(2) In spite of clinical improvement it is uncertain that evidence of complete cures from any form of treatment will be found.

Summary

The bladder neck, including the posterior urethra, is considered in some detail as a potential focus of chronic infection in recurring cystitis in women.

Some practical points in relation to urethroscopy are discussed.

There are common patterns of incidence and pathology in decades for cases of chronic frequency and cystitis.

The cervix uteri is considered.

Attention is called to the occurrence of gland structures resembling prostatic tissue in the posterior urethra of females.

A general survey of cystoscopic appearances in frequency and cystitis is made.

The efficacy of local treatment is based on the need to provide the best possible drainage from the infected focus. Residual urine which resists other forms of treatment sometimes calls for bladder-neck resection.

The uncertain value of urine reports is discussed.

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LYMPHOGRANULOMA VENEREUM

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Lymphogranuloma venereum is a venereal disease, usually acquired in tropical or subtropical regions, caused by a filterable virus which is related morphologically and antigenically to the virus of psittacosis. There are even more descriptive synonyms for the condition than is usual, including lymphopathia venereum, lymphogranuloma inguinale, poradenitis venerea, climatic bubo, and Nicolas-Favre disease. It should be distinguished from granuloma inguinale (venereum), an infection by the Gram-negative pleomorphic organism *Donovania granulomatis*.

Although some of the classical studies of the disease were published in Britain (Stannus, 1933; Findlay, 1933; Hanschell, 1938), the number of cases diagnosed in this country is not high; thus new patients seen in special treatment centres in the five years 1951 to 1955 inclusive and enumerated in the annual reports of the chief medical officer of the Ministry of Health total only 363.

Stannus (1933), who suggested that John Hunter in 1786 and William Wallace, of Dublin, in 1833 may have

described cases of the bubonic form of lymphogranuloma venereum, thought that the scarcity of reports of infection in Great Britain was due to the lack of recognition of the disease by the medical profession. The experience of King *et al.* (1956) supports this view. Frei tests were performed on all patients attending the venereal diseases clinic of the London Hospital during a 13-months period. Active infection with lymphogranuloma venereum, as shown by a positive skin test and a complement-fixation test positive at a serum dilution of 1 in 32 or more, was found in 23 out of 1,119 patients (2%). Almost half of the patients with positive reactions had clinical evidence of infection. However, in spite of a more widespread appreciation of the clinical features of the disease, and in spite of the greater facility with which complement-fixation and skin tests for the disease can be carried out, there were, until the above-mentioned report, fewer than 20 instances in the literature of patients who have acquired the infection in this country and in whom the diagnosis is indubitable (see Subsidiary References).

Hanschell (1938), who had a considerable experience of the disease, reported that in 19 years of observation in a London dockside hospital he had seen no cases of indigenous infection. The disease is apparently transmitted in exudates from ulcerated lesions which in the male are usually present for only a short time. Males constitute the bulk of travellers from the tropical and subtropical areas where lymphogranuloma venereum is endemic, and the short incubation and infectious phases will often be completed during the journey to this country. It has been suggested that the infectious phase is for practical purposes further curtailed by the fact that the man is rendered *hors de combat* for much of this time by the concomitant painful buboes (Stannus, 1933). It is probable, therefore, that hitherto infectious cases have rarely reached this country and that "reservoirs" of infection have not developed here. With the increasing use of air travel and with the influx of immigrants from the West Indies, where lymphogranuloma venereum is extremely common, this situation may be altered.

In this paper the cases of two patients who acquired lymphogranuloma venereum in this country and who presented in the immediate post-primary stage are reported, together with details of four other cases which also attended this hospital during a recent period of four months and which illustrate other syndromes of the disease.

Case 1

A West Indian negro aged 39 while in his early teens had had swellings in the left groin which had discharged and healed, leaving some linear scars. He admitted several sex contacts before this. Since coming to this country three years ago he had been treated on two occasions for acute gonorrhoea. Three weeks before admission he had intercourse with a coloured West Indian woman whom he met casually. About ten days later he developed an itching blister on the glans penis. The blister was broken by scratching, but healed within a few days, at which time bilateral inguinal swellings developed; these increased in size and became painful. He came to hospital complaining of the painful groin swellings and of headache.

