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A CLINICAL STUDY ON 29 CASES OF DEBATABLE STS AND TPI SEROREACTIONS IN GREENLAND

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Abstract. Some doubtful lipid-serological reactions (STS) in Greenlandic patients occasioned a more routine study of the sera by TPI. This disclosed a large number of persons who, despite a negative or faintly positive STS, had a positive or faintly positive TPI, yet no history of syphilitic infection. Twenty-nine persons of this category and 109 of their primary and secondary contacts were subjected to a careful clinical and anamnestic venerealogical study. Eleven of the 29 patients and 12 of the 109 seronegative contacts had or had had symptoms which could not be rejected as syphilitic, but there was no clinical evidence of syphilis in any case. Owing to an extraordinarily high incidence of gonorrhoea and owing to the extensive use of antibiotics, it is reasonable to assume, but has not yet been proved, that we are dealing with syphilitic infections which have been masked—and possibly cured—by antibiotics at a very early stage.

The first report on syphilis in Greenland appeared in 1829 (11). During the period 1872–90 about 50 cases occurred in the village of Arsuk near the cryolith mine of Ivigtut (3, 5). The next time that syphilis was diagnosed in Greenland was not until 1947, and the epidemic, this time at Frederiksdal, was limited to 6 cases (12).

During the subsequent 18 years only sporadic cases occurred. In the next epidemic, in 1965, 13 cases of fresh syphilis were diagnosed in the three medical districts of Southern Greenland (15). This epidemic was apparently contained and controlled (15). Nevertheless, several new cases of syphilis were found during the subsequent years, where the incidence of syphilis in Greenland has been about seven times higher than in Denmark in 1972, per 10 000 inhabitants (Table I).

The ever-increasing use of antibiotics during recent years, covering 8 000–9 000 penicillin-treated cases of gonorrhoea annually, may also, as stated by Lomholt & Berg (9) and by Aagaard Olsen (15), have created a possibility of the occurrence of numerous antibiotic-masked cases.

However, there have been only a very few studies to elucidate the extent and significance of antibiotic masking. Siboulet & Egger (18) demonstrated primary or secondary syphilis in 77 out of 9 057 patients with gonorrhoea who were monitored for more than 3 months. In a therapeutic trial in the Rudolph Bergh Hospital, Copenhagen, Hallinger (4) demonstrated that 1 g probenecid combined with 5 mega units sodium penicillin G could suppress primary syphilis for from 4 to 11 weeks in 7 out of 8 patients. This has been the standard treatment for gonorrhoea in Greenland since 1964. In the eighth patient there was still no clinical recurrence or lipid-serological reactivity at the end of 17 weeks, only TPI reactivity.

This combination of a negative STS with a positive TPI is a well-known serological finding months or years after antibiotic treatment of early, especially secondary syphilis.

Some doubtful lipid-serological reactions in Greenlandic patients occasioned a more routine study of the sera by TPI. In this way a fairly large number of persons were found showing a negative (or very faintly positive) STS and a positive or faintly positive TPI, but whose history gave only atypical or no signs of syphilis (Table II).

The reasons why the occurrence of atypical cases of syphilis may be expected especially in Greenland are, apart from the increasing use of antibiotics (17). The Greenlanders often do not consult a doctor for genital ulcers (9). The promiscuity among parts of the population and the intense traffic between the various municipalities during recent years have afforded a good soil for the spread of venereal

Table I. *Annual number of cases of syphilis in Greenland, 1965–1972*

1965	1966	1967	1968	1969	1970	1971	1972
28	4	9	5	4	11	37	195

diseases. Moreover, the health authorities have to contend with great difficulties. There are no doctors specialized in venereal diseases, and in the villages the treatment of gonorrhoea is mainly in the hands of midwives who have a very limited medical education.

Up to 1969 only "classical", i.e. clinically and serologically typical, cases of syphilis had been diagnosed in Greenland.

Before I arrived in Greenland in August 1969 three cases of primary syphilis and one case of secondary syphilis had been diagnosed, and 24 persons had been found to exhibit the above-mentioned combination of a negative STS with a positive TPI, and without any history of syphilitic infection.

