CLINICAL MICROBIOLOGY REVIEWS, Oct. 2004, p. 942–964 Vol. 17, No. 4
0893-8512/04/$08.00+0 DOI: 10.1128/CMR.17.4.942–964.2004

Role of Microglia in Central Nervous System Infections

R. Bryan Rock, Genya Gekker, Shuxian Hu, Wen S. Sheng, Maxim Cheeran, James R. Lokensgard, and Phillip K. Peterson*

Neuroimmunology Laboratory, Minneapolis Medical Research Foundation, and University of Minnesota Medical School, Minneapolis, Minnesota

"Inflammatory processes of any nature are soon to be manifested in the reaction of microglia. In cases of meningitis and meningoencephalitis the microglia of the affected areas undergoes changes corresponding to the early stages of mobilization and phagocytic intervention." Pio del Rio-Hortega (97)

INTRODUCTION

Historical Background

The early years of research on the nature of microglia, the resident macrophages of the nervous system, are noteworthy for the remarkable insights of many illustrious anatomists and neuropsychiatrists (reviewed in reference 300), including Gluge (who in 1841 identified phagocytic cells of mesodermal origin in the damaged brain), Virchow (who in 1846 observed phagocytes ["foam cells"] contributing to a disease process termed congenital encephalitis), His (who in 1890 described amoeboid mesodermic corpuscles which entered the developing brain of human embryos in the second month, colonized both grey and white matter, and emitted protoplasmic radiations), Nissl (who in 1899 suggested that glial cells in the brain have similar functions to macrophages in other tissues), Robertson (who in 1900 distinguished "neuroglia" and "mesoglia," the latter cells, derived from mesoderm, displaying phagocytic activity in pathological conditions such as chronic brain degeneration), Alzheimer (who in 1904 believed that glial cells became amoeboid in certain acute infections and were destined to combat the infection), and Cajal (who in 1913 recognized mesoglia as the "third element" of the central nervous system [CNS]). However, it was the Spanish neuroanatomist Pio del

* Corresponding author. Mailing address: Department of Medicine, Hennepin County Medical Center, 701 Park Ave., Minneapolis, MN 55415. Phone: (612) 873-2877. Fax: (612) 904-4299. E-mail: peter137@umn.edu.

Rio-Hortega who in 1932 earned the title "father of microglia biology." He was the first to demonstrate (in 1919 to 1922) that mesoglia were composed of microglia, which are of mesodermal origin, and oligodendroglia, which, along with astroglia and neurons, are of neuroectodermal lineage. In his classic treatise published in 1932 (97), Rio-Hortega framed a "modern conception of microglia" that remains relevant to this day.

Following this era of vigorous scientific inquiry, the field of research on microglia experienced an eclipse that lasted half a century. Over the past 15 years, however, a phenomenal reawakening of interest has erupted (a Medline search reveals more than 1,800 articles published during this period with the term "microglia" in the title). This rebirth of interest is due in no small part to the recognition of the role of microglia in neurodegenerative disorders, such as human immunodeficiency virus (HIV)-associated dementia (HAD) and, ironically, the disease named after one of the earliest researchers, i.e., Alzheimer disease. During this same period, a number of reviews have appeared on various aspects of microglia biology (10, 27, 122, 194, 200, 224, 262, 264, 273, 278, 340, 341, 343, 350). With the exception of articles focusing on HIV, however, the literature on the role of microglia in defense against and pathogenesis of CNS infections has not been critically evaluated; such an evaluation is the principal aim of this review. It is also the intent of this review to highlight concepts that have been evolving in recent years, such as the pivotal role of microglia in innate immunity of the nervous system, the controversy over the protective versus destructive activities of activated microglia, and the tropism of certain microorganisms for microglia versus macroglia (astrocytes and oligodendrocytes) and neurons.

Definition, Derivation, and Distribution

The term "microglia" refers to cells that reside within the parenchyma of the nervous system, that share many if not all the properties of macrophages in other tissues, but that in their nonactivated or resting state have a characteristic "ramified" morphology not seen in resident macrophages of other organ systems. Although microglia are "brain macrophages," they are distinguished by their parenchymal location and certain functional differences from other types of brain macrophages such as meningeal and perivascular macrophages (264, 290, 291) and perivascular cells or pericytes (351, 376), which are enclosed by a perivascular basement membrane within blood vessels and are not part of the CNS parenchyma.

The origin of microglia was a matter of intense controversy in Pio del Rio-Hortega's day (97). Although it is still a somewhat contentious issue, most authorities now agree on the correctness of his concept of mesodermal glial cells invading the parenchyma during embryonic development followed by the ingress of bone marrow-derived blood monocytes in the postnatal period (89, 172, 224). Thus, microglia are currently regarded as members of the "mononuclear phagocyte system." Another of his concepts that has withstood the test of time is that of three phases of microglia reflecting their plasticity: an amoeboid phase found in the fetus, a ramified (resting) phase found in the nervous system framework, and a third phase of recovery of amoeboid properties and motility "necessary for active discharge of their macrophagic function" (97).

As Rio-Hortega recognized, the penetration and migration of microglia takes place very quickly, and postnatally, microglia are to be found in every location within the nervous system (97). Often not appreciated, however, is the fact that the brain is composed primarily of glial cells. While about 15% of the cells in the brain are neurons, it is estimated that microglia are found in roughly equivalent numbers (341). In a recent study of the local density of microglial cells in the normal adult brain, ramified microglia bearing markers such as CD68 and major histocompatibility complex (MHC) class II antigen were found to be more concentrated in white matter than in grey matter, and significant regional differences were observed, with microglia ranging from 0.5 to 16.6% of all the cells within various areas of the brain parenchyma (250). Grey matter of the cerebellum had the lowest density of microglia, while the highest level of CD68- and MHC class II-positive cells was found in the medulla.

