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SPECIAL REPORT

Contradictory Concepts in the Etiology and Regression of Kaposi's Sarcoma*

The Ferenc Györkey Memorial Lecture

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The Introduction is an overview of 3 decades of works performed by Professor Ferenc Györkey† (in many cases in collaboration with the author) and aimed at the elucidation of viral participation in the etiology of arteriosclerosis, SLE, hairy cell leukemia, HD, AIDS and KS. Controversial issues surrounding the etiology, treatment and regression of KS are discussed in terms of paracrine and autocrine loops of growth factors; protooncogene-oncogene activations, immunosuppression and retro- and/or herpesviral etiology. In regressing KS lesions the roles played by Fas, Bcl-2, Bax, TNFß; apoptotic-antiapoptotic events; and antiangiogenesis agents especially that of Hu-r-IFNα are elaborated on. (Pathology Oncology Research Vol 2, No 4, 249–267, 1996)

Key words: Growth factor cascade, human herpesvirus 8, apoptosis, protooncogenes-oncogenes, retro-lentiviruses

Introduction

It is a sad occasion but certainly a great honor for me that I may dedicate this presentation to our deceased friend Professor Ferenc Györkey *(Fig.1)*. He and his gracious wife Phyllis *(Fig.2)* at the Veterans Administration Hospital (Medical Center) and Baylor College of Medicine Houston TX had mightily contributed to our factual knowledge and theories concerning the viral etiology of systemic lupus erythematosus (SLE), hairy cell leukemia, Hodgkin's disease (HD) and AIDS and Kaposi's sarcoma (KS). Ferenc Györkey with the assistance of his devoted wife Phyllis and his faithful technician Alex (Sandor) Gergely worked in his laboratory 14h days and week-ends until his death. He died three years ago of complications of multiple myeloma at MD Anderson Hospital.

It was in 1968 that I had carried to Ferenc freshly removed tissues of a patient of mine who died with an unusually malignant case of SLE involving his brain and spinal cord. It was in this case that we sitting side by side observed first the abundance of those cytoplasmic structures *(Fig.3)* that occur without exception in every case of SLE. I am responsible for calling these structures unenveloped viral ribonucleoprotein strands believing that we observed an incomplete myxo-, paramyxo- or retrovirus: the causative agent of SLE! However this notion remains without proof. Similar structures occur in many other pathological entities (in AIDS-KS or in Paget's osteitis deformans etc) and can be induced to form in lymphocytes exposed to interferons alpha or beta (but not to gamma) (IFNα,ß,γ). Up to this date no one concentrated these structures from tissue extracts by differential centrifugation to study their immunohistochemistry and/or biological activities; thus this project remains open for the next generation of scientific investigators. It is still possible that SLE is caused by an incomplete endogenous retrovirus *(Fig.3bc)* whose switched off genomic sequences become activated to encode antigenic peptides and/or to recombine with an apathogenic exogenous retrovirus. Endogenous retroviral sequences reside in the human genome (including KS cells, *vide infra*)[1-3] and antibodies to polypeptides encoded by such sequences are formed in patients with SLE. *Blood* rejected our manuscript (the common fate of original discoveries) but we published the case history of our first patient in the *Texas Reports on Biology & Medicine*[1,2,3] and wrote a Letter to the

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Editor of the *New England Journal of Medicine*[*45] when we found similar structures in every patient with SLE.[44]

In the late '60s we like others tried to induce "focus formation" and "antigenic conversion" in cultures of

Figure 1. *Professor Ferenc Györkey at his Philips electron microscope (VA Medical Center, Houston TX) in 1991.*

human sarcoma cells: these elusive phenomena implied the presence of a filterable (viral) agent.[124] While we could not isolate and identify human sarcomagenic viruses, electron microscopy showed subviral structures and mature virions resembling retroviruses in these cultures.[40] Szakacs and Ruttgers Szakacs confirmed the presence of retrovirus-like particles in human sarcomas.[138]

Thereafter Ferenc found herpes virus type particles in cells of hairy cell leukemia. These viral particles turned out to be those of the Epstein-Barr virus (EBV) *(Fig.4)*, persisted in cultured cells, and coexisted with cytoplasmic tubuloreticular structures.[119,128] Occasionally delicate cytoplasmic tubuloreticular structures and budding retrovirus-like particles were also seen *(Fig.5)*. We never could isolate these retroviruses but other hairy cell leukemic patients yielded isolates of human T cell leukemia virus type 2 (HTLV-2). Isolating HTLV-2 from a few cases of (atypical) hairy cell leukemia[105] does not prove etiological relationship since most B hairy leukemia cells were devoid of HTLV-2 genomic sequences.[73]

Our attention then was turned to Reed-Sternberg (RS) cells of HD. In this entity Ferenc and I observed intranuclear herpes viral nucleocapsids *(Fig.6)*[118] long before the association of EBV with RS cells was proven by immunohistochemical and molecular biological means.

[*] Dr. Györkey submitted our letter to the Editor with the authors' names listed as F Györkey, Sinkovics, Men and P Györkey. The editors admitted that due to an error at type setting my name had become the third in line: they published a correction.[41]

Table 1. **EBV in human malignancies**

Lymphoproliferative
African Burkitt's lymphoma cells
Lymphomas AIDS-associated (especially those in CNS)
Large cell diffuse lymphomas in transplanted liver and hearts consisting of recipient's cells
Hodgkin's Reed-Sternberg cells
Hairy leukemia cells
Pyothorax associated lymphoma cells[59]
Nasal T cell lymphoma[39]
Leiomyosarcoma
AIDS associated pediatric; in transplanted livers[78,80]
Nasopharyngeal carcinoma ("lymphoepithelioma")[61,96,113]
Squamous carcinoma cells fused with cells of lymphoid stroma[29]

With diligent search we also found budding retroviral particles in RS cells *(Fig.7)*. Soon experimental data emerged in my laboratory showing that a retrovirus existed in HD tissue extracts revealing itself as an envelope-donor to an incomplete murine retrovirus.[112,117] We could detect antibodies directed to these viral envelopes in patients with HD (but Ferenc could not complete the immunoelectron microscopic studies). These observations allowed us to view RS cells as "natural hybridomas" formed by the fusion of a retrovirally infected mononuclear HD cell (probably an antigen-presenting dendritic cell) with reactive or bystanding naive B or T lymphocytes. The unique relationship of antigen-presenting cells with lymphocytes allows for such a reaction *(vide infra* "conjugate formation" in AIDS). Some RS cells are

Figure 2. *Dr. & Mrs. Ferenc & Phyllis Györkey are honored at a medical convention (1990).*

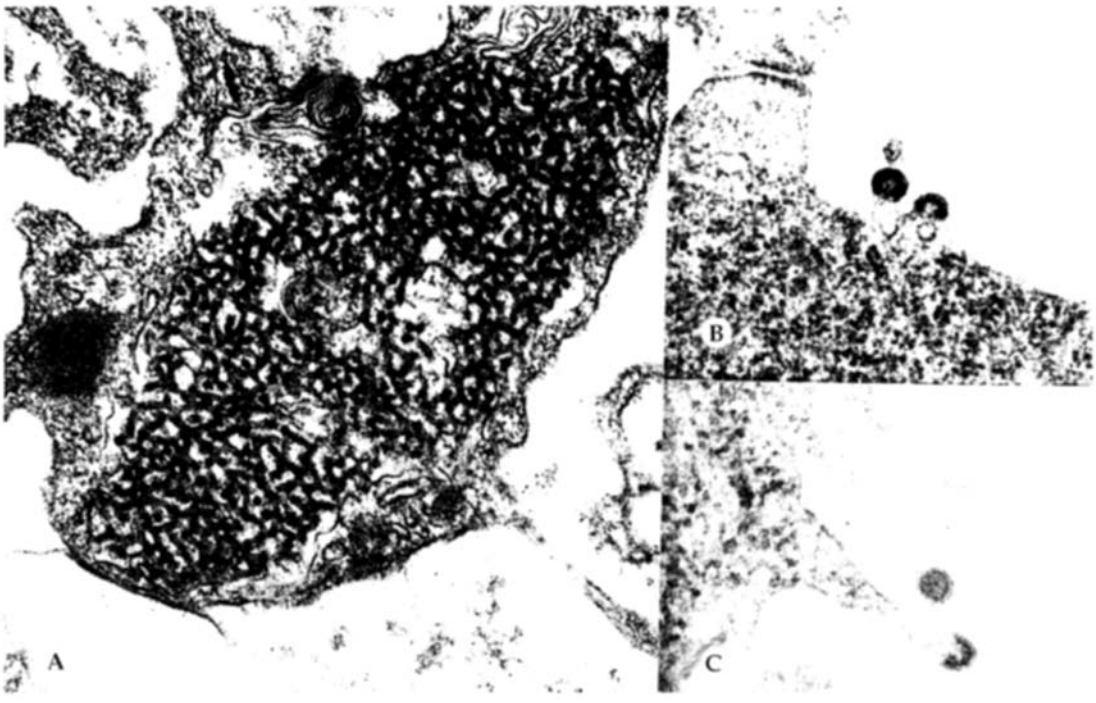

Figure 3a, b, c. *The cytoplasmic tubuloreticular structures of SLE measuring 200-220A in width and up to 1000 Å in length in a kidney glomerular cell (1971).[44] EM, original magnification x34,000 (enlarged in print: approx x120,000). Budding retroviral particles in primary cultures of skin from a case of discoid lupus (b) and kidney from SLE (c) (1982). EM, original magnifications x85,000 (b) and x112,000 (c).*

