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PROPOSAL FOR A STUDY OF THE INCIDENCE AND OCCUPATIONAL
DISTRIBUTION OF TESTICULAR NEOPLASMS IN
UNITED STATES AIR FORCE PERSONNEL

By

Emmet Paul Murphy, B.A., M.D.



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Spurgeon H. Neel, M.D., M.P.H.

Dedicated, for their love, patience, and enormous understanding to

My wife, Marilyn

My children, Eric, Kristin, Heather, and Ryan

and

For endless lessons on the meaning of excellence

to

The Men and Women of the United States Air Force

PROPOSAL FOR A STUDY OF THE INCIDENCE AND OCCUPATIONAL
DISTRIBUTION OF TESTICULAR NEOPLASMS IN
UNITED STATES AIR FORCE PERSONNEL

By

EMMET PAUL MURPHY, B.A., M.D.

PROJECT PROPOSAL

Presented to the Faculty of the University of Texas

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in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF PUBLIC HEALTH
Houston, Texas
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Submitted: April 12, 1988

PROPOSAL FOR A STUDY OF THE INCIDENCE AND OCCUPATIONAL
DISTRIBUTION OF TESTICULAR NEOPLASMS IN
UNITED STATES AIR FORCE PERSONNEL

Emmet Paul Murphy, B.A., M.D.
The University of Texas
School of Public Health, 1988

Supervising Professor: Robert O. Oseasohn, M.D.

Testicular cancer is a relatively rare neoplasm which affects males of any age but predominantly those 15-44 years old. While age-adjusted mortality in the US has not varied significantly over the past 50 years, age-adjusted incidence has quadrupled over the same time period. The only strongly positive risk factor for testicular cancer, accounting for less than 10% of cases, is cryptorchidism. Many other risk factors have been suggested in the clinical and epidemiologic literature but supporting evidence is inconclusive since most researchers are hampered by small populations making it difficult to test any single hypothesis.

This proposal suggests utilizing the large (500,000) high risk (20-44 years of age) male population of the United States Air Force (USAF) to conduct a 10-year (1975-1984) historical cohort study of testicular cancer in active duty USAF personnel. Data from the USAF Manpower and Personnel Center, Randolph AFB, Texas and Wilford Hall USAF Medical Center, Lackland AFB, Texas would be used to calculate crude, age, race, rank and occupation specific incidence rates for the USAF. Comparison of USAF testicular cancer incidence rates against US national rates calculated from the Surveillance, Epidemiology and End Results Program would be accomplished. In addition, a case comparison study nested in the historical cohort would look for association of testicular cancer with occupations, using the Armed Forces Specialty Code (AFSC), as a broad indicator of job type.

From analysis of this data specific, testable hypotheses as to testicular cancer etiology could be developed. If significant differences are noted between USAF and national incidence rates, or if a strong association, as reflected by an increased odds ratio, is found with specific occupational codes further analytic studies could be designed and conducted on other populations

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SECTION I

BACKGROUND

Introduction

The lifetime probability of developing testicular cancer in the white male is about 0.2% as compared with 3.8% for prostatic cancer.⁽⁵⁵⁾ Of specific epidemiological interest are its unusual age distribution (figure 1), large racial differences (figure 2), and the dramatic changes in incidence and mortality over time. The age-specific mortality and incidence rates in both blacks and whites is bimodal, with a peak in the 24-36 year age range and a lesser peak beginning after the age of 70, but the age-adjusted incidence and mortality of blacks is one-fourth that of whites. While the age-adjusted mortality in the United States has not varied significantly in the past 40 years, over the past several decades there have been dramatic increases in the age-adjusted incidence of testicular cancer, the most striking increases occurring among white men 15-44 (figure 3).⁽⁷⁾ Comparable data for tumors of the ovaries have shown little change for ovarian cancer (epithelial and nonepithelial) over the past 30 years in women between the ages of 25-44.⁽²⁶⁾

Is this change the result of a new carcinogen or increased exposure to an

FIGURE 1
Age-specific incidence rate of testicular cancer
Surveillance, Epidemiology, and End Results Program

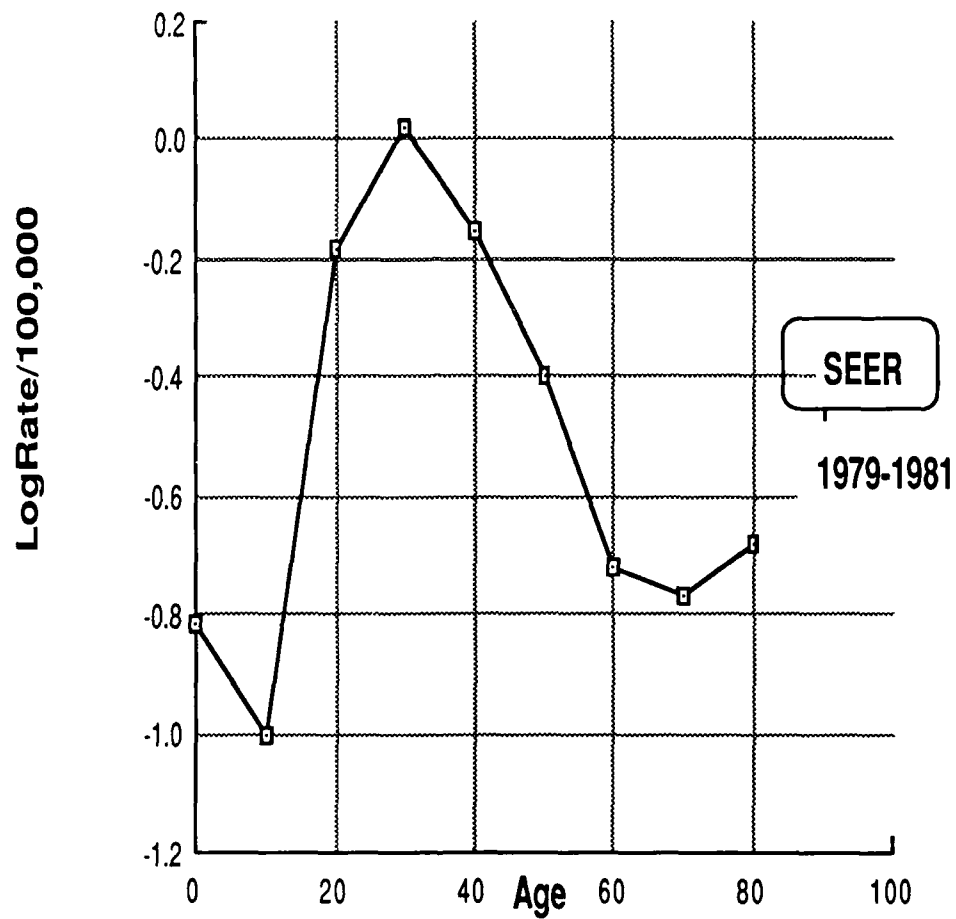


FIGURE 2

Age-specific rates of testicular cancer .

