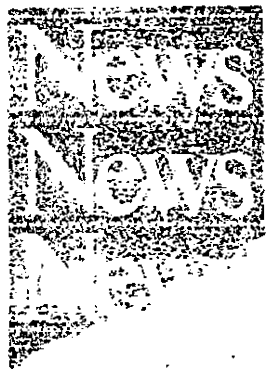


relative risk of 1.1 of testicular cancer for Army troops and a 1.3 risk for Marines who served in Vietnam.

Other mortality studies conducted during the mid 1980s have seen no difference in testicular cancer deaths in Vietnam veterans or have not looked at the tumors. Hayes said some of those studies simply did not address the issue of testicular cancer when they reported their findings. A 1988 study by the Centers for Disease Control "saw an unexplained but significant decrease" in sperm motility and concentration of "normal sperm cells" in Vietnam war veterans.

Richard L. Schilsky, M.D., of the University of Chicago Medical Center wrote in an August 16, 1989, editorial in this Journal that "The great majority of patients with testicular cancer also had diminished sperm production before therapy is initiated." He said that biopsies of the contralateral, non-tumor-bearing testis found abnormalities including "hyalinzed tubules, spermatogenic arrest, absence of germinal epithelium, and carcinoma in situ," leading Schilsky to speculate that a common genetic or environmental factor may be responsible.

The Armed Forces Institute of Pathology necropsy reports on the dogs provided data for the Hayes study. AFIP's files are a unique resource for epidemiologists, Hayes said.

Most of the dogs were German Shepherds, entered the military under 3 years of age, and had to pass rigorous physical examination. Each of the dogs was tattooed and permanent health records kept. When a dog died, regardless of circumstances of death or duty location, a necropsy was performed by a veterinarian and a standardized set of tissue specimens and major organs were sent to the Armed Forces Institute of Pathology in Washington, DC.

—By Francis X. Mahaney, Jr.

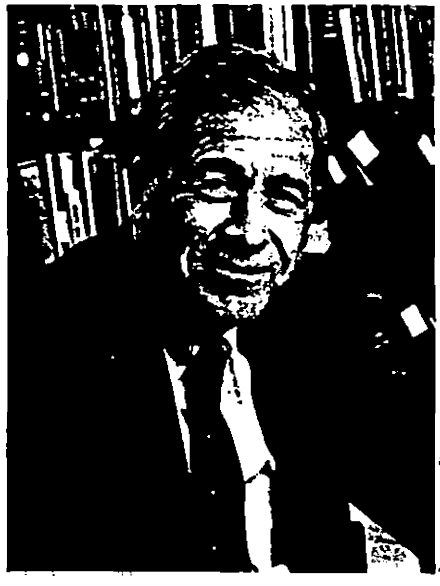
Tamoxifen With or Without Chemotherapy?

The American Society of Clinical Oncology meeting in Washington last month was the forum for results from two major studies of adjuvant therapy for node-positive breast cancer patients which, in effect, yielded contradictory results. The researchers involved, however, agreed that the studies couldn't really be compared in the first place.

Chemo Plus

A regimen of chemotherapy and tamoxifen was found far superior to tamoxifen alone in a study headed by Bernard Fisher, M.D., director of the National Surgical Adjuvant Breast and Bowel Project and professor of surgery at the University of Pittsburgh.

"Patients who received chemotherapy in combination with hormone therapy had significantly increased disease-free and distant disease-free survival and significantly reduced mortality rates when compared with women who received the standard treatment of hormone therapy alone," explained Fisher.



Dr. Bernard Fisher

More than 1,100 women over 50 years of age with "tamoxifen-responsive" tumors were randomized to tamoxifen alone, or Adriamycin, cyclophosphamide, and tamoxifen. The group receiving ACT had a 50% reduction in mortality and a 41% reduction in treatment failure compared to those receiving tamoxifen alone.

"Clearly, postmenopausal breast cancer patients who are node-positive will have a greater chance of survival and less chance of disease recurrence if they are given a chemotherapy regime in addition to tamoxifen," said Fisher.

Only Tamoxifen

Meanwhile, Saul E. Rivkin, M.D., of the Swedish Hospital Medical Center Tumor Institute in Seattle, presented results of an Intergroup trial of chemotherapy verus tamoxifen versus both where all three treatment arms were equal in efficacy.