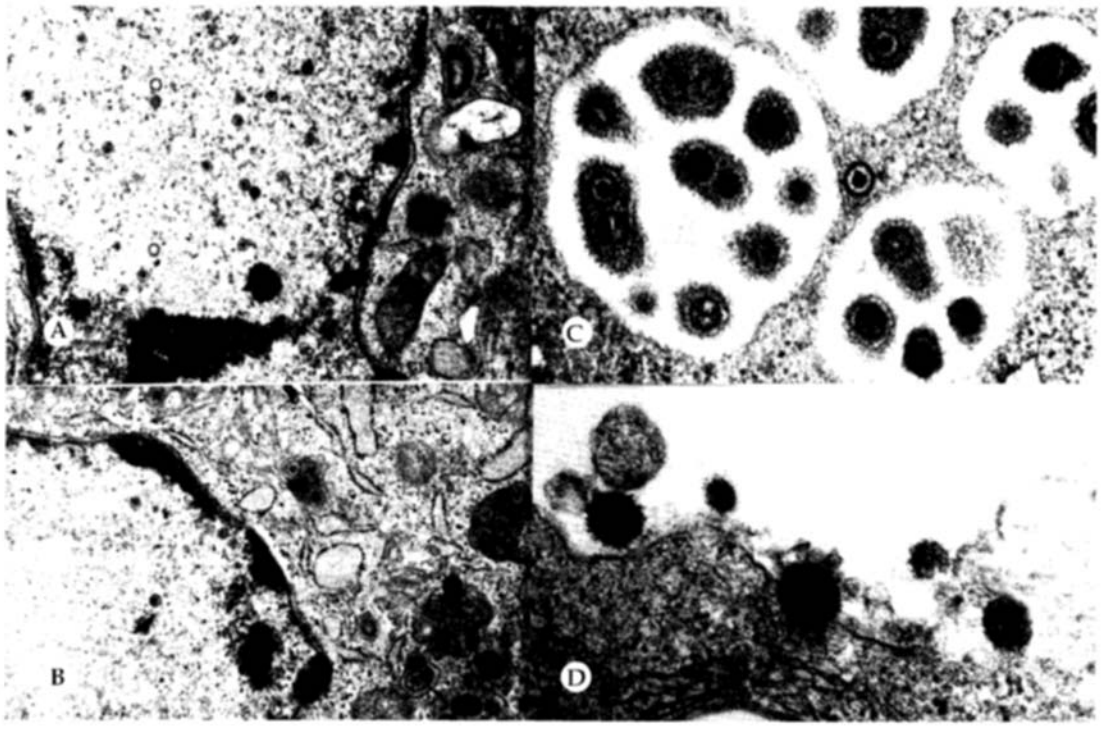

Figure 4a, b, c, d. *Herpesviral unenveloped nucleocapsids in the cell nucleus (a); developing herpesviral particles in the cytoplasm (bc); and mature enveloped herpesviral (EBV) particles leaving the cell (d) in cultured tartrate-resistant B-hairy leukemia cells (1975).[119] EM, original magnifications x40,000 (a and b); x112,000 (c); and x100,000 (d).*

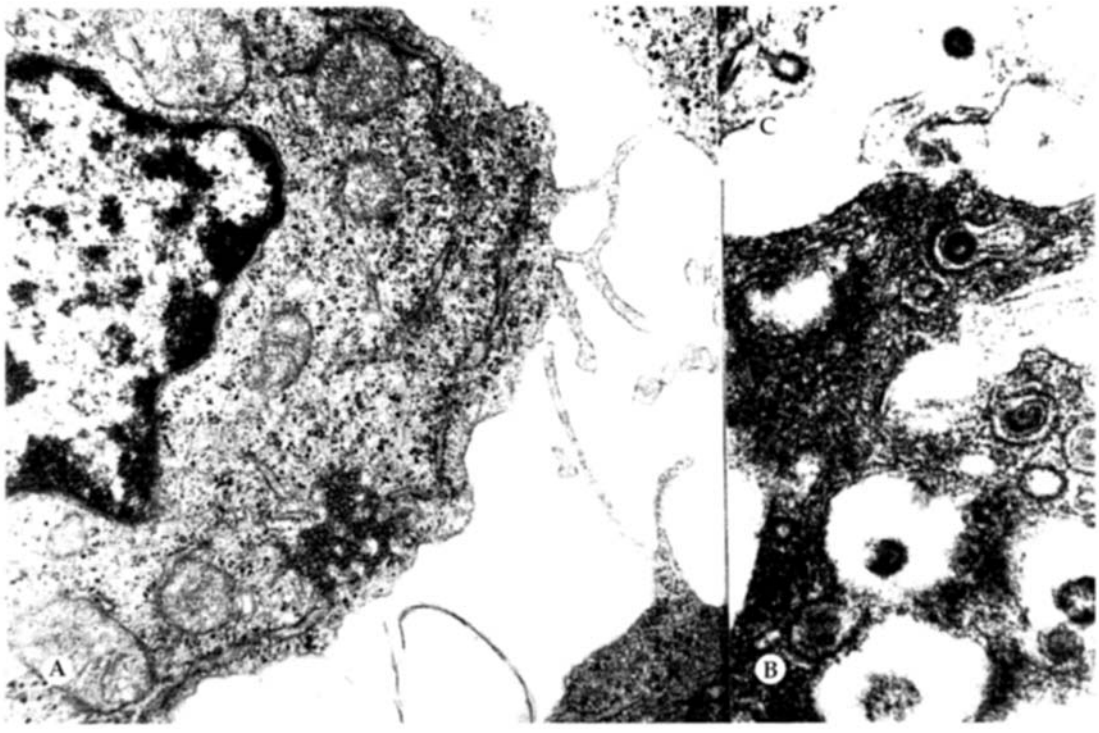

Figure 5a, b, c. *Unidentified viral particles with the appearance of "budding" in hairy leukemia B-cells. EM, original magnification x45,000. Delicate tubuloreticular structure in the cytoplasm of a B hairy leukemia cell (1974). EM, original magnification x25,500.*

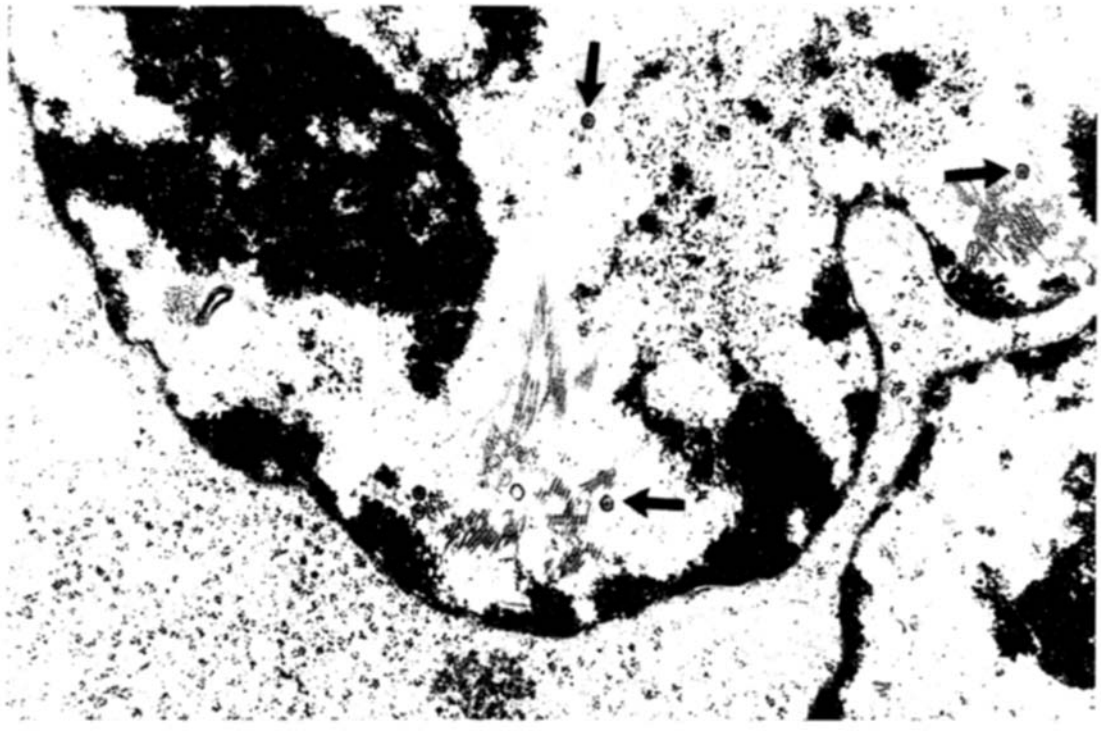

Figure 6. *Unenveloped EBV nucleocapsids in the nucleus of a RS cell of HD (1990). EM, original magnification x37,500.*

formed by fusion with B lymphocytes: we proposed that EBV enters RS cells at this point contributing to the malignancy of RS cells by the activities of EBV genomic sequences BHRF-1 and BNFL-1 imitating those of the *bcl*-2 gene (inducing antiapoptotic events) and encoding latent membrane protein (adding to the malignant phenotype), respectively. After the entry of EBV into RS cells lentiretroviral expressions decline as EBV expressions prevail. Other RS cells were proposed to be formed by fusion of the retrovirally infected dendritic cell with T lymphocytes (like in nodular sclerosis HD). This theory recently received support by the observation of p53 mutation in only one nucleus of the multinucleated RS cell.[35] When B cell Ig gene or T cell receptor gene rearrangements are detectable in RS cells,[50,67] we propose that the mononuclear HD cells fused with oligoclonally expanding reactive B or T lymphocytes: when such gene rearrangements are not detectable,[107] the fusion partner is a naive lymphocyte. *Table 1* summarizes those human malignancies in which EBV appears to have a prominent role either by initiating or by contributing to the malignancy. It is remarkable that in many human (or simian *vide infra*) pathological entities herpes type and lenti-retroviral pathogens coexist (hairy cell leukemia; Hodgkin's disease; AIDS-KS) so much so that when one of the pair is present it is worthwhile to search for its partner (infectious mononucleosis,[122] Burkitt's lymphoma; AIDS-associated lymphomas and body cavity lymphomas; AIDS-associated leiomyosarcoma). Ferenc was deprived of the extra time needed for such search.