A priori it was not known whether patients having these serological characteristics, called STS −/TPI + below, represented: (1) very fresh cases of syphilis in which TPI reactivity had just started to appear; (2) somewhat older cases subjected to such intensive antibiotic treatment for other diseases that

Table II. *Results of TPI test on sera from Greenland, 1965–1970*

Non-reactive: < 20 %, weak reactive: 20 % ≤ 49 % immobilisation, reactive: ≥ 50 % immobilisation

Year	No. of sera	Non-reactive in TPI test		Weak reactive in TPI test
		n	%	*n*
1965	468	184	39.3	24
1966	177	152	85.9	8
1967	105	90	85.7	7
1968	104	84	80.8	5
1969	1 233	982	79.6	56
1970	1 516	1 023	67.5	62
Dec. 1970	92	80	87.0	2

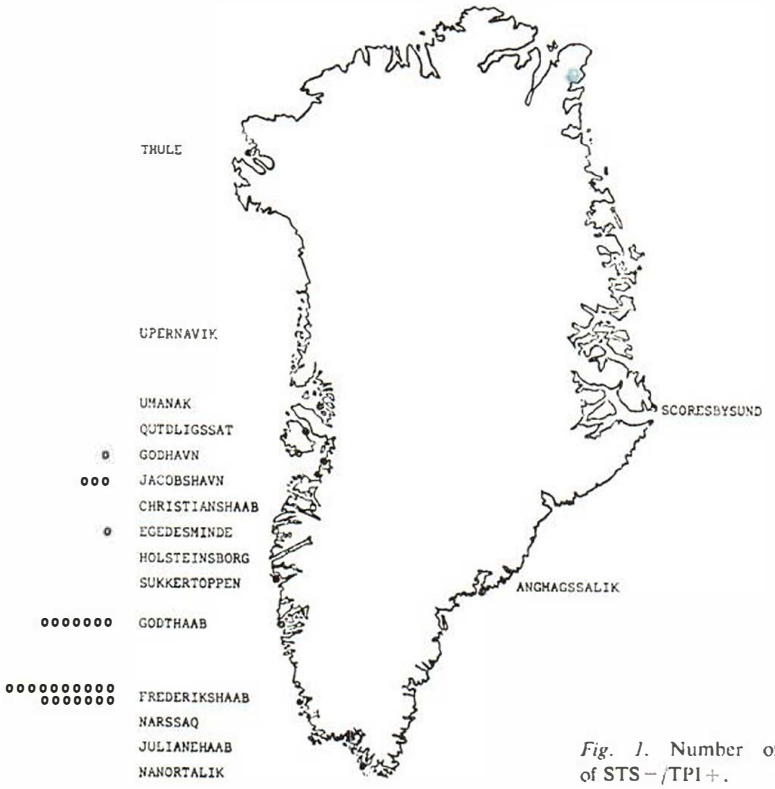

Fig. 1. Number of STS −/TPI + patients. o, One case of STS −/TPI +.

	Reactive in TPI test		Inconclusives	
%	*n*	%	*n*	%
5.1	34	7.3	226	48.3
4.5	6	3.4	11	6.2
6.7	4	3.8	4	3.8
4.8	4	3.8	11	10.6
4.5	37	3.0	158	12.9
4.1	26	1.7	405	26.7
2.2	7	7.6	3	3.2

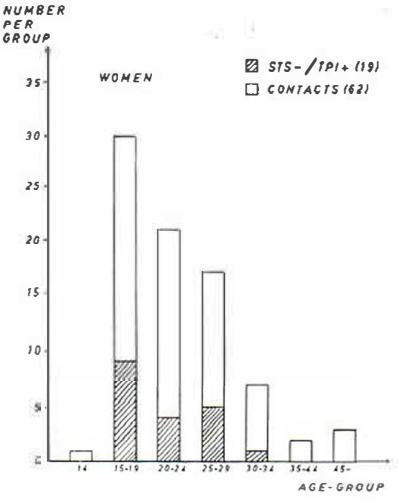

Fig. 2b. 81 women divided into age groups.

it had completely or almost suppressed the lipid-serological reactivity, or (3) hitherto unknown examples of non-specific TPI reactivity.

If these questions were to be answered, the history had to be supplemented with respect to clinical symptoms, including the Herxheimer reaction, and medication. A thorough venereological study had to be carried out and new blood samples had to be obtained. As many contacts as possible had to be traced and examined.

MATERIAL

In five districts of Western Greenland I examined clinically 21 out of the 24 STS−/TPI+ patients and 117 out of their 219 known contacts (Fig. 1). The majority of patients examined were located in that area where the syphilis epidemic took place in 1965.

