LYMPHOPATHIA VENEREUM IN THE SOUTH AFRICAN BANTU FEMALE

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Lymphopathia venereum is a venereal disease not well known in this country. Amongst Europeans it is extremely rare, but an investigation undertaken at the Baragwanath Hospital reveals that this is not true of the South African Bantu.

Historical. The disease was first described as a specific entity by Durand, Nicholas and Favre in 1913. Further knowledge of it was developed by Frei, who introduced a specific intradermal test in 1925. In 1930 Hellerstrom and Wassen discovered the causative virus. Pus obtained by them from enlarged inguinal lymph nodes of Frei-positive cases was injected cerebrally into monkeys and a meningo-encephalitis produced. From these experimental lesions a virus was obtained with which the disease could be transmitted to animals.

Present Investigation. For a long time the gynaecological wards at Baragwanath Hospital were presented with several unusual pathological conditions of the vulva where no diagnosis could be made. The patients were treated empirically with antibiotics without improvement. A diagnosis of lymphopathia had been suggested in these cases, but no positive response to the Frei test could be evoked. After consultation with the South African Institute for Medical Research, a new batch of antigen was obtained, which in 2 cases gave a strongly positive Frei test. Since then a careful study has been made of 16 fully investigated cases.

All the cases studied were admitted to the hospital under erroneous diagnoses, and only because one was on the look-out for the disease, was the correct diagnosis ultimately made.

Lymphopathia venereum affects relatively young people, especially at the age of the greatest sexual activity. Of the 16 cases 12 were under the age of 40. It is generally agreed that in the vast majority, infection is transmitted through sexual intercourse. The disease occurs in

patients who are prone to sexual promiscuity, and it is therefore not unreasonable to expect that in many cases the other venereal diseases would accompany the lymphopathia. This was borne out in the present investigation, where 5 cases of the 16 were definitely known to have suffered also from both syphilis and gonorrhoea.

The primary lesion of lymphopathia venereum is a small, erosive herpetiform vesicle or infiltrated papule, which is usually painless and appears 2-5 days after exposure on any part of the external genitalia, vagina or cervix. Rapid spontaneous healing takes place and, because of its painless nature, the patient is often unaware of the lesion and the doctor is unlikely to encounter it.

CLASSIFICATION

The clinical features of the disease can conveniently be grouped in the following proposed classification:

(1) Bubonic
(2) Vulval and Clitoral
  (*a*) ulcerative.
  (*b*) elephantiac.
  (*c*) perforating.
(3) Rectal
  (*a*) early.
  (*b*) late.
(4) Destructive
  (*a*) fistula-in-ano.
  (*b*) recto-vaginal fistula.
  (*c*) vesico-vaginal fistula.

(1) *Bubonic.* Since lymphopathia is a disease of the lymphatic system it is not unreasonable to expect bubonic manifestations. Nevertheless, only 2 cases with tender fluctuant masses in the inguinal region were encountered. These represented the acute bubonic type and, if left untreated, the condition would almost certainly have passed into the chronic phase with multiple discharging sinuses, a not uncommon feature in cases of long-standing infection.

(2) *Vulval and Clitoral.* In this group there were 3 distinct types. The ulcerative and the elephantiac were not uncommonly encountered in the same patient. For many years any indolent ulcer of the vulva was called 'esthiomene'. Today this term is confined to the *ulcerative lesion* of lymphopathia (Fig. 1). The ulcer is usually situated in the region of the clitoris or on the surface of the labia minora. The base of the ulcer is usually covered with multiple irregular fleshy granulations, which may bleed if vigorously scraped. Puckering may be observed, which is an expression of the healing process. Occasionally a completely healed ulcer is encountered, exhibiting very marked fibrosis, the contractures of which present a spider's-web appearance.

The *elephantiac lesion* is the commonest vulval type (Fig. 2). Its most striking feature is lymphoedema involving the labia minora and clitoris. Multiple flattened areas are elevated to contrast with intervening sulci, thus imparting a lobulated appearance to the lesion. The sulci are the result of long-standing fibrosis and contracture.

