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AIDS, Alcohol, Endothelium, and Immunity

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WITTE, M. H., P. BORGS, D. L. WAY, G. RAMIREZ, JR., C. L. WITTE AND M. J. BERNAS. *AIDS, alcohol, endothelium, and immunity*. ALCOHOL 11(2) 91-97, 1994. — Analogies are drawn between important unknowns in AIDS and alcohol research, related to underlying common pathogenetic mechanisms, immunodysregulation, cofactors, and prominent vascular manifestations. The central role of the blood and lymphatic vasculatures and specifically their endothelial lining in many facets of the immune response is reviewed. Evidence is presented that both alcohol and HIV (as well as other coinfecting viruses in AIDS) target and alter endothelial cells and the angiogenic process. These concepts are further illustrated by a serendipitous viral epidemic among rats on continuous long-term alcoholic and control nonalcoholic diets, where synergism between alcohol and virus appeared to underlie multiple vascular proliferative lesions in the liver. In AIDS and alcoholism/alcoholic liver disease (ALD), the prominent features of dysregulated angiogenesis point to the endothelium as a key player in pathogenesis of these seemingly disparate disorders and potentially in immunomodulation.

AIDS Alcohol Endothelium Immunity HIV Angiogenesis Kaposi's sarcoma Cofactors

IN a recent issue of *Science* (5) focusing on "Unanswered Questions," leading AIDS researchers identified the key questions remaining or newly posed about this devastating epidemic. Contrary to most reports over the past decade, this issue concentrated on what is or remains unknown about this acquired syndrome—more suitably termed an immunodysregulation than an immunodeficiency. The key question posed was "What is the central immune defect in AIDS?" In this current Research Society on Alcoholism (RSA) symposium, and increasingly in the field of alcohol research, a similar question is also being posed: What, if any, is the central immune defect following chronic alcohol ingestion and its relationship to alcoholic liver disease (ALD)? These two parallel unanswered questions, identified in seemingly unrelated fields, are embodied within a larger question addressing the role of cofactors, including drugs of abuse, alcohol, and viruses (HIV and others) and their interactions in the pathogenesis of full-blown AIDS and progressive ALD. The early findings of immunostimulation and hyperreactivity followed by progressive immunodeficiency (primarily of the cellular type) characterize both AIDS and ALD along with heightened susceptibility to opportunistic infections, intense angiogenesis, fibrosis, and benign and malignant neoplasms (including tumors of endothelial origin). Are alcohol and viral infection merely associations or do they interact to produce additive and/or synergistic deleterious effects on the immune system?

We explore this commonality of mechanism and the role of endothelium as a common target through which a spectrum of physiologic sequelae are mediated.

ENDOTHELIUM AND IMMUNE DEFENSE

The University of Arizona NIAAA-supported Alcohol Research Center has been focusing on the effect of alcohol, alone or in combination with cofactors such as other drugs of abuse or viral infection, on 1) immune cells, lymphocytes and macrophages; 2) soluble immune mediators, growth factors, and cytokines; and 3) disease resistance to opportunistic infections and neoplasms in man and experimental animals. Our own research has centered on the endothelial cell—the cell lining the blood vasculature and lymphatic channels and an often neglected player in the immune defense system. Fig. 1 illustrates a variety of processes in which endothelium is thought to play a role, many crucial to the immune response and potentially modulated by alcohol and/or virus exposure, including leukocyte adhesion and transmigration, macromolecular and fluid permeability, coagulation cascading, particulate phagocytosis, antigen presentation and cytokine activation, lymphoid cell trafficking, and proliferative events leading to new vessel or tumor growth. The extent of homeostatic and immune defense dysregulation following pathologic perturbation of the endothelium and its processes is immediately