Eight of the contacts proved to belong also to the category STS−/TPI+. Thus, the material which forms the basis of the following analysis was increased to 29 STS−/TPI+ patients and 109 totally seronegative contacts.

Age distribution and sex ratio

The age and sex distributions are given in Fig. 2*a* and *b*.

Tracing of contacts

Tracing of contacts went back at least 1 year. Some of the patients could even state the names of their sexual partners within the past 4 years. All the traceable contacts, a total of 109 or almost 50% of all, were examined.

Twenty out of the 29 STS−/TPI+ patients were primary or secondary contacts to one or more of the other STS−/TPI+ persons, whereas no information was available about

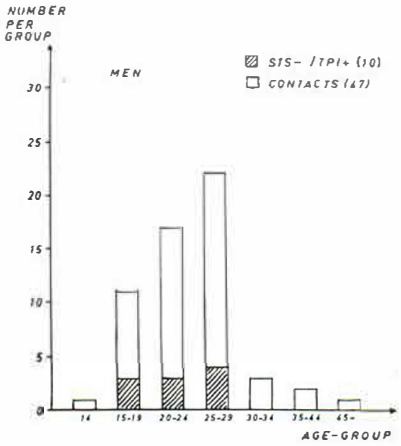

Fig. 2a. 57 men divided into age groups.

Table III. *Clinical symptoms*

	STS−/TPI+ ♂	STS−/TPI+ ♀	Serol. neg. contacts ♂	Serol. neg. contacts ♀
Genital ulcer	0	0	2	2
Genital scar	3	0	0	0
Anal ulcer	0	0	0	2
Balanoposthitis	0		3	
Erosion of the cervix		1		1
Herpes genitalis	0	0	1	0
Condyloma acuminatum	0	1	2	0
Molluscum contagiosum	1	1	3	0
Stomatitis	0	0	0	1
Fibroma of tongue	0	0	0	1
Local lymphadenitis	0	1	1	0
Total	4	4	12	7

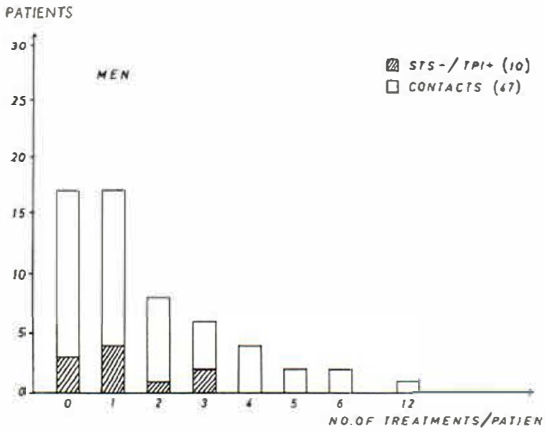

Fig. 3a. Number of standard treatments for gonorrhoea per male patient, 1965–69.

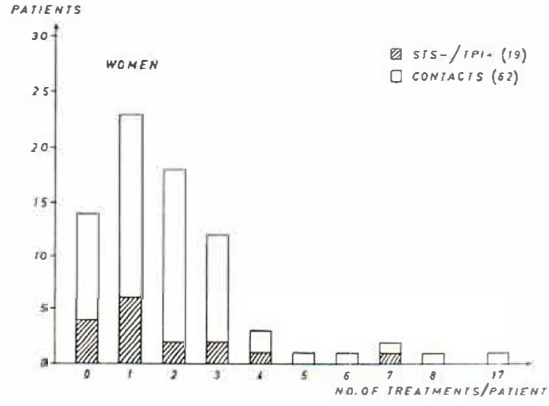

Fig. 3b. Number of standard treatments for gonorrhoea per female patient, 1965–69.

sexual contact with the remaining 9 STS−/TPI+ patients or between these 9 mutually. The patient who had secondary syphilis was not known to have been in sexual contact with any of the 29 STS−/TPI+ patients.

Serological findings

Thirteen of the patients designated as STS−/TPI+ were completely negative lipid-serologically. 1 patient was KR 1, but WR and MR negative. 15 patients were WR −, KR −, and MR ±. The TPI reactivity ranged from slightly over 20% to 100% immobilization. In 13 cases it was ≥ 50%. For details of the technique, consult Nielsen & Reyn (13).

