

# STUDIES ON GRANULOMA INGUINALE

## VII. SOME EPIDEMIOLOGICAL CONSIDERATIONS OF THE DISEASE\*†

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Granuloma inguinale as a disease entity is poorly understood and its epidemiology is even less clear. The method of transmission is still in doubt and because or perhaps in spite of this, concepts of transmission have been proposed which are at variance with each other and supported by little evidence. The reasons for this state of uncertainty are two-fold:

(a) It was only recently that the nature of the aetiological agent of the disease became known with any degree of certainty. Although Donovan bodies have been known to be associated with the disease since 1905, when Donovan first described them, it was not until 1943 that it was clearly shown that the Donovan bodies were bacterial in nature. This bacterium, provisionally named *Donovania granulomatis*, could be isolated from cases of granuloma inguinale. Not only did they resemble Donovan bodies morphologically but, when prepared as antigen, they reacted in a positive manner with a high percentage of sera from patients with the disease and not with sera from patients with a wide variety of other diseases (Anderson, 1943; Goldberg, Weaver, Packer, and Simpson, 1953). The isolated bacterium has not yet been shown to be able to initiate the disease when inoculated into many different laboratory animals and human volunteers. Although the Postulates of Koch are still not yet fulfilled, the data are strong enough to allow us to assume the aetiological significance of the *Donovania*, granting that other factor(s) may be necessary for the initiation of the disease.

(b) Because of the genital location of the majority of lesions in granuloma inguinale, the concept developed that the disease was venereal in nature, although there was very little definitive information

to support such a hypothesis. This emphasis upon the venereal nature of the disease minimized efforts to investigate the non-venereal aspects. We will show below that, if a venereal disease is defined as one which is transmitted from patient to patient by close physical contact, usually during sexual intercourse, then there is good evidence that granuloma inguinale may not be venereal. However, because the venereal concept is so well established in the literature, we will briefly review the evidence.

The main points which have been presented in favour of sexual transmission of the disease are:

- (1) History of sexual exposure before the appearance of the lesion.
- (2) Increased incidence of the disease in age groups in which sexual activity is the highest.
- (3) Lesions found on the internal genitalia, such as the cervix, without any other lesions.
- (4) Lesions found only around the anal orifice in patients who practice passive pederasty.
- (5) Genital or peri-genital location of lesions, the commonest site being on or about the external genitalia.

(1) The fact that most patients with granuloma inguinale give a history of sexual exposure before the appearance of the disease is of little value. In any population the frequency of sexual exposure is so great that one would expect to find sexual activity recorded in any sample thereof. Our data indicate that the frequency of coitus and total number of sexual contacts are no greater in persons with granuloma inguinale than in persons belonging to the same socio-economic stratum who have never had granuloma inguinale.

(2) Similarly, the fact that granuloma inguinale is more common in the sexually-active age groups is of little significance as a proof of venereal transfer of the disease. The span of sexual activity, especially

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in the socio-economic stratum in which granuloma inguinale occurs, starts at 5 to 6 years of age and continues until the sixth or seventh decade of life; it is thus to be expected that the majority of those sampled from this population will be in the sexually-active years.

(3) The existence of cases with lesions of the cervix only might at first suggest venereal transfer, but the possibility of the aetiological agent being present in the vaginal tract and inducing lesions cannot be ruled out.

(4) Similarly, the anal lesions observed in passive pederasts are not conclusive proof of venereal transmission. If the aetiological agent were present in the intestinal tract, then these lesions might indicate auto-inoculation rather than venereal transfer.

(5) The high frequency of lesions in the peri-genital or genital regions cannot be questioned. All authors agree that these are the most common sites in which the lesions appear. What is usually not emphasized, however, is that cases with genital lesions only are less common. D'Aunoy and von Haam (1937) reported that, of 294 cases of granuloma inguinale, the lesions were solely genital in only 128 (43 per cent.). Nair and Pandalai (1934) reported that only 39 of 73 cases (53 per cent.) were solely genital, and Rajam and Rangiah (1954) reported that only 478 of 858 cases (56 per cent.) were solely genital. Some patients have non-genital lesions not only near the anus and other parts of the trunk, but also on the forearm, thigh, feet, etc., and in others the sites are mixed.

The data which do not support the venereal transfer of the disease may be listed as follows:

- (1) Occurrence of the disease in very young children and sexually-inactive persons.
- (2) Rarity of the disease in prostitutes.
- (3) Occurrence of non-genital lesions in both homosexuals and heterosexuals.
- (4) Rarity of the disease in the sexual partners of patients with open lesions.