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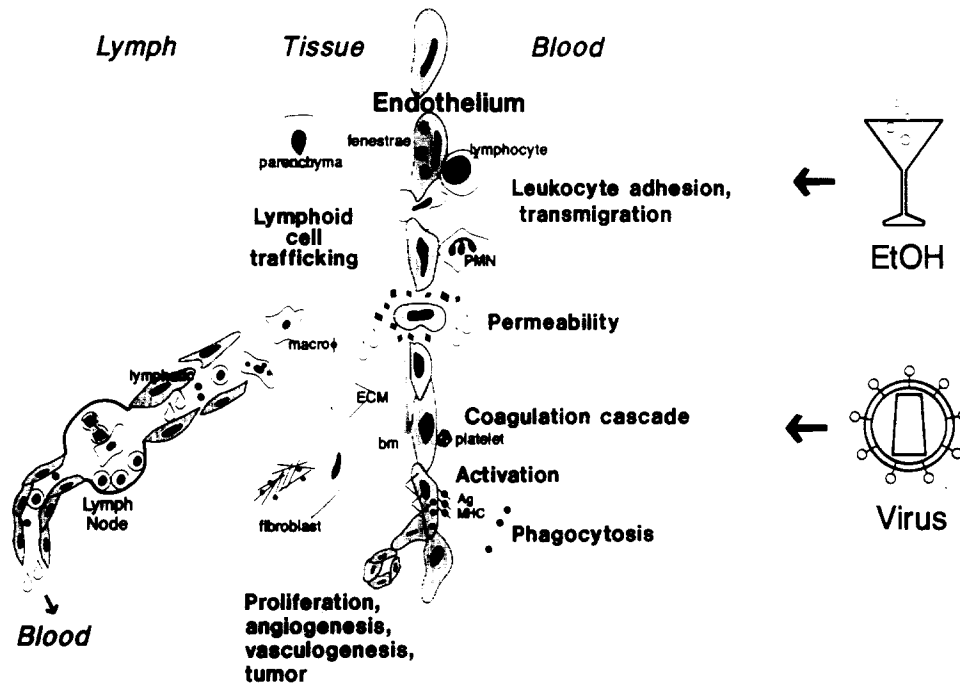


FIG. 1. Schematic of the relationship between blood and lymph vascular endothelium, parenchymal and extravascular connective tissue, migrating leukocytes, transcapillary fluid and macromolecule movement, and foreign particulates, including their relative anatomy and emphasizing the variety of endothelium-mediated homeostatic and immune defense processes potentially influenced by alcohol and viruses. PMN = polymorphonuclear leukocyte, macro ϕ = macrophage, ECM = extracellular matrix, bm = basement membrane, Ag = antigen, MHC = major histocompatibility complex, EtOH = ethanol (alcohol), filled black rectangles represent macromolecules, drops represent fluid (plasma, interstitial or lymph), filled black circles represent exogenous particulates. See text for further explanation.

apparent. Arising from a common primordium in the mesenchymal anlage, blood and lymph vascular endothelium interact with immunocompetent cells by directing lymphocyte recirculation through binding to specific constitutive and inducible cell surface receptors or vascular "addressins" (1) and by producing colony-stimulating activity which differentiates hemopoietic stem cells into granulocytes and monocytes (3). Also, endothelium regulates leukocyte attachment, transmigration, and extravascular accumulation; inducibly expresses class II MHC surface molecules; phagocytoses and presents antigen; and increases Fc and C3 receptor expression upon viral infection exhibiting a capability for controlling tissue entry and killing of pathogens. Immunocompetent cells, fibroblasts, and adipocytes secrete angiogenic factors and share growth factor surface receptors with endothelium that in wound healing and scarring interact functionally as they produce the structural and biochemical components of desmoplasia. Properly functioning endothelium, therefore, is fundamentally implicated in initiation and development of regional immune responses, defense against invading microbes, and wound repair, remodeling, and revascularization while facilitating small solute and macromolecular transport, directing physiologic cell migration, stabilizing pro- and anticoagulatory cascades, and regulating the biosynthetic maintenance of extracellular matrix components. Heterogeneity, related both to vessel caliber and organ-specific characteristics, and transdifferentiating capabilities, emulating a variety of morphologic and functional phenotypes, imply a further level of adaptation for the aforementioned myriad of endothelial pro-

cesses. Thus, endothelium plays a key role in disease containment as well as progression, while also representing a potential target for immunomodulation.