On admission he had an intermittent fever to 100.6° F. (38.1° C.) with a pulse rate of 70-84 a minute. There was no neck stiffness. On the dorsum of the glans penis adjacent to the corona there was a depigmented area indicating the site of the recent lesion. There were tender enlarged glands in both groins above and below the inguinal ligaments, with oedema and induration of the surrounding subcutaneous

tissue and overlying skin. Each swelling was divided by a deep skin groove (see Fig.). The changes were more obvious on the right side, where the external iliac glands were also palpable and slightly tender. A few small glands were palpable in both axillae. The scar of a recently healed boil was present on the right wrist and there was a small discharging pustule in the left suprapubic region. Proctoscopy demonstrated mucopus lying on an inflamed rectal mucous membrane. The Frei skin test was positive: an area of induration 8 mm. in diameter was present at 48 hours.

Case 1. Note groove in bubo and depigmented area on glans penis.

A complement-fixation test for lymphogranuloma venereum was positive at a serum dilution of 1 in 16, the titre falling to 1 in 8 12 days later.

Other investigations showed: haemoglobin, 106%; white blood cells, 5,100 per c.mm. (neutrophils 80%), E.S.R. 41 mm. in one hour (Westergren); total serum proteins, 7.9 g./100 ml. (albumin 4.8 g., globulin 3.1 g.); electrophoresis of serum proteins showed prominent alpha-2 and gamma-globulin bands; after two weeks the serum globulin had risen to 3.7 g./100 ml. Serum Wassermann and Price precipitation reactions were negative, and the chest radiograph was normal. The episode of inguinal suppuration in adolescence in this case was thought to be due to a chancroidal bubo; this suspicion was confirmed by a positive dmelcos skin test for infection with *Haemophilus ducreyi*.

Forty-eight hours after treatment was started with tetracycline, 500 mg. every six hours by mouth, some reduction in the swelling and tenderness in the groins was apparent. On the fourth day of treatment the patient became, and subsequently remained, afebrile. Tenderness had disappeared within six days of starting treatment, and after 14 days there remained only slight inguinal-gland enlargement without apparent periadenitis. The dosage of tetracycline was reduced to 250 mg. every six hours after five days and to 250 mg. every 12 hours after a further eight days; the antibiotic was stopped on the nineteenth day after a total of 20 g. had been given.

Between the times of his extramarital exposure and of the appearance of symptoms the patient had had intercourse with his wife. Her Frei test and lymphogranuloma venereum fixation test were normal three weeks after this coitus. She failed to attend subsequently for the tests to be repeated.

Case 2

A male West Indian negro aged 31 was referred to the department of venereal diseases with tender enlarged glands in the groin. Two years previously he had been treated for acute gonorrhoea. He had suffered from bouts of mild central abdominal pain for some years and from a cough for about one year. Since his arrival in England some six months earlier he had had night sweats. His weight had not changed. Eleven days before admission he had felt feverish and a tender swelling had appeared in the right groin. He became constipated and complained of headache and dysuria. Four days later a swelling developed in the left groin. On the day before admission he coughed up some blood-stained sputum.

On examination he had an irregular intermittent fever to 103° F. (39.4° C.) without comparable tachycardia (pulse rate 80–100 a minute). A few glands were palpable in all areas, including both epitrochlear regions. Lying below and parallel to the right inguinal ligament was a chain of enlarged, slightly tender lymph nodes, the most medial of which showed periadenitis with adherence to the skin. A smaller but similar chain of glands was palpable in the left groin, and the right external iliac glands were also enlarged. There was a mild urethritis with no gonococci demonstrable on examination of the urethral discharge by smear and culture. The rectal mucosa was normal on proctoscopy. The Frei test was positive, with an area of induration 10 mm. in diameter after 48 hours. The complement-fixation test for lymphogranuloma venereum was positive at a serum dilution of 1 in 32.

Other investigations showed: haemoglobin, 106%; white blood cells, 6,000 per c.mm. (neutrophils 49%, lymphocytes 34%, monocytes 9%, eosinophils 8%); E.S.R., 15 mm. in one hour (Westergren); total serum proteins, 8.4 g./100 ml. (albumin 5.8 g., globulin 2.6 g.); electrophoresis of serum proteins showed a prominent gamma-globulin band. Dmelcos skin test was positive. Serum Wassermann and Price precipitation reactions were negative and the chest radiograph was normal. Tetracycline was given in the same dosage pattern as in Case 1. After 72 hours the patient was afebrile and had no headache; the right external iliac glands were no longer palpable and the tenderness of the inguinal glands had disappeared. Before the patient defaulted nine days later, the groin glands were becoming smaller and more mobile.