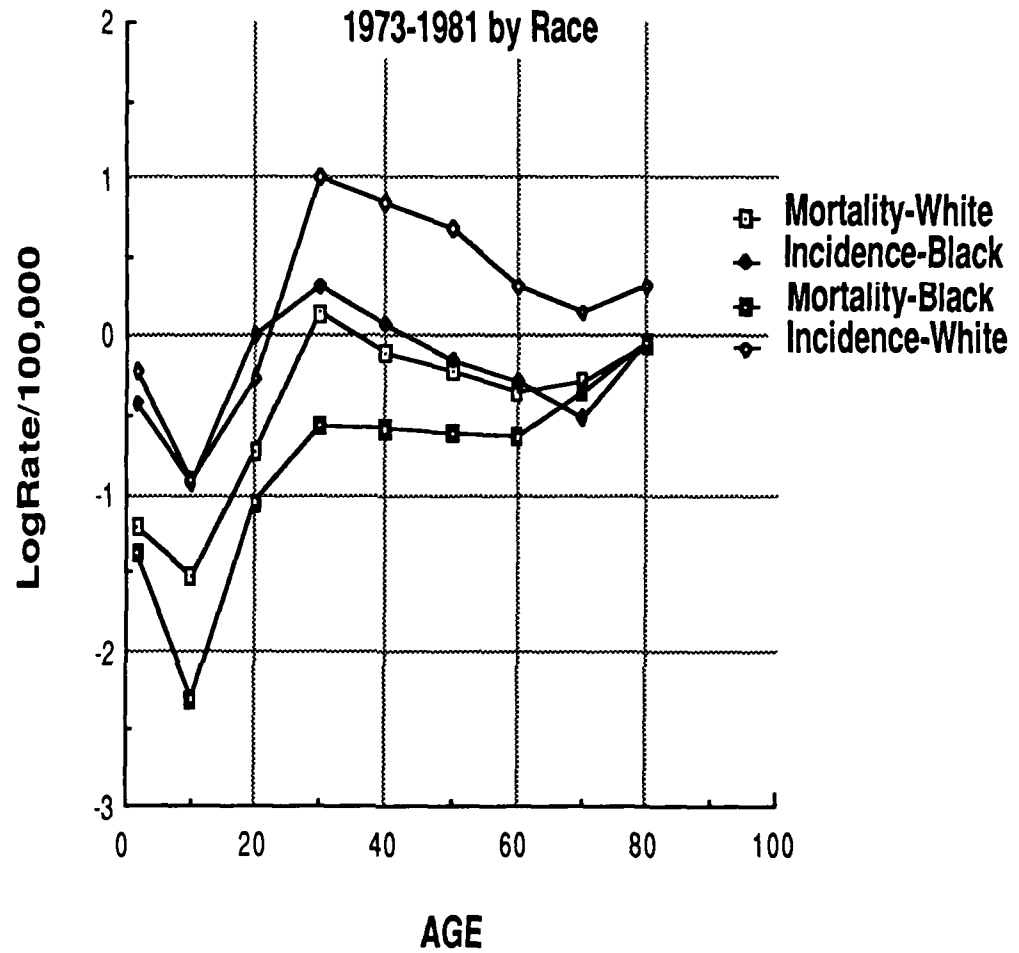
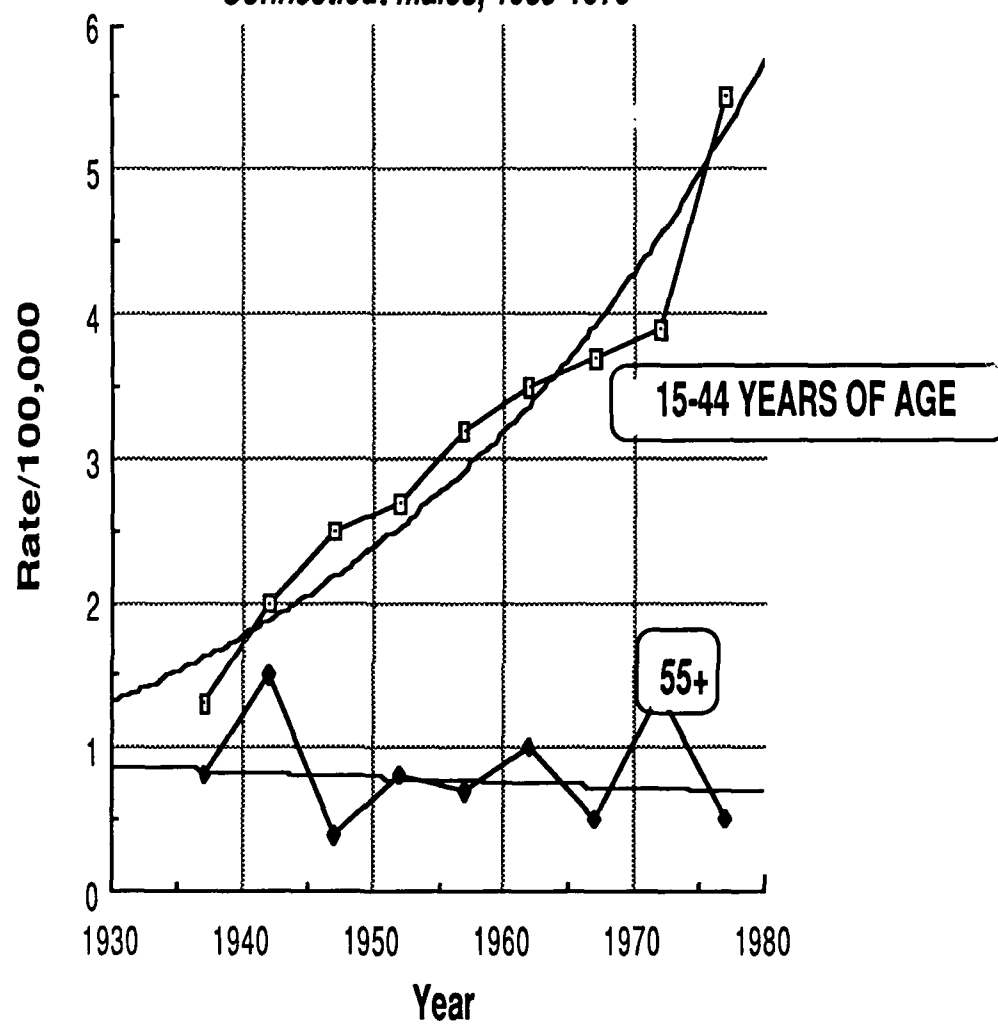


FIGURE 3
Average annual age-adjusted rate of testicular cancer
Connecticut males, 1935-1979



testicular cancer has been so rapid, following an exponential growth line, that the statement "epidemic of testicular cancer" should not be considered an overstatement.

Testicular cancer is a wide and aggressively studied condition with literally hundreds of prospective, retrospective, descriptive, analytic and case comparison reports in the literature. An etiological role for undescended testis, groin hernias, testicular trauma, mumps, mumps orchitis, elevated testicular temperature, hormonal, both pre and perinatal, exposure and occupational factors in the development of young adult testicular cancers has been suggested by any number of studies. Most researchers have been hampered by small study populations which make it difficult if not impossible to test any single hypothesis.

The United States Air Force (USAF) offers a unique opportunity for the study of this neoplasm. With a total active day to day population of 750,000 persons, the vast majority of whom are of the appropriate sex and age to be considered at high risk for testicular cancer it offers an excellent data base. All force structure information is retrievable via computer accessed files which can rapidly sort data by sex, age, race and rank. The USAF has a single medical treatment facility, Wilford Hall USAF Medical Center (WHMC) to which all suspected cases of testicular cancer are referred for final diagnosis and initial treatment. The Department of Urology at WHMC maintains a cancer registry on all confirmed cases of testicular neoplasm. These sources offer the opportunity to study a large population on many different variables from accurate, accessible data.

Classification of Testicular Neoplasm

Classification of testicular neoplasm is a area of considerable disagreement and confusion. Naming these tumors is a difficult exercise, both mechanically, for the pathologist, and in nomenclature assignment. This is an important issue since, no matter what classification system is used there are definite age patterns apparent for various tumors of the testis frustrating the efforts of the epidemiologist when pooled data from different sources with different classification are in use. This has been noted in the epidemiologic literature⁽⁵⁵⁾ but aggregate data (all histologies) covering all age ranges are nevertheless frequently used without specific notation that such data reflect a mixture of tumor types.^(15,38,49) Therefore it is necessary to establish a standard nomenclature for the various types of testicular neoplasms.

Pathologically, testicular cancer can be divided into nine categories.

1. Germ cell tumors
2. Gonadal stromal tumors
3. Tumors and tumor like lesions containing both germ cells and gonadal elements
4. Miscellaneous tumors
5. Lymphoid and hematopoietic tumors
6. Secondary tumors
7. Adenexal tumors
8. Unclassified tumors
9. Tumor like lesions

Tumors of germ cell origin comprise 95% of primary testicular tumors⁽⁵⁵⁾ whereas, in contrast, germ cell tumors account for less than 5% of ovarian cancers.⁽⁶²⁾ Of the nongerminial tumors, malignant lymphoma of the testis is the second most common type. It is found most often in patients over 50 years of age being almost unknown in younger populations. The secondary peak in the incidence rate of testicular cancer seen after the age of 70 (figure 1) is entirely a reflection of increasing rates of testicular lymphoma and not of germ cell malignancies arguing for separate etiologies for testicular tumors of germ cell origin as compared to tumors of lymphoid origins.

More than two thirds of germ cell tumors contain two or more histological types. In 1973 Mostofi⁽⁴⁵⁾ proposed a pathologic classification of germ cell testicular tumors. It recognized a number of basic histological types, and emphasized the clinical need to distinguish between tumors of one histologic type and those of more than one histologic type, and proposed that each type be recorded. With slight modifications this complex classification system was adopted by the World Health Organization in 1977.⁽⁴⁶⁾ Much of the literature published in the world today uses this classification system although papers preceding this date and present day British work use other nomenclature. Essentially though, germ cell tumors can be sub-classified in simplest terms as (1) seminomas (2) embryonal carcinoma (3) teratomas (4) choriocarcinomas (5) yolk sac tumors and (6) mixed tumors.(Table 1)

There has always been curiosity on how so many different tumor types could

arise from exactly the same tissue. A hypothesis, first published in the 1930s, that the type of testicular cancer observed in any individual is a function of the age at which malignant transformation takes place in the testis.⁽²⁰⁾ If the malignant transformation occurs while the germ cells are capable of expressing totipotentiality than a mixture of embryonal carcinoma, teratoma, and choriocarcinoma is produced. Germ cells which have lost the ability to express totipotentiality develop into the relatively uniform proliferation of cells termed seminoma. Tumors containing both embryonal carcinoma and seminoma arise when malignant transformation occurs with germ cells present which have both characteristics. This theory offers an explanation of the differences in testicular cancer histopathology without necessarily invoking multiple etiologies for these apparently different neoplasms all arising from the same tissue.

