is under discussion in Italy (Milan and Bologna Cancer Centres). Additionally, a very detailed 'vanguard' study is presently under planning at the University of Wisconsin (1500 volunteers, aged 55–69) to address the main issues of long-term tolerability and side-effects of tamoxifen.

Alberto Costa
European School of Oncology
20133 Milan, Italy

Richard R. Love
University of Wisconsin
Madison, U.S.A.

1. Craig Jordan V, Dowse LJ. Tamoxifen as an antitumour agent: effect on oestrogen binding. *J Endocrinol* 1976, **68**, 297–303.
2. Fisher B, Costantino J, Redmond C *et al.* A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have oestrogen-receptor-positive tumours. *N Engl J Med* 1989, **320**, 479–484.
3. Powles TJ, Hardy JR, Ashley SE *et al.* A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* 1989, **60**, 126–131.
4. Love RR. Prospects for antioestrogen chemoprevention of breast cancer: Commentary. *JNCI* 1990, **82**, 18–21.
5. Maltoni C, Pinto C, Paladini G. Project of experimental bioassays on chemoprevention agents performed at the Bologna Institute of Oncology: report on tamoxifen control of spontaneous mammary tumours on Sprague–Dawley rats. *Cancer Invest* 1987, **6**, 59–74.

Eur J Cancer, Vol. 26, No. 6, pp. 657–659, 1990.
Printed in Great Britain

0277-5379/90$3.00 + 0.00
Pergamon Press plc

The Conundrum of Kaposi's Sarcoma

INTRODUCTION

KAPOSI'S SARCOMA (KS), first described by the Hungarian pathologist Moritz Kaposi in 1872 [1], is an increasingly challenging puzzle. Is KS a genuine malignancy or a hyperplastic response to angiogenic growth factors? Why is its incidence increasing outside the risk groups for AIDS, as reported from Sweden by Bendsöe and colleagues [2] (p. 699)? Why is it prevalent in homosexuals with AIDS but not in haemophiliacs? Why does the classical pre-AIDS form of KS occur ten times more frequently in men than women? Is there a transmissible KS agent?

CELL BIOLOGY

KS lesions have two main cellular components, endothelial layers and aggregations of spindle cells [3, 4]. It is not clear whether the endothelial cells are of vascular or lymphatic origin, or whether the spindle cells derive from endothelium or smooth muscle. The use of cell markers has been inconclusive [5, 6], though it appears that most KS cells of both types are positive for CD34 antigen, which is characteristic of bone marrow stem cells and vascular endothelium (J.J. Brooks, J. Armes and C. Fisher, pers. comm.). Only recently have KS cells been propagated in long-term culture [5, 6], and these appear to be endothelial [5, 7].

The concept of KS as a malignant tissue of clonal origin has been questioned, with suggestions that early lesions at least are hyperplastic [8, 9]. KS lesions are frequently multicentric, but seldom resemble metastases. Early lesions regress spontaneously or following withdrawal of iatrogenic immunosuppression in organ transplant recipients. Lesions often disappear within days after the onset of chemotherapy. The pattern of KS growth is consistent with a hyperplastic response to local angiogenic growth factors. Nevertheless, a malignant, clonal lineage of cells may exist as a minority cell population in the tumour, but not be apparent morphologically, as Reed–Sternberg cells are in Hodgkin's lymphoma; these cells could have a paracrine angiogenic effect. Alternatively, the lesions may be polyclonal, similar to lymphoblasts in infectious mononucleosis; conceivably, late stage KS lesions may then allow the emergence of a true malignancy as a further step in transformation.

There have been reports of oncogenes in KS detected by DNA transfection [10, 11]. Transfected murine 3T3 cells developed KS-like angiosarcomas following inoculations into mice [10]. Nude mice injected with cultured human KS cells also develop KS-like tumours composed of murine cells [12]. The one oncogene identified in KS is homologous to the *hst* oncogene belonging to the fibroblast growth factor family [11]. However, it was not active in the original KS lesion and may have arisen as an artefact of the DNA preparation.