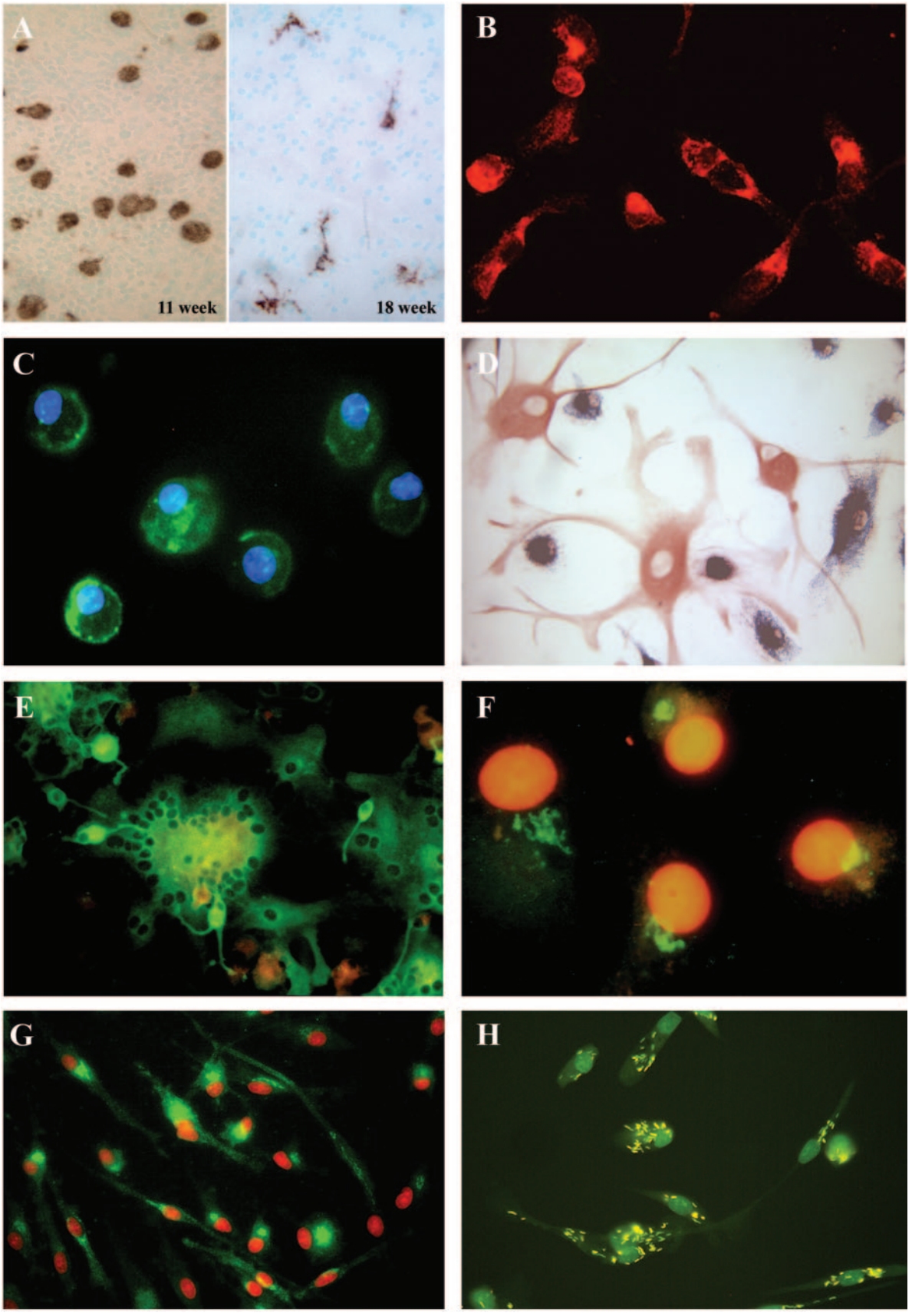
Consistent with the concept of Rio-Hortega (97), amoeboid, ramified, and reactive microglia are currently viewed as different forms of a single cell type. Amoeboid microglia are active macrophages during development and are precursors of resting or ramified cells, which can, in response to a variety of insults such as infection, traumatic injury, or ischemia, reactivate in the postnatal brain, assume an amoeboid shape, and move to the site of injury (350). Early in human fetal brain development, microglia are mainly amoeboid in appearance, whereas by 18 weeks of gestation, a ramified morphology predominates (Fig. 1A). Consistent with the ability of these cells to assume an amoeboid morphology, upon isolation and culture, a homogenous population of amoeboid microglia can be obtained for in vitro studies (Fig. 1B and C).

Astrocytes are the predominant cell type within the CNS, and astroglia-microglia interactions appear to play an important role in microglial cell biology. For example, in vitro studies have shown that blood monocytes and amoeboid microglia develop branching processes when layered on astrocytes, suggesting that astrocytes induce the morphology of resting or ramified microglia (301, 307). Moreover, amoeboid and even fully ramified microglia have been shown to migrate rapidly when seeded on a confluent layer of astrocytes (307). Although astrocytes differ morphologically (Fig. 1D) and functionally from microglia, the two glial cell types appear to act in concert as the intrinsic immune system of the CNS (326).

FUNCTIONS OF MICROGLIA

Ramified (Resting) Microglia

The term "glia," derived from the Greek word for "glue," suggests that microglia share with astroglia and oligodendroglia the property of brain support and, more particularly, the support of neurons. However, such a supportive role in the healthy brain is better appreciated for astroglia, which make important contributions to neurotransmitter metabolism, and for oligodendroglia, which are the source of myelin, than for ramified (resting) microglia. While it seems likely that ramified microglia also contribute to the well-being of neurons, this "neuronocentric" view may underestimate the importance of neuronal support of microglia. Nonetheless, amoeboid microglia are thought to have a crucial scavenger function in the


A
11 week
18 week
B
C
D
E
F
G
H

developing brain by removing the large number of cells in the neocortex that die in the course of normal remodeling of the fetal brain (364). Scavenger receptors have been identified on neonatal murine microglia, whereas this class of cell surface protein is not detected on microglia in postnatal mouse or normal human adult brain (163). Further evidence of a supportive role of microglia has been shown in the facial nerve axotomy paradigm, in which the recovery of injured neurons is dependent on the trophic function of activated microglia (264, 340).

Activated Microglia

As already mentioned, certain cell surface markers of importance in immune regulation, such as MHC class II molecules, are constitutively expressed on ramified microglia in the normal adult brain (250). However, in response to a variety of CNS insults such as microbial invasion, ramified microglia have the capacity not only to dramatically change their morphology to reactive or amoeboid forms but also to rapidly up-regulate a large number of receptor types and produce a myriad of secretory products that are thought to contribute to the defense of and, potentially, damage to the infected brain.

The state of microglial activation represents a continuum that is reflected by in vitro studies, with relatively minor changes being observed just in the process of preparing and culturing amoeboid microglia, which express CD14 (Fig. 1C), a marker not found in ramified microglia. At the far end of the activation spectrum, marked alterations are seen following stimulation with microbial products such as lipopolysaccharide (LPS). Because activated microglia are regarded as a pivotal cell in both defense against and immunopathogenesis of infections and inflammatory diseases of the CNS, numerous in vitro studies of the regulatory factors involved in microglial activation have been reported (reviewed in reference 260), and in recent years, techniques to identify activated microglia in vivo have been applied to studies of various pathological conditions (23, 24, 371).

Cell membrane receptors. As already mentioned, immune recognition molecules, such as MHC class II, can be identified on ramified (resting) microglia in the undisturbed brain (250). Relatively few studies of other cell membrane receptors involved in immune responses have been carried out with ramified microglia. However, activated microglia have been the focus of many studies, and in this functional phase they have been shown to express a number of such receptors, e.g., members of the immunoglobulin superfamily, complement receptors, cytokine/chemokine receptors, and Toll-like receptors (TLRs) (Table 1). In addition to MHC class I and II glycoproteins and costimulatory molecules (269, 385), a population of microglia that have properties of dendritic cells may arise during infectious and inflammatory conditions (110). It has been suggested that these dendritic cell-like microglia may present antigens to Th1 lymphocytes and thereby participate in chronic inflammation of the nervous system (110).

TABLE 1. Microglial cell membrane receptors[a]

Scavenger receptors
Cell adhesion molecules
Immunoglobulin (Ig) superfamily
Ig Fc receptors (FcγRI, RII, RIII)
MHC class I glycoproteins
MHC class II glycoproteins
CD4 receptors
Intercellular adhesion molecule 1 (ICAM-1)
Integrins
Leukocyte function-associated antigen 1 (LFA-1; CD11a/CD18; CR1)
Mac-1 (CD11b/CD18; CR3)
p150, p95 (CD11c/CD18; CR4)
Complement receptors: C1q, C5a
Cytokine/chemokine receptors
IFN-α, IFN-β, IFN-γ
IL-1, IL-6, IL-10, IL-12, IL-16
TNF-α
M-CSF, GM-CSF
CCR, CXCR, CX3CR
Toll-like receptors
CD14 receptors
Mannose receptors
Purinogenic receptors
Opioid receptors (μ, κ)
Cannabinoid receptors
Benzodiazepine receptors (mitochondrial membrane)

[a] Receptors reported in the literature, whose expression may be influenced by the state of activation as well as by the anatomic location, age, and animal species from which the microglia are derived.

