Radiation therapy for seminoma of the testis: results in British Columbia

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Between 1942 and 1978 radiation therapy was given to 362 patients with seminoma of the testis, 40 (11%) of whom had a history of maldescent of either testis. The disease was classified retrospectively according to the extent of the primary tumour, the involvement of the regional lymph nodes and the presence of distant metastases (the TNM system), and the results of treatment were analysed according to the classifications. Among the 275 patients referred for treatment at least 5 years before this analysis the 5-year survival rates were 87% overall, 96% for those with a T1 or T2 (relatively localized) tumour but no evidence of nodal involvement or distant metastases and 62% for the 24 with palpable or distant metastases at the time of clinical presentation. Of the 28 patients in whom the disease recurred 15 were successfully treated. A second primary testicular tumour developed in the contralateral testis of eight patients. The incidence of other cancers was not increased over the expected rate in the general male population of the same age.

Entre 1942 et 1978 la radiothérapie a été administrée à 362 malades souffrant d'un séminome testiculaire, dont 40 (11%) présentaient une histoire de cryptorchidie. La maladie fut classifiée rétrospectivement selon l'étendue de la tumeur primaire, l'atteinte des ganglions lymphatiques régionaux et la présence de métastases éloignées (le système TNM), et les résultats du traitement furent analysés en rapport avec cette classification. Parmi les 275 patients dirigés pour traitement au moins 5 ans avant cette analyse les taux de survie à 5 ans ont été de 87% globalement, 96% pour ceux ayant une tumeur T1 ou T2 (relativement localisée) mais sans signe d'atteinte ganglionnaire ou de métastases éloignées et de 62% pour les 24 patients présentant des métastases palpables ou éloignées au moment de la consultation. Sur les 28 patients ayant subi une récidive, 15 ont été traités avec succès. Une seconde tumeur testiculaire primaire est apparue dans le testicule contralatéral chez huit malades. L'incidence des autres cancers n'a pas été supérieure au taux prévu pour la population générale mâle du même âge.

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Radiotherapy in British Columbia is limited to two centres (the A. Maxwell Evans Clinic, Vancouver, and the Victoria Cancer Clinic) now joined in the Cancer Control Agency of British Columbia; the agency's third centre (the Interior Cancer Clinic, Kamloops) does not offer radiotherapy. This paper reports the province's experience in the treatment of seminoma of the testis during the past four decades. The treatment results are related to the TNM (tumour–nodes–metastases) classification, and the patterns of failure are examined in detail.

Patients and methods

Patient population

During the years 1942 through 1978, 400 patients with seminoma of the testis were referred to the agency's clinics in British Columbia. Thirty-eight of the patients had been treated elsewhere and were referred for follow-up only. The remaining 362 were treated by the agency and are the subject of this analysis.

The patients' age distribution was typical (Fig. 1).

Forty patients (11%), three of whom had bilateral tumours, gave a history of testicular maldescent (Table I). Of the 25 patients who had received no treatment for maldescent the problem was unilateral in 22, and in all but 3 the tumours developed on the affected side. In the three patients whose undescended testis eventually descended spontaneously the seminoma developed on the affected side. Surgical correction of the maldescent had been undertaken in 12 patients: in the 2 whose undescended testis was removed the

tumour obviously occurred in the opposite testis; among the 6 who underwent unilateral orchidopexy (surgical fixation of the testis in the scrotum) four ipsilateral and four contralateral tumours developed 10 to 32 years after the surgical procedure; and in the 4 patients who underwent bilateral orchidopexy the tumours developed 6 to 50 years later. The average interval between spontaneous descent or surgical correction and development of the seminoma was 24 years. In over one quarter of the patients with a history of unilateral maldescent the seminoma developed on the opposite side.

Before the seminomas were diagnosed 238 patients had fathered 598 children and 109 patients had not fathered children; for the other 15 patients there was no record on this matter. Our records did not allow an assessment of postradiation fertility.

In all patients the disease was classified retrospectively according to the TNM system[1] (Tables II and III) by careful review of the pretreatment hospital record. In most (82%) of the patients the primary tumour was classified T1 or T2. Since lymphography was not available before 1964, in many cases the disease was classified NX because involvement of the regional lymph nodes could not be assessed. In seven patients supradiaphragmatic nodes were involved at the time of presentation (N4), and in five there was evidence of extranodal metastases (M1).