In the *perforating type* the lesion consists of one or more punched-out perforations in the labia minora. These are either circular or oval and have clear-cut

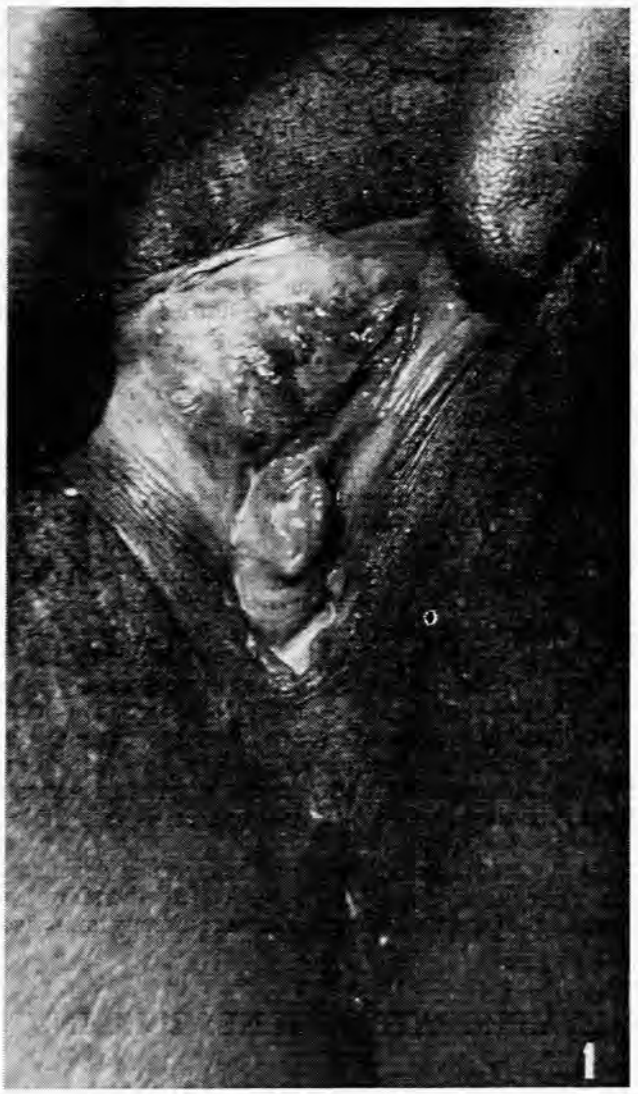

Fig. 1.

edges, as if punched-out. Since lymphopathia is known to destroy involved tissues, it is not surprising that a lesion of this nature is encountered; however, in the perusal of the literature we have not found any description of this type.

(3) *Rectal.* Classically, lymphopathia attacks the rectal region more commonly than any other site. This is also true for the South African Bantu. The most vulnerable sites are the lymphatic channels along the utero-sacral ligaments. At first an effusion into these ligaments takes place; as the disease progresses the effusion is converted into a fibrotic process which encircles the rectum and produces the well-known picture of rectal stricture. Thus the rectum is initially attacked from without, and it is only in the later stages that the mucosa is affected. Generally one does not see the cases in the early stages, or when seen early the diagnosis is usually missed. Two early cases were