In this trial, 966 postmenopausal, node-positive, estrogen-receptor positive women were treated with cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone alone, CMFVP and tamoxifen, or tamoxifen alone.

"CMFVP chemotherapy alone, or in combination with tamoxifen, was not shown to prolong survival or disease-free survival compared to tamoxifen alone, in ER-positive, node-positive, postmenopausal breast cancer," summed Rivkin.

"The study results suggest that tamoxifen is the standard against which

Excess of Seminomas Observed in Vietnam Service U.S. Military Working Dogs

Howard M. Hayes, Robert E. Tarone, Harold W. Casey, David L. Huxsoll*

During the Vietnam War, US military working dogs served with their companion dog handlers in close proximity, sharing common exposures to war-related activity, many zoonotic infectious agents, chemical pesticides, phenoxy herbicides, and extensive use of therapeutic drugs. To gain insight into the effects of the Vietnam experience, we investigated the occurrence of neoplasms in military working dogs based on standard necropsy examination by the Armed Forces Institute of Pathology. We observed that these dogs experienced significant elevated risks for testicular seminoma and, independently, testicular dysfunction. Experimental evidence shows testicular dysfunction and impaired spermatogenesis in laboratory animals exposed to phenoxy herbicides, dioxin, or tetracycline, an antibiotic used extensively in military working dogs in Vietnam. Because an unexplained significant decrease in sperm quality in Vietnam veterans has been observed by the Centers for Disease Control, further research is warranted if we are to clarify military service in Vietnam as a risk factor for testicular dysfunction. The testis should be made a priority site in the study of Vietnam experience-related cancers. [J Natl Cancer Inst 82:1042–1046, 1990]

US military working dogs (MWD) proved to be sentinels for the presence of zoonotic infectious agents in their military dog handlers in southeast Asia (*1,2*). Because the dog has been demonstrated to be a useful indicator of carcinogenic risk to humans (*3–5*), examination of the occurrence of neoplasia in MWDs serving in southeast Asia may be useful in an assessment of whether service in Vietnam led to increased cancer risk in humans. To determine if service in that country led to increased cancer risk in dogs, we compared their experience with that of MWDs that served in the continental United States (CONUS) during the same time.

Materials and Methods

During the Vietnam conflict, MWDs were purchased by the US government from private citizens. Most of these animals were phenotypic German shepherds, although occasionally other breeds were obtained for special purposes. Each dog had to be 1 to 3 years of age, have suitable body conformation, and pass a rigorous physical and medical examination (*6*). About 91% of the MWDs were intact males.

Each animal accepted for the MWD program was tattooed with a unique identity number which, with permanent administrative and health records, accompanied the MWD throughout its duty (*7*). Most MWDs either worked as scouts with forward elements or as sentries in security units at fixed installations (*7,8*).

Each MWD was assigned to a military handler who was responsible for its immediate care, feeding with standard rations, and day-to-day evaluation of performance. Outpatient care was provided by a trained veterinary technician, who also updated the medical records; serious medical problems were referred to a military veterinarian (*9*).

When an MWD died, regardless of the circumstances of death or the duty location, a necropsy was performed by a veterinarian, and a standardized set of tissue specimens and major organs was submitted to the Armed Forces Institute of Pathology (AFIP) in Washington, D.C. for histopathologic evaluation (*10*). Evaluations were made by at least two veterinary pathologists, including one who was board certified; final necropsy reports were maintained for historical purposes. One co-author (Casey) personally reviewed or supervised over 90% of all the histologic diagnoses considered in this study. Each necropsy report contains the MWD's breed (99% were German shepherds), tattoo number, name, age, sex, date and circumstances of death, and duty location at time of death (*11*).

Permanent military service records, which could be used to identify all MWDs with Vietnam service, are not available for computer access. Thus we could identify unequivocally as dogs with Vietnam service only those animals listed on necropsy reports as having died in Vietnam, and 199 additional MWDs identified from military correspondence as having been returned alive from Vietnam in 1971–1973, usually to the United States. Sixty-four of these 199 dogs have been described in detail (*2*).