In the first years of the 1980s middle aged veterans started to succumb to dreadful multiple infections with cytomegalovirus (CMV), *P. carinii*, cryptococcus and others.[12] It was in this patient population where Ferenc found KS in their lymph nodes[42] and budding retroviral particles in their lymphocytes, macrophages, megakaryocytes and platelets, brain cells and vascular endothelial cells *(Fig.8)*. He and Dr. Melnick reported most of these observations.[36,38,39] In 1983 at the International Congress for Infectious Diseases held in Vienna Austria I had the opportunity to show a series of our EM pictures depicting two different types of retroviruses and herpes virus particles in various organs of AIDS patients.[121] (Not knowing this then, we now believe some of these patients harbored both HIV and HTLV infections!)[28,58] When this co-infection occurs, the lentivirus HIV is able to infect resting cells since its reverse transcription (pre-integration) complex can enter the non-dividing nucleus, whereas retroviruses enter the nucleus during cell division when the nuclear membrane is broken down.[133] Dr. R. Gallo sitting in the first row observed these pictures and promptly invited me to deliver the same lecture at his department: I was pleased to comply. The as yet unidentified viral particles we observed were by then in the earliest of their cultures in Dr. Gallo's laboratory.

Soon we observed an association of herpes type and retroviral particles in AIDS-KS cells. For long we knew of the association of herpes type viruses with KS *(Fig.9)*: we attended some 50 patients with classical Mediterranean KS in the pre-AIDS era at MD Anderson Hospital.[6] We like others[7] isolated CMV and grew B lymphocyte cell lines harboring EBV from these tumors.[120] Now budding retroviral particles structurally different from HIV-1 appeared in some of these tumors *(Fig.10)*;[43] these particles failed to react immunologically as HIV-1 or HTLV-1. The occurrence of similar retroviral particles in KS were reported elsewhere very seldom: once relating these particles to the viruses of avian leukemia and once in Greece (Raffensberger et al; Spandidos et al; cited in[125]) in a cluster of cases of HIV classical KS. HIV isolates from epithelial cells of the uterine cervix[140] and HTLV type IIIB infections of the thymic epithelial cells[103] do exist thus cells other than the lymphatic system could possibly be carriers of these viruses. AIDS-KS cells also contained an abundance of tubuloreticular cytoplasmic structures[41] entirely similar to those previously found in SLE. Dr. Zucker-Franklin who described HTLV-1-like viral particles in mycosis fungoides and related entities[160] wrote a most complimentary editorial[158,159] concerning the discovery of these structures even though the nature and biological function, if any, of these structures remains unknown.

Ferenc Györkey could not finish several of his projects. Some of these concern the finding of CMV in arteriosclerotic plaques with the suggestion that this virus is among the most important causative co-factors of these lesions.[37] The foremost expert on CMV pathogenesis Dr. Eva Gönczöl has recently given credit to Dr. Györkey for this discovery.[32]

When we first observed that human lymphocytes can kill autologous and allogeneic tumor cells either by cytoplasmic lysis or nuclear DNA clumping I submitted cultured human tumor cells dying under lymphocyte attack to Dr. Györkey. In many other laboratories perforins and other enzymes of lymphocyte origin were found to be responsible for complement-like cytoplasmic lysis, whereas nuclear clumping induced by an active suicidal process led to programmed cell death (apoptosis). To Ferenc's great sorrow he could not keep up with the rapid development of this field. So much more he wanted to do and he was not ready to die. However, Ferenc coauthored a paper of mine that was presented first in the form of a lecture in 1969 and appeared in print in 1970.[125] In this paper several original observations were presented: these observations re-emerged as 3 major discoveries (in other laboratories!) in the 1970s. In this paper we reported first that not only lymphocytes of patients with cancers but also lymphocytes of healthy donors could kill cancer cells in vitro: these healthy lymphocytes were characterized later elsewhere as "natural killer cells". We showed slides and

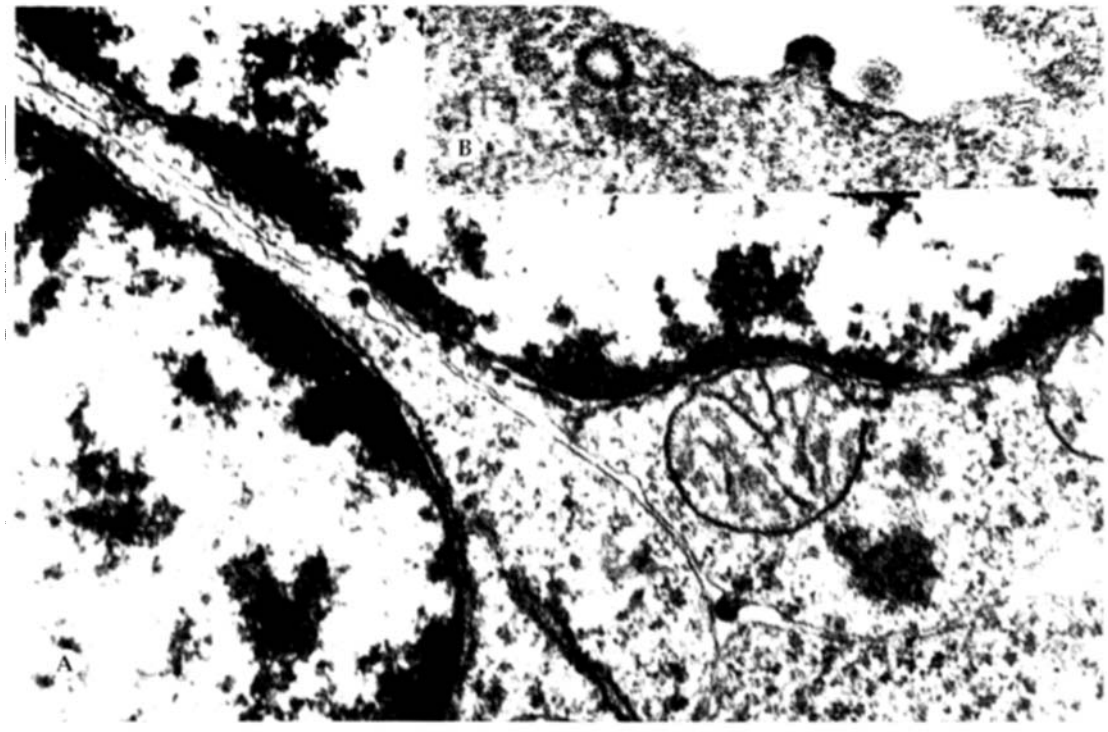

Figure 7. Budding retroviral particles at the cytoplasmic membrane of a RS cell of HD (a); and enlargement of another budding virus particle (b) (1990).[117] *EM, original magnifications x55,000 (a) and x85,000 (b).*

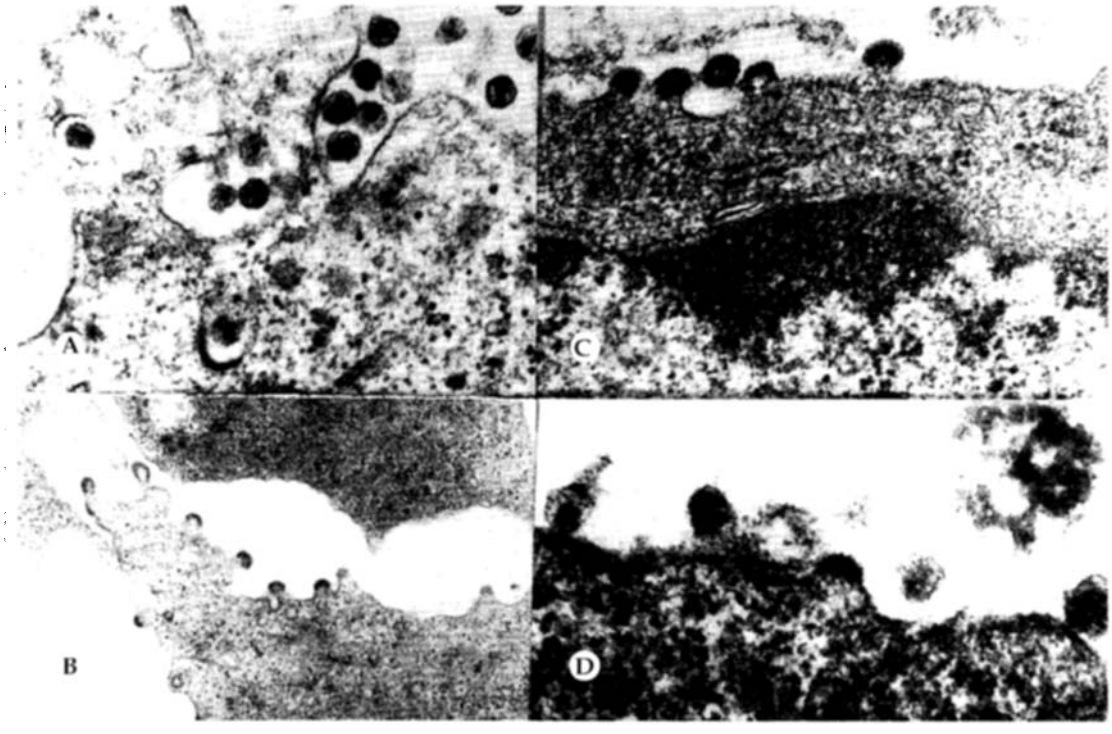

Figure 8a, b, c, d. *Extracellular HIV particles with bar-shaped core in the brain of a patient with AIDS (a) and unidentified retrovirus particles budding from a dendritic cell of the same brain (b) (1983). EM, original magnification x110,000 (a) and x87,500 (b). Unidentified budding retrolentiviral particles in a lymph node cell of a patient with AIDS (c) and in a cell from an AIDS-lymphoma (d) (1985). EM, original magnifications x112,000 (c) and x142,000 (d).*

pictures depicting the mode of target cell killing by lymphocytes either by cytoplasmic lysis or by nuclear clumping: the first mode of killing was shown elsewhere to be mediated by perforins and the second mode of killing was an example of the phenomenon described elsewhere later as programmed cell death or apoptosis induced by serin proteases or granzymes;[47,137] when induced by cytotoxic lymphocytes, this phenomenon is also mediated by TNFαβ (lymphotoxin).[116]