Not only do microglia contribute to acquired immune responses through their interactions with $CD4^+$ and $CD8^+$ lymphocytes which enter the nervous system during infection or inflammation, but also they are a key cell in the innate immunity of the nervous system (264). In this regard, activated microglia have been demonstrated to express TLRs (54, 184, 264), CD14 (280), and mannose receptors (228), all of which play a role in recognition of so-called pathogen-associated molecular patterns, such as LPS of the gram-negative bacterial cell wall and peptidoglycan and teichoic acid of the gram-positive bacterial cell wall.

Little is known about the signals that induce the transformation of microglia from an amoeboid to a ramified form, although cytokines such as granulocyte-macrophage colony-

FIG. 1. Human microglia. (A) Microglial cells in fetal brain tissue at 11 weeks' gestation are predominantly amoeboid in shape (left panel), whereas by 18 weeks they have assumed a ramified morphology (right panel) (stained with anti-CD68 antibodies, a macrophage marker). (B and C) Microglia in cell cultures isolated from 18-week fetal brain tissue have assumed an amoeboid morphology (CD68 antibody positive) (B) and up-regulate CD14 antigen (a marker not seen in nonactivated ramified microglia) (C). (D) A double-stained mixed culture of microglia (anti-CD68 antibody positive, dark blue) and astrocytes (anti-GFAP antibody positive, red) from 18-week fetal brain tissue shows differences in morphology and size. (E) Microglial cell cultures infected for 14 days with HIV-1 assume a multinucleated giant cell morphology (stained with anti-p24 antigen antibodies, green). (F and G) LPS (100 ng/ml)-stimulated microglial cell cultures express intracellular CXCL8/IL-8 (green) (F) and intracellular CXCL10/IP10 (green) (G). (H) Microglial cell cultures are shown after 18 h of incubation with nonopsonized *M. tuberculosis* H37Rv (tubercle-to-cell ratio, 10:1) (auramine-rhodamine stain).

TABLE 2. Secretory products of microglia[a]

Cytokines (IL-1α, IL-1β, IL-6, IL-10, IL-12, IL-16, IL-23, TNF-α, TGF-β)
Chemokines
CC: CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, CCL5/RANTES
CXC: CXCL8/IL-8, CXCL9/MIG, CXCL10/IP-10, CXCL12/SDF-1α
CX3C: CX3CL1/fractaline
Matrix metalloproteinases (MMP-2, MMP-3, MMP-9)
Free radicals: superoxide, nitric oxide
Eicosanoids: PGD_2, leukotriene C_4
Growth factors: nerve growth factor, fibroblast growth factor
Proteases: elastase, plasminogen
Cathepsins B and L
Quinolinic acid, glutamate
Amyloid precursor protein
Complement factors: C1, C3, C4

[a] Secretory products reported in the literature, whose generation is influenced by the state of activation as well as by the anatomic location, age, and animal species from which the microglia are derived.

stimulating factor (GM-CSF) can do so in vitro (278). Similarly, the mechanism underlying the change in morphology from a ramified to an activated or amoeboid form is poorly understood. However, Rio-Hortega had determined more than half a century ago that amoeboid microglia were capable of migrating in a directed fashion toward areas of brain injury and, once there, "discharge their macrophagic function" (97). A major contribution of the recent renaissance of research on microglia has been an understanding of the critical role of cytokine/chemokine receptors (Table 1) and their cognate ligands (Table 2) in directing the migration and the activation of microglial cells, topics that have been reviewed elsewhere (17, 19, 86, 94, 112, 143, 149, 171, 173, 196, 338).

Insights into the functional consequences, both physiological and pathophysiological, of up-regulation in activated microglia of cytokine/chemokine receptors and their ligands have emerged from a variety of in vitro and in vivo paradigms of infection, as well as neuroinflammatory and neurodegenerative disorders. Although much remains to be learned, it appears that these receptors and their ligands not only contribute to shaping the development of the normal fetal brain (84, 187, 300) but also may be involved in infection-related neurodevelopmental damage (154).

So far, activated microglia have been shown to express many of the receptors and ligands belonging to the three major chemokine families, i.e., the CC (5, 6, 12, 26, 41, 76, 96, 116, 125, 147, 156, 169, 239, 257, 283, 327–329, 333, 334), CXC (5, 6, 12, 75, 96, 102, 103, 169, 298, 334), and CX_3C (40, 77, 83, 145, 221, 246, 265) families (Tables 1 and 2). Many of these receptors and chemokines can also be expressed in astrocytes, suggesting that chemokines may serve as communication signals between microglia and astrocytes; it has been proposed that CX_3CR1 and its ligand (CX_3CL1/fractaline), which are also expressed in neurons (40, 77, 83, 145, 221, 246, 265), play an important role in neuronal signaling of microglia.

While chemokines modulate many functions of microglia in addition to chemotaxis, other members of the cytokine superfamily appear to contribute most importantly to their state of activation. Activated microglia can express receptors and the cognate ligands for both proinflammatory, e.g., interleukin-1 (IL-1) (73, 179, 217, 240, 259, 278), IL-6 (217, 259, 295), IL-12 (11, 31, 272, 337), IL-16 (320), IL-23 (198), and tumor necrosis factor alpha (TNF-α) (67, 179, 217, 240, 259, 295), and anti-inflammatory, e.g., transforming growth factor β (TGF β) (88, 292) and IL-10 (190, 211, 377), classes of cytokines (Tables 1 and 2). The role of these cytokines in CNS infections is discussed more fully later in this review, but it is important to note that although microglia possess receptors for and can be activated by alpha, beta, and gamma interferons (IFN-α, IFN-β, and IFN-γ), it appears that microglia are incapable of generating appreciable quantities of these critical activating cytokines.

ATP is a major factor mediating intercellular communication in the immune and nervous systems, and recent studies have shown that microglia possess purinigenic receptors (268, 362), whose stimulation markedly affects a number of microglial cell functions, such as chemotaxis and cytokine production, that are involved in defense as well as brain damage (165). Since ATP is considered to be the dominant extracellular messenger for astrocyte-to-astrocyte communication, it has been proposed that ATP may also serve a similar function in astrocyte-to-microglial cell communication (362).

Recent studies have shown that activated microglia can express receptors such as opioid receptors of the μ (72) and κ (65) classes, cannabinoid receptors (365), and peripheral-type benzodiazepine receptors (212), whose stimulation affects a number of functional activities of microglia involved in the pathogenesis of infections of the nervous system (63, 69, 157, 159, 160, 203, 215, 216, 279, 281). It has been postulated that these receptors may be activated not only by endogenous opioids and cannabinoids but also by plant derivatives, e.g., opium and cannabis, and drugs that target these same receptor sites.

Secretory products. As already noted, activated microglia release a number of cytokines/chemokines that, through paracrine and autocrine actions, contribute to both defense against and neuropathogenesis of CNS infections. In addition to these mediators, a number of other secretory products of activated microglia, which can contribute to immunologic and inflammatory processes, have been described (Table 2). Of these, matrix metalloproteinases (MMPs) have been recognized most recently for their potential role in blood-brain barrier (BBB) breakdown, leukocyte emigration into the nervous system, and tissue destruction. MMPs are a family of zinc-dependent enzymes capable of degrading proteins found in the extracellular matrix, and a rapidly growing literature related to CNS infections, neuroinflammatory/neurodegenerative disorders, and hypoxic, traumatic, or toxic insults of the nervous system has shown that activated microglia can secrete MMP-2, MMP-3, and MMP-9, as well as the their natural inhibitors, in response to a variety of stimuli (14, 36, 85, 124, 135, 136, 164, 210, 218, 222, 231, 305, 306, 384).

