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## Lymphopathia venereum

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LYMPHOPATHIA VENEREUM

SENIOR THESIS

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## CHAPTER I

### INTRODUCTION

Climatic bubo, long recognized in the tropical countries, and lymphogranulomatose inguinale subaigue, described by Durand, Nicolas, and Favre of Lyon in 1913, now more commonly known as lymphogranuloma inguinale or as lymphopathia venereum, have been demonstrated to be a single entity. The first and the latter group of designations now merely serving to indicate in a rough way, the part of the world where the infection was acquired. Clinically and pathologically, they are identical, their etiology is the same; they are due to an infection with an ultra-microscopic, filterable virus.

Still more recently, the series of conditions, heretofore described under various terms, but which may appropriately be designated as esthiomene and elephantiasis vulvae, elephantiasis penis et scroti, certain types of inflammatory rectal stricture, combination of which are commonly referred to as genito-ano-rectal syndrome, and lastly, extragenital cases, have been shown to possess the same pathogeny, a similar histological picture and to yield the same virus, a virus usually communicated venereally. Further, it has been shown that this series of conditions may be associated with the inguinal adenopathy of climatic bubo or lymphogranuloma inguinale.

All these conditions are manifestations of a single disease and as such, they deserve and demand the notice, not only of the tropical specialist and the venereologist, but also of the dermatologist, the proctologist and the gynecologist as well as the public health officer.

In the preparation of this paper, an attempt has been made to clarify, as much as possible, the present status of the knowledge of this disease, which seemingly is vaguely understood by most physicians, but which is shown not to be so rare and presenting a problem in treatment when it is encountered.

#### DEFINITION AND NOMENCLATURE

Lymphopathia venereum is a specific, subacute or chronic, fairly well localized, infectious disease of the lymphatic system, caused by a filterable virus, usually communicated venereally and affecting the regional lymph nodes with abscess formation and fibrosis and is characterized in many cases by a transitory primary lesion followed by gradual destruction of the affected lymph glands, with or without sinus formation or sometimes resulting in elephantiasis, ulceration and fibrosis of the involved region, occasionally manifested as a rectal stricture.

If the term venereal is applied strictly to a disease which is communicated by illicit sexual relation, then the term is not correctly used by most authors. Furthermore, since this term is generally applied to diseases which are usually transmitted

by sexual contact, the use could not practically be limited to a disease which is transmitted in no other way, as no disease can be confined to such iron-clad limitations, if it is to be considered as an etiologic entity.

Lymphopathia venereum has been called by many authors "The Fourth Venereal Disease", implying that syphilis, gonorrhoea and chancroid constitute the other three. Stannus (40) says "If to syphilis, gonorrhoea and ulcus molle, be added 'The Fourth Venereal Disease' of some American writers (the genital infection with Vincents' organism) and granuloma inguinale, then in the disease under consideration, one has a sixth venereal disease." If lymphopathia venereum referred to by number, certainly the logic of Stannus' argument should be carried out.

The name "Lymphopathia Venereum" was suggested by Wolf and Sulzberger (54) who pointed out that besides the condition described by Nicolas, Favre and Durand, this designation will include those cases of esthiomene, genito-ano-rectal syndrome, elephantiasis of the penis and scrotum as well as stricture of the rectum.

Many authors, on writing on this condition, have originated their own terms for the disease. The following are terms found in the literature which have been applied to the disease: Durand-Nicolas-Favre disease; lymphogranuloma inguinale; fourth venereal disease; tropical bubo; climatic bubo; non-venereal bubo; strumous buboes of the groin; lymphogranulomatoser

schanker; venerisches adenogenes Geschwür; non-tuberculous  
granulomatous lymphadenitis; lympho-adenopathia inguino-cruralis  
epidemica; lymphogranulomatose inguinale aigue cutanee l'origine  
genitale and paradenitis inguinalis acuta.

Since "climatic bubo" and "lymphogranuloma inguinale"  
are the terms used by the large majority of authors, especially  
American authors, these two names are used in this paper, more  
in the effort to preserve the individuality of a given author's  
report than to support the use of the terms.

This writing ardently supports the name introduced by  
Wolf and Sulzberger above, by virtue of the argument they pro-  
pose, and encourage a more widespread adoption of the term for  
those reasons.



## CHAPTER II

### HISTORY

The occurrence of lymphopathia venereum previous to its description as a clinical entity, is rather strongly indicated in writings by various observers back over an indefinite period of time. Descriptions of disease conditions by early writers in many cases are sufficiently characteristic to warrant suspicion that this disease was observed by many of these writers though these were essentially on clinical evidence, before laboratory facilities were available.

According to Zakon (55) and Hoffman (27), Hellerstrom found descriptions of indolent buboes among the writings of the early Greeks and Romans, and Galen classified buboes and called the subchronic adenitis of the groin "strumous bube." Also, Celsus found these strumous buboes hard to treat. Salicetti and Angelana in the thirteenth and fourteenth centuries, pointed out the causal connection between venereal lesions and inguinal buboes and the term bube began thereafter to be more and more employed as exclusively for venereal conditions. In 1786, John Hunter, cited by Cormia (10) and Zakon (55), though he brought chaos into venereology by confounding gonorrhoea and syphilis, still emphasized the distinction between venereal and non-venereal buboes.

Bloom (4) states that according to Hellerstrom, the des-

cription of some buboes given by Greek, Roman and Arabian physicians coincides with the clinical picture of lymphogranuloma inguinale. Ricard, in 1838, cited by Zakon (55), considered the strumous bube as a symptom of scrofulous or tuberculous dyscrasia of the blood. In 1859, a French Surgeon, Chassaignac, cited by Bloom (4), described this condition as a disease entity.

Cormia (10) and Stannus (40) in their review of the literature, mention Trousseau (1865) as being the first to accurately describe the disease now known as lymphogranuloma inguinale. Cole (9) quotes from this French Clinician as follows:

"I must not forget to say a few words about a lymph node infection which I have often observed in young Creoles, and more particularly in the Creoles of Réunion and Maurice. In adolescence, and more in the boys, we see the superficial and deep nodes in the groin swell up on one or both sides. Symptoms of the disease come on in cycles lasting one, two or three months, and separated by intervals, it may be, of several months. Then comes a violent paroxysm and the nodes suppurate. In certain of the cases the suppuration extends to several of the nodes or to the entire mass. The patient is thus bedridden for a long time and the suppuration may last for a year. In most of the cases the disease comes in the virile years."

Cole (9) and Burney (6) state that Scheube, in 1867, while independently writing of this trouble as seen in Japan, gave it the name "climatic bube." The condition now generally referred

to in England as climatic bubo, appears, according to Findlay (20) to have been first described in 1879 by Bodnar and by Ruber in 1880, who believed that the adenitis was a malarial manifestation, while in 1882, Jouet, in Indo-China, cited by Cole (9), described a suppurating bubo not accompanied by a portal of entry. Stannus (40) states that the condition was noted by Guerin in 1883 in Tonkin, by Segard in 1886 in Madagascar, by Martin in 1889 in Sumatra, all believing in malaria as the cause.

Nelaton in 1890 published his observations, cited by Zakon (55) and by Hansmann (25), in which he was the first to clearly separate this disease from tuberculosis. His differentiation was on clinical lines and he gives a very good clinical description. His reason for believing these cases non-tuberculous was the occurrence of local lesions followed by glandular enlargement. He noted in one of his former cases that a small lesion on the little finger preceded axillary lymphadenitis of this variety. He operated and found that suppuration took place within the lymphatic glands, and discovered that excision led to cure. In this case, further mentioned by Bloom (4), the little finger showed an insignificant erosion and the tumor was almond sized, slightly painful and covered with normal skin. The histologic examination of the tumor revealed the picture of the adenitis of lymphogranuloma inguinale. This case incidently is the first, or one of the first fairly authentic cases of extragenital involve-

ment of this disease.

The first reasonably reliable report of this disease in this country appears to be that of Klotz, cited by Zakon (55) and by Bloom (4). In the same year as Nelaton published his report, Klotz, who as physician at the German Hospital in New York, had seen about 120 cases of inguinal adenitis of this kind within ten years, reported his personal experience with the disease. He did not consider these cases syphilitic and he gave a good clinical description of the disease. While extirpating one of these inguinal tumors, called at that time "strumous bubo", he injured the tip of his left index finger slightly with a sharp hook. Four weeks later he noticed a swelling of the glands at the outer edge of the pectoralis major muscle. A few days later fever and rheumatoid pains in the joints developed. An operation was performed by a colleague who removed all the glands of the axilla and below the clavicle. These glands showed numerous military and a number of confluent pus foci. Hence, we have here, another fairly reliable history of an extragenital infection.

Findlay (20) and Hoffman (27) mention the report of Ruge who in 1896 caused a furor by reporting an epidemic on board a German man-of-war anchored off Zanzibar, which in the light of present knowledge would merely call for investigation. Both of these authors also mention Marion and Gandy, who in 1901 published excellent clinical, histologic and bacteriologic observations on

this disease which they called "l'adenitis subaigue." They gave a very good histological description and were so impressed by the close resemblance of the histology of this condition to the histology of tuberculosis that they disregarded their negative results from the animal inoculations which they had attempted and considered the process to be tuberculous.

The report of Tanton and Pigeon in 1906 is referred to by Zakon (55), Hausmann (25) and Hoffman (27). These workers published a report of one hundred and forty-seven cases of sub-acute inguinal adenitis which they observed in Algeria and proved conclusively the non-tuberculous character of this particular type of lymphadenitis by injecting one hundred and twenty guinea pigs with pus from lesions and not a single guinea pig died of tuberculosis. They also examined one hundred and forty freshly made smears from one hundred and forty-seven cases and found no organisms.

Stannus (40) and Bloom (4) mention the report of Rost in 1912 of climatic buboes in Eastern Asia and The West Indies and to him, credit is given for first suggesting the initial penile lesion, which had been observed by many writers before, was the portal of entry for some infection acquired by coitus with colored women, who harbored the virus in the vagina, an opinion confirmed by Muller and Justi in 1914 who gave a very excellent description of the disease. Rost mentioned that

axillary, cubital or cervical glands seem to be involved only exceptionally and that this fact is quite strange and, in regard to the etiology, worthy of notice.

However it was left to Durand, Nicolas and Favre to describe in detail in 1913 the clinical and histological features of subacute inguinal adenitis. Reference to the work of these authors has been made by writers of most of the articles on this disease since and the disease has been named after them. They emphasized that the condition is a symptom of a uniform, independent, infectious disease. They gave it the name "lympho-granulomatose inguinale subaigue," on account of the granulation tissue found histologically on which they based their most reliable diagnosis.

Little progress was made in the following several years, however, as the World War seemed to cause a lapse in the study of the condition. Bory, in 1921, cited by Zakon (55) studied the local lesion histologically as did Phylactos, who wrote a valuable paper covering the literature on the subject up to 1922 and his description corresponded with that of Bory. Phylactos made a strong point of the identity of subacute granulomatous lymphadenitis and climatic bube and insisted on the venereal origin of the disease.

In 1921 Ravaut and Scheikevitch (36) reported the study of six more cases in France and were unable to find anything to suggest syphilis, soft chancere, tuberculosis or find any

etiological agent. Later in the same year Ravaut (35) encountered eight more cases and reported seeing cells with ameboid movement in the pus from one case. This marked the beginning of the use of emetine in treatment which was taken up by many authors.

Other authors were reporting cases during this time from various parts of the world. Tschirky (48) in 1922 described cases which he considered a tropical disease occurring exclusively in men after intercourse and characterized by an ephemeral ulcer on the penis and claimed a complete cure in fourteen days by the use of intravenous tartar emetic.

In 1922 Nicolas and Favre (33) reported further findings in which they described partner transmission from a man to a woman and a definite case of accidental inoculation though they considered the disease as one essentially of the adult male. They reported the incubation period of the disease and a study of the histopathology and determined the choice of treatment to be radiotherapy, complete curettage or surgical excision. They believed the disease to be universally distributed.

Miskjian, quoted by De Wolf and Van Cleve later did their work, observed a number of cases of unusual inguinal adenitis which he termed "hypertrophic bube". He was not certain that the clinical picture was identical with the disease described by Nicolas, Favre and Durand.

In the United States the first reference to this disease is alluded to in the report of Klotz above and while Butler (7)

in 1924 wrote on climatic bubo as found in the United States Navy and Whitmore (51) reported twenty six cases in the Naval Hospital in Florida, they did not emphasize any relation of the disease described by Nicolas, Favre and Durand.