Host defense against infection depends upon intravascular and extravascular events involving humoral and cellular elements within the vascular lumen as well as along the blood vessel and lymphatic lining, working in concert with immune cell populations in lymphoid and nonlymphoid tissues. Physical and biochemical interactions, particularly cytokine release, mediate the acute and chronic inflammatory response, which is associated with a mobilization cascade of the white blood cell series. Effective responses to invading microorganisms include engulfment, killing, neutralization, and subsequent generation of specific antibody and delayed-type hypersensitivity. These reactions take place in part within the extracellular fluid and tissue matrix (the intermediate milieu of the blood-lymph loop) and are closely coordinated with events occurring within blood vessels as well as in regional lymphatic channels and nodes. If the endothelial lining becomes "dysfunctional," this orderly process becomes unhinged, and the entry, proliferation, and dissemination of invading microorganisms escapes this important gateway of control.

One postulated sequence of events regarding the development of ALD and eventual cirrhosis (the "intact cell hypothesis") serves as an example of an endothelium-directed pathomechanism (29). Initially, high levels of circulating alcohol directly damage the normally highly permeable endothelium of the liver sinusoids, leading to a process of capillarization. Such endothelial cell damage and ensuing hepatic vascular

remodeling may not be specific to alcohol or its metabolites, but instead could be a common pathophysiologic sequel of liver injury, whether from inflammation, viral infection, ischemia, carbon tetrachloride, or graft-versus-host reaction. Capillarization, identified by several ultrastructural features such as the loss of sieve plates, defenestration, basal lamina deposition, and collagenization of the spaces of Disse (8,20), converts the liver sinusoid into a nonliver microcirculation, a transdifferentiating response of the endothelium reflecting a "dynamic mutability" similar to the transformation potential of immature hepatocytes and the metaplasia of mature bile duct cells to hepatocytes. The endothelial dysfunction and disordered microcirculation of the capillarized sinusoid in ALD are characterized functionally by lowered hepatic lymph protein concentrations relative to plasma (31), altered foreign particulate filtering, impaired microcirculatory safety valve functioning in response to elevated intravascular pressures, and a contracted extravascular albumin distribution space (24,25). The accompanying dysregulated sinusoidal hemo- and lympho-dynamics, aggravated by cycles of inflammation, promote disordered angiogenesis or neovascularization leading to 1) parenchymal cell damage, 2) fibrosis characteristic of ALD and cirrhosis, 3) portal hypertension, and 4) edema or ascites formation. Moreover, sinusoidal capillarization would be expected to result in defective neutralization of opsonized pathogens; chemotaxis and phagocytosis by granulocytes and Kupffer and endothelial cells; immune hyperreactivity and subsequent immune "exhaustion" associated with immune complex deposition in the perisinusoidal areas; and even full-blown immune complex disease, reflecting dysregulation or loss of hepatic immunity. The immune reaction including the involvement of endothelial lining cells would also liberate cytokines, which in turn stimulate angiogenesis, progressive fibrosis, and mitogenesis, further promoting portal hypertension and vascular hypoplasia and neoplasia as the end result. Thus, not only intrahepatic and extrahepatic portal hypertension but also hepatic parenchymal dysfunction and immune dysregulation are, according to the "intact cell theory," consequences of early and progressive microcirculatory endothelial injury and vascular remodeling. While hepatic histopathology in AIDS has not been well described, many of these features of ALD have also been reported in AIDS patients.

NEOANGIOGENESIS AND VASCULAR MANIFESTATIONS IN AIDS AND IN ALCOHOLISM

Neoangiogenic phenomena are prominent features of both AIDS (30) (Fig. 2) and alcoholism (Fig. 3) particularly in ALD and portal hypertension. The most prominent vascular lesion in AIDS, affecting predominantly the homosexual population, is Kaposi's sarcoma (KS) (Fig. 2, C and D), in successive stages from plaques and papules to lymphangiohemangioma-toid nodules and frankly fibrosarcomatous lesions. The clinical course is typically aggressive, involving all parts of the body, particularly the face, trunk, extremities, oral cavity, genitalia, gastrointestinal tract, lung, and liver, with attendant complications of edema, serous effusion, and hemorrhage. KS-like angiogenic reactions are even more commonly seen in lymph nodes of many, perhaps the majority, of AIDS patients and may produce a prominent angioproliferative and even angioimmunoblastic lymphadenopathy. In addition, prominent neovascularization is also observed in AIDS in a variety of localized cutaneous lesions such as angiomas, angiofibromas, angiolipomas, pyogenic granulomas, and epithelioid or histiocytoid angiomas. Vascular dilatation is often widespread as telangiectasia of the skin and peliosis in the liver and other