In the adult patient seminoma is the most common testicular tumor, accounting for 35%-45% of all tumors of the testis in various studies.^(11,13,34) It is believed to arise from the seminiferous epithelium of the mature or maturing testis although rare cases are recorded in younger children. The peak incidence is in the fourth decade of life. Testicular seminoma is characterized by its prompt and marked response to radiation. There is less information in the response of disseminated seminoma to chemotherapy although it has been generally assumed that the

TABLE 1
Histological Classifications of Testicular Cancer

I Tumors showing a single cell type

Seminoma

Teratoma

Embryonal carcinoma

Choriocarcinoma

Yolk sac tumor

II Tumors showing more than one histologic pattern

Embryonal carcinoma with teratoma(teratocarcinoma)

Embryonal carcinoma with seminoma

Embryonal carcinoma with teratoma and seminoma

Teratoma plus seminoma

Any combination with choriocarcinoma

radiosensitivity of the tumor is paralleled by a sensitivity to chemical agents. Its excellent survival (90% five year) is largely a reflection of the high numbers of patients who present with early disease (secondary to high testicular mass), its low metastatic potential, and the sensitivity of the tumor to available treatment.

About 40% of testicular tumors are composed of a combination of more than one of the patterns described below as embryonal, teratoma, and choriocarcinoma. In many studies testicular germ cell tumors are grouped into two broad areas: "seminomas" and "other germ cell tumors". This "all other" category contains the remaining five types of germ cell tumors of the testis, each with age-specific incidence rates different than seminoma.

The designation, teratoma, refers to a group of complex tumors having various cellular or organoid components reminiscent of normal derivations of more than one germinal layer. They occur at any age, from infancy to adult life, but are also most common in young adults under age thirty. In adults the pure tumors comprise about 10% of testicular neoplasms and can be classified into their variants: (1) benign cystic (dermoid) teratoma, (2) mature (differentiated) solid teratoma which may be benign but are often malignant and (3) immature or embryonic (undifferentiated) solid teratoma which is almost always malignant. Additionally the most common constituent of mixed tumors is the teratoma. A mixture of teratoma with any of the other forms of testicular cancer has the designation of teratocarcinoma.

Embryonal carcinoma in its pure form is seen mostly in the second and third

decades of life and constitutes less than 3% of germinal tumors but is a common constituent found mixed with other cells. Embryonal/teratomas comprise 25% of all testicular neoplasms. Therefore, many highly complex, multipatterned, embryonal carcinomas could be regarded as teratocarcinomas. Thus there is much confusion, histologically, about where embryonal carcinoma ends and teratocarcinoma begins. Less often an embryonal carcinoma has varying components of seminoma or choriocarcinoma. Even being seen so infrequently, from thousands of pathological specimens over many years there is wide spread agreement that the elements of teratoma and or choriocarcinoma seen in germ cell tumors of the testis are usually derivatives of embryonal carcinoma.

The yolk sac tumor is a rare, rapidly growing tumor which, in its pure form, occurs almost exclusively in the testis of infants and young children. This pure form rarely occurs in adults but its frequency in association with other testicular cancers is common. This tumor is almost invariably associated with elevated serum levels of alpha feto protein.

Choriocarcinoma is the most aggressive of the testicular tumors. Its clinical manifestations are characterized by presentation with metastatic symptoms (hemoptysis, hematemesis, and central nervous system signs) without any symptoms referable to the testis. This tumor is also uncommon in its pure form accounting for between 2% and 5% of all testicular tumors, again with the most common age group affected being under thirty years of age. In a significant number of testicular tumors,

particularly embryonal, meticulous pathologic examination will reveal foci of choriocarcinoma. Since pathologists tend to label a tumor by the most malignant component, many tumors in the past have been mislabeled choriocarcinomas causing over representation of this tumor in incidence statistics.

Literature Review

Testicular cancer, although it accounts for only 1% of all cancers in males in the United States, is thought to account for 20% of all cancers among 20-34 year olds and is the most common cancer in white males ages 15-24.⁽³⁰⁾ There is strong evidence that the incidence of testicular cancer among white U.S. males has doubled over the past four decades.^(13,17,65) Although the incidence of this cancer is relatively low throughout the world, there is considerable geographic variation. The highest national average age-adjusted (world population standard) rates occur in Switzerland (9.9/100,000), Denmark (6.7/100,000), and the Federal Republic of Germany (5.4/100,000).⁽¹⁰⁾ The highest racial group rate occurs in the native Maori peoples of New Zealand at greater than 12/100,000.⁽⁵⁰⁾ In the United States the incidence ranges from less than 0.1/100,000 for prepubescent white males to 9.7/100,000 for white males ages 25-29. The average annual age-adjusted rate in the U.S. is approximately 5/100,000.⁽¹³⁾

The majority of the etiologic information on testicular cancer has come from the clinical literature. Although numerous case-comparison studies have been published to date, these have failed to substantiate some of the associations suggested by clinical reports. Suggested risk factors for testicular cancer are listed in table 2. Poor evidence is available for most while conflicting evidence exists for the following potential risk factors: inguinal hernia, mumps orchitis and occupational

TABLE 2
Suggested Risk Factors for Testicular Cancer

Urologic anomalies
Cryptorchidism
Inguinal hernia
Ectopic kidneys
Other anomalies
X-Linked ichthyosis
Steroid sulfase deficiency
Polythelis
Testicular trauma
Mumps orchitis
Occupation
Professional/skilled occupations
Farming
Oil and natural gas extraction
Military service
Podiatrist
Aircraft repairman
Genetic factors
Familial history
Twin concordance
HLA type
Klinefelter's syndrome
Race
Prenatal factors
In utero DES exposure
Other exogenous hormones
Bleeding during pregnancy
Endogenous hormones (nausea)

exposures. On the other hand the most consistently documented risk factor been cryptorchidism.

Both the clinical and the epidemiological literature have established that cryptorchidism is the major risk factor for testicular cancer. This was first recognized in 1918 by Gordon-Taylor who saw two patients with malignant growths in undescended testes.⁽²³⁾ Numerous case-control studies since have documented that the risk of testicular cancer among men with uncorrected, undescended testes, which occur only about once in 500 men, is in the order of 20 to 48 times greater than men with normally located scrotal testes. Abdominally situated testes are at even higher risk of becoming malignant, as a fivefold increased risk for cancer development has been noted over testes in a pelvic location.^(10,21,56) Age at correction of the undescended testis may also influence testicular cancer risk. In a recent case comparison study, it was noted that the risk of testicular cancer increased with increasing age at correction, with the highest risk for men whose cryptorchid testis was never corrected.⁽⁵¹⁾ In addition a higher incidence of testis cancer may occur in the contralateral normally descended testis of patients with cryptorchidism. In retrospective studies of patients with testicular cancer and cryptorchidism, the incidence of neoplasia in the contralateral, normally descended testis, has varied from 1% to 20%.^(21,29)

Other evidence that the contralateral, normally descended testis, is abnormal in patients with unilateral cryptorchidism comes from studies of spermatogenesis. Cryptorchidism is frequently associated with bilateral testicular dysgenesis; a failure of

the normal development of the testis, even in the normally descended testis. In one study, spermatogenic arrest occurred in all patients with bilateral cryptorchidism and 81% of patients with a unilateral cryptorchid testis.⁽²⁾ This suggests some underlying systemic factor affecting both testes. There is also an association of low fertility or infertility in patients with testicular cancer, particularly carcinoma in situ. A high incidence of intratubal malignancy has been described in patients undergoing testicular biopsy for investigation of infertility.⁽⁶⁴⁾ Finally, atrophy, a common feature associated with cryptorchid testes, is also independently associated with an increased risk of malignancy.⁽²¹⁾

Seminoma is the most commonly occurring testis cancer in patients with cryptorchidism. Seminoma was present in 72% of testes tumors of cryptorchid patients compared to 57% in the tumors of patients with normally descended testes.⁽⁴⁰⁾ A somewhat lower incidence of seminoma was found in a recent review of 125 patients with testicular cancer and cryptorchidism where 43% had seminoma, with teratocarcinoma being more common in those patients below the age of 30 years.⁽³⁾

Factors suggested to play a role in the increased incidence of testicular tumors in cryptorchid testes include: elevated testicular temperature, interference with testicular blood supply, endocrine disturbances and gonadal dysgenesis. Much of the evidence seems to point in the direction of embryonic or endocrine causes. However, there is no conclusive evidence as to which of these factors is responsible for the increased incidence of testicular cancer among cryptorchid men. Cryptorchidism

accounts for only about 10% of patients with testicular cancer. This risk is not new, and should not have made a major contribution to the rising incidence of testicular neoplasms.

In addition to testis cancer and testicular dysgenesis, other urogenital anomalies occur more frequently in cryptorchid patients. Among 70 children with testis cancer inguinal hernia was present in 21% and other urogenital anomalies (including duplication of the ureters, hypospadias and ectopic kidney) in 6%.⁽³⁴⁾ Pottern reports on 73 testicular cancer patients seen in the Washington D.C. area, 24 of whom (32%) were determined to have major urogenital anomalies such as gross renal ectopia (5.5%), or minor urogenital anomalies such as hypospadias and ureteral duplication.⁽⁵²⁾ Among 100 consecutive urograms performed on cryptorchid boys anomalies were present in 12%.⁽²⁴⁾ The significance of these minor urologic anomalies is uncertain because of the heterogeneity of these defects and their unknown prevalence in the general population. These findings do suggest though that an array of genitourinary anomalies including but not limited to cryptorchidism may be associated with testicular cancer.

