

THE EFFECTS OF PREPARATIONS OF HUMAN CHORIONIC GONADOTROPIN ON AIDS-RELATED KAPOSI'S SARCOMA

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ABSTRACT

Background Kaposi's sarcoma is the most common cancer in patients with the acquired immunodeficiency syndrome (AIDS). Recently, certain preparations of human chorionic gonadotropin (hCG) have been shown to inhibit the growth of Kaposi's sarcoma cell lines in vitro and in immunodeficient mice.

Methods After in vitro evaluation of four commercially available hCG preparations, the most active product was evaluated in 36 patients with AIDS-related Kaposi's sarcoma. In a phase 1-2 trial, 24 patients received intralesional injections of hCG three times a week for two weeks at doses of 250, 500, 1000, or 2000 IU (6 patients each). In each patient three nodular lesions were injected, two with the drug and one with diluent alone. In a double-blind trial, 12 additional patients were randomly assigned to receive intralesional injections of 2000 IU of hCG or diluent alone (6 patients each; two lesions per patient). At the conclusion of therapy, the lesions were measured, their gross appearance assessed, and biopsy specimens evaluated.

Results A.P.L. (Wyeth-Ayerst), which had the most in vitro activity against Kaposi's sarcoma cell lines, was selected for the clinical investigation. Treatment with A.P.L. was well tolerated at all doses. In the cohorts given 250, 500, 1000, and 2000 IU, 1, 5, 5, and 10 of the 12 injected lesions responded, respectively ($P=0.03$ for trend). Complete tumor regression was observed in one lesion each at the 250-IU and 500-IU doses, in two lesions given the 1000-IU dose, and in five lesions given the 2000-IU dose. In the double-blind study, none of the 12 lesions in the six patients injected with diluent had responses, as compared with 10 of the 12 lesions in the six patients injected with hCG ($P=0.015$). Microscopical evidence of apoptosis was observed only in hCG-treated lesions. The percentage of cells that died increased in a dose-dependent manner ($P<0.001$). Serum levels of follicle-stimulating hormone ($P=0.002$) and luteinizing hormone ($P=0.001$) declined after the last injection of hCG, but there was no effect on these hormones in the diluent-treated patients.

Conclusions The intralesional injection of hCG induces the regression of AIDS-related Kaposi's sarcoma lesions in a dose-dependent manner. The response of these tumors appears to be mediated by the induction of apoptosis. (N Engl J Med 1996;335:1261-9.)

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K APOSI'S sarcoma is the most common tumor in patients with the acquired immunodeficiency syndrome (AIDS).¹⁻³ The treatment of patients with AIDS-related Kaposi's sarcoma is only palliative and includes radiotherapy, interferon alfa, and systemic chemotherapy.⁴⁻¹⁰ Toxic side effects limit the usefulness of chemotherapy and interferon alfa, particularly when they are given concurrently with antiretroviral agents.^{6,8,10} Therefore, other drugs are needed for the treatment of AIDS-related Kaposi's sarcoma.

Experiments with long-term cultures of spindle cells from patients with AIDS-related Kaposi's sarcoma have identified several factors that regulate tumor growth.¹¹ The subcutaneous injection of such cells into nude (athymic) mice usually results in angiogenic lesions that resemble human AIDS-related Kaposi's sarcoma lesions histologically but consist of cells of mouse origin.¹² This finding indicates that Kaposi's sarcoma cells secrete factors that induce vascular proliferation. Further experiments identified a variety of growth factors for AIDS-related Kaposi's sarcoma in this model, including interleukin- 1β , interleukin-6, tumor necrosis factor α , platelet-derived growth factor, oncostatin M, basic fibroblast growth factor, and vascular endothelial growth factor.¹³⁻¹⁹

The spindle cells used in these studies have a normal diploid set of chromosomes and limited in vitro growth. By contrast, two recently isolated lines of AIDS-related Kaposi's sarcoma cells have overt neoplastic properties.²⁰ KSY-1 and KS-SLK²¹ (the second of which is derived from a patient with Kaposi's sarcoma who was negative for the human immunodeficiency virus type 1 [HIV-1]) are aneuploid and produce tumors in nude mice. In addition, KSY-1 cells metastasize and provoke angiogenesis.²² An unusual property of KSY-1 cells is that they fail to grow in pregnant mice. A pregnancy-related hormone,

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most likely chorionic gonadotropin, is thought to be responsible for this antitumor activity.

On the basis of this finding, we conducted a phase 1–2 dose-escalation study and a double-blind, randomized study of the effect of intralesional injection of a commercial preparation of human chorionic gonadotropin (hCG) on AIDS-related Kaposi's sarcoma.