Although military dog handlers usually rotated out of Vietnam after about 1 year of service, the MWD typically remained to be teamed with a new handler. This process, which involved evaluation and possibly retraining, often took place in Okinawa. A considerable number of Vietnam MWDs undergoing reevaluation did not perform at acceptable levels and were euthanized. Thus many MWDs with Vietnam service were reported on the AFIP records as having died in Okinawa. In other Asian duty stations (e.g., Japan, Korea, and Thailand), new dog handlers were usually united with their military dogs "in-country," thereby minimizing the possible diversion of MWDs to Vietnam and vice versa.

Our analysis was restricted to the results of necropsies conducted on MWDs 3 years of age and older who were identified by a complete tattoo number. The AFIP records were searched for necropsy reports of all such MWDs that died in CONUS, Vietnam, Okinawa, Japan, Korea, or Thailand from 1968, the first year of complete data available for study, through 1973. Identified were 1,167 MWDs with known Vietnam service, 437 that died in Okinawa and thus may have served in

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H. M. Hayes, R. E. Tarone, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Md.

H. W. Casey, Department of Veterinary Pathology, School of Veterinary Medicine, Louisiana State University, Baton Rouge, La.

D. L. Huxsoll, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Md.

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**Correspondence to:* Howard M. Hayes, D.V.M., Environmental Epidemiology Branch, Executive Plaza North, Rm. 443, National Institutes of Health, Bethesda, MD 20892.

Vietnam, 483 that died in either Japan, Korea, or Thailand and probably did not see service in Vietnam, and 791 that died in CONUS and had no known Vietnam service. Of the 199 Vietnam veteran MWDs known to have left Vietnam alive, 18 were identified in AFIP records as MWDs dying in CONUS or elsewhere between 1971 and 1973; these 18 were included in the Vietnam service cohort.

We computed the prevalence of neoplasms at necropsy for each group and compared the prevalence rates from Asian duty stations with those from CONUS. Conditional maximum likelihood estimates of prevalence odds ratio (OR) were calculated, with associated exact 95% confidence intervals (CI), and adjusted for age and sex (*12*). Generally, the relationship between rates for tumor incidence and prevalence at necropsy for occult tumors is not a simple one (*13*). For nonlethal tumors such as seminomas in the dog, however, there is a direct relationship between incidence and prevalence rates (*13*), so that elevated prevalence ORs indicate elevated relative risks for tumor incidence.

Results

There were no significant differences in the occurrence of tumors in general, malignant neoplasms of any cell type, carcinomas of any site, soft tissue sarcomas, or malignant lymphomas in any of the duty locations, compared with the CONUS referent MWDs (table 1). No present evidence indicates that service in Vietnam led to increased risk in MWDs for soft tissue sarcoma or lymphoma, cancers for which herbicide exposure has been proposed to be a risk factor in Vietnam veterans. However, statistically significant elevations in ORs were evident for all testicular tumors combined and for testicular seminomas among MWDs with known Vietnam service and those that died in Okinawa (table 1).

To corroborate or refute the excess relative risk for testicular seminoma among MWDs with known Vietnam service dying between 1968 and 1973, we searched AFIP records through 1978 (the last year complete data were available for this study) for necropsy results about those Vietnam veteran MWDs known to have left Vietnam alive. Identified were 96 unneutered males that died between 1974 and 1978. With the same analytic method and using the necropsy reports of 682 CONUS MWDs without known Vietnam service dying in the period 1974–1978 as the standard (OR = 1), we observed the 96 Vietnam veteran MWDs to have a significant excess risk for seminoma, which supported the findings in the earlier period. The incremental ORs by age for seminoma in Vietnam veteran MWDs are presented for both periods in table 2. Combined analysis of both cohorts, adjusted for age and time, gives an overall OR of 1.9 (CI = 1.4, 2.8) for seminoma in MWDs known to have served in Vietnam.

