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Human immunodeficiency virus and the autonomic nervous system: A study of cardiovascular reflexes

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HUMAN IMMUNODEFICIENCY VIRUS AND THE AUTONOMIC NERVOUS SYSTEM: A STUDY OF CARDIOVASCULAR REFLEXES

by

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STATEMENT BY AUTHOR

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

Page

LIST OF TABLES

Page

ABSTRACT

Recent reports suggest that human immunodeficiency virus (HIV), the virus causing AIDS, may cause autonomic nervous system (ANS) dysfunction. ANS abnormalities on cardiovascular reflex tests have been demonstrated in HIV+ persons, persons infected with HIV, who have signs of illness or have used intravenous drugs. In this study cardiovascular reflex function of 11 HIV+ homosexual or bisexual males who met the Centers for Disease Control criteria for absence of illness was compared to that of 11 uninfected homosexual or bisexual males of similar ages. Additionally, somatic, depression and fatigue differences between the two groups were assessed using an ANS symptom checklist, the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS). Six of the 11 HIV+ subjects had impaired cardiovascular reflexes. Differences on the BDI and POMS were not attributable to a depressive mood or despair, but rather to presence of mild symptoms of HIV infection and fatigue.

INTRODUCTION

The spectrum of neurological dysfunction attributed to human immunodeficiency virus (HIV) continues to grow. In 1987 reports of autonomic dysfunction in individuals infected with HIV began to appear (Craddock, Bull, Pasvol, Protheroe, & Hopkin, 1987; Evenhouse et al., 1987; Lin-Greenberg & Taneja-Uppal, 1987; Miller & Semple, 1987; Villa, Foresti, & Confalonieri, 1987). Autonomic nervous system (ANS) abnormalities on cardiovascular reflex tests have been demonstrated in HIV+ persons, persons infected with HIV, who have signs of illness or who have used intravenous drugs. This thesis addresses the question of whether persons who are infected with HIV who are not yet clinically ill and do not have a history of intravenous drug use have cardiovascular reflex abnormalities.

AIDS HISTORY

In 1981 the Centers for Disease Control (CDC) reported the development of Pneumocystis carinii pneumonia, a disseminated form of Kaposi's sarcoma, and other "opportunistic" infections in previously healthy young homosexual males in New York and San Francisco (Gottlieb, Schanker, Fan, Saxon, & Weisman, 1981; Friedman-Kien et al., 1981; Gottlieb, Schroff et al., 1981; Masur et al., 1981; Siegal et al., 1981). These infections are rare in persons with normal immune function, and therefore indicated a deficit or deficiency in the immune system. Thus, the "acquired immunodeficiency syndrome", AIDS, was identified.

In 1983 the retrovirus causing AIDS was identified at the Pasteur Institute in France and named lymphadenopathy associated virus (LAV) because the virus isolate came from the lymph nodes of an AIDS patient (Barre-Sinoussi et al., 1983). In 1984 the National Cancer Institute reported the identification of another retrovirus: human T-cell lymphophotropic virus (HTLV-III) (Gallo, Salahuddin et al., 1984). Also in 1984, Levy et al. at the University of California at San Francisco discovered AIDS-associated retrovirus (ARV). Subsequent biochemical analyses indicated that these three viruses were all variants of one virus: what is now called human immunodeficiency virus (HIV) (Brown, 1986; Coffin et al., 1986).

CLINICAL MANIFESTATIONS OF HIV INFECTION

AIDS is only one of several manifestations of exposure to HIV. Those exposed to the AIDS virus fall into two categories: seronegative (HIV-), and seropositive (HIV+). HIV+ individuals have antibodies to HIV in their blood and are by this criteria said to be "infected" with HIV. The presence of these antibodies is not indicative of disease, but rather reveals that the individual has been exposed to HIV at some time. In HIV- individuals, however, antibodies to HIV are not detected. Seronegativity indicates that either the individual has not had HIV in the bloodstream or that the individual has not yet developed antibodies to HIV. HIV+ individuals are at risk for developing AIDS or other HIV-related illnesses.

For surveillance purposes the CDC (1986) divides HIV+ individuals into five groups: those with acute infection, those with no symptoms of illness, those with persistent generalized lymphadenopathy, those with other HIV-related diseases, and those with AIDS. The order of the foregoing groups is consistent with the progression of the stages of HIV-related illness. Individuals need not go through all stages, but progression is considered to be irreversible.

Acute Infection

Individuals may have an acute infection associated with seroconversion from the HIV- to HIV+ state (CDC, 1986; Cooper et al., 1985; Ho et al., 1985). In a prospective study, Cooper et al. (1985) found that 11 of 12 subjects had an acute mononucleosis-like illness at the time of seroconversion. The syndrome had a sudden onset, lasted 3 to 14 days, and was characterized by fevers, sweats, malaise, lethargy,

anorexia, nausea, sore throat, diarrhea, and generalized lymphadenopathy. There were also changes in immune function consistent with the presence of a viral infection. Since one subject had no such syndrome, it is possible that this indicator of seroconversion is either not present or of a subclinical nature in some individuals.

Absence of Illness

Following seroconversion there may be an indefinite period during which the individual shows no systemic illness (CDC, 1986). At this stage the individual is still infected despite apparent health. It is possible that some individuals will never manifest further HIV-related symptoms; epidemiological studies of long-time asymptomatic individuals are of particular importance in this regard.

Persistent Generalized Lymphadenopathy

HIV+ individuals with a lymph node enlargement of 1 cm or greater, at 2 or more extra-inguinal sites, lasting for more than 3 months, in the absence of any other explaining illness are said to have persistent generalized lymphadenopathy (CDC, 1986). The sites may not be inguinal since lymph nodes in inguinal areas frequently become enlarged following exposure to other sexually transmitted diseases. Should the lymphadenopathy resolve after more than three months, the individual is still diagnosed as having persistent generalized lymphadenopathy.

Other HIV-Related Diseases

Persistent diarrhea and/or fever lasting for more than one month, or loss of more than 10 percent of baseline body weight, or presence of certain other infectious diseases or cancers in seropositive individuals with or without lymphadenopathy characterizes this group

(CDC, 1986). Once related diseases appear, the diagnosis is not changed even if the symptoms are no longer present. These diseases can also be diagnosed by exclusion: an HIV+ individual who is clinically ill and does not meet diagnostic criteria for having AIDS is classified as having an HIV-related disease.

AIDS

As of September 1987 the Centers for Disease Control revised the Surveillance Case Definition for Acquired Immune Deficiency Syndrome (CDC, 1987). According to the new definition, the diagnosis of AIDS can be made with positive, negative, and unknown or inconclusive laboratory evidence of HIV infection. Following is a summary of the process for diagnosis of AIDS. It is important to recognize that at all stages of diagnosis other causes of immunodeficiency must be actively ruled out.

With positive laboratory evidence of HIV, meaning that the serum of the individual in question has been tested for antibodies and is HIV+, the diagnosis is AIDS if any of the indicators in TABLE 1 are present. In the presence of unknown or inconclusive laboratory findings, a definitive diagnosis of any of the diseases listed in numbers 1-12 constitutes an AIDS case. However, other possible causes of immunodeficiency must first be ruled out, and diagnoses of Kaposi's sarcoma and/or lymphoma are valid indicators of AIDS only when the individual in question is less than 60 years old.

TABLE 1

CRITERIA FOR THE DIAGNOSIS OF AIDS

1. candidiasis of the esophagus, trachea, bronchi, or lungs
2. cryptococcosis, extrapulmonary
3. cryptosporidiosis with diarrhea persisting > 1 month
4. cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient >1 month of age
5. herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient > 1 month of age
6. Kaposi's sarcoma
7. lymphoma of the brain (primary)
8. lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia affecting a child < 13 years of age
9. mycobacterium avium complex or M. kansasii disease, disseminated
10. Pneumocystis carinii pneumonia
11. progressive multifocal leukoencephalopathy
12. toxoplasmosis of the brain affecting a patient > 1 month of age
13. bacterial infections, multiple or recurrent, of specific types, affecting a child < 13 years of age.
14. coccidioidomycosis, disseminated
15. HIV encephalopathy
16. histoplasmosis, disseminated
17. isosporiasis with diarrhea persisting > 1 month
18. other non-Hodgkin's lymphoma of B-cell or unknown immunologic phenotype and of specific histologic types
19. any mycobacterial disease caused by mycobacteria other than M. tuberculosis, disseminated
20. disease caused by M. tuberculosis, extrapulmonary
21. Salmonella (nontyphoid) septicemia, recurrent
22. HIV wasting syndrome (emaciation)

When there are negative laboratory findings, other causes of immunodeficiency must be sought. In the absence of another cause, an individual with a definitive diagnosis of Pneumocystis carinii pneumonia is considered to have AIDS. In addition, any individual who has any disease listed in numbers 1-12 in TABLE 1 (Kaposi's sarcoma and/or lymphoma must, once again, occur in persons less than 60 years of age) is also considered to have AIDS when there is no other cause of immunodeficiency, and the T-helper lymphocyte count is $< 400/mm^3$.