METHODS

Growth-Inhibition Assays

We studied the inhibition of growth of AIDS-related Kaposi's sarcoma cell lines caused by four commercial preparations of hCG: A.P.L. (Wyeth–Ayerst, Radnor, Pa.); Profasi (Serono, Randolph, Md.); and generic forms manufactured by Schein (Brewster, N.J.) and Goldline (Miami), using methods described previously.²³

Studies of hCG in Tumor-Bearing Mice

KSY-1 cells (5×10⁵) were injected subcutaneously into immunodeficient (Xid) beige mice. The mice received intralesional injections of various preparations of hCG at doses of 100 IU in a volume of 0.2 ml each day for seven days. The animals were killed after three to four weeks and examined grossly and microscopically for the presence of tumor, angiogenesis, and metastasis.²²

Patients

Patients with serologic evidence of HIV-1 infection and biopsy-proved Kaposi's sarcoma who had at least three nodular cutaneous lesions were enrolled in the study. The study was approved by the institutional review board of the Los Angeles County–University of Southern California Medical Center. The criteria for

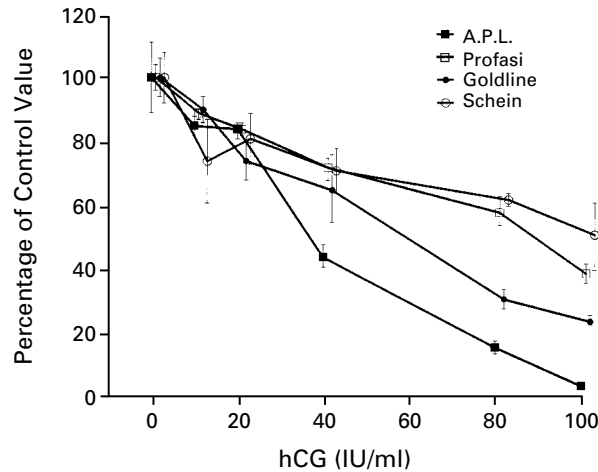


Figure 1. Effect of Four Preparations of hCG on the Growth of KSY-1 Cells in Vitro.

The cells (100,000 cells per well) were seeded in 24-well gelatin-coated plates and treated with one of the preparations (A.P.L., Profasi, and two generic brands, one from Goldline and one from Schein) at various concentrations on days 1 and 3. The cell counts were performed on day 6. The results shown are the means and standard deviations obtained, expressed as a percentage of the values in the control wells (those with no drug). The assays were performed in triplicate.

TABLE 1. CHARACTERISTICS OF THE 36 STUDY PATIENTS WITH KAPOSI'S SARCOMA.

CHARACTERISTIC*	VALUE
Age — yr	
Median	36
Range	26–56
No. of months since 1st KS lesion	
Median	8
Range	1–85
KS lesions — no. of patients (%)	
>50	7 (19)
25–50	11 (31)
<25	18 (50)
Lymphedema — no. of patients (%)	5 (14)
Prior therapy — no. of patients (%)	
Systemic chemotherapy	3 (8)
Interferon alfa	5 (14)
Local therapy†	12 (33)
Prior opportunistic infections — no. of patients (%)	12 (33)
B symptoms — no. of patients (%)‡	9 (25)
CD4 cell count <200/mm ³ — no. of patients (%)	29 (85)§
Concurrent antiretroviral therapy — no. of patients (%)	
Zidovudine alone or in combination	12 (33)
Other	13 (36)
None	11 (31)

*KS denotes Kaposi's sarcoma.

†Local therapies were defined as radiation therapy, intralesional injections with vinblastine or vincristine, and treatments of individual lesions with liquid nitrogen.

‡B symptoms included the presence of fevers of unknown origin, drenching night sweats, or unintentional weight loss exceeding 5 percent of body weight.

§Base-line CD4 lymphocyte counts were not available for two patients.

inclusion were an age over 17 years; adequate hepatic, renal, and bone marrow function (absolute granulocyte count, >750 per cubic millimeter; platelet count, >75,000 per cubic millimeter); a Karnofsky score for performance status of 50 or above; no acute infection; and no therapy, local or systemic, for AIDS-related Kaposi's sarcoma during the two weeks before entry into the study.

One patient who received only a single injection of the hCG preparation had a worsening of cytomegalovirus retinitis that necessitated reinduction treatment. This patient was replaced in the study and removed from all the analyses.

Study Design

In the phase 1–2 dose-escalation trial, 24 consecutive patients were treated with 250, 500, 1000, or 2000 IU of A.P.L., with 6 patients receiving each dose. The therapy consisted of intralesional injections of the hCG preparation or diluent (sterile water) three times a week for two weeks. In each patient, two lesions were injected with the study drug and a third lesion was injected with diluent. Only discrete, nodular lesions with clear margins were selected for injection. The dose of the hormone preparation was fixed in each cohort; no patient was allowed to receive increasing doses. The volume of the injection of either hormone or diluent was also fixed at 0.2 ml for all doses.

In the double-blind trial, 12 additional patients were randomly assigned to receive either hCG at a dose of 2000 IU or diluent alone (6 patients each). In each of these patients, two nodular lesions were injected three times a week for two weeks. After a two-week washout period, the patients who had been randomly assigned to receive diluent alone were allowed to cross over to receive the active drug as described above.

The hCG preparation was freshly reconstituted and adminis-

TABLE 2. RESPONSES TO hCG THERAPY AND LESION SIZES AFTER THERAPY, ACCORDING TO THE DOSE OF hCG, IN THE PHASE 1-2 DOSE-ESCALATION TRIAL.

VARIABLE	hCG-DOSE GROUP			
	250 IU	500 IU	1000 IU	2000 IU
Responses to therapy				
No. of patients	6	6	6	6
No. with responses*	1	3	4	5
No. of lesions treated with hCG	12	12	12	12
Overall no. of responses†	1	5	5	10
Lesions with biopsy-confirmed complete responses	1	1	2‡	5
No. of lesions treated with diluent	6	6	6	6
Overall no. of responses†	1	0	1	4
Complete responses	1	0	0	4
Size of hCG-treated lesions				
Responding lesions				
No.	1	5	5	10
Median size (mm ²)	66	91	98	53
Size range (mm ²)	—	25-180	49-324	35-112
Nonresponding lesions				
No.	11	7	7	2
Median size (mm ²)	62	84	144	245
Size range (mm ²)	10-1053	50-132	75-400	49-440
P value	0.76	0.78	0.19	0.52

*P=0.03 for the comparison of dose cohorts by the Cochran-Armitage test for trend.