The report of Williams (52) of four cases of undiagnosed pelvic tumors in women might suggest an unrecognized pelvic involvement of this disease. However, what is usually considered the first report of the disease in this country was made in the same year (1924) by Hansmann (25) who reported four cases under the name of "Non-Tuberculous Granulomatous Lymphadenitis." The next report of the disease in this country appears to be that of Hillsman, Wilshusen and Zimmerman (26) who reported a case with autopsy and pathological study in 1928.

According to De Wolf and Van Cleve (17), De Bellard in Venezuela in 1924 apparently was the first to transmit the disease to a monkey by preputial inoculation.

During these years there was much difference of opinion among the different observers as to whether the disease described by Nicolas, Favre and Durand was identical with the well recognized climatic bubo of the tropics. Most of the French workers believed the two conditions were the same. Hoffman, quoted by Pardo-Castello (34), had rather extensive experience with the disease and believed they were identical and that it was imported into France by colonial troops during the World War.

Since 1922, the study of lymphogranulomatosis inguinalis



has been pursued with great zeal in different countries. Zakon (55) states that the disease was first described in Germany by Frei in 1925; in England by Mc Donogh in 1924; in Italy by Gamma in 1923; in Austria by Fuhs and Musger in 1927, and was later reported from Russia, Poland, Roumania, Spain, Portugal, Norway and Finland.

In 1925, Frei (21) gave one of the most valuable contributions to the study of this disease when he reported a skin reaction obtained with an antigen prepared from the pus from the bube in nine cases of the so-called inguinal lymphogranuloma. The complement fixation tests with the serum from these patients were negative. This test was readily adopted and confirmed by other workers and according to Berkovsky (3) Sulzburger was the first to apply the test in this country.

In same year (1925), according to Coutts and Bianchi (12), Frei and Kappel studied the ano-rectal syndrome following esthiomene vulvae in relation to lymphogranulomatosis venerea, and were able to establish that patients suffering from this condition reacted positively to intracutaneous inoculation of their specific antigen. Jersild, Nicolas, De Gregario, Seneque, Fischer, Langer, Bensaude, Viscarrondo, Villela, Reyna Miranda and Alvarado confirmed this finding.

At this point in the history we may look back on the history of the genito-ano-rectal conditions as related to this disease. This has been reviewed by Stannus (40) who states that

the literature dealing with these other conditions embracing ano-vulvar elephantiasis and ulceration and inflammatory stricture of the rectum tells much the same story as above. Though recognized clinically, they have defied elucidation until recent years. Part of the difficulty arose from the fact that the pathological changes might be minimal in degree and limited in extent in one case, and in another the pathological process might be maximal and involve the whole genito-ano-rectal region.

Huguier is generally acclaimed as the first author to have delineated definitely this syndrome, but there are excellent references to cases by Desruelles (1844) and Bays de Loury and Costilhes (1845). Huguier, in a communication to the Academic de Medecine (1848), entitled "Memoire sur l'Esthiomene ou Datre rongeante de la region vulvo-anal", says:

"This chronic malady which lies in some intermediate position between the elephantiasis of the Arabs, syphilis, cancer and scrofula, and to be distinguished from the latter, is characterized by the leaden or violaceous color of the affected parts; their deformation, thickening and induration; the ulceration and destruction, at the same time infiltration and hypertrophy, so that the orifices and passages of the vulva and anus may be at the same time the seat of ulceration and enlargement as well as stricture, while the folds of the skin and mucous membrane manifest thickening, fibrosis and ulceration of variable degree and

distribution, without pain or tenderness; without menacing life, and without even injuring the general health, at all events for a very long time."

Huguier recognized the difficulty of assigning a definite etiology and suggested that an alteration in the humours determined by a scrofulous diathesis alone or combined with a degenerated, mitigated syphilitic poison was a factor. He purposely decried the use of the word "lupus" and invented "esthiomene" in its place. He believed--and he has been proved right only after a lapse of eighty years--that the disease was neither syphilitic, tuberculous nor cancerous.

Inflammatory stricture of the rectum unassociated with the other elements of the complete syndrome was first described by the Danish surgeon Larsen (1849) and considered by him to be syphilitic. Since these earlier records, individual cases or short series of cases have been published in every country in Europe and in America, generally under the designation "elephantiasis vulvae," "lupus vulvae," "esthiomene," "syphilome ano-rectale" (Fournier) and non-malignant stricture of the rectum. On this subject may be mentioned a clinical lecture by Bernutz at the Charite in Paris (1874), a paper by Angus Macdonald in Edinburgh (1884), a paper by Matthews Duncan before the Obstetrical Society of London the same year, and an excellent article by Koch of Breslau (1896). Tuberculosis, syphilis, gonorrhoea,

ulcus molle, chronic irritation, trauma, severally or in combination, have in turn been invoked as the etiological cause, not only of the vulval conditions but also of the rectal stricture when met with alone.

The vast majority of cases have been seen in the prostitutes and clandestines of the lower classes according to Cohen's monograph quoted by Stannus (40), on elephantiasis vulvae and herein lies the explanation of the etiologies which have been adduced. It had usually been a case of putting forward the finding of chronic inflammatory lesions as evidence of tuberculosis. In regard to stricture of the rectum, the discussion of Sir Charters Symonds in 1923 and of Henri Hartmann in the same year covers the subject and brings out the fact that this condition still belonged to the group of diseases of unknown etiology.

No satisfactory explanation was forthcoming of the female sexual incidence of genital elephantiasis and rectal stricture noted by nearly all writers, and as remarkable as the male incidence for climatic bube and lymphogranuloma inguinale.

Here an allusion must be made to a wide gap in our knowledge of the geographical distribution of these genito-ano-rectal conditions. It would be expected that they would be found widespread among native women in areas where climatic bube is known. While this is likely, few references have been made to them. Branfoot (1902) apparently observed them in Madras, Roegholt

(1926) and Joachimovits (1929) found many cases in the Dutch East Indies. There are references to many cases in China and some in Ceylon and Stannus (40) himself has seen cases in East Central Africa.

Returning now to the general history, we find that in 1927, Koppel, quoted by Saenz (38), first described the occurrence of erythema nodosum in association with lymphopathia venereum.

Hanschell (24), writing on climatic bubo described very good results in a series of cases observed between 1919 and 1926, by the use of intravenous TAB. vaccine and he denounced the surgical treatment of the disease.

Hellerstrom did considerable work in advancing the knowledge of this disease and in 1930, cited by DeWolf and Van Cleve (17), he reported successful intracerebral inoculation of monkeys and transmission through eleven passages with the production of a meningo-encephalitis and then using the brain tissue successfully as antigen in known human cases. Levaditi and other French workers confirmed this work the following year. Later Hellerstrom demonstrated the filterability of the virus through Berkefeld and Chamberlain filters and showed that immune or convalescent serum, when mixed with the virus and injected intracerebrally in monkeys, had a neutralizing effect and prevented infection from developing.

In 1932 Findlay (20) confirmed the work of Hellerstrom and the French workers and added much information concerning the properties of the virus. He also produced undisputable evidence to demonstrate the identity of lymphogranuloma inguinale and climatic bubo, showing that the disease as found in different parts of the world was a single entity. It is interesting to note however that Stannus and Findlay (41) reported in 1933 the first case to be diagnosed by laboratory work in England.

In July 1933, Coutts and Bianchi (11) reported a series of cases from Chile, which, from their study, claimed two strains of the virus exists, giving different cutaneous reactions, different clinical course and different clinical syndromes. They divided their cases into two groups, those which showed a primary lesion and those which did not. They found that antigen made from patients of one group reacted positively on the whole group but negatively on the other group. The following year they reported further work in detailing these syndromes, which work will be dealt with more under that section on clinical syndromes in this paper. This work is not widely understood and has not been confirmed yet.

The first and only report of successful culture of the virus, found in this survey of the literature, was made by Tamura (44) in August 1934. He reported the transference of pus, by sterile aspiration of the inguinal glands of known cases, to the tissue-Tyrode medium used by Maitland and his co-workers for the cultivation of the vaccinia virus. The virus produced a cloudiness

in the media and was transmitted in serial cultures or in serial cultures alternating with guinea pig inoculations. He demonstrated the filterability of the virus from these cultures. He showed accurate results with the use of the heated culture in diagnostic skin tests and reported good therapeutic results by using the heated culture in subcutaneous injections.

In December 1934, Grace (22) contributed to the knowledge of the antigen by studying and reporting the possibilities with the use of dried antigen.

Probably the last contribution is that of Reiss (37) who described a new diagnostic test which serves as a check on our not-infallible Frei test, and may aid in the diagnosis earlier in the course of the disease.

## CHAPTER III

### INCIDENCE

The large majority of reported cases of this disease being from tropical and subtropical countries shows its incidence to be much higher in warmer climates, but in recent years, the disease has been found to be not rare in temperate climates. It is interesting to note, however, that a surprisnly large proportion of the cases discovered in the temperate zones are cases which have recently been south. This observation, together with the fact that the condition is found preponderantly in the lower social levels explains the higher incidence of the disease in the larger seaports and clinics of the larger cities.

Cases of lymphopathia venereum have been reported from nearly every important tropical and subtropical country, these cases being reported as "climatic bubo" because they were diagnosed on clinical grounds, due to the fact that the identity of climatic bubo and lymphopathia venereum was not so generally known and because the Frei test was not known to the workers or that they were unable to apply the test to their cases.

The total number of reported cases was estimated by Cormia (10) in 1934 to be about 2,000. The marked increase of reported cases in temperate climates in the past few years is due mainly to the more widespread use of the Frei test, which in many instances has clarified the etiological diagnosis of



cases previously undiagnosed or on which a doubtful diagnosis had been placed. Co-incidentally, this has stimulated many workers to be on the lookout for these cases in later years.

Findlay (20) comments on a curious point in the geographical distribution of lymphopathia venereum in that it is extremely rare in England. Very few autochthonous cases have been reported and then only in large seaports as London and Bristol. Yet the disease is not rare in France, Germany and Scandinavia and cases have been reported in Spain and Italy. Gibson, quoted by Findlay, showed that one per cent of the naval personnel of the British Station in China are said to have it.

Whitmore (51) in 1927, in commenting on the epidemiology, states that the disease is endemic though cases occur in small groups suggesting small epidemics. Many observers have noted the disease to be unusually prevalent in the West Indies. Butler (7), in 1924, in writing on climatic bubo, stated that the disease has its greatest incidence among white soldiers and sailors serving in the tropics but it was not limited to the tropics. He stated that in the United States Navy there were cases of apparently non-venereal bubo which occur in northern climates. These cases were increased in incidence for ships stationed in the tropics and for the personnel of many tropical shore stations. It may be stated in general, however, that most all observers in the last few years agree, and emphasized by Wilmoth (53), that climatic

bears no relation to the course or nature of the disease.

Cormia (10) states that cases described in temperate climates have usually occurred in the summer months or have been acquired by contacts recently returned from warmer climates. In his series of twenty-four cases studied in Indianapolis, Dalton (14) studied the seasonal incidence to compare his observations with several reports which showed that around seventy per cent of cases occurred between March and September, and found in his series that fifty-eight per cent occurred between May and October, forty-one per cent occurring between October and May. These figures however probably have little significance due to the seasonal variation in the amount of travel and contact of people.

Most all reports of the age incidence are harmonious and point to the fact that the highest incidence occurs during the height of sexual activity. Wilmoth (53) in twenty-seven cases studied, finds the ages to range from twenty-one to thirty-nine years with an average of twenty-seven and two tenths years. He mentions Arrillaga's report of the condition in both men and women in which the ages ranged from seventeen to forty-five years. In Dalton's cases the ages ranged from seventeen to fifty-two years with an average of twenty-eight and six tenths years. Thirty-three per cent occurred in the five year period between twenty and twenty-five years of age and eighty-three per cent occurring under the fortieth year. The only cases reported in

children that could be found by this author were reported in Klinische Wochenschrift for Aug. 13, 1932, reporting two female children, ages six and seven years, who were sleeping in a bed with an infected female cousin. Dalton's series showed sixty-six per cent were single or separated from their marital partners. Of the thirty-three per cent who were married, all admitted extra-marital exposures and his cases were equally divided between white and colored patients.

As regards the sex incidence, many of the earlier writers, especially those writing on climatic bubo, described the disease as peculiar to the male. Hanschell (24), in 1926, stated that he had never seen a case in a woman. The introduction of the Frei test, however, changed the views. Ives and Katz (28) state that before the use of the Frei test, the ratio of the condition known as lymphogranuloma inguinale in males and females was thought to be about seven to one, but since the use of the Frei test, the disease in some form has been shown to occur equally in both sexes.