Summary

In summary, the diagnosis of AIDS and HIV-related illness is a complex process. The syndrome is by definition progressive, and the factors influencing progression are not understood. Finally, assuming that each individual manifests the disease similarly is erroneous; manifestations are multiple and varied.

HIV AND THE NERVOUS SYSTEM

History

Since the beginning of the "AIDS epidemic" (Landesman, Ginzburg, & Weiss, 1985), clinicians and research scientists have been curious about nervous system involvement in this syndrome. About 40 percent of adult AIDS patients have some neurological impairment (Snider et al., 1983; Koppel et al., 1985; Levy, Bredesen, & Rosenblum, 1985; Levy, Bredesen, & Rosenblum, 1988). Navia, Jordan, and Price (1986) reported that more than half of the 70 AIDS patients they studied showed some cognitive, motor, and/or psychological changes during the course of their illnesses. Upon autopsy 70-80 percent of AIDS patients have neuropathological changes (Moskowitz, Hensley, Chan, Gregorios, & Conley, 1984; Petito, Cho, Lemann, Navia, & Price, 1986). Additionally, neurological impairment may be the presenting complaint in subsequent AIDS patients (Levy, Bredesen, & Rosenblum, 1988), and in some cases this impairment may be the only feature suggesting disease related to HIV during life (Navia & Price, 1987).

Initially, these neurological alterations in AIDS patients were attributed to opportunistic infections (Snider et al., 1983; Moskowitz et al., 1984; Nielson, Petito, Urmacher, & Posner, 1984) or mistaken for depression (Johnson & McArthur, 1986; Price, Navia, & Cho, 1986). While some nervous system impairment in AIDS patients can be attributed to opportunistic infections (see Levy, Bredesen, & Rosenblum 1988) and lymphomas (see Rosenblum et al., 1988), neither they nor depression explain the many neuropathological or clinical central nervous system

(CNS) disturbances that may follow primary HIV infection (Navia, Jordan, & Price, 1986; Navia, Cho, Petito, & Price, 1986).

Clinical Presentation

Memory loss, difficulties concentrating, and mental slowing were frequently reported early cognitive impairments in 46 patients with progressive dementia studied by Navia, Jordan, and Price (1986). Patients also reported motor impairments including unsteady gait, leg weakness, loss of coordination, impaired hand writing, and tremor. Finally, some described changes in behavior such as depression, apathy, agitation, and confusion.

Signs related to these early symptoms were detected on mental status and neurological examinations. In some patients, the mental status examinations revealed psychomotor slowing, and difficulty with the "serial sevens" task or tasks designed to test recent memory. The neurological examinations showed cases of rapid movement impairment, gait ataxia (impaired tandem gait, rapid turns), and/or leg weakness. Hyperreflexia, dysarthria, and impairment of smooth pursuit eye movements were also recurrent problems.

The late manifestations in Navia, Jordan, and Price's (1986) patients included moderate to severe dementia, and confusion. Psychomotor slowing with verbal response delays and near or absolute mutism accompanied by a vacant stare were common. Patients were often distractible, disinhibited, unaware of their illness, and showed evidence of organic psychosis. Neurological examination indicated weakness in the extremities with legs affected to a greater degree than arms. Pyramidal tract signs included spasticity, hyper-reflexia, and

extensor plantar responses. Ataxia, urinary and fecal incontinence, myoclonus and seizures were also present.

Since this was a retrospective study, individuals with other focal lesions or confounding metabolic processes reported or discovered at autopsy were not included. Still, nearly two thirds of the remaining AIDS patients showed signs of dementia. Thus, this study, in addition to providing a list of the common clinical features of dementia in AIDS patients, provided evidence that dementia resulted from the presence of HIV.

McArthur (1987) prospectively studied 39 patients previously identified as having dementia. Behavioral change (90 percent), memory loss (80 percent), depressive symptoms (30 percent), apathy (15 percent), and motor complaints (20 percent) were most frequently reported by the 20 patients studied with early AIDS-related dementia. These early manifestations were not detected by the routine bedside examinations. Later dementia was characterized by global deterioration in cognitive function with development of psychomotor retardation, incontinence, and mutism. Neurologic abnormalities in the 19 patients studied included diffuse hyperreflexia (77 percent), hypertonia (35 percent), impaired rapid alternating movements (27 percent), release signs (41 percent), and myelopathy with signs of spastic paraparesis (41 percent).

Neuropathology of the Central Nervous System

HIV enters the CNS and invades cells there. HIV has been isolated in cerebrospinal fluid (CSF) (Ho et al., 1985; Levy, Shimabukuro, Hollander, Mills, & Kaminsky, 1985; Goudsmit et al., 1986) and brain

deoxyribonucleic acid (DNA) (Shaw et al., 1985). Most HIV in the brain has been found in monocytes, macrophages, and multinucleated giant cells (Koenig et al., 1986; Gabuzda, et al., 1986; Pumarola-Sune et al., 1987). In addition, immunohistology and in situ hybridization techniques have been used to isolate HIV antigens in neural tissue and CSF, and nucleic acids in neural tissues (Vazeux et al., 1987). Additionally, synthesis of HIV-specific antibody may occur within the CNS (Resnick et al., 1985). All of these findings indicate that HIV both enters the brain and may induce a specific infectious process there. Finally, based upon a study in which HIV from the brain was distinguishable from peripheral blood HIV, Cheng-Mayer and Levy (1988) suggest that HIV in the brain may be a distinctive subtype of HIV.

HIV-associated histopathological abnormalities in the CNS are most frequent in subcortical structures. The central white matter and deep gray structures including the basal ganglia, thalamus, brainstem and spinal cord are most vulnerable; the cerebral cortex is relatively spared (Navia, Cho, Petito, & Price, 1986). Studies investigating the location of viral protein (Pumarola-Sune et al., 1987) and viral ribonucleic acid (RNA) (Stoler, Eskin, Benn, Angerer, & Angerer, 1986) in the brain support these findings. Viral protein and RNA are concentrated in the white matter and basal ganglia; they are predominantly found in macrophages and multinucleated giant cells, occasionally found in astrocytes and oligodendroglia, and rarely found in neurons. In both gray and white matter there may be loss of astrocytes, but loss of oligodendrocytes or neurons is uncommon (Navia, Cho, Petito, & Price, 1986).

Navia, Cho, Petito, and Price (1986) reported that less than 10 percent of 70 autopsied brains from adult AIDS patients were histologically normal. The brains were characterized by diffuse pallor of white matter (decreased myelin density), multinucleated giant cell encephalitis, and vacuolar myelopathy. Pallor of white matter, the most frequent finding, was more prevalent in the central and periventricular areas, and the degree of pallor usually correlated with the severity of previously reported neurological symptomatology. Multinucleated giant cells, markers for HIV replication (Gartner et al., 1986), were found in patients who, during life, had more severe clinical disease. Macrophage, microglial, and lymphocyte reactive brain infiltrates also tended to be present in these patients, and infiltrates were most often found in white matter and deep gray structures (viz., the basal ganglia, thalamus, and pons). Vacuolation, cavity formation, was typically found in the spinal cord, but extended into the brain stem of some patients. Though the severity of vacuolar myelopathy correlates with the signs and symptoms of spinal cord disease (Petitio et al., 1985), it does not directly correspond with the amount of brain pathology (Price, Brew, Sidtis, Rosenblum, Scheck, & Cleary, 1988).

Cerebral atrophy, marked by ventricular dilatation and occasional white matter abnormalities (e.g., diffuse attenuation of white matter), may be detected with computed tomography (CT) scanning and magnetic resonance imaging (MRI) (Navia, Jordan, & Price, 1986; Grant et al., 1987). In a review of CT scans from 200 neurologically symptomatic AIDS patients, Levy, Rosenblum, and Perret (1986) found no

abnormalities in 39.5 percent, diffuse atrophy in 35 percent, and focal lesions in 25.5 percent of cases. In this study, the risk of neurological progression was three times greater for patients with diffuse atrophy alone than for patients with normal CT scans.

Though CT has been used more frequently than MRI, MRI is generally a more sensitive detector of intracranial pathology in AIDS patients with known neurological symptoms (Levy, Mills, Posin, Moore, Rosenblum, & Bredesen, 1986). When the results of MRI and CT scans were compared in 98 adult AIDS patients with CNS symptoms, MRI detected cerebral lesions which were not detected by CT in 44 percent of the cases (De La Paz & Enzmann, 1988). McArthur (1987) reported that the number of white matter lesions and degree of cerebral atrophy on MRI increase as AIDS patients clinically deteriorate.