Case 3

A coloured West Indian woman aged 32 had for three months, since shortly after her arrival in England, been the regular consort of the previous patient (Case 2). Her attendance at hospital for investigation as a contact was therefore arranged and she was subsequently admitted. She had given birth to a child a year before and since delivery had had leucorrhoea. There were no symptoms suggestive of infection with lymphogranuloma venereum, but for four months she had suffered from a cough. Two weeks before admission there had been pain in the right chest and on one occasion she had produced blood-streaked sputum.

On examination she had a fever to 99.6° F. (37.6° C.). There were a few palpable but not very large glands in the axillae and groins. A small irregular punched-out ulcer was present on the inner surface of the right labium minus. Proctoscopy revealed a slight purulent proctitis. The Frei test was positive, with an area of induration 12 mm. in diameter. The complement-fixation test for lymphogranuloma venereum was positive at a serum dilution of 1 in 256. Examination of her blood showed: haemoglobin, 96%; white cells, 7,700 per c.mm. (neutrophils 38%, lymphocytes 34%, monocytes 10%, eosinophils 17%); E.S.R., 28 mm. in one hour (Westergren); total serum proteins, 8.6 g./100 ml. (albumin 4.8 g., globulin 3.8 g.); electrophoresis of serum proteins showed a prominent gamma-globulin band. A radiograph of the chest showed slight shadowing of doubtful significance at the extreme left apex. The sputum was negative for tubercle bacilli on smear and contained no ova or mites.

Before investigation or treatment could be completed the patient took her own discharge because her consort failed to visit her in the ward. She had then received 10 g. of tetracycline during five days and the vulval ulcer had almost healed.

Case 4

For about one week before his admission, while travelling from Jamaica, a male negro aged 48 was treated in the ship's hospital for central abdominal pain and diarrhoea. A more accurate history was unobtainable owing to the patient's low

intelligence. His temperature was 98.4° F. (36.9° C.) and his pulse rate 80 a minute. Tenderness and guarding were present in the right iliac fossa. On rectal examination there was tenderness on the right side of the pelvis. A scar was present in the right groin.

Acute appendicitis was suspected and appendicectomy was performed through a McBurney incision. The appendix was firm and pale. There was at least 5 oz. (140 ml.) of clear straw-coloured fluid in the peritoneal cavity. A Meckel's diverticulum was sought but not found. There were some slightly enlarged mesenteric glands. Macroscopic section of the appendix showed thickening of the submucosa, and microscopically there were the changes of mild chronic inflammation. The ascitic fluid contained no acid-fast bacilli on smear, and a Löwenstein culture was negative.

Post-operatively the patient had an irregular intermittent fever to 102° F. (38.9° C.), and in view of the indefinite changes found at operation further investigations were made: haemoglobin, 108%; white blood cells, 4,100 per c.mm. (neutrophils 85%); E.S.R., 18 mm. in one hour (Westergren). The serum Wassermann and Price precipitation reactions were negative. On the sixth post-operative day he complained of suprapubic pain; albumin and pus cells were found in the urine and a course of sulphadimidine (21 g. over six days) was given. A mid-stream specimen of urine, obtained before this treatment started, was later reported to contain no albumin, only a few white blood cells and epithelial cells, and to be sterile on culture. He was then found to have bilateral moderately enlarged and slightly tender inguinal glands with some tenderness over the right external iliac glands. On proctoscopy a small piece of mucus was seen on the anterior rectal wall. A Frei test was positive. Complement fixation test for lymphogranuloma venereum was positive at a serum dilution of 1 in 16.

Fifteen days after admission the E.S.R. had risen to 35 mm. in one hour (Westergren); the total serum proteins were 7.8 g./100 ml. (albumin 4.3 g., globulin 3.5 g.); electrophoresis of serum proteins showed increased gamma-globulin. Tetracycline, 250 mg. every six hours, was given for the next five days, during which time the affected glands became smaller and less tender. A fortnight after finishing this treatment the glands were no longer palpable.

Case 5

A male Jamaican aged 27, who had lived in the United Kingdom for one year, was admitted to hospital with abdominal pain. This had been present for three days accompanied by anorexia, occasional vomiting, constipation, and fever. At first the pain had been of an aching character and had been situated in the lower abdomen, but it had gradually become more severe and had spread over the whole abdomen.

On examination the patient lay with his knees drawn up; his temperature was 103.2° F. (39.6° C.) and pulse rate 104. There was diffuse abdominal tenderness, maximal in the right iliac fossa, with guarding and rigidity. There was no tenderness on rectal examination. A small ulcerated papule was present on the prepuce dorsally, adjacent to the coronal sulcus, and the inguinal lymph nodes on both sides were enlarged and firm but not tender. He admitted having had a sore on the penis about three weeks before.