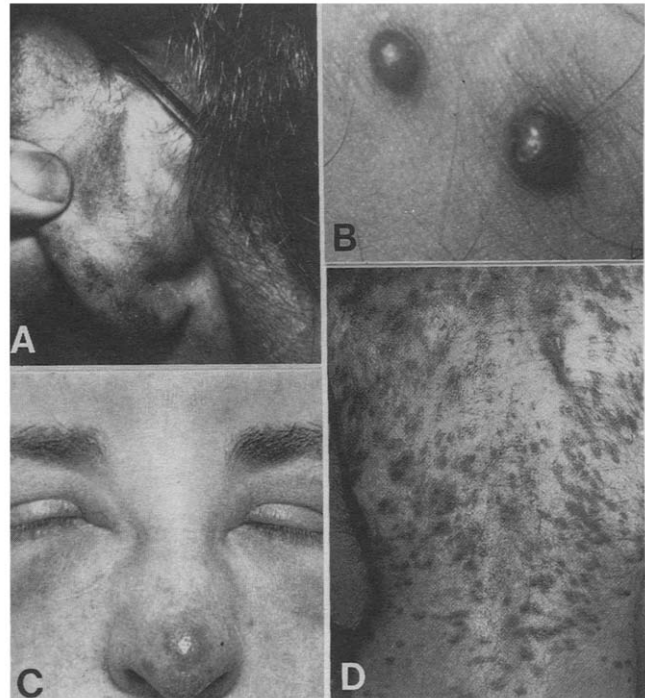


FIG. 2. Cutaneous vascular lesions in AIDS include (A) telangiectasia as shown here behind the ear, suddenly appearing before *Pneumocystis carinii* infection (13); (B) histiocytoid hemangioma-like lesions resembling pyogenic granulomas (16); and Kaposi's sarcoma presenting as (C) severe facial lymphedema associated with macules on the nose (7) and (D) brownish purple plaques spreading over the torso (9).

sites. Thrombophlebitis in the extremity occurs in the presence and absence of KS. A sclerotic process producing marked thickening of blood vessel walls with luminal narrowing may present clinically as a "stroke," which may also follow thromboembolism. Diffuse vascular calcification is also common. Generalized purpura and renal failure have been attributed to immune complex and leukoclastic vasculitis, which may also underlie poorly understood dysfunction of other organ systems. The lymphatic vasculature is prominently involved in KS, which characteristically shows lymphatic dilatation and obstruction and, not uncommonly, striking lymphedema (Fig. 2C). A discrete Whipple's disease-like syndrome with intestinal lymphangiectasia and protein-losing enteropathy has also been described.

Some of the foregoing and other vascular manifestations in AIDS derive from opportunistic infections associated with immunosuppression or immunodysregulation, including those due to viruses such as herpes zoster and simplex and cytomegalovirus (CMV); bacteria such as *Chlamydia* and mycobacteria, fungi, and protozoan parasites such as *Pneumocystis carinii* and *Toxoplasma gondii* may also be involved. Of particular interest is the identification and isolation of a rickettsia, *Rochalimaea henselae*, from bacillary angiomatosis and peliosis hepatis lesions in AIDS patients (19). Abuse of recreational drugs with potent vasoactivity, such as volatile amyl and butyl nitrite or "poppers," may also play a role (11). In addition, disorders of the blood and lymph circulation may underlie tissue fibrosis and sclerosis in diverse locations. Finally, the relationship of these and other vascular manifesta-

tions to circulating angiogenic factors generated directly by viral or other opportunistic infections or indirectly by the host immune response is intriguing but poorly understood. For example, KS and other vascular lesions such as telangiectasia appear in other acquired and congenital immunodeficiency states and may disappear after immunorestitution. Furthermore, opportunistic invaders, including viruses, bacteria, parasites, and rickettsia, promote vascular lesions that may regress with specific antimicrobial treatment.