Additionally, normal controls can be distinguished from AIDS dementia patients on the basis of regional brain glucose metabolism using positron emission tomography (PET). Rottenberg et al. (1987) found that basal ganglion and thalamic glucose hypermetabolism appeared early in the dementia, and progression of dementia was associated with cortical and subcortical hypometabolism. In this study, alterations in subcortical metabolism correlated with deficits in fine motor control, and alterations in cortical metabolism correlated with verbal fluency and visuoconceptual/visuomotor tracking deficits.

Some persons show diffuse slowing of the electroencephalogram (EEG) in later stages of HIV dementia (Enzensberger, Fischer, Helm, & Stille, 1985; McArthur, 1987). EEG abnormalities have been reported in patients with AIDS and AIDS-related illnesses who have dementia and/or

opportunistic infections, and in patients without apparent neurological disease (Gabuzda, Levy, & Chiappa, 1988). To date, there have been no reported attempts to apply presumably more sensitive computerized EEG analyses (e.g., John, Prichep, Fridman, & Easton, 1988) with AIDS patients. Delayed brainstem auditory evoked potentials in infected persons who do not have AIDS have also been reported; this suggests an early central defect (Smith, Jakobsen, Gaub, Helweg-Larson, & Trojaborg, 1988). Further cerebral electrophysiological research appears needed in order to determine the sensitivity and specificity of EEG and evoked potential measures in HIV nervous system involvement.

HIV and the Peripheral Nervous System

HIV also affects the peripheral nervous system (PNS). De la Monte et al. (1988) described the clinical and pathological features of peripheral nerve disease in 21 patients with AIDS or AIDS-related diseases. The clinical spectrum of disease ranged from asymptomatic to a chronic progressive and debilitating syndrome. However, the occurrence, severity, and nature of peripheral neuropathy were not correlated with diagnosis or duration of AIDS or AIDS-related diseases, the presence of subacute encephalitis of AIDS, or opportunistic infections.

Of the 21 patients in this study, 11 had symptomatic peripheral neuropathies; 10 had sensory deficits with painful dysesthesias or numbness and paresthesias; 7 were weak; and 2 had symptoms suggesting autonomic instability (postural hypotension for example). Nineteen of 20 patients had histopathological lesions in the peripheral nerves. These lesions were patchy in distribution, seldom involved large areas

of a single nerve, and occurred in various parts of the body. The peripheral nerve lesions showed one or more of the following characteristic lesion types: demyelination, axonal degeneration, inflammation. Mononuclear inflammatory cell infiltrates were present in the inflammatory lesions while multinucleated cells were not. Finally, HIV was isolated from several peripheral nerve samples.

Additionally, there were changes in both the dorsal root ganglia and skeletal muscles of some patients. The dorsal root ganglia, part of the sensory pathway, showed patchy inflammation, loss of ganglion cells, and fibrosis in some cases. Leg muscles showed evidence of denervation with atrophy and/or lymphocytic inflammation in perivascular spaces.

There are a number of possible causes of HIV-related peripheral neuropathy. The absence of multinucleated giant cells, however, suggests that PNS pathological processes are not identical to those within the brain. The PNS does show signs of inflammation similar to those in the brain and demyelination as in the spinal cord and lower brain stem. Since HIV has been isolated from peripheral nerves (de la Monte et al., 1988; Ho et al., 1985), lymphocytes (Popovic et al., 1983) and macrophages (Wiley, Schrier, Nelson, Lampert, & Oldstone, 1986), any or all of these cell types could be responsible for peripheral neuropathy.

De la Monte et al. (1988) suggest two possible etiologies for PNS histopathology. First, HIV might infect Schwann cells causing a T-cell mediated immune attack on the infected cells. Demyelination would follow necrosis of the Schwann cells, and a secondary axonopathy might

follow in areas of immune-mediated nerve damage. A second possibility assumes that the nerves themselves are infected with the virus and that T cells or macrophages attack the myelin and/or axons in an autoimmune demyelinative process.

HIV AND THE AUTONOMIC NERVOUS SYSTEM

Though ANS dysfunction can accompany many disorders, autonomic neuropathy has been most commonly associated with diabetes mellitus (Ewing, Campbell, & Clarke, 1980), renal failure (Tyler, 1974), amyloidosis (Cohen & Benson, 1975) or alcohol-related thiamine deficiency (Low, Walsh, Huang, & McLeod, 1975). In 1987 five separate reports of ANS dysfunction associated with AIDS appeared in letters to the editors of Annals of Internal Medicine (Lin-Greenberg & Taneja-Uppal, 1987; Evenhouse et al., 1987) and Lancet (Craddock et al., 1987; Miller, & Semple, 1987; Villa et al., 1987). Given the benefit of hindsight, the knowledge that the ANS is a diffuse network with both CNS and PNS components, and documentation of HIV's involvement in both of these systems, ANS involvement associated with HIV infection is not surprising.

Common signs and symptoms of ANS dysfunction include circulatory reflex abnormalities such as orthostatic hypotension, difficulties with the pupils and eye lids, absence of tears and secretions, erectile failure and retrograde ejaculation, digestive problems, bladder dysfunction, and sweating disorders (Gudesblatt, Goodman, Rubenstein, Bender, & Choi, 1985; Ewing & Clarke, 1986; McLeod & Tuck, 1987a). Additionally, the first symptoms of progressive ANS failure are often insidious; initial complaints of weakness, postural dizziness or faintness may be overlooked (Bannister, 1983). Finally, since ANS activity accompanies all voluntary and involuntary body actions, autonomic disorders pose a serious problem.

Lin-Greenberg and Taneja-Uppal (1987) reported the case of a 62-year-old homosexual man who had orthostatic hypotension, impotence, urinary urgency, relative anhydrosis, and an abnormal response to an autonomic nervous system test. Since there was no evidence of other causes of ANS dysfunction such as diabetes mellitus or alcoholism, the authors suggested that "dysautonomia...be added to the spectrum of neurologic abnormalities observed in HIV infection" (p. 167).

Craddock et al. (1987) reported that four of five AIDS patients with lung infections had syncopal reactions following percutaneous needle aspiration of the lung for diagnostic purposes. One of these patients died of cardiorespiratory arrest following the procedure. This reaction had not previously been reported following this procedure leading the investigators to suspect ANS dysfunction since cardiorespiratory arrest had been known to follow general or epidural anesthesia in patients with diabetic neuropathy (Page & Watkins, 1978). Subsequently, the performance of one of the original four patients with a syncopal reaction and four other patients with a history of opportunistic infections on formal battery of ANS tests (Ewing & Clarke, 1986, tests described in the following section) demonstrated autonomic dysfunction.

Further reports confirmed the presence of symptoms of ANS dysfunction in a variety of symptomatic HIV carriers. Miller and Semple (1987) described an AIDS patient with autonomic neuropathy in association with parkinsonism and dementia. This is not implausible since autonomic dysfunction has been reported in both Parkinson's disease and in progressive autonomic failure with parkinsonian features

(McLeod & Tuck, 1987a). Evenhouse et al. (1987) reported three cases of orthostatic dizziness and hypotension out of 25 symptomatic HIV patients. These 3 patients had persistent diarrhea which could, but need not be, attributed to ANS dysfunction.

Villa et al. (1987) studied 15 drug addicts participating in a methadone treatment program. Of the 10 HIV+ addicts, 1 was asymptomatic, 5 had persistent generalized lymphadenopathy, and 4 had a weight loss greater than 10 percent of baseline. Although none of the participants showed signs or symptoms of autonomic and/or peripheral neuropathy, 2 HIV+ subjects were "borderline" and 2 were "impaired" on a single test of autonomic function. The authors concluded that preclinical ANS dysfunction could be detected in drug addicts using ANS tests. However, since 2 HIV- subjects were also "borderline", other etiologies cannot be ruled out. Additionally, it is generally recommended that more than one test of ANS dysfunction be used to detect ANS neuropathy (Hilsted, 1984; Ewing & Clarke, 1986; Johnson, Lambie, & Spalding, 1987).

MEASURING ANS FUNCTION

Signs and symptoms of autonomic dysfunction and neuropathy usually involve a combination of sympathetic and parasympathetic dysfunction (Appenzeller, Arnason, & Adams, 1965). The initial descriptions of autonomic neuropathy (in diabetes mellitus) were provided by Jordan in 1936 and Rundles in 1945. During the 1950s and 1960s a variety of complex invasive methods to detect autonomic dysfunction were developed; in the 1970s simple non-invasive cardiovascular reflex tests became available (Ewing & Clarke, 1986). It is assumed that abnormalities in cardiovascular reflex tests indicate diffuse autonomic damage throughout the nervous system since abnormalities of cardiovascular reflexes correlate with other autonomic abnormalities (Campbell et al., 1977; Channer et al., 1985; Pfeifer et al., 1985; Martyn & Ewing, 1986; Ewing, Bellavere et al., 1986).