Laparotomy was performed through a right lower paramedian incision. There was no ascitic fluid, and no localized lesion was found other than injection of the peritoneal coat of the whole of the small gut. The appendix, which appeared normal, was removed. The fever settled by lysis during the next three days. The Frei test was negative, but the complement-fixation test for lymphogranuloma venereum was positive at a serum dilution of 1 in 128. Two days after operation the E.S.R. was 70 mm. in one hour (Westergren); total serum proteins were 7.8 g./100 ml. (albumin 4.2 g., globulin 3.6 g.); electrophoretic pattern—increased alpha-2 and gamma-globulins.

Case 6

A married white woman first attended hospital in 1937 at the age of 35, shortly after her arrival from Barbados, where she was born. She complained of rectal discomfort with a slight rectal discharge and of difficulty in defaecation for the previous eight years. She was found to have rectal strictures at 2 and 5 in. (5 and 12.5 cm.) from the anus; these required dilatation by the passage of rectal bougies every few weeks. For about six years she suffered repeated attacks of arthritis in her knees. In 1944 a Frei test was positive.

She now (1957) complains of urgency of defaecation with slight faecal incontinence, although there is little evidence of rectal stenosis; her complement-fixation test for lymphogranuloma venereum is positive at a serum dilution of 1 in 16.

Discussion

The clinical picture in Case 1 is typical of the early stages of lymphogranuloma venereum in the male, while Case 2 provides a similar but less complete example of the syndrome. The primary lesion is usually described as a herpetiform vesicle or ulcer, often situated in the region of the coronal sulcus. The lesion, which is painless and often unnoticed by the patient, appears between 3 and 21 days after the infecting coitus and disappears spontaneously in a few days. No palpable scar is produced, but an area of discoloration may result, as in Case 1. The inguinal bubo appears usually between 7 and 30 days, although occasionally months, after infection. These buboes, which are bilateral in a quarter to a third of the cases, have several unusual features which together form an almost pathognomonic picture. Lymph nodes in all sections of the superficial inguinal group are involved, and soon periadenitis with inflammatory obstruction of adjacent lymphatic vessels produces induration of the subcutaneous tissue and of the overlying skin, which may become discoloured. The resulting elongated swelling has its long axis parallel to the inguinal ligament, and is typically grooved in this axis. The principal groove appears to be due to enlargement of lymph nodes above and below the groin fold, which persists owing to the normal adherence here of the superficial fascia to the inguinal ligament. Lesser grooves are due to inflammatory attachment of the skin to deeper structures.

If untreated the bubo begins to fluctuate at several sites owing to patchy suppuration and necrosis. Finally, multiple sinuses without inflamed or ulcerated orifices appear. The external iliac glands often become palpable but do not break down. Constitutional symptoms such as fever and headache are not infrequent. Splenomegaly, arthritis, iridocyclitis, meningitis, or a typhoidal state may occur. Acute abdominal episodes form another rare but well-recognized group of manifestations of systemic involvement (Longmire, 1944). The symptoms may be those of diffuse pelvic peritonitis, or the pain and clinical signs may be more intense in the right upper or lower abdominal quadrants. A local granulomatous lesion may be found at laparotomy, but often only a serous effusion is discovered. Cases 4 and 5 would seem to be examples of this condition. Law (1943) believes that the syndrome which mimics acute appendicitis may occur when the deep iliac and lumbar glands are extensively involved.

Anorectal disease is not as common in the male as in the female, and if present may be due to direct infection following homosexual contact. This does not seem likely in Case 1, in which the infection presumably reached the rectal mucosa via the pelvic lymphatics. Such spread is the rule rather than the exception in the female, for the primary lesions are commonly situated in the upper vagina or on the cervix; as a result of this, pelvic rather than inguinal lymph vessels and nodes become involved in the post-primary stage. This anatomical distribution of the lesions probably accounts for the fact that the early stages of the disease are often symptomless in women. Our Case 3 had no symptoms likely to be due to lymphogranuloma. The vulval ulcer might

represent the secondary genital ulceration described by Greenblatt and Wermer (1945). The very high dilution of this woman's serum at which fixation of complement occurred suggests that the disease had been present for a considerable time, while her consort's symptoms were those usually seen within a few weeks of infection; it seems probable, therefore, that the woman was the infecting partner, especially as it is believed that in women the infectious phase is longer than in men. Although the cause of the cough and haemoptysis in Cases 2 and 3 has not been proved, these symptoms are probably unrelated to the venereal infection.

