CENTERS FOR DISEASE CONTROL . Jan 82 .

COMPUTED TOMOGRAPHY OF THE CENTRAL NERVOUS SYSTEM

A symposium entitled "Update on Computed Tomography of the Central Nervous System" will be held at the Acapulco Princess Hotel in Acapulco, Mexico, February 25-March 2. The fee is $385.

Contact the Program Coordinator, Office of Continuing Education, Upstate Medical Ctr., State University of New York, 750 E. Adams St., Syracuse, NY 13210; or call GRO-C

PEDIATRIC DERMATOLOGY

The Ninth Annual Pediatric Dermatology Seminar will be held at the Carillon Beach Hotel in Miami Beach, Fla., February 25-28. The fee is $190.

Contact Dr. Guinter Kahn, 16800 N.W. 2d Ave., Miami, FL 33169; or call GRO-C

CLINICAL GENETICS

A symposium entitled "Clinical Genetics for Primary Care Physicians" will be held at the University of Wisconsin in Madison on February 26 and 27. The fee is $180.

Contact Sarah Z. Aslakson, Continuing Medical Education, 465B WARF Bldg., 610 Walnut St., Madison, WI 53706; or call GRO-C

MOTOR SKILLS

A seminar entitled "Ender Nailing: A Motor Skills Course with Hans Ender, M.D." will be held at the University of California–Davis Medical Center in Sacramento on February 26 and 27. The fee is $200.

Contact Ardi Neiswonger, Office of Continuing Medical Education, School of Medicine, University of California, Davis, CA 95616; or call GRO-C GRO-C

CLINICAL SYMPOSIUM

St. Jude Children's Research Hospital will hold its Sixteenth Annual Clinical Symposium on February 26 and 27 in Memphis. Registration is limited. There is no fee.

Contact the Associate Director for Clinical Research, St. Jude Children's Research Hospital, Box 318, Memphis, TN 38101; or call GRO-C

CARDIOLOGY

A seminar entitled "Acute MI — The First Six Hours" will be held at the Tampa Marriott Hotel in Tampa, Fla., on February 26 and 27.

Contact the American Heart Assoc., Hillsborough County Chapter, P.O. Box 4835, Tampa, FL 33677; or call (813) 253-0023.

CANCER AND VITAMINS

The First International Symposium on the Modulation and Mediation of Cancer by Vitamins will be held at the University of Arizona in Tucson, February 23-26.

Contact Mary Humphrey, University of Arizona Cancer Ctr., Tucson, AZ 85724; or call GRO-C

OCCUPATIONAL SAFETY AND HEALTH

The Occupational Safety and Health Winter Institute will be held in Daytona Beach, Fla., February 22-26.

Contact Larry D. Hyde, Occupational Safety and Health Educational Resource Ctr., University of North Carolina, 109 Conner Dr., Suite 1101, The Professional Village (346A), Chapel Hill, NC 27514; or call GRO-C

CORRECTION

Recurrent Genital Herpes: Reinfection or Reactivation? (1981; 305:1586-7, Dec. 24). In the reply by Corey, Holmes, and Reeves on page 1587, the next to the last sentence in the second paragraph should have read as follows: "New sexual partners were reported by 36 per cent of patients who did *not* have recurrences, as compared with 14 per cent of those who *did* ($P<0.05$)." We regret the error.

SPECIAL REPORT

EPIDEMIOLOGIC ASPECTS OF THE CURRENT OUTBREAK OF KAPOSI'S SARCOMA AND OPPORTUNISTIC INFECTIONS*

SINCE June 1981, the Centers for Disease Control (CDC) has learned of an increased occurrence of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and other serious opportunistic infections concentrated among homosexual men in the United States. After receiving the initial reports,[1,2] the CDC formed a task force to undertake surveillance for these disorders and conduct epidemiologic and laboratory investigations. This report describes these surveillance activities and summarizes current knowledge of the epidemiologic aspects of this outbreak.