Currently there are five simple non-invasive cardiovascular reflex tests used to access autonomic neuropathy (Hilsted, 1984; Ewing & Clarke, 1986): blood pressure (BP) responses to standing up and sustained handgrip, and heart rate (HR) responses to the Valsalva maneuver, standing up and deep breathing. These tests have been categorized as sympathetic when control of BP, and parasympathetic when control of HR, is involved (Ewing, 1983; Watkins & Edmonds 1983; Hilsted, 1984). However, since cardiovascular reflex pathways contain both sympathetic and parasympathetic fibers, this conceptualization is not physiologically accurate (Ewing & Clarke, 1986). Additionally, no single test is sufficient to detect ANS impairment (Hilsted, 1984; Ewing & Clarke, 1986; Johnson et al., 1987). Since impairment on two

or more of these cardiovascular reflex tests or other non-invasive ANS function tests correlate well with abnormalities detected by invasive ANS tests (McLeod & Tuck, 1987b), Ewing and Clarke (1986) suggest that the five cardiovascular reflex tests be used together to describe ANS involvement. These tests are described below.

BP Response to Standing

When a person stands, pooling of the blood in the legs causes BP to fall; this is rapidly corrected by a reflexive peripheral vasoconstriction (Ewing & Clarke, 1986). In a normal subject the systolic BP falls less than 10 or 15 mm Hg (Currens, 1948); in persons with orthostatic hypotension the systolic, diastolic, and pulse pressures fall (Johnson et al., 1987) and remain low (Ewing & Clarke, 1986). In severe cases unconsciousness may occur within seconds after standing; in mild cases the BP may fall substantially causing few or no symptoms (Johnson et al., 1987).

To test this cardiac reflex, BP is measured while the subject is lying down, and then one minute after standing up. A fall in systolic pressure of 10 mm Hg or less is normal; a fall of 11-29 mm Hg is a borderline response; a fall of 30 mm Hg or more is abnormal (Ewing & Clarke, 1986). While measuring this response the arm must be extended horizontally when the subject stands to prevent a falsely elevated BP reading (Webster, Newham, Petrie, & Lowell, 1984). An abnormal response is mainly caused by a lack of increase in peripheral vascular resistance upon standing due to denervation of sympathetic vasoconstrictor nerves (Hilsted, 1984). Abnormal responses may also occur in patients taking antihypertensive drugs or other medications,

and persons with adrenal insufficiency and hypovolemia (McLeod & Tuck, 1987b). Finally, lack of activation of the sympathetic nervous system in central nervous system disease my also be responsible (Hilsted, 1984).

BP Response to Sustained Handgrip

During isometric exercise BP increases because of increased cardiac output and increased peripheral vascular resistance in nonexercising limbs (Lind, Taylor, Humphreys, Kenelly, & Donald, 1964). To do this test a subject maintains handgrip at 30 percent of his/her maximum voluntary contraction on a handgrip dynamometer for up to five minutes; the diastolic BP before the handgrip begins and just prior to release is measured (Ewing & Clarke, 1986). A diastolic BP increase of less than 15 mm Hg has been considered indicative of sympathetic neuropathy (Ewing, Irving, Kerr, Wilsmith, & Clarke, 1974). This response is not affected by age (McLeod & Tuck, 1987b). For clinical ANS testing, an increase of 16 mm Hg or more is normal, increases of 11 to 15 mm Hg are borderline, and increases of less than 10 mm Hg are abnormal (Ewing & Clarke, 1986).

HR Response to the Valsalva Maneuver

The Valsalva maneuver is the change in HR that follows brief forced expiration against a closed glottis or mouthpiece. Normally during the forced expiration the BP falls and HR rises; after release the BP rises over the resting value while HR falls (Ewing & Clarke, 1986). The HR response to the Valsalva maneuver depends on vagal control as well as the parasympathetic and sympathetic tone of the heart (Hilsted, 1984). In individuals with ANS damage the BP falls during forced expiration

and returns to normal slowly after release with a compensatory increase in BP or change in HR (Ewing & Clarke, 1986).

To perform the maneuver (Ewing & Clarke, 1986) the subject sits quietly, takes a breath and after a normal expiration blows into an aneroid manometer at 40 mm Hg for 15 seconds. The ratio of the longest beat to beat (R-R) interval at the beginning of the maneuver to the shortest R-R interval during the maneuver is calculated from an electrocardiogram (EKG). The average ratio from 3 successive Valsalva maneuvers gives the final score. The response is age-dependent (McLeod & Tuck, 1987b), but for diagnostic purposes a Valsalva ratio of 1.20 or less is abnormal while a value of 1.21 or more is normal (Ewing & Clarke, 1986).

HR Response to Standing

When a person stands unaided from the lying position there is a rapid increase in HR that reaches a peak about 15 beats after standing followed by a bradycardia at about 30 beats (Ewing & Clarke, 1986). The ratio of the R-R intervals from an EKG corresponding to the thirtieth and fifteenth heart beats following standing is called the 30:15 ratio (Ewing, Campbell, Murray, Neilson, & Clarke, 1978).

This response depends upon both sympathetic and parasympathetic systems; a large increase in HR within 3 seconds after standing excludes vagal neuropathy, while no increase indicates combined parasympathetic and sympathetic neuropathy (Hilsted, 1984). The 30:15 ratio decreases with age (McLeod & Tuck, 1987b). For diagnostic purposes a 30:15 ratio of 1.04 or more is normal, of 1.01-1.03 is borderline, and of 1.00 or less is abnormal (Ewing & Clarke, 1986).

HR Response to Deep Breathing

In healthy persons HR varies with respiration, but in persons with autonomic neuropathy there is either a reduction or absence of HR variation (Ewing & Clarke, 1986). The increase in HR during inspiration is caused by decreased cardiac vagal activity (McLeod & Tuck, 1987b). The magnitude of normal variation, sinus arrhythmia, declines with age (Smith, 1982) and may decrease or disappear in disorders affecting either central or peripheral autonomic pathways (McLeod & Tuck, 1987b).

To test HR variation (Ewing & Clarke, 1986), the subject sits quietly and breathes deeply and evenly at six breaths per minute using 5 seconds to inhale and 5 seconds to exhale while an EKG is recorded. The differences between the maximum (on inspiration) and minimum heart rates (on expiration) from each of three consecutive 10-second cycles are averaged to determine HR variation. Variations of 15 beats/min or more are normal, 11 to 14 beats/min are borderline, and 10 beats or less are abnormal.

Scoring Cardiovascular Reflex Tests

Ewing and Clarke (1986) suggest two methods of classification of severity of ANS dysfunction in individuals. According to the first scheme, normal function requires 5 normal tests or 4 normal tests and one borderline. Early involvement is defined as 1 of 3 HR tests abnormal or 2 borderline. Definite involvement is indicated by 2 or more abnormal HR tests. Severe involvement requires 2 or more HR test abnormalities and 1 or both BP tests abnormal or borderline. An

atypical pattern is any other combination of abnormal tests, but only 6 percent of Ewing's diabetic patients fell into this category.

The second strategy is to give each of the five cardiovascular reflex tests a score of 0, 1, or 2, depending on whether they were normal, borderline, or abnormal, respectively. This allows each test to carry an equal weight in scoring while providing a numerical value. Additionally, this procedure allows for the expression of atypical patterns which may not be present in diabetics but may be present in other populations suffering from ANS disturbances.

SUMMARY AND HYPOTHESIS

Currently, ANS abnormalities have been demonstrated in homosexuals (Lin-Greenberg & Taneja-Uppal 1987; Craddock et al., 1987; Miller, & Semple, 1987), hemophiliacs (Craddock et al., 1987), bisexuals (Evenhouse et al., 1987), and drug addicts (Villa et al., 1987) who are infected with HIV and have other symptoms of HIV infection. Additionally, de la Monte et al. (1988) reported 2 cases of orthostatic hypotension in their study of HIV+ persons with peripheral neuropathy. Further, there is some indication that HIV+ drug addicts may perform abnormally on ANS function tests without showing any overt signs or symptoms of ANS dysfunction (e.g., Villa et al., 1987). This is consistent with findings in other populations with progressive ANS dysfunction (Bannister, 1983; Ewing & Clarke, 1986).

Considering the documented cases of ANS dysfunction in HIV+ persons, evidence suggesting the possibility of early nervous system (both central and peripheral) involvement following HIV infection, the possibility of a clinically silent autonomic neuropathy, and the lack of a study using more formalized ANS testing with an appropriate control group, experimental study of HIV and the ANS is warranted. In particular, one might expect that, as a group, HIV+ persons who do not have AIDS, AIDS-related diseases, or lymphadenopathy to perform more poorly on cardiovascular reflex tests than a group of persons from a demographically similar HIV- control group. Further, since not all HIV+ persons have neurological difficulties, every HIV+ individual would not be expected to have ANS difficulties. Finally, since HIV has been documented to have a number of effects in both the CNS and PNS,

and since abnormalities in cardiovascular reflex tests indicate diffuse autonomic damage throughout the nervous system, isolating a particular pattern of ANS dysfunction is unlikely.