Abnormalities of spermatogenesis are common at the time of diagnosis of testis cancer in man (*14,15*); it has been suggested that common genetic or environmental factors are responsible for the impaired spermatogenesis and the development of germ cell tumors of the testis (*16,17*). An examination of the AFIP necropsy records for MWDs dying between 1968 and 1973, excluding those with known endogenous factors related to altered spermatogenesis (i.e., those with testicular neoplasm, hypoplastic testis, orchitis or epididymitis, or those that were cryptorchid), revealed that testicular dysfunction (degeneration, atrophy, and/or oligospermatogenesis) was diagnosed significantly more often in MWDs in Vietnam (OR = 1.7; CI = 1.1, 2.6) and in Okinawa (OR = 2.0; CI = 1.2, 3.3), when compared with those in CONUS.

Discussion

No obvious sources of bias could have led to a spurious finding of increased risk of testicular dysfunction and testis tumors in Vietnam MWDs. If selection for service in Vietnam was based on factors or characteristics that are also related to testicular tumor risk, this could have resulted in bias. Dogs were allocated to Vietnam in groups as needed, without consideration being given to characteristics of individual animals. For example, no difference was noted in the percentage of female MWDs serving in Vietnam and other duty stations. Bias also could have resulted if a cause of death was more common in Vietnam and Okinawa than in CONUS, and if this was positively associated with testicu-

Table 1. Percent (%) frequency and prevalence OR, adjusted for age and sex, of certain neoplasms observed among necropsied MWDs by duty experience, 1968–1973*

Neoplasm	CONUS		Vietnam			Okinawa			Other Asian countries†		
	%	OR	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
Tumor, any cell type	15.2	1	13.3	1.1	(0.8, 1.4)	21.5	1.3	(1.0, 1.9)	14.8	0.8	(0.6, 1.1)
Malignant tumor, any cell type	4.7	1	3.3	0.9	(0.5, 1.5)	5.5	1.1	(0.7, 2.0)	7.6	1.6	(0.9, 2.6)
Soft tissue sarcomas	2.0	1	0.8	0.5	(0.2, 1.3)	2.5	1.2	(0.5, 2.8)	2.3	1.0	(0.4, 2.4)
Carcinoma, any site	1.6	1	1.5	1.2	(0.5, 2.7)	2.1	1.2	(0.5, 3.1)	2.5	1.4	(0.6, 3.3)
Malignant lymphoma	0.8	1	0.4	0.6	(0.2, 2.4)	0.5	0.5	(0.1, 2.6)	1.2	1.3	(0.4, 4.5)
Testis tumor, any cell type	7.3‡	1	8.5	1.8§	(1.2, 2.7)	15.4	2.2§	(1.5, 3.4)	5.8	0.7	(0.4, 1.2)
Seminoma	4.7	1	6.3	1.9§	(1.2, 3.0)	11.2	2.6§	(1.6, 4.3)	4.2	0.8	(0.4, 1.5)
Interstitial cell tumor	2.1	1	2.0	1.7	(0.8, 3.6)	3.7	1.8	(0.8, 3.9)	1.1	0.5	(0.2, 1.5)
Sertoli cell tumor	1.4	1	1.0	1.0	(0.4, 2.6)	2.2	1.6	(0.6, 4.3)	0.9	0.6	(0.2, 2.2)

*Of the MWDs identified, 791, 1,167, 437, and 483 served in CONUS (known Vietnam veterans excluded), Vietnam, Okinawa, and other Asian countries, respectively.

†Data for Japan, Korea, and Thailand are combined.

‡Data are sex specific; for unneutered male dogs: CONUS = 727, Vietnam = 1,086, Okinawa = 402, other Asian countries = 450.

§$P < .05$.

Military Working Dogs May Be A Sentinel for Human Cancer

Military working dogs and their handlers who served in Vietnam faced more risks than those from the enemy, a report in this issue indicates. (*See* page 1042).

The dogs and their handlers were exposed in Vietnam to Agent Orange and other phenoxy herbicides, chemical pesticides, zoonotic infections, and "the extensive use of therapeutic drugs" to fight off bacterial infections. For example, from 1965–1970, more than 11 million gallons of Agent Orange were sprayed over Vietnam during "Operation Ranch Hand."

Until now, few studies have been able to quantitate the health effects of the environmental exposures associated with the Vietnam experience.

Testicular Cancer

But Howard M. Hayes, D.V.M., of the National Cancer Institute, and his coauthors believe that military working dogs who served in Vietnam may be a "sentinel" for the related health effects of the Vietnam experience in humans.