†These numbers include both complete and partial responses.

‡Both lesions were in the same patient.

tered immediately to avoid its becoming inactivated with time. For intralesional administration, a 27- or 30-gauge needle was placed immediately under the skin overlying the Kaposi's sarcoma lesion. The fluid was injected slowly to develop a weal. The injected lesions were measured and photographed before the first dose, after the sixth dose, and one week thereafter. One week after the final injection, one hCG-treated lesion and the diluent-treated lesion were studied at biopsy (with 3-to-5-mm punch biopsies) in all consenting patients to assess pathological changes and evidence of apoptosis in situ. These analyses were conducted blindly in the double-blind trial.

Only injected lesions were assessed for their response to therapy. In the double-blind trial, the lesions were evaluated without the investigator's knowledge of the treatment assignment. A complete response was defined as the absence of detectable disease in an injected lesion, as confirmed by biopsy. A partial response was a decrease of more than 50 percent in lesional size in two dimensions or the complete flattening of a nodular lesion. Progressive Kaposi's sarcoma was defined as an increase in the size of an injected lesion by at least 25 percent. Stable Kaposi's sarcoma was defined as present when a lesion did not fulfill any of these criteria.

Laboratory Studies

Complete blood counts, analyses of serum chemistry, and assessments of T-cell subgroups (CD4 and CD8) were performed before entry and at the completion of therapy. In 23 patients, serum testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured before therapy and within 24 hours after the sixth dose.

In situ staining of the biopsy specimen was performed to determine whether cells with DNA fragmentation were present.

Slides of tumor tissue were processed and evaluated without the investigator's knowledge of the treatment assignment. The assays were performed according to the instructions of the manufacturer (Oncor, Gaithersburg, Md.).²²

Statistical Analysis

To determine whether there was a relation between the dose of hCG and the proportion of patients who had responses, a Cochran-Armitage test for trend was performed.²⁴ Differences in response between the two groups in the double-blind study were assessed by Fisher's exact test.²⁵ The lesions with responses and those without responses were compared with regard to size by Student's t-test.²⁴ Changes in the mean serum levels of testosterone, FSH, and LH from base line to the end of therapy were compared by a paired Student's t-test.²⁶ An analysis of variance was used to assess the changes in hormone levels according to dose, as well as the effect of the dose on apoptosis.²⁴

RESULTS

Effects of Various Preparations of hCG

We examined the effects of four commercial preparations of hCG on the growth of KSY-1 cells in vitro. All four preparations inhibited such growth, with the 50 percent inhibitory concentration ranging from 40 to 100 IU of hCG per milliliter (Fig. 1). The A.P.L. preparation selected was the most active preparation. Its effects were also studied in three nude mice injected with KSY-1 cells. In all three animals there was a marked reduction in the growth of subcutaneous tumors, with the lesions measuring 1 mm by 1 mm, as compared with lesions measuring 28 by 25 mm, 27 by 30 mm, and 29 by 31 mm in three diluent-treated mice.

Study Patients

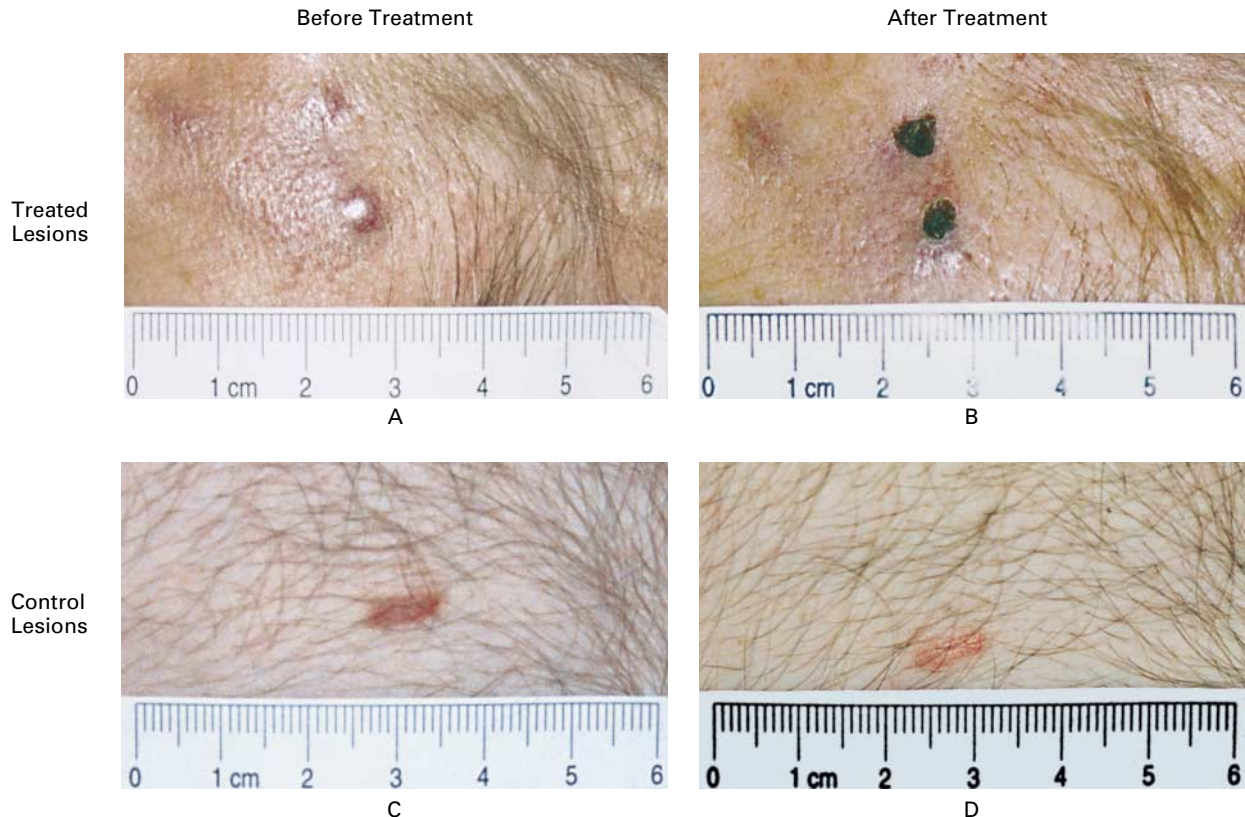
Thirty-six homosexual or bisexual men were enrolled in the study. Table 1 shows their characteristics. No patient had symptomatic visceral Kaposi's sarcoma at study entry. The median CD4 lymphocyte count at enrollment was 31 cells per cubic millimeter (range, 5 to 405).