On the other hand, the vascular manifestations of alcoholism and particularly ALD are well recognized as "stigmata" of the disease and central to its pathogenesis. In the form of the portal hypertension syndrome with varix hemorrhage and ascites, these aberrations are the major cause of morbidity and mortality in hepatic cirrhosis secondary to alcoholism and also viral hepatitis. In addition to cutaneous angiomas, telangiectasia, and palmar erythema (Fig. 3, A-C), portosystemic neocollateralization is prominent on the abdominal wall (Fig. 3D) and as venous varices along the length of the gastrointestinal tract. As a hallmark of cirrhosis and portal hypertension, striking increases in hepatic, intestinal, and thoracic duct lymph flow have been observed with massively dilated lym-

phatic collaterals associated commonly with ascites and, occasionally, pleural effusions. Furthermore, peliosis hepatis, a variety of vascular tumors, and vascular sclerosis and thrombosis (particularly involving hepatic and portal veins) have been described and, rarely, pulmonary vascular plexopathy, a lesion recently also observed in AIDS.

AIDS AND ALCOHOL: INFECTING AND AFFECTING ENDOTHELIUM

What then is the evidence that endothelium is targeted and/or damaged by viruses such as HIV and coinfecting viruses (and other microbes) in AIDS and by alcohol (and other environmental pollutants and drugs of abuse)?

Viruses and Endothelium

Not only have HIV-infected cells of the lymphocyte series been identified within the lumen of lymphatics and blood vessels on histologic section by *in situ* hybridization techniques, but endothelial cells lining the vasculature also harbor virus.

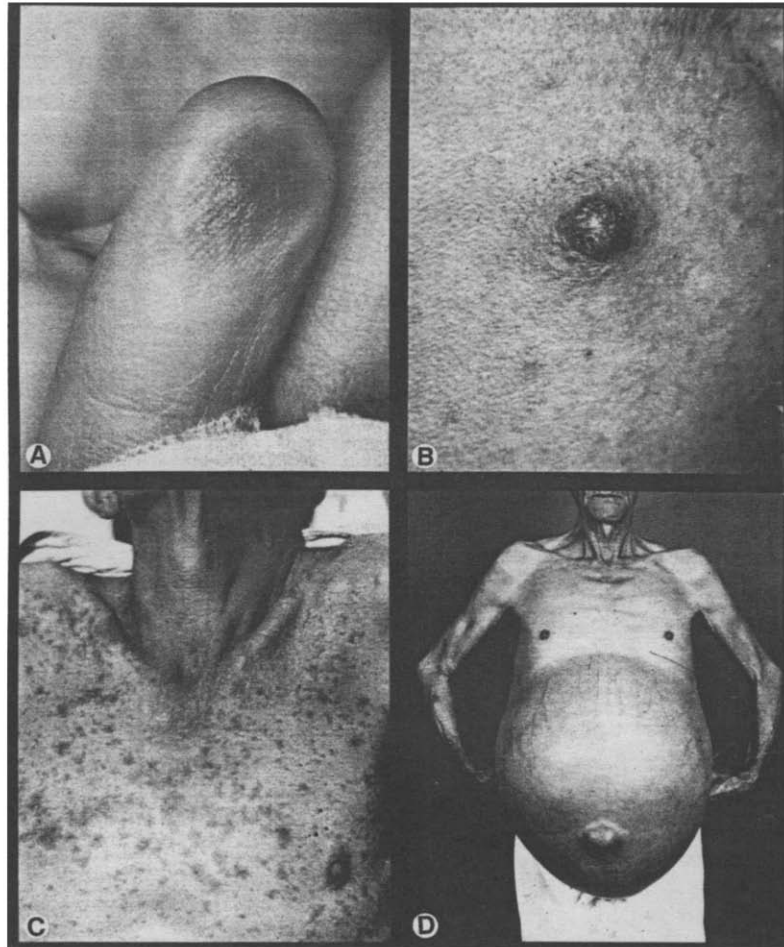


FIG. 3. Cutaneous vascular manifestations in chronic alcoholism and alcoholic liver disease. Angiomas of the (A) finger and (B) cheek and (C) extensive telangiectasia of the chest wall; (D) prominent portosystemic venous collaterals along the abdominal wall with caput medusae (umbilical vein collaterals) associated with massive ascites.