In particular, Hayes said, the dogs may be a "useful indicator of carcinogenic risk" to the Vietnam war veteran.

Hayes and his colleagues report they found a two-fold excess of testicular tumors and independently, testicular dysfunction in military working dogs who served and died in Vietnam.

Of the 96 male dogs that returned intact and alive from Vietnam and died between 1974-1978, 25 were diagnosed with testicular tumors, again a two-fold excess. According to Hayes, the military dogs were exposed to herbicides and insecticides for longer periods of time than their soldier handlers who were usually rotated out of Vietnam within a year.

In addition, high doses of tetracycline were given to the dogs. The antibiotic has been shown in vitro to lead to reduced sperm quality in man and dog, and testicular atrophy has been reported in the rat and the dog, the authors said.

The anatomic development of the male genital tract, testis descent and tunica albuginea relationship in the dog closely parallel man, Hayes said. Histologically, canine seminomas are identical to the classic testicular tumors found in man, except that in the dog they are usually benign.

And the Vietnam Vets

An ongoing study conducted by the U.S. Air Force on Air Force veterans involved in the spraying of herbicides during Operation Ranch Hand so far has identified three cases of testicular cancer among 995 veterans in the Ranch Hand group and no testicular cancers in 1,299 Air Force controls, Hayes said. Additionally, a mortality study of West Virginia veterans by the West Virginia Health Department in 1986 "did find a significant increase in testicular cancer deaths (3 cases observed versus 0.6 expected) among Vietnam veterans compared to Vietnam-era veterans who did not serve in Vietnam," Hayes added.

Another study by the Veterans Administration showed a nonsignificant

Infantry scout dogs bring up the rear during the Tet offensive on February 1, 1968. Photo by Jim Doyle.

Table 2. Frequency of testicular seminoma, by age, observed among MWDs by necropsy period; prevalence OR, adjusted for age, for seminoma in Vietnam MWDs

Age (yr)	MWDs, 1968-1973					MWDs, 1974-1978				
	CONUS		Vietnam		OR	CONUS		Vietnam veteran		OR
	No. of cases	No. of necropsies*	No. of cases	No. of necropsies*		No. of cases	No. of necropsies*	No. of cases	No. of necropsies*	
3-4	1	135	6	313	2.6	1	30	0	0	—
5-6	1	126	17	317	7.1†	1	51	1	5	12.5
7-8	11	229	28	307	2.0	10	133	4	22	2.7
9-10	17	197	17	137	1.5	48	309	14	45	2.5†
11-12	3	37	0	11	0	35	148	6	24	1.1
13-14	1	3	0	1	0	3	11	0	0	—
			Summary OR = 1.9 (95% CI = 1.2, 3.0)					Summary OR = 2.0 (95% CI = 1.2, 3.5)		

*Values represent total number of necropsies of unneutered male dogs.
†95% CI excludes 1.

lar tumor risk. No evidence was seen for such a source of bias, and the finding of an increased risk of testis tumor in Vietnam veteran MWDs dying in CONUS during 1974–1978 argued against such a bias. Given the strength of the observed associations and the lack of identifiable sources of bias, we conclude that some factor(s) or exposure(s) associated with service in Vietnam had a deleterious effect on the testes of MWDs and led to increased testicular tumor risk.

The anatomic development of the male genital tract, testis descent, and tunic relationships in the dog closely parallel that in man (*18*). Man and dog also share most of the same epidemiologic features regarding tumor development, although they differ in cell type frequencies and overall frequency of occurrence. Embryonal carcinomas and teratomas predominate in children and seminomas in adults, but Sertoli cell and interstitial cell tumors, which occur in equal proportion to seminoma in the dog, are very rare in man (*19*). Man and dog share many of the known risk factors, including the strong association with cryptorchism and to a lesser extent inguinal hernia (*19,20*), and occasional familial tendencies (*21*). Histologically, canine seminoma is identical to the classic seminoma seen in man, except that in the dog it is usually benign, as are most canine testis tumors (22). Because of a significant predisposition to seminoma development in the German shepherd (*23*), MWDs may be a particularly sensitive sentinel for exposure(s) leading to increased seminoma risk in man.