The more advanced the primary tumour, the more likely was the patient to have metastatic disease. Excluding the patients in whom the nodal status was not fully assessed, between one quarter and one third of the patients with T1 or T2 tumours had evidence of nodal involvement or distant metastases at the time of presentation. However, more than half of those with T3 or T4a tumours had nodal involvement or distant metastases.

No patient presented with bilateral tumours, but in eight patients a tumour of the contralateral testis developed later in the course of their disease.

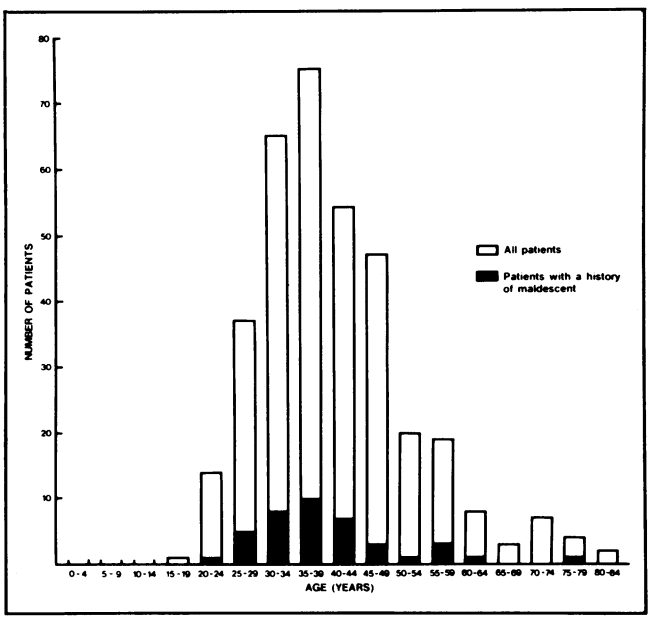

FIG. 1—Age distribution of 362 patients with seminoma of the testis.

Treatment techniques

All but five patients received radiation treatment. In the absence of supradiaphragmatic disease at the

Table I—Laterality of seminomas in patients with testicular maldescent

	Laterality of tumour		
Maldescent	Ipsilateral	Contralateral	Bilateral
Unilateral	24	6*	3
Bilateral	7	—	—

*Includes seminomas developing in two patients whose opposite testis had previously been removed.

Table II—TNM classification of seminoma of the testis[1]

T (primary tumour)

- TX: The minimum requirements to assess the extent of the primary tumour cannot be met.
- T0: No evidence of primary tumour.
- T1: Tumour limited to the body of the testis.
- T2: Tumour extends beyond the tunica albuginea.
- T3: Tumour involves the rete testis or epididymis.
- T4: Tumour has invaded the spermatic cord or scrotal wall or both.
  - T4a: Invasion of spermatic cord.
  - T4b: Invasion of scrotal wall.

N (regional and juxtaregional lymph nodes)

- NX: The minimum requirements to assess the regional lymph nodes cannot be met.
- N0: No evidence of involvement of regional lymph nodes.
- N1: Involvement of one homolateral regional lymph node, which, if inguinal, is mobile.
- N2: Involvement of contralateral or bilateral or multiple regional lymph nodes, which, if inguinal, are mobile.
- N3: A palpable abdominal mass is present or there are fixed inguinal lymph nodes.
- N4: Involvement of juxtaregional lymph nodes.

M (distant metastases)

- MX: The minimum requirements to assess the presence of distant metastases cannot be met.
- M0: No evidence of distant metastases.
- M1: Distant metastases present.
  - M1a: Evidence of occult metastases based on biochemical or other tests.
  - M1b: Single metastasis in one organ.
  - M1c: Multiple metastases in one organ.
  - M1d: Metastases in multiple organs.

Table III—Retrospective TNM classification of the disease in 362 patients (1942–78)

	TX or T0	T1 or T2	T3	T4a	Total
NX	–	115	12	6	133
N0	–	131	12	8	151
N1	–	0	2	0	2
N2	–	38	6	1	45
N3	8	6	2	3	19
N4	1	4	1	1	7
M1	1	3	1	0	5
Total	10	297	36	19	362

time of presentation orthovoltage radiation was directed to the ipsilateral pelvis and the para-aortic region until 1954. With the introduction of cobalt therapy separate parallel opposed fields of radiation to the ipsilateral pelvis and the para-aortic region were used. The total dose, given over 5 to 6 weeks, was usually 3000 to 4000 rad between 1955 and 1963 and 3000 rad between 1964 and 1970. From 1970 to 1976 the pelvis and para-aortic region were irradiated together, with a dose of 3000 rad given over 5 to 6 weeks. The scrotum and remaining testis were normally excluded from treatment. Prophylactic supradiaphragmatic irradiation was not given. Variations in dose and treatment time as well as the relatively small numbers of patients made statistical comparison of these treatment techniques impossible. However, for the patients treated between 1942 and 1954 the overall 5-year crude survival rate was 79%, and for those treated between 1970 and 1974 it was 88%.