SURVEILLANCE AND REPORTING METHODS

Case-report forms were completed for biopsy-proved cases of Kaposi's sarcoma in persons under 60 years of age without underlying immunosuppressive disease or therapy. Reports were also completed on all life-threatening or fatal opportunistic infections documented by biopsy or culture from patients with no known underlying illness or history of immunosuppressive therapy. The cases summarized below fit this case definition and were reported to the CDC between June 1 and November 10, 1981. For each case reported, an epidemiologist interviewed the attending physician by telephone and recorded both demographic data (age, race, marital status, sexual preference, and residence) and clinical information (e.g., illnesses, dates and methods of diagnoses, presence and dates of onset of signs and symptoms, history of predisposing conditions, and outcome of therapy).

To examine the incidence of Kaposi's sarcoma before 1980, we contacted epidemiologists associated with selected tumor registries in New York, California, and Georgia. Information was obtained from the National Cancer Institute Surveillance Epidemiology and End Results registries in the San Francisco Bay and Atlanta areas through 1979. Additional data were provided by the New York State Tumor Registry, the New York University Coordinated Cancer Registry, and the University of California Tumor Registry.

Task-force epidemiologists or officers of the CDC's Epidemic Intelligence Service actively surveyed physicians in 18 major metropolitan areas in the United States by letter and telephone to inquire about Kaposi's sarcoma in persons under 60 years of age or opportunistic infections in patients without a known predisposing factor since January 1979. At a minimum, heads of infectious disease, dermatology, oncology, and pathology departments from all major hospitals in these communities were contacted. In several of the metropolitan areas, physicians who served large numbers of homosexual men were known by the staff of clinics for sexually transmitted diseases or by other health-care personnel. When we obtained

*Report of the Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections:

The members of the Task Force include David M. Auerbach, M.D., John V. Bennett, M.D., Philip S. Brachman, M.D., Glyn C. Caldwell, M.D., Salvatore J. Crispi, James W. Curran, M.D. (Coordinator), William W. Darrow, Ph.D., Henry Falk, M.D., David S. Gordon, M.D., Mary E. Guinan, M.D., Harry W. Haverkos, M.D., Clark W. Heath, Jr., M.D., Roy T. Ing, M.D., Harold W. Jaffe, M.D., Bonnie Mallory Jones, Dennis D. Juranek, D.V.M., Alexander Kelter, M.D., J. Michael Lane, M.D., Dale N. Lawrence, M.D., Richard Ludlow, Cornelia R. McGrath, James M. Monroe, David M. Morens, M.D., John P. Orkwis, Martha F. Rogers, M.D., Wilmon R. Rushing, Richard W. Sattin, M.D., Mary Ellen Shapiro, Thomas J. Spira, M.D., John A. Stewart, M.D., Pauline A. Thomas, M.D., and Hilda Westmoreland. Address reprint requests to Dr. Curran at Technical Information Services, Centers for Disease Control, Atlanta, GA 30333.

the names of these physicians, we attempted to contact them as well. In early August 1981, a formal request was made to all state health departments to notify the CDC of illnesses suspected of fitting the case definition. Several of these agencies have begun active surveillance.

Since November 1967, the CDC has been the sole United States supplier of pentamidine isethionate for the therapy of *P. carinii* pneumonia. Although trimethoprim-sulfamethoxazole has replaced pentamidine as the initial therapeutic agent, many patients still require pentamidine therapy. Routinely collected data on the patients' underlying conditions were reviewed from January 1, 1976, to November 10, 1981.

Results

There were 159 documented cases of Kaposi's sarcoma, *P. carinii* pneumonia, and other serious opportunistic infections reported to the CDC between June 1 and November 10, 1981 (Table 1). Sixteen additional cases have been excluded because of possible predisposing illnesses or systemic immunosuppressive therapy. The majority of the cases were detected through follow-up of reports to the CDC and requests for pentamidine or through active surveillance in New York City and California. Active surveillance in 15 metropolitan areas outside New York and California revealed no cases fitting the case definition that had not been reported previously. Searches of available tumor registries in New York, California, and Georgia indicated that Kaposi's sarcoma was an uncommonly reported cancer in these areas, rarely occurring in persons under the age of 50. No increased incidence of Kaposi's sarcoma was noted through 1979. From January 1, 1976, through June 1980 there was one questionable request to the CDC for pentamidine isethionate to treat an adult without an underlying disorder. From July through December 1980, there were nine such requests, all of which are included in this report. At this writing in 1981, 42 requests for pentamidine have been filled for men without underlying disorders. This represents 37 per cent of all the requests for pentamidine for the treatment of adults in the United States in 1981 (42 of 114 requests).