Growth factors influence the proliferation of KS cells. Some virally transformed cells in culture release angiogenic factors which have a mitogenic effect on KS cells [6]. Of particular interest is the finding that a secreted form of the tat protein of HIV acts as a mitogen on certain KS clones [13]. This observation indicates that HIV may act to promote KS growth by a more direct means than by immunosuppression. Transgenic mice expressing the *tat* gene of HIV developed lesions not dissimilar to KS [14]. The *tat* gene was expressed in dermal or epidermal cells, not in the proliferating endothelial cells, suggesting a paracrine effect. Curiously, only male mice transgenic for *tat* had KS-like nodules [14].

EPIDEMIOLOGY

Before the AIDS epidemic, KS was known to occur sporadically in elderly men in Europe and more frequently in younger men, and occasionally women and children in central and East Africa [3, 4]. KS also occurred with significantly increased relative risk in recipients of renal transplants under immunosuppressive therapy [15]. The sudden appearance of KS in previously healthy homosexual men, first noted by A. Friedman-Kien in New York, led to the recognition of AIDS [16]. It soon became apparent that endemic KS in Africa was not due to HIV infection, but that the vast increase in aggressive, disseminated KS was indeed associated with HIV [17, 18].

In the years since AIDS first appeared, a distinctive pattern of KS presentation has been observed. The incidence of KS in AIDS cases in Western countries varies remarkably according to the risk group, being most prevalent in homosexual men (21%), rare in intravenous drug users and transfusion recipients (3–4%), and very rare in haemophiliacs (1%) [19]. Moreover, the proportion of new homosexual AIDS cases with KS has fallen from approximately 70% to 20% between 1982 and 1989. KS is four times commoner in women with AIDS reporting sex with bisexual men than those whose partners were intravenous drug users [19]. In addition, the incidence of KS has not only risen two-fold in the general HIV-negative population over the past 25 years [2] but occasional HIV-negative KS cases are being recorded at a higher rate among homosexual men [20], indicating that this is also a risk group independent of HIV infection.

Together, these data indicate that an agent other than HIV causes KS. This agent would be sexually transmissible particularly among the most promiscuous, but less frequently transmitted by whole blood and hardly at all by concentrated clotting factors [19]. The KS agent would be latent in many more individuals than those developing KS, and would present as KS in immunosuppressed transplant and AIDS patients. The higher incidence of KS among AIDS cases in some risk groups than among transplant patients would be compounded by the higher exposure to a sexually transmitted agent, and possibly also by the KS cell-growth-promoting property of the HIV tat protein [13].

There is a strong male bias of KS even in Africa where one might presume the putative agent is heterosexually transmitted. Therefore, hormonal influences may affect KS growth. However, the occurrence of KS in African children (where the sex ratio of cases is nearer unity) challenges both the theories of sexual transmission and the hormonal effects. Possible maternal transmission of a KS agent should not be ignored.

SEARCHING FOR THE KS AGENT

If these epidemiological arguments are correct, it will be important to search for the aetiological agent of KS. Studies to date have not successfully linked known viruses with KS, although cytomegalovirus came under suspicion in the 1970s [4]. I expect that there is an unknown KS agent awaiting discovery. What sort of agent might that be?

There are two animal models that bear comparison to KS. Dictor and Järplid [21] have pointed out that haemangiomatous tumours, resembling KS histopathologically, often develop in chickens infected with certain strains of avian leukosis virus. By this analogy, a C-type retrovirus, distinct from HIV, might be sought in KS. An alternative animal model epidemiologically redolent of KS is the canine transmissible venereal sarcoma [22]. Unlike KS, it usually presents on the external genitalia, but similar to KS it spontaneously regresses except in conditions of immunosuppression, when it becomes widely disseminated [23]. Chromosomal and oncogene markers indicate that the transmissible agent is the tumour cell [24, 25]. In other words, the cancer cell itself has adapted to spread as a parasite.

To explore this analogy with canine transmissible venereal sarcoma, we attempted to test whether cells of foreign genetic origin might be present in KS lesions. Given the predominance of KS in men we predicted that a transmissible tumour cell would originally have had a male provenance and we therefore probed DNA from female KS biopsies for Y-specific sequences, following amplification by the polymerase chain reaction (H. Jaffe, T.J. Schulz, J. Hoad, R.A. Weiss, unpublished observations). The results were negative, indicating that the tumour was female, had lost the Y chromosome sequences or, most likely, that the canine model of transmission is inappropriate for KS.