Adverse Effects

The intralesional injections of hCG were well tolerated; there were only mild side effects in some patients. One patient receiving 250 IU reported vertigo, mild dizziness, and nausea that resolved after stopping the drug. One patient receiving 1000 IU reported headache, nightmares, and fatigue, all of which resolved by the second week of therapy. A second patient, also receiving 1000 IU, reported mild fatigue. One patient receiving 2000 IU had injection-related pain after one dose and declined further therapy.

Responses of the Kaposi's Sarcoma Lesions

Table 2 shows the responses of the AIDS-related Kaposi's sarcoma lesions in the dose-escalation study. In one patient treated with 250 IU of hCG, one of the two injected lesions flattened completely and contained no evidence of disease on biopsy. The



diluent-treated lesion in this patient, located very near the treated lesion that responded, also flattened and contained no evidence of disease on biopsy. No other responses were observed in lesions treated at that dose of hCG.

Three patients had lesions that responded to treatment with 500 IU of hCG. One patient had biopsy-confirmed complete remission of both hCG-treated lesions. In another patient there were partial remissions in both treated lesions. The biopsy of one of these lesions showed central necrosis, with residual Kaposi's sarcoma in the periphery. In a third patient, one of the two hCG-treated lesions had a partial response. Two of these three patients had tumor-associated edema and pain when they entered the study, and in both the edema lessened and the pain resolved during treatment.

Five AIDS-related Kaposi's sarcoma lesions in four patients responded to treatment with 1000 IU of hCG, and one of these responded completely. In this patient, both of the hCG-treated lesions showed no histologic evidence of Kaposi's sarcoma (Fig. 2). The diluent-treated lesion in this patient became flat but had evidence of tumor on biopsy. In each of three other patients, one of the two hCG-treated lesions had a partial response, whereas none of the other injected lesions responded.

At the 2000-IU dose, one patient withdrew from the study after the first day because of injection-related pain. On follow-up, no response was observed in any lesion in that patient. Among the remaining five patients, all 10 hCG-treated lesions had responses, with necrosis and scab formation. Four of the five diluent-treated lesions in these patients flattened completely but did not show tissue necrosis. Biopsies of the five diluent-treated lesions revealed no evidence of Kaposi's sarcoma in four of the five. Biopsies of hCG-treated lesions, one in each of the five patients studied, showed no evidence of Kaposi's sarcoma. Overall, there was a statistically significant dose-response relation ($P=0.03$).

Twelve additional patients were recruited to take part in the double-blind, randomized trial; they were randomly assigned to treatment with either 2000 IU of hCG or diluent alone. In six patients, two lesions were injected with the preparation of hCG, and in the other six, two lesions were injected with diluent alone. The treatment assignments were blinded by the pharmacist, and the physicians and nurses who evaluated the patients were unaware of them. The pathologist who examined the tumor-biopsy specimens was also unaware of the treatment assignments.

All six patients treated with hCG showed macroscopic regression of the AIDS-related Kaposi's sarco-