Some other anomalies have been noted to be associated with cryptorchidism and testicular cancer. Supernumerary nipples (polythelia) were noted in 11% of the 73 testicular cancer patients noted above compared with a 0.4% to 2.7% prevalence of polythelia in other populations. Patients with polythelia and testicular cancer generally have not had undescended testis. Thus polythelia may be an independent

marker for dysgenesis of the testis or testicular cancer.⁽⁵²⁾

Another dermatologic condition, X-linked ichthyosis, may be associated with the development of testicular cancer. In one series of 25 men with this condition seven (28%) had cryptorchidism and testicular cancer was noted in the normally descended testis of two of the men with this trait.⁽³⁷⁾ This suggests that X-linked ichthyosis may be risk factors for both cryptorchidism and testicular cancer.

Inconsistent findings regarding the degree and significance of the risk of testicular cancer associated with groin hernia have been reported. Henderson and coworkers⁽²⁵⁾ reported a twofold excess of developing testicular cancer among subjects who reported ever having a hernia repair, although this risk was not statistically significant and the sample was small. Also, their analysis did not exclude cryptorchid men, preventing one from drawing conclusions concerning the risk of testicular cancer associated with hernia alone. Two other studies, which controlled for history of cryptorchidism, (one of which used military medical records) compared a history of hernia operation prior to the age of 15 among case subjects and control subjects. Among the non-cryptorchid subjects, those who had a hernia operation were 2.9⁽⁴³⁾ and 2.7⁽¹⁴⁾ times as likely to develop testicular cancer than those who had not had hernia operations. In another study⁽⁵¹⁾ the effect of hernia operation on the risk of testicular cancer appeared to be dependent on the age of repair with a RR of 2.1 for those hernias repaired after the age of 7 compared to a RR of 0.7 for those repaired at an age less than 7 years. Several studies though have found no relationship at all

between hernias and testicular neoplasm. In particular Brown,⁽⁷⁾ in collaboration with Pottern, found no association using essentially the same population/case control studies as reference number 70. There are two possible explanations for these findings: 1) they may be due to chance, a common problem with subgroup analysis which all these studies used; and 2) it may indicate that, similar to cryptorchidism, failure to undergo correction until relatively older ages results in an elevation of testicular cancer risk. Further studies are needed to investigate the possible contribution of inguinal hernias to the risk of testicular cancer in the normally descended testis.

There are indications that testicular cancer has a genetic component. Family clusters of testicular cancer have been noted by clinicians for many years. Data from a case control study in 1985 with a comprehensive review of the literature⁽⁶⁰⁾ found 6 of 269 testicular cancer patients and 1 of 259 control subjects had a first degree relative with testicular cancer. This suggests a six times increase in the risk for testicular cancer in the brothers and sons of men with the condition. A total of 52 case reports of testicular cancer in first degree relatives was found in the literature; 11 twin brothers, 31 non-twin brothers and 10 father-son pairs. The difference in age at diagnosis was least for twins and greatest for father-son pairs. Cryptorchidism was present in 4 of the 11 twin pairs, 6 of 62 non-twin brother pairs and 1 of 10 father-son pairs.

Epidemiologically, testicular cancer is extremely rare in black populations throughout the world⁽⁶¹⁾ suggesting that genetic susceptibility has an impact on

expression of the disease. The incidence of testicular cancer in black Kenyan Africans is 0.09/100,000 males compared to 0.1/100,000 black males in the United States but, the proportional distribution of primary testicular germ cell neoplasms (type of neoplasm) is much the same as in the United States.⁽⁶⁶⁾ The fact that incidence rates do not change appreciably upon migration of the black population from Africa seems to favor the role of genetic rather than environmental factors in the etiology of this neoplasm.⁽²⁷⁾ In counterpoint, although testicular cancer occurrence among hispanic men is closer in incidence to that whites (5.5/100,000 compared to 10/100,000 at age 26) than blacks,^(54,57) higher rates of testicular cancer among indigenous New Mexico hispanics relative to their migrant counterparts indicate that environmental factors could be pivotal to the etiology.⁽⁵⁹⁾ Ethnic differences in incidence are least evident at the extremes of age where yoke sac tumors in the young and lymphoma in the aged predominate.

Mumps and mumps orchitis have been investigated as a possible cause for testicular cancer. Mumps orchitis can cause permanent damage to germinal epithelium, Leydig-cell function and is likely to cause tubular damage when it occurs in adults rather than before puberty. Orchitis appears to be a risk factor but not a major one. A study of 132 men with a history of mumps orchitis at the Mayo Clinic from 1935 to 1974 found two cases of testicular cancer.⁽⁴⁾ Three case comparison studies^(58,34,7) found increased testicular cancer risks for men with a history of mumps orchitis with relative risks (RR) ranging from 5.8 to 12.7. An association

between mumps and the subsequent development of testicular cancer has been suggested by a few clinical studies.⁽³⁰⁾ but the balance of the evidence does not suggest that mumps, without clinical orchitis, raises the risk of testicular tumor. One small case comparison study⁽³⁶⁾ found a RR of 1.3 to 5.9 depending on the source of the information (subject for the former and subject mother for the latter) while two larger case comparison studies found no association between a history of mumps and testicular cancer.

The relationship between occupation, social class and education as related to testicular cancer is being increasingly studied. The most consistent association has involved the professional and technical occupations and the upper social class groupings. This has been proposed as the basis for the higher rates of testicular cancer in the western industrialized nations as compared to the developing world, but this difference could also be explained on a foundation of genetic difference. The best studies in this area come from England, with its large and well organized governmental statistics offices and national cancer registries. A study based on medical records review from England⁽⁴⁸⁾ found a marked difference in the incidence of testicular cancer between predominately non manual occupations (as determined by social class from the British Office of Population Census and Surveys) and manual ones. A death certificate study also from England⁽³⁸⁾ of all testicular cancer deaths between 1971 and 1980 in England and Wales (2334 cases) found an increased risk of mortality for professional workers (RR 1.44) farmers (RR 1.85) printers (RR 1.48) and

the armed forces (1.21) although the latter two were nonsignificant. In addition the most recent British Registrar General's study⁽³⁵⁾ found high SMRs for the farming and skilled occupations and highest rates in professional ranks and the armed forces. These findings were a repeat of the findings of prior Registrar General's studies. From New Zealand a case comparison study⁽⁵⁰⁾ with data from the national cancer registry found professional workers exhibiting an odds ratio (OR) of 1.09 (non-significant), sales and service workers at a 1.38 OR and physicians at an OR of 6.50 for testicular cancer. The higher OR among sales and service workers was primarily a function of elevated risks for policemen and armed forces personnel. From the United States come three studies. A medical record case comparison study of the upstate New York population⁽³⁴⁾ showed an increased risk for professional occupation of 1.85 and 2.29 (seminoma versus all other tumor types), findings which duplicated a similar study from a San Francisco based population.⁽⁶³⁾ Results from the Los Angeles County Cancer Surveillance Program⁽⁷⁷⁾ also showed a positive association between testicular cancer and higher social class for whites. Finally a case comparison study from the Dallas area found a strong (OR 6.27) association between agricultural occupation and testicular cancer and a weaker one (2.29) with a history of work in the oil and natural gas exploration industry.⁽⁵⁷⁾

There have also been 2 reported time space clusters of testicular cancer which might have an occupational association. Four cases of testicular cancer in 1225 graduates of a school of podiatry with an expected number in a population of this size

of 0.62 and 7 cases of this neoplasm among workers in 2 U.S. Navy shops engaged in the repair of F-4 aircraft airframes. (53,18)

Most of the data seems to indicate that occupation by itself has a minimal role in the etiology of testicular cancer. Environmental factors such as higher testicular temperature secondary to constant sitting have been postulated as contributing etiology. Some have theorized that there are two stages to the cancerous process, induction and promotion, so that exposure to some hazard in the workplace might promote the growth of an already induced tumor.

It has been postulated that exposure to an abnormal hormonal environment, either exogenous or endogenous, during pregnancy may subsequently lead to testicular cancer in male offspring. Several observations have led numerous groups to investigate this potential risk factor. The discovery of an increased incidence of clear cell adenoma of the vagina in female offspring of mothers who took diethylstilbestrol (DES) during pregnancy focused an intense spotlight of attention on this area. Normal testicular development, in utero and following birth, is dependent on and sensitive to hormonal influences. The high potential for testicular cancer in males with cryptorchidism is possibly due to an abnormal hormonal milieu. Might it be possible for testicular cancer to develop secondary to hormonal imbalance independent of any sign of cryptorchidism?