Finally we observed the fusion of a diploid murine malignant lymphoma cell, producer of leukemia virus particles budding through its cell membrane, with a plasma cell secreting antibodies specific to the virus.[125] The fusion product was an immortalized tetraploid cell that grew in suspension cultures in spinner bottles or in the abdominal cavities of mice in the form of fatal ascites tumors and continued to secrete the antibodies: the first recognition of the "hybridoma principle" (even though we did not coin this term in 1969-70 to our antibody-producer tetraploid cells). These are examples of my research projects Ferenc was invited to contribute to but could not. Yet it gives me great satisfaction now that he remains a co-author of this seminal paper!

Ferenc Györkey MD, professor of pathology, pharmacology and virology at Baylor College of Medicine and chief of laboratory services at Houston's VA Medical Center died leaving behind the legacy of his life time of work for the benefit of his coworkers whose studies he so powerfully advanced and of the patients he served.

Controversial Issues Concerning KS

Growth Factor Cascade

While dermatologists-immunologists considered activated lymphocyte-driven cell proliferations, for example in the case of psoriasis,[147] where growth factors released by T cells reacting to streptococcus superantigens promote proliferation, maturation and scale formation of keratinocytes, in the pathogenesis of KS such concepts emerged only after HIV-1- or HTLV-1 or 2- infected CD4 lymphocytes were shown in Dr. Gallo's laboratory to release growth factors (GF) for vascular endothel cells.[22,89] While such a concept explains the initiation of AIDS-KS[3] (or that of rare cases of KS associated with HTLV-1- induced diseases),[33] it fails to account for the initiation of cases of KS in HIV$^-$/HTLV-1,2$^-$ patients. However paracrine GF-driven cell proliferations are not considered to be malignant. A multistage process is emerging in AIDS-KS: initiation by paracrine GF loops which is converted into growth driven by autocrine loops due to "second hits" on the vascular endothelial cells. Prominent in the initiation phase are IL-1,[72] IL-6,[83] oncostatin-M, TGFβ, scatter factor (SF)[77,97] and HIV-1 Tat.[1,22,148] However the role of IL-6 and leukemia inhibitory factor (LIF)/oncostatin-M has been weakened by showing that KS cells frequently do not express receptors (R) for IL-6 and LIF/OSM.[87] The importance of IL-1β as a KS GF is best shown by complete inhibition of KS cell growth by IL-1RA (antagonist).[74] Prominent in the "second hit" process occurring in the target cells are IL-6, oncostatin-M (OSM), basic fibroblast GF (bFGF),[18,34,101,130,154] c-*met* encoding receptor for hepatocyte growth factor or SF,[97] vascular endothel GF[8,90,152] and platelet activating factor.[10] Protooncogene-oncogene transformation in vascular endothelial cells could apply most to *int* encoding the bFGF family with KSbFGF;[18] and c-*met* encoding R for SF.[97] Indeed, bFGF and receptor overexpression is common in endothelial cells providing an autocrine loop for angiogenesis. Weak, variable and uncertain GF are IL-4, GM-CSF and platelet-derived GF (PDGF).[135] However the c-*sis* gene encoding PDGF is an established protooncogene whose role in Kaposi sarcomagenesis remains to be proven. Chemokines interact with endothelial cells but their specific roles in KS induction is unknown.[93] In HIV infection chemokines interfere with viral entry into and postbinding fusion of infected cells.[106]

Unanswered questions of Kaposi sarcomagenesis are what constitutes the initiation phase in HIV$^-$ cases? What provides the "second hit" in the targeted endothelial cells? KS tumors harbor numerous pathogens *(vide infra)*. It is not certain at all which one can induce autocrine loops of GF in these cells. Is it conceivable that more than one pathogen(s) is needed for the proper sequence and composition of the GF cascade?[127]

Cells of Origin and Culture of KS Cells

Attempts to grow classical (Mediterranean) KS cells in permanent cultures was unsuccessful in the 1970s.[95,120] Technics resulting in the growth of numerous soft tissue and osteogenic sarcoma and other human tumor cell lines failed to yield KS cell lines.[120] Perhaps diligent changes of media (including week ends) deprived our primary cultures of GF essential for the initiation of growth. Conditioned media support early growth of KS cells in culture. Taken out of its interaction with its matrix a KS cell may behave differently in culture than in its natural environment. Cellular adhesion molecules (CAM) including E-selectin are expressed by KS cells only after the proper stimulation.[157] Some of the stimulator molecules occur in the natural environment of KS (IL-1β, TNFα). Others (polyI:C, lipopolysaccharides) stimulate ICAM-1, VCAM-1 etc expressions when added to KS cell cultures. Spindle shaped KS cells circulating in blood of patients expressed endothelial cell markers (VE-cadherin; CD31) and macrophage markers (CD68; mannose-R; CD14) and contained genomic sequences of HHV-8 *(vide infra)*. Cultured KS cells express fibroblastic antigen TE7 and smooth muscle-specific actin-alpha.[151] Heterogeneity of the spindle cells in KS lesions speak against monoclonality:[57] rather polyclonal GF-driven proliferation of mesen-

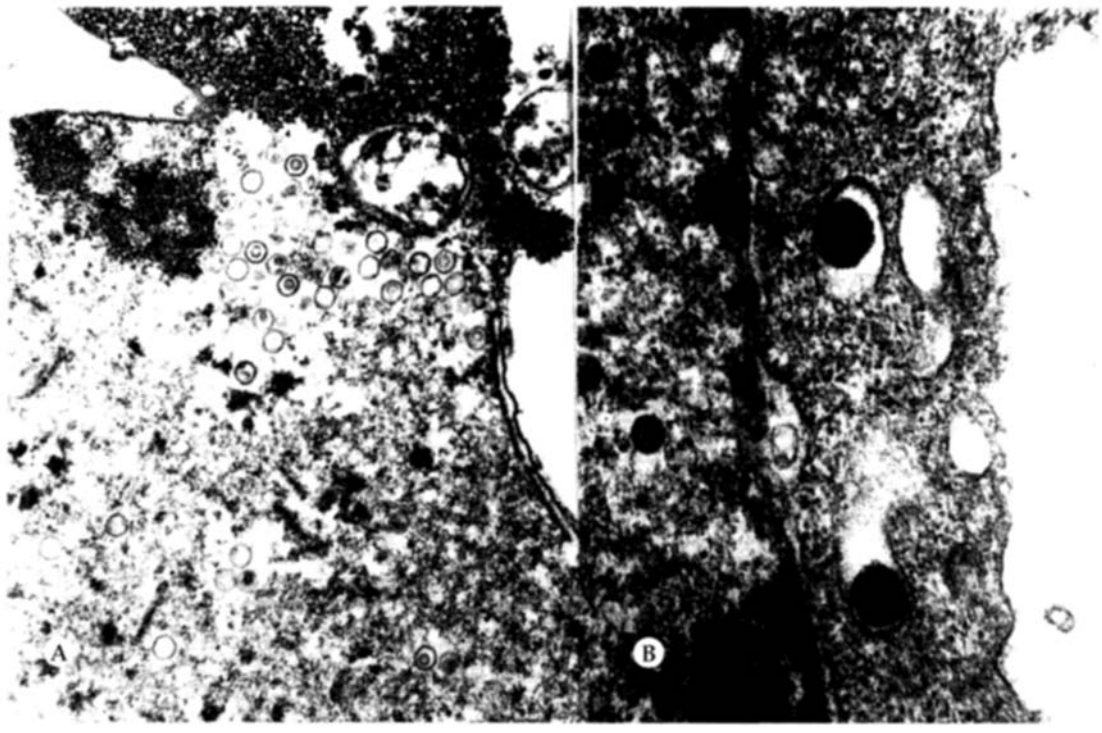

Figure 9a, b. *Cytopathogenic unidentified herpes-like virus particles in classical (Mediterranean) KS: unenveloped viral nucleocapsids in the nucleus of a cell denuded of cytoplasm (a); unenveloped immature intranuclear and enveloped maturing herpes-like virus particles in cytoplasm of a KS cell (b) (1974).[21] EM, original magnifications x65,000 (a) and x105,000 (b).*