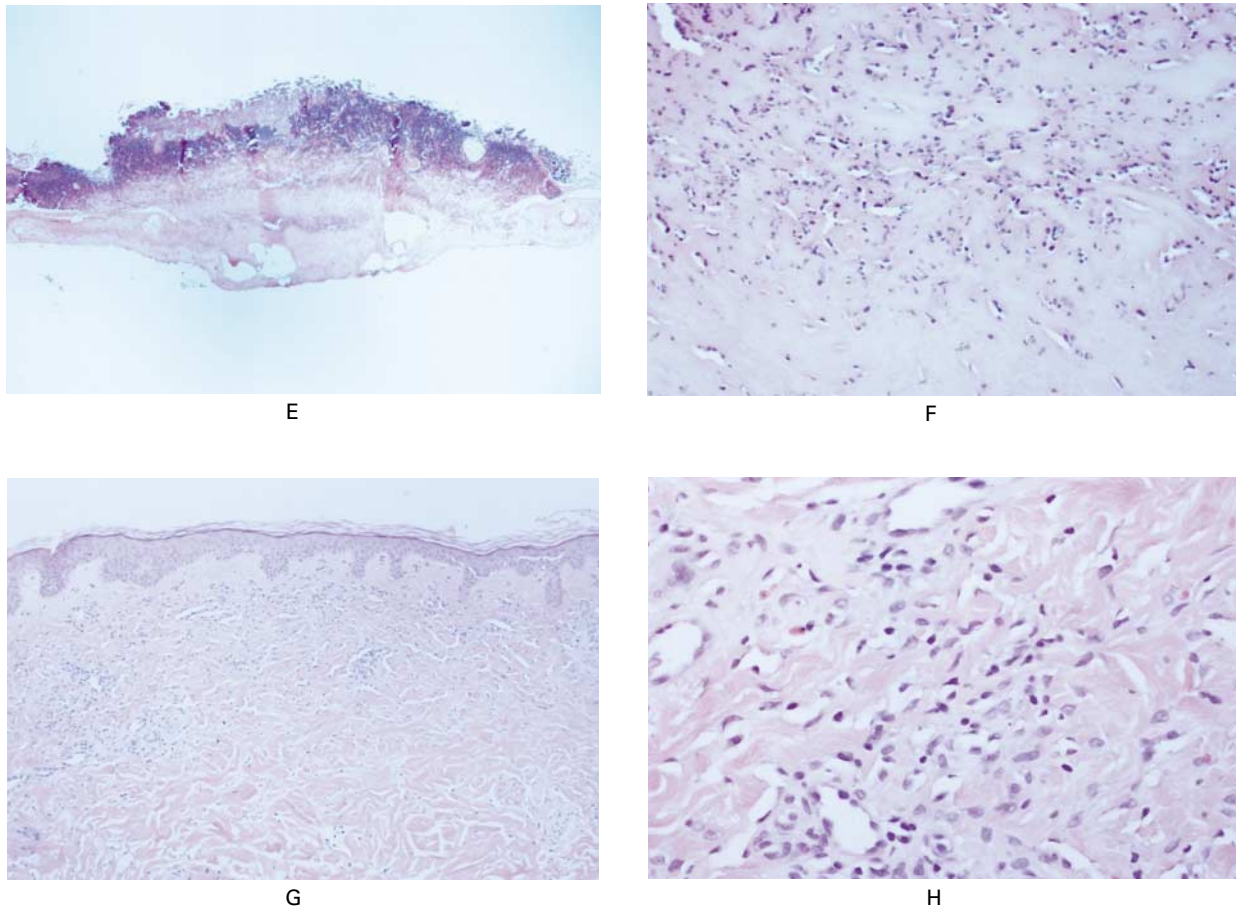


Figure 2. Clinical and Pathological Response of Kaposi's Sarcoma Lesions in a Patient Treated with 1000 IU of A.P.L. Panel A (facing page) shows representative lesions before treatment. Panel B shows the same lesions after treatment with six injections containing 1000 IU of hCG each. Tumor necrosis and scab formation are visible. Panel C shows a representative lesion in the same patient before an injection of diluent. Panel D shows the same lesion after six injections of diluent. Panel E shows one of the lesions treated with intralesional hCG. Necrotic tissue is visible ($\times 100$). Panel F shows that this hCG-treated lesion consists of necrotic tissue, a few cells, and abundant collagen and contains no evidence of Kaposi's sarcoma ($\times 400$). Panel G shows a biopsy specimen of the diluent-treated lesion ($\times 100$), and Panel H shows the same lesion at higher power ($\times 400$); there are minimal residual Kaposi's sarcoma cells.

ma lesions. Ten of 12 lesions injected with hCG responded macroscopically. Histologic evaluation showed complete responses in five of six biopsy specimens (Fig. 2). None of the diluent-injected lesions showed either macroscopic or pathological evidence of a response ($P=0.015$).

The five patients with biopsy-proved responses in the double-blind trial were followed for up to five months. In three, neither of the hCG-injected lesions relapsed after follow-up periods lasting two, four, and five months. However, the patient followed for five months was given systemic chemotherapy one month after his response to hCG was documented. In two other patients, lesions recurred at the injection sites two and three months after the initial response. Five of the six patients initially assigned to diluent were later given open-label treatment with hCG. Lesions

in all five flattened completely and thus showed at least partial responses to the hCG injections, although the lesions were not studied at biopsy to confirm that complete responses had occurred. None of the injected lesions recurred after four months in two of these patients and after five months in the remaining two. One patient was lost to follow-up.

Apoptosis

Tumor specimens obtained before treatment and at the completion of therapy were studied for evidence of apoptosis in situ. The slides were reviewed with the examiner unaware of the treatment assignments. Tumor tissue from diluent-treated lesions showed the same amount of cell death as tissue from untreated lesions (less than 2 percent) (Table 3 and Fig. 3). The hCG-treated lesions had dramatically

TABLE 3. BIOPSY-PROVED APOPTOSIS IN AIDS-RELATED KAPOSI'S SARCOMA LESIONS AFTER hCG THERAPY.*

VARIABLE	hCG (DOSE PER LESION)				
	DILUENT ALONE	250 IU	500 IU	1000 IU	2000 IU
No. of patients studied by biopsy	3	5	4	4	4
Percentage of cells undergoing apoptosis	<5	20, 22, 23, 27, 30	40, 44, 46, 50	70, 78, 79, 80	90, 95, 98, 100

* $P < 0.001$ for the increase in apoptosis in relation to the hCG dose, by analysis of variance.

higher percentages of cells undergoing apoptosis, and these proportions correlated with the doses, ranging from 20 to 30 percent for lesions treated at the 250-IU dose to 90 to 100 percent for those treated at the 2000-IU dose ($P < 0.001$) (Table 3).

