Studies in Malignant Tumors of the Testis

IV. Bilateral Testicular Cancer. Incidence, Nature, and Bearing upon Management of the Patient with a Single Testicular Cancer*

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(Received for publication November 13, 1941)

In a previous communication we (7) suggested that testicular tumors, lymphosarcomas not included, possess a pronounced tendency to bilaterality. The man with cancer of one testis is exceptionally prone to development of cancer in the other testis. Thus, although the general incidence of testicular tumors among living males is approximately only 0.0013 per cent, the likelihood of involvement of the second testis is manifoldly greater, 0.7 per cent, in men who have had one testicular cancer. If the testes be ecticpic the chances reach the grave values of 15 per cent with inguinal cryptorchidism, and 30 per cent with abdominal cryptorchidism. The tendency to bilateral tumors appears all the more pronounced in view of the fact that the majority of the patients live but a short time after the appearance of the first testicular tumor, and so afford limited opportunity for a later development of neoplasm in the other testis. Implications of these facts in the etiology of testicular cancer, and especially in the choice of management of the patient with cancer of the testis, have led to the following attempt to evaluate (a) the nature of the neoplasms which involve both testes of the same individual, (b) the possibilities of congenital predisposition to testicular cancer, and (c) certain basic facts in management.

Incidence.—Attempts at exhaustive examination of the literature from the time of Livingstone (17) in 1805 to La Manna (16) in 1939 resulted in the collection of 144 instances of bilateral testicular tumors, or 2 per cent of the approximately 7,000 total reported number of men with testicular tumors. That, despite the usually early death of individuals with testicular cancer, the incidence of bilateralism is as high as 2 per cent might seem on superficial appraisal to be ascribable to preferential reporting of the rather dramatic instances when both testes are cancerous. To test this possibility a survey was made of series from various hospitals in which only consecutive cases and not less than 10 patients were reported. The incidence of bilateralism in 1,466 such consecutive cases was 1.6 per cent, which serves to corroborate the high proportion of bilateralism in the other reports of testicular cancer.

The proportion of bilateral cancer is great in undescended testes; therefore the incidence of bilateralism will vary sharply, dependent upon the number of cryptorchid individuals included.

Pathological types.—In bilateral testicular cancer the relative percentages of the various types of tumors are similar to those which occur unilaterally save for the absence of chorionepitheliomas (Table I). The fact that no particular type of tumor is especially concerned in bilateral involvement is contrary to any hypothesis that bilateralism is due in large extent to metastases, for similar metastatic potentialities could scarcely be expected in dissimilar types of tumors.

Age distribution.—The distribution of cases according to the ages of the patients is shown in Fig. 1. The highest peak of incidence falls in the fourth decade, being between 30 and 44 years in almost 4 per cent of all cases. In 116 cases, the average age of the patient when the first tumor was found was stated to be 40.6 years. It is noteworthy that a fourth of all cases with bilateral tumors were in men more than 50 years of age, a period of life at which unilateral cancer is much less frequent. A completely satisfactory explanation for this latter point is not obvious, but matters involved to some extent are the absence of bilateral chorionepitheliomas (a type restricted to the age of reproductive activity and infrequent in men over 40 years of age) and the relatively high incidence of bilateral teratomas during late years of life.

The youngest case was an 8-months' foetus with teratomas (23), the oldest a man 76 years of age who had unicellular cancer (3).

Figs. 2, 3, and 4 show that the increased incidence of testicular cancer during the years of reproductive activity applies to all types of tumors. The augmented occurrence of bilateral tumors during these years is due, however, chiefly to unicellular tumors, as shown in Fig. 5. Especial stimulation of unicellular types of...
TABLE I: COMPARISON OF BILATERAL AND UNILATERAL CASES OF TESTICULAR CANCER WITH REGARD TO PERCENTAGE OCCURRENCE OF VARIOUS TYPES IN DESCENDED AND IN RETAINED TESTES *

<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>Bilateral Tumors</th>
<th>Unilateral Tumors</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Per cent</td>
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<tr>
<td>Ectopic</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Abdominal</td>
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<td>55.5</td>
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<tr>
<td>Scrotal</td>
<td>71</td>
<td>65.7</td>
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<tr>
<td>Total</td>
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<td>62.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
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<tr>
<td>Scrotal</td>
<td>543</td>
<td>64.0</td>
</tr>
<tr>
<td>Total</td>
<td>927</td>
<td>66.1</td>
</tr>
</tbody>
</table>

* Figures for instances of bilateralism and ectopy represent attempts at complete culling of reported cases. A limited series of 848 cases of unilateral cancer in scrotal testes is included for purposes of comparison.