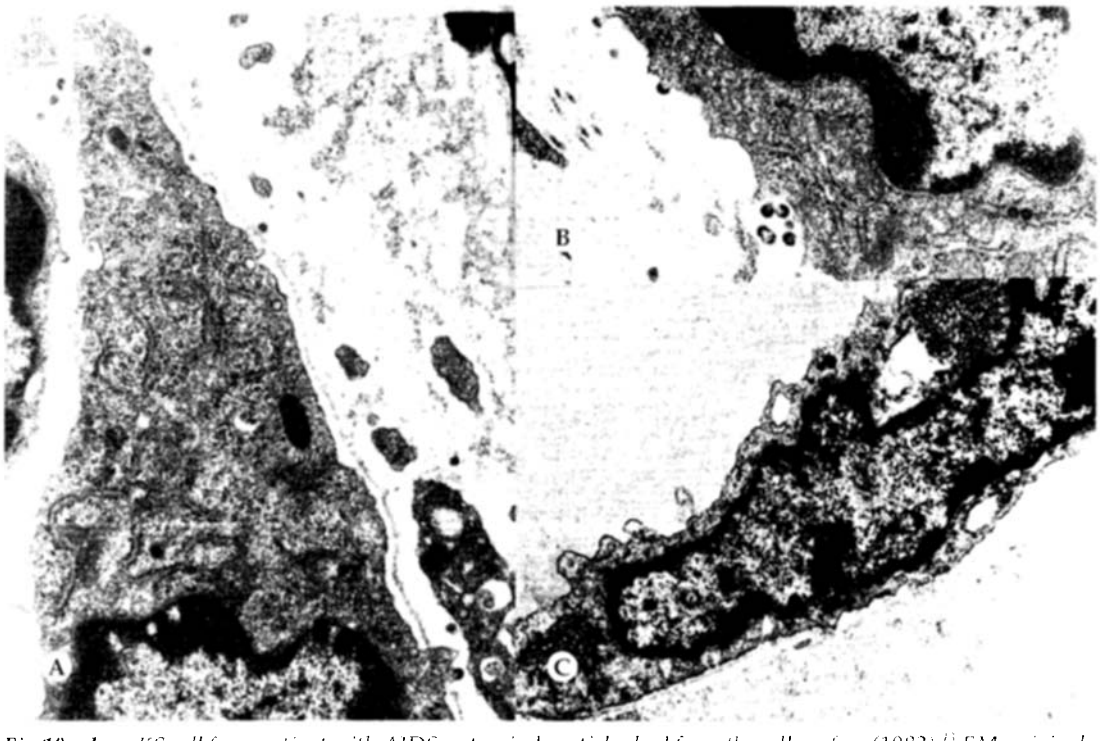

Fig 10a, b, c. *KS cell from patient with AIDS: retroviral particles bud from the cell surface (1983).[1] EM, original magnification x30,000 (a) and x42,000 (b). AIDS-KS cell: cytoplasmic tubuloreticular structures (1981).[41] EM, original magnification x27,500.*

chymal-endothelial cells is the case (but this finding does not exclude the assumption of clonal growth later like in some AIDS-KS lesions of African women).

KS lesions are rich in dermal dendritic cells expressing XIIIa.[91] If these cells actually contribute to the formation of KS, then as in monocyte-macrophage lineages susceptibility to infection with lenti-retroviruses (HIV included) becomes an attribute of these cells.[145] KS in culture (on matrigel) continued to excrete GM-CSF, TNFα, IL-1β and IL-6. These elongated cells were positive for actin.[151] KS-bFGF enhanced, pentosan polysulfate inhibited their growth.[153] Dexamethasone increases, the glucocorticoid receptor antagonist RU486 decreases the growth rate of cultured KS cells.

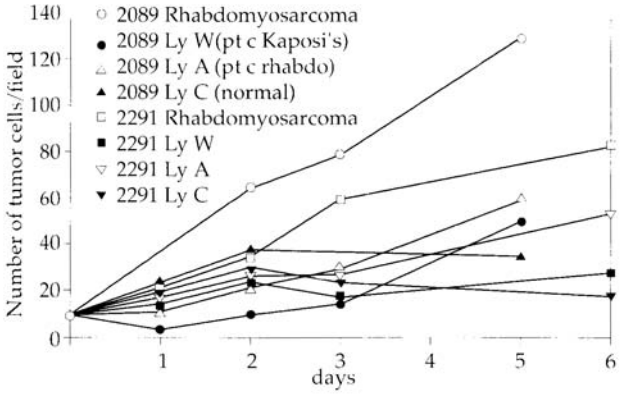

Figure 11. *Lymphocyte-mediated cytotoxicity assay with allogeneic rhabdomyosarcoma cell targets. Two target cell lines show good outgrowth in control cultures. Lymphocytes of a patient with classical KS; another patient's with rhabdomyosarcoma; and a healthy control's inhibit target cell growth more or less equally. This experiment was among the first of those contradicting the ruling tenet of the early 1970s holding incorrectly that only patients with cancer circulated lymphocytes cytotoxic to the patient's type of tumor and thus predicting correctly the existence of NK cells in the healthy human blood[*]. The patient with classic KS tested here showed no lack of NK cells.*

Some established KS cell lines may not represent the cells the cultures were initiated from. A cell line became HHV-8$^-$, remained CD34$^+$, assumed tetraploid and highly malignant karyo- and phenotype and suffered gene loss (3p14$^-$).[76,99] Tetraploid malignant cells are suspect of being fusion-products. Endomitosis is always possible but much neglected is the consideration of "natural hybridoma" formation either in vivo or in vitro in the primary culture. Murine natural hybridomas are fusion products of immortalized lymphoma cells expressing budding retroviral particles and reacting plasma cells secreting antibodies specific to the retroviral particles.[112,125] Due to antigen-antibody reactions at the cell surfaces two such cells each of diploid karyotype originally can fuse and form a tetraploid and highly malignant cell that conceals its retroviral neoantigenicity by covering budding viral particles with self immunoglobulins. In another murine lymphoma,[69] the lymphoma cell fused with a macrophage and thus gained increased malignancy. Not only myxo-, paramyxo- and retroviruses but also EBV may induce cell fusions.[9] We proposed that tetraploid Burkitt's lymphoma (BL) cells re-emerging in immunocompetent hosts are natural hybridomas (EBV-expressor diploid BL cells fusing with reactive B cells that are producers of anti-EBV immunoglobulins).[112] The resulting tetraploid BL cell acquires immuno-resistance by concealing EBV antigens as these antigens are covered by antibodies now produced by the same cell that expresses the antigen. However these cells are still attacked by macrophages recognizing antigen-antibody complexes: hence the "starry sky" appearance of those lymphomas in which such cell fusions i.e. natural hybridoma formation, occur.

Lenti-retrovirally infected dendritic cells readily fuse with reactive T cells: the so called "conjugate formation" in AIDS lymph nodes.[11,26,98] This reaction is so extensive in AIDS that large syncytia are formed. We proposed a similar phenomenon in HD (before AIDS "conjugates" were discovered): the lenti-retrovirally infected mononuclear HD cell fuses with reactive (or bystanding naive) lymphocytes (see above).[112] Tetraploid RS cells may fuse with one and other: quadroma formation (resembling early syncytia).

It should be considered that KS cells may gain growth advantage especially when it comes to in vitro cultures through cell fusions resembling natural hybridoma formation. Macrophages are so numerous in KS lesions and often are HIV-carriers[39] that their fusions with vascular endothelial cells plausibly can occur. Diploid malignant cells almost always gain increased malignant potential when they subvert macrophages for fusion.[86] In this new unison the macrophages' defensive molecular mediators, even TNFα, could serve the natural hybridoma as an autocrine loop of GF. Could even the TNF-related apoptotic Fas ligand-Fas-ICE/Bax-TGFβ-p53 etc. pathway *(vide infra)* be diverted in certain FasL$^+$, Fas$^+$, bcl-2$^+$ malignant cells from its regular course into an autocrine loop of signal transduction (activating c-*myc*; c-*met*; c-*sis*; deactivating p53) and thus leading to cell proliferation? After all the defensive molecule TNF has already been subverted to serve neuroblastoma (and other tumor like sarcoma) cells as their autocrine GF.[31]

Viral Etiology

KS tumors harbor large numbers of potential pathogens (papilloma and other papova viruses; 4 herpes type viruses: CMV, HHV-6, EBV in B cells infiltrating these tumors and HHV-8; hepatitis B viral genomic sequences; *Mycobacterium avium intracellulare* inducer of IL-6; tubuloreticular cytoplasmic structures; retroviral particles other than HIV-1 or HTLV-1).[127] The strong candidate for

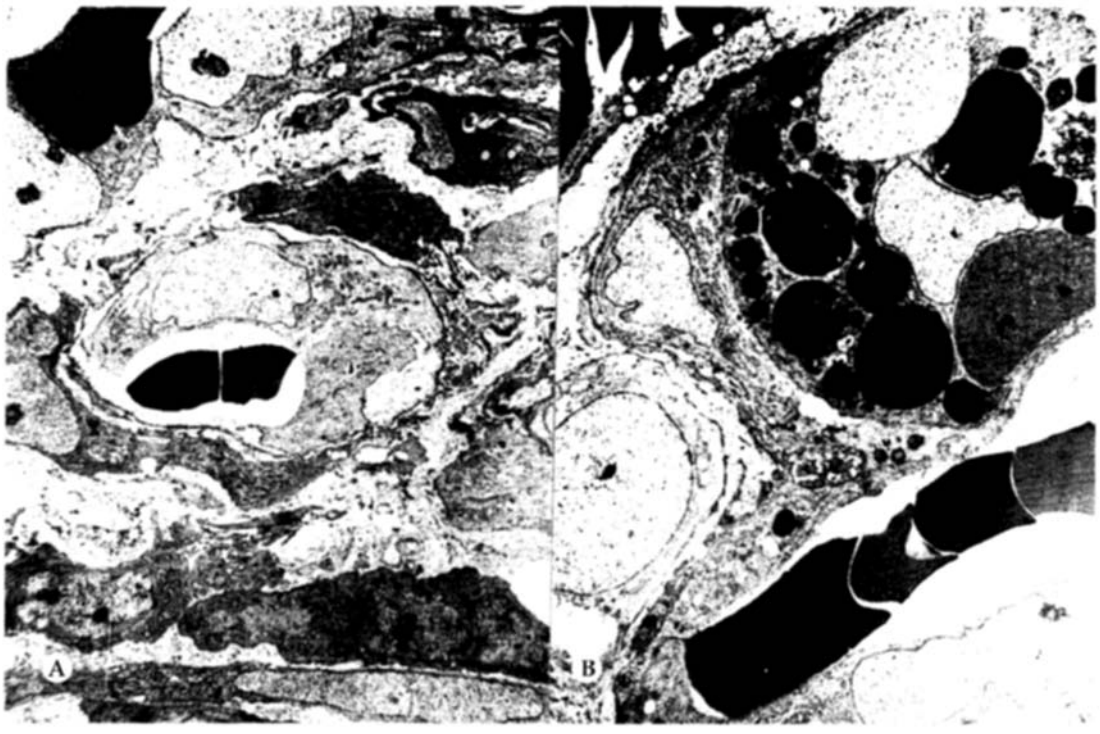

Figure 12a, b. *Proliferating vascular-lymphatic endothelial cells recognizable in low grade perianal AIDS-KS.*[12] *EM, original magnification x2,000 (a) and x2,500 (b).*