Martin (32) studied twenty-five cases of rectal stricture, all of which occurred in negro females, the youngest being twenty-two years and the oldest, forty-eight. Twenty of the twenty-five cases showed a positive Frei test and in this series he found a higher incidence of lymphopathia venereum than of syphilis, gonorrhoea or tuberculosis. In comparison of the incidence in general, in all types of cases, lymphopathia venereum was estimated as

by Coutts and Bianchi (12) as lower than that of syphilis, gonorrhoea or chancroid.

Of the fifty-eight cases reported by DeWolf and Van Cleve (17) in Cleveland, thirty-one were seen while they showed active inguinal adenitis. Of this group ten were white males, twenty were colored males and one was a colored female. Only three cases of the ano-rectal disease were found in the fifty-eight cases.

To date, Cameron (8) has seen a total of twenty-four cases in Omaha, comprising eighteen colored males with inguinal adenitis, one white male with inguinal adenitis, four ano-rectal syndromes, all in colored women, and one colored woman with active rectal fistulae. All but three of these cases have been discovered in Omaha in the past two years, which shows that the disease is not a rarity in the middle-west.

## CHAPTER IV

### ETIOLOGY

#### THE VIRUS:

Much work has been done in the past three decades to determine the cause of lymphopathia venereum or climatic bubo but the etiology was considered unknown until the past few years when extensive animal inoculation experiments were done which proved the organism to be an ultra-microscopic filterable virus.

Mention has already been made, in the historical survey in this paper, of attempts by various workers to find the causative organism in smears and stained sections and to prove or disprove a tuberculous etiology by animal inoculation, all of which have consistently proved negative. Such also was the findings of Ravaut (36) though he caused some confusion for a while by reporting in 1921 (35) that in a second series of investigations in the same year, he saw cells which on the warmed stage, had ameboid movement and believed that these cells were amebae. He thought that they resembled *ameba coli* rather than *ameba histolytica*. This finding though later shown to be of no etiological significance prompted the use of emetin in treatment which was done by this author and followed by other investigators.

Further work by various investigators consistently showed negative results until 1930 when Hellerstrom and Wassen,

discussed by Cormia (10) and Hoffman (27), conclusively demonstrated the filterable nature of the organism. This work was duplicated and confirmed by the French workers Levaditi, Ravaut et al, the next year.

The bacteriologic research of lymphopathia venereum can be briefly summarized by stating that up to the present time no visible organism has been discovered as an etiological agent. Various organisms have been found occasionally in cultures and by direct examination of pus; *Bacillus fluorescens putridus* or *liquifaciens*, ameba and pseudodiphtheria bacilli but none of this have been shown to have any etiological significance. The vast majority of attempts at culture have been entirely negative. The same is true of auto-inoculation experiments, which have been of such great value in the study of the bacillus of Ducrey.

Animal inoculation has been utilized for many years, but only in recent years has any real advance been made in a positive direction. On one negative fact all workers are in complete agreement; namely that tuberculosis is not the cause of lymphopathia venereum for no animal inoculated with pus of infected glands of this disease has ever developed tuberculosis. De Wolf and Van Cleve (17) state that in 1924 Det Bellard in Venezuela, apparently successfully transmitted the disease to a monkey by preputial inoculation and that in 1930 at the International Dermatological Congress in Copenhagen, Hellerstrom

reported the successful transmission of the disease to monkeys by intracerebral inoculation. He was able to transmit the disease from one monkey to another through eleven passages producing in them a meningo-encephalitis. When cerebrospinal fluid and an emulsion of the meninges and the brain of infected animals were used as antigen, strongly positive intracutaneous tests were obtained on known cases in humans. In 1931 Levaditi, Marie and Lepine inoculated a patient with dementia paralytica in the prepuce with material from an infected monkey, the twelfth successive passage animal, and after thirty-five days, without observable change at the site of inoculation, the patient developed bilateral adenitis of lymphopathia venereum. Hellerstrom has more recently shown that the virus is filterable through Berkefeld and Chamberlain filters and he has been able to infect monkeys intracerebrally with the filtrate.

De Wolf and Van Cleve made smears of local lesions with negative results. Pus obtained by aspiration or from glands removed surgically have been examined in stained smears and by dark field illumination with negative results. The same is true of examination of many tissue sections stained for acid fast organisms and for spirochetes. Attempts at culture on various types of aerobic media have been negative except one case in which a culture of an acid-producing bacillus, probably *Bacillus acidophilus*, was only on Loeffler's serum agar.

In 1932 Findlay (20) reported the results of his experiments, and which have been reviewed by Hoffman (27). Findlay studied the properties of the virus and confirmed the fact that it could successfully be transmitted to animals. He injected bacteriologically sterile material from human buboes intracerebrally into monkeys and mice and in the groins of guinea pigs and obtained results corresponding with those of Hellerstrom and Wassen and the same as Levaditi, Ravaut, Lepine and Schoen.

He found that the following species of monkeys were susceptible: The green monkey (*Cercopithecus colletrichus*); the brown capcuhn (*Cerbus fatuellus*); the sooty Mangabey (*Cercocebus fuliginosus*); the common marmoset (*Callithrix jacchus* and *Callithrix pennicillata*). The common rhesus monkey, *sinicus rhesus* (*Macacus rhesus*) is less susceptible, and of eight rhesus monkeys inoculated, only one died from the intracerebral infection.

While cultures from the brains of these monkeys remained bacteriologically sterile, it was possible to show that the virus does not remain localized to the central nervous system but is present in the liver, spleen, kidneys, inguinal nodes and to a less extent in the blood. In mice, as in monkeys, the virus was found not to remain localized in the central nervous system and one strain has been transferred for ten mouse passages. Intracerebral injection of material from human buboes in the brain of guinea pigs failed to produce infection but injected into the groin of the guinea pigs, infection followed. Findlay



was unable to infect rats or rabbits by injection either intracerebrally or in the groin. Contrary to the findings of Findlay, De Wolf and Van Cleve (17) injected a few guinea pigs subcutaneously, intraperitoneally and in the groin and state that they showed no evidence of the disease either grossly or microscopically.

Cormia (10) states that the French have recently isolated different strains of the virus which, when inoculated intracerebrally in monkeys have a variable virulence corresponding with what is seen clinically in man. The Kamm strain, the most virulent, has been passed through twenty monkeys without attenuation.

A careful study of the brains of infected monkeys has convinced Levaditi that the virus is mesoblastotropic, and a further study of the characteristics of the virus by him demonstrated that the virus differed greatly from the neurotropic type of virus. Levaditi further found that in intracerebrally inoculated monkeys the virus became disseminated to the bones, lymph glands and various viscera but the blood was not infected. Dissemination does not occur, according to Findlay when the monkeys are inoculated on the prepuce or in the groin. Findlay found that intraperitoneal inoculation of mice was followed by a general dissemination of the virus to various viscera, but no evidence of neurotropism occurred.

In studying the properties of the virus, Findlay ob-

served the filterability of the virus as determined experimentally in monkeys and mice. A capuchin monkey inoculated intracerebrally with a filtrate of infected monkey brain developed symptoms on the eighth day after the injection and was killed on the tenth day when moribund. The histologic changes in the brain were those characteristic of climatic bubo, while the brain was infected for mice. An emulsion of infected brain in broth at pH 7.2 was filtered through an L<sub>3</sub> candle and .05 cc. of filtrate was inoculated intracerebrally in five mice which died with characteristic symptoms in fourteen, twenty-three, fifty-one and fifty-four days respectively. Brain material from these mice was infected for other mice.

Infected mouse brain preserved in fifty per cent glycerine in saline and kept at a temperature of 40 degrees C. was virulent after seven, but not after fourteen days. Findlay finds the virus is killed by heating to 60 degrees C. for thirty minutes but survives for about ten days at 30 degrees C.; drying inactivates it is not easily destroyed by the usual antiseptics except formaldehyde up to 1:1,000 (U.S.P.). He also finds that unlike many neurotropic viruses the concentration of this virus in infected mouse brain does not appear to be very great, as dilutions greater than 1:1,000 failed to kill although the histologic examination of brains of mice injected with a 1:100 dilution gave evidence of a slight degree of infection.

According to Dorne and Zakon (18), Koch demonstrated the relationship between lymphopathia venereum and esthiomene by preparing an extract of a piece of proliferating tissue from the genital zone of a patient with typical esthiomene (Frei positive) and injected the extract intracerebrally into an ape, in which there developed specific lymphofranulomatous meningo-encephalitis. This shows the virus to be alive during the later manifestations of the disease.

The only report, found in the literature, of successful culture of the virus, was made by Tamura (44) in August 1934. He reported having transferred aseptically aspirated pus from the glands of known cases in the tissue-Tyrodé medium used by Maitland and his co-workers for the cultivation of the vaccinia virus. Since work which he has done with this cultured material appears to have great possibilities in diagnostic and therapeutic work and especially in facilitating the obtaining of antigens by workers in the more isolated districts, on account of his methods is herein indicated.

When the aseptically aspirated pus is proved bacteriologically sterile, it is diluted 1:5 with sterile saline solution. When .02 to .03 cc. of the diluted pus is planted in the Tyrodé solution containing a sterile piece of guinea pig liver and incubated at 37.5 degrees C., a peculiar cloudiness appears throughout the supernatant fluid in from thirty-six to forty-eight hours. Control tubes of the medium incubated at the same time

remain perfectly clear. The cloudiness can be transmitted from tube to tube and in one instance was carried through twenty-four subcultures, when the procedure was discontinued. When the cloudy supernatant fluid in the tissue-Tyrase medium is examined or cultured on the ordinary aerobic and anerobic media, nothing resembling ordinary bacteria is to be found. The appearance of the cloudiness is followed by a slow disintegration of the tissue. Such disintegration does not occur in control tubes.

When transfer is made from twelve day old cultures it is successful. In a fourteen day old culture the cloudiness seems to settle out and when the clear supernatant fluid is subcultured it no longer produces cloudiness.

Attempts to see the etiologic agent in the cloudy fluid have failed, with the exception that peculiar granules are brought out with Giemsa's stain and these are absent in controls. Subcultures from a 1:1,000 dilution of pus produced a growth but from a 1:10,000 dilution, there was a failure to produce any growth.

When the cloudy supernatant fluid in culture was passed through a Berkefeld N filter, the filtrate produced cloudiness on the subculture. The etiologic agent has been passed from culture to guinea pig, then from guinea pig to the medium, from this culture to a subculture and then back to a guinea pig as often as four times.

## TRANSMISSION:

The usual means by which lymphopathia venereum is contracted, as is implied throughout this paper, is by sexual exposure to an infected person, and, as stated by Wolf and Sulzberger (54) is generally accepted now as of venereal origin.

Accidental inoculation through an abrasion in the skin has apparently been sufficiently established to list this as a means of transmission and is discussed in other parts of this paper. Also in this paper has been taken up extragenital cases which show the practices of cunnilingus and fellatio to be a means of transmission. Coutts and Bianchi (11) believe the viruses are also of buccal origin and report a case showing an ulcer on the tongue and penis at the same time. Hellerstrom, quoted by Cormia (10), believes that prostitutes may be carriers without having active manifestations. Cases of rectal stricture occurring in males have been reported, in which the patients admitted having practiced sodomy and Lee and Staley (30) consider that cases of rectal stricture in the male, due to lymphopathia venereum, are either the result of infection through sodomy or else due to the passage of the virus along the collateral lymphatic vessels from the primary lesion located on the glans penis or prepuce.

Cases of spread to marital partners have been observed by many authors, Dalton (14) having observed one such instance and determined in his series of twenty-four cases a demonstrable

partner spread of twelve and one half per cent. The only occurrence of the disease in children, found in the literature by Dalton was a report in Germany where two female children, ages six and seven years, who were sleeping in a bed with a known infected female cousin.

Coutts and Bianchi (12) state that they and others have shown by clinical evidence that the virus resides in the mouth and was of buccal origin but was adapted to the vagina. These authors have investigated the existence of pediculi in a large proportion of patients with lymphopathia venereum and its possible importance in the transmission of the disease. Microscopic study of pediculi for parasites and study of the intestine of pediculi revealed nothing. An emulsion of pediculi, from lymphogranulomatous patients, sterilized in alcohol and injected in guinea pigs caused regional lymph node inflammation reaching its height on the seventh to the tenth day while an emulsion from pediculi from persons not having the disease, when injected into guinea pigs gave negative results. This may show little significance except to stimulate further investigation.

In the literature covered, as listed in the bibliography, no mention has been found of any cases of congenital lymphopathia venereum.