CONCLUSIONS

KS is an endothelial growth that is probably polyconal and responsive to paracrine and angiogenic growth factors. The response of KS cells in culture to HIV *tat* gene products [13] does not explain the epidemiological data that only the HIV infected persons in sexual risk groups have a high incidence of AIDS-linked KS [19]. It seems likely that a sexually transmissible agent is a key factor for KS. That agent remains to be found.

Robin A. Weiss
Chester Beatty Laboratories
Institute of Cancer Research
Fulham Road
London SW 3 6JB
U.K.

1. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. *Arch Dermatol Syph* 1872, **4**, 265–273.
2. Bendsöe N, Dictor M, Blomberg J, Ågren S, Merk K. Increased incidence of Kaposi sarcoma in Sweden before the AIDS epidemic. *Eur J Cancer* 1990, **26**, 699–702.
3. Hutt, MSR. Kaposi's sarcoma. *Br Med Bull* 1984, **40**, 355–358.
4. Armes JA. Review of Kaposi's sarcoma. *Adv Cancer Res* 1989, **53**, 73–87.
5. Roth WK, Werner S, Werner R, Remberger K, Hofschneider PH. Cultured, AIDS-related Kaposi's sarcoma cells express endothelial cell markers and are weakly malignant *in vitro*. *Int J Cancer* 1988, **42**, 767–773.
6. Nakamura S, Salahuddin SZ, Biberfeld P *et al.* Kaposi's sarcoma cells: long-term culture with growth factor from retrovirus-infected CD4$^+$ T cells. *Science* 1988, **242**, 426–430.
7. Werner S, Hofschneider PH, Roth WK. Cells derived from sporadic and AIDS-related Kaposi's sarcoma reveal identical cytochemical and molecular properties *in vitro*. *Int J Cancer* 1989, **43**, 1137–1144.

8. Costa J, Rabson AS. Generalised Kaposi's sarcoma is not a neoplasm. *Lancet* 1983, i, 58.
9. Brooks JJ. Kaposi's sarcoma: a reversible hyperplasia. *Lancet* 1986, ii, 1309–1311.
10. Lo SC, Liotta LA. Vascular tumors produced by NIH/3T3 cells transfected with human AIDS Kaposi's sarcoma DNA. *Am J Pathol* 1985, **118**, 7–13.
11. Delli Bovi P, Curatola AM, Kern FG, Greco A, Ittmann M, Basilico C. An oncogene isolated by transfection of Kaposi's sarcoma DNA encodes a growth factor that is a member of the FGF family. *Cell* 1987, **50**, 729–737.
12. Salahuddin SZ, Nakamura S, Biberfeld P *et al.* Angiogenic properties of Kaposi's sarcoma-derived cells after long term culture *in vitro*. *Science* 1988, **242**, 430–433.
13. Ensoli B, Barillari G, Salahuddin SZ, Gallo RC, Wong-Staal F. Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. *Nature* 1990, **345**, 84–86.
14. Vogel J, Hinrichs SH, Reynolds RK, Luciw PA, Jay G. The HIV *tat* gene induces dermal lesions resembling Kaposi's sarcoma in transgenic mice. *Nature* 1988, **335**, 606–611.
15. Penn I. Kaposi's sarcoma in immunosuppressed patients. *J Clin Lab Immunol* 1983, **12**, 1–10.
16. Centers for Disease Control. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. *MMWR* 1981, **30**, 305–308.
17. Biggar RJ, Melby M, Kesterns L *et al.* Kaposi's sarcoma in Zaire is not associated with HTLV-III infection. *Lancet* 1984, ii, 1051–1052.
18. Bayley AC, Downing RG, Cheingsong-Popov R, Tedder RS, Dalgleish AG, Weiss RA. HTLV-III serology distinguishes atypical and endemic Kaposi's sarcoma in Africa. *Lancet* 1985, i, 359–361.
19. Beral V, Peterman TA, Berkelman RL, Jaffe HCW. Kaposi's sarcoma among persons with AIDS: a sexual transmitted infection? *Lancet* 1990, **335**, 123–128.
20. Friedman-Kien AE, Saltzman BR, Cao Y *et al.* Kaposi's sarcoma in HIV-negative homosexual men. *Lancet* 1990, **335**, 168–169.
21. Dictor M, Järplid B. The cause of Kaposi's sarcoma: an avian retroviral analog. *J Am Acad Dermatol* 1988, **18**, 398–402.
22. Hayes HM, Biggar RJ, Pickle LW, Hoover R, Toft JD. Canine transmissible venereal tumour: a model for Kaposi's sarcoma? *Am J Epidemiol* 1983, **117**, 108–109.
23. Cohen D. The biological behaviour of the transmissible venereal tumor in immunosuppressed dogs. *Eur J Cancer* 1973, **9**, 253–258.
24. Cohen D. The canine transmissible venereal tumor: a unique result of tumor progression. *Adv Cancer Res* 1985, **43**, 75–112.
25. Katzir N, Arman E, Cohen D, Givol D, Rechavi G. Common origin of transmissible venereal tumors (TVT) in dogs. *Oncogene* 1987, **1**, 445–448.