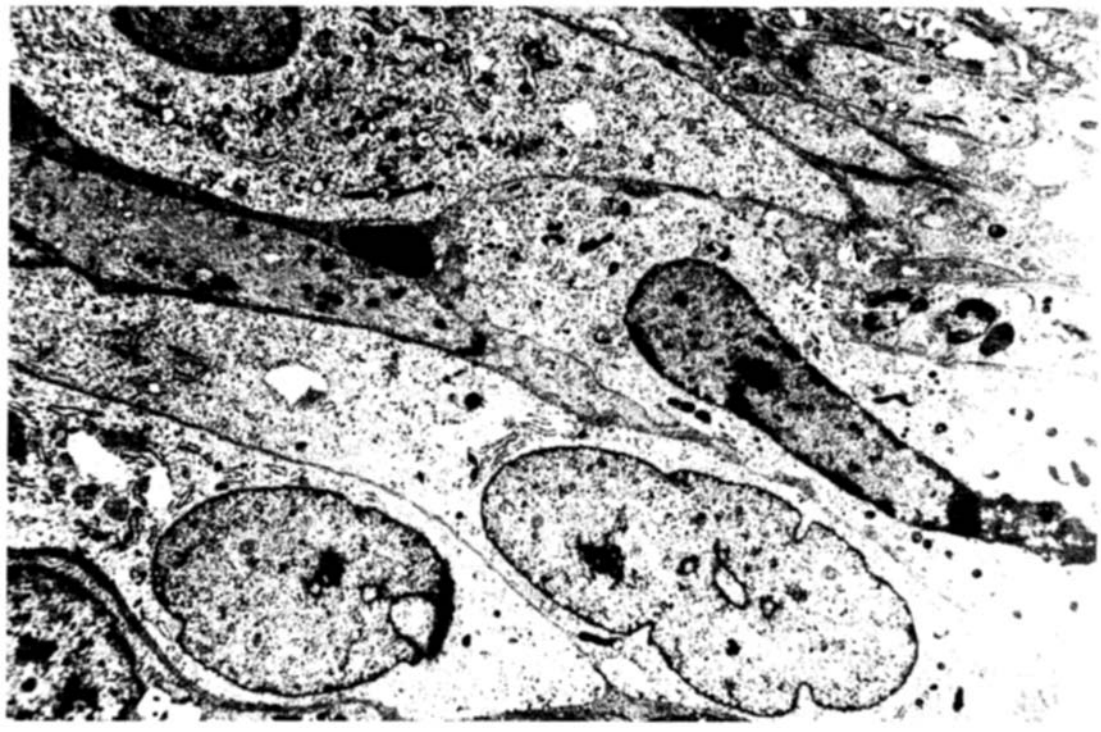

Figure 13. *Dense network of elongated sarcoma cells in a case of classical (Mediterranean) KS of an HIV man (courtesy of Dr. J. Szakacs).*[13] *EM, original magnification x3,800.*

etiological role CMV was dropped when endemic African KS cells failed to show genomic sequences of this virus in their genome.[2] HHV-8 emerges as the strongest candidate for etiological role in KS. This is a B-lymphotropic gamma herpesvirus[51] (like EBV). It has approximately 50% DNA sequence homology with *HV saimiri* a T cell lymphoma-inducer virus in New World squirrel monkeys. In retroperitoneal fibrosis of pigtailed macaques (*M. nemestrina*) a gamma herpes virus showing some 80% DNA sequence homology to HHV-8 was found.[51,131] One DNA segment of HHV-8 encodes a capsid protein and the viral enzyme thymidine kinase; another segment encodes herpes viral interrelated envelope antigens p140 and p160; a cyclin D-related protein. HHV-8 is able to infect spindle cells and it was detected in the prostate and seminal fluid and saliva[7] of patients with KS. In spindle cells the virus exists in the form of extrachromosomal covalently closed circular episomes whereas in B lymphocytes linear forms of the viral genome characteristic of replicating virions are present.[16] It is still debated if this virus is confined to a small segment of the human population or if it is ubiquitous like EBV. It is present in angiosarcoma in HIV$^-$ patients,[46] in multifocal angioproliferating follicular Castleman's disease and in AIDS-associated (and HIV$^-$) lymphomas of body cavities such as pyothorax-associated lymphomas consisting of large cells with multilobulated nuclei[12] and in various skin lesions of immunosuppressed organ transplant recipients.[102] AIDS-associated Burkitt's-like lymphomas often carry EBV (brain lymphomas always!), seldom if ever show c-*myc* translocation and very frequently also harbor genomic sequences of HHV-8.

Patients developing antibodies to HHV-8 antigens (p40 butyrate-induced; or latent nuclear antigen) prior to the clinical diagnosis of KS have a high chance to develop KS later.[60] A preponderance of currently available seroepidemiological evidence indicates that viral distribution is not ubiquitous, it is highly common in HIV-infected male homosexuals (but not in HIV-infected hemophiliacs)[78] and antibodies to HHV-8 occur worldwide.[27] While mature HHV-8 particles replicate in tetradecanoyl phorbol-13-acetate-treated cultures,[104] a model system is still missing in which HHV-8 or some of its genomic sequences or gene product proteins were shown to be neoangiogenic, mitogenic or mutagenic- transforming.

As the Australopithecines evolved in Africa some 3 million years ago they might have been decimated by viruses like an ancestral EBV. Indeed this virus has followed the migration of *Homo habilis* out of Africa and established with *Homo sapiens* a host-virus relationship that is harmless to the host (with rare exceptions). Even in African BL the c-*myc* translocation t(8;14) (q24;q32) appears to carry more weight in furthering malignancy than the presence of EBV in these cells. When did HHV-8 evolve to be a human pathogen? All KS cells (classic; iatrogenic; endemic African; epidemic AIDS-associated)[17,19,92] harbor this virus yet contrary to EBV, it does not appear to be a ubiquitous human parasite. If it co-evolved with mankind in Africa, how did it acquire a substantial length of genomic sequences homologous to certain herpesviruses of New World monkeys (marmosets) or Indian-Asiatic simian species (macaque)? KS is rare in Asia. If this virus followed the migration of *Homo habilis* toward Mesopotamia, those migrating toward the West (the CroMagnons) must have carried it to the Mediterranean basin, whereas those moving to the East were not carriers of this virus. Or did a branch of *Homo sapiens* evolve in Asia independently from the *Homo habilis* migrating out of Africa and remained relatively free of HHV-8? Co-evolution and coexistence of man with Asiatic and New World monkeys could have had established this virus in more recently evolved human communities. If it is not an ancient virus co-evolving with mankind in Africa, was it trade that might have introduced this virus in relatively recent times to Africa and Europe (out of Asia and/or the New World)? Encounter with a new virus just a few centuries ago produced a disease more virulent in Kaposi's time in Europe or earlier this century in pre-AIDS Africa than the indolent classical KS is today? As we find simian AIDS and herpes viruses in coexistence, we must trace the origins of HHV-8 among Old World and/or New World monkeys in order to better understand our relationship with this pathogen: is it more ancient than EBV and co-evolved with mankind in Africa or does it represent a more recent introduction into human communities coming from the New World?

The gene product protein of p53 is the target for binding with early antigens of oncogenic DNA viruses:[139] large T antigen of SV40; E6 protein of HPV; EBNA5 of EBV; and E1B of adenovirus 5. *HV saimiri* encodes the tyrosine kinase interacting protein Tip. Tip interacts with cellular protein p56^{lck}: Lck. The normal function of Lck is signal transduction through tyrosine phosphorylation of several membrane proteins that characterize activated T cells that also produce IL-2. Amplified and/or point-mutated (?) lck functions as an oncogene for T cells. Tip-bound Lck could be downregulated: in Jurkat T cells the Tip-Lck complex blocked tyrosine phosphorylation and in fibroblasts it was anti-oncogenic.[56] In contrast[82] in normal human CD8 cells transformed by *HV saimiri* Tip mediated IL-2-independent growth and NK cell-like cytotoxicity of these cells; it increased tyrosine phosphorylation by p56^{lck}. Another human T cell line immortalized by *HV saimiri* was activated by IL-12.[62] Does HHV-8 encode a Tip protein which interacts with Lck in those lymphoid cells that transform in HIV-infected patients or in body cavities of HIV patients? Any such interaction in KS cells?

Not only HHV-8-related but also EBV-related herpes viruses exist in cynomolgus monkeys (*Macaca fascicularis*).[72] These EBV-related viruses are present in SIV-related lymphomas and contain DNA sequences related to

EBV's EBNA5 (which binds to p53 and Rb proteins). The LMP2A gene product protein of human EBV exerts down-regulation of signal transduction in B cells: an effect analogous to Tip-Lck mediated signal transduction in Jurkat T cells. There appears to be a continuing interaction (antagonistic or cooperative) between lymphotropic retrolentiviruses and gamma herpes viruses as they co-evolved with humans in Africa and thereafter as *Homo erectus* and *Homo habilis* left Africa. It appears to be worthwhile to search for retrolentiviral copathogens in infectious mononucleosis, BL, HD, leukemic reticulo-endotheliosis and other entities shown in *Table 1*.