Proctitis, as seen in very mild form in Cases 1, 3, and 4, may, if the patient is not treated by antibiotics, lead after many months or years to stricture formation. This syndrome, which is commoner in women, is exemplified by Case 6. This patient's recurrent arthritis is similar to the arthritis described in other patients with lymphogranuloma venereum; the knees are among the joints most commonly affected (Longmire, 1944). Many sufferers from lymphogranulomatous strictures also have anorectal or rectovaginal fistulae, which characteristically open internally close to the stricture on its anal side. Another late manifestation of lymphogranuloma seen in women is the condition known as esthiomene, in which ulceration and elephantiasis of the external genitalia produce gross deformities.

The diagnosis in our cases is confirmed by the raised titres of the complement-fixation tests and, in all but one case, by the positive Frei intradermal tests. The Frei test becomes positive usually between 7 and 40 days after the appearance of adenitis, and may remain positive for life. It is uncertain as yet whether antibiotic treatment may cause a reversal. The criteria on which a diagnosis can be made, using the complement-fixation test, are less well established. After investigating this problem, Bedson *et al.* (1949) concluded that, in a patient with symptoms compatible with a diagnosis of lymphogranuloma venereum, a titre of 1 in 32 or over indicates active infection and a titre of 1 in 16 is suggestive of infection. There is no typical leucocyte response to lymphogranuloma venereum or to any particular manifestation thereof. Eosinophilia has been reported, but the presence of parasites cannot be excluded as a cause of the eosinophilia in Cases 2 and 3. Hyperglobulinaemia without other evidence of liver disorder is a well-recognized accompaniment of lymphogranuloma venereum; the gamma fraction largely accounts for the increase, the degree of which is related to the activity and duration of the disease. The greatly increased sedimentation rates sometimes found in lymphogranuloma are probably dependent on this change in the plasma globulin.

The tetracycline group of antibiotics provides specific therapy. In the earlier manifestations of the disease dosages of 250 mg. four times a day for from 15 to 30 days produce complete control of the infection with disappearance of the buboes and healing of open lesions without subsequent recurrence. In the later stages, with strictures, fistulae, and elephantiasis, prolonged antibiotic therapy should precede any surgical procedure. There were no toxic complications from the use of tetracycline in any of the four cases we treated with this drug. The sulphonamide drugs also have some therapeutic action in lymphogranuloma venereum, and the course of the disease in Case 4 was probably modified by the sulphadimidine given him for the suspected urinary infection.

Summary

To the small group of patients recorded as having acquired lymphogranuloma venereum in Great Britain are added two with the inguinal syndrome seen in the immediate post-primary stage.

The cases of two other male patients who illustrate the rare pseudo-appendicitis syndrome, that of a woman with the late anorectal syndrome, and that of a symptomless but probably infectious female patient are also reported.

The recent influx of West Indian immigrants of both sexes and the greater likelihood, with the rapidity of air transport, of males reaching Great Britain in the infectious state may make lymphogranuloma venereum a commoner clinical problem in this country.

Our thanks are due to Mr. R. H. Boggon and Professor J. B. Kinmonth for permission to publish details of cases under their care.

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CAUSE OF ANOMALOUS RESULTS IN THE ERYTHROCYTE SEDIMENTATION RATE USING WINTROBE'S METHOD

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In current clinical practice the erythrocyte sedimentation rate (E.S.R.) is usually measured by either the Westergren method (Westergren, 1921), using citrated and diluted blood, or by the Wintrobe method (Wintrobe and Landsberg, 1935), using oxalated undiluted blood. While the latter method has some practical advantages in that haematocrit readings can be made in the same tube and the oxalated blood specimen can be used for other routine haematological investigations, there is evidence that the Westergren method provides a more reliable index of disease activity and progress (Gilmour and Sykes, 1951; Goldberg, Glynn, and Bywaters, 1952; Goldberg and Conway, 1952; Alexander and Andrews, 1957). These authors have pointed out the occasional failure of the Wintrobe method to reflect the clinical state of the patient when the disease process is very active; the anomaly is seen of a high Westergren rate associated with a normal or near normal Wintrobe rate.

The Wintrobe method continues to be widely used, and it was felt that further information on the incidence and causes of such anomalous readings would be of value.

Incidence of Anomalous Wintrobe Readings

For the past five years all in-patients in this unit have had weekly E.S.R.s measured by both the Westergren and the Wintrobe method simultaneously, together with the