(1) There is little doubt that the disease does occur in sexually-inactive individuals. It has been reported in a 2-year-old child as well as in newborn infants.

Nair and Pandalai (1934) reported the case of an adult male who had had his penis amputated 16 years before acquiring the disease. It is reasonable to assume that methods of transmission other than venereal were at work in these cases.

(2) Pfeiffer (1939) stated that in his experience prostitutes rarely had the disease. This is also true in Jamaica where we have observed very few cases in prostitutes (Goldberg and Sutherland, n.d.).

(3) Various authors have reported that cases with solely non-genital lesions occur with a low but regular frequency. We have seen several such cases with positive smears for Donovan bodies. Many authors have noted anal and peri-anal lesions in male homosexuals. Marmell (1958) reported that nine of ten patients with granuloma inguinale of the anus were admitted passive pederasts, and in a review of the literature cited 44 out of 48 cases of anal granuloma inguinale in which passive pederasty was admitted. Goldberg and Bernstein (1964) reported granuloma inguinale of the anal region in two homosexuals who denied ever having had a heterosexual contact.

(4) The incidence of granuloma inguinale in the sexual partners of those with the disease is very low. Packer and Goldberg (1950) reported that the sexual partner was infected in only two of approximately 500 cases of granuloma. Allison (1946) reported that only one sexual partner was infected in over 200 cases. Sutherland (1963) found only six in 1,000 cases in Jamaica. Greenblatt, as reported by Barrow (1958), stated that in his experience of over 300 granuloma inguinale patients, only a half-dozen or so of the marital partners also had the disease. Tiedemann (1962) was able to follow several individuals with granuloma inguinale with open lesions and their sexual partners for varying periods of time (before the antibiotic era). In one case the couple were examined repeatedly for approximately 3 years, and the sexual partner did not develop granuloma inguinale in spite of continued sexual contacts with the patient. It would seem therefore that, in the United States and Jamaica at least, the sexual transmission of the disease is rare.

A few authors nevertheless vigorously maintain that conjugal transmission of the disease is not so rare. Serma (1957) found nineteen conjugal cases in 157 patients with the disease. Rajam and Rangiah (1954) reported that thirty partners of 250 patients were affected. Rake (1955) stated that he was shown cases in Madras in which husband, wife, and children were all infected with granuloma inguinale, but unfortunately, he did not state whether these lesions exhibited Donovan bodies. In a personal communication, Rangiah (1962) stated that, in his experience in southern India, conjugal cases of granuloma inguinale were not rare. Prof. Rangiah is a very experienced venereologist and it is unlikely

that his cases are misdiagnosed. It is possible that more than one organism may cause the disease, although at this time there is no evidence to support this view, and we still do not feel that the available evidence supports the concept of venereal transmission.

If the disease is not venereal and the habitat of the organism is not the skin lesions, what evidence is there to support an alternative hypothesis? De-Montreun and Goodpasture (1933) isolated a bacterium (a member of the genus *Aerobacter*) from the lesion of a case of granuloma inguinale. They were not able (by the intradermal inoculation of the bacterium into laboratory animals) to produce lesions comparable to those observed in man, but were so impressed with the morphological similarity that they suggested that the *Aerobacter* organism (found in the faeces) was the aetiological agent. They further pointed out that the lesions of granuloma inguinale were usually located in areas where faecal contamination could easily occur. Anderson, De Montreun, and Goodpasture (1945) isolated a bacterium from the lesions of three cases of granuloma inguinale, which was found to react with a large number of sera from proven cases of granuloma inguinale but not with sera from a wide variety of controls. Later, Rake (1948) proposed a similar faecal habitat, although his reasoning was based on entirely different grounds. He and his associates, using an antigen produced from a modified strain of *Donovania granulomatis*, noted that sera from patients with varicose ulcers reacted with their antigen. Additional work established the fact that an antigen prepared from *Klebsiella pneumoniae* (a bacterium closely related or perhaps identical with *Aerobacter*) would react with sera from patients with granuloma inguinale. This antigenic similarity so impressed Rake that he put forward the hypothesis that the *Donovania* were members of the *Enterobacteriaceae*, postulating that the *Donovania* were extremely tissue-trophic forms of an enteric organism. Goldberg and others (1953) were able to confirm that the *Donovania* (certain strains at least) had a common antigen with some members of the *Enterobacteriaceae*, but that there was antigenic variation among strains (Goldberg, 1954).