The agency's present policy is to treat the pelvic and para-aortic nodes together, using parallel opposed fields of megavoltage x-rays or cobalt, in a dose of 3000 rad given in 20 treatments over 4 weeks. For patients with extensive para-aortic node involvement prophylactic irradiation of the mediastinum and supraclavicular areas is recommended.

Table IV—Five-year survival of 275 patients referred for treatment before 1974: influence of N and M classifications

Classification	No. (and %) of patients				
	Total	Alive*	Died		
			Lost to follow-up	Of other causes*	Of seminoma
Any T and M0					
NX	127	109 (86)	1	11	6 (5)
N0	95	91 (96)	0	2	2 (2)
N1	2	2 (100)	0	0	0 (0)
N2	27	22 (81)	1	1	3 (11)
N3	16	12 (75)	0	1	3 (19)
N4	5	3 (60)	0	0	2 (40)
Any T, any N and M1	3	0 (0)	0	0	3 (100)
Total	275	239 (87)	2	15	19 (7)

*Without evidence of recurrent seminoma.

Table V—Five-year survival of 222 patients with NX or N0 disease referred for treatment before 1974: influence of T classification

Classification	No. (and %) of patients				
	Total	Alive*	Died		
			Lost to follow-up	Of other causes*	Of seminoma
NX					
T1 or T2	112	95 (85)	1	10	6 (5)
T3 or T4	15	14 (93)	0	1	0 (0)
Total	127	109 (86)	1	11	6 (5)
N0					
T1 or T2	86	83 (97)	0	1	2 (2)
T3 or T4	9	8 (89)	0	1	0 (0)
Total	95	91 (96)	0	2	2 (2)
NX or N0					
T1 or T2	198	178 (90)	1	11	8 (4)
T3 or T4	24	22 (92)	0	2	0 (0)
Total	222	200 (90)	1	13	8 (4)

*Without evidence of recurrent seminoma.

Table VI—Overall results of 5-year follow-up

Classification	No. (and %) of patients				
	Total	Alive*	Died		
			Lost to follow-up	Of other causes*	Of seminoma
NX, N0, N1 or N2	251	224 (89)	2	14	11 (4)
N3, N4 or M1	24	15 (62)	0	1	8 (33)
Total	275	239 (87)	2	15	19 (7)

*Without evidence of recurrent seminoma.

Results of radiation treatment

Five-year survival

The 275 patients referred to the agency before 1975 whose data were available for analysis 5 years or more after treatment had a crude survival rate of 87% (Table IV). Only three patients died of seminoma more than 5 years after the initial treatment; in Tables IV, V, VI and VII they are counted as having died within 5 years.

Ignoring the classification of the primary tumour we see that as the extent of metastatic involvement increased the survival rate decreased: in the absence of known metastases (N0, M0) 96% of the patients survived for 5 years without recurrence of the disease, and both of the patients with N1, M0 disease survived this long (Table IV).

In the absence of known metastases the extent of the primary tumour alone did not influence survival or the risk of dying of malignant disease (Table V): of the 222 patients classified as having NX or N0 disease, only 8 died of seminoma within 5 years, and all had T1 or T2 disease; none of the 24 patients with T3 or T4 disease died within 5 years.

Of the 251 patients without palpable disease following orchidectomy and without evidence of distant metastases 224 (89%) survived without recurrence of

Table VII—Sites of recurrent disease in 28 patients

Site	No. of patients
Lymph nodes	
Groin	3
Mediastinal or supraclavicular, or both	13
Axillary	3
Para-aortic	3
Lung	10
Bone	8
Subcutaneous	2
Bowel	1
Brain	1
Epidural	1

the disease and only 11 died of seminoma, whereas of the 24 patients presenting with palpable abdominal disease or distant metastases 15 (63%) survived for 5 years and 8 died of seminoma (Table VI).

Actuarial estimates of survival

In order to study the survival of all 362 patients treated by the agency, we prepared actuarial survival curves using an approximation of the product-limit estimate of survival,[2] including all patients who died, whether or not from seminoma, and all patients lost to follow-up. No correction was made for age.

