effects on Kaposi's sarcoma in the absence of a CG-like molecule in mice?

Of potentially more importance, the biological function of hCG is mediated by the αhCG/βhCG dimer and not by the free βhCG subunit, but the same function and receptors are being proposed for hCGβ as for hCG by Lunardi-Iskandar *et al.* This contradiction could be clarified by conventional radioreceptor assays or by direct demonstration of LH/hCG-receptor gene expression, but not by an immunohistochemical demonstration of receptors with a polyclonal antiserum against the ligand, as performed by Lunardi-Iskander *et al.* The hormonal profiles of pregnancy sera differ vastly from sera of non-pregnant humans and mice, not only with respect to hCG. The investigators should have included some conclusive specificity controls such as immunoneutralization by monoclonal antibodies against both hCG and its subunits[9,10]. The same applies to the crude hCG preparations used in their bioassays, especially as they did not rely on highly purified material (for example, hCG CR-127, 14,900 IU per mg), which is made available by their own research institution, NIH. Whether it is really CG, or even more surprisingly free βhCG, which exerts antioncogenic effects on Kaposi's sarcoma is therefore not resolved.

Finally, by definition, βhCG is not a pregnancy hormone, as claimed by Lunardi-Iskandar *et al.* It is at best a pregnancy marker whose serum levels are at least 100–1,000-fold less during gestation[11]. Furthermore, a "purified native hCG preparation containing 80% βhCG and 20% αhCG" is a contradiction in terms and certainly not a biologically active holo-hormone.

We believe that hCG-like molecules have a potential for additional functions, especially as βhCG and alternative messenger RNA splice products with open reading frames have been shown to be expressed, not only in the placenta, but also eutopically in the testis[12]. Moreover, the main metabolic product of hCG, the βhCG core fragment, has a striking structural similarity to nerve growth factor and other members of the superfamily of 'cystine-knot' growth factors, suggesting a distinct biological function[13]. The suggestions of Lunardi-Iskandar *et al.* are, however, not yet proven.

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LUNARDI-ISKANDAR *ET AL.* REPLY — Rabkin *et al.* state in their analyses the interesting observation that pregnancy does not protect against Kaposi's sarcoma (KS). We agree that it is likely that factors other than hCG explain the male/female differential in this disease. In pregnancy, hCG levels peak only for a short period, and even that peak would be insufficient for long-lasting effects. Rather, we propose LH, and not hCG, as a candidate for a hormonal contribution to the sex differential in Kaposi's sarcoma[1], because the LH β-chain is 85% homologous to the β-chain of hCG[14,15], and because LH is higher in women than in men and much higher at some stages of the menstrual cycle[16]. Moreover, we find that LH has some of the same effects we reported for some hCG preparations (unpublished results).

Berger and Dirnhofer are concerned that because mice do not have hCG, but do have LH-like molecules, the inhibitory factor in mouse sera cannot be the same as in humans, namely βhCG. Mice may not have the corresponding βCG gene nor a placental hormone similar to CG, but sera of pregnant mice and women have an anti-KS factor, especially in early pregnancy. This activity is present in some preparations of hCG; it resides in the β-chain, as demonstrated using purified native βhCG[1] and also purified βhCG recombinant peptides (our unpublished data). Berger and Dirnhofer note that LH carries a related activity. Because of the homology between βhCG and βLH, we assume that if mice do not have CG, the anti-KS activity in mouse sera may well be LH or LH-like.

They also state that the reproductive biological effects of hCG are associated with the dimer. This is indeed the case; however, several workers have shown that the β-chain alone can induce signal transduction[6,17–19] and also that βhCG competes with the dimer for receptor binding[13], so there is good evidence that the β-chain alone contains some biological activity.

With respect to the presence of hCG receptors, all our preliminary results indicate that the Kaposi sarcoma cells have hCG receptors (unfortunately, there was a mistake in our figure legend: the polyclonal sera were not to the ligand but to the receptor), but it is possible that the mechanism for the effect of βhCG could be independent of these. Berger and Dirnhofer note the similarity of βhCG to some growth factors[20], and we believe that one interpretation of our results (N. W. Isaacs, personal communication) is competition of βhCG for a growth factor needed by these tumour cells.

We disagree with Berger and Dirnhofer's contention that results with monoclonal antibodies to hCG would be more conclusive than those presented. We feel that the use of purified native βhCG and purified recombinant peptides of βhCG is sufficiently strong evidence to draw the conclusions made in our paper.

Finally, let us reiterate the novelty of our paper: Kaposi's sarcoma Y-1 cells are the first proven malignant cells obtained from HIV-associated Kaposi's sarcoma and they are killed by purified βhCG peptides. A possible additional novelty is the hypothesis of a gender susceptibility difference based on LH.

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Erratum

IN the Scientific Correspondence "Non-invasive bird tagging" by D. Michard, A Ancel, J-P Gendner, J Lage, Y Le Maho, T Zorn, L Gangloff, A Schierer, K Struyf and G Wey (*Nature* **376,** 649–650; 1995), the reference list was inadvertently omitted. It is given below. Also, the surname of Alfred Schierer was misspelt.

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