In the following study the cardiovascular reflexes of a group of HIV+ males meeting the CDC criteria for absence of illness were compared to that of a group HIV- homosexual males. The reliabilities of the five cardiovascular reflex tests were also examined. Additionally, subjects completed a medical history, an ANS symptom checklist, the Profile of Mood States, and the Beck Depression Inventory. These measures were used to examine the relationships between the cardiovascular reflex measures, and reports of symptoms, fatigue, and depression.

METHODS

Subjects

Twenty two homosexual or bisexual male volunteers who knew their HIV antibody status (11 HIV+, 11 HIV-) and were between the ages of 23 and 39 were recruited through local community agencies and screened via an initial telephone interview and an HIV/ANS symptom checklist (see Appendix A). All persons with a history of intravenous drug use were excluded from the study. Persons reporting a current respiratory infection, inability to stand or walk unaided, a history of hypertension, diabetes, or consumption of more than two alcoholic beverages daily were excluded from the study. Subjects were not ill or taking prescribed medications at the time of study.

Based on the telephone interview and HIV/ANS symptom checklist, persons who were HIV+ and met the CDC criteria (1986) for absence of illness, were selected for the experimental group. They did not have AIDS and had not been diagnosed with or, to their knowledge, had any AIDS-related illness or had lymph node enlargement lasting over a month. None of the HIV+ subjects had participated in clinical trials for experimental drugs or previously used AZT.

Since a number of the cardiovascular reflex measures are related to age, HIV- subjects were selected so that there was no significant difference in age between groups. HIV- subjects had been tested for antibodies to HIV less than six months prior to participating in the study and, by self-report, had no reason to suspect they were carriers of HIV. Three of these subjects had been tested twice (with the second test at least 6 months after the first).

All subjects were paid twenty dollars for participating and treated in accordance with the "Ethical Principles of Psychologists" (American Psychological Association, 1981).

Materials

Four questionnaires were used: an HIV/ANS symptom checklist (Appendix A), an HIV medical history (Appendix B), the Profile of Mood States, and the Beck Depression Inventory. The HIV/ANS symptom checklist and the HIV medical history were used to place subjects in appropriate groups and for descriptive purposes.

The Profile of Mood States (POMS) measures six mood states: Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigor/Activity, Fatigue/Inertia, and Confusion/Bewilderment. The POMS has 65 adjectives, each of which is rated on a five-point scale (0=not at all, 1=a little, 2=moderately, 3=quite a bit, 4=extremely). A score is obtained for each mood state by summing the responses of the adjectives defining that particular mood state as determined by factor analytic grouping during test construction (McNair, Lorr, & Droppleman, 1971). For this study the 15 Depression/Dejection adjectives were used as a measure of depression, and 7 Fatigue/Inertia adjectives were used as a measure of fatigue.

The Beck Depression Inventory (BDI) was also used (see Beck, Steer & Garbin, 1988). Each of the 21 items on the BDI consists of a series of 4 graded self-evaluative statements. Within each item the statements are ordered to reflect a range of severity for each symptom or attitude from neutral (0) to maximum severity (3). The items measure each of the following symptoms and attitudes: sadness,

pessimism/discouragement, sense of failure, dissatisfaction, guilt, expectation of punishment, self-dislike, self-accusation, suicidal ideation, crying, irritability, social withdrawal, indecisiveness, body image distortion, work retardation, insomnia, fatigability, anorexia, weight loss, somatic preoccupation, and loss of libido (Stehouwer, 1985). To score the BDI, the values (0 to 3) of the most severe statements endorsed within each item are summed.

A sphygmomanometer with a digital printout (Takeda Medical Digital Blood Pressure Meter, Model UA-751), a polygraph machine (Grass Model 7B with Wide Band AC EEG Amplifier Model 7P5B and Polygraph DC Driver Amplifier Model 7DAF) and supplementary supplies required for 3 EKG leads, an aneroid pressure gauge attached to a disposable mouthpiece by a tube, and a stop watch were required for cardiovascular reflex testing. A ruler, calculator, and IBM compatible computer with statistical software were used to analyze results.

Design and Procedure

Following the telephone interview, a two hour testing session was scheduled. Upon arrival subjects were shown the testing facility, given a consent form to sign, and provided with an opportunity to ask questions. The HIV/ANS symptom checklist was administered, again, along with the HIV medical history. Initial HR and BP measurements were made on each arm, and three EKG electrodes were applied. Cardiovascular reflex testing using the method suggested by Ewing and Clarke (1986) followed. Tests were given in the order in which they are described, and the first administration took less than 35 minutes.

HR Response to Valsalva Maneuver. The subject was asked to sit quietly, take a normal breath, expire, and then blow into a tube connected to an aneroid pressure gauge at the pressure equivalent of 40 mm Hg. The subject practiced maintaining this level of Hg for 15 seconds. After the practice session the subjects was asked to sit quietly, inspire, expire and then blow into the tube for 15 seconds while the polygraph was running. When the pressure reached 40 mm Hg, the experimenter started the stopwatch. After 15 seconds the experimenter instructed the subject to "relax." The subject relaxed for a minute before repeating the maneuver. The maneuver was performed 2 more times.

HR Variation During Deep Breathing. While sitting, the subject breathed "slowly and regularly" taking 5 seconds to inhale and 5 seconds to exhale so each breath took 10 seconds. The experimenter prompted the subject every 5 seconds saying "in" when the subject was to inhale and "out" when the subject was to exhale, and marked the polygraph on each inspiration and expiration. Six cycles (a total of one minute) were recorded.

BP Response to Sustained Handgrip. The experimenter measured the subject's resting BP with the sphygmomanometer. Then the subject was given a handgrip dynamometer and asked to squeeze as hard as possible. The experimenter calculated 30 percent of the maximum voluntary contraction and asked the subject to maintain that grip strength until instructed to stop. The experimenter took BP readings just prior to starting and at three minutes. After the reading at the third minute was complete, the subject was instructed to release the grip.

HR and BP Responses to Standing. These two tests were performed simultaneously for convenience and last since they require the subject to stand up. After the subject had been lying down for two minutes, a BP reading was taken from the dominant arm. The polygraph was started and the subject was asked to stand while keeping the arm with the sphygmomanometer cuff parallel to the floor. One minute after standing another BP reading was taken (with the arm parallel to the floor).

Subsequently, the subject completed the POMS and the BDI, in that order, by selecting the answer in each item best describing how they felt over the past week, including the day of the experiment. When the questionnaires were completed, another sitting BP and HR measurement was made on each arm, and the cardiovascular tests were repeated as described above. The second administration took 25 to 30 minutes.

Scoring and Analyses

The HIV/ANS checklist and the HIV medical history were used to ensure that subjects had been correctly assigned to groups and for descriptive purposes. The POMS and BDI were scored conventionally. From the POMS, only the Fatigue/Inertia and Depression/Dejection scale scores were used.

BP and associated HR values (baseline measures, hand grip test, response to standing) were printed out as they were measured. HR values obtained during the cardiovascular reflex testing (Valsalva maneuver, responses to standing and deep breathing) were calculated from the EKG record using a millimeter ruler and calculator according to the method described by Ewing and Clarke (1986, see previous discussion). The experimenter scored and recorded values from each EKG

record twice: The first scoring occurred immediately following each individual testing session. A second blind scoring occurred after all the data had been collected. When the results of the two scorings were compared, there were only three disparate values (one measurement and two calculation errors) and these errors were subsequently corrected.

Mean sitting HR and BP values were determined by averaging the HR and BP pressure values taken prior to each round of cardiovascular reflex testing (i.e., 2 measures from the dominant and 2 measures from the nondominant arm were used). Mean supine HR and BP values were formed by averaging the two measures taken prior to testing the HR and BP response to standing. To elucidate baseline differences between groups that might influence or aid in the interpretation of the cardiovascular reflex test results, t tests were performed on the HR and BP values as well as subject ages.

Test-retest reliability values were calculated for each of the cardiovascular reflex measures. Multivariate Analysis of Variance (MANOVA) was employed to test the significance of group differences on the cardiovascular reflex tests and the self-report measures of depression and fatigue. Variables included in the MANOVA for cardiovascular reflexes were the HR response to Valsalva's maneuver (Valsalva Maneuver), HR variation during deep breathing (Deep Breathing), BP response to sustained handgrip (Hand Grip), and HR and BP responses to standing (HR Stand and BP Stand, respectively). For a given subject, these variables were formed by averaging the two scores obtained from repeated test administration on each cardiovascular reflex test. Variables included in the MANOVA for depression and

fatigue were the scores from the BDI, the Depression/Dejection (Depression) and Fatigue/Inertia (Fatigue) scales of the POMS. The MANOVAs were followed up by univariate tests of significance (t tests).