## CHAPTER V

### MORBID ANATOMY

Most authors agree that the variation in cases is due to the differences in lymph drainage in the male and female. Cormia (10) gives a good discussion in which he explains that in the male the primary lesion is usually in the coronary sulcus. The infection passes up the penile lymphatics, occasionally causing a lymphangitis, and extends to the inguinal glands, thence to the crural and iliac groups and rarely penetrating the intrapelvic glands. In the female, if the primary lesion is on the upper two-thirds of the vulva, the infection passes to the inguinal glands. If it is on the posterior surface of the vulva, the infection commonly spreads to the intrapelvic glands. The vulval and vaginal lymphatics have further ramifications to the cervix, ano-rectal glands and those in the pouch of Douglas and to those in the broad ligament. Because of this distribution of lymphatics, the female is subject to inguinal involvement and intrapelvic involvement with subsequent rectal stricture, also intra-abdominal gland involvement with abscess formation in the loin and perimetritis and perisalpingitis.

The histology of the primary lesion according to Hoffman (27), is that of a small ulcerated area beneath which there is a heavy infiltration of inflammatory cells, mostly plasma cells. Few neutrophils are seen. Marked infiltration of plasma cells

is seen along the lymphatics. In these lesions are many newly formed bloodvessels with some thickening of the walls of the smallest vessels.

The gross pathology of the glands as described by Zakon (55), show the affected glands matted together. The surface is of a tinge ranging from red to violet, so-called wine-red or gray-red. Even macroscopically, a number of abscesses are seen up to the size of a pea, filled with yellowish-green, rather thick pus. The glands never caseate.

Histopathology of the lymph glands: The description given by Nicolas and Favre (33) state that the glands show on microscopic section, miliary gummas and lenticular abscesses with giant and epithelioid cells at their border; as well as great numbers of giant and epithelioid cells isolated throughout. There is a disappearance of the normal structure of the glands which is replaced by all types of cells, including lymphoid, mononuclears, connective tissue, large acidophils, polymorphonuclear neutrophils and eosinophils which characterize the granuloma, from which the name "lymphogranulomatosis" was originally chosen, but which it is better to drop because of the confusion with the German disease, malignant ganglionic granuloma, in which the suppurative adenitis is distinctly different.

The histopathologic cytology is described by Hoffman (27) under eight points as follows:

- "1. Numerous large and small areas of circular or ir-



regular outline composed of light staining cells of large size but with relatively small vesicular nuclei. These large areas have a remote resemblance to the characteristic epitheloid cell tubercle, but without any characteristic giant cells. The cells are to be interpreted as histiocytes of the reticulo-endothelial system in harmony with the present concept of the nature of typical tubercles. Their cytoplasm is remarkably clear and unstained, resembling lipoid-containing cytoplasm, but fat stains show lipoid only in certain more extensively degenerated areas.

2. Within these areas are necrotic and purulent centers with marked karyorrhexis and pyknosis of nuclei.

3. Very sparse small hemorrhagic areas.

4. Complete obliteration of normal architecture of lymph nodes including the germinal centers.

5. Remarkable deposits of typical and atypical plasma cells in dense groups and scattered throughout the tissue. These cells vary in size and many are multinucleated.

6. A small group of cells with large hyperchromatic nuclei, many of which are in mitosis, but with a narrow ring of cytoplasm. These are probably lymphoblastic in character and represent germinal center cells.

7. Remarkably large numbers of small vascular channels with very hyperplastic vascular endothelium giving the entire structure much resemblance to ordinary granulation tissue.

8. The periglandular tissue contains inflammatory cellular

exudate, principally lymphocytes and plasma cells."

Other authors, including Zakon (55) and Amtman and Pilot (2), describe histologic pictures similar to the above. Ives and Katz (28) state that within the same chain, different lymph nodes show various stages of development of the disease process.

The clinical-pathological picture of lymphopathia venereum in the conditions besides the inguinal adenitis, especially regarding rectal stricture, has been excellently discussed by Bloom (5), who states that the problem of this type of stricture is inseparable from the problem of esthiomene. Esthiomene consists of obstinate chronic ulceration of the vulva associated with elephantiasis and sclerosis of the vulva, the anal region, and the rectal wall, the latter involvement producing anal fistulae and rectal strictures. In esthiomene, one finds enormous dilatation of lymph spaces and lymph vessels of the labia and obliteration of the regional lymph glands.

The infection of the deep glands may take place simultaneously with the development of the inguinal adenitis or alone without any external manifestation. Even in men, together with the inguinal adenitis, the iliac gland involvement may be felt in the beginning of the illness as a firm mass deep in the iliac fossa. In women in the majority of cases the lymphogranuloma inguinale infection is not manifested by inguinal adenitis, for the lymph vessels lead from the primary lesion on the genitals mostly directly to the deep pelvic glands, omitting the inguinal

lymph nodes. The glands invaded by the virus are destroyed and this leads to chronic lymphostasis in the regions draining into these glands. These regions are the genitals, the anal region and the rectum. Upon the extent of destruction of these glands, depends the extent of the lymphostasis. The genital, anal and rectal regions may be affected together or separately.

That the sequellae of lymphogranuloma inguinale; namely, elephantiasis of the genitals and anus, and rectal stricture do not occur in men as frequently as in women is also understood, for the lymph vessels of the genitals in men lead mostly and primarily to the inguinal glands. If the involvement of the deep pelvic glands takes place, it is in most cases only secondarily and not in such a degree as in women. Besides, there is the fact mentioned by Roegholt, that in men there are abundant anastomoses between the lymphatics of the right and the left sides and the deep and superficial vessels, so that the result of lymphostasis might not be developed in such a marked degree as in women where there are a few anastomoses.

The chronic lymphostasis leads to disturbance in nutrition of the affected region. The disturbance might manifest itself in a regressive form, leading to chronic ulceration associated usually with the productive form, the proliferation of connective tissue, resulting in elephantiasis and finally in shrinkage producing stricture of the rectum.

Whether this affection of the rectum is the result of lymphostasis only or whether the specific virus has some part in the causation, is a question on which the opinions of investigators are divided. Loehe and Rosenfeld, further cited by Bloom (5), believe that it is quite possible that there is not only obstruction of lymph ways but also retrograde transportation of the infectious material from the pelvic glands to the skin of the affected regions and into the rectal wall, so that the resulting changes are at least partly specific ones due to the virus. Another point of evidence in favor of the retrograde lymph transport is the presence in reported cases of bubonuli occurring in the dorsal lymph trunk of the penis several weeks after superficial and deep inguinal infection, and pus from which bubonuli gave positive reactions on known cases. In another case, Bloom has seen subcutaneous infiltrations ulcerate in the triangle of Scarpa in the thigh.

Barthels and Biberstein, quoted by Bloom, believe there is also a specific process in which the virus causes a proliferation stimulus as in filariasis. They have found the same structure in elephantiasis tissue as in glands recently infected with the virus of lymphopathia venereum. According to Bloom, this latter opinion is held by Nicolas, Favre, Massia and Lebeuf while Jersild and Frei are inclined to the conception that those changes are the result of lymphostasis alone, perhaps supported by secondary infection.

**ASSOCIATED PATHOLOGY:**

Due to the fact that this disease has not been shown to become generalized in humans and since, in the literature covered, no reports have been found pertaining to the pathologic nature of the transient changes occurring during the course of the constitutional symptoms seen in the acute stage of the disease, the subject of associated pathology necessarily is very limited.

The changes occurring in the blood picture and to a certain extent, the cutaneous manifestations of the disease, have been discussed elsewhere in this paper. However further elaboration of the cutaneous lesions may appropriately be mentioned here.

Erythema nodosum has been observed by a number of authors and according to Cormia (10), Gans noted it in ten per cent of cases. It usually occurs after operative interference. This author also states that an enlarged spleen was found by Neumann. Rheumatic manifestations are frequently seen but apparently no pathological studies of this have been reported. Dalton (14) observed one patient who showed a purpura with the onset of the gland swelling.

Saenz (38) in discussing the skin lesions in his study of the allergy of this disease states that the lesions adopt the features characteristic of erythema multiforme or erythema nodosum and are localized on the extensor surfaces of the extremities, seldom invading the trunk and face. The conjunctiva and mucous

membranes of the mouth and anal region are sometimes involved.

The lesions are discrete, have a red or red-cyanotic tint, infiltrating the cutis and subcutis. Their evolution is strikingly transient as they almost fade in a week or two and show little tendency to recur.

## CHAPTER VI

### SPECIFIC REACTIONS AND ANTIGENS

The intracutaneous test devised by Wilhelm Frei (21) in 1925 has proved to be specific for lymphopathia venereum. A little later, as cited by Cormia (10), Frei and Koppel applied this reaction in the diagnosis of rectal stricture due to lymphopathia venereum and soon after in the clarification of the etiology of the genito-ano-rectal syndrome.

Preparation of Frei antigen, as given by Coutts and Bianchi (12), is made as follows: Lymph node pus obtained by aseptic aspiration through a sterile syringe is mixed, 1 c.c. with 10 c.c. of sterile normal salt solution, placed in a sterile glass bottle containing sterile glass pellets and well shaken for one-half hour. It is then placed in a water bath at 60 degrees C. for two hours during three successive days. It is then submitted to sterility proofs, both in aerobic and anerobic media. If found sterile, it is placed in ampules and is ready for use.

These authors find that antigen prepared in this way is not reliable after three months. Patients from whom pus is obtained for this antigen must have both Wassermann and Kahn tests negative as well as negative gono-reaction and Itowon Reenstierna intracutaneous test.

Saenz (38), in an excellent review of allergy in this

disease, enumerates other antigens used for intracutaneous tests: Dind's Antigen is an extract of the tissues of lymphogranulomatous glands, obtained by surgical extirpation, triturated and pressed with physiologic serum or bouillon. After being filtered through muslin instead of through paper, it is prepared as is the Frei antigen. Nicolas-Favre's Antigen is made by drying glands of a lymphogranulomatous patient according to Pasteurs technique and keeping in a solution of equal parts of glycerin and distilled water. The antigen is prepared when needed, by triturating the glands with physiologic serum.

Antigen from spinal fluid and brain: These antigens have no clinical use and were used only in experimental researches by Hellerstrom, Levaditi, Freund and others. The spinal fluid and brains of infected animals are prepared in the same manner as Frei's antigen and have been discussed in this paper under the section on etiology.

Antigens from serum of bullas: In cases of lymphopathia venereum presenting eruptions of erythema multiforme or erythema nodosum, antigens have been prepared either from a fluid obtained by producing vesication with cantharides over the lesions or by trituration of the lesions with physiologic serum.

Tamura (44) recently reported successful intracutaneous testing by using a heated culture of the virus which he prepared. He reports accurate results and undoubtedly in the near future,



attempts will be made to duplicate his work.

In Tamura's work, the cloudy supernatant fluid from the subcultures was heated to 60 degrees C. for two hours on one day and at the same temperature for one hour on the following day. When such heated culture antigen preserved in 1:10,000 merthiolate is injected intradermally into patients, it gives just as marked reactions as Frei antigen. When the twenty-third subculture in one series was heated for antigen, it was found to be just as active as antigen prepared from earlier subcultures. The culture antigen gave no reaction in normal individuals.

Since it is difficult to obtain cases free from tuberculosis, syphilis and who have not had soft chancre or gonorrhoea, and due to the fact that the antigen is not reliable after three months, when prepared in the above manner, Coutts and Bianchi (12) decided to try the Bardet-Gengou complement fixation test in relation to the different syndromes of this disease, employing as receptor, an antigen prepared from lymphogranulomatous lymph nodes. Surgically excised nodes are reduced to pulp and mixed, one gram with 30 c.c. of one-half per cent carbolic acid in normal salt solution. The mixture is well shaken for one-half hour and next centrifuged for ten to twenty minutes. The supernatant liquid is drawn by a pipette and put in a water bath at 56 degrees C. for one hour. The titre of the antigen is then determined and used as required for the reaction. Alcoholic extracts have been

insufficient. The results, not yet published at the writing of these author's paper, are, according to the authors, encouraging.

Hoffman (27), in preparing antigen in the manner as Coutts and Bianchi, above, finds that heating to 80 degrees C. produces a less active antigen and 100 degrees C. kills all the diagnostic properties. The antigen should be kept in a cool dark place. He states that DeWolf and Van Cleve have successfully used antigen for ten months at the end of which time it suddenly lost its ability to react.

The technique of applying the test as done by Hoffman at the Los Angeles County General Hospital, Urology Service, is as follows: (1) Clean the upper forearm with alcohol and let dry; (2) use an insulin syringe and fine needle; (3) inject 0.1 c.c. of normal saline solution intradermally; (4) about three centimeters below this, inject 0.1 c.c. antigen intradermally; (5) read the test in twenty-four, forty-eight and seventy-two hours. If the reaction is positive, in twenty-four hours, there will be an inflammatory papule that is tender and can be palpated better than seen. It is usually less than one-half centimeter in diameter and usually itches. In forty-eight hours the papule is usually larger than one-half centimeter and still more tender and inflamed, showing a surrounding zone of erythema.