The estimated survival rates at 5 and 10 years respectively (Fig. 2) were 91% and 87% for the entire group, 96% and 94% for those with N0 disease, 90% and 87% for those with N1 or N2 disease and 88% and 81% for those with N3 disease. There were too few patients with N4 or M1 disease to extend the analysis to 10 years, but at 5 years the estimated survival rate of this group was 44%.

Patterns of treatment failure

In all five patients presenting with distant metastases both radiotherapy and chemotherapy failed to control the disease.

In 28 patients the disease recurred after orchidectomy and radiotherapy. The most frequent sites of recurrence were mediastinal and supraclavicular lymph nodes, then lung and then bone (Table VII).

The risk of recurrent disease in the mediastinal or supraclavicular lymph nodes was directly related to the original nodal classification. Of the 13 patients with such disease 4 had originally been classified as having NX disease (risk of recurrent disease 3% [4/133]), 2 N2 disease (risk 4% [2/45]) and 7 N3 disease (risk 37% [7/19]). None of the patients originally classified as having N0 or N1 disease had recurrent disease in these nodes.

Although most of the patients with recurrent disease were not subjected to further biopsy, in three patients the disease was shown to be embryonal carcinoma. One of the three had metastatic disease in the brain. In none of the other patients were intracranial metastases known to be present, though in two there were metastases to the orbit and the base of the skull.

In 15 of the patients with recurrent disease further treatment was successful; 11 of these patients had lymph node metastases, although patients with orbital, base of skull and pelvic bone metastases were also successfully retreated. Only 3 of the 10 patients with pulmonary metastases were successfully retreated.

The recurrent disease appeared to be nodal alone in 11 patients and hematogenous alone in 9 patients; in 5 patients the two types of metastases appeared simultaneously, and in the other 3 nodal metastasis was followed by hematogenous spread.

The results of chemotherapy for distant metastases was disappointing. Of the 10 patients treated with a single agent (chlorambucil, nitrogen mustard, cyclophosphamide or melphalan) or a combination of vinca alkaloids, cyclophosphamide and actinomycin D, only 3 had a temporary partial response.

Second primary testicular tumours

In British Columbia it has been customary not to irradiate the remaining testis unless there are special indications, and in only 28 patients in this series was irradiation of the remaining testis called for. In none of the 28 has another malignant testicular tumour developed, but such a tumour has appeared in 8 (2.4%) of the other 334 patients after an average of 8 years (range 2 to 18 years). In four the second tumour was a seminoma (appearing after an average of 10 years), and all four patients were successfully treated. In the other four the second tumour was an embryonal carcinoma (appearing after 3 to 5 years); one of the tumours was mixed with a teratoma and another teratocarcinoma. Three of the patients were successfully treated, but the fourth died of widespread malignant disease within a year.

Long-term effects of radiotherapy

Many of our patients have been followed up for a long time, the longest being 30 years, and all but five have received radiotherapy, principally to the abdomen. We therefore had a good opportunity to investigate the long-term risks of large-volume radiotherapy, particularly the risk of carcinogenesis.

Apart from the second primary testicular tumours there were 11 second malignant tumours, 4 in the abdomen (2 in the pancreas, 1 in the stomach and 1 in the large bowel), and there were no instances of leukemia. This is probably an accurate statement since only four patients were lost to long-term follow-up. Of the 22 patients dying of incidental disease two thirds died from cardiovascular disease.

Discussion

It has been estimated that persons with undescended

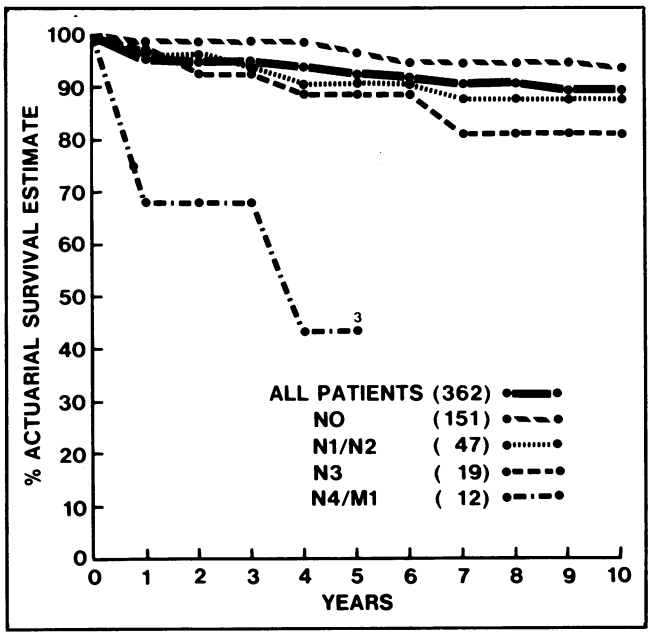

FIG. 2—Actuarial estimates of survival by N and M classifications of TNM (tumour–nodes–metastases) system.