Systemic Effects of hCG

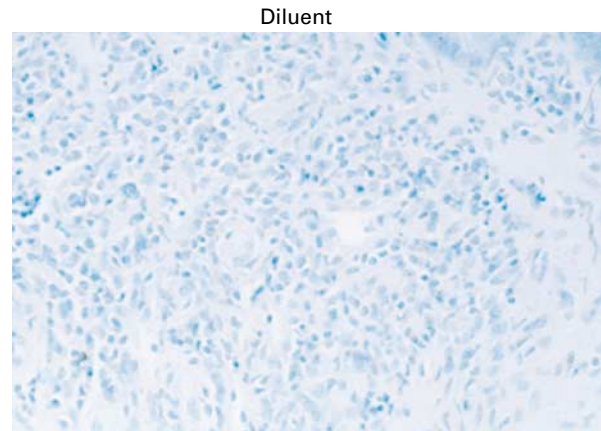
The systemic effects of hCG therapy included increased appetite in five patients, with weight gains of up to 2.7 kg (6 lb) in three. Two patients reported increased energy, and one reported increased libido. In one patient chronic diarrhea resolved immediately after the start of treatment and recurred after the therapy ended.

Effects on Serum Hormone Levels

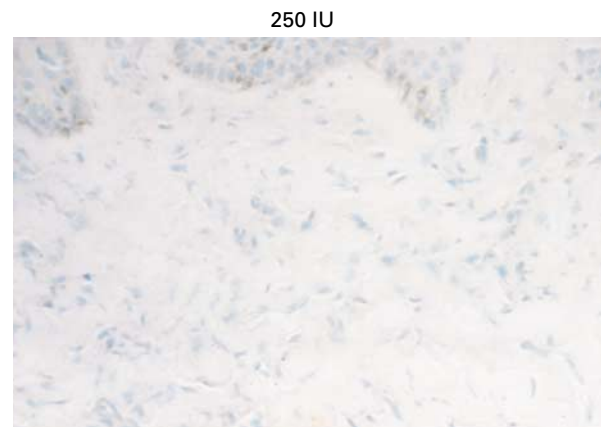
In 23 patients, including all 12 patients studied in the randomized trial, serum levels of testosterone, FSH, and LH were measured before the first injection and after the final injection. Of these 23 patients, 17 were treated with hCG (3 patients each at 500 and 1000 IU and 11 patients at 2000 IU), and 6 were given diluent. There were significant declines in the levels of FSH ($P = 0.002$) and LH ($P = 0.001$) in all 17 patients after the final dose (Fig. 4), although the declines did not differ significantly among the three doses tested. In the six patients who received diluent, there were no significant changes in hormone levels. Thirteen of the 17 patients given hCG had increased levels of testosterone, but the increases were not statistically significant ($P = 0.55$).

DISCUSSION

This clinical investigation originated with studies of a cell line, KSY-1, that was isolated from the pleural fluid of a patient with AIDS-related Kaposi's sarcoma. KSY-1 cells induce Kaposi's sarcoma tumors, angiogenesis, and metastases in immunodeficient mice that are similar to those in humans.²⁰ Another cell line, KS-SLK,²¹ obtained from a patient with an HIV-1-negative form of Kaposi's sarcoma, also in-



A



B

duces tumors in immunodeficient mice.²⁰ Interestingly, both cell lines have the same chromosome marker.²⁷ The failure of these cell lines to grow in nude mice in the early stage of pregnancy led to studies showing that certain commercial preparations of hCG inhibit the in vitro growth of Kaposi's sarcoma cells. Moreover, Kaposi's sarcoma cell lines and cells from primary tumors in patients with AIDS-related Kaposi's sarcoma were found to express the receptor for LH and hCG.²²

We tested four commercial preparations of hCG at equivalent doses and found that they did not all have the same antitumor activity. Moreover, different lots of the same preparation varied in their activity. To determine whether the antitumor activity in the preparations was caused by hCG or by a degradation product, we tested a highly purified hCG heterodimer. Its in vitro inhibitory activity was minimal, with 10 to 20 percent cell killing. We then studied overlapping β -hCG peptides and found that certain of them inhibited Kaposi's sarcoma cell lines both in vitro and