Each subject's score on each of the five cardiovascular reflex tests was also classified as normal, borderline, or abnormal based on the clinical cutting scores employed by Ewing and Clarke (1986). Subsequently, a chi-squared analysis, using the number of impaired (having an abnormal score on at least one test, or borderline scores on at least two tests) and normal (receiving 5 normal, or 4 normal and 1 borderline test scores) HIV- subjects as the expected values and the number of impaired and normal HIV+ subjects as the observed values was performed.

For exploratory purposes, a correlation matrix was examined. A total of 16 variables were correlated including the descriptive measures (age, sitting resting systolic and diastolic BP, supine resting systolic and diastolic BP, resting sitting and supine HR), the cardiovascular reflex test scores (Valsalva Maneuver, Deep Breathing, Hand Grip, HR Stand, BP Stand) the number of symptoms on the HIV/ANS symptom checklist, and the depression and fatigue self-report measures (BDI, Depression, and Fatigue).

RESULTS

Descriptive Information

Seven HIV+ subjects had a history of other sexually transmitted diseases, while only 3 HIV- subjects did. At the time of study, 5 of the HIV+ subjects smoked (cigarettes-3, marijuana-2), 9 drank alcohol, and 2 used other drugs (cocaine-1, amyl nitrite-1). In the HIV- group, one subject smoked (cigars), 8 drank alcohol, and 1 used other drugs. Four of the HIV+ and 9 of the HIV- subjects engaged in regular aerobic exercise (more than one hour a week).

Excluding the first question, all HIV+ subjects answered two or more questions on the HIV/ANS symptom checklist affirmatively (range 2 to 9), while all HIV- subjects answered "no" to all questions. A summary of the symptoms, the subject numbers of the HIV+ subjects endorsing them, and the overall frequency of each symptom are provided in TABLE 2.

Since there were no missing data, for all statistical analyses, unless otherwise stated, N equals 22 (11 HIV+, 11 HIV- subjects). TABLE 3 reports summary statistics and the results of the t tests on age and the baseline measures of BP and HR. The two groups were not statistically different in age or on baseline measures of BP. However, the HIV+ group had statistically higher HR both while sitting ($t=8.70$; $df=1,20$; $p=.008$) and supine ($t=7.85$; $df=1,20$; $p=.011$).

TABLE 2

HIV/ANS SYMPTOM CHECKLIST: RESPONSES OF HIV+ SUBJECTS

Symptom	Subjects Endorsing	Frequency
Lymphadenopathy	2, 3, 5, 7, 9	5
Fever	3, 9	2
Fatigue	6, 7, 8, 9, 11	5
Weight loss	3, 5, 6, 7, 8, 9, 10	7
Cough	5, 7	2
Dyspnea	3	1
Diarrhea	2, 5, 7	3
Night sweats	3, 5, 7, 8, 9	5
Rash	1, 3, 4, 6, 8, 11	6
Mouth problems	1, 2, 3, 5, 6, 8, 9, 10	8
Anxiety	3, 4, 5, 10	4
Sleep disturbance	3, 7, 8, 11	4
Depression	4, 10, 11	3

TABLE 3

BASELINE MEASURES OF AGE, BP AND HR

Measure	Descriptive Stats			t Test		
	Group	Mean	SD	DF	t	Prob.
Age	HIV+	31	5.6	1,20	.02	.880
	HIV-	31	5.4			
Systolic	HIV+	121	13.1	1,20	1.15	.296
Sitting	HIV-	127	12.3			
Diastolic	HIV+	77	9.9	1,20	.00	.981
Sitting	HIV-	77	7.3			
Systolic	HIV+	119	12.2	1,20	.66	.425
Supine	HIV-	123	10.2			
Diastolic	HIV+	71	7.5	1,20	2.03	.169
Supine	HIV-	67	6.1			
HR	HIV+	78	8.0	1,20	8.70	.008
Sitting	HIV-	66	10.9			
HR	HIV+	71	6.6	1,20	7.85	.011
Supine	HIV-	60	10.2			

Within the descriptive variables, there were significant correlations between mean sitting systolic and diastolic BP (r=.36, p=.052), mean supine systolic and diastolic BP (r=.43, p=.022), sitting and supine systolic BP (r=.78, p<.000) and sitting and supine diastolic BP (r=.64, p=.001). Mean sitting and supine HR were also significantly correlated (r=.88, p<.000).

Cardiovascular Reflex Tests

The test-retest reliabilites and levels of significance for the cardiovascular reflex tests by group (HIV+, HIV-) are shown in TABLE 4. Reliabilities for Valsalva Maneuver, Deep Breathing, Hand Grip, and HR Stand were all significant; the reliabilities for BP Stand were not. In subsequent statistical analyses the cardiovascular reflex scores from the test and retest were averaged into a single score.

The group main effect for the overall MANOVA on the cardiovascular reflex tests scores was not statistically significant using an alpha level of .05 (Wilks lambda=.58181; approximation of F=2.30; df=5,16; p=.094). Of the five subsequent univariate tests, two were significant (see TABLE 5). The HIV+ group had relatively poorer scores on both Valsalva Maneuver (t=4.46; df=1,20; p=.047) and BP Stand (t=4.72; df=1,20; p=.042). The univariate test for Hand Grip approached significance (t=3.40; df=1,20; p=.080).

TABLE 4

CARDIOVASCULAR REFLEX TESTS: TEST-RETEST RELIABILITIES

Measure	HIV+	HIV-
Valsalva Maneuver	.77*	.80**
Deep Breathing	.68*	.65*
Hand Grip	.84**	.84**
HR Stand	.81**	.93**
BP Stand	.51	.32

Note. * = significant at .05 level (tabled value=.62);

** = significant at the .01 level (tabled value=.79);

significance values are those for two-tailed tests.

TABLE 5

CARDIOVASCULAR REFLEX MEASURES

Measure	Descriptive Stats			t Test		
	Group	Mean	SD	DF	t	Prob.
Valsalva Maneuver	HIV+	1.29	.118	1,20	4.46	.047
	HIV-	1.43	.182			
Deep Breathing	HIV+	23.4	7.1	1,20	.02	.884
	HIV-	23.8	5.9			
Hand Grip	HIV+	16.9	9.9	1,20	3.40	.080*
	HIV-	28.9	19.2			
HR Stand	HIV+	1.30	.225	1,20	1.97	.175
	HIV-	1.45	.277			
BP Stand	HIV+	-9.4	9.5	1,20	4.72	.042
	HIV-	-1.7	6.9			

Note. * = group variances not homogeneous (Cochran's C).

Examination of the correlation matrix revealed that HR Stand was the only variable correlated with other variables in the group of cardiovascular reflex tests. The correlation values and probabilities were as follows: Valsalva Maneuver r=.38, p=.040; Deep Breathing r=.52, p=.007; Hand Grip r=.37, p=.047; and BP Stand r=.49, p=.011. For the descriptive variables and cardiovascular reflex test scores there were significant correlations between mean sitting HR and Valsalva Maneuver (r=-.52, p=.006), HR Stand (r=-.50, p=.009), and BP Stand (r=-.37, p.=.045). Mean supine HR was correlated with Valsalva Maneuver (r=-.50, p=.009), Hand Grip (r=-.39, p=.037), and HR Stand (r=-.44, p=.020). Mean sitting systolic BP was correlated with BP Stand (r=.41, p=.030).

Individual Subject Results

Subject's average scores (average of test and retest scores) on each of the five cardiovascular reflex tests are presented in TABLE 6. Borderline and abnormal scores, based on the cutting scores employed by Ewing and Clark (1986), are indicated in TABLE 6 (borderline by ^{b}, abnormal by ^{a}). It made no difference whether individual test scores (test or retest) or the average of the two scores was used to lable subjects as borderline or normal. The individual categorization was the same in all cases.