Estrogen administration can directly induce testicular cancer in certain strains of mice and, DES administered to pregnant animals, has produced

incomplete development of the male genitalia, including testicular hypoplasia and maldescent.^(1,39) DES has been shown, in humans, to cause clear cell adenoma of the vagina in female offspring as well as anatomic and functional genitalia tract abnormalities in the male offspring.⁽⁶³⁾ In a follow up study of the offspring of DES exposed mothers, male children had a significantly higher incidence of epididymal cysts, hypoplastic testis and induration of the testicular capsule when compared to unexposed controls. No malignant testicular tumors were found in the exposed males.⁽⁶⁾ This raises a question of whether there were sufficient follow-up intervals to permit tumor formation or discovery.

Though several case comparison studies have attempted to examine the association between testicular cancer and in utero exposure to DES and other hormones, to date, evidence for such an association is weak. In a case comparison study of 108 patient-mother and control-mother pairs, a significant association was found for hormone exposure in the first trimester of pregnancy. Nine cases and two control mothers had taken hormones during pregnancy.⁽¹⁶⁾ Two of the case mothers and none of the control mothers had taken DES. Henderson and associates published a case control study in 1979 of 131 cases of testicular cancer cases. It reported exogenous hormone exposure during pregnancy to be a risk factor for testicular cancer with a RR of 5.00. This was not a significant finding though since the one sided p-value was .11.⁽²⁵⁾ Schottenfeld, in an analysis of data on 190 testicular cancer patients and 166 controls, reported a nonsignificant elevated risk of 1.8 associated with use of DES

and other hormones during pregnancy.⁽⁵⁵⁾ In another case comparison study of 202 mothers of patients with testicular cancer and mothers of 206 control subjects there was no risk associated with exogenous hormone use during pregnancy.⁽⁸⁾ Finally there was a report from the University of California San Francisco of another case comparison study involving 273 case-subject, mother-subject pairs showing no association with the mothers hormone or DES exposure during pregnancy.⁽⁴⁴⁾

There have also been several studies which reported an excess risk for testicular cancer associated with nausea during pregnancy, particularly in the first trimester, thus implicating endogenous estrogen exposure. The results though, on close scrutiny, have shown non-significant increased risks^(16,25,58) or no association^(9,44,55)

It has been suggested in clinical reports that trauma to the testis might be a risk factor for testicular cancer. In the majority of patients it is difficult to assess if reported trauma preceded tumor development, since testicular injury may increase the likelihood of detecting an asymptomatic testicular tumor. In addition, cancer patients might be motivated to recall a minor injury to the testis to explain the development of their tumor. Only one case comparison study has attempted to address this issue. Coldman and colleagues⁽¹⁴⁾ used questions regarding specific sports activity as a means of assessing trauma. Bicycles and horses were ridden more frequently by cases than controls to a significant degree. Testicular cancer associated with this sort of activity would have to be based on a very rapid malignant induction and could not

explain the very rapid rise in testicular cancer in of past three to four decades.

Several other groups have looked for iatrogenic effects or prenatal infections analogous to congenital rubella syndrome as possible etiologies, by examining birth months of men with cancer of the testis. The benchmark study by Knox⁽²⁸⁾ found strong evidence of a four month cycle, analogous to the school term related cyclical component identified in other diseases, thus suggesting a prenatal infection etiology. However, two follow up studies by other groups^(5,32) based on larger population groups, were unable to reproduce these results.

There have been many reports of space-time clusters of patients with such conditions as Hodgkin's disease, childhood leukemia and Burkitt's lymphoma. Space-time clusters of malignant disease often have been cited as evidence of a viral etiology of the disease in question. Space-time clusters also suggest the possibility of some non-infective environmental carcinogen. There is little information in the literature concerning testicular cancer and space-time clusters. As mentioned there have been two reports of clusters among podiatrists and aircraft repairmen, which could also be considered as occupationally related.^(15,53) Otherwise, at this time, there are only two other reports of pure space-time occurrences. A journal reported in 1978 concerning a family physician who diagnosed three cases of seminoma of the testis in a small town in Mississippi.⁽²²⁾ Secondly, a geographic cluster of four testicular seminomas was reported in 1983.⁽¹⁹⁾ All patients lived in the same neighborhood, within a one block area. The only analysis done was to note the presence, within one-half mile, of a city

incinerator and sewage disposal plant. The significance of these reports is unclear and unfortunately there is not enough information to make an informed guess as to etiology in these cases.

There has been some study of the incidence of testicular cancer in relation to marital status. This originates from findings of different incidence rates for some cancers associated with marital status. Again the evidence is lacking in quality and inconclusive. Two studies report small elevations in risk for testicular cancer (seminoma) associated with married status as compared to never married^(24,42) while two other studies report risks of a similar magnitude for never married as compared to ever married.^(49,57)

A personal observation is in order to explain my own interest in this area. While assigned to a USAF Base in Europe from July 1984 to July 1987 there were three new cases of testicular cancer diagnosed in the base population. All of these cases occurred in active duty personnel on flying status. In addition two individuals on flying status with a history of testicular cancer were noted. There were no other new cases diagnosed during this time period. The total active duty population of the base was approximately 7500 persons of whom 15% were female. The total number of personnel on flying status at any one time for this base is approximately 500 persons all of whom are male. What is the probability that this event happened by more than chance alone? Ignoring the two cases with prior diagnosis of testicular cancer the question asked is: what is the probability in a population of 500 males,

20-45 years of age, that three new cases of testicular cancer would be diagnosed in three years if the incidence rate for testicular cancer in the U.S. male population is approximately 10cases/100,000 person years at risk? The solution, from the Poisson distribution indicates that there are 5 chances in 10,000 of this particular event happening by chance alone. (See appendix A for the calculations) I wondered, with this very low probability, if there might be something inherent in the occupation of flying or working around military aircraft that predisposed to a higher risk of testicular cancer.

Summary of Literature.

At this time there are few absolute statements which can be made concerning the epidemiology of testicular cancer: 1) the incidence is rising in young adults (ages 15-44) and has been doing so for at least the past four decades; 2) there has been no substantial rise in the incidence of rates of childhood testicular cancer; 3) cryptorchidism is the most important known risk factor for cancer of the testis with increased risk both in the maldescended and contralateral testis; 4) there has been no substantial increase in the incidence of cryptorchidism in the past 40 years, at least not of the magnitude necessary to explain the epidemic increase in testicular cancer; 5) there is a definite relationship between socioeconomic status and the incidence rate of testicular cancer with higher socioeconomic groups having considerably higher rates; 6) there is a definite relationship between race and the incidence of testicular cancer with blacks having a much lower incidence rate, worldwide, than whites; and 7) the incidence of cryptorchidism is not associated with socioeconomic status.

Cryptorchidism is the most important known risk factor for cancer of the testis. Although there are several theories for the high incidence of testicular cancer in the cryptorchid testis, since maldescent is related to events in utero, much of the available evidence seems to suggest maternal hormonal imbalance. On the other hand, if it is the environment in utero, or even in childhood, which is critical, it is puzzling that familial cases are not more common. In contrast to the general pattern of a rise in

incidence and mortality from testicular cancer in young adults the rate in children under 15 years of age has not changed. Neither has the rate of cryptorchidism. This suggests that if prenatal factors are etiological for adult testicular cancer they are either different prenatal factors from those responsible for childhood cancer or they are not the cause of the increasing trend. The evidence so far available is against the former explanation.

It seems reasonable to suppose that any socioeconomic factor responsible for the increased incidence in testicular cancer in developed countries, ignoring the possible effect of race, could be responsible for the strong association of the cancer with social class, and for lower incidence in less developed countries. It is also consistent with this being a postnatal factor, since childhood testicular cancer has showed no increase in incidence nor a higher incidence in developed as compared to undeveloped countries.

Taken in conjunction with the general trends most of this data suggests that the overall increase in testicular cancer incidence since the 1940s is related to some feature of modern life which has gradually become more common throughout society but affects men in the higher social classes more than manual workers. A bewildering range of features of modern life could fit this definition and might be relevant, including sedantary way of life, central heating, changes in diet or earlier sexual maturation.

Statement of Research Problem.

It is clearly important to define more precisely the cause of the growing incidence of testicular cancer in young men. The increases do not appear to be related to improved diagnostic practices nor to most of the risk factors so far addressed. It is doubtful that any other cancer shows as much provocative variation as does testicular cancer. For some time there has been speculation that the marked peak of testicular cancer incidence in young adults might be due to some unrecognized factor(s). The profound increase over time in young adult males suggests that an environmental factor which has similarly varied over time might be responsible. Given the magnitude of this increase one would expect that this factor should have been identified by analytical studies. However to date the factor(s) responsible for its dramatic increase remain elusive. Substantial epidemiological variation should provide powerful clues for the development of specific testable hypotheses. Identification of the agents responsible for these patterns is a challenge which needs to be taken on.

The objective of this proposal, is to use the large high risk population base of the United States Air Force, with its corresponding excellent centralized data base, to search for such clues. After a preliminary analysis of the data, specific hypothesis will be formulated and analytic studies designed to test them in a different population.