MWDs that served in Vietnam were exposed to many infectious zoonotic agents (*1,2*) and native parasites; harsh ambient working conditions; extensive therapeutic treatment with drugs, particularly tetracyclines (*24*); and levels of man-made chemicals not experienced by their CONUS counterparts. It is unclear whether any of these factors affected the increased risk of testicular dysfunction and seminoma in Vietnam MWDs, but some of the exposures have been demonstrated to have adverse affects on sperm quality, spermatogenesis, and testicular tissue.

Many Vietnam MWDs received extensive treatment with tetracyclines for ehrlichiosis, a parasitism caused by a tick-borne rickettsial organism. No immunity was imparted following recovery (*25*), and thus many Vietnam MWDs received regimens of tetracycline two or more times during one duty tour. No mention was made of testis pathology with canine ehrlichiosis prior to the Vietnam era (*26,27*), and no association was observed in this study between ehrlichiosis and testicular dysfunction or seminoma.

Tetracycline is known to be strongly absorbed by mammalian spermatozoa in vivo and in vitro (*28,29*). Testicular atrophy has been reported in the tetracycline exposed rat and dog (*30,31*), as has impaired spermatogenesis in in vivo rat studies (*32–34*). Furthermore, in vitro exposure to tetracycline has led to reduced sperm quality in man and dog (*35,36*). Thus extensive tetracycline exposure may have contributed to the increased risk of testicular problems observed in Vietnam service MWDs.

Testicular involvement and dysfunction have been observed in laboratory animals exposed to phenoxy herbicides used extensively in Vietnam. Feeding studies with rats have shown chlorinated dibenzo-*p*-dioxin in the testis (*37*). Furthermore, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induces arylhydrocarbon hydroxylase activity (*38*) and binds to receptor proteins in the rat testis (*39*). Investigators (*40–47*) have demonstrated testicular dysfunction in six laboratory animal species after exposure to phenoxy herbicides or dioxin. Although some have argued that these abnormalities are a secondary effect due to wasting (*42,43*), abnormally reduced androgen levels (*48*), decreased steroidogenesis (*49*), and enhanced lipid mobilization and peroxidation (*50*) have been identified in rats as likely being responsible for the testicular effects rather than nutritional deprivation.

Available evidence, although limited, shows that other chemicals sprayed extensively in Vietnam [picloram (*51*), a component of the herbicide Agent White, and malathion (*52–54*), an insecticide used to control mosquitos] also cause testicular atrophy and damage to the seminiferous tubules in laboratory animals. MWDs in Vietnam and Okinawa received considerable direct exposure to malathion, as they were regularly dipped in a 0.5% solution for tick control following the *Ehrlichia* epizootic in 1968–1969 (*8,55*).

Epidemiologic studies of cancer risk in Vietnam veterans have, for the most part, assessed mortality. For the most part, mortality has been assessed in epidemiologic studies of cancer risk in Vietnam veterans. However, high survival rates of testicular

cancer patients (*56*) limits the power of mortality studies to detect increased testis cancer risk in Vietnam veterans. A mortality study in West Virginia did reveal a significant increase in testicular cancer deaths (three cases observed vs. 0.6 expected) among Vietnam veterans compared with Vietnam-era veterans who did not serve there (*57*). Another such study conducted by the Veterans Administration reported nonsignificant elevated relative risks of 1.1 for US Army personnel and 1.3 for US Marines who served in Vietnam (*58*). Other mortality studies have shown no difference in testicular cancer death rates between veterans of Vietnam and those who did not serve there (*59,60*) or have not addressed the issue (*61–63*).

One ongoing study (*64*) of cancer incidence in Vietnam veterans is the prospective investigation of US Air Force veterans involved in the spraying of herbicides in Operation Ranch Hand (RH). A recent update from the RH incidence study notes three confirmed cases of testicular cancer in 995 individuals in the RH group and none in 1,299 US Air Force controls (Michalek J: unpublished results). The recent Vietnam Experience Study of the Centers for Disease Control that evaluated veteran physical health by medical examination (*65*) noted unexplained differences in semen quality of veterans 15+ years after leaving that country, including a decrease in sperm motility and significant decreases in sperm concentration and the average proportion of morphologically "normal" sperm cells. Semen evaluation of the RH cohorts, however, showed no difference in sperm count or percentage of abnormal sperm between RH members and their matched controls (*66*). However, a decrease in sperm concentration, although not significant, has been reported among selected Vietnam veterans from Texas, thought to have received high exposures to Agent Orange (*67*). Low sperm counts also have been reported in a self-selected group of Vietnam veterans claiming exposure to this herbicide (*68*).