Table 1. Outcome of Cases of Kaposi's Sarcoma, *Pneumocystis carinii* Pneumonia, and Other Serious Opportunistic Infections Reported to the Centers for Disease Control from June 1 to November 10, 1981.

Disease	No. Alive	No. Dead	Total No.	% Dead
Kaposi's sarcoma	62	11	73	15.1
P. carinii pneumonia	24	37	61	60.7
Both	8	7	15	46.7
Other infections	4	6	10	60.0
Total	98	61	159	38.4

The high mortality rate among the patients with *P. carinii* pneumonia accurately reflects the severity of their illness as well as the general debilitation of many of these men. Among 76 men with *P. carinii* pneumonia, 30 (39.5 per cent) died of the initial infection. Of the survivors, 13 subsequently died, including four of the eight who had recurrent *P. carinii* pneumonia. The remainder of the subsequent deaths were attributed to Kaposi's sarcoma or to other opportunistic infections. Forty-three of 76 initial episodes of *P. carinii* pneumonia and all eight recurrent episodes required therapy with pentamidine. Among the 15 patients with both Kaposi's sarcoma and *P. carinii* pneumonia, Kaposi's sarcoma was diagnosed first in six, *P. carinii* pneumonia was diagnosed first in six, and the diagnoses were made during the same month in the remaining three. In some patients, the diagnosis of *P. carinii* pneumonia preceded that of Kaposi's sarcoma by six months or longer.

The 10 patients with other serious opportunistic infections included four with progressive or disseminated herpes simplex virus infections, three with toxoplasmosis of the central nervous system, one with cryptococcal meningitis, and two with disseminated cytomegalovirus infection. Over 40 per cent of the remaining 149 patients with Kaposi's sarcoma, *P. carinii* pneumonia, or both were reported to have other serious opportunistic infections, including 10 of 73 patients with Kaposi's sarcoma alone, 42 of 61 with *P. carinii* pneumonia alone, and 12 of 15 with both Kaposi's sarcoma and *P. carinii* pneumonia. Patients with *P. carinii* pneumonia alone were significantly more likely to be reported as having opportunistic infections than were those with Kaposi's sarcoma alone ($P<0.00001$ by Fisher's exact test). These infections include 24 clinically important cytomegalovirus infections confirmed by virus isolation or biopsy, six progressive or disseminated herpes simplex virus infections, five cryptococcal meningitis infections, 12 invasive gastrointestinal candida infections, seven disseminated mycobacterial infections (two with *Mycobacterium tuberculosis* and five with other species), and 10 other infections. These data are incomplete; they reflect only the coexisting infections that were well documented and were reported to the CDC.

Data generated by CDC surveillance indicate a secular increase in the number of reported cases by month of onset, month of confirmed diagnosis, and month of death (Fig. 1). The patients with both Kaposi's sarcoma and *P. carinii* pneumonia are represented in the diagnosis curve according to their first diagnosed illness. A considerable delay occurred between the initial onset of symptoms and diagnosis in both the Kaposi's sarcoma and *P. carinii* pneumonia groups. For Kaposi's sarcoma, the time from the onset of symptoms to diagnosis ranged from one to 30 months (median, 5.5); for *P. carinii* pneumonia, the range was one to 18 months (median, 3.5). Fifty-three per cent of the patients (84 of 159) had the onset of their illness after January 1981, whereas 88 per cent became ill after January 1980. Seventy-five per cent of the cases (119 of 159) were diagnosed during 1981, and 74 per cent of the deaths (45 of 61) occurred during 1981. The decline in the onset curve probably reflects the average three to six-month delay from the onset of symptoms to diagnosis. Late declines in the diagnosis and death curves may represent delay in reports to the CDC.

