictures; topical application of balsam of Peru to areas of ulceration on the external genitalia or anorectal regions; x-ray to the groin or rectum; medicated enemata and general supportive measures. None of these procedures afforded ideal treatment. The most satisfactory results followed the use of Frei antigen, by the subcutaneous or intravenous routes, but only a small proportion of the cases dealt with in this manner responded well.

In 1938 Gjuric[32] reported good results in the treatment of twenty-three inguinal cases of lymphogranuloma by the use of a combination of fuadin and sulfanilamide. Shropshear[33] and Shaffer and Arnold,[34] in the same year, showed that the anorectal cases did unusually well following sulfanilamide therapy.

Between July 1938 and May 1940, thirty-one ambulatory cases showing various manifestations of lymphogranuloma were treated with sulfanilamide at the New York Hospital. The drug was given orally, usually commencing with 0.3 gm. to 0.6 gm. three times daily and increasing to 0.9 or 1.2 gm., three times daily. The exact dose depended upon the tolerance of the patient. Rest periods of 1 to 2 weeks were given on an average at 6 weekly intervals. In several cases, however, it was found necessary to discontinue the drug for a short time following 1 to 3 weeks' administration. Other patients, however, were able to take sulfanilamide continuously for 12 to 24 weeks without ill ef-

fects. When changes in the blood picture occurred, the duration of the rest period was extended. The average length of treatment, including rest periods, was, for the inguinal variety of the disease, 4 weeks, and for the anorectal, 29 weeks. No other treatment was employed except aspiration of fluctuant buboes. Of the inguinal cases 80 per cent were completely well within 3 to 6 weeks after beginning treatment and the remainder within 16 weeks. An average total dose of 52 grams of the drug were required. In the case of the anorectal variety, 39 per cent were completely healed within 9 to 79 weeks by the use of a total average dose of 172 grams of sulfanilamide. Improvement to a marked degree occurred in another 39 per cent and no less than 92 per cent of all the anorectal cases showed benefit from the treatment. The maximum total amount of the drug given to any healed patient was 330 grams during a period of 39 weeks. One individual, who did not respond at all to treatment, received 584 grams of sulfanilamide in 53 weeks. Untoward reactions, all minor in degree, occurred in 57 per cent of the individuals treated, and consisted of dizziness, headache, nausea and secondary anemia. There was no demonstrable relationship between the sulfanilamide content of the blood and the ultimate therapeutic effect of the drug.

Symptomatic relief coincided with the improvement in the proctoscopic appearance of the anorectal lesions, which began on an average 5 weeks after starting treatment. The passage of mucopurulent and bloody stools gradually diminished and finally ceased altogether; rectal, perianal or abdominal pain subsided; difficulty with bowel movements vanished and a feeling of well-being returned accompanied by a gain in weight and the disappearance of systemic manifestations including arthralgia and myalgia. Fibrous stricture of the rectum was not affected by sulfanilamide.

Frei tests were performed upon a number of persons in the group, before and after sulfanilamide therapy. No significant change in the degree of cutaneous reactivity resulted from the treatment.

Since May 1940 sulfathiazole has replaced sulfanilamide in the treatment of lymphogranuloma in our clinic. The dose employed has been 1.5 grams three times daily for 2 weeks, then 1.0 gram three times daily for the next 3 weeks. A rest period occupies the succeeding 3 weeks after which treatment is resumed, beginning with 1.5 grams three times daily as above. Inguinal cases of the disease do not usually require a

second five-week course of therapy. Results, to date, show a slightly more rapid response to sulfathiazole than was found with sulfanilamide. This may be due to the fact that the amount of sulfathiazole administered in a given time to any patient, has been almost double that previously employed in the case of sulfanilamide. No toxic manifestations have yet been observed with sulfathiazole.

The marked beneficial effect which has attended the use of sulfanilamide and sulfathiazole in the treatment of lymphogranuloma springs from the virostatic effect of these chemicals upon the etiological agent of the disease.

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