Based on these categorizations each subject was classified as impaired (having an abnormal score on at least one test, or borderline scores on at least two tests) or normal (receiving 5 normal, or 4 normal and 1 borderline test scores). Impaired subjects are indicated on TABLE 6 by a * following the subject number. By these criteria,

TABLE 6

INDIVIDUAL CARDIOVASCULAR REFLEX SCORES

Subject	Valsalva Maneuver	Deep Breathing	Hand Grip	HR Stand	BP Stand
1+*	1.13[a]	13[b]	19	1.17	1
2+	1.32	23	30.5	1.21	-11.5[b]
3+	1.38	19.5	20	1.31	-8.5
4+	1.41	33.5	17	1.67	4.5
5+	1.31	30.5	16	1.31	-13.5[b]
6+*	1.14[a]	15	18	.96[a]	-22.5[b]
7+*	1.12[a]	19	11[b]	1.07	-7
8+*	1.37	26	-6[a]	1.3	-10
9+*	1.23	28	9[a]	1.6	2
10+	1.45	18	22.5	1.17	-25.5[b]
11+	1.37	32	28.5	1.56	-12.5[b]
1-	1.43	21.5	24.5	1.21	-13[b]
2-	1.51	28	35	1.41	7.5
3-	1.58	26.5	10.5[b]	1.06	-9
4-	1.33	27	19	1.07	2.5
5-	1.32	14[b]	23.5	1.46	-5
6-	1.55	19.5	22	1.52	1
7-	1.21	32.5	15.5	1.8	.5
8-	1.34	16.5	78	1.57	-7.5
9-	1.44	21	14	1.39	8
10-	1.83	31.5	46	1.97	2.5
11-*	1.20[a]	24	29.5	1.52	-6.5

Note. *=impaired, [a]=abnormal, [b]=borderline

1 HIV- subject was impaired and 10 were normal; of the HIV+ subjects, 5 were impaired and 6 were normal. Based on the frequency of impairment of the HIV- group, the frequency of impairment in the HIV+ subjects was significantly greater than expected (chi-square=17.6, df=1, $p<.01$).

Of the 5 impaired HIV+ subjects, 2 had histories of other sexually transmitted diseases (1+, 8+), 2 smoked (cigarettes-7+, marijuana-8+), 4 drank alcohol (1+, 6+, 7+, 9+) , one used other drugs (cocaine-1+), and 2 engaged in regular aerobic activity (1+, 9+). In addition to the ANS symptoms reported in TABLE 2, the impaired subjects reported memory loss (1+, 8+, 9+), frequent headaches with recent onset (1+, 6+, 9+), and periodic leg cramps (6+, 8+). Unimpaired subjects also had complaints of memory loss (3+, 5+, 11+) and headaches (3+, 5+), but not of leg cramps.

Depression and Fatigue Differences

The group main effect in the MANOVA for depression and fatigue measures was statistically significant (Wilks lambda=.42591; approximation of F=8.08; df=3,18; p=.001). Of the three subsequent univariate tests, two were significant (see TABLE 7). The HIV+ group had higher scores on both the BDI (t=14.98; df=1,20; p=.001) and POMS Fatigue (t=6.01; df=1,20; p=.024). POMS Depression was not significant.

TABLE 7

DEPRESSION AND FATIGUE MEASURES

Measure	Descriptive Stats			t Test		
	Group	Mean	SD	DF	t	Prob.
BDI	HIV+	11.4	6.5	1,20	14.98	.001*
	HIV-	3.0	2.0			
Depression (POMS)	HIV+	10.5	10.6	1,20	.53	.473
	HIV-	7.9	5.5			
Fatigue (POMS)	HIV+	10.7	6.7	1,20	6.01	.024*
	HIV-	5.3	3.2			

Note. * = group variances not homogeneous (Cochran's C).

The small number of impaired (5) and unimpaired (6) HIV+ subjects precluded further statistical analysis of differences between these subgroups. However, for descriptive purposes, the means (M) and standard deviations (SD) were as follows: BDI-impaired M=14, SD=8.1; unimpaired M=9.2, SD=4.3. POMS Depression-impaired M=15, SD=13.9; unimpaired M=6.8, SD=6.3. POMS Fatigue-impaired M=13.4, SD=6.7; unimpiared M=8.5, SD=6.3. The number of items endorsed on the HIV/ANS symptom checklist was the same in each of these subgroups: impaired M=5, S.D.=2; unimpaired M=5, S.D.=2.4.

The depression and fatigue measures were significantly correlated: BDI and POMS Fatigue ($r=.75$, $p<.001$), BDI and POMS Depression ($r=.67$, $p<.001$), and POMS Fatigue and POMS Depression ($r=.50$, $p=.009$). There were also significant correlations between the number of symptoms reported on the HIV/ANS checklist and the BDI score ($r=.78$, $p<.001$) and POMS Fatigue ($r=.50$, $p=.009$), but not POMS Depression. Both the BDI scores and the number of symptoms on the HIV/ANS checklist correlated with the sitting (BDI $r=.45$, $p=.018$; ANS $r=.49$, $p=.011$) and supine (BDI $r=.42$, $p=.026$; ANS $r=.52$, $p=.007$) resting HR. Additionally, the BDI score correlated with BP Stand ($r=-.46$, $p=.015$), and the number of items endorsed on the HIV/ANS checklist correlated with Valsalva Maneuver ($r=-.35$, $p=.052$) and Hand Grip ($r=-.41$, $p=.028$).

DISCUSSION

Cardiovascular Reflex Changes

In this study 45 percent (5 of 11) of the HIV+ subjects were impaired on cardiovascular reflex tests. These results suggest that HIV+ persons who meet the CDC (1986) criteria for absence of illness may have cardiovascular reflex abnormalities. Additionally, consideration of the group differences on reflex test performance, individual test scores, and patterns of individual performance across tests suggest that ANS dysfunction in HIV+ persons is not a unitary entity.

Although the cardiovascular reflex measures themselves, with the exception of BP Stand, are fairly reliable, they are not highly correlated. Thus, while these measures may correlate with other measures of ANS function, these five cardiovascular reflex test do not measure the same underlying processes.

Though findings of this study suggest ANS dysfunction, the underlying pathology cannot be elucidated for a number of reasons. First, both the sympathetic and parasympathetic systems, which make up the ANS, have central and peripheral pathways. The sympathetic system has origins in the thoracolumbar spine, and the parasympathetic has cranial and sacral origins (Johnson et al., 1987). McLeod and Tuck (1987a) provide a straightforward account of these systems which is summarized in the following paragraphs.

The sympathetic nervous system's main control center is in the hypothalamus, but there are also connections to the bulbar reticular formation, cingulate gyrus, cerebral cortex, amygdala, and other

structures. The descending pathways of this system synapse with the cells of the intermediolateral columns which extend from thoracic vertebra one to lumbar vertebra two; there is progressive loss of these intermediolateral cells with increasing age. The sympathetic axons leave the spinal cord via the ventral roots and join the PNS made up of white and gray rami, sympathetic paravertebral and other ganglia. Preganglionic fibers are myelinated and synapse in the ganglia; postganglionic fibers are unmyelinated and run to visceral structures or with peripheral nerves to blood vessels (in muscle and skin) and to sweat glands. In the sympathetic nervous system the preganglionic fibers are cholinergic, and the postganglionic fibers are mostly noradrenergic.

The parasympathetic nervous system is also under the control of the hypothalamus and other suprabulbar centers. Fibers from this portion of the ANS exit the CNS either from the brainstem via the third (oculomotor), seventh (facial), ninth (glossopharyngeal), and tenth (vagus) cranial nerves, or the sacral portion of the spinal cord through the second, third and fourth sacral nerves. The ganglia in the parasympathetic system lie closer to the innervated structures than the ganglia of the sympathetic system resulting in shorter postganglionic fibers. Both pre- and postganglionic fibers in this system are cholinergic.

Second, there are complex interactions between the sympathetic and parasympathetic system and other systems. For example, the regulation of BP (see Feuerstein, Labbe & Kuczmierczyk, 1985) depends not only on sympathetic and parasympathetic activity, but also the circulatory,

respiratory, and endocrine systems, and many interactions (e.g., neuronal, hormonal) between these systems. Third, HIV is an infectious agent which disrupts functions in many systems. For example, changes in the cardiovascular system could also alter cardiovascular reflex function, and recently Levy, Simon, Rios, and Ross (1989) reported that 36 percent (9 of 25) HIV+ persons who did not have AIDS had cardiac abnormalities. Thus, different patterns of cardiovascular reflex abnormalities may very well reflect different patterns of HIV involvement.

Depression and Fatigue Differences

Based on the BDI scores alone, one might conclude that HIV+ subjects are more depressed than HIV- subjects. However, further consideration suggests that this interpretation is an oversimplification. Several points have merit here. First, though 3 HIV+ subjects said they were depressed (see TABLE 2), the remaining 8 said they were not depressed. Second, differences between groups on POMS Depression did not reach statistical significance. Third, HIV+ persons have reason to be preoccupied with somatic issues, and HIV+ subjects in this study all had other symptoms that are probably related to HIV infection. Finally, HIV+ subjects were significantly more fatigued that HIV- subjects. Thus, differences between the two groups are probably not strictly attributable to a depressive mood or despair. HIV+ subjects have more reason to worry about their health, have mild symptoms of illness, and experience greater fatigue than HIV- subjects. Differences in fatigue and depression between HIV+ persons who are and are not impaired on cardiovascular reflex tests remain to be examined.