If positive, a reaction can be read for about a week but usually reaches its height on the third day. In about one-half of the positive reactions, the center becomes necrotic and appears

similar to a small boil. In Hoffman's series, he did not observe syphilis or any other venereal infection to have any effect on the test, but noted that all cases do not give a positive reaction early in the course of the disease.

Lehman and Pipkin (31), experimenting with the preservation of antigen, obtained 100 c.c. of pus under sterile aspiration and made antigen in different ways as follows:

1. Specimen containing no preservative.
2. Specimen containing one-fourth per cent phenol.
3. Specimen was made up to 1:10,000 merthiolate.
4. Specimen kept at room temperature in white glass container.
5. Specimen kept at ten degrees C.

Any of these variations had not affected the potency of the antigen over a period of nine months and no variation of reaction of antigens preserved in these ways in the same patient occurred.

In 1929, E. H. Hermans, cited by Wolf and Sulzberger (54) and by Coutts and Bianchi (12), prepared two types of antigens from different cases of lymphopathia venereum which he called I and II, that did not give positive skin reactions simultaneously when tested on one or other case. He concluded a second group of cases exists which does not react positively to the ordinary Frei vaccine but does react to vaccine prepared in the same manner from pus of its own group, while never the less, these cases are clinically identical with the others.

Coutts and Bianchi noted in their cases that antigen

made from patients not having a primary lesion would produce positive skin allergy only on patients of this class (Antigen B). Hence they made an antigen from each of the two types (those without a site of lesion and those with a site of lesion). These authors now test new patients by applying an intradermal test of each of the two antigens in the same arm and a control injection of a sterile suspension of leukocytes, soft chancre vaccine and normal salt.

Grace (22) in 1934 reported some excellent experimental work with dried antigen. He found that pus from lymphogranulomatous buboes can be dried in vacuo from the frozen state without loss of the property present in the fresh pus of producing a Frei reaction in lymphogranulomatous persons. Appreciable Frei reactions are produced with the dried material in dilutions as high as from 1:4,000 to 1:100,000, with an average of 1:50,000. The titre is somewhat lower in antigens prepared from fresh material than in those prepared from dried material and ranges from 1:3,000 to 1:20,000 with an average figure of 1:7,500. The difference in titre may be due to, (1) removal of inert material by drying, or (2) to an inferior keeping quality of antigens prepared from fresh material or to a combination of these. This author further showed that both dried and fresh antigens give the same degree of reaction in all dilutions in both the inguinal and the anorectal types of the disease.

A very recent contribution has been made by Reiss (37) in

1935 in Shanghai, China. This author noted occasional failure of the antigen, the antigenic properties sometimes being missing in the pus of a clinically evident case, a fact which was also noted by Nicolau and Bancini. Reiss, working on the well known fact that a mixture of serum from convalescent patients with Frei antigen neutralized the Frei reaction, realized this to be of diagnostic importance in some cases. He reasoned that if one assumes that the serum of convalescent patients contains the antibodies from the third to the sixth month, it can also be taken for granted that there is a period before the production of antibodies when antigenic substances circulate in the blood. Starting from this idea, Reiss has investigated the blood serum of patients with lymphopathia venereum in the second or third week of the illness, while there was still apparent activity of the disease on the antigenic action. His investigation has not yet been carried to the point of determining if the antibodies are also attached to the blood cells.

The technique used by Reiss was the taking of blood from clinically typical, Frei positive cases, separating the serum, mixing the serum with 0.5 per cent phenol solution and kept in an icebox. The serum was then proved culturally sterile. On each patient tested, four tests were applied; (1), the control of .5 phenol in normal salt; (2), the Frei antigen; (3), a mixture of .05 c.c. Frei antigen with .05 c.c. of the prepared blood serum; (4), .1 c.c. of the prepared blood serum. He observed no

reactions to the control solution, the Frei antigens gave typical positive reactions, the Frei antigen and serum caused a more marked reaction than the Frei antigen alone and the reaction to the serum is similar to the Frei action alone. The reaction to the serum reaches its height in forty-eight hours and disappears in from eight to ten days. Control experiments carried out on syphilitic and rheumatic patients remained negative.

From Reiss' work, it is evident that the blood serum of lymphopathia venereum patients has antigenic properties and antibodies are absent in the serum because of the increased or accumulative effect instead of a neutralizing effect is seen when the serum and Frei antigen are mixed. Hence a new, apparently specific, diagnostic reaction is made available for the diagnosis of lymphopathia venereum.

## CHAPTER VII

### ALLERGY AND IMMUNITY

The intradermal reaction of Frei is admittedly a standby for the confirmation of the clinical diagnosis of lymphopathia venereum. Cormia (10) in his excellent discussion of the allergy of this condition, states that Ravaut used the antigen intravenously and found that only proved cases of the disease reacted with fever, joint pains and other allergic symptoms. He also states that Frei believes that there are no false positive reactions, although negatives not infrequently occur in certain situations. The reaction usually becomes positive in from two to four weeks after the onset of the adenopathy, and like the tuberculin test, is apt to remain so for years after the active process has subsided. A striking demonstration of this is cited by Bloom (4) who stated that in 1929 Hellerstrom reported the case of a surgeon who in 1904, while preparing for an operation on a resistant strumous bubo, injured himself slightly under the left thumb-nail with the point of a nail file. He had forgotten this injury until some time later when a small tender ulcer appeared under the nail; this healed under simple treatment. Soon after this, however, the glands in the left axilla became enlarged and the characteristic clinical picture of lymphopathia venereum developed. The glandular mass was enucleated and the surgeon recovered. In 1927, twenty-three years later, a Frei test was done on this surgeon and gave a positive reaction, while the test for ulcus molle was negative.

The glands which were preserved from 1904 were examined by Hellerstrom who found the characteristic histologic picture of lymphopathia venereum.

According to Cormia, the mechanism of its production is unknown but the skin is undoubtedly hyperergic (strong positive Frei test) in a large proportion of cases. This hyperergy can be explained on the basis of Jadassohn's theory of blood-carried sensitivity from within. Early in the disease the blood carries antigenic elements.

The immunological mechanism reacts with the production of antibodies. Toxic properties of the antigen-antibody union are deposited in the skin. The Frei test now becomes positive.

Gottlieb has demonstrated, according to Cormia, these blood-carried antibodies. He found that the blood serum of an active case of lymphopathia venereum, when mixed with a Frei antigen of known reactivity, had definite neutralizing powers and would prevent the development of a positive Frei reaction. It is seen that this principle is analogous to the findings of Hallerstrom, Ravaut and Findlay in their animal experimentation described previously in this paper. These antibodies are probably present in the blood for only a limited period of time which may explain the failure of Calatayud to duplicate Gottlieb's work.

Where further dissemination of virus elements occurs in a case with a previously sensitized skin, multiple focal cutaneous Frei reactions are developed and the patient presents clinically



an erythema nodosum. The conclusions reached by Saenz (38) were that the intensity of a cutaneous reaction is in direct relation to changes in the skin above the involved glands, and to the existence of general disturbances. The allergy is greatly increased by roentgen therapy to the groins in inguinal adenitis cases. Saenz believes that cutaneous manifestations are rather rare and in most of the cases, the cutaneous manifestation developed after the intracutaneous test was done. He believes that in these cases, the antigen stimulates the allergy of the skin, the cutaneous lesion resulting from a powerful immunizing activity on the part of the cutaneous structure. In most instances the eruption is noticeable in from six to ten weeks after lymph gland involvement. Increased allergic reaction of the skin causes a transient exaggeration of the symptoms of the affected glands, followed by more rapid recovery and healing. This demonstrates and supports the rationale of the use of antigen in therapy.

Sometimes temporary cutaneous anergy (negative Frei reaction) occurs. Nicolas, Favre and Lebuef, cited by Cormia (10), noted a temporary suppression of the Frei test in active tuberculosis, in early florid syphilids, in high fevers, sometimes during the premenstrual period and sometimes in chancroids. Chevallier observed that in a relapse with presumably a coincidental lowered resistance, tests with Frei antigen were negative. In one instance in which there was previously tuberculosis in the involved glands, the lymphogranulomatous infection lighted up the tuberculous process and

the Frei test was temporarily negative.

The question of hyperallergy and anergy in lymphopathia venereum are not yet entirely clear. The Frei test has been invaluable. It has not been used prognostically, however, except in a rough way. It would be interesting to note graded responses to different dilutions, though some work has been recently reported by Grace, which has been described previously in this paper, and to correlate these variations in allergic reactivity with the prognosis in individual instances. As in syphilis, the role of immunity has not been definitely settled. Cormia cites the report of Kitcher and Vatz who reported a case which was reinfection or recurrence.

Contributions to the knowledge of immunity in lymphopathia venereum are found in small bits scattered throughout the literature on the subject. Patients infected with this disease seem to be immune to further inoculation, according to De Wolf and Van Cleve (17), yet the disease is inoculable in humans aside from its usual sexual transmission; for example, accidental inoculation in surgeons.

The large number of reports of satisfactory therapeutic reports effects with the use of the vaccine treatment of the disease certainly has its immunologic significance. The report of Wolf and Sulzberger (54) shows that cases in the United States react positively to vaccines from cases in Germany and Sweden and the report of Findlay (20) shows that Germany and Southeastern Asia react positively to cases in England. This demonstration of the uniformity

of the disease regardless of the geographical area has also been shown by various other investigators.

That the sera of patients with lymphopathia venereum possesses protective properties when injected into mice inoculated with the virus, has been demonstrated by Levaditi, Ravaut and Shoen, cited by Hoffman (27) and confirmatively demonstrated again by Findlay (20). If the incidence of this disease continues to expand as it has in the past few years, further immunological work on humans is certainly indicated.

## CHAPTER VIII

### CLINICAL COURSE, SYMPTOMS

#### AND CLINICAL SYNDROMES

Recently, a few authors have given evidence that two types of the disease exist, differing in specificity of cutaneous tests and differing clinically in some respects. Due to this present status of uncertainty of the newer findings, a survey of the clinical picture of the disease as it is understood by most authors, will be given, then a description of the proposed subdivisions, though it necessitates some repetition. The late manifestations are well recognized by most authors but will be taken up under the discussion of the clinical syndromes.

The incubation period is quite variable, ranging from a few days to a few weeks. Cormia (10) finds that in a few days to to three weeks following exposure, a small transient and often herpetiform lesion appears on the genitalia. Hoffman (27) found in the literature, a division of the primary lesion, in the male, into four types of lesions on the glans penis, coronary sulcus, prepuce or in the urethra: (1), ulcerative type; (2), nodular type; (3), papular type; (4), lymphogranulomatous urethritis. The primary lesion is transitory and often overlooked. The lesion occurs singly, except in the herpetiform type. In the female, the primary lesion, if found, is seen in the fourchette, in folds of labiae, or in the vagina, as a small clean lesion. The primary lesion is usually subjectively free from symptoms.

Dalton (14) reports that recurrent herpetiform eruptions of the genitalia during the course of the disease have been reported and stated that eight and one-third per cent of his series of twenty-four cases showed this. He also states that twelve and one-half per cent of this series showed herpetiform lesions from twenty-one to sixty days after the regional glands were involved.

Coutts and Bianchi (12) state that Buschke and Boas found a site of inoculation in the genital organs in most of a series of fifty-nine cases; Gibson studied thirty-seven cases and found a site of inoculation absent in nearly all cases; Nicolas and Banciu studied thirty-six cases and found a site of penetration in eighteen; Flammerich found genital ulceration in two out of six cases and Vegas found no ulceration in eight cases, while Coutts and Bianchi studied 150 cases and found no initial lesion in forty-eight.

Lehman and Pipkin (31) state that ten to twenty per cent of the patients give a history of a primary lesion. Various other authors report proportions ranging about as the above reports.

The same variation holds true in the reports of various workers on the observation of the incubation period. Nicolas and Favre (33) determined it as ten to twenty-five days; Wolf and Sulzberger (54) state that the primary lesion appears in from ten to thirty days after infection and is followed by lymph node swelling in from two to three weeks; 21.8 per cent of Dalton's (14) series showed a primary lesion present in from two to twenty-eight

days (average of seventeen and one-half days) before the occurrence of the secondary gland process and twelve and one-half per cent of the series noted primary and glandular lesions simultaneously, fifty-eight and one-third per cent showed a unilateral inguinal gland involvement and forty-one and two-thirds per cent a bilateral inguinal process, 45.8 per cent showed extension to the iliacs and sixteen and two-thirds per cent showed spread toward the fossa ovalis chain. Ives and Katz (28) find the primary lesion occurs two weeks after exposure and the lymph nodes become involved in ten days to six weeks. Lehmann and Pipkin find the period from exposure to appearance of primary lesion to be from seven to ten days and the period from exposure to the onset of the adenitis to be from ten to thirty days.