Goldberg (1959), using four strains of *Donovania granulomatis*, found that a low oxidation-reduction potential was necessary for growth, and that the egg-yolk material required for *in vitro* growth of the *Donovania* may be replaced by enzymatic digests of bovine albumin or soya meal. These results were felt to strengthen the postulated faecal habitat of *Donovania*. Goldberg (1962) reported that he was

able to isolate a bacterium from the faeces of a patient with granuloma inguinale; and this bacterium was morphologically similar to *D. granulomatis*, had identical cultural characteristics, and when prepared as antigen reacted with sera from patients with granuloma inguinale to the same degree as antigens prepared from known strains of *D. granulomatis*. In addition, this bacterium was shown (by the use of complement-fixation tests utilizing unabsorbed and absorbed antisera) to contain antigens similar to the prototype strain of *D. granulomatis*.

These results strengthened the hypothesis that the *Donovania* are faecal organisms and that the natural habitat is the intestine rather than the skin.

The question naturally arose: If the *Donovania* exist as faecal organisms, how are they transferred to the skin, particularly to the skin on or about the genital area? There seemed to be two possibilities: direct contact, such as occurs during rectal intercourse, and indirect contact, such as would occur if the vaginal tract was contaminated by faeces or faecal organisms. This latter possibility might allow transmission during normal coitus.

During the past years, in interviewing patients with granuloma inguinale, we noted that a high percentage admitted to heterosexual rectal coitus. Because the number was small, we were hesitant to draw any conclusions until we had more data concerning this type of sexual activity in the same socio-economic stratum as that of the granuloma inguinale patients. To determine the extent of heterosexual rectal coitus, 525 male Negro patients were interviewed in two venereal disease clinics, 273 at Kingston, Jamaica, and 250 at the Social Hygiene Clinic of Chicago, Illinois. The interview lasted 60 to 90 minutes and questions pertinent to the sexual activities of the patient were asked. Table I (opposite) shows that heterosexual rectal coitus is not a rare event.\* In the Kingston sample, 24.4 per cent. of the patients had had heterosexual rectal coitus at least once and in the Chicago sample, 25 per cent. In both groups only about 20 per cent. of these indulged "occasionally" or "regularly". It is thus apparent that, while heterosexual rectal intercourse represented only a relatively small percentage of the total sexual activity of the persons concerned, it occurs frequently enough to account for the transmission of the disease. Rectal intercourse might account for the entire transmission of the disease, but it seems probable that other methods are also in operation. Previous attempts to isolate gonococci

\* (Homosexual rectal coitus is also not rare. 17 per cent. of the patients in the Chicago sample admitted this type of activity during their adult lives. This aspect will be discussed in another paper.)

TABLE I  
HETEROSEXUAL RECTAL COITUS—BY MALES

Venereal Disease Clinic	Age Group (yrs)	Frequency					
		Never	At least Once	Six times or Less	Occasionally	Often	Not Stated
Kingston, Jamaica	16-20	47	22	11	1	2	8
	21-25	66	42	23	0	6	13
	26-30	37	14	6	1	3	4
	31-35	19	3	1	0	0	2
	36-40	7	3	3	0	0	6
	41+	2	3	3	0	0	0
	Unknown	1	1	1	0	0	0
	Total	179	94 (34.4%)	48	2	11	33
Chicago	16-20	30	11	7	0	2	0
	21-25	66	23	15	2	1	5
	26-30	40	15	10	0	4	1
	31-35	19	6	6	0	0	0
	36-40	11	1	1	0	0	0
	41+	11	2	2	0	0	0
	Total	177	58 (24.7%)	41	2	7	6

from the female vaginal tract had indicated that enteric organisms were present. In order to estimate the occurrence of enteric bacteria in the vaginal tract, 793 female patients were selected at random at the Chicago Social Hygiene Clinic, and the venereal disease clinics of St. Louis and Kingston, Jamaica. During the pelvic examination of these patients, cervical specimens were obtained using sterile cotton swabs. The swabs were immersed in 2 ml. sterile heart infusion broth and transferred to the laboratory. On arrival, they were gently rotated in the broth and the fluid removed by gently pressing the swab against the side of the tube. The tubes were then incubated at 37°C. for 24 hours and aliquots placed both on eosin methylene blue agar and on 5 per cent. sodium chloride heart infusion agar. After 24 hrs' incubation at 37°C., the EMB plates were examined and all colourless colonies, as well as those showing lactose fermentation, were picked off and inoculated into Kligler's slants. Gram stains were also done at this time. Gram-negative, non-spore-forming rods, fermenting dextrose and lactose, and the production