Generation by microglia of free radicals, such as reactive oxygen intermediates (ROIs) and reactive nitrogen intermediates (RNIs), has been regarded as an important mechanism both of defense of the nervous system against intracellular microorganisms and, when these toxic molecules are released into the extracellular milieu, of potential damage to neurons. Microglia isolated from rat brains were initially recognized in 1987 to release the ROI superoxide on stimulation with phorbol myristate acetate or opsonized zymosan (81), and in vitro

studies of murine (161), swine (158), and human (280) cells have demonstrated that activated microglia from all three of these species share the capacity to produce superoxide. Animal species differences, however, appear to prevail in the generation of the RNI nitric oxide (NO) by microglia. While microglia isolated from rat and mouse (167, 256) brains yield substantial amounts of NO when activated, the picture is less clear for human microglial cells. On stimulation with cytokines and LPS, human microglia release little or no appreciable NO (47, 99, 168, 282), a finding which is consistent with the hyporesponsiveness of the human inducible NO synthase (iNOS) gene reported for other populations of human mononuclear phagocytes.

MICROGLIA-MICROBE INTERACTIONS

Early observations demonstrating a poor alloreactive response to tissue engraftment within the CNS led to the concept of the brain as an "immunologically privileged" organ. Characteristics of the healthy brain that support this notion include a BBB composed of highly specialized endothelial cells and astrocytes that limit the passage of leukocytes and immune mediators from the circulation into the CNS, a relatively low level of expression of MHC class I and II molecules, and the absence of resident lymphocytes within the brain parenchyma. Nonetheless, the brain is routinely and effectively surveyed by the immune system (151), and when one considers the number of microglia within the parenchyma of the nervous system, which function as intrinsic immune effector cells, the CNS may be more properly regarded as a specialized immune organ.

Despite what appears to be a marvelous strategy for keeping microbes out of the brain parenchyma, when looked at from the perspective of the large number of viruses, bacteria, fungi, parasites, and proteinacious pathogens that are "neurotropic," i.e., that have a predilection for infecting the nervous system (Table 3), the brain could be considered an "immunologically underprivileged" organ. Thus, an evolving concept of microglia is that when it comes to defense of the CNS against invading microorganisms, they do not function on their own but rely on their ability to "call in the troops," i.e. lymphocytes, monocytes, and neutrophils. In the sections that follow, literature is reviewed which highlights what is currently viewed to be the role of microglia and their allies in defense against and pathogenesis of infectious disease agents.

TABLE 3. Neurotropic infectious agents

Viruses	*Borrelia burgdorferi*
Retroviruses	*Nocardia asteroides*
HIV	*Leptospira*
Human T lymphotropic virus type 1	*Brucella*
Herpes group	*Rickettsia*
HSV	*Mycoplasma*
CMV	*Ehrlichia*
Epstein-Barr virus	Parasites
Human herpesvirus 6	*Cysticercus*
B virus	*Toxoplasma gondii*
Enteroviruses	*Trypanosoma*
Polioviruses	*Entamoeba histolytica*
Coxsackieviruses	Free-living amebas
Echoviruses	*Echinococcus*
Arboviruses	*Schistosoma*
Rabies virus	*Angiostrongylus cantonesis*
Mumps virus	*Gnathostoma spinigerum*
Lymphocytic choriomeningitis virus	Fungi
Measles virus	*Cryptococcus neoformans*
Rubella virus	*Coccidioides immitis*
Nipah virus	*Histoplasma capsulatum*
Hendra virus	*Blastomyces dermatitidis*
JC virus	*Candida*
	Zygomycetes
	Aspergillus
Bacteria	*Sporothrix schenckii*
Mycobacterium tuberculosis	
Treponema pallidum	Prions

[a] Human pathogens that have the capacity to invade, multiply, and elicit a pathologic response within the brain parenchyma. This list does not include the bacteria that most commonly cause meningitis and brain abscesses or the parasite *Plasmodium falciparum*, which is the cause of CM.

Viruses

Human immunodeficiency virus. HAD is characterized by cognitive, behavioral, and motor deficits ranging from mild disease to profound dementia. Since the introduction of highly active anti-retroviral therapy, the incidence and prevalence of HAD have decreased dramatically (229). A considerable amount of attention has been focused on the factors involved in the development of HAD over the last 20 years, and the neuropathogenesis of HIV has been extensively reviewed elsewhere (120, 132, 262, 274, 379). A key element in the development of HAD appears to be infection of mononuclear phagocytes with HIV-1, including infection of microglial cells, which are the only brain cell type that is productively infected with this virus. It has also become clear that neurotoxic mediators released from brain macrophages/microglia play a pivotal role in HIV-1 neuropathogenesis.

HIV-1 enters the CNS early after infection (90), and productive replication and macrophage invasion occur years later and only in certain individuals (274). Microglia are the principal target for HIV-1 (82, 178, 373) and HIV-2 (254) in the brain, although there is limited evidence of infection in neurons, oligodendrocytes, and astrocytes (9, 267, 310, 355). This low level infection in astrocytes may serve as a reservoir of HIV (245, 353). Although parenchymal microglia are actively infected (8, 82), some have suggested that the more specific targets for HIV-1 are perivascular macrophages or infected monocytes infiltrating the CNS (90, 111, 285, 378, 379), and these cells have been implicated as a possible mechanism for HIV-1 entry into the CNS (90, 185). HIV-1-infected microglia are primed by HIV-1 (266), demonstrate cytopathic features and form multinucleated giant cells, but are not necessarily killed by the virus (205). Infected microglia harbor viral particles intracellularly, reflecting their potential as a reservoir (379). When histopathological features of HAD have been examined, the number of activated microglia and macrophages in the CNS is a better correlate with HAD than is the presence and amount of HIV-1-infected cells in the brain (131), and microglial activation is a better correlate of neuronal damage than is productive HIV-1 infection in the CNS (2). These observations demonstrate the importance of activated microglia/macrophages in HIV-1 neuropathogenesis.

HAD is associated pathologically with HIV-1 encephalitis. HIV-1 encephalitis is characterized by multinucleated giant

cell formation, microglial nodules, and macrophage infiltration into the CNS (274). Multinucleated giant cell formation is mirrored by HIV-1 infection of microglia in vitro (Fig. 1E). Active infection of microglia is ultimately associated with astrogliosis, myelin pallor, and neuronal loss (274).

HIV-1 can enter the microglial cell via CD4 receptors and chemokine coreceptors such as CCR3, CCR5, and CXCR4 (147, 186), with CCR5 being the most important of these (7, 323). Interestingly, humans with double allelic loss of CCR5 are virtually immune to HIV (311). IL-4 and IL-10 enhance the entry and replication of HIV-1 in microglia through up-regulation of CD4 and CCR5 expression, respectively (368). The chemokines CCL5/RANTES, CCL3/MIP-1α, CCL4/MIP-1β, all of which bind to CCR5, are inhibitory to HIV-1 replication in microglial cells, apparently by their ability to block viral entry (177, 327). GM-CSF and macrophage-colony stimulating factor (M-CSF) stimulate the production of these β-chemokines but actually inhibit the antiviral properties of these chemokines when added to microglial cell cultures (327).