The secondary lesion is manifested in the male, and in rare instances in the female, by an inguinal adenitis and, according to Hoffman (27) is followed closely by iliac adenitis. In the female, the adenitis may simulate a salpingitis with tenderness throughout the lower abdomen. He states that there are no symptoms until the secondary lesion is evident, but when the secondary lesions occur, the symptoms are: Malaise and fever, the glands enlarge and become tender and periadenitis ensues. Suppuration occurs in fifty per cent of cases, with sinus formation and with the overlying skin attached to the glands. The skin over the unruptured glands becomes of a red to purplish color. The iliac glands are involved in nearly every case, a point which may serve

in differential diagnosis as they are noted as a mass above and behind Poupart's ligament. The iliac glands do not suppurate, though they do contain tiny abscesses upon biopsy. During the periadenitis, the patient shows the toxic picture of an ordinary infection. The temperature sometimes reaching 104 degrees F. and cases of delirium have been reported.

Dalton noted that during the lymph node enlargement, loss of weight, nausea and vomiting, weakness and rheumatic pain. He noted no generalization of adenopathy. In one of his patients, he noted a purpura with the onset of the glandular swelling. The leukocyte counts were normal to slightly elevated with a high monocyte count in some cases. Fifty per cent of his cases fistulized following either spontaneous rupture or surgical incision and forty-one and two-thirds per cent of the fistulized group remained under observation until healed, the time required for healing varied from 92 to 577 days (average 278 days) from the onset to healing.

Wilmoth (53) found that the average time between the onset of tender glands and the time the patients sought medical attention was twenty days. Pain was seldom severe enough to keep the patient awake at night. He found no definite associated blood picture, the leukocyte count being normal before central necrosis occurs, then fever and the leukocyte count both go up correspondingly, the average white cell count in his series being 12,700 and the differential showed 70.1 per cent of neutrophils. There was usual-

ly a slight secondary anemia.

The majority of authors agree on the presence of a mild leukocytosis and while some report an increase in mononuclear cells, others report varying degrees of eosinophilia. Goldstein and Byars (23) report a case which itself one week after the onset of the adenitis and showed a primary lesion and also on the shaft of the penis were two areas of nodular enlargement not unlike a sebaceous cyst. The patient also had a urethral discharge. No gonococci were found and the serology was negative. These authors cite a report by Nicolas and Bancin of two cases of this suppurating lymphitis of the penis accompanying a lymphogranulomatous bubo.

In a small percentage of cases, many authors have observed an accompanying erythema nodosum or erythema multiforme. Since these have been discussed in this paper in the section on Allergy in lymphopathia venereum, they will not be repeated here. Lehman and Pipkin (31) have noted a generalized papular or papulo-macular eruption in some cases during the period of malaise.

The acute stages of the lymphadenitis subside gradually in three or four weeks, as described by Amtman and Pilot (2) and in the cases which go on to suppuration, the glands may discharge several months, the pus changing from the characteristic thick yellow to pus of a thinner type with the occurrence of secondary infection. In some cases multiple fistulae form which may drain for a year or more. The inguinal gland form of the disease lasts



from several months to one or more years, leaving only the scars resulting from suppuration. No report has been found showing any difference in the duration of the inguinal form of the alleged two types of the disease.

A number of authors have offered classifications of the late manifestations of lymphopathia venereum, or conditions other than the inguinal involvement of the disease, excluding extragenital cases. Cormia (10) classifies these conditions as (1) elephantiasis of the male pudenda, (2) esthiomene or vulvar elephantiasis, (3) rectal stricture in both sexes and urethral stricture in women, (4) rectal elephantiasis, ulceration or anal fistulae, and (5) a chronic perimetritis and salpingitis type of syndrome.

Wolf and Sulzberger (54) list these conditions as (1) esthiomene or *ulcus chronicum elephantasticum vulvae*, the condition known as "syphiloma" anorectale, and (2) a certain type of high rectal stricture, occurring especially in women.

Dorne and Zakon (18), in writing on the late manifestations of this disease, divide them into those occurring in women and those occurring in men. In the former they include, (1) esthiomene--a chronic ulceration of the vulva with elephantiasis, (2) genito-ano-rectal syndrome, often referred to as ano-rectal syphiloma, and (3) a certain type of rectal stricture. In the latter group, those occurring in men, they consider only elephantiasis of the penis and scrotum.

With regard to the infrequency of early diagnosis of the disease in women and the uncommon occurrence of the inguinal adenopathy in the female, Sulzberger and Wise (43) explain that as there are no severe subjective symptoms and no visible lesions, due either to the primary lesion or to the lymphatic involvement, the entire course of the active phases of the disease frequently escapes notice. The infection does not cause any manifestations until the retractile scarring has brought about the sequelae. These often first appear years later. These authors state that the position of the strictures following lymphopathia venereum is usually high in the rectum and are generally just to be reached by the end phalanx of the palpating finger, both in male and female cases.

Before taking up the syndromes as presented by Coutts and Bianchi, the question of extragenital cases might be conveniently taken up at this point. From such case reports found in the literature, it appears that two main types of extragenital cases are seen; those which are contracted by accidental inoculation through a break in the skin as in the case of surgeons injuring themselves while operating on lymphogranulomatous patients, and those cases of oral infection developing a cervical adenitis, which cases are usually found to be sexual perverts acquiring the disease through cunnilingus or fellatio.

In the case of accidental inoculation, the course of the disease is essentially like that of the inguinal infection, the

regional glands becoming involved and following the course of events described in the inguinal form.

In the cases of oral infection, Coutts and Bianchi describe a case which will be referred to subsequently, in which the primary lesion was of transitory nature. However, Curth (13) and Bloom (4) have both reported cases in which the primary lesion persisted and was refractory to any type of treatment. The case reported by Curth showed an ulcer on the tongue and submaxillary gland involvement similar to that of the inguinal type. The glands were finally removed but the anterior two-thirds of the tongue remained enormously swelled and the primary ulcer remained unchanged regardless of treatment and the condition compared with elephantiasis vulvae. This author cites the case of Buschke, in Berlin, in which the lesion of the tongue was still present after nine months. The case reported by Bloom was very similar. The lesion was on the tip and left side of the tongue and appeared as a superficial, irregularly outlined and eroded area with redness, swelling and slight infiltration, covered with grayish-yellow pus. The glands were removed and the neck healed but the lesion on the tongue persisted.

The following is the description and classification of the syndromes of lymphopathia venereum as given by Coutts and Bianchi (12), who have done extensive work on this disease in South America and who have taken close and accurate observations in

working out these groups of symptom-complexes:

#### A AND B SYNDROMES

##### I SYNDROME A.

Under this group, are included the lymphogranulomatous conditions occurring in cases in which a primary lesion has existed. Under this heading are included lymphogranulomatosis inguinalis, cervicalis, etc.; esthiomene vulva; elephantiasis penis et scroti; genito-ano-rectal syndrome of both male and female, and in a few cases reported, of a lymphogranulomatous glossitis marginata, of somewhat doubtful nature and probably belonging under the heading of lymphogranulomatosis cervicalis, above.

1. Lymphogranulomatosis Inguinalis: This is the most frequently seen clinical type, occurring mostly in males and rarely in females. Usually in from five to twenty-five days after exposure, there appears a small, soft, painless, dark red ulceration on the glans penis or prepuce, or there may be several vesicles like herpes progeneralis or sometimes a sterile urethral discharge with reddening of the urinary meatus. These various primary lesions have been classified above. Darkfield examination of the primary ulceration, herpes or urethral discharge is negative. Ulcerative lesions soon disappear under any local treatment but not the urethral discharge, for, when present, it may last for many months, especially when complicated by staphylococcus or micrococcus catarrhalis infection. Urethroscopic examination reveals a varying degree of edema of the whole extent of the anterior

urethral mucosa. The appearance of the primary lesion is followed by regional lymph node inflammation in six to thirty days. Lymph node inflammation begins very slowly. The patient usually has his attention first called to it by a discomfort in the upper thigh and there finds a small, round, painless mass in the groin. The mass increases slowly and other small masses are found surrounding the first one so that in one or two weeks a diffuse hard mass is felt under and over the inguinal ligament. The deep iliac lymph nodes are not commonly involved but when they are involved, it is long after the inguinal process that they can be felt as small, hard, painless in the iliac fossa.

During the first period the temperature may rise one-half to one degree, lassitude sets in and walking becomes slightly impaired. After two or three weeks, the lymph node mass increases very little in size but gets harder and becomes of a scirrhous consistency. Soon soft zones appear in the mass, some of which gradually make contact with the skin, showing by signs of inflammation and finally break out spontaneously, the expelled material being formed of leukocytes and tissue debris.

If untreated, the lymph nodes suppurate through sinuses for months, the process eventually ends owing to fibrosis, the inflamed nodes reduce gradually in size and the sinuses close up leaving umbilicated scars.

Schulman, cited by Coutts and Bianchi, has recently described abortive forms of this syndrome, such as inflammation of

the urinary meatus with slight inguinal inflammation, simple edema of the urinary meatus without lymph node involvement.

Bilateral lymph node involvement occurred in only five per cent of Coutts and Bianchi's cases while they report that Foncea of Chile found bilateral involvement in a higher percentage and Nicolas and Bancin noted bilateral involvement in 13.1 per cent of cases.

2. Extragenital Cases: These authors studied two cases of cervical adenopathies infected through cunnilingus. The primary lesion on the tongue is a small superficial ulceration, slightly painful and of rapid evolution toward healing. Two weeks after the appearance of the primary lesion both of these cases noticed a small painless lump in the superior carotid triangle which slowly increased in size. Treatment was instituted when soft zones could be felt in the mass and these did not break out.

3. Esthiomene and Elephantiasis Vulvæ: While Frei was the first to call attention to the lymphogranulomatous nature of this syndrome, most authors describe it as rare but information from gynecologic clinics and venereal disease dispensaries have shown an increase incidence, especially in women twenty to twenty-five years of age.

4. Elephantiasis Penis et Scroti: As mentioned in the historical survey of this paper, Barthels and Biberstein, in 1931 first placed among the lymphogranulomatous syndromes, a certain

of elephantiasis penis et scroti and although they described only one case, they based their arguments on the presence of a positive Frei test and on the similarity of histological findings with those of histological findings with those of elephantiasis vulvae. Coutts and Bianchi have studied three cases. One case studied histologically showed marked separation of connective tissue cells, pachydermatosis and numerous plasma cells. In the other case, the skin test with antigen A was definitely positive. The third case showed a positive antigen A skin test and a similar histological picture. None of these cases showed filiarisis nor a positive Wassermann or Kahn. In all three cases, the skin of the penis, scrotum and suprapubic region appeared considerably thickened, owing to hard organized edema which does not leave digital impression on pressure. The symptoms were only in relation to difficulty during coitus. All three of the patients were over fifty years of age and all three had had the edema several years before they were seen by these authors.

5. Genito-ano-rectal syndrome: In females, it is usually related to esthiomena and elephantiasis vulvae. Coutts and Bianchi state that for many years, and following the studies of Larson and Fournier, inflammatory strictures of the rectum were attributed, in a large proportion of cases to syphilis (ano-rectal syphiloma of Fournier). The absence of lyphilis in the anamnesis, the negative serologic test in most patients and the inefficiency of anti-luetic agents in the treatment of this condition awakened suspicion

as to the importance of syphilis as the causative agent.

The formation of abscesses and fistulae in the perineal and perianal regions, the presence of giant cells in the inflamed tissues, gave rise to the tuberculosis theory which was soon replaced by the theory that the condition was ano-rectal gonorrhoea until failure to demonstrate gonococci in the rectal secretion and then an attempt was made to explain the condition as determined by traumatism following frequent anal coitus. Dysentery, Chronic constipation, hemorrhoids, etc., have been considered the cause of rectal stricture. Mention has been made in this paper under the historical survey of the work done in establishing the relation of this condition to lymphopathia venereum.

Coutts and Bianchi, after their study of several cases of this condition in males, concluded it presents two forms: One that begins with abscesses and fistulae in the lower perineum, which are not in relationship to the urethra and where the ano-rectal symptoms appear some years after, and another where fistulae appear when the ano-rectal stricture is already established and can be diagnosed by simple digito-rectal examination.

The course of the perineo-rectal type, as determined by these authors, is such that patients do not remember any special symptoms prior to the appearance of one or more abscesses on the perineum. These abscesses are slightly painful and after a vary-



ing period of time, break out spontaneously. Resulting fistulae pour out a sero-purulent matter. They may heal and break out again. Urine does not pass out through them. Rectal symptoms appear in two to three years and are the same as those described in ano-rectal lymphogranulomatosis.