Fig. 1.—Comparison is made of the age distribution (when the first testicular cancer appeared) between 116 cases with bilateral cancer and 1,403 men with unilateral cancer. The average and the modal ages are greater in patients with bilateral testicular cancer than in those with a unilateral distribution of these tumors, and bear somewhat less of a relation to the years of reproductive activity.

Figs. 2, 3, AND 4.—The age of the patients at the onset of the first tumor is compared for different types of bilateral cancer: unicellular (Fig. 2 of 1,090 cases) and teratoma (Fig. 3 of 414 cases). Comparison of these two types of tumor shows that the incidence is restricted more to the years of reproductive activity in unicellular tumors, although not as exclusively so as in chorionepithelioma (Fig. 4 of 85 cases). As neoplasms of chorionic tissue have never been observed bilaterally, the comparison represented in Fig. 4 is of unilateral cases only.
tumors, like stimulation of cells in the seminiferous tubules, might be expected during the years of reproductive life, but the preponderance of this type among bilateral tumors and the restricted period of years during which a man may develop chorionepitheliomas, are other noteworthy facts that need further examination with regard to the effect of endocrine substances.

Site of tumors.—The tumors were located in the scrotum in 108 instances, in the inguinal region in 3, in the abdomen in 18, and in a mixed distribution in 5 cases (Table 1). The location was not stated in 12 reports. The frequency of bilateralism in abdominal testes is striking. Although the ratio of the abdominally-retained to the inguinally-retained testes (uncomplicated by cancer) is only 1 to 8, the ratio of occurrence in bilateral cancer is 6 to 1, a preferential incidence nearly 50 times greater than expected by chance association. This supports the previous suggestion of Gilbert and Hamilton (7) that the propensity for carcinogenesis is greatest in abdominally-retained testes. In the previous report in which unilateral and bilateral cancer had been considered jointly, the frequency of bilateralism in abdominal testes is striking. Although the ratio of the abdominally-retained to the inguinally-retained testes (uncomplicated by cancer) is only 1 to 8, the ratio of occurrence in bilateral cancer is 6 to 1, a preferential incidence nearly 50 times greater than expected by chance association. This supports the previous suggestion of Gilbert and Hamilton (7) that the propensity for carcinogenesis is greatest in abdominally-retained testes. In the previous report in which unilateral and bilateral cancer had been considered jointly, the frequency of bilateral cancer in abdominal testes was about six times greater than expected from the ratio of the incidence of uncomplicated cryptorchidism in the abdomen and inguinal.

Etiology of testicular cancer.—As shown previously, the correlation between maldescent and cancer is high, more than 1 in every 10 instances of cancer being in an improperly descended testis, an association held to be about 48 times that expected as coincidental. No proof was found, however, that residence in ectopy per se rendered the testis potentially malignant. On the basis of these facts, the logical queries concern (a) the nature of the influences causing the maldescent and congenital defects, and (b) the possibility that those influences may predispose the testis to later malignant growths.

A survey of data concerning bilateral testicular tumors in comparison with testicular cancer in general suggests that prenatal factors are of even greater significance in bilateral than in unilateral cancer. Thus, 1 in every 5 instances of bilateral cancer occurs in congenitally undescended testes, an exceedingly high figure in view of the fact that the incidence of cryptorchidism is only 0.23 per cent and bilateral cryptorchidism only a small fraction of this. Moreover, 12.5 per cent of all bilateral cancer is in abdominally-retained testes, an exceedingly rare type of retention which represents the more severe form of maldescent. It is noteworthy that 1 of every 8 instances of bilateral testicular cancer occurs in the probably less than 0.005 per cent of men who have bilateral abdominal cryptorchidism.

Even though the number of cases is small, it is noteworthy that the percentage incidence of teratomas is twice as high in bilateral as in unilateral testicular cancer. This is interpreted as a further indication of a relationship between congenital factors and bilateral testicular cancer.