SECTION II

METHODS

Overview of Research Proposal

The goal of this research proposal will be to develop testable hypotheses as to the etiology of testicular cancer. This goal will be accomplished by meeting the following objectives. 1) Describe the incidence and distribution of testicular cancer in United States Air Force (USAF) personnel overall and according to several demographic and occupational parameters. 2) Compare crude and specific rates of testicular cancer in USAF personnel with U.S. national rates. 3) Look for statistically significant differences between crude and specific testicular cancer incidence rates in USAF personnel and the U.S. population. 4) Compare crude and specific incidence rates of testicular cancer between selected social (commissioned/enlisted) and occupational (flying/non flying) USAF groups. 5) Conduct a case comparison analysis of USAF testicular cancer cases by Armed Forces Speciality Code.

The design of this study will be a statistical analysis of a historical cohort with a case comparison study nested in the larger cohort study.

This study will look at the incidence of testicular cancer in the USAF from 1 January 1975 to 31 December, 1984. This interval was chosen for three reasons.

1) The Surveillance Epidemiology and End Results (SEER) Program is a continuing project of the Biometry Branch of the National Cancer Institute (NCI). The Program was initiated in 1973 with 8 original participants collecting data on cancer incidence and mortality. Two other groups began collecting data in 1974 and the last of the 11 long term participants initiated coverage with 1975 diagnoses. Therefore 1975 is the first year for which complete SEER data is available.

2) Manpower and Personnel Center (MPC), Randolph Air Force Base, Texas began computerization of the USAF personnel operation in the late 1960's. Complete automation with total electronic retrieval was not achieved though until 1973-74. The first year that complete automated recall of force structure is available from MPC is 1975.

3) 1985 is chosen as the final year of the study interval because of the unavoidable time lags in data collection and analysis by the SEER Program. The final data for any calendar year are due from the 11 participants no more than 11 months following the end of the reporting period. Data for 1985 would not be available for SEER Program analysis until November 1986. The SEER Program then needs another year to sort, code and enter the information on computer tape. Copies of this tape are then made available to the public, approximately two years following the close of the time period under study.

There will be one main population and several subsets of that population for the two studies to be conducted under this proposal.

In the historical cohort analysis the study population will be all males 20-45 years of age serving in the United States Air Force during the specified study period. This age range is chosen for two reasons. 1) Age-specific incidence rates for testicular cancer are highest during these life years thus yielding the largest number of cases and 2) the vast majority (90%) of males on active duty in the USAF are included by this range.

For the nested case comparison the case population includes all active duty USAF males 20-44 years of age with a diagnosis of testicular cancer admitted to the Urology service at WHMC from 1975-1984 and listed in the testicular cancer registry. The comparison population will be a sample of active duty USAF males 20-44 years of age admitted to the Urology service at WHMC from 1975-1984.

The dependent variable for both the historical and the nested case comparison study will be new cases of testicular cancer which are diagnosed during the defined time period.

The independent variables (exposure) for both the historical and the case comparison study will be:

- 1) Occupational history; specifically the flying status (Those USAF members assigned to work positions requiring/not requiring frequent and regular participation in aerial flight) of the patients and the controls.

- 2) Armed Forces Speciality Code (AFSC); a 4 digit number code which identifies the military occupational speciality of individual USAF members. The first

number identifies the major career field (9 for medical 7 for administration and so forth). The second number identifies enlisted members (0) or commissioned officers (1thru9) general career fields (93 for preventive medicine or 92 for primary care). The third number identifies specialized career fields (935 for aerospace medicine physican or 924 for family pratice). The last number indicates the level of experience of the individual (an AFSC of 9351 is less than 2 years of pratice as an areospace medicine physican while an AFSC of 9356 is more than 2 years of experience).

3) Rank (social status) of the patients and controls in terms of officer of enlisted.

To conduct the proposed cohort analysis data will need to be collected to from the following sources.

Denominators for the historical cohort analysis (person years at risk) will come from the Manpower and Personal Center, Randolph Air Force Base, Texas. This separate operating agency of the USAF maintains a computerized data base which contains force demographic statistics. This agency can generate accurate numerical data, upon request on almost any variable force structure providing exact, age-specific information on the numbers of males on active duty by; 1)race, 2)rank (commissioned /enlisted), 3)Flying status (flying/nonflying), for the period January 1, 1975 to December 31, 1984.

Numerators for the historical cohort analysis will come from the Wilford Hall USAF Medical Center (WHMC), Department of Urology, testicular cancer registry. The

Department of Urology at WHMC maintains a cancer registry with a complete listing of all cases of testicular cancer seen at WHMC. The tumor registry was initiated in 1968 with the establishment of Graduate Medical Education in Urology at WHMC. WHMC has the only urology residency training program in the USAF. Therefore, for resident training purposes, all suspected cases of testicular cancer in active duty personnel are sent to WHMC for definitive diagnosis and initial treatment. A review of the registry to identify all cases of testicular cancer diagnosed between January 1, 1975 and December 31, 1984 will be made. Data to be extracted from the registry will include: 1) age, 2) race, 3) rank, 4) flying status, and 5) histology of tumor.

Expected number of cases for various USAF groups will be calculated from national age specific testicular cancer incidence rates extracted from the Surveillance Epidemiology and End Results Program (SEER) of the National Cancer Institute, Department of Health and Human Services. Because of the nature of the SEER database these national testicular cancer incidence rates will be best estimates only because of the original major goals of the SEER Program which are: 1) Determine periodically the incidence of cancer in selected geographic regions of the United States with respect to demographic and social characteristics of the population, 2) Estimate cancer incidence for the United States on an annual basis.

Participants in the SEER Program were selected on the basis of their ability to operate and maintain a population based cancer reporting system and for the unique population subgroups that each of them offered. Thus, participants were selected with

forethought of subgroups within the defined populations which were epidemiologically interesting, rather than on the basis of being representative with respect to various demographic characteristics of the United States population. The populations being reported on represent slightly more than 10% of the total population of the United States and are fairly representative with respect to age. Blacks though are underrepresented, whereas other minority populations (Chinese, Japanese, and American Indian) are overrepresented. Rural populations, especially rural blacks are also underrepresented. Therefore, extrapolating the crude and age specific/race specific incidence data of the SEER Program to U.S national rates is not as precise as I would like. This is the most comprehensive and accurate information on U.S cancer rates available though and has been used by other investigators in the same manner.

To conduct the case comparison analysis data will be collected from the following sources.

Case identification and information (AFSC, age, race, rank and year of diagnosis) for the case comparison study will come from the WHMC Department of Urology testicular cancer registry. Controls selection will be from the admissions and dispositions (A&D) records of WHMC from 1975 to 1984. Comparison subjects will be selected; 2 controls for each case; as the first 2 age race and rank matched active duty USAF personnel admitted to the Urology service in the month and year of diagnosis of each case of testicular cancer.

Study Approval

Approval authority for this proposal rests with two separate authorities. First with an Institutional Review Board or Committee for the Protection of Human Subjects. Because all data will come from secondary sources, which precludes contact with or identification of individuals, there should be no requirement for approval by one of these groups. Second, military regulations, tradition and courtesy require that approval for any project involving military resources be requested and approved through the chain of command. To obtain this permission the following steps will be taken.

Request to the Office of the Surgeon General, United States Air Force for the following: 1) permission to conduct the study using USAF Medical Service resources, 2) introduction to the Commander Manpower and Personnel Center Randolph Air Force Base Texas, 3) Introduction to the Commander of the Joint Military Medical Command San Antonio Area, Randolph Air Force Base Texas

Official request, from the principle investigator to; 1) Commander Manpower and Personnel Center, 2) Commander of the Joint Military Medical Command, 3) Commander WHMC, 4) Chairman of the Department of Urology, WHMC for permission to use the resources of their organizations for data collection.

Consideration of Confounding Variables

A confounder is a variable that; 1) is causally related to the disease under study and 2) is associated with the exposure under study in the study population but is not a consequence of this exposure. From this definition there are several confounders which could affect the interpretation to this studies results.

Because testicular cancer is age dependent, both in the histology seen and incidence rates, it should be considered. The age range chosen for this study (20-44years) covers the major life years at highest risk for testicular cancer. The peak incidence though, occurs in the 20-26 year age range group. The historical cohort portion of this study proposes to describe the incidence of testicular cancer in USAF personnel and to compare testicular cancer incidence rates between officer/enlisted personnel (as a reflection for social class) and between flyers/nonflyers (as a broad occupational indicator) while the nested case comparison portion will examine the strength of association (odds ratio) of testicular cancer with major Armed Forces Speciality Code occupational areas. For a number of reasons there are disparities between the age means for officers compared to enlisted and flyers compared to nonflyers. Enlisted personal, may join the military at 17 years of age. A high percentage of enlisted personal will therefore be grouped in the younger age ranges. Officers, with the requirement of a college degree for commissioning, will have fewer if any personnel in the younger age groups. In addition the age distribution between

flying status AFSC's and non-flying status AFSC's will be unequal because the vast majority of personnel on flying status come from the commissioned ranks.

To control for disparities in age distributions, age-specific testicular cancer incidence rates for will be computed in five year increments; (20-24), (25-29), (30-34), (35-39), and (40-44) for the historical cohort portion of the study and cases will be matched with controls on the basis of age in the case comparison analysis.