testes have a 20- to 40-fold increased risk of testicular tumours.[3] However, no such tumours have been reported in patients undergoing orchidopexy before the age of 6 years.[4] Twelve percent of our patients gave a history of maldescent, but Collins and Pugh[5] have reported a rate of 6%. Peckham and McElwain[6] stated that one in five tumours occurring in persons with undescended testes arises in a normal testis; in our series the ratio was one in four. The longest reported interval from orchidopexy to appearance of a tumour is 34 years.[7] In one of our patients the interval from bilateral orchidopexy to tumour formation was 50 years, but the average interval was 24 years.

Seminoma of the testis is both radiosensitive and radiocurable, and the generally good results of radiotherapy have been confirmed by our study. The 5-year disease-free survival rate reported from several large series has averaged 85% for all patients (Table VIII). (Some of the investigators relied on actuarial estimates of survival, and one assessment was done at 3 years.) Our crude 5-year survival rate, 87%, is consistent with this average. Since accurate staging has been available only since the early 1960s some of the centres calculated separate rates for patients without palpable evidence of metastatic disease or evidence of hematogenous metastases (NX, N0, N1 or N2 and M0 disease) at the time of presentation; the rates, 90% each, were comparable to our 89%.

More accurate assessment of lymph node status not only improves assessment of prognosis but also helps to identify patients needing prophylactic irradiation of the mediastinum and supraclavicular fossae. Of 27 patients without palpable abdominal metastases but with lymphangiographic evidence of involvement of the para-aortic lymph nodes (N2 disease) 3 died from seminoma and in 2 there was subsequent development of mediastinal or supraclavicular lymph node involvement. Of 16 patients with palpable para-aortic nodes at the time of presentation (N3 disease) 12 were successfully treated by radiotherapy. Nevertheless, 7 of the 19 patients originally classified as having N3 disease (Table III) went on to show evidence of mediastinal or supraclavicular disease. We therefore now recommend prophylactic radiotherapy to the mediastinum and lower neck for all patients with N3 disease.

Table VIII—Five-year survival of patients with seminoma of the testis

Year of report	Total no. (and % surviving 5 years)	
	All patients	Patients with no palpable or distant metastases
1973[8]	336 (90)	– –
1974*	201 (80)	153 (90)
1975[6]	133 (90)	– –
1975[9]	141 (81)†	– –
1976[10]	257 (82)	203 (90)
Total (and average)	1068 (85)	356 (90)
1980 (this series)	275 (87)	251 (89)

*R. Gibb: personal communication, 1979.
†Three-year survival rate.

The evidence for prophylactic radiotherapy is not so strong for patients with N2 disease, but we believe it is sufficient to justify such treatment in those with extensive N2 disease.

The prognosis for patients with disease of various classifications at the time of presentation is illustrated by the actuarial estimates of survival in Fig. 2. The estimated 10-year survival rate for patients without metastases at the time of presentation was 94%. For those with N1 or N2 and M0 disease the prognosis was still excellent, with 90% expected to survive for 10 years. With more advanced disease the prognosis worsened. However, even in the presence of palpable abdominal metastases at the time of presentation (N3) the 10-year survival rate was 81%. Patients with supradiaphragmatic disease at the time of presentation clearly had the worst prognosis, with an estimated survival rate of 44% at 5 years; there were not enough patients in this group to predict the 10-year survival rate, but, in view of the rarity of seminoma recurrence after 5 years, the 10-year survival rate should be about 35%.

Tumours in the contralateral testis have been reported to occur in 2.5% of patients with testicular tumours.[5] Peckham and McElwain[6] described 10 patients with second tumours (a frequency of approximately 6%); in 6 of these patients the original tumour was a seminoma, but in only 2 was the contralateral tumour of a similar pathological type. We are not aware of any reports of tumours occurring in the contralateral testis after this structure was included in the area initially irradiated. None of the eight patients in our series in whom second testicular tumours (four seminomas and four embryonal carcinomas) developed had received radiotherapy to the contralateral testis; thus, the frequency of a second tumour in the nonirradiated testis was 2.4%.