Clinical symptoms

The present study disclosed the changes shown in Table III. None of these findings was suspicious at the time of investigation. None of 9 dark-field examinations disclosed *Treponema pallidum*. There was a history of genital ulcers during the previous months of 1969 in another 6 of the STS−/TPI+ patients and in 2 of the seronegative contacts.

Antibiotic consumption

Antibiotics are defined here as antibiotics with antisyphilitic action. The antibiotic therapy prescribed by doctors was analysed for the period 1965–69 (Figs. 3 and 4) and separately for the two previous, presumably most important years, 1968 and 1969 (Table IV). These must be minimum figures, since non-recorded self-prescribed drugs may have been taken, especially in the villages.

In the analysis of the antibiotic therapy before the positive TPI was ascertained, a distinction is made between treatment of gonorrhoea and other antibiotic treatment.

1. *Treatment of gonorrhoea*

Some 40 (70%) of the men and 67 (83%) of the women had been treated, once or more times, for gonorrhoea during the period 1965–69 (Fig. 3*a* and *b*).

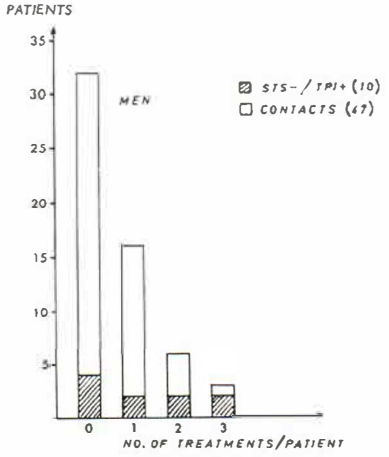

Fig. 4a. Treatment by antibiotics for other diseases, 1965–69, males.

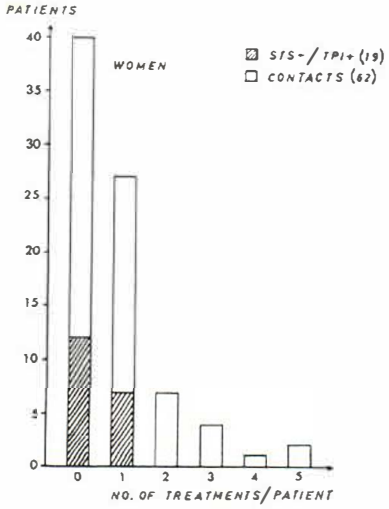

Fig. 4b. Treatment by antibiotics for other diseases, 1965–69, females.

The treatment used seems to have been the standard treatment recommended in 1964, i.e. 1 g probenecid combined with 5 mega units sodium penicillin G. Because of penicillin allergy one patient had received tetracycline instead and another one Ledermycin.

2. *Other antibiotic medication*

As is apparent from Fig. 4*a*, *b*, 25 (44 %) of the men and 41 (51 %) of the women had received antibiotics for other diseases (often tonsillitis or pyoderma) during the period 1965–69.

The antibiotics used were: Sodium penicillin G in doses ranging from 1 mega unit × 1 to 2 mega units × 14 i.m. Procaine penicillin in doses from 600 000 units × 3 to 1 mega unit × 5 i.m. Phenoxy-methyl penicillin K tablets of 500 000 units × 3–6 for up to 6 days, and tetracycline 1–1.5 g × 7 by mouth.

Antibiotic treatment 1968–69

Table IV gives the analysis of the antibiotic consumption for 1968 and the first approx. 9 months of 1969 (up to my arrival).

From this table it is apparent that the STS −/TPI + patients had received fewer antibiotic treatments than the serologically negative controls, though the difference is not significant.

Comments. According to Aagaard Olsen's calculations (16) of the delivery of antibiotics to Greenland, single persons aged 15 years and over were "allotted" in 1968 and 1969 about 3 times as many antibiotic treatments as the patients of the present material could be found to have had received. Accordingly, there is a statistical basis for the assumption that they have also received non-recorded antibiotic treatment.

Four of the STS −/TPI + and 14 of the contacts had not received any form of antibiotic therapy in 1968–69 before the positive TPI was ascertained. Unfortunately at least 18 of the STS −/TPI + patients had received antisyphilitic treatment during the last few months prior to the present study.

In 14 cases temperature curves were available from the institution of this antisyphilitic therapy. Neither the history nor these temperature curves afforded any evidence of a Herxheimer reaction.

Other drugs

To assess whether the STS −/TPI + patients might be hitherto unknown examples of non-specific TPI reactivity, it was important to investigate whether they had received drugs which might be imagined to have affected the serological reactions, e.g. corticoids (2) or metronidazol (1).