Race could profoundly influence the final findings. The incidence of testicular cancer in blacks is very low compared to whites. Additionally the distribution of blacks, with respect to the variables being studied, is not representative of the general U.S. population. The percentage of blacks are over represented in the U.S. military as compared to their percentage of the total U.S. population, and this over representation is confined almost exclusively to the enlisted ranks and non-flying positions.

There are two ways to control for this. Blacks could be excluded from the analysis. The incidence rate in blacks is so low nationally and internationally that the contribution of this racial group to the final statistics would be negligible. Or, separate incidence rates (race-specific) for black USAF members could be calculated. This course presents some difficulties. because, when looking at the subgroups of commissioned officers and flying status, there are proportionately so few blacks available in these study sets, and the rate of testicular cancer is so low in this racial group, that no cases may be found for analysis over the ten year period.

Therefore an effort will be made to calculate age-specific incidence rates and

risk ratios for blacks separately from whites. If the number of cases is not adequate for accurate statistical analysis, this part of the study will be dropped.

Consideration of Bias

In this study there are at least two areas of possible bias. Several aspects USAF (or military recruits in general) personnel might differ from the U.S. population.

There is some indication from review of the literature that a relationship between higher social class and the higher incidences of testicular cancer exists. Level of education could be considered a reflection of social class. In the USAF, acceptance for service is predicated on attaining at least 12 years of schooling (high school diploma), and in the past five years, 98% of all new recruits to the USAF have possessed at least this level of education. Figures as high as 25% are frequently quoted for the number of adolescents who fail to graduate from high school. It is commonly accepted that this drop out rate is a function of the social status (values) of the families of these young people. Is there any reason why the USAF experience, albeit biased by education would hurt the results to be obtained, i.e.; will this affect the validity of this studies findings? Possibly. How, or whether to adjust for this possible bias is the question. The U.S. has no traditional method of assigning social class such as the British do. Additionally, SEER figures do not separate their incidence statistics on the basis of social class, In the final analysis this source of bias should be noted when interpreting the findings of the study.

For decades the chauvinism of interservice rivalries precluded sending members of a one branch of the armed forces to the medical treatment facilities of

another branch for treatment, except in the most dire of emergencies. This included persons stationed overseas, who were almost always transferred to parent service facilities in the United States for diagnosis and treatment in lieu of using a rival services hospital which might be closer. However in the past few years, with the initiatives for interservice cooperation and increased cost effectiveness, military medical treatment facilities are being treated as interchangeable. Therefore new cases of testicular cancer in USAF personal, particularly those with an initial diagnosis made overseas, are not sent to WHMC automatically. They are sent to the closest military hospital with the capability of handling the diagnosis and treatment. This policy should not have great impact on this proposal. The final year of population study will be 1984. The new regulations on "closest available facility" were published in January of 1984 and were not implemented fully for 12 months.

Unfortunately, with this move towards interservice cooperation by mandated sharing of medical resources, the high quality service specific information which is used for this study will never again be available unless the Department of Defense Office of Health Affairs directs that an Armed Forces wide cancer registry is established.

SECTION III

MATERIALS

USAF Demographics

A computer generated report from Manpower and Personnel Center will give the following demographic data.

1. Number of males 20-44 years of age in the USAF total and by 5-year age group 1975-1984
2. Number of males 20-44 years of age in the USAF by race: total and by 5-year age group 1975-1984 (black/white)
3. Number of males 20-44 years of age in the USAF by rank: total and by 5-year age group 1975-1984. (commissioned/enlisted).
4. Number of males 20-44 years of age in the USAF by flying status: total and by 5-year age group 1975-1984, (flying/non-flying).
5. Number of males 20-44 years of age in the USAF total and by 5-year age groups for these subgroups: 1975-1984.
 - a. White/Commissioned/Flyer
 - b. White/Noncommissioned/Flyer
 - c. White/Commissioned/Nonflyer
 - d. White/Noncommissioned/Nonflyer

- e. Black/Commissioned/Flyer
 - f. Black/Noncommissioned/Flyer
 - g. Black/Commissioned/Nonflyer
 - h. Black/Noncommissioned/Nonflyer
6. Number of males 20-44 in the USAF grouped by major AFSC heading.

National Incidence

U.S. national age and race specific testicular cancer incidence rates from:

1. *SEER Program Incidence and Mortality in the United States.* DHHS

Publication # (NIH) 85-1837 Washington D.C.

2. Computer tapes containing most recent unpublished SEER data on US

national age and race specific testicular cancer incidence rates from
Demographic Analysis Section
Biometry Branch
National Cancer Institute
Bethesda, Maryland 20205

Hardware

Processing of the data will be done by microprocessor using the following hardware Microprocessor: Macintosh Plus, MC 68000 32 bit internal architecture, 1 megabyte RAM, 128 thousand bytes of ROM, 800 thousand bytes double sided 3.5 inch disc.

Software

The data will be entered and processed using the following software program.

- A. Statview 512+ available from
Brain Power Inc.
24009 Ventura Blvd
Suite 250
Calabasas, CA 91302

SECTION IV

DATA ANALYSIS

Historical Cohort: Variables to be Analyzed

Using data from MPC (person years at risk: total and by race, rank and flying status, for the period 1975 to 1984) and the WHMC Department of Urology Testicular Cancer Registry (new cases of testicular cancer:, for the period 1975 to 1984) incidence density rates (crude age, race rank and occupation specific) of testicular cancer for the USAF will be calculated.

Using data extracted directly from SEER Program reports U.S. incidence rates (crude and age specific by race) for testicular cancer will be calculated

Combining USAF incidence density rates and U.S. national incidence density rates calculate incidence density ratios (crude and age specific) for the total force and by race, rank and occupation. The risk of disease is sufficiently small (under 0.05 for both the exposed and unexposed groups) the value of this "rate ratio" will be nearly identical to a calculated odds or risk ratio and should give an accurate indication of the magnitude of the association between USAF service and the risk of testicular cancer.

Using data from MPC (person years at risk total and by race, rank and

occupation, 1975 to 1984) and the SEER Program (U.S. incidence rates crude and age specific by race the expected number of testicular cancer cases (crude race, rank and flying status specific) will be calculated.

Case Comparison: Variables to be Analyzed

For cases, using the WHMC testicular cancer registry, extract the year of diagnosis, age, race, rank, and armed forces speciality code data for all cases of testicular cancer in active duty USAF males between the ages of 20-44 diagnosed from 1975-1984 listed in the testicular cancer registry.

For control subjects using the WHMC admissions and dispositions data base identify by month of admission all active duty USAF males between the ages of 20-44 admitted to the WHMC Urology Service from 1975-1984 and, for each case of testicular cancer, identify the first 2 patients matched for month and year of admission, age, race, and rank as controls and extract information on armed forces speciality code.

Historical Cohort Statistical Analysis.

Differences (statistically significant) between the observed number of cases of testicular cancer, taken from the testicular cancer registry, and the expected number of testicular cancer cases, calculated from the SEER data, in the non age standardized groups will be tested against the null hypothesis (H_0) : observed = expected.

A level of significance $p < 0.05$ will be set: i.e. values of p smaller than 0.05 indicate that the probability of observed = expected is very small and that observed $\neq$ expected is more likely. Or, smaller p -values give stronger evidence for the alternative hypothesis H_A (observed $\neq$ expected) over the null hypothesis H_0 (observed = expected)

The equation is
$$Z = \frac{(\text{OBSERVED \# of CASES}) - (\text{EXPECTED \# of CASES})}{(\text{EXPECTED \# OF CASES})^{1/2}}$$

Next the age-standardized incidence rates (SIR) for USAF commissioned members, black and white, will be compared to the SIR for USAF enlisted members, black and white and the SIR for USAF members flying status, black and white will be compared to the SIR of USAF members non-flying status, black and white looking for statistically significant differences.

The notations, equation and significance level are given on the next two pages.

$X_{fc/bw}$ = Observed incidence rate of testicular cancer in flying status or commissioned members black or white by five year age group.

$X_{ne/bw}$ = Observed incidence rate of testicular cancer in non-flying status or enlisted members, black or white by five year age group.

X = $X_{fc/bw} + X_{ne/bw}$

$PY_{fc/bw}$ = Person years at risk in flying status or commissioned, black and white

$PY_{ne/bw}$ = Person years at risk in non-flying and enlisted, black and white.

PY = $PY_{fc/bw} + PY_{ne/bw}$

$E_{fc/bw}$ = $X(PY_{fc}/PY)$ = Expected number of case in flying status or commissioned black and white

$E_{ne/bw}$ = $X(PY_{ne}/PY)$ = Expected number of cases in non flying or enlisted black and white

Test for significant differences by assuming that there is no difference between the underlying age specific rates in any two groups. (Null Hypothesis) Thus, assume there is no difference between the observed incidence rates in flyers vs nonflyers (black and white) and the observed incidence rates in officers vs enlisted (black and white). The level of significance will be set at $p < 0.05$. i.e.: If p value is less than 0.05 then the probability that the underlying age specific rates between any two groups is equal is very small and the probability that the underlying rates are different

is high. Therefore there is a significant difference.