Seminoma may metastasize by both lymphatic and hematogenous routes. However, it is difficult to predict which tumours will metastasize by only one route. The prognosis for those with hematogenous spread is poor: only 3 of 10 patients with pulmonary metastases in our series were successfully treated. It is hoped that with recent advances in chemotherapy these prospects may improve. Patients with spread by the lymphatic route alone may be successfully treated: 8 of 11 patients with nodal metastases in our series had their disease controlled by further therapy.

We compared the overall incidence of other cancers and the incidence of abdominal cancer in this group of relatively young men receiving large-volume radiotherapy with the expected rates in 362 Canadian men of the same age in the same follow-up period;[11] the rates were, respectively, 11% and 4% in our group and 11% and 2% in the comparison group — not significantly different.

We acknowledge the contribution of the many urologists and radiation oncologists in British Columbia who treated these patients over the years. The analysis was made possible by a summer student grant from the British Columbia Cancer Foundation to Mr. Olivotto.

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Intestinal parasitic infections in homosexual men: prevalence, symptoms and factors in transmission

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In a controlled study 67.5% of 200 homosexual men but only 16% of 100 heterosexual men were found to be infected with intestinal parasites. *Entamoeba histolytica* was isolated from 27% of the homosexual and 1% of the heterosexual men, and *Giardia lamblia* was isolated from 13% of the homosexual and 3% of the heterosexual men. The presence of symptoms could not be correlated with infection except when the infection was caused by more than one organism, including *G. lamblia*. Symptoms were much more common in both infected and uninfected homosexuals than in heterosexuals. Among the homosexual men recent foreign travel, living in a homosexual household and promiscuity were not correlated with intestinal parasitic infection, but cleansing of the anus before anal sex was associated with a significantly lower prevalence of infection. These findings suggest that the male homosexual community may be an important reservoir of potentially pathogenic protozoa.

Dans une étude contrôlée une infection à parasites intestinaux a été retrouvée chez 67.5% de 200 homosexuels mâles comparativement à seulement 16% de 100 hétérosexuels du même sexe. *Entamoeba histolytica* a été isolé chez 27% des homosexuels et 1% des hétérosexuels, et *Giardia lamblia* a été isolé chez 13% des homosexuels et 3% des hétérosexuels. La présence de symptômes n'a pu être reliée à une infection sauf lorsque l'infection était causée par plus d'un organisme, incluant *G. lamblia*. Des symptômes étaient beaucoup plus fréquents chez les homosexuels infectés ou non infectés que chez les hétérosexuels. Chez les homosexuels un voyage récent à l'étranger, la résidence dans un foyer homosexuel et la promiscuité ne montrèrent pas de corrélation avec une infection parasitaire intestinale, mais le lavage de l'anus avant l'intromission anale fut associé à une prévalence significativement plus faible d'infection. Ces observations indiquent que la communauté homosexuelle mâle peut constituer un important réservoir de protozoaires potentiellement pathogènes.

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In the past 10 years several individual case reports and a few retrospective studies have hinted at the problem of sexual transmission of pathogenic intestinal viruses, bacteria and parasites in the male homosexual community.[1-9] Shigellosis and viral hepatitis appear to be growing problems among homosexual men. In 1967 Most,[10] in his presidential address to the American Society of Tropical Medicine and Hygiene, first suggested the association of amebiasis with homosexuality. Recently giardiasis has also been reported with increasing frequency in this group.[11,12]

To assess the prevalence of sexually transmitted intestinal parasitic infections among homosexual men in Toronto we carried out a controlled study.

Method

From May until August 1978, mail-in stool containers along with leaflets outlining the purpose of the study were placed in a bookstore, a church, a public bath and the waiting rooms of a community clinic and a private physician, all of which were frequented predominantly by homosexual men. Similar containers were distributed to heterosexual male members of two Metropolitan Toronto fire departments, who served as a control group. Participation in the study was strictly voluntary.

Each volunteer completed a questionnaire (anonymity was optional) outlining the following information: age, foreign travel in the past year (excluding the United States), specific gastrointestinal or systemic symptoms, and sexual orientation. The homosexual men completed a more detailed section on the sexual orientation of members of their household, their methods of cleansing before anal sex, the number of sexual