There is also some evidence to suggest that the depression, fatigue, and somatic measures are related to cardiovascular reflex scores. The BDI score correlated with BP Stand, and the number of items endorsed on the HIV/ANS checklist correlated with Valsalva Maneuver and Hand Grip. Interestingly, these were the same variables that were significant (Valsalva Maneuver, BP Stand) or approached significance (Hand Grip) when group differences on cardiovascular reflex tests were examined. However, given the small sample size and the low reliability of BP Stand, these findings must be viewed as tenuous. Finally, the fact that the depression and fatigue measures employed in this study were highly correlated further tempers interpretation of findings.

Other Differences

In comparison to the HIV- subjects, HIV+ subjects had elevated sitting and supine HR rates. This difference could be related to pathophysiology. For example, elevated mean resting HR has been associated with vagal damage, and been reported in diabetics with parasympathetic abnormalities and in alcoholics with other evidence of vagal neuropathy (Johnson et al., 1987). Hypovolemia also might increase HR without altering BP. Additionally hypovolemia is one cause of abnormalities in BP response to standing (McLeod & Tuck, 1987b), and in this study the HIV+ group had a poorer response than the HIV- group.

On the other hand, HIV- subjects may exercise more and thus have a lower resting HR (see Feuerstein, Labbe, & Kuczmierczyk, 1985) or there may have been a situational increase in "resting HR" in HIV+ subjects attributable to 'the significance of the situation' (Duffy, 1972, p.

595) since participation in this experiment probably had a different psychological meaning to the HIV+ subjects. The finding of a relatively higher resting HR without concomitant changes in BP remains to be replicated and, if replicated, explained.

Additionally, there were more smokers, drug users, and persons with a history of other sexually transmitted diseases in the HIV+ group. However, 3 nonsmokers, 3 subjects who did not use drugs, and 3 subjects without a history of other sexually transmitted diseases had cardiovascular reflex abnormalities. Thus, though other etiologies cannot conclusively be ruled out, the most parsimonious explanation for the findings of cardiovascular reflex abnormalities in the HIV+ subjects in this study is that the reflex abnormalities are related to the presence of HIV.

Finally, although subjects in the HIV+ group met the CDC (1986) criteria for absence of illness, they all had more than one complaint on the HIV/ANS symptom checklist. Thus, this group fits that CDC criteria for "absence of illness" by exclusion in that subjects were HIV+ and had not been diagnosed with lymphadenopathy, AIDS-related diseases, or AIDS. Therefore the presence of a truly "clinically silent" ANS dysfunction without any ANS symptoms cannot be addressed by this study. However, HIV+ subjects in this study were relatively healthy in comparison to the HIV+ persons previously reported to have ANS dysfunction (no opportunistic infections or intravenous drug use). Still, 45 percent of these subjects were impaired.

Summary and Research Directions

HIV+ persons who do not have AIDS, AIDS-related illness, or lymphadenopathy may have cardiovascular reflex abnormalities. This has several implications. First, these HIV+ persons with ANS involvement run the risk of syncopy or cardiorespiratory arrest during invasive medical procedures or stressful events. Second, the presence of symptoms such as disordered sweating, diarrhea, and fatigue in HIV+ individuals could be related to ANS neuropathology, though this relationship remains to be demonstrated.

Further, as Villa et al. (1987) suggested, cardiovascular reflex abnormalities may be an early indicator of neurological involvement in HIV+ persons. However, the type of involvement has yet to be described, and the determinants, correlates and prognostic value of this involvement remain to be elucidated. Villa et al. also suggested that one might find signs of autonomic neuropathy before the clinical manifestations of HIV infection appear. This was not confirmed in this study since subjects, despite "absence of illness", did have symptoms, albeit mild ones, that could be attributed to ANS involvement.

Craddock et al. (1987, p. 18) suggested that "if effective antiviral therapy is developed, measurement of autonomic function may provide an objective and non-invasive indicator of disease activity and response to treatment in some patients." Perhaps in the future this utility will be demonstrated. However, in the meantime, there is much to learn about HIV's actions in the ANS. Considering the complexity of the ANS and the multiple manifestations of HIV infection, this promises to be a challenging task. Still, research in this area may contribute

to our understanding of ANS function, the pathology of HIV infection, and lead to better care for HIV+ patients.

APPENDIX A:

HIV/ANS SYMPTOM CHECKLIST

Have you ever received a positive result on a blood test for AIDS virus antibodies?

In the last 3 months have you noticed any persistent lumps or swelling in your neck, jaw, or armpits?

In the last 3 months have you had any fevers that lasted for more than a week?

In the last 3 months have you experienced any period of more than a week when you were so tired that you could not go to work or perform your normal activities?

In the last 3 months have you lost any weight without meaning to?

In the last 3 months have you notice any period of more than a week when you had a persistent, strong, dry cough?

In the last 3 months have you noticed any period of more than a week when you got severely short of breath during normal activities such as walking across a room?

In the last 3 months have you noticed any period of more than a week when you had watery diarrhea every day?

In the last 3 months have you had any episodes of sweating so heavily at night that you soaked the bed sheets?

APPENDIX A

In the last 3 months have you noticed any unusual or persistent skin conditions?

In the last 3 months have you noticed any problems in your mouth such as sores, coating on your tongue, bleeding gums, or a persistent, unpleasant taste?

In the last 3 months have you noticed any periods of time when you found yourself worrying about AIDS so much that you could not concentrate on other things, or worrying so much that you noticed symptoms such as sweating, rapid pulse, chest pains, upset stomach, or headache?

In the last 3 months have you noticed any change or disturbance in your normal sleep pattern?

In the last 3 months have you noticed any significant change in your general mood?

APPENDIX B

HIV MEDICAL HISTORY

Subject Number_____
City_____ # Years_____ Education_____

SEX M F AGE_____ DOB___/___/___ RACE_____

Risk group_____ Diagnosis: NEG ASX PGL ARD FBA

Support Systems: organizations_____
home: lives alone___ w/s.o.___ w/family___ other___

Family History self or family member / age onset/ descrip
Diabetes_____
Hypertension_____
Cardiovascular_____
Allergies_____
Asthma_____
TB_____
Cancer_____
Seizures_____
Arthritis_____
MS_____
SLE_____
Other_____
_____

Disease History
Date of test ___/___/___ Acute (flu, mono) ___/___/___
HIV+ partner ___/___/___ SX onset ___/___/___

Symptoms:			Days/Mo w/sx	
Fever	Y	N	_____	
Night Sweats	Y	N	_____	
Nausea/Vomiting	Y	N	_____	
Thrush	Y	N	_____	
Lymphadenopathy	Y	N	_____	
Fatigue	Y	N	_____	
Diarrhea	Y	N	_____	# stools/day_____
Weight Loss	Y	N	_____	norm wt____ wt now____
Appetite Loss	Y	N	_____	Special Diet_____

Meals/day_____
Sleep Pattern _____ Naps/day _____

APPENDIX B

Infection/Cancer History

	Date/Rx		Date/Rx
Kaposi's Sarcoma	_____	Gonorrhea	_____
Pneumocystis	_____	Syphilis	_____
Herpes Simplex	_____	Aspergillus	_____
Herpes Zoster	_____	Giardia	_____
Candidiasis	_____	Trichomiosis	_____
Hepatitis	_____	Chlamydia	_____
Cocci	_____	Nocardia	_____
Cytomegalovirus	_____	Toxoplasmosis	_____
Cryptosporidiosis	_____	Histoplasmosis	_____
Epstein Barr Virus	_____	MAI	_____
Mononucleosis	_____	Meningitis	_____

Recreational Drug Use

1=never
2=1/year
3=monthly
4=weekly
5=daily

marijuana	_____	amphetamines	_____
cocaine	_____	IV drugs	_____
nitrites	_____	alcohol	_____
opiates	_____	other_____	_____

Current Medications

Medicine	Dose	Schedule	Date Started

Other treatments (vitamins, relaxation, hypnosis, etc.)

_____
_____
_____
_____

APPENDIX B

Patient Complaints

HEENT: lymph nodes, sore throat, mouth ulcers/lesions

SKIN: itching, dryness, rashes, ulcers, moles, vesicles, nodules, lesions

RESP: SOB, DOE, cough, hemoptysis, sputum, sinus problems
smoker? amt_____

CARD: HTN, chest pain, pressure, stiffness, palpitations, fainting, peripheral edema

GI: anorexia, nausea, vomiting, hematemesis, diarrhea, constipation, blood/mucous in stool, abd pain, perianal ulcers/fissures, loss of bowel control

GU: dysuria, UTIs, hesitancy, kidney stones, pyelonephritis, hematourea, loss of bladder control

MUS/SK: arthritis, joint-swelling, pain, stiffness

PAIN: location:_____
duration:_____
alleviation:_____

NEURO: vision, blind spots, floaters, seizures, dizziness, weakness, headaches, memory loss, confusion, numbness/tingling in extremities, strength, coordination

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