of acid and gas were considered to be coliform. Other enteric organisms were identified by routine methods. The 5 per cent. salt-agar plates were incubated for an additional 24 hrs and after this period all colonies which appeared were picked off, Gram-stained, and examined microscopically. The identification of the staphylococci was done on morphological grounds. Table II shows that a high percentage of the 793 females sampled, regardless of geographical area, had enteric bacteria in the vaginal tract; 48 per cent. had coliform organisms and in an additional 10 per cent. other enteric bacteria were present. (Many, of course, had both.) Thus 58 per cent. had enteric bacteria present on or about the cervix at the time of examination. It is likely that, if the vaginal area closer to the orifice had been sampled, even greater percentages would have been shown to be contaminated. The data clearly indicate that, in the socio-economic stratum sampled, enteric organisms are present in approximately six out of ten females, enough to indicate that this may be another method of transmission of the *Donovania*. In 64 per

TABLE II  
ISOLATION OF VARIOUS BACTERIA FROM THE VAGINAL TRACTS OF FEMALE PATIENTS FROM THREE VENEREAL DISEASE CLINICS

Clinic	No. of Patients	Coliform or Other Enteric Bacteria		Negative for Coliform Positive for Other Enteric Bacteria		Staphylococci	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Chicago	440	235	53.4	45	10.2	285/394	71.9
St. Louis	69	29	42	10	14.5	18	26
Kingston, Jamaica	284	117	41.1	24	8.5	21/43	50
Total	793	381	48	79	10	324/506	64

cent. of the females sampled staphylococci were also present in the vaginal tract; 7 per cent. were coagulase positive, an indication of pathogenicity. The presence of pathogenic cocci in the vaginal tract with the possibility of superficial infection always present may be one method by which a weakly invasive organism may enter the tissues and initiate further changes.

We have also found that fully 50 per cent. of all patients with granuloma inguinale that we have tested show a diagnostically positive serological test for lymphogranuloma venereum (complement-fixation test with Lygranum antigen titre of  $>1:40$ ). There is little doubt that, in the socio-economic stratum in which granuloma inguinale is found, multiple venereal diseases infection tends to occur.

### Discussion

Rectal coitus, both hetero- and homosexual in nature, is probably much more common than most societies are willing to admit. In homosexuals, rectal intercourse seems to be the most common form of sexual activity. Thus, it should not surprise us, if we consider granuloma inguinale to be a faecally transmitted disease, to find that the literature on granuloma inguinale contains numerous references to anal lesions in passive pederasts. De Souza Araujo (1917) reported five passive pederasts among 59 cases of granuloma inguinale. Vogel (1928) related the high incidence of granuloma inguinale in the Marandmois tribe of Dutch New Guinea with the widespread practise of pederasty and uninhibited sexual orgies. Serma (1957) reported three pederasts with anal lesions in 157 cases. Secca (*see* Forkner, Coats, Grace, Rake, and Speiser, 1955) stated that, while the disease was somewhat rare in Brazil, there was a widespread opinion among physicians that it was definitely a venereal disease and in many cases connected with homosexual practices. The findings of Marmell (1958) and of Goldberg and Bernstein (1964) are reported above.

Rectal coitus is undoubtedly much less common among heterosexuals than among homosexuals, but is still practised to an appreciable extent. Peruvian pottery indicates that this type of sexual activity was well known in ancient times. The *Kama Sutra* (trans. S. C. Upadhyaya, 1961), states that ". . . The people of the south also indulge in 'Adhorata' or 'the congress in the anus' (it can be indulged in either with another man or another woman. . .)".

It is interesting to note that in southern India the incidence of granuloma inguinale is much higher than elsewhere. Jensen (1953) reported that 25 of 45 females with gonococcal proctitis, admitted to the

practice of rectal coitus. The Institute for Sex Research (Kinsey Group) found that 6.8 per cent. of 132 white males with 0 to 12 years of schooling had had rectal coitus (personal communication).