Several facts suggest that an abnormal influence by steroid substances, such as estrogens for example, is associated with cryptorchidism. In rodents according to Burrill, Greene, and Ivy (5), and in opossums as shown by Burns (4) prenatal treatment with estrogens prevents proper testicular descent. In man cryptorchidism is sometimes accompanied by hypospadias, an effect known to be produced in young female and male rats by estrogens, as described by Hain (10) and by Greene, Burrill, and Ivy (8).

Testicular cancer appears chiefly during the years of reproductive activity, suggesting that the endocrine stimuli existent during this period of life may be implicated also in the carcinogenesis. Any immediate conclusion that gonadotropic substances are directly and solely responsible, however, cannot be accepted, for androgens and some other substances stimulate at least the seminiferous tubules. Nevertheless, testicular cancer bears a high correlation with cryptorchidism, and at least in animals bilateral cryptorchidism is characterized by excessive secretion of gonadotropins. It is perhaps more than coincidental that testicular tumors (a) occur mainly during the years after gonadotropins have begun to be secreted in the greatest quantity and (b) are characteristically frequent in the cryptorchid state which has a tendency at least in animals to allow over-production of gonadotropins. Moreover, the maldescended testis resides in an environment where in rodents it is known to function ab-
normally and to react peculiarly to androgens and to gonadotropins as shown by the investigations of Hamilton and Leonard (12) and Mimpriss (20). Finally, cancer occurs only infrequently, if at all, in eunuchoid men whose testes are stimulated by only small quantities of gonadotropic substances.

The significantly lesser frequency of carcinogenesis in inguinal than in abdominal cryptorchism contradicts the claims that traumatic forces play a large role in the induction of cancer in the ectopic testis. Protection provided by the abdomen would be expected to cushion the blows and prevent much of the stress from muscular movement of the abdominal wall.

Recognition and pre-operative duration.—The average pre-operative interval between the first tumor and removal of one or both testes was 16 months. The duration of the condition prior to consultation was, on the right side, 14.4 months, on the left, 10.3 months.

Clinical grades.—There were 82 cases which, when observed at the appearance of the first tumor, were classified in group I (operable cases stated to have no metastases) and underwent orchidectomy. It is eminentiy significant that 66 of these had bilateral orchidectomy with the findings of a usually unsuspected tumor in the second testis. In group II, consisting of 26 cases which were operated upon despite metastases, 21 of the men were orchidectomized bilaterally, while 5 had only unilateral orchidectomy performed.

Pathological types.—Definite histological data are available in 126 cases, excluding 11 tumors classified only as clinically malignant. There were 88 unicellular tumors, 30 teratomas, and 8 miscellaneous tumors, the last-named group including 4 adenomas, 2 interstitial cell tumors (in brothers) (14), one classified as adrenal carcinoma (24), and one as spindle cell sarcoma (15). A summary of data from the case records of these types of tumors follows.

I. Unicellular tumors.1—There were 88 such tumors. The average age of 76 patients was 41.8 years. The site was stated to be as follows: scrotal, 71; inguinal, 2; and abdominal, 10. Mixed distribution was scrotal and abdominal in two men, abdominal and inguinal in one man. This group includes one pseudohermaphrodite described by Christophe and co-workers (6).

The average pre-operative duration, as stated in reports of 60 cases, was 18.2 months; in 34 instances where the right side was involved, the average was 16.5 months, whereas with 24 tumors on the left side, it was 12.5 months. The average post-operative duration in cases terminating fatally, as stated in operative notes at the time, had castration phenomena, gynecomastia, and indurated atrophic testes which were described as adenomatous. Two pseudohermaphrodites (18, 26) had adenomas.

The second tumor was recognized in 18 instances at an average of 55.5 months after removal of the first tumor. Of these, 5 patients died at an average of 4 years after the first operation, the longest survival before development of the second tumor being 12 years (21). The remaining 13 patients survived an average of 5 years before the second tumor developed, but no further follow-up is available; the longest survivals before the second tumor appeared in this group were 10, 12, 14, and 23 years.

There were 60 patients in group I, of which 46 had bilateral, 4 right- and 4 left-sided, orchidectomy. Group II comprised 13 patients, of whom 10 had bilateral, and one each right or left orchidectomy. Sixteen patients with bilateral tumors were considered inoperable, and no surgery was attempted.