As viruses and other infectious agents gain access to the lymphatic apparatus and the bloodstream directly through portals of entry in the gastrointestinal, respiratory, and genitourinary tracts and are disseminated by hematogenous (systemic and portal) and lymphogenous pathways, it is not unexpected that these agents can be found in the endothelial lining of the blood vasculature and lymphatics. Although great emphasis has been placed on the T-helper lymphocyte as the prime target of the AIDS virus, increasing attention has turned to other cell types serving as HIV reservoirs. Thus, HIV has been detected in cerebral blood vessels (28) by monoclonal antibody and in situ hybridization techniques and also in hepatic sinusoidal endothelium of AIDS patients. Moreover, HIV infects endothelial cells in vitro (22). Viruses producing co-infections in AIDS have also been demonstrated in endothelial cells in tissue sections by polymerase chain reaction, in situ hybridization, or ultrastructural detection of viral particles, and these include CMV, herpes simplex virus (HSV), human papillomavirus (HPV), and, recently, hepatitis B virus (HBV). These viruses have been documented in blood vessel or lymphatic endothelial cells from a variety of sites in vascular lesions of AIDS patients, other patients without AIDS, and in experimental animals infected with these viruses. Particularly interesting in this regard is the course of experimental frog hepatitis viral infection (15,21), which denudes the sinusoidal endothelium allowing other types of viruses not phagocytosed by Kupffer cells to reach the hepatic parenchyma and produce fatal hepatitis; with the endothelium intact, these same viruses have no effect, highlighting the crucial role of intact endothelium as a barrier and the complex interrelationships between endothelium and other cell types. In vitro, viruses exert a variety of direct effects on endothelial cells: activating histocompatibility complex receptors and, specifically in HSV infection, increasing production of extracellular matrix associated with heightened DNA and RNA synthesis (14). Viremia also stimulates morphologic transformation to high venous endothelium primed for cell trafficking and promotes growth factor and cytokine secretion, which flood surrounding tissues. Chronic mitogenesis promotes phenotypic and even genotypic changes in endothelial cells. Thus, alterations in endothelial cells themselves (cytotoxicity, altered metabolism or permeability, mitogenesis) and through their other cell-cell interactions mediated in part by cytokines such as IL-1 and IL-6 and growth factors could produce profound immune system dysregulation including immunodeficiency. Furthermore, angiogenesis and oncogenesis are probably closely linked. In spontaneous avian leukosis virus infection with immunodeficiency and angiomas (6) as well as angiosarcomas resembling Kaposi's sarcoma, the retroviral insert appears next to the fibroblast growth factor gene. Although both CMV and HPV have been reported in the vascular lining or spindle cells of KS lesions (but not cultured KS cells), these and other transmissible viral agents are generally not accepted as the causative agent of KS. Nonetheless, cultured AIDS-KS cells are thought to represent transdifferentiated lymphatic or blood vascular endothelium altered either by cytokines released during HIV infection or other immunodysregulated states. These influences, in turn, then alter cell shape and function, promoting endothelial spindling and migration with disordered angiogenesis.

Alcohol and Endothelium

Prolonged alcohol exposure, in both experimental and clinical ALD, is similarly characterized by sinusoidal capillarization, specifically defenestration, basement membrane forma-