FIGURE 4

MODIFIED MANTEL HAENSZEL TEST STATISTIC

To test H_0

$$Z = \frac{\{\sum \text{of } X_{fc/bw} \text{ from } 20-24 \text{ to } 40-44\} - \{\sum \text{of } E_{fc/bw} \text{ from } 20-24 \text{ to } 40-44\}}{\sum \text{ from } 20-24 \text{ to } 40-44 \text{ of } \{ (X_{fc/bw} + X_{nd/bw}) \times \frac{PY_{fc/bw}}{PY} \times \frac{PY_{ne/bw}}{PY} \}^{1/2}}$$

Case Comparison Statistical Analysis

All cases of testicular cancer in active duty 20-44 year old males will be sorted by major career field (AFSC first digit identification number). All controls will also be sorted on the same basis. Then 2x2 tables will be constructed for each of the major AFSC career fields vs positive or negative for testicular cancer.

		TESTICULAR CANCER		
		+	-	
SPECIFIC AFSC	+	A	B	S
	-	C	D	N-S
		N1	N2	N

Then odds ratios for each of the major AFSC career fields will be calculated by the method AC/BD . 95% confidence limits for the odds ratio will be calculated by the following method:

FIGURE 5

The 95% confidence interval for $p_1 - p_2$ is

$$\underline{(p_1 - p_2) \pm 1.96 \times \text{standard error (se) of } (p_1 - p_2)}$$

where

$$p_1 = A/N_1$$

$$q_1 = C/N_1$$

$$p_2 = B/N_2$$

$$q_2 = D/N_2$$

$$\text{se}(p_1 - p_2) = \{p_1 q_1 / N_1 + p_2 q_2 / N_2\}^{1/2}$$

SECTION V

DISCUSSION

The goal of this research proposal is to develop enough information on the distribution of testicular cancer in USAF males to propose specific analytic studies.

Parameters presented for suggested analysis in this proposal are: 1) Comparison of USAF crude and age-specific testicular cancer incidence rates by race occupation and social class with crude, age, and race specific U.S. national testicular cancer incidence rates for significant differences. 2) Comparison of USAF crude, age and race specific testicular cancer incidence rates between officers with enlisted personnel and between flying and non-flying occupations. 3) Comparison between armed forces speciality codes of the strength of association with testicular cancer.

From information available in the literature several preliminary predictions could reasonably be made. Testicular cancer incidence (age and race specific) will probably be higher in the USAF than in the U.S. population, and rates of testicular cancer in the commissioned ranks should be higher than enlisted and U.S. national rates. This would be expected from the constant finding across many studies of higher rates of testicular cancer in higher social classes. Higher educational levels and higher rank can generally be associated with higher social class. For this reason the USAF population as a whole will generally be of higher social class than the U.S.

population and officers of a higher class than enlisted personal. What is not as clear is whether there will be any differences between flying and non-flying rates or higher rates of testicular cancer within major AFSC's groups.

It will be interesting if there are very large differences between the USAF rates and national rates or, within the Air Force, between subgroups, i.e. officer >> than enlisted or flyer >> than non-flyers or higher rates in certian AFSC groups, where occupational exposures might be related to the etiology of the neoplasm. If this were the finding then maximal investigational attention could be focused, on these areas. An immediate possiblity, if occupational etiology in USAF members was suspected from the case comparison analysis of AFSC's, would be to start an analysis of the various high risk occupations using the USAF's occupational exposure/AFSC catalog, maintained by the Air Force Logistics Command at Wright Patterson Air Force Base Ohio. All available current information on significant hazardous occupational exposures are filed and cross referenced in this catalog by AFSC. Particularly close attention could be focused in looking for frequent exposure to some common suspicious work exposure such as electromagnetic radiation from radio or radar work. This would necessitate a hypothesis of early life testicular cancer initiation followed by some occupational exposure acting as a promoter, a concept which follows nicely from much of the recent work on cancer development.

Significant difference in testicular cancer rates, whether across the entire Air Force or within specific groups should be reported through administrative channels to

the highest levels of the USAF Medical Service immediately. Notice from the USAF Surgeon General's Chief of Clinical Services to all medical treatment personnel of higher rates of testicular cancer in military persons would sensitize physicians to closer examination of the testis during physical examinations and, where appropriate, during office visits. Additionally as stressed by public health philosophy, the possible benefit of self examination could be stressed and taught. The major determinant of successful treatment and cure of testicular cancer is early detection.

The results of this study, particularly if results positive for a correlation between military service and testicular cancer were found, should be published in a journal with a broad military physician audience. The Journal of Aviation Space and Environmental Medicine or the Journal of Military Medicine would be the primary choices. If the results are positive only for already known and appreciated risk factors then publication would be sought in the Journal of Epidemiology and Community Health or the International Journal of Epidemiology.

SCHEDULES

Time Schedules

Because of the centralized availability of the needed data time requirements for the actual project should be relatively short term. The greatest amount of effort and time will be expended making official written and personal contact with the responsible authorities.

1. Written explanations of the project with accompanying request for permission to conduct the study to

- a. The Office of the Surgeon General United States Air Force.
- b. The Commander of Manpower and Personal Center.
- c. The Commander of Wilford Hall Medical Center.

1 Month

2. Written clarifications of questions and personal contacts and granting of approvals.

6 to 8 months

3. Coordination of approvals between the agencies involved.

1 Month

4. Data collection and analysis.

3 Months

Budget

The cost breakdown for this project should be limited to two major items.

I. Manhours

A. Investigator

1. Requests for permission

a. 1 month at 10% **16 hours**

2. Clarification/personal contact/approvals

a. 6 to 8 months at 2.5% **24 to 36 hours**

3. Coordination

a. 1 month at 15% **24 hours**

4. Data collection/analysis

a. 3 months at 50% **240 hours**

B. Personal specialist/Computer operator

1. Data Collection at MPC

a. 1 week at 100% **40 hours**

II. Main frame computer time

A. MPC computer data retrieval and collation **2.5 to 5 hours**

Software, microprocessor, SEER DHHS reports, are personal inventory of the investigator.

Appendix 1

Testicular cancer incidence rate for U.S white males ages 20-44.

$$\approx 10 \text{ cases}/100,000 \text{ persons/year} = 10 \text{ cases}/100,000 \text{ person years}$$

USAF base, 3 year period, July 1984 to July 1987.

3 Cases of testicular cancer in flying personal

Total flying population on base (male) ≈ 500 persons

Total person years at risk

$$\underline{500 \text{ persons} \times 3 \text{ years} = 1500 \text{ person years at risk}}$$

Equation for probability under the Poisson distribution

$$\Pr[x=k] = (e^{-\mu} \mu^k)/k!$$

Where

μ = the mean of the number of expected cases

k = the number of cases seen

x = the mean of the number of sample cases

Expected number of cases

$$\underline{10 \text{ cases}/100,000 \text{ person years} \times 1500 \text{ person years at risk} = .15 \text{ cases}}$$

If the $\Pr[x>3] = 1 - \Pr[x \leq 2] = \Pr[0] + \Pr[1] + \Pr[2]$ then

$$\begin{aligned} 1 - \Pr[x \leq 2] &= 1 - (e^{-\mu}) + (e^{-\mu} \mu) + (e^{-\mu} \mu^2 / 2) = 1 - (e^{-.15}) + (e^{-.15} \cdot .15) + (e^{-.15} \cdot .15^2 / 2) \\ &= 1 - (0.8606 + 0.12911 + 0.00968) = \mathbf{0.00050} \end{aligned}$$

There is less than 0.5 chances in 1000 of this event (three cases of testicular cancer in a three year period in a population of 500) occurring if the observation and study group had been defined *a priori* and the observations made later.

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VITA

Emmet Paul Murphy [REDACTED] He is the eldest child of Dorothy Mae ([REDACTED]) Murphy and Paul John Murphy also of Minnesota. After graduating from El Cajon Valley High School in June 1968 he served three years in the United States Army. In 1975 he was awarded an Associate of Arts degree from Grossmont Community College, El Cajon California. In 1976 he entered the University of California at San Diego and graduated in June of 1978 Magna Cum Laude with a Bachelor of Arts degree in Biology. In 1979 he began medical studies at the University of California San Diego School of Medicine graduating with a Doctor of Medicine in June 1983. From June of 1983 to June of 1984 he completed the first year of residency in Internal Medicine through the University of California at San Francisco School of Medicine. In 1984 he was awarded his Flight Surgeon rating in the United States Air Force and was posted to RAF Lakenheath in the United Kingdom where he was Officer in Charge of Flight Medicine. In June of 1988 he graduated with a Masters of Public Health from the University of Texas at Houston. He is presently in the second year of the Residency in Aerospace Medicine at Brooks Air Force Base, Texas.

He is Married to Marilyn Jeanne ([REDACTED]) Murphy and they have four children: Eric, [REDACTED]; Kristin, [REDACTED]; Heather, [REDACTED]; and Ryan, [REDACTED]

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