In contrast to herpes viruses, lenti-retroviral pathogens appear to have had been left behind in Africa. HTLV-1 and 2 probably moved out of Africa toward Japan and Asia with Portuguese sailors just a few hundred years ago. Slave trade mobilized HTLVs out of Africa to the Caribbean basin and from there to the American continents especially to SE USA. HIV was still lurking behind. Late in this century extensive air travel and most liberal sexual practices converted a latent and sporadic disease of native Africans into a world epidemic. Dr. Koprowski rejected the ill-conceived idea that green monkey kidney cell culture-grown live attenuated polio vaccines of the Wistar Institute initiated the African AIDS epidemic.[64]

Even if we discovered a new human pathogen in the form of HHV-8, we do not know how to protect ourselves against it and once we acquired this virus and become carriers of it how can we get rid of it? Is anti-herpes viral chemotherapy for KS feasible?[50,51]

Immunosuppression

There is no doubt that patients receiving immunosuppressive therapy (for example for SLE) and for allowing retention of an allogeneic graft (especially cyclosporin-treated patients with kidney transplants) often develop KS (incidence over 150-fold higher than that of classical KS). These tumors regress upon cessation of immunosuppressive therapy clearly indicating that immunological control of the disease prominently exists. Immunosuppression due to depleted CD4 cells in HIV-infected individuals (and due to the production of acid labile alpha interferon and/or antiinterferon agents)[53] is one of the most important co-factor in Kaposi sarcomagenesis in AIDS whether KS is induced in the epidemic African or Western type disease. High levels of IFN-gamma and low levels of IL-2 and IL-12 form the background for advancing AIDS and KS.[3] However a good number of patients with AIDS are on record who developed KS before they developed any significant immunosuppression. It is not easy to document immuno-suppression in patients with classical Mediterranean KS who tolerate indolent KS for a decade or so but without succumbing to it or to the usual infectious complications that accompany AIDS-KS. We observed lymphocytes cytotoxic to allogeneic sarcoma cells in patients with classical KS *(Fig.11)*; these tests might have been among the earliest documentations of natural killer (NK) cells.* Hungarian authors found subtle immunodeficiencies in patients with classical KS (Dobozy et al cited in [111]). There is no easy explanation why the classical disease described by Kaposi as fatal (Kaposi in his original paper: "die Krankheit führt zum Tode") has become indolent in Central Europe within a century (unless HHV-8 had been newly introduced into European and African communities and is on its way to undergo some attenuation imitating what happened between EBV and its host during a much longer coexistence).

In pre-AIDS African endemic KS studies showed immunosuppression only in florid (and may be in infiltrative) but not in nodular disease. On the other hand those African patients are continuously stimulated (probably to exhaustion) by various pathogens of the tropical climate. Could immunologically active but not virally infected lymphocytes release GF that may initiate KS lesions that "transform" when receive the "second hit" by HHV-8? After all even in organ transplant recipients there are T cell clones mobilized to reject the graft. Could viruses infecting white blood cells (CMV; EBV; HHV-8) induce the production of such GF? Is it possible that certain infections other than those with HIV or HTLV start KS-inducing GF cascade?

Dr. Jeno Szakacs of the Moffitt Cancer Center, Tampa FL communicated to this author[126] his observation that KS lesions seen in AIDS patients were much better differentiated than those deriving from HIV patients with classical KS *(Fig.12,13)*. Could it be that a host with classical KS is so much less immunosuppressed than the host with AIDS-KS that a low grade lesion can overcome the latter host while the former host can resist lesions of much higher grades? This interesting notion calls for systematic studies.

Regression of KS Lesions

The cytokine cascade responsible for the induction of KS is much better understood than those events that take place in regressing KS lesions. Is it abrupt cessation of GF production and supply that lead to apoptotic death of KS cells? For example if interferons alpha deactivate the *int* oncogenes the production of neoangiogenic bFGF comes to a halt. When it was observed that KS lesions regress without immunoreconstitution in AIDS patients treated with interferons alpha (but not with gamma), we immediately proposed that anti-neoangiogenic effects of interferons alpha were at work.[113,114] Deactivation of the bFGF-encoding *int* genes by IFNα was considered to be the prime mechanism of this effect.[113,115] Indeed IFNα

* See debate in *Oncology Times* 18/7:2–4 July; 18/11:4 Nov 1996.

and ß downregulate bFGF mRNA and proteins in human tumor (kidney carcinoma) cells.[23] However this issue remains controversial because IFNα together with IL-2 synergistically enhanced bFGF synthesis[15] and therapy with these 2 agents exacerbates the disease! Customarily GF-dependent cell populations undergo programmed cell death upon deprivation of the GF. In endothelial cells dephosphorylation of certain cellular proteins starts the apoptotic process; in general these genes become activated: ICE, TRPM-2, TGFβ. Regressing KS lesions often show large numbers of apoptotic bodies[127] *(Fig.14)* but gene activation processes were not as yet studied in these cells.

KS cells are often Fas$^+$ (expressing Fas receptor) yet they resist Fas ligand- or anti-Fas monoclonal immunoglobulin-mediated apoptosis.[84] NK cells expressing the Fas ligand fail to kill these KS cells. However apoptosis-resistance is not mediated by amplified *bcl*-2: its mRNA is down-regulated. In AIDS-KS cells Fas-associated phosphatase (FAP) is significantly upregulated. Actinomycin D inhibiting FAP synthesis renders KS cells sensitive to apoptosis-induction. Transfection of KS cells with cDNA of FAP increases resistance to apoptosis. Interferon gamma failed to induce apoptosis in these cells (and failed in the treatment of AIDS-KS). The authors did not test if interferon alpha could overcome apoptosis resistance. More recently in some aggressive KS lesions *Bcl*-2- and Bcl-xl-mediated resistance to programmed cell death was also documented.[85] Bax or Bcl-xs promote, Bcl-2 and Bcl-xl antagonize apoptosis. In proliferating AIDS-KS cells resisting apoptosis more Bcl-xl is expressed than Bcl-2.[25] The expression of these cell survival gene product proteins and their antagonists were not as yet studied in regressing KS lesions. Would in regressing lesions, KS cells switch to apoptosis-promoting Bax or Bcl-xs expression? Do KS cells or certain lymphoma cells express the Fas ligand (FasL)? Such malignant cells could repel or actually kill Fas receptor (APO; CD95) positive lymphocyte populations attempting to launch a cytotoxic attack on these neoplastic target cells.

The functions of TGFβ in the induction and regression of KS so far evaded clear understanding. This molecular mediator is produced by HIV- or other retrovirally infected lymphocytes and by KS cells.[14,108] It is mitogenic to KS cells. In the healthy bone marrow it preserves the CD34$^+$ stem cell population by exerting antiproliferative effect. How come that CD34$^+$ KS respond to TGFβ and proliferate? This molecular mediator prevents phosphorylation of the Rb gene product protein and hypophosphorylated Rb protein acts as a brake in the cell cycle. Thus loss of response to TGFβ could lead to cell proliferation. The activities of TGFβ are mediated by p15 inhibiting cyclin-dependent kinases phosphorylators of the Rb protein.[110] The matter of growth stimulation versus inhibition appears to relate more to TGFß receptor expression than to the production of the ligand. TGFß receptors I and II must be coexpressed for the transduction of the antiproliferative signal. AIDS-KS cells are frequently TβRI (do not express receptor I) while remain TßRII$^+$. Thus these cells evade the antiproliferative signal. TBRIII captures the ligand (consuming it) but it is a nonsignaling receptor; its overexpression can pre-empt antiproliferative effects of TGFβ. When TGFβ suppresses cell growth it acts through the RB gene that it maintains in the cell cycle-arresting hypophosphorylated state. TGFβ also downregulates cyclins and SF. TGFβ antagonizes IL-2 and protects cells against the cytotoxicity of lymphocytes expanding under the effect of IL-2. In a most paradoxical manner TGFβ1 under special circumstances could exert LAK cell-attractant activity.[68] Cessation of TGFβ production would allow access of cytotoxic lymphocytes to their target cells. TGFβ is active in apoptotic cells (for example in androgen hormone-dependent prostatic carcinoma cells undergoing apoptotic death upon the withdrawal of the hormone; or in hepatoma cells).[111] We do not know but presume similar activity in KS cells undergoing apoptosis. Thus TGFβ may be needed for apoptotic death of KS cells; it should not be present when cytotoxic lymphocytes kill KS cells; and if KS cells do not express TßRI they escape TGFβ-induced antiproliferative effect (but may stop growth if both TßRI and II are co-expressed).

It is a paradoxical observation that early KS are heavily infiltrated by lymphocytes and macrophages (providing more GF than actually rejecting the lesion?). When fully developed dedifferentiated lesions are viewed these infiltrating cells are not present as spindle cells of KS form a dense network. Even when apoptotic death of KS occurs direct attachment of lymphocytes to the dying KS cell is seldom seen but HIV-infected macrophages may be in close vicinity *(Fig.14a; 15)*. KS regresses in AIDS patients treated with interferon alpha without restoration of immunocompetence. From fragmentary pieces of information we must conclude that growth factor deprivation (for example cessation of KSbFGF production) rather than an immune attack is the prominent factor in regressing KS lesions. But if an immune attack could be documented what are the antigens: HHV-8 or oncoproteins? Will LAK cell or TIL infusions be therapeutically beneficial or detrimental (providing GF)? Regressing KS lesions are more difficult subjects to study than expanding early KS lesions.

