and may make an individual susceptible or resistant to a particular disease. Also, the MHC region is densely packed with genes, many of which are important for function. Hence, mutations in this region of the genome are more likely to result in a disease than mutations in a region of the genome that has very few coding regions. Furthermore, the MHC region may be a "hot spot" for mutagenesis. Finally, the polymorphic nature of this region means that a mutation in or near the MHC complex is likely associated with a specific HLA type that is not found in many people. Hence, specific HLA types can serve as markers that are linked with defective genes in this region.

While diseases have been known to be correlated with specific HLA loci for some years, recent advances in molecular biology have resulted in the discovery of many more disease associations. Classic serologic techniques define an HLA type by reactivity of an antibody or antisera with HLA molecules. DNA analysis has shown that one classic HLA type can be further subdivided into a set of alleles with slightly different sequences. These alleles are known as subtypes of an HLA type. If a disease is associated with only one particular HLA subtype, then studies employing classic serologic techniques might fail to establish a statistically significant correlation between the disease and HLA markers. In these cases, molecular techniques can determine HLA subtypes and might establish that one HLA subtype is associated with the disease.

HLA studies can help investigators classify diseases. Juvenile rheumatoid arthritis (JRA), for example, can have several presentations. Researchers proposed classifying JRA into various subtypes based on clinical features and then found that different JRA subtypes correspond with different HLA subtypes. This provides evidence that different forms of JRA arise from different pathophysiologic mechanisms and may be responsive to different therapeutic interventions.

Diseases that are associated with specific HLA types or subtypes include ankylosing spondylitis, type 1 diabetes mellitus, Behçet's disease, celiac disease, Grave's disease, Hashimoto's thyroiditis, Hodgkin's disease, idiopathic membranous nephropathy, idiopathic nephrotic syndrome, multiple sclerosis, narcolepsy, C2 deficiency, C4 deficiency, congenital adrenal hyperplasia, idiopathic hemochromatosis, gluten-sensitive enteropathy, pemphigus vulgaris, cicatrical pemphigoid, Goodpasture's syndrome, juvenile rheumatoid arthritis, and rheumatoid arthritis. In addition, susceptibility to malaria infection and rapid or slow progression of HIV infection are associated with specific HLA types.

For most diseases, molecular techniques that determine HLA subtypes provide the most useful information. These studies can be complicated, however, because in some diseases, such as type 1 diabetes, certain HLA subtypes (DQA1*0301, for example) are associated with an increased risk of contracting the disease but other subtypes (DQA1*0102, for example) are associated with a decreased risk of contracting the disease.

Some of the diseases with the strongest associations with specific HLA genotypes in the general population are ankylosing spondylitis, narcolepsy, and celiac disease. HLA typing can be useful in many other diseases, however. Often when a family member has a disease, the family and physician want to know the likelihood that other family members will develop the disease. In these cases, comparing the HLA type of the proband with relatives can provide useful information even if the disease does not have a strong correlation with particular HLA subtypes in the general population. Also, in specific clinical situations, HLA testing may help refine a differential diagnosis or predict the progression of an illness.

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Kaposi's Sarcoma–Associated Herpesvirus (KSHV): A New Viral Pathogen Associated With Kaposi's Sarcoma, Primary Effusion Lymphoma, and Multicentric Castleman's Disease

KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS (KSHV), also known as human herpesvirus 8 (HHV-8), is a member of the gammaherpesvirinae subfamily of herpesvirus that are characterized by the ability to replicate in lymphoblastoid cells. KSHV is related to Epstein-Barr virus (EBV) and herpesvirus saimiri (HVS) and is the first member of the genus *Rhadinovirus* known to infect humans. Viral DNA was first discovered in Kaposi's sarcoma lesions by Chang and Moore, who used representational difference analysis to identify KS330Bam and KS631Bam fragments. As shown by ELISA for HHV-8 antibody, the prevalence of KSHV is much lower than other human herpes viruses (EBV, HHV-6, cytomegalovirus, herpes simplex virus 1). Less than 20% of normal adult donors and 33% of HIV-negative homosexual men have antibodies to KSHV. Both HIV-positive and -negative patients with Kaposi's sarcoma have antibodies to KSHV (titer >1280 in most cases), and seroconversion has been documented before the development of Kaposi's sarcoma. KSHV also is now known to be associated with a new lymphoma subtype, primary effusion lymphoma, and with lymphoid proliferations resembling angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) and multicentric Castleman's disease.