One interesting discrepancy noted in HIV-1 encephalitis is the limited number and localization of HIV-1-infected microglia in comparison to the diffuse CNS abnormalities that occur in HAD (205). This paradox suggests that diffusible factors that are released from macrophages and microglial cells are contributing to neuronal loss. It has become more and more apparent that HIV-1-infected microglia and macrophages actively secrete both endogenous neurotoxins such as TNF-α (266), IL-1β (18), CXCL8/IL-8 (382), glutamate (170), quinolinic acid (150), platelet-activating factor (123), eicosanoids (266), and NO (1), as well as the neurotoxic viral proteins Tat (263), gp120 (46), and gp41 (1). In addition to inducing neurotoxicity, these viral proteins can affect microglial cell function (148, 322). The chemokine CX_3CL1/fractaline appears to be neuroprotective against gp120 neurotoxicity (246). At least one of these neurotoxic mediators, TNF-α, can be inhibited in vitro by pentoxifylline, dexamethasone, or thalidomide (67, 276, 284), and insulin-like growth factor 1 protects neurons from TNF-α-induced damage (383). Infected microglia can also enhance the recruitment of additional microglia and macrophages to the site of infection by inducing endothelial cells to produce adhesion molecules and by release of CCL2/MCP-1, CCL3/MIP-1α, and CCL4/MIP-1β (205, 262, 275). Although the initial stimulus for secretion of neurotoxins appears to be microglial activation by HIV-1 or viral proteins, interactions with astrocytes, neurons, and monocytes may regulate this secretion (38, 205). Furthermore, microglia may require a secondary trigger, such as opportunistic organisms, neoplasms, cytokines, and CNS-specific regulatory elements, to bolster secretion of these neurotoxic factors (205). Ultimately, the complex interactions among activated microglia/macrophages, astrocytes, and neurons trigger the onset and progression of CNS damage. Despite a large body of evidence pointing to a neuropathogenic role of activated microglia in the development of HAD, recent data have suggested some neuroprotective capabilities of microglia, at least in early-stage HIV disease (137, 358).

Overall, microglia are the principal target of HIV-1 in the brain parenchyma, and when activated by HIV-1 or viral proteins, they secrete or induce other cells to secrete neurotoxic factors; this process is accompanied by neuronal dysfunction or apoptosis. Although HIV-1-associated CNS injury is a complex process and probably involves numerous pathways and neurotoxic agents, it is clear that activated microglia contribute greatly to this neuropathogenic process.

Cytomegalovirus. Human cytomegalovirus (HCMV) causes congenital encephalitis and encephalitis in patients with AIDS, but is rare in other immunocompromised individuals (15). Sequelae of HCMV encephalitis include cognitive deficits, delirium, cranial nerve palsies, ataxia, and death (330). In patients with advanced AIDS, CNS infection due to HCMV results in two distinct neuropathological patterns: microglial nodular encephalitis and ventriculoencephalitis (138), which in turn have distinct clinical manifestations. Micronodular encephalitis consists of diffuse microglial cell syncytia, aggregates of astrocytes, and cytomegalic cells. Although the clinical importance of HCMV-related micronodular formation is unknown, it was initially implicated as an important cause of HCMV-associated dementia in AIDS patients. The second major type of HCMV encephalitis, ventriculoencephalitis, is a necrotizing infection of the ependyma and subependymal layers, but focal necrosis may also be found deep in the brain parenchyma. Most cases of rapidly progressing HCMV brain disease appear to manifest as ventriculoencephalitis. The current state of knowledge regarding the pathogenesis of HCMV encephalitis is based largely on clinical features and postmortem studies, which reflect the final stages of disease progression. More recent work has evaluated the role of glial cell-mediated defenses against HCMV.

Key cells in the defense against HCMV include microglia and T lymphocytes (76, 297). There is evidence that murine CMV (MCMV) productively infects murine microglia and that IFN-γ suppresses this infection (319). In the human CNS, however, HCMV appears to infect primarily astrocytes and ultimately leads to cell destruction (153, 213, 235), although neuroepithelial precursor cells and differentiating neurons are permissive to HCMV infection, suggesting that the fetal CNS is especially vulnerable to HCMV-induced injury (233, 289). HCMV-infected astrocytes in turn secrete chemokines, primarily CCL2/MCP-1, that recruit microglial cells to the area of infection (76). Microglia, however, do not show signs of productive infection or cytopathic changes (213). Nonetheless, microglial cells, but not astrocytes, produce the antiviral cytokine TNF-α, which suppresses HCMV replication in astrocytes (76). Nonproductive infection of human microglial cells also elicits the production of the T-lymphocyte chemoattractant CXCL10/IP-10, which then recruits T lymphocytes to the area of infection (75). These activated T lymphocytes can then secrete IFN-γ, which also inhibits HCMV replication in astrocytes (74). The anti-inflammatory cytokines IL-10 and IL-4 inhibit this T-lymphocyte recruitment process, as does the HCMV-derived cmvIL-10 (180), which is a viral analogue of human IL-10. This viral analogue therefore demonstrates a mechanism for HCMV to negatively impact the antiviral capabilities of human microglia.

Infection with HCMV may impact coinfection with other agents, such as HIV. Early studies explored the relationship of HCMV to AIDS-related dementia. From these earlier evaluations, HCMV infection does not appear to contribute significantly to HAD (294, 366). However, the HIV entry coreceptor CCR5 is suppressed in astrocytes, microglia, and monocyte-

derived macrophages infected with HCMV (189). In monocyte-derived macrophages this process impaired HIV infection, although in astrocytes and microglia this was not apparent. In contrast, HCMV superinfection in astrocytes infected with certain strains of HIV actually increased p24 production, suggesting a stimulatory effect on HIV expression (234).

In summary, productive infection of astrocytes by HCMV appears to initiate a cascade of events that ultimately facilitates the antiviral activities of both microglial cells and activated T lymphocytes. This process can be diminished by anti-inflammatory cytokines as well as by HCMV gene products.

Herpes simplex virus. Herpes simplex virus (HSV) causes a devastating CNS infection in neonates and immunocompetent adults, which results in acute focal necrotizing encephalitis with severe neuroinflammation and swelling of the brain (214). Despite reductions in mortality with the use of acyclovir or vidarabine therapy, fewer than 20% of patients with herpes encephalitis recover without significant long-term neuropathologic manifestations (237, 331). The mechanisms responsible for the sequelae following herpes encephalitis appear to involve both direct virus-mediated damage and indirect immune-mediated processes. During herpes encephalitis in both humans and experimental animal models, the virus load in the cerebrospinal fluid or brain tissue does not correlate well with the severity of structural damage or clinical findings (372). Studies have shown that long-term neuroimmune activation and cytokine production persist after HSV infection in patients (16) and after experimental infections in mice (59, 141, 247, 324, 325). These studies suggest that herpes encephalitis and its neuropathologic sequelae are related at least in part to an inflammatory process within the CNS.

Human HSV encephalitis has been modeled in rats experimentally by inoculation of virus in peripheral nerves (105, 370). HSV moves along peripheral neurons, achieving widespread distribution in the brain by days 8 to 10 postinfection. Granulocytes, T lymphocytes, and monocytes/microglia infiltrate the sites of infection early. Microglial cells express increased MHC class I and class II glycoproteins and have a wide distribution throughout the brain, including areas separate from the productive infection. In some instances, this focal microglial cell reaction remains for several weeks (105).

Productive viral infection by HSV is observed in cultures of purified primary human astrocytes as well as neurons and is ultimately cytopathic in both cell types (217). Despite a productive infection, unlike HCMV infection, neither of these cell populations produces chemokines or cytokines in response to HSV. In contrast, human microglial cells infected with HSV provide only limited replication followed by a rapid decline in infectious virus. This is associated with high levels of both the immediate-early antigen ICP4 and reporter gene expression (LacZ) from recombinant viruses, and a minority of infected microglial cells display late viral antigen (nucleocapsid) expression (217). Despite limited viral replication, cytopathic effects are evident in HSV-infected microglia, with death mediated through an apoptotic pathway. Additionally, microglia produce considerable amounts of TNF-α, IL-1β, CXCL10/IP-10, and CCL5/RANTES, together with smaller amounts of IL-6, CXCL8/IL-8, and CCL3/MIP-1α, in response to nonproductive infection. TNF-α inhibits HSV replication in astrocytes (217), and CXCL10/IP-10 inhibits replication in vivo (223) and in neurons (217).