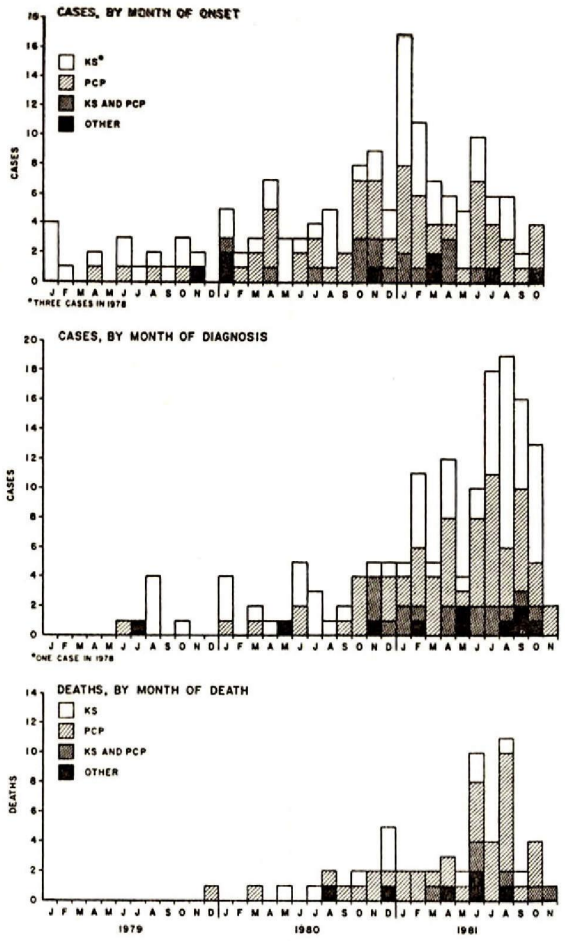

Figure 1. Incidence of Kaposi's Sarcoma (KS), *Pneumocystis carinii* Pneumonia (PCP), and Other Opportunistic Infections in the United States, 1979–1981.

Table 2 shows selected signs or symptoms in patients with Kaposi's sarcoma, *P. carinii* pneumonia, or both. The frequency of lymphadenopathy, fever, and weight loss in the group with Kaposi's sarcoma attests to the often generalized nature of the disease. In each group, many patients were reported to have had a prodromal illness lasting for weeks to months and characterized by weight loss, lymphadenopathy, fever, and diarrhea. This prodrome was more consistently present and severe in patients with *P. carinii* pneumonia.

All but one of the 159 reported cases occurred in men. Ninety-two per cent of these men (136 of 148) were reported to be homosexual or bisexual when sexual preference was known (Table 3). Patients' ages ranged from 15 to 57 years, with a median of 35. Eighty-two per cent of the men were in the 25 to 44-year-old group. Seventy per cent of the men were white (not Hispanic), 16 per cent Hispanic, and 14 per cent black. There were no significant differences in age or race between the disease categories.

Although cases were reported from 15 states, the District of Columbia, and two foreign countries, over three fourths of the patients were living in New York City, San Francisco, or Los Angeles at the time of diagnosis (Table 4). Since over half the cases were reported from the New York City metropolitan area, we compared the residence of patients whose onset of symptoms was early with that of patients whose symptoms began later in the epidemic. There was no significant difference in residence in metropolitan New York City between patients whose symptoms began before January 1, 1980 (17 of 24, 70.8 per cent), and those whose symptoms began after that date (70 of 135, 51.9 per cent) ($P>0.10$).

Discussion

The current outbreak of Kaposi's sarcoma, *P. carinii* pneumonia, and other opportunistic infections is highly unusual. Kaposi's sarcoma is a rare, malignant neoplasm, predominantly affecting elderly men and seldom causing death.[3] Although precise rates are unavailable, the annual incidence in the United States has been estimated to be 0.021 to 0.061 per 100,000 population.[4,5] In one large series, Safai et al. reported a 3:1 male-to-female ratio and a mean age of 63 years among patients with Kaposi's sarcoma.[6] Precise incidence estimates specific for sexual preference are not available, because the number of homosexual men living in cities where Kaposi's sarcoma has occurred is unknown. Nonetheless, the highly localized occurrence of 88 cases among men under 60 suggests at least a 100-fold increase in age-specific risk among homosexual men in the cities reporting cases, as compared with previous estimates of incidence. Although *P. carinii* causes several hundred cases of severe pneumonia in the United States annually, these cases were previously found almost exclusively in patients whose immunity was severely compromised by underlying disease, immunosuppressive therapy, or both.[7,8] After reviewing requests for pentamidine in the period from 1967 to 1970, when pentamidine was the only recommended treatment for *P. carinii* pneumonia, Walzer et al. discovered only one case of confirmed *P. carinii*

Table 2. Signs or Symptoms Reported in Patients with Kaposi's Sarcoma, *P. carinii* Pneumonia, or Both.