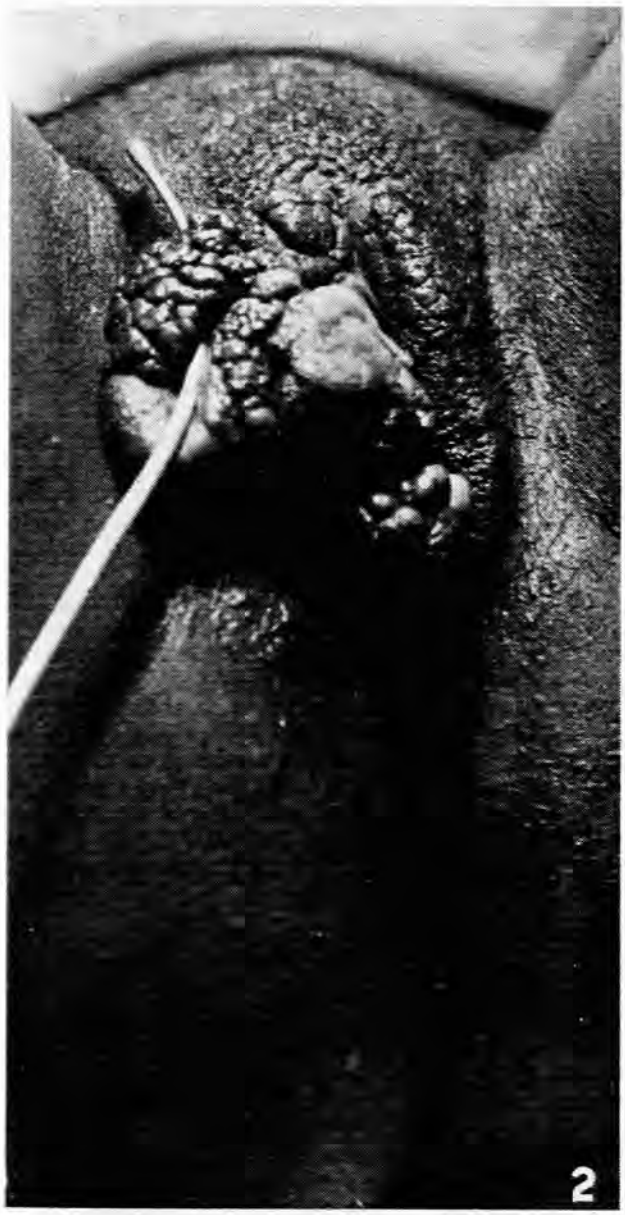

Fig. 2.

encountered in this series, and the diagnosis suspected (and later confirmed) simply because there was no response to antibiotic treatment.

The 2 *early cases* both presented with very gross infiltration along the utero-sacral ligaments and no other clinically detectable pathology. It is felt that if they had been left untreated they would ultimately have entered the chronic phase, with stricture and possibly fistula formation.

Eight *late cases* were encountered (constituting one-half of the series of lymphopathia under report) 3 with rectal stricture only and 5 with stricture and fistula formation. The rectal strictures were situated one or two inches from the anus and varied in thickness.

The presenting symptoms in these cases were: (1) passage of blood and mucus during and after defaecation, (2) pain in anus and rectum during and after defaecation (3) difficulty during defaecation, (4) progressive decrease in the diameter of the stools, and (5) alternating diarrhoea and constipation. There was gross mechanical obstruction to defaecation; yet despite this the general health remained good and there was no evidence of any interference with normal metabolic functions.

(4) *Destructive Type.* Alongside the reparative process in the nature of fibrosis, which is characteristic of lymphopathia, is a progressive process of destruction of tissue. There is a definite tendency towards the breakdown of involved tissues, with the result that sinuses and fistulae are produced, besides strictures.

Fistulae-in-ano and recto-vaginal fistulae. The posterior vaginal wall is much more commonly involved in the destructive process of lymphopathia than the anterior wall. Involvement of the anus may lead to the formation of single or multiple fistulae-in-ano. They are superficially situated and generally end blindly. It is not certain what part secondary infection plays in these destructive lesions.

Recto-vaginal fistulae were situated $\frac{1}{2}$-1 inch from the anus; none were encountered higher up. They vary in size from that of a pin's head to 1-2 inches in diameter. The presenting features of these cases are very much the same as those described under rectal stricture but, in addition, a history of the passage of faeces *per vaginam* is often obtained. As a general rule, when the patient is constipated she passes stools *per rectum*, but during a bout of diarrhoea the faeces escape *per vaginam*.

Vesico-vaginal fistulae. Involvement of the anterior vaginal wall with the production of a vesico-vaginal fistula is rare in lymphopathia. Only one case occurred in this series.

DIAGNOSIS

The diagnosis of lymphopathia venereum is based on the clinical picture outlined above, confirmed by a positive Frei test. The test remains positive for many years, even after adequate treatment. It is stated that the test is positive in 90-95% of cases. It is carried out in the following manner:

With a tuberculin syringe 0·1 ml. of normal saline is injected intradermally in the anterior surface of the left forearm as a control, and an equal quantity of Frei-antigen, prepared from suppurative inguinal lymph nodes, into the right forearm (the injection must be intradermal; a subcutaneous one may produce a negative response). A positive response is manifested by erythema and induration, which reaches a maximum in 48-72 hours. It must be of the order of 1 cm. in diameter or more to be accepted as positive; it is often better felt than seen. The nodule persists for approximately one week, after which it gradually diminishes in size and eventually disappears.

In one case only, what was possibly a general reaction to the test ensued; the patient developed diarrhoea with blood and mucous in the stools. This, however, may have been coincidental.

Investigations

Frei Test. Every patient in the series gave a positive Frei test.

Stool Examinations. No significant results were obtained.

Proctoscopy and Sigmoidoscopy were carried out in all cases where there was no stricture. Eight cases were carefully sigmoidoscoped, the instrument being passed for 20 inches. No pathological condition was detected.