Cytokine-induced neurotoxicity may be a mechanism underlying HSV-related CNS damage. Cytokines produced by microglia are toxic to neurons (61, 66, 68, 71). Although microglia-derived cytokine toxicity has not been elucidated completely as a mechanism for CNS damage as a result of HSV infection, activated microglial cells in HSV encephalitis patients do persist for more than 12 months after antiviral treatment (58).

Overall, productive HSV infection occurs primarily in astrocytes and neurons, and activated microglia appear to be involved both in inhibition of viral replication and in neurotoxicity. The contrasting forms of viral encephalitis produced by the herpesviruses CMV and HSV demonstrate the dual nature of microglia: they contribute to the defense of the CNS but may also bear responsibility for CNS damage.

Bacteria

Lipopolysaccharide. *Neisseria meningitidis* and *Haemophilus influenzae* are the most important causes of gram-negative bacterial meningitis. The major component of the outer membrane of the gram-negative bacterial cell wall, LPS (302), is a potent stimulus of many secretory products of microglia including cytokines (TNF-α, IL-1β, and IL-6), chemokines, and prostaglandins (4, 67, 260) and often has been used for activation of microglia in vitro (260). Examples of microglial cell stimulation by LPS include the induction of the chemokines CXCL8/IL-8 (Fig. 1F) and CXCL10/IP-10 (Fig. 1G). Although astrocytes are capable of cytokine production (278), microglial cells are substantially more responsive to LPS than are astrocytes (195). In contrast to microglial cells from adult brain tissue (357), amoeboid microglial cells express CD14 receptors, which, along with TLR4 (183), are the main plasma membrane binding sites for LPS-induced cytokine expression (117). Although LPS has been used as a classic activating agent, a recent study of rat microglia demonstrated that prolonged LPS exposure induces a distinctly different activated state from that in microglia acutely exposed to LPS (4). The microglial cells demonstrated a degree of adaptation to repetitive exposure to LPS, with diminishing TNF-α and NO, but persisting prostaglandin E_2 (PGE_2) production. Interaction between TLR4 and TLR2 may play a role in this adaptive response (183). These observations imply that microglia possess a level of plasticity when faced with bacterial products, which may ultimately affect the resolution of brain inflammation.

***Streptococcus pneumoniae*.** *Streptococcus pneumoniae* is the most common and most serious cause of bacterial meningitis, with a mortality rate of 30% and neurologic sequelae in 30 to 50% of survivors (101, 287). *S. pneumoniae* meningitis is localized primarily to the subarachnoid space, but cytokines and chemokines are produced by cells lining the brain side of the BBB (313), most probably by microglia and astrocytes. Also, intracerebral edema, which is a major cause of death and sequelae in *S. pneumoniae* meningitis, may result from inflammatory processes triggered by intraparenchymal glia (313). Investigations into the role of microglial cells as the source of neuronal damage in pneumococcal meningitis have centered on murine and rat models.

The contribution of activated microglia to defense against the pneumococcus is probably similar to that for other infectious agents, i.e., functioning in the initial immune response and recruitment of cells of the peripheral immune system (neutrophils, monocytes, and T lymphocytes) to the site of infection. Since pneumococci can cross the BBB (303), microglia may respond directly to intact bacteria or to pneumococcal cell wall. In the murine model, the pneumococcal cell wall induces microglia to produce TNF-α, IL-6, IL-12, keratinocyte-derived chemokine, CCL2/MCP-1, CCL3/MIP-1α, CXCL2/MIP-2, and CCL5/RANTES, as well as soluble TNF receptor II, a TNF-α antagonist (144). The induction of these inflammatory mediators involves activation of the extracellular signal-regulated protein kinases 1 and 2 (ERK-1 and ERK-2) mitogen-activated protein kinase intracellular signaling pathway (144). The implications of this profile of cytokine release by microglia include recruitment of leukocytes into the CNS for the purpose of defense, as well as inflammatory mediator-induced neuronal damage. With the influence of IFN-γ produced by T lymphocytes that have entered the brain, the chemotactic profile shifts from favoring neutrophils to a preferential recruitment of monocytes and T lymphocytes (146), which is also seen during the clinical course of bacterial meningitis.

Neuronal damage in the rat model is caused at least partially by the production of NO by activated microglia and astrocytes, which is greatly attenuated by dexamethasone in vitro (176). More recent work suggests that permanent loss of neurons by the induction of apoptosis in the dentate gyrus of the hippocampus probably contributes to the poor outcome of pneumococcal meningitis (43, 386). Although neuronal apoptosis is triggered in part by the inflammatory process via caspase activation, pneumococci can also directly induce apoptosis in primary rat hippocampal and cortical neurons and in human microglial and neuronal cell lines (44). The proposed mechanism involves the release of apoptosis-inducing factor, leading to rapid and massive damage to neuronal mitochondria (44). Additional studies identified several pathogenic factors unique to *S. pneumoniae* that are involved in mediation of this apoptotic process. These include the exotoxins hydrogen peroxide (H_2O_2) and the pore-forming molecule pneumolysin, which induces apoptosis via translocation of intracellular calcium and apoptosis-inducing factor (45). Either pneumolysin or H_2O_2 is sufficient to trigger mitochondrial damage and apoptosis in vitro, and inactivation of these toxic mediators effectively prevents this damage (45).

***Staphylococcus aureus*.** Brain abscesses are a serious CNS infection, accounting for 1 in every 10,000 hospital admissions in the United States (354). The most common etiologic agents of brain abscesses in humans are *Streptococcus milleri* and *Staphylococcus aureus* (230). A limited number of studies have addressed the factors involved in the acute CNS response to these organisms. An in vivo murine model of experimental brain abscess demonstrated that *S. aureus* leads to the rapid and sustained expression of numerous proinflammatory cytokines and chemokines (174). It also underscored the importance of both the neutrophil-attracting chemokine CXCL1/Gro-α and neutrophils in the acute host response to *S. aureus* in the CNS (174).

As immune effector cells of the brain, microglia facilitate neutrophil recruitment into the CNS. This was demonstrated by recent work of Kielian et al. (175) showing that murine microglia have bactericidal activity against *S. aureus* and that *S. aureus* is a potent inducer of TNF-α, IL-1β, and CXCL1/Gro-α gene expression in microglia. Also, a number of microglial cell genes were suppressed, including those for CXCR4, mannose receptor, and tissue inhibitor of metalloproteinase 2 (175). The findings by these authors also suggest that intact *S. aureus* and peptidoglycan boost TLR1, TLR2, TLR6, and CD14 expression in murine microglia, which may serve to augment microglial activation during CNS infection (175).

***Mycobacterium tuberculosis*.** CNS tuberculosis accounts for 1 to 10% of all cases of tuberculosis and clinically manifests as meningitis or intraparenchymal infection (tuberculoma); it carries a high mortality (87, 197). The causative agent in most cases is *Mycobacterium tuberculosis*, which appears to enter the subarachnoid space via rupture of an adjacent parenchymal tubercle rather than by hematogenous spread (197) as is seen in acute bacterial meningitis.