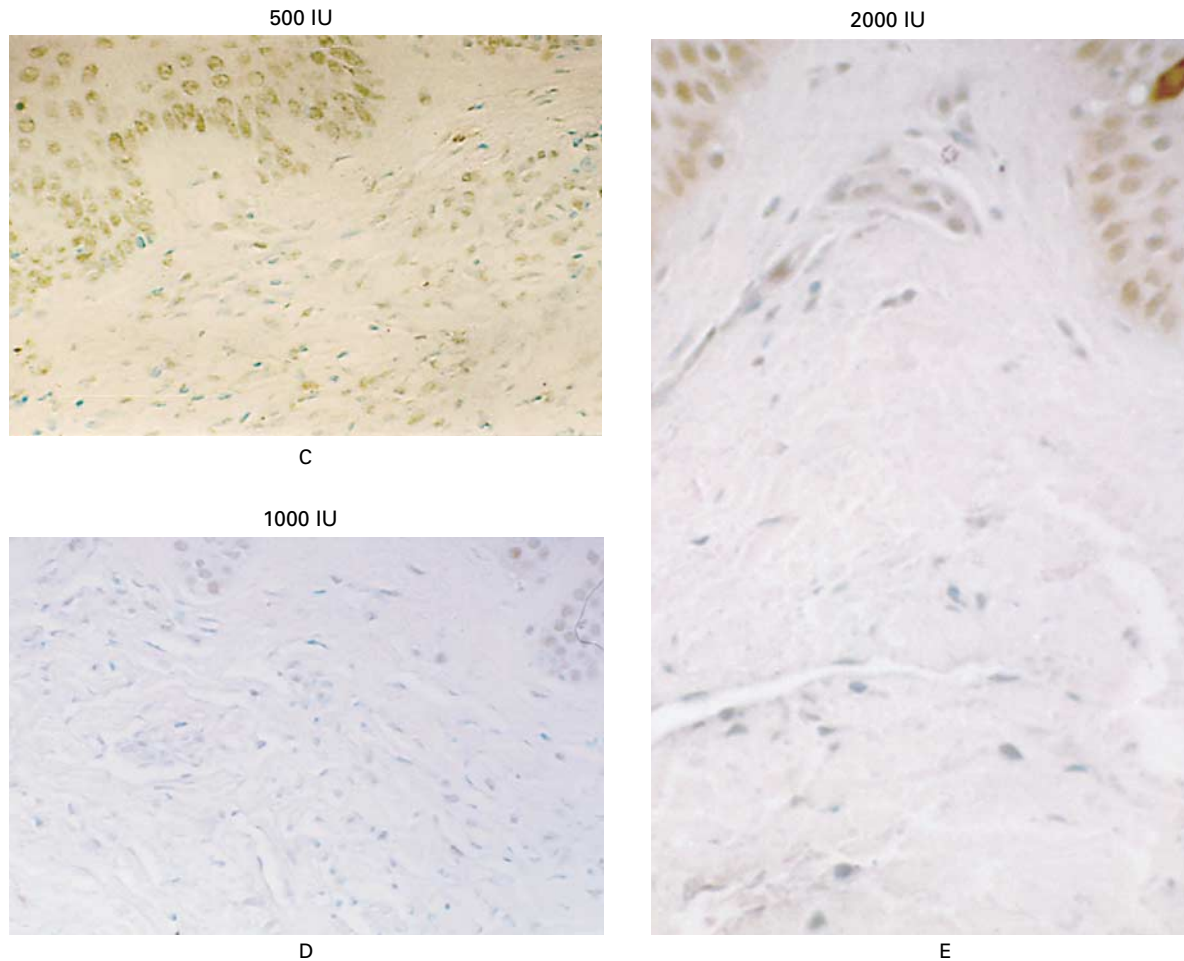


Figure 3. Apoptosis in Kaposi's Sarcoma Lesions Treated with A.P.L.

Panel A (facing page) shows a diluent-treated lesion, with no evidence of apoptosis. There was a progressive increase in the percentage of cells undergoing apoptosis and a decrease in tumor cellularity with increasing doses of hCG (Panels B, C, D, and E). The A.P.L. preparation was administered in each case.

in the mouse model. An analysis of commercial preparations showed the presence of free hCG peptides, but their biologic activity is unknown (unpublished data).

These laboratory findings led to clinical trials of the effects of hCG administered intralesionally in patients with AIDS-related Kaposi's sarcoma. Some preparations of A.P.L. were used because they were the most active of the four products we tested in vitro and in the mouse model. We found that these preparations of hCG can be safely injected into AIDS-related Kaposi's sarcoma lesions at doses of 250 to 2000 IU per lesion three times weekly for two weeks. The side effects were mild and included dizziness, nausea, headache, anxiety, and pain at the injection site.

We found a significant relation between the anti-tumor activity of the preparation and the dose, with responses to treatment in 8 to 83 percent of patients.

There was complete resolution of AIDS-related Kaposi's sarcoma lesions in 10 of 12 patients with the highest dose of hCG used in the testing. We did not expect to see systemic antitumor effects because of the short duration of the treatment, but there was complete resolution of five diluent-treated lesions in the dose-escalation trial. These responses may be due to a systemic effect of the hormone when it is injected locally. In the double-blind trial, none of the tumors injected with diluent alone responded, whereas those injected with hCG did respond. It should be noted that the lesions treated in this trial were relatively small. Large or confluent lesions were not studied. Furthermore, since only three of the patients studied had had cytotoxic chemotherapy, we cannot predict the influence of such therapy on the response of AIDS-related Kaposi's sarcoma lesions to hCG.