The cause of the ano-rectal type (ano-rectal lymphogranulomatosis) seems to develop in latent form in occasional cases with a feeling of rectal fullness accompanied by slightly painful discharge of muco-pus from the anus. Once the stricture is established, bowel movements are difficult and several days may elapse between one bowel movement and another. Patients must use cathartics or enemata. Rectal suppuration of varying intensity appears. Intense and persistent constipation develop and feces become ribbon shape. Later the stricture is accompanied by abscess and resulting fistulae.

On examination, around the anus there can be seen small and hard condylomatous excrescences, the skin is pachydermatous and sometimes small papillomatous strips follow the anal folds. Digeto-rectal examination reveals just beyond the anus or immediately above, thickening of the wall and loss of elasticity, small vegetating proliferations and a progressive narrowing which renders the examination painful. Proctoscopy reveals a dark red uneven mucous membrane with cicatricial spots, vegetations, hemorrhagic zones and ulcers. As the narrower portions are approached, the stiffness increases and the gray color of the

surface contrasts with that of the mucous membrane lower down. Radiograms clearly demonstrate the extension of the stricture. Coutts and Bianchi find nearly all cases of both types of the genito-ano-rectal syndrome are between twenty-five and thirty years of age.

6. Lymphogranulomatosis Glossitis Marginata: Coutts and Bianchi include include this condition in this group of syndromes. It is found in persons practicing cunnilingus or fellatio. Lesions on the tongue are not typical. Sometimes the tongue is enlarged, margin appears thickened and furrowed and with zones of cicatricial retraction. In other cases these symptoms are very mild but there is, on the dorsum, deep and extensive grooves and several well limited zones of intense dark red color with loss of superficial epithelium or opaque grayish papules. Regional lymph nodes are only slightly involved. Lymphogranulomatosis of the mouth is often and easily mistaken for lichen planus of the mouth.

## II SYNDROME B.

The outstanding fact about this syndrome is the absence of any primary lesion, in or about the genitals.

The course begins with symptoms not unlike any common infection. A few days before the lymph node syndrome appears, the patient feels general malaise, headache, lumbar and articular pain. Fever accompanies the onset of the lymph node enlargement.

Coutts and Bianchi believe the clinical picture is established in one week and the patient usually enters with the symptoms of fever, persistent and higher in the evening, intense pallor, slightly furred tongue and rapid pulse. Headache is worse during the prodromal stage and leaves by the time of full development of the clinical picture. Mesenteric, cervical, epitrochlear and lumbo-aortic glands may be involved and palpated in the developing stage of the disease. The urine is negative and the blood shows an eosinophilia.

In a few weeks the general symptoms subside but the fever and inguino-iliac lymph node inflammation remains. In certain cases, during the second or third weeks of the disease, arthritis of one or more joints sets in. It starts suddenly and stops suddenly and while its clinical appearance is similar to gonococcus arthritis, its swiftness and rapid restitution of all movements is contrary to gonococcus arthritis. In three or four weeks fever disappears and lymph node inflammation subsides but it may take two to six months for the lymph node inflammation to subside. Eosinophilia is one of the most persistent symptoms throughout the length of the disease. The degree of eosinophilia varies in reports of different authors from two per cent to twenty-five per cent though usually around ten per cent or less.

## CHAPTER IX

### DIAGNOSIS

The clinical diagnosis of the inguinal involvement with this disease is not difficult but should be considered uncertain until confirmed by an intracutaneous test. The essential points as given by Zakon (55) and by Wilmoth (53) are: A history of a painless, transient, superficial ulcerating primary lesion or the finding of such lesion; the history of gradual onset of enlarging lymph glands, with or without history or the primary lesion or contributory lymphangitis; the history of a recent visit to the West Indies, South or Central America is suggestive.

The Frei test is the most reliable point in the diagnosis, though it should be realized that this does not become positive until lymph gland involvement is well under way. The serum reaction recently described by Reiss, discussed in the section of specific reactions in this paper may prove to be of value for an earlier diagnosis. The Frei test, however, should be done with both the known A and B antigens. One negative Frei test is not sufficient to rule out lymphopathia venereum.

The finding of clinical evidences of the forms of this disease other than the inguinal adenitis should be good indications for a Frei test. Certainly all cases of rectal stricture deserve a skin test which should show a positive reaction if due to lympho-

pathia venereum, for by the time the stricture manifests itself, the allergy is well developed.

The nature of a rectal stricture, as determined by digital examination, may give a clue as to its etiology. Streicher (42) classifies this stricture as annular-tubular with the apex of the stricture at about three or four centimeters from the anal orifice with the tubular formation of the stricture distal to the annular constriction and the apparently normal recto-pelvic colon proximal to the stricture. The finger meets with immediate obstruction on rectal examination and is of a leather-like consistency, almost stony hard and simulates syphilis of the rectum except for rectal fistulae which are usually absent in syphilis. Rectal fistulae may be present with rectal stricture and no inguinal gland involvement and the reverse is true. Also the inguinal adenopathy and stricture but no fistulae.

#### DIFFERENTIAL DIAGNOSIS

Chancroid: The primary soft chancre, according to Hoffman (27), is chronic and the patient is aware of its presence, and Tomlinson and Cameron (47) bring out the point that the lesion of chancroid can be proved to be auto-inoculable and the exudate contains the Ducrey Bacillus. These authors as well as Lehman and Pipkin (31) state that in the bubo of chancroid, the gland process is very painful, more acute and develops to suppuration more rapidly. The adenitis is a complication in chancroid rather

than a secondary lesion and the bacillus of Ducrey can be found in seventy-five per cent of cases. The bubo suppurates usually into one cavity. The Ito-Reenstierna intradermal test is positive while the Frei test is negative unless there is a mixed infection. The dirty appearance of chancroid and the odor are characteristic.

Syphilis: Hellerstrom, quoted by Zakon (55), found syphilis present in thirty per cent of his cases. Hoffman points out that the glands are hard but discrete and painless. There is history of a hard chancre or visible evidence of one from which a darkfield examination may be done or a darkfield study of material from gland aspiration. The glands do not have the same tendency to suppurate that is seen in lymphopathia venereum, also in the latter disease there is no secondary skin eruption. The diagnosis however depends mainly on the laboratory tests, the Wassermann usually being positive by the time a luetic adenitis is seen. Also the course of lymphopathia venereum is not affected by antiluetic treatment. In the later manifestations of the two diseases, it may be impossible to distinguish them on clinical grounds and in these conditions, the laboratory tests are reliable and diagnostic in a very high percentage of cases but it must be remembered that, as reported by Burney (6) occasionally early cases of lymphopathia venereum may give a weak positive Wassermann for awhile and that, as has already been brought out, active second stage syphilis may cause anergy in intracutaneous Frei tests.

Hodgkins Disease: As brought out by Hoffman, the glands here are discrete, hard and have little tendency to become fixed or to break down and suppurate. Often too, other glands than the inguinal group are involved and here it is seen that Hodgkin's disease would offer a greater problem in differentiating from the extragenital cases of lymphopathia venereum. In Hodgkins the spleen is enlarged and the microscopic picture from biopsy is diagnostic.

Tuberculosis: Like lymphopathia venereum, tuberculous adenitis is chronic, the glands suppurate and sinuses form but tuberculosis usually gives a history of systemic symptoms of longer standing. The diseases may be confusing even in microscopic sections but, according to Amtman and Pilot (2), careful study will show differences even in the presence of Langhans cells. Further, lymphogranulomatous glands never caseate. Smears for acid-fast bacilli are helpful, guinea pig inoculation is valuable and tuberculin tests are useful, particularly if negative in the adult, thus disproving a tuberculous etiology in a given case. The laboratory work probably being the most valuable in the ano-rectal cases.

Granuloma Inguinale: This disease causes much confusion, due mainly to the present similarity in the names of the two diseases. In granuloma inguinale, as emphasized by Tomlinson and Cameron (47), there is ulceration of the skin over the glands without glandular suppuration; the disease is characterized by the presence of Donovan bodies in the large mononuclear cells of the pus from the

granulation tissue surface of the ulceration. It does not begin as an adenitis, but as an ulcerating lesion of the skin and involving the subcutaneous tissue and increasing in area if untreated. Involvement of the lymph glands is rare according to Amtman and Pilot (2). Also, this disease responds more readily to intravenous antimony and potassium tartrate.

Neisserian Infection: The history or finding, in the male, of an acute, purulent urethritis and in the female, an urethritis, vaginitis, Bartholinitis or cervicitis, even incases where the gonococcus can not be found in smears, usually cause little confusion. The gonorrhoeal bubo is uncommon and when it does occur, it is very acute and there is evidence of gonorrhoea on examination of the genitalia. Intrapelvic involvement of lymphopathia venereum however may be difficult to distinguish from a chronic gonorrhoeal infection, mainly cervicitis and salpingitis, especially with the high incidence of gonorrhoeal history in lymphopathia venereum patients. The Frei test of course should always be used to prove or disprove the presence of the latter. This as well as microscopic study of smears should be done in cases of rectal involvement.

Plague: Here the process of bubo formation is much more acute, twenty-four hours after exposure according to Hoffman (27), the constitutional symptoms more marked and laboratory findings by direct smear, culture and animal inoculation eliminate confusion of the two diseases, using aspirated pus from the buboes.



Simple Pyogenic Adenitis: This might be confusing but a primary focus of infection can be found and bacteriologic studies clear up the etiology. Also a pyogenic bubo produces one large, rather than numerous small abscesses if the process extends to that stage of development. In pyogenic adenitis of the groin due to lesions of the lower extremity, the adenitis will be femoral rather than inguinal.

Other conditions mentioned by Burney (6), which must be ruled out but which do not cause sufficient confusion to warrant detailed consideration are tularemia, chronic glanders, malignant growths, herpes genitalis, actinomycosis and acute leukemia. In cases showing elephantiasis, filariasis may need to be ruled out by examination of the blood, urine and chylous fluid for the microfilariae, though a Frei test should be sufficient if corroborated by clinical study. Coutts and Bianchi (12) state that lymphopathia venereum of the mouth may easily be mistaken clinically for lichen planus of the mouth.

## CHAPTER X

### PROGNOSIS

The prognosis in this disease is good though the course may be subacute or chronic, especially if not properly treated. However, the different types of treatment with varying results, still make the course indefinite. Zakon (55) says the prognosis is never grave though the long duration and the therapeutic resistance render it a troublesome condition. Only one case having resulted in death--a few weeks after an operation for the removal of the glands. The necropsy report showed abscesses and hemorrhagic infarcts, verrucous endocarditis, purulent nephritis and a persistent thymus.

However, since Zakon's report in 1932, Wein and Perlstein (50) have reported a case with autopsy findings which gave pathological confirmation of the course of the disease as it occurs in the female.

## CHAPTER XI

### TREATMENT

The treatment of lymphopathia venereum is yet variable in the hands of most authors who report their results of different methods. Due to the difference of results obtained in employing any one kind of treatment, no one method has been generally established as superior. Many authors state that spontaneous cure occurs rather frequently.

The main types of treatment and the results reported by different writers may be listed under the following headings:

#### SURGICAL:

Most authors having had experience in the surgical treatment of the inguinal form of the disease conclude that removal of the affected glands is much more satisfactory in shortening the course of the disease than is incision and drainage. DeWolf and Van Cleve (17) believed that surgical removal of the glands offered better results than any other form of treatment. Wilmoth (53) excised the glands in twenty cases and found this to be more effective than incision and drainage. In his series, disability after excision averaged twenty-seven and one tenth days as compared with an average disability of thirty-five and two tenths days in cases in which incision and drainage had been done. He observed that a rather severe reaction may follow either incision or excision and occasionally involvement of the deeper, more proximal group of glands follows with slow recovery. Such involvement of the deeper glands is charac-

terized by continued rise of fever with tenderness on deep pressure in the lower abdomen. Post-operatively, there is always a rise of the temperature curve to usually about two degrees above the highest pre-operative point, which declines to normal in five to nine days. He concluded that early resection of the involved glands is preferable.

Whitmore (51) expresses surgery as the choice of treatment. He treated twenty cases by surgery and in some he removed all the glands and sutured the wound shut. About one-half of these healed by primary intention. In others there was prolonged drainage but the course seemed shorter than in those who had incision and drainage.