Table V lists the information given about such treatment during the period 1965–69. It concerns 12 STS −/TPI + patients and 41 serologically negative contacts, whereas according to the information at hand the remaining persons had not been treated by such drugs.

As may be seen, none of the STS −/TPI + patients had been treated with metronidazol or with corticosteroids. Psychotropic medication, if any, had been mainly by meprobamate.

DISCUSSION

In the present study it was *a priori* not particularly likely that clinical signs of syphilis would be demonstrable, as at least 27 of the 29 STS −/TPI + patients concerned had received either antisyphilitic treatment (procaine penicillin 600 000 units × 10 in two series with an interval of 14 days) or antibiotics for other diseases within the past 2 years. Entirely fresh infections may be cured by smaller doses and more short-lasting treatment (6, 8, 10). At all events, it was of great importance to try to decide whether the STS −/TPI + patients represented cases of syphilis cured or suppressed by coincidental antibiotic therapy or hitherto unknown examples of non-specific TPI reactivity.

A retrospective diagnosis of syphilis in Greenland has to rest upon a number of uncertain criteria.

The age distribution and sex ratio of the present material are characteristic of a venereal clientele in Greenland (9).

Despite the intensive antibiotic therapy that the majority had received, there must have been frequent possibilities of transmitting infection because of the pronounced sexual activity. None of the STS −/

Table IV. *Antibiotic treatment (1968–69) in 29 STS −/TPI + patients and 109 seronegative contacts*

	STS −/TPI +	Serol. neg. contacts
Number of standard treatments for gonorrhoea	38	150
Number of treatments by antibiotics for other diseases	9	75
Total number of treatments by antibiotics	47	225
Mean number of treatments per patient	47/29 = 1.6	225/109 = 2.1

Table V. *Drugs other than antibiotics during the period 1965–69*

	Number of treatments	
	STS −/TPI +	Serol. neg. contacts
Antacids	1	10
Antihistamines	1	4
Corticosteroids	0	1
Metronidazol	0	3
Psychotropic drugs	1	13
Phenylbutazone	0	2
Salicylates	5	5
Sulphonamides	1	15
Vagitoria	1	3
Various drugs	6	14
Total number	16	70

TPI + patients of the present material had had known contact with persons having "classical" syphilis, but among STS −/TPI + cases found later the author is aware of at least one definite example of such contact.

Where clinical symptoms and signs were present, they were either atypical or they were other diseases, such as condyloma acuminatum and molluscum contagiosum. More importance can be attached to the attenuation of the serological reactions following antibiotic therapy that could be demonstrated in 15 of the cases.

The diagnosis antibiotic-masked syphilis had to be considered more likely in some cases than in others, but it could not be definitely excluded on the basis of the data available in any of the STS −/TPI + patients.

Prior to 1965 there had been minor epidemics of syphilis in the towns of the south-western coast. During recent years, cases of classical syphilis as well as of STS −/TPI + have been scattered all over the inhabited coast of Greenland.

In a population with many cases of syphilis and a large consumption of antibiotics, there must be most chances of finding signs of syphilis in those persons who have received the fewest antibiotic treatments. The STS −/TPI + patients may be one such group.

The scepticism among the doctors of Greenland as to whether the STS −/TPI + patients have in fact had syphilis is presumably due to the relatively large number of cases of STS −/TPI + found during the period 1965–69 (7) plus the fact that some of the rubber stoppers used had given rise to false positive TPI reactions.

The Treponematoses Department, Statens Serum-institute, Copenhagen, where all the serological tests were made, investigated this problem for the first 6 months of 1970 and found that if the blood samples as recommended had been send in polystyrene tubes with polypropylene stoppers, there would possible have been 17 fewer weak reactive sera—and two less reactive sera in the TPI test (Table II).

In December 1970 nearly all tests were sent in plastic materials. The last line in Table II shows the results.

However, there does not seem to be any reason for doubting the specificity of the majority of the reactions for this so-called TPI epidemic in Greenland (14).

Routine control with lipid-serological test 2 or 3 months after treatment for gonorrhoea has disclosed very, very few cases of masked syphilis infection in Denmark itself. It is at the present time not known whether a routine control with the TPI test would disclose more cases. Studies concerning that question are going on at present time in the Treponematoses Department, Statens Seruminstitute.

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