Treatment

KS is a radio- and chemotherapy-sensitive tumor.[149] Excision, cryo- and radiotherapy, photodynamic therapy, and intralesional chemotherapy are applicable to single lesions or to locoregional disease of limited extent. The disease is often multifocal and systemic. Mildly cytotoxic and non-immunosuppressive chemotherapy is preferred. Bleomycin, vincristine, dacarbazine, cisplatin, metho-

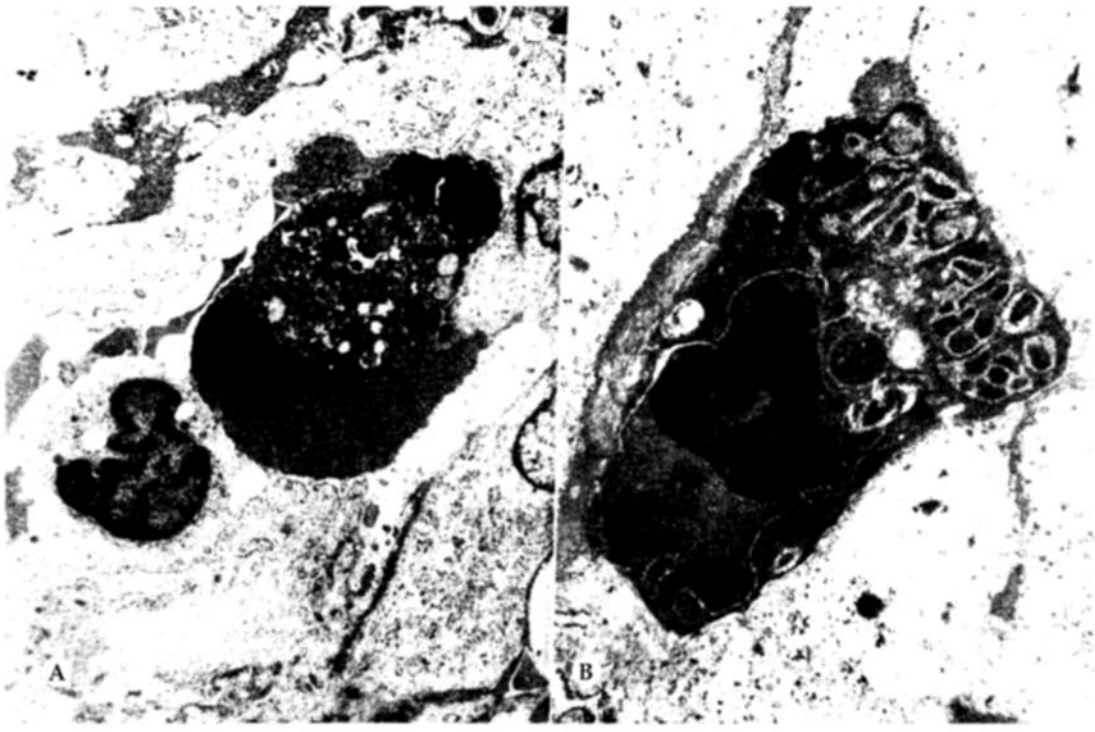

Figure 14a, b. *Apoptotic bodies in regressing AIDS-KS: one sarcoma cell undergoing programmed cell death next to a mononuclear cell (a) (courtesy of Dr. J. Szakacs). EM, original magnification x7,800 (a) and x17,800 (b).*

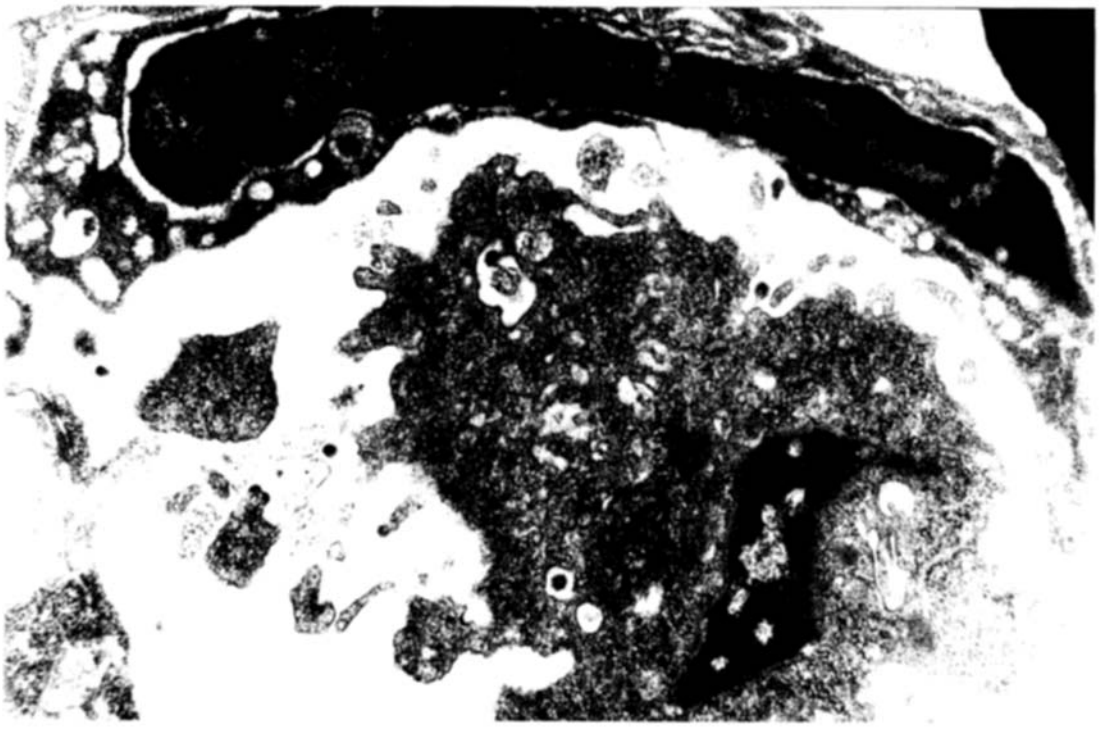

Figure 15. *Elongated KS cell with massive nuclear clumping and cytoplasmic blebbing lying next to a retrolentivirally infected mononuclear (monocyte-macrophage) cell (1985).[114] EM, original magnification x37,800.*

trexate with leucovorin rescue are useful for this purpose. Cytocidal and immunosuppressive therapeuticals (adriamycin, etoposide, vinblastine, paclitaxel etc)[7,144] singly but especially when combined are highly effective in inducing up to 80% remission rates but at the price of increased susceptibility of the host to opportunistic infections. Liposome-encapsulated anthracyclins (doxorubicin (Adriamycin) or daunorubicin (Cerubidine) remains highly effective with reduced toxicity.[100,136]

Among biologicals interferon alpha in substantial dosage induces the best responses: long term, lower dosage interferon therapy may maintain remissions. Interferon gamma (suppressor of acid FGF) fails to induce remissions of KS lesions. Interferon beta and IL-2 together may induce exacerbations.[66] Interleukin-1R antagonist goes into clinical trials since in vitro it stops growth of KS cells.[74] Human chorionic gonadotropin beta (hCGß) emerges as a potential therapeutic agent since it mediated the rejection of some tetraploid KS cell lines in the nude mouse.[76] KS occurring in pregnant women (producers of the hormone) and some adverse reactions to it deplete the initial enthusiasm.[143,155]

Antiherpesviral chemotherapeuticals especially when combined with interferon or with anti-HIV therapy (protease inhibitors; reverse transcriptase inhibitors) may fail, may stabilize or may induce remission of KS.[21,30,51]

Immunotoxins appear on the scene. IL-4 and pseudomonas exotoxin fusion protein works in clonogenic assays.[52] The fusion proteins IL-2 and diphtheria toxin or IL-6 and diphtheria toxin[79] both inhibit KS cell proliferation *in vitro*. The former immunotoxin is in clinical trial against malignant lymphomas expressing the p55 component of the IL-2R.[71]

Antiangiogenesis agents attack the blood supply of developing tumors and the tumor itself when it consists of transformed vascular-lymphatic endothelial cells. In addition to the quite toxic suramin the list of these agents include angiostatin;[94] platelet factor 4;[132] fumagillin-derivative AGM-1470 inhibitor of vascular endothelial GF;[146] *Arthrobacter* sp-derivative AF25 (tecogalan)[70] inhibitor of bFGF-binding to its receptor;[88] antagonists to $\alpha v\beta_3$-integrin serving as receptor to vitronectin (ligand) and mediating bFGF-induced angiogenesis;[48] pentosan polysulfate inhibitor of KS-bFGF[153] and others. Vascular endothelial GF-diphtheria toxin fusion protein (immunotoxin) is a powerful inhibitor of neoangiogenesis in the chorioallantois membrane. Batimastat a synthetic inhibitor of matrix metalloproteinases[142] also inhibits the growth of KS cells and vascular growth in mouse models. Antisense oligonucleotides targeting mRNA of bFGF inhibited KS cell growth in nude mice.[21,55] Some of these and other major efforts to curb tumor neoangiogenesis may eventually translate into clinical trials.

All-trans-retinoic acid administered orally or applied topically in gel-form induced improvements and partial remissions as reported in several abstracted lectures at the XI International Conference (Vancouver, Canada) on AIDS 1996.*

Cytotoxic T cells administered as adoptive immunotherapy do not handle well HIV infection.[5,63] Are there any cytotoxic LAK or immune T cells that play an important role in the rejection of KS? If so could these lymphocyte populations be collected, mobilized and reinfused (expanded with IL-2 and/or other GF) into patients with multifocal visceral and rapidly advancing KS?

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* For good narrative report see *Oncology Times* 18/10:49–53 Oct 1996.

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