The limited research on microglial interactions with *M. tuberculosis* has focused on the mechanisms of ingestion and the factors that influence this process. A distinctive characteristic of *M. tuberculosis* is its capacity to enter and replicate within macrophages. Human microglial cells are productively infected with *M. tuberculosis* and may in fact be the principal cell target in the CNS (87, 280). In our laboratory we have found that challenge of purified human microglia and astrocytes is associated with selective infection of microglia by *M. tuberculosis* (Fig. 1H). We also have found that ingestion of nonopsonized *M. tuberculosis* by human microglia is facilitated by the CD14 receptor (280), although this appears not to be the case with human monocyte-derived macrophages (321). This receptor, along with the β_2-integrin CD-18 and TNF-α, is also involved in the formation of histologically characteristic multinucleated giant cells by porcine microglia infected with *M. bovis* (277).

A recent study demonstrates that human microglia are more efficient at ingesting *M. tuberculosis* than virulent and avirulent strains of *M. avium* and that following infection with *M. tuberculosis*, there is a significant, lasting inhibition of both IL-1 and IL-10 production (87). The authors suggested that mycobacterial infection induces immunosuppressive effects on microglial cells, which is more evident with more virulent species.

Examination of external influences on *M. tuberculosis* uptake by microglial cells has been limited. Although opiate addiction has been identified as a risk factor for clinical tuberculosis, treatment of human fetal microglial cell cultures with morphine stimulates the phagocytosis of nonopsonized *M. tuberculosis* through an interaction with G-protein-coupled receptors on microglial cells (281). It was suggested that such a phenomenon could favor the intracellular growth of tubercle bacilli.

***Borrelia burgdorferi*.** Lyme disease has been associated with inflammatory damage within the CNS. However, little work has been done on the role of microglial cells in neuroborreliosis. Rasley et al. demonstrated that *Borrelia burgdorferi* stimulates the production of IL-6, TNF-α, and PGE_2 by murine microglia (296). This effect was also shown to be associated with an increased expression of TLR2 and CD14, which are receptors known to underlie spirochete activation of other immune cell types. Their conclusion was that microglia are a source of inflammatory mediators following challenge with *B.*

burgdorferi and that this phenomenon may play an important role during the development of neuroborreliosis.

***Nocardia asteroides*.** An in vitro study examining murine microglia and astrocytes showed that *Nocardia asteroides* productively infects astrocytes but not microglia after phagocytosing the organism (30). In the course of a lethal infection, there appears to be a propensity for growth within the soma of neurons and their axonal extensions, and there is evidence of demyelinization and axonal degeneration. It is postulated that this compartmentalization of nocardiae within neurons could contribute to their failure to induce an inflammatory response or a cytopathic effect (29). Overall, the role of microglia may simply be in clearing the organism in nonlethal infections.

Fungi

***Cryptococcus neoformans*.** *Cryptococcus neoformans* is a ubiquitous, opportunistic fungus that has a pronounced predilection for the CNS, which is less likely to be the result of tissue tropism than the result of the ability of cryptococci to grow unimpeded in the CNS. Defending the CNS against this microbe requires both innate and adaptive immunity. $CD4^+$ T lymphocytes are critical to the anticryptococcal capability of the murine CNS (152), and perivascular macrophages and microglial cells appear to cooperate in this defense against *C. neoformans*. Murine studies support this hypothesis by demonstrating that lymphocyte-mediated resistance to *C. neoformans* brain infection occurs through interactions with $CD4^+$ T lymphocytes and replenishable perivascular macrophages that lie in close proximity to cerebral vasculature (3). Although T lymphocytes may augment the antifungal activity of parenchymal microglia via stimulation with inflammatory cytokines such as IFN-γ, expression of MHC class II on parenchymal microglia does not appear necessary for effective anticryptococcal activity. This observation argues that direct lymphocyte-yeast interactions, independent of MHC class II restriction, are not an important means of host resistance to *C. neoformans* in vivo.

In addition to the interaction of perivascular macrophages with T lymphocytes, the phagocytic role of microglia has been established. Microglia can ingest and inhibit the growth of *C. neoformans* (39, 192). Porcine (201) and murine (39) microglia ingest nonopsonized cryptococci, but opsonization is required for human microglia to ingest cryptococci (192, 203), and the ingested yeast can eventually lyse the microglial cell (193). Enhanced phagocytosis and killing of cryptococci by IFN-γ-stimulated microglia has been established in vitro in experiments with murine cells (39), but even though cryptococcal growth is arrested, actual killing of the cryptococcus does not occur in human microglia, even with the addition of IFN-γ (204). This animal species-related difference appears to be associated with the relatively inefficient generation of NO by cytokine-activated human microglia compared to that by murine microglia (64, 282).

In the absence of specific antibody, *C. neoformans* fails to elicit a chemokine response, but in the presence of specific antibody, human microglia produce CCL3/MIP-1α, CCL4/MIP-1β, CCL2/MCP-1, CXCL8/IL-8, and low levels of CCL5/RANTES via Fc-receptor activation (133). The cryptococcal polysaccharide component glucuronoxylomannan (GXM) does not induce a chemokine response even when specific antibody is present, and it actually inhibits CCL3/MIP-1α induction associated with antibody-mediated phagocytosis of *C. neoformans* (133). The authors of this study hypothesize that GXM-specific antibody complexes elicit different signals from those due to *C. neoformans*-specific antibody complexes and that soluble GXM found in the brain and cerebrospinal fluid of patients with cryptococcal meningoencephalitis may elicit an immunosuppressive effect by inhibition of chemokine production by microglia. Interestingly, GXM also elicits CXCL8/IL-8 production by human microglia but effectively blocks migration of neutrophils into the CNS (202).

C. neoformans elicits a wide range of tissue inflammatory responses, and there is evidence that this variability is due to both host immune status (191) and attributes of fungal cells, including the polysaccharide capsule and phenotypic switching (134). Granulomatous inflammation is the tissue response usually associated with control of infection (191), although in most AIDS patients, cryptococcal meningoencephalitis is associated with minimal inflammation (13).

In addition to antifungal therapy, other agents have demonstrable effects on cryptococcal-microglial cell interactions. Uptake of cryptococci by human microglia is enhanced by morphine via both μ-opioid receptors and complement receptors (203), whereas morphine suppresses porcine microglial uptake of cryptococci (335). Also, chloroquine enhances the anticryptococcal activity of the murine microglia-derived cell line BV2 in vitro (232).

Parasites

***Toxoplasma gondii*.** Toxoplasmic encephalitis (TE) is a condition that affects AIDS patients as well as other immunocompromised individuals with defective cell-mediated immunity. In AIDS patients, TE is most often due to reactivation of latent infection, resulting in disruption of tissue cysts followed by proliferation of tachyzoites. This breakdown in the containment of latent cysts probably stems from impaired T-cell immunity as well as impaired IFN-γ production (258). A comprehensive review of host resistance to *Toxoplasma gondii* infections of the brain has been provided by Suzuki (344). Briefly, $CD8^+$ T cells, $CD4^+$ T cells, and NK cells work in concert with resident cell populations of the CNS, including microglia, astrocytes, and neurons, to suppress the proliferation of *T. gondii* tachyzoites in the CNS, primarily through the actions of IFN-γ. Furthermore, both host genetic factors and *T. gondii* strain differences play a role in the development of TE. Murine microglia, as well as astrocytes, neurons, and oligodendrocytes, are susceptible to infection with tachyzoites, and all but oligodendrocytes produce latent cysts after infection with bradyzoites (109). In the rat model, intracerebral replication of *T. gondii*, as well as spontaneous conversion of tachyzoites to bradyzoites, occurs primarily within neurons and astrocytes. Activated microglia appear to effectively inhibit growth (219).