Sign or Symptom	% with Sign or Symptom		
	Kaposi's sarcoma (n = 73)	*P. carinii* pneumonia (n = 61)	Both (n = 15)
Skin or mucosal lesions	80.8	8.2	86.7
Lymphadenopathy	43.8	23.0	40.0
Fever	23.3	93.4	86.7
Weight loss	19.2	70.5	53.3
Diarrhea	17.8	34.4	40.0
Dyspnea	5.5	88.5	100.0
Oral thrush	6.8	41.0	26.7

Table 3. Sexual Preference of Men with Kaposi's Sarcoma, *P. carinii* Pneumonia, or Other Serious Opportunistic Infections Reported to the CDC.

Disease	Homosexual or Bisexual	Heterosexual	Unknown	Total
		no. of patients		
Kaposi's sarcoma	66	2	5	73
P. carinii pneumonia	49	9	3	61
Both	15	—	—	15
Other infections	6	1	2	9
Total	136	12	10	158

pneumonia in a patient without a known underlying condition.[7] Our recent review of requests for pentamidine confirms the rarity with which this disease has been previously diagnosed among adults without underlying conditions.

The simultaneous occurrence of Kaposi's sarcoma and *P. carinii* pneumonia among homosexual men of the same age and racial groups who live in the same geographic areas strongly suggests the occurrence of a single epidemic of underlying immunosuppression in these men. As noted previously, *P. carinii* pneumonia is typically a disease of immunocompromised patients. The incidence of Kaposi's sarcoma is greatly increased among recipients of renal allografts[9-12] and others receiving immunosuppressive therapy.[13-15] The natural history of the currently reported cases of Kaposi's sarcoma among these homosexual men is similar to that among transplant recipients, in that it more frequently involves the visceral organs and has a poor prognosis.[12,15a] When Kaposi's sarcoma occurs in allograft recipients, the tumor often spontaneously regresses with cessation or reduction of immunosuppressive therapy.[10,12]

The high mortality rate among young men with these disorders indicates a serious public-health problem. The magnitude of the current epidemic is understated by the data presented on biopsy-confirmed cases of Kaposi's sarcoma and *P. carinii* pneumonia. Young men presenting with interstitial pneumonia without an underlying disorder may not have received a definite diagnosis or specific therapy for *P. carinii* pneumonia; others may have received empirical therapy with trimethoprim–sulfamethoxazole. The rather benign, inconspicuous appearance of many of the skin and mucous-membrane lesions of Kaposi's sarcoma in these men suggests that this disease may also be underdiagnosed.

If immunosuppression is the underlying cause of these conditions, then Kaposi's sarcoma and *P. carinii* pneumonia may represent the "tip of the iceberg" including other conditions that are less readily recognized or have longer latency periods. While investigating this outbreak, we have received numerous physicians' reports on young homosexual men with nonfatal opportunistic infections, unexplained prolonged lymphadenopathy, or lymphoreticular neoplasias. Although sporadic case reports of lymphoreticular neoplasms are difficult to interpret, these reports are a cause for concern, since Safai et al. have noted that Kaposi's sarcoma is frequently associated with other primary tumors.[6] In their series, 37 per cent of the patients with Kaposi's sarcoma had other primary cancers; specifically, the authors noted a 20-fold increase in lymphoreticular neoplasms. Clinicians caring for homosexual men should be alert for signs and symptoms of other infections and neoplasms associated with immunodepression, in addition to Kaposi's sarcoma and *P. carinii* pneumonia.

Although it is possible that the concentration of reported Kaposi's sarcoma, *P. carinii* pneumonia, and other opportunistic infections among homosexual men living in New York and California represents a reporting artifact, we consider this possibility unlikely. Most of the reported cases were from tertiary-care facilities — the same type of facility included in our survey of 18 cities. If the geographic clustering of cases is in fact real, it suggests that risk factors for these diseases are not randomly distributed in the homosexual community.