Acknowledgement—I thank the Cancer Research Campaign for support.

Eur J Cancer, Vol. 26, No. 6, pp. 659–660, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Morpholinyl Anthracyclines: Option for Reversal of Anthracycline Resistance

ANTHRACYCLINES are potent chemotherapeutic drugs whose mechanisms of action are still intriguing. The most widely used are doxorubicin and daunorubicin. Intrinsic or acquired anthracycline resistance in tumours hampers their clinical effectiveness. Efficacy, toxicity and drug resistance may be related to different parts of the anthracycline molecule. Helen Coley and her colleagues (p. 665) add to our knowledge of newly synthesized anthracycline derivatives which have several attractive features.

Anthracyclines may be cytotoxic to cells at the outer cell membrane [1]. In general, however, to be cytotoxic, the drug has to enter the cell. One of the earliest proposed mechanisms is DNA intercalation. The anthracycline chromophore fits stereometrically between two base-pairs, preventing replication and transcription and leading to cell death [2]. Another possible mechanism is the ability to turn topoisomerases into cellular toxins [3]. This, also, is not a full explanation because the *in vitro* capacity to inhibit topoisomerase II is not linearly related to cytotoxicity [3]. Anthracyclines can induce DNA damage. After exposure to anthracyclines, DNA–DNA crosslinks, DNA–protein crosslinks, and single-stranded and double-stranded breaks can be detected. This could, at least in part, be due to the generation of free radicals by the quinone moiety [4]. None of these mechanisms can be seen as the principal cause of cytotoxicity; all probably participate to varying extents depending on the structure of the anthracycline.

The cell membrane plays, in contrast to its limited role in cytotoxicity, an important part as a first-line defence in drug resistance. The most extensively studied mechanism is multidrug resistance (MDR) mediated by P-glycoprotein. The P-glycoprotein mediated membrane pump removes anthracyclines that have entered the cells by diffusion through the lipid compartment of the membrane [5]. The result is decreased intracellular drug concentrations. Other membrane pumps have also been described [5]. Alternative mechanisms of anthracycline resistance include decreased topoisomerase II activity and enhanced detoxifying enzyme activities, including raised glutathione peroxidase and glutathione S-transferase [5–8].

The ideal anthracycline should have several properties. It should have at least the same anti-tumour activity as the parent compound. Therefore, all the supposed mechanisms of action should be present and additional mechanisms would be welcome. In addition, the compound should not be affected by anthracycline resistance mechanisms. Several drugs partly fulfil these requirements. In *in vitro* systems, these drugs have good anti-tumour activity and also show activity in cell lines with various resistance mechanisms [9]. Their greater effectiveness is primarily due to increased lipophilicity, itself leading to higher intracellular drug levels. Some of these drugs have been tested in clinical trials. Examples include idarubicin, detorubicin and esorubicin. However, the advantage of the analogues over doxorubicin is limited [10].

Interesting analogues are the 3′ *N*-morpholinyl substituents. These drugs have several of the required properties. Morpholinyl anthracyclines are highly lipophilic, diffuse rapidly through the cell membrane, and reach high intracellular levels [11].