Microglia are major effector cells in the prevention of *T. gondii* tachyzoite proliferation in the brain. Previous studies by our laboratory have shown that both murine (62) and human (64) microglia inhibit the proliferation of tachyzoites following treatment with IFN-γ plus LPS. NO mediates the inhibitory effect of activated murine microglia on intracellular replication

of tachyzoites. Simultaneous treatment of microglia with IFN-γ plus LPS and *N*G-monomethyl-L-arginine, which blocks the production of NO, abrogates their antitoxoplasmic activity (62). Furthermore, IFN-γ plus TNF-α inhibits *T. gondii* multiplication in a dose-dependent manner and TGF-β suppresses this antitoxoplasmic activity of murine microglia by interfering with NO generation (70, 278). Freund et al. (115) reported that murine microglia stimulated by IFN-γ and TNF-α inhibited *T. gondii* replication via both an NO-dependent and a separate IFN-γ-dependent mechanism. This separate mechanism was not associated with the creation of ROIs or degradation of tryptophan. Deckert-Schlüter et al. (91) reported that murine microglia are activated primarily through IFN-γR signaling pathways in vivo and that production of TNF-α by murine microglia is strictly dependent on IFN-γ. Using experimental knockout mice, they concluded that signaling through TNFR1 provides the required stimulus for protective NO production (92). They later demonstrated that mice lacking TNF-α or lymphotoxin-α had reduced production of iNOS and succumbed readily to intracranial toxoplasmosis, thus indicating the essential role of these cytokines (317). Overall, murine microglia appear to respond to IFN-γ in two ways: by inhibiting tachyzoite proliferation through both IFN-γR and TNFR1 signaling mechanisms that stimulate NO production and by a separate pathway that is NO independent. GM-CSF, but not M-CSF, also activates murine microglia to inhibit tachyzoite replication via the generation of NO (108).

Despite widespread activation, only murine astrocytes and microglia restricted to inflammatory infiltrates actually produce chemokines that actively recruit inflammatory leukocytes (339). Blood vessel-associated astrocytes are the main source of CXCL10/IP-10 and also produce CCL2/MCP-1. Parenchymal microglia produce CCL5/RANTES, CXCL9/MIG, and limited amounts of CXCL10/IP-10, but only in full-blown TE. This interplay of chemokines and immune response is heavily dependent on the presence of IFN-γ, and $CD4^+$ and $CD8^+$ T cells are the single most important source of this cytokine in TE. The chemokine profile produced by glial cells preferentially selects for $CD4^+$ and $CD8^+$ T cells in addition to macrophages. Among T cells, only activated and memory T cells are actually recruited into the brain (339). Overall, microglia may perform a fine-tuning function of chemotaxis by augmenting the type of cells recruited and directing inflammatory leukocytes to the actual location of parasites within the brain.

Microglia produce IL-10 (316), and neutralization experiments reveal that IL-10 facilitates persistence of the parasite in the brain by suppressing the CNS immune response (93). Interestingly, a *T. gondii*-triggered regulatory mechanism involving PGE_2 secretion by astrocytes and IL-10 secretion by microglia may reduce host tissue inflammation, thus avoiding neuronal damage during the host immune response (309). Therefore, IL-10 may be necessary to prevent the immunopathological effects of an uncontrolled immune response.

T. gondii may use many methods to evade host defense in the CNS, but it has specifically demonstrated its ability to downregulate activation-induced MHC class II expression in infected rat microglia and astrocytes (220). Additionally, different strains of *T. gondii* may augment the CNS susceptibility to TE in different ways (155, 345).

In contrast to the observations with murine microglia, our laboratory reported that NO is not involved in the antitoxoplasmic activity of activated human microglia (64). Rather, the host defense activity of human microglia against *T. gondii* is dependent primarily on the activating properties of IFN-γ, TNF-α, and IL-6, which reduced the entry of *T. gondii* into microglia. Once tachyzoites gain entry into human microglia, however, cytokine treatment has little or no effect on tachyzoite replication (64). In humans, therefore, $CD4^+$ and $CD8^+$ T cells may play an even more prominent role in the defense against *T. gondii*.

***Plasmodium falciparum*.** One of the most serious complications of *Plasmodium falciparum* infection is cerebral malaria (CM), with approximately 1 million deaths annually (95). Pathological features of CM include cerebral venules filled with infected erythrocytes, microhemorrhages, local and global ischemia, and glial proliferation, which culminates in the formation of astrocyte and microglial aggregates called Dürck's granulomas (95). CM is primarily a hematogenously derived infection, which places endothelial cells and the BBB as the first line of defense. It is the interplay of the parasitized erythrocytes with endothelial cells, disruption of the BBB, microhemorrhage, and formation of glial aggregates that is thought to promote clinical CM (95).

The pathogenesis of human CM is still debated and has been reviewed thoroughly elsewhere (95). One hypothesis is that CM is the result of an excessively vigorous immune response. $CD4^+$ T cells, cytokines, and ROI are involved in the development of the cerebral complications of malaria (243). Within the murine CNS parenchyma, astrogliosis, degeneration of astrocytes, activation of microglia, an increase in the amount of c-fos, and an increase in TNF-α expression have all occurred in CM and may be important in the initiation and perpetuation of the cerebral complications associated with this disease (241). Additionally, examination of the cerebrospinal fluid of Kenyan children with CM demonstrated increased levels of excitotoxins (100).

Recent investigations have implicated microglia in the pathogenesis of CM. A prominent feature of human CM is widespread activation of microglial cells (315). The most widely utilized murine model of CM is a "fatal" model involving CBA/T6 mice infected with *P. berghei* ANKA (CBA-PbA). This fatal murine cerebral malaria (FMCM) model exhibits neurological and histological changes similar to those in human CM (242). Essential components of the immunopathogenesis associated with FMCM are T lymphocytes, monocytes, and cytokines, especially TNF-α. Using a retinal whole-mount technique, microglia were found to have morphologic changes very early in FMCM (242). These changes included a decrease in process length, an increase in soma size, an increasingly amoeboid appearance, and vacuolation. Redistribution of the microglia to the venous side of the vascular endothelium, with compromised barrier properties, was also noted (242). These less ramified microglia increased in numbers until the terminal stage of the disease (242). TNF-α production by microglia, astrocytes, peripheral blood monocytes adherent to the meningeal vessels, and cerebrovascular endothelial cells prior to onset of cerebral symptoms was also detected (243). Other investigators have also found TNF-α production in human CM cases at autopsy, along with IL-1β (53). More specifically,

human microglia were also found to express the immunosuppressive cytokine TGF-β_2 in Dürck's granulomas (95).

An experimental increase in BBB permeability in the FMCM model was sufficient to elicit thickening of microglial processes and redistribution of microglia toward the vasculature, but microglia with amoeboid and vacuolated morphology were not observed (241). Microglia are not activated by circulating malaria parasites in the absence of an immune response, however. This was demonstrated by early treatment with dexamethasone, which resulted in fewer activated microglia, and this coincided with less severe neurological symptoms without affecting parasite growth (241). This led the authors to conclude that a likely course of events in FMCM involves the malaria parasite producing a vasoactive factor that increases BBB permeability, which initiates a redistribution of microglia and astrocytes toward the blood vessels. Concurrently, dexamethasone-sensitive immunopathological events further activate microglia, which release TNF-α and eventually lead to irreversible cerebral complications (241). The serine protease urokinase-type plasminogen activator receptor, which is important in cell adhesion and spreading, was isolated to macrophages and microglia in the same sites (106), as well as endothelial cells