II. Teratoid tumors.—In 30 cases with teratomas histological examination (not always serial) revealed no evidence of choriogenic components. The average age of the patient, stated in 25 instances, was 39.1 years. The pre-operative duration for 20 cases was 8.6 months. The length of life when the right testis was first involved averaged 10 months in 15 instances, 6 months in 11 cases when the first site was the left testis. The post-operative duration of 14 fatal cases averaged 24.4 months, the total duration 320 months. Fourteen patients were reported alive at an average of 84.3 months, 9 of these lived 9.5 years, while 5 were alive with metastases or a second tumor, after an average of 28.6 months. Six patients survived 5 years or more, with an average of 140 months (12 years); 4 of these were alive at an average of 144 months (12 years), one with metastases at 8 years. Two died later, due to involvement of the second testis, 10 and 13 years respectively after an initial orchidectomy (22, 11).

In 9 cases the second tumor developed at an average of 8 years after unilateral orchidectomy; 6 of these men remained alive at an average of 86 months before the second tumor developed. Six patients developed the second tumor from 2 to 60 months after orchidectomy.

There were 13 patients in group I, 12 undergoing bilateral and 1 right orchidectomy. Group II comprised 11 patients, 9 with bilateral and 2 with left-sided orchidectomy. Group III contained 6 patients, 2 being pseudohermaphrodites (1, 2, 9).

III. Malignant testicular tumors.—Eleven tumors were classified as clinically malignant without specific pathology even in cases where autopsies were done. One patient (25) developed the second tumor 72 months after removal of the first testis, but no further follow-up is available. One pseudohermaphrodite is included (19).

IV. Miscellaneous tumors.—Seven individuals with these tumors underwent bilateral orchidectomy. Five were in group I, and one in group II; only one had no surgery performed (13). No significant clinical data are given, except that in one instance of an interstitial cell tumor the second tumors became involved 3 years after removal of the first testis (14). This patient's brother also had bilateral orchidectomy because of an interstitial cell tumor. The case reported by Hermanns, without operative notes at the time, had castration phenomena, gynecomastia, and indurated atrophic testes which were described as adenomatous. Two pseudohermaphrodites (18, 26) had adenomas.

SUMMARY AND CONCLUSIONS

In men with one testicular cancer, the likelihood of cancer in the second testis is from several hundred to several thousand times greater than expected in chance association.

Abdominally-retained testes are especially prone to bilateral cancer. One of every 8 men with bilateral
testicular cancer had abnormally-retained testes, a condition which can be estimated to occur in probably much less than 0.005 per cent of men. The pronounced carcinogenic tendency of abdominal testes can also be ascertained differently. Although the incidence of cancer in inguinal testes is high, the occurrence in abdominal testes is some 50 times higher, as seen by comparison with the ratio of abdominal and inguinal testes in uncomplicated cryptorchidism.

Bilateral tumors occur predominantly in the reproductive years of life, but the first tumor usually occurs later in life than in unilateral cases. The greatest number of both unilateral and bilateral tumors, especially those occurring during the reproductive years, are unicellular types.

The relative percentages of the various types of tumors are the same in bilateral as in unilateral cancer, save for the fact that chorionepitheliomas are not found bilaterally.

Further evidence is advanced to the effect that prenatal factors are significant in the predisposition to testicular cancer. It is possible that estrogens might play a role in the instigation of cryptorchidism and gonadotropins in the stimulation to carcinogenesis during the reproductive years of life.

Management of the case with cancer of one testis must be concerned with the possibility of primary involvement of the other testis. Despite the usual rapidly fatal course in the patient with testicular cancer, a tumor has appeared in the other testis in 15 per cent of those with inguinal testes and 30 per cent of those with abdominal testes. The second testis of a man with a bilateral cryptorchidism and cancer of one testis must be viewed as a site of a potential carcinogenesis.

REFERENCES

References to all bilateral cancers of the testis will be included in a complete bibliography in a forthcoming monograph. Specifically cited reports are given below.

4. Burns, R. K., Jr. Sex Differentiation During Early Pouch Stages of Opossum (Didelphys virginiana) and Comparison of Anatomical Changes Induced by Male and Female Sex Hormones. J. Morphol., 65: 497-547. 1939.

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*Cancer Res* 1942;2:125-129.

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