At present, we have no convincing evidence that service in Vietnam led to increased risk of testicular cancer in veterans. However, the magnitude of the observed excess risk of testicular seminoma and dysfunction in MWDs serving in Vietnam strongly suggests that military service in Vietnam be considered a risk factor for testicular cancer.

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Phase I Trial of 5-Day Continuous Venous Infusion of Oxaliplatin at Circadian Rhythm-Modulated Rate Compared With Constant Rate

Jean-Pierre Caussanel, Francis Lévi, Silvano Brienza, Jean-Louis Misset, Moshe Itzhaki, René Adam, Gérard Milano, Bernard Hecquet, Georges Mathé*

The toxic effects and tissue uptake of both cisplatin and oxaliplatin—[(1*R*, 2*R*)-1,2-cyclohexanediamine-*N*,*N*'] [oxalato(2-)-*O*,*O*']platinum—were previously shown to vary similarly according to dosing time in mice. A 4-hour infusion of cisplatin resulted in fewer side effects and allowed administration of higher doses at 16 hours than at 4 hours in patients with cancer. We hypothesized that the continuous venous infusion of oxaliplatin for 5 days would be less toxic and would deliver a higher dose to the patient if the drug were infused at a circadian rhythm-modulated rate (peak at 16 hr; schedule B) rather than at a constant rate (schedule A). We tested this hypothesis in a randomized phase I trial. We escalated the dose of oxaliplatin to the patient by 25 mg/m^2 per course. Courses were repeated every 3 weeks. An external, multichannel, programmable-in-time pump was used for the infusions. Toxicity was assessable for 94 courses in 23 patients (12 patients with breast carcinoma, nine with hepatocellular carcinoma, and two with cholangiocarcinoma). The incidence of neutropenia of World Health Organization grades II–IV and the incidence of distal paresthesias were 10 or more times higher ($P < .05$) with schedule A than with schedule B. In addition, vomiting was 55% higher ($P = .15$) with schedule A than with schedule B. Furthermore, with schedule B, the mean dose of oxaliplatin ($P < .001$) and its maximum tolerated dose ($P = .06$) could be increased by 15% over those doses with schedule A. An objective response was achieved in two of the 1[illegible] patients with previously treated breast cancer. We recommend that the dose of oxaliplatin for phase II trials be 17[illegible] mg/m^2, delivered according to the circadian rhythm-modulated rate. [J Natl Cancer Inst 82:1046–1050, 1990]

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J.-P. Caussanel, F. Lévi, Unité de Recherc[illegible] Associée, Centre National de la Recherche Scie[illegible]tifique, Chronobiologie-Chronopharmacologie, Fo[illegible]dation A. de Rothschild, Paris, France.

J.-P. Caussanel, F. Lévi, S. Brienza, J.-L. Miss[illegible] M. Itzhaki, G. Mathé, Service des Maladies Sa[illegible]guines Immunitaires et Tumorales, Institut du Canc[illegible] et d'Immunogénétique, Association Clauc[illegible] Bernard, Hôpital Paul-Brousse, Villejuif, France.

R. Adam, Surgery Department, Hôpital Pa[illegible] Brousse, Villejuif, France.

G. Milano, Laboratorie d'Oncopharmacolog[illegible] Centre A. Lacassagne, Nice, France.

B. Hecquet, Laboratoire de Pharmacodynam[illegible] Centre O. Lambret, Lille, France.

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**Correspondence to:* Francis Lévi, M.D., Ph.[illegible] Unité de Recherche Associée, Centre National de Recherche Scientifique, Chronobiologie-Chron[illegible]pharmacologie, Service des Maladies Sanguines I[illegible]munitaires et Tumorales, Institut du Cancer d'Immunogénétique, Hôpital Paul-Brousse, 16, [illegible] Paul-Vaillant-Couturier, 94804 Villejuif Céd[illegible] France.