Giraldo et al. first suggested an association between Kaposi's sarcoma and cytomegalovirus infection when they isolated cytomegalovirus from one of eight tissue-culture cell lines from patients with Kaposi's sarcoma.[16] They subsequently demonstrated a serologic association of Kaposi's sarcoma with cytomegalovirus in American and European patients, but not in African patients.[17,18] Finally, they found that three of eight tumor-biopsy samples were positive for cytomegalovirus DNA by DNA-DNA reassociation kinetics.[19] Cytomegalovirus is often associated with *P. carinii* pneumonia in immunosuppressed hosts, especially among renal-transplant recipients.[20] Furthermore, cytomegalovirus induces transient abnormalities in cellular immune function in otherwise healthy persons.[21] Since serologic evidence of cytomegalovirus infection and active shedding of cytomegalovirus in the urine have been shown to be more common among homosexual men than among heterosexual men of the same age,[22] further investigation of cytomegalovirus in the cases reported here is important. On the other hand, cytomegalovirus infection is very common in the United States and has not been

Table 4. Metropolitan Area of Residence at the Time of Diagnosis in Patients with Kaposi's Sarcoma, *P. carinii* Pneumonia, or Other Serious Opportunistic Infections.

Disease	New York City	San Francisco	Los Angeles	Other	Total
			no. of patients		
Kaposi's sarcoma	40	12	4	17	73
P. carinii pneumonia	34	5	10	12	61
Both	7	2	2	4	15
Other infections	6	0	1	3	10
Total	87	19	17	36	159

shown to have such devastating effects on other populations. Since reactivation of cytomegalovirus is common among immunocompromised hosts, the role of this virus will not be easily defined in this outbreak.

In a recently published study, Masur et al. described 11 cases of *P. carinii* pneumonia in immunocompromised men without underlying disorders or therapy.[23] Although six of these men were homosexual, five others were reported to be drug abusers (using heroin, methadone, alcohol, or cocaine). Opiate addiction has been associated with alterations in cellular immune status in vitro,[24,25] but it had not previously been associated with *P. carinii* pneumonia.

The interest in a causal role for inhalants containing amyl nitrite or isobutyl nitrite or both ("poppers," as they are commonly called) stems from the hypothesis that they are used as sexual stimulants or recreational drugs by some homosexual men. In a recent survey of 420 men attending clinics for sexually transmitted diseases in New York, San Francisco, and Atlanta, we found that 86.4 per cent of homosexual and bisexual men (242 of 279), as compared with 14.9 per cent of heterosexual men (21 of 141), reported the use of nitrite inhalants within five years. However, the frequency of nitrite use was closely correlated with the number of sexual partners reported during the previous month. This suggests that the use of nitrites may be associated with other hypothetical etiologic factors, such as sexually transmitted infections, antimicrobial agents for treatment or prevention of these infections, types of sexual behavior, attendance at places where partners are encountered, and perhaps the use of other drugs. Studies undertaken to determine what role (if any) nitrites may have as risk factors for Kaposi's sarcoma and *P. carinii* pneumonia and immunosuppression must carefully consider the confounding effects of these other variables.

In collaboration with investigators in New York, California, and Georgia, the CDC task force is completing a national case-control study to identify risk factors for Kaposi's sarcoma and *P. carinii* pneumonia among homosexual men. We are continuing surveillance for these disorders and conducting other clinical and laboratory investigations.

This sudden, highly focal occurrence of Kaposi's sarcoma and *P. carinii* pneumonia provides an opportunity to investigate the relations among life style, environment, host immune responses, and oncogenesis and suggests the potential for prevention of these diseases if risk factors can be identified.

Note added in proof: Between November 10, 1981, and January 13, 1982, 57 additional cases were reported, bringing the total to 216 (89 cases of Kaposi's sarcoma, 91 of *P. carinii* pneumonia, 18 of both, and 18 of other infections). At least 88 (40.8 per cent) of these patients have died.

We are indebted to the physicians reporting cases and to Drs. Donald F. Austin, Erwin Braff, James W. Buehler, James Chin, J. Lyle Conrad, Selma Dritz, Diane M. Dwyer, Shirley L. Fannin, Yebuda M. Felman, Stephen M. Friedman, Robert A. Gruin, John P. Hanrahan, Robert J. Kingon, Michael D. Mallison, Stanley I. Music, Mark A. Roberts, Alain J. Roisin, Richard B. Rothenberg, and R. Keith Sikes for their roles in active surveillance.

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