In view of the data presented above, a tentative concept of the aetiology, epidemiology, and transmission of granuloma inguinale may be expressed as follows:

Granuloma inguinale is a specific, granulomatous reaction in the skin of the host to the presence of a bacterium, *Donovania granulomatis*. The cellular response of the host to the presence of the *Donovania* is by the production or migration of monocytes into the area of involvement. The presence of the *Donovania* within these monocytes (phagocytosis?) results in the Donovan body which is pathognomonic for the disease. The normal habitat of the *Donovania* is the intestine where it apparently causes no pathological changes. When conditions are appropriate and the bacterium is introduced into the skin the sequence of changes which results in clinical lesions is initiated. The exact conditions necessary for the *Donovania* to initiate growth are not known, but trauma and/or previous or concurrent bacterial infections are likely possibilities. The actual transmission of the bacterium from the intestinal tract to the skin could occur either by auto-inoculation or by venereal transfer.

#### (1) AUTO-INOCULATION

(a) *Associated with Coitus*.—Before the sexual act, the *Donovania* may be mechanically transferred from the intestine to the genital area and during sexual activity the bacterium may be introduced into the skin. This would not be venereal transmission in the strict sense, for the transfer is not from patient to patient. A similar situation would arise with those who practise passive pederasty.

(b) *Not associated with Coitus*.—It is possible that, in some sites, the cervix for example, the bacteria are introduced by faecal pollution and non-sexual trauma or infection may lead to the production of clinical lesions of granuloma inguinale.

#### (2) VENEREAL TRANSFER

(a) *Associated with Normal Heterosexual Coitus*.—It is possible that a contaminated vaginal tract might be the means by which the organism is transferred from one individual to another. This may also apply to those who indulge in active pederasty.

(b) *Material transferred from a Lesion to the Sexual Partner.*—This is true venereal transfer, which we believe to be rare.

This widened concept of the transmissibility of granuloma inguinale would explain the following problems:

(1) The rarity of granuloma inguinale in the sexual partners of those with the disease. The rare sexual partner who does have the disease could have acquired it at the same time as did his partner, or they may have acquired it later, not from the lesions but from the same area that first supplied the bacterium for introduction into the patient.

(2) The sporadic appearance of cases in areas in which there is little or no known granuloma inguinale.

(3) The infrequency of cases in the higher socio-economic (more hygienic) levels.

(4) The rarity of the disease in prostitutes; most prostitutes douche regularly, and this would tend to reduce faecal contamination of the vaginal tract.

(5) Anal lesions in passive pederasty; this mode of sexual activity occurs in an area heavily contaminated with faecal material and subject to trauma during the act.

This hypothesis would not, however, explain the familial occurrence reported in southern India. Until more is learned about this particular situation, further discussion would be unrewarding.

### Summary

The pertinence of previously published data to the mode of transmission of granuloma inguinale is discussed. It is concluded that venereal transmission of the disease is not consistent with the observable facts. The evidence presented to support the faecal habitat of *Donovania granulomatis* is believed to be strong enough to warrant the assumption that the *Donovania* are essentially faecal organisms, with their normal habitat in the intestinal tract. In two venereal disease clinic population samples (Kingston, Jamaica, and Chicago, Illinois), heterosexual rectal intercourse had been practised by 25–34 per cent. of those interviewed, often enough to account for the transmission of the disease. In addition, enteric bacteria were isolated from the vaginal tracts of 58 per cent. of the female patients in the same clinics. These findings favour the concept that the disease may be initiated by auto-inoculation by a faecal organism rather than by venereal transmission,

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### Étude du granulome inguinal

#### VII. Considérations épidémiologiques

##### RÉSUMÉ

On discute la relation des données déjà publiées sur la question de la transmission du granulome inguinal. On en tire la conclusion que les faits observés n'indiquent pas que cette maladie peut être transmise par voie vénérienne. Le témoignage de l'habit fécal du *Donovania granulomatis* semble établir que ces organismes habitent les intestins.

Parmi la clientèle mâle de deux cliniques anti-vénériennes (à Kingston, Jamaica, et à Chicago, Illinois), 25 à 34% des malades examinés reconnurent avoir pratiqué la pénétration rectale hétérosexuelle assez souvent pour expliquer la transmission de l'infection.

La bactérie entérique fut isolée des vagins de 58% des femmes fréquentant les mêmes cliniques.

Ces données supportent l'idée que cette maladie peut commencer par l'autoinoculation d'un organisme fécal et non pas par la transmission vénérienne.