Some years ago, Nicolas and Favre (33) claimed the choice of treatment to be radiotherapy, complete curettage or excision. Berkovsky (3) also recommends wide excision and massive xray dosage, while Cole, according to Burney (6), recommends only partial excision to prevent elephantiasis. According to this author, Hellerstrom says that the danger of elephantiasis in total extirpation may be avoided if care is taken not to excise all the inguinal and subinguinal glands. Cole considers the best results are obtained by rest in bed, free drainage, partial extirpation of the nodes plus the use of antimony and potassium tartrate intravenously.

Dalton (14) treated sixty-two and one-half per cent of his twenty-four cases by complete or partial excision, lancing or aspiration, and of the healed cases, those with complete extirpation required an average of sixty-one days from operation to healing.

Those who had had excision without previous lancing required thirty days as against one hundred twenty-three days in those that had previously been either lanced or partially excised, especially in cases of bilateral involvement, because of the resultant lymphatic block. Further, Hanschell (24) in 1926 even denounced any surgical approach beyond aspiration of large and fluctuant glands. Hoffman (27) believes that surgery alone does not cure. He treated the suppurating glands by aspiration. If the lesion was large, small parallel incisions were made in the mass and the pus pockets broken down with the finger but the glands were not removed or destroyed. Small penrose drains were put in. He argues that this technique avoids having large wounds which have to granulate in and it saves the glands to prevent a later complication of elephantiasis.

#### TREATMENT WITH THE ANTIGEN:

This treatment can be applied in whatever form the disease may manifest itself and probably is of value in preventing the late manifestations. Alley (1) has used antigen in the treatment of four cases in the pre-stenotic stage of rectal involvement and he states that the results are encouraging. The technique of the treatment is simple and is essentially the same as the diagnostic test: With a tuberculin syringe and small needle, preferably dry-sterilized, 0.1 c.c. of antigen is injected intradermally. He believes the intradermal treatment to be more effective than the subcutaneous or intramuscular injections. The dose is repeated twice a week. Two of his four cases had activation of rectal symptoms, shown by increased

bowel activity, diarrhea and tenesmus following the first few injections. The most striking change in these four cases, who had had fifteen to thirty injections each, was the better general feeling and the diminution of rectal discharge and discomfort.

An important and interesting point in the intradermal treatment was brought out by Wein and Perlstein (49) who used intradermal antigen and noted that the reactions in the patients arms became negative after repeated injections but the reaction to injection on the hip was actively positive. In their cases treated with intradermal antigen, these authors noted that new lesions ceased forming, sinuses stopped discharging and healing and fibrosis were hastened. They state that with the intradermal method, results are obtained in less time than when the antigen is given subcutaneously. Further, the intradermal method requires less antigen, which is a point to be appreciated, considering the difficulty with which fresh antigen is obtained.

Perhaps this problem might be largely relieved in the future since Tamura (44) has shown results with cultured antigen. At the time he reported his successful culture of the virus, he had nine cases showing active inguinal manifestations of the disease. He was treating them with heated culture vaccine, given subcutaneously. Of these, three cases showed such marked improvement they were considered cured in eight weeks. The other cases showed improvement. The effects of this antigen given intradermally remains to be reported.

#### INTRAVENOUS TARTAR EMETIC:

This method of treatment has been rather widely used with

fair success but according to Cormia (10), Hellerstrom does not find it comparable with operative results. Coutts and Bianchi (12) report good results in the early stages of the disease with the combined use of deep Xray therapy and intravenous tartar emetic.

Hoffman (27) found tartar emetic very efficaceous except in one case of his series. As soon as the diagnosis was established, his cases received the intravenous antimony and potassium tartrate in sterile one per cent solution, 3c.c. given on the first day, 5 c.c. on the second day, 8 c.c. on the third day and 10 c.c. on the fourth day. If the patient could be observed for toxic symptoms of nausea and vomition, 10 c.c. were given daily until healing was evident and then repeated two or three times a week until healing was complete.

Apparently the tartar emetic treatment was originated in 1925 by Destefano and Vaccarezza (16) who reported excellent results in seventy-two cases over a period of two years. Bilateral involvement occurred in twenty-six cases. They used the one per cent solution intravenously twice a week for from four to ten injections usually, and sometimes up to fifteen or more were given in some cases. According to their report the lesions retrogressed under this treatment alone and the general health of the patients improved so it was unnecessary even to incise the abscesses. They concluded that the action of this drug is so manifest and so constant that it should be ranked as a specific. They report all their cases were cured or improved. The only contraindications being kidney disease.

Sorley and Gibson (39) treated a large number of cases and after using intravenous tartar emetic, excision and protein shock therapy, abandoned the latter two. They made a modification of the original method of giving the drug as used by Destefano and Vaccarrezza. The original method is as follows: The injections are given every three or four days, the dose of the drug in the first injection being one-half grain; in the second, one grain; and in the third, one and one-half grains. The latter is the maximal dose. The duration of the treatment is, of course, regulated by the results. The patient is prepared before each injection by the achievement of a free bowel movement and by the administration of glucose on the night previous to, and also on the morning of the injection. The glucose acts as a guard against tissue injury, especially hepatic.

It is essential that the tartar emetic solution should be made up fresh on each day of injection. The exact amount of the drug is weighed out and placed in a sterile glass beaker. The solvent for making the solution is sterile distilled water, and the volume of solution for each injection is 10 c.c. The injection is given very slowly in an attempt to avoid any reaction which takes the form of a dull aching at the elbow and shoulder of the arm in which the injection is being given, and after the injection is finished, laryngeal irritation with violent coughing. Nausea and vomiting may also rarely be caused. In order to reduce the chance of a reaction to a minimum, the injection should take at least five minutes.

The modification of this method, devised by Sorley and Gibson, differs from the original method in the time employed in



giving the injection. It appears that to get the best results, according to these authors, it is desirable to produce in the patient a well-marked but transient reaction. The symptoms produced do not seem to be of serious pathological significance. The modification then, consists of giving the drug rapidly enough to insure the production of a reaction. The progress of cases in which a reaction was produced with every injection was consistently more satisfactory than that of cases in which the temporary comfort of the patient was considered and the injections slowed to obviate any reaction. The average time of injection required to produce a reaction is three minutes.

These authors have abandoned even aspiration and consider it essential to avoid, if possible, any break in the skin over the bubo, even in the presence of fluctuation. In most cases treated with tartar emetic, absorption of the pus and resolution of the inflammatory reaction in the bubo occurred gradually but surely. If by chance, a bubo leaked or underwent a spontaneous rupture, the opening was well cleansed with spirits and closed by a collodian dressing. This principle of non-interference with the bubo, according to these authors, seems to be an important point in the tartar emetic treatment. The table of results by these observers shows the average disability period in cases treated by the original method to be thirty-four and two tenths days as against an average of twenty-three and three tenths days in cases treated by their modified method.

**NON-SPECIFIC FEVER THERAPY:**

This method of treatment was strongly advocated a decade ago by Hanschell (24). Most of the work with this form of therapy in this disease has been done by the British workers. Hanschell reported excellent results with bed rest and intravenous typhoid vaccine. One dose and a second and third if needed. If the glands are large and fluctuant so they look like they might break through, they may be aspirated. Hanschell says his own experience with this treatment was confirmed by Dr. G. C. Low and Dr. P. H. Manson-Bahr at the Hospital for Tropical Diseases, in London.

Low and Cook, cited by Burney (6), recommend foreign protein in the form of TAB vaccine given in increasing doses at intervals of four to eight days, beginning with fifty million to a hundred million organisms. The doses are increased until three hundred million are given at one injection. The size of the dose and the intervals between injections are regulated by the condition of the patient, the amount of reaction and progress of the patient, aspiration being done if there is pus.

In the treatment of forty-three patients by the intravenous vaccine method, Sorley and Gibson (39) were unable to get the results claimed by Hanschell. In the forty-three patients treated by this method, they determined an average disability period of forty-six and six tenths days as against one of twenty-eight and eight tenths days in thirty-six patients treated with intravenous tartar emetic.

**EMETINE TREATMENT:**

Ravaut (35) originated this treatment. He reported a rapid

cure with subcutaneous and intravenous injections in one case and later noted good results in later cases, including one case of glandular involvement of the neck. Other observers subsequently reported fair results with this drug but in recent years its use in this disease has largely been abandoned.

#### MISCELLANEOUS AND NON-SURGICAL LOCAL TREATMENT:

Treatment of the primary lesion is ignored by most workers on account of its superficial and evanescent character. Usually ordinary cleanliness is considered sufficient. Hanschell (24) in his report, claims to have healed the primary lesion in his cases in twenty-four hours by swabbing with ninety per cent methylated spirits. No reports of other workers to duplicate this have been seen.

Wilmoth (53) concluded that local treatment of the adenitis was of little avail as far as the course of the disease is concerned, but it may add to the comfort of the patient. He states that some recommend lead lotion, ichthyol ointment, tincture of iodine, ice bag and hot water bottle. Others recommend the quartz lamp or injections of mercury salts or injections locally of iodoform emulsion or similar emulsions. Potassium iodide by mouth and intravenous arsphenamine are no good.

The treatment of a case reported by Davies, King and Findlay (15) consisted of rest, hot fomentations to both groins, repeated aspirations as fluctuation appeared and two intramuscular injections of manganese butyrate, one to one and one-half c.c., given three days apart, and saline dressings on the prepuceal sore. At the end of six

weeks the patient had only thickened glands and brown staining of the skin over the glands.

The use of fuadin has been tried by some workers and Coutts and Bianchi (12) report good results with it. Dalton (14) treated seven patients medically, four of which received tartar emetic (two early cases and two with fistulae) and three received fuadin but the comparative results did not reveal anything either in a positive or a negative way.

Thomas and McCarthy (46) treated one case with an autogenous filtrate in bouillon applied by soaking dressings on the wound where the patient showed no tendency to heal after having had the groin incised some time before. They reported rapid and complete recovery by this trial.

Coutts and Bianchi (12) state that when fistulae have become established, Xray therapy and local treatment with ten per cent iodoform-glycerine accelerates cicatrization. According to Cormia (10), Xray, preferably filtered, has been extensively used by Favre, Frei, Poutrier, Lohe and Rosenfeld and others and according to Burney (6), Pardo-Castello recommends radio-therapy before suppuration, or excision after suppuration has occurred. Cormia states that ten per cent sodium iodide, sodium salicylate and Lugols solution have been popular in France, while in Germany, solgonal (a gold preparation) has been strongly recommended by Nauman, Lohe and Rosenfeld.

#### TREATMENT OF THE LATE MANIFESTATIONS:

The treatment of the late manifestations of lymphopathia venereum is mainly a surgical problem in handling a mechanical ab-

normality, though the logic of first treating the disease itself, if still active, is obvious. Also it is generally recognized that treatment of the disease itself has no effect on the late manifestations when once they have developed but is important in the prevention of these complications. Therein lies the importance of early diagnosis of this disease, especially in women who are more prone to develop a late genito-ano-rectal involvement.

Streicher (42) states that treating the disease itself has no effect on the rectal stricture after it has formed and Alley (1) believes that in the advanced stages with dense fibrous stricture of the rectum, colostomy is necessary as a life preserving measure. He has used antigen in the treatment of four cases in the pre-stenotic stage and feels that the results are encouraging.

Templeton and Smith (45) reported a case of a male with rectal stricture and fistula in ano and extensive ulceration around the anus. The stricture was divulsed after cutting it with the cautery and opening the fistula with the cautery. The stricture was gradually dilated and diathermy used. Also two drachms of saturated solution of potassium iodide three times a day and intradermal injections of Frei antigen. The patient progressed to complete healing. Lash (29) reports a case showing a growth on the labia minora six years after a colostomy had been done. A vulvectomy was done and the patient sent home. Martin (32) studied twenty-five cases of rectal stricture in colored women, twenty of which reacted positively to the Frei test. He concluded that colostomy is the best treatment.

## CHAPTER XII

### CONCLUSIONS

In the foregoing chapters, an attempt has been made to present a comprehensive study of lymphopathia venereum in all its phases and to clarify, as much as possible, the present status of the knowledge of the disease, by compiling the pertinent facts established to date.

The study of one case in January 1934 served as a stimulus for the preparation of this paper. The case, a colored female, age thirty-eight years, showed a rectal stricture and a recto-vaginal fistula which had been unsuccessfully repaired four times before the presence of lymphopathia venereum was discovered. The patient then had a permanent colostomy performed. Undoubtedly many more comparable cases are presenting such a problem and warrant physicians and surgeons to be constantly on the lookout for their occurrence.

The facts presented in the text suggest that some work may well be done in culturing the virus of each of the two types of the disease; namely, the A and B syndromes. If each can be successfully cultured, much knowledge can be gained of the specificity of these two types, provided such can be more firmly established. Further, this culture antigen might be prepared and put in sterile ampules to supply many workers finding difficulty in obtaining antigen both for diagnostic and therapeutic purposes.

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