Blood Counts. The haemoglobin was estimated in all cases and no evidence of anaemia was found. The average haemoglobin level was 13·7 g.%. This finding is contrary to the statement of some authors that lymphopathia induces an anaemia (Wassen 1935). From the routine examination of every case it appears that lymphopathia *per se* produces neither leucocytosis nor leucopenia; but the former was evident in one case of secondary infection with salpingitis and another with basal pneumonia. In the differential white-cell count, the only significant feature was that 10 of 14 cases thus investigated had an eosinophil count of 4% or more. In only 1 of the 10 cases were ova of Ascaris encountered.

Liver Function Tests. The total proteins were all between 7 and 9 g.%. Of the 13 cases investigated, 10 had a definite reversal of the albumin/globulin ratio. Hyperglobulinanaemia may thus be a diagnostic aid in lymphopathia. The thymol turbidity was significantly raised in 12 of 14 cases investigated. Thymol flocculation was +++ or ++++ in 9 out of 12 cases, and all cases investigated gave a positive response to the Takata-Ara test. These tests substantiate the reversal of the albumin/globulin ratio. Their exact significance in the Bantu requires further investigation, but it is probable that lymphopathia venereum does produce these changes, and that they may be used as an aid in diagnosis.

Lumbar Puncture was performed in 3 cases only. These random samples did not reveal any deviation from normal, though changes have been described in the literature (Finberg 1949).

TREATMENT

From time to time, various drugs have been used in the treatment of lymphopathia. Frei antigens (Gay-Prieto 1932), tuberculin, antimony (Shaffer *et al.* 1938) and fuadin were all tried, with unsatisfactory results. Then came a phase of heroic radical surgical onslaught, such as permanent colostomies and abdomino-perineal resections.

Sulphonamide Drugs. Many favourable reports on the effects of sulphonamides in lymphopathia have been published (Stein 1940), Schamberg 1941, Graham 1941). For this reason 15 cases in this series were tested against a course of sulphadiazine. In none of them was there any appreciable response.

Penicillin treatment was tried in 10 cases, with uniformly poor results.

Streptomycin was tried in only one case, without any response.

AUREOMYCIN THERAPY

Wong and Cox (1948) found that, although aureomycin had little or no viricidal activity *in vitro*, there was a remarkable protective effect in chick embryos and mice infected with the virus of lymphopathia. Wright *et al.* (1948) concluded that aureomycin is the drug of choice for lymphopathia venereum. Robinson *et al.* (1950) treated 9 cases with unimpressive results; there was some improvement in 3 only. Alergant (1950) presents 6 cases, with improvement in only 4.

Adams (1948) writes: 'The unsatisfactory results obtained with palliative measures in the treatment of lymphopathia in Baltimore led to the practice of more aggressive measures. In line with generally accepted principles that inflammatory conditions of a different aetiology and involving other parts of the bowel should be subjected to resection, removal of the rectum for lymphopathia was attempted, and resection was performed.'

Thus the reports on the efficacy of aureomycin therapy are very conflicting. It is possible that only certain strains of the lymphopathia virus respond to aureomycin. How would the disease react in the South African Bantu? To answer this question all the patients were subjected to aureomycin therapy.

Dosage. The optimum dosage of aureomycin is extremely difficult to determine. For purposes of standardization, all cases received 3 courses of treatment with a break of 4-6 days between the courses. Each course consisted of 250 mg. of aureomycin at 4-hourly intervals for 5 days, a total of 7½ g. In nearly every case the results achieved with one course were as good as with 3 courses. The effects of the drug were noted within 48-72 hours and whatever improvement occurred later was slight as compared with the initial response. It can generally be stated that the more acute the condition the more rapid the response.

Response to Aureomycin

Bubonic Type. In both cases the swelling resolved within 2-3 days. A residual brownish pigmentation remained in both cases, but there was no scarring. Thus the 2 cases of bubonic type, while not responding to sulphadiazine or penicillin, underwent a complete clinical cure with aureomycin within a short time.

Vulval and Clitoridal Type. Of the cases of this type the ulcerative cases responded best. The ulcers, which were insensitive to all other drugs used, healed completely within 2-5 days. Where the ulcers ran a more chronic course, radial scarring remained.

In the elephantiac cases the response was less dramatic. Nevertheless, in nearly every case the lymphoedema was considerably reduced and the persistent discharge disappeared. What remains is a shrunken lymphoedematous lesion, which is non-tender, and symptomless.

Of the cases of this type the least response was noted in the perforating cases. It is in fact not to be expected that an anatomical defect of this nature would be corrected by any drug. Aureomycin in these 2 cases did not materially alter the punched-out holes in the labia, although there was a considerable reduction in the swelling of the labia minora in both cases. The vaginal discharge disappeared.