tion, interstitial collagenization in the space of Disse, and spreading interstitial fibrosis. These changes, as previously outlined, are postulated to temporally precede and pathomechanistically induce hepatocellular damage. Relatively normal hepatocellular features, biliary excretion, and reticuloendothelial function (as displayed on hepatobiliary scintiscanning) and only minimally elevated serum transaminase activities despite the microcirculatory changes support that microcirculatory injury, as distinct from hepatocellular damage, is a primary mechanism of ALD. This process, seen in rats on high levels of alcohol delivered by continuous intragastric infusion (18,23), can, in part, be reproduced in vitro through the demonstration of morphological and functional abnormalities even after brief exposure of endothelial cells (human umbilical vein, omental microvasculature, rat hepatic sinusoid and bovine lymphatic) to high levels of ambient alcohol comparable to peak peripheral and portal blood levels in binge drinkers (0.5-1.0 vol%). Cell margins retract reversibly and transmonolayer albumin permeability increases, probably through reversible alterations in cell membrane fluidity. Sustained high concentrations of alcohol affect endothelial cell cycle progression by acting as a specific $G_{1/0}$ blocking agent in endothelial cells derived from rat sinusoids and human umbilical vein but not in AIDS-KS cells (26,27). The relative resistance of KS cells to chronic alcohol exposure suggests a possible mechanism for their selective survival advantage in AIDS patients who are also alcohol abusers. This cell selection may be key to exuberant angiogenesis, teratogenesis, neoplasia, and carcinogenesis with chronic alcohol abuse. In some endothelial cell types, short-term in vitro alcohol exposure, associated with reversible morphologic changes (4), is followed by a burst of proliferative activity suggesting that the G_1 block also is reversible. The response of endothelial cells to the high levels of blood alcohol attainable in the hepatic sinusoid, as suggested by these in vitro studies, would initiate a pattern of cyclic morphologic shape changes, defenestration, and arrests in proliferation followed by proliferative bursts of growth, a transdifferentiating response that would promote progressive change from a fenestrated sinusoid to a nonliver capillary. It is noteworthy that a variety of hydrocarbon environmental pollutants, most notably vinyl chloride, act as vigorous angiostimulatory agents producing a spectrum of vascular hyperplasia and neoplasia including peliosis, angiomas, and angiosarcoma in both man and experimental animals.

VIRAL-ALCOHOL SYNERGY?

We have recently serendipitously observed what appears to be an even closer link or synergy between alcohol and viral infection in the continuous intragastric alcohol infusion rat model (17). In an experimental group consisting of four alcohol-fed rats and a control group of four rats identically fed except for isocaloric substitution of glucose for alcohol in the liquid diet, an epidemic of a provisionally identified salivary gland coronavirus infection swept unexpectedly through the rat colony 10 weeks into the feeding regimen. All eight rats were serologically positive for the virus at the time of killing. In each of the alcohol-fed rats, but in none of the rats fed a control diet, vascular proliferative lesions with neoplastic features and variable endothelial marker Factor-VIII-related antigen positive staining were identified in multifocal nodules distributed throughout the liver. Viral particles, ultrastructurally resembling the size, shape, and staining of a strain of parvovirus, were visible in the sinusoidal endothelium of both the alcohol- and non-alcohol-fed rats but were most promi-

nent in the proliferative vascular lesions found only in the alcohol-fed group. The latter finding suggests that alcohol—the only clear variable in these experiments—was acting as a cofactor (insufficient alone) promoting a proliferative vascular response to a putative viral infection. Of interest, the viral particles detected in the endothelium morphologically resembled parvoviruses identified recently in AIDS patients (2) and suspected as contaminants in a number of commercial vendor sources of rodents (10,12).

CONCLUSION

In summary, endothelium has been highlighted as playing a pivotal role in vascular homeostasis and the immune response. Evidence has been provided that the endothelial cell directly participates in HIV infection and other opportunistic infections in AIDS as well as in the sequelae of chronic alcohol exposure and progressive ALD. Indeed, the blood and lymphatic vasculatures represent “portals of entry” and “dissemination-distribution” of both virus and alcohol as well as the

stage upon which protective and self-destructive events in AIDS and ALD, both intimately involved and affecting the immune system, are played out. Dysfunctional and functional endothelium, its proliferation and related angiogenesis, generate prominent features of the underlying immunodysregulation seen in both disorders and promote not only opportunistic infections (some of which in turn target the blood and lymphatic vasculature) but also prominent vascular manifestations, including neoplasms. Clearly, more work is needed to explore these important unanswered questions about the role of endothelium in the pathogenesis of AIDS and ALD and also to consider this cell and the angiogenic process as suitable targets for immunomodulation.

ACKNOWLEDGEMENTS

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