Primary effusion lymphoma occurs predominantly in HIV-infected male patients; the primary symptom is lym-

phomatous effusions (pleural, pericardial, or ascitic) without a contiguous tumor mass. Primary effusion lymphomas mainly occur in older patients (most in the fourth decade of life) and with more advanced disease than Burkitt-like lymphomas. The patients are usually severely immunosuppressed (T cells <100/mm^3), and most have prior manifestations of AIDS, including opportunistic infections. Morphologically, the tumors resemble B cell immunoblastic and large-cell anaplastic lymphomas. In most patients, disease is limited to body cavities, but occasional cases have involved adjacent organs such as the lung, soft tissues, regional nodes, and bone marrow. KSHV-associated lymphomas have also been identified in the central nervous system and the gastrointestinal tract, in HIV-negative men, and in women. The prognosis is poor, and the majority of patients die within 1 year of diagnosis.

Phenotypically, primary effusion lymphomas express leukocyte common antigen (CD45), but most are negative for other B and T cell–associated antigens including CD20, CD19, and immunoglobulins. The cells have activation antigens including HLA-DR and CD30. Molecular analysis confirms derivation from late differentiating B cells, possibly at the immunoblast, plasmablast, or preplasma cell stage. Herpesvirus particles consisting of 100- to 115-nm capsids with central cores have been identified within neoplastic cells. Most cases in HIV-seropositive individuals are also positive for EBV (type A or B). Unlike most EBV-associated lymphomas, however, there appears to be no involvement of c-*myc*. They also lack *bcl-6* gene rearrangements and *ras* oncogene or *p53* tumor suppressor gene mutations. Cytogenetic studies reveal multiple chromosomal abnormalities. Preliminary data suggest that involvement of two potential oncogenes, one a cellular type D cyclin similar to the PRAD 1 oncogene involved in mantle cell lymphomas, and one homologous to the cellular G protein–coupled receptor (GCR) family of proteins. The virus contains proteins similar to human macrophage inflammatory protein (MIP) chemokines and interleukin-6 (viral IL-6), which may play a role in the pathogenesis and clinical syndrome of multicentric Castleman's disease.

KSHV has been associated with benign lymphoid proliferations from HIV-positive and -negative patients with AILD and multicentric Castleman's disease. KSHV is present in almost all cases of Castleman's disease in patients with AIDS and in approximately half the cases in HIV-seronegative patients. KSHV sequences have also been detected in peripheral blood lymphocytes from patients with Castleman's disease. Multicentric Castleman's disease occurs most often in older patients, predominantly men, and is associated with lymphadenopathy and constitutional symptoms. We have detected KSHV sequences in a child with familial multicentric Castleman's disease, and other children have been seropositive for KSHV. Patients with Castleman's disease may develop secondary malignancies, most commonly Kaposi's sarcoma and non-Hodgkin's lymphoma. In HIV-infected patients with Castleman's disease, there is a strong association between KSHV and sexual transmission, as well as the development of Kaposi's sarcoma.

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Cocaethylene: A Novel Cocaine Homolog

COCAETHYLENE (CE) is a pharmacologically significant homolog of cocaine, formed by transesterification of cocaine with ethanol when the two are ingested concurrently. This reaction is mediated by a hepatic carboxylase which, in the absence of ethanol, catalyzes the production of benzoylecgonine, the major urinary metabolite of cocaine.

As is the case for cocaine, CE binds to the dopamine transporter and inhibits dopamine uptake into synaptosomes. The behavioral pharmacology as well as the psychomotor stimulant effects of CE are similar to those of cocaine, but the toxicity of CE is greater than that of cocaine, and its LD_{50} is much lower. Furthermore, the plasma half-life of CE in humans is longer than that of cocaine, and plasma concentrations of CE often exceed those of cocaine itself. Taken together, these factors make CE a compound of toxicological importance.

Recent work has demonstrated that CE binds with high affinity to human serum alpha-1 acid glycoprotein (orosomucoid) and with low affinity to serum albumin. Human brain, heart, liver, and placenta also bind both cocaine and CE.

Both cocaine and CE can be quantitated simultaneously in plasma and urine by high-pressure liquid chromatography. Thin-layer chromatography of urine is useful for the qualitative detection of cocaine and CE if a solvent system consisting of hexane (65 ml):toluene (20 ml):diethylamine (5 ml) is used. Both compounds can be readily visualized as reddish-brown spots after the plate is sprayed with iodoplatinate (cocaine, R_f 0.44; CE, R_f 0.51). Furthermore, both are metabolized to benzoylec-