Rectal Type. The diagnosis in the 2 early cases was only considered after intensive penicillin and sulphadiazine therapy had failed to make the slightest difference

to the condition. On further investigation both cases gave a very strongly positive Frei test. They were then treated with aureomycin. Within 3-4 days the utero-sacral infiltration had almost completely disappeared in both cases, and pain and tenderness on rectal examination had disappeared. It thus seems that in reasonably early cases of the early rectal type a complete cure is possible with aureomycin.

The late rectal cases represent a very advanced stage of lymphopathia venereum, with very gross fibrosis. Until the introduction of aureomycin there was no satisfactory treatment for these patients, except perhaps an extensive surgical procedure. Although one cannot claim a cure with aureomycin, the results obtained show very considerable palliation. Firstly, in all cases complete disappearance of symptoms took place. Pain, difficulty on defaecation, and the passage of blood and mucus in the stools, disappeared in all cases where these were the presenting symptoms. A considerable increase in the diameters of the stools were noted in all cases where a previous narrowing had been complained of. Anatomically, the rectal stricture although still present, imparted a softer feel to the examining finger. Secondly, after aureomycin therapy any surgical procedures undertaken in dealing with the stricture yielded good functional as well as anatomical results.

Destructive Type. In this group also aureomycin therapy is successful in the relief of symptoms. The pain, tenderness and discharge disappear. In recto-vaginal fistula the passage of faeces *per vaginam* ceases. Fistulae-in-ano, although anatomically still present, become asymptomatic.

A striking feature is that, although in none of the cases did the fistula close, the leakage *per vaginam* ceased after aureomycin therapy. The most striking response to aureomycin occurred in a case where spontaneous closure of a vesico-vaginal fistula took place. This case illustrates the importance of administering aureomycin in all cases of lymphopathia before operation, no matter what the nature of the lesion.

THE PLACE OF SURGERY IN LYMPHOPATHIA VENEREUM

Although there is no apparent necessity for heroic surgery in lymphopathia, certain minor surgical procedures are of great value.

The dilatation of rectal strictures in cases of lymphopathia is not entirely without hazard; sudden death due to rupture of the bowel has been recorded. Bleeding during a dilatation generally occurs fairly early in the procedure. It has been repeatedly noticed that after aureomycin therapy dilatation is a relatively easy procedure; there is seldom any bleeding if the dilatation is not taken beyond a no. 20 dilator. This is probably due to the softening of the stricture which occurs after aureomycin. Five cases were dilated, with gratifying results.

Cases of fistula-in-ano were treated by complete excision after aureomycin therapy. All healed well.

Recto-vaginal fistulae were repaired in the usual manner. After aureomycin therapy the fistulae were excised and converted into third-degree tears. The usual perineal reconstruction was then done. Healing was by first intention. Three cases were thus treated.

Although there does not appear to be any need for surgery to the vulva, for psychological reasons excision of a lymphoedematous portion is justifiable. Satisfactory cosmetic results are achieved.

PATHOLOGY

Although the tissue response to invasion by the agent of lymphopathia venereum tends to follow a definite pattern, the microscopic appearance is not patho-gnomonic. The conservative pathologist reports that the appearance of the tissue is consistent with, but not diagnostic of, this infection.

In the elephantiac type the epithelium generally shows considerable hyperplasia with hyperkeratosis. The corium is oedematous and infiltrated with leucocytes, plasma cells, lymphocytes and occasional eosinophils. In some sections giant cells with peripherally situated nuclei are present, but tubercle formation and caseation are absent, which distinguishes the condition from tuberculosis.

In the early phase oedema and cellular infiltration are the predominant features. As the disease progresses fibroblasts appear and subsequent sclerosis and hardening of the involved region occurs. As a direct result of fibrosis, obstruction to the lymphatic flow occurs. Histologically, therefore, dilatation of lymph channels is a prominent feature in the more advanced case.

The above features have been noted in most of the sections examined, irrespective of the site involved.

SUMMARY AND CONCLUSIONS

1. An investigation of lymphopathia venereum in the South African female Bantu is presented.

2. A classification based on the clinical material is suggested.

3. The clinical features are described and the diagnosis is discussed.

4. Various treatments are outlined. It appears that aureomycin is the drug of choice in the treatment of the condition in the South African Bantu.

5. Heroic surgery in lymphopathia appears to have an extremely limited field. Minor surgical procedures, aimed to restore the local anatomy to as normal a condition as possible, seems to be justifiable from both the functional and the psychological point of view.

6. Aureomycin should be administered to all patients before surgery is undertaken.

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