We paid careful attention to drug stability, the size of the needles used in the injections, and the tech-

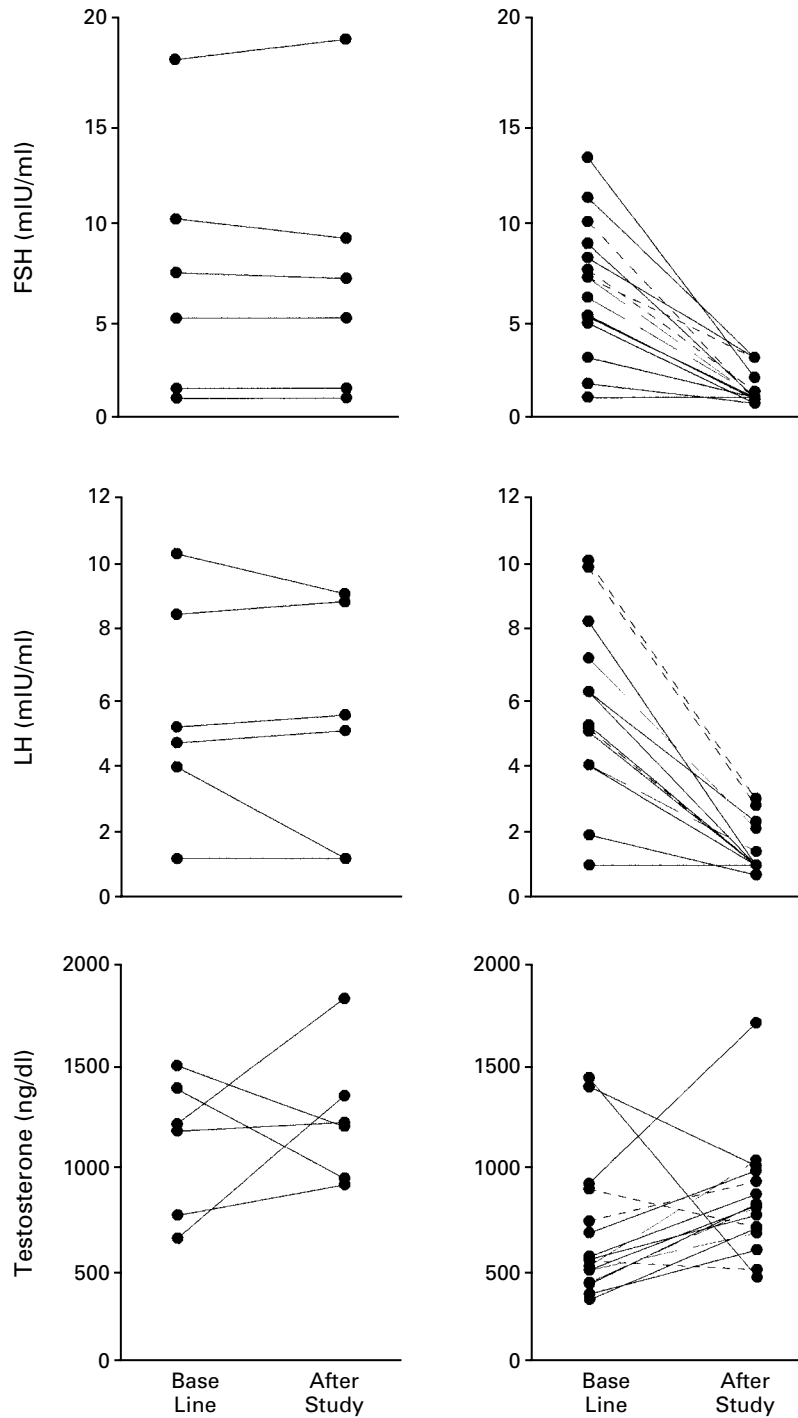


Figure 4. Levels of FSH, LH, and Serum Testosterone before the Start of hCG Treatment (Base Line) and within 24 Hours after the Final Injection.

The left-hand panels show the values for six patients treated with diluent alone in the double-blind, randomized study. The right-hand panels show the values for 17 patients treated with 500 IU (dotted lines), 1000 IU (dashed lines), and 2000 IU (solid lines) of hCG.

nique of injection. The hCG preparation was reconstituted and used immediately to avoid degradation of the active material. A fine needle (27- or 30-gauge) was used to minimize injection-related pain and reduce the efflux of the drug from the injection site. The hCG was injected under the skin immediately over the lesion in order to raise a weal that covered the whole lesion.

We also studied the effects of intralesional hCG injections on blood levels of FSH, LH, and testosterone. At doses of 500 to 2000 IU, hCG lowered the serum levels of FSH and LH in blood drawn within 24 hours after the final dose of hCG, as compared with the base-line levels. Serum testosterone levels rose, but not significantly so, in 17 of 23 patients. No alteration in hormone levels was observed in the patients who received diluent alone.

Tumor-biopsy specimens obtained after the final administration of the hCG preparation revealed apoptosis, an effect analogous to the effects of hCG on human Kaposi's sarcoma cells in vitro and in the mouse model.²² The proportion of cells that underwent apoptosis was positively correlated with the dose of the hCG preparation. These findings suggest that the antitumor activity of the hCG preparation is mediated by direct cytotoxic effects of the active moiety on the tumor cells. There was no evidence of infiltration of the tumor with mononuclear cells, a fact that argues against an immune-mediated response.

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CORRECTION

The Effects of Preparations of Human Chorionic Gonadotropin on AIDS-Related Kaposi's Sarcoma

The Effects of Preparations of Human Chorionic Gonadotropin on AIDS-Related Kaposi's Sarcoma . On page 1264, the sentence that begins in line 7 of the left-hand column should have read, "One patient had biopsy-confirmed complete remission of *one hCG-treated lesion*," not "*both hCG-treated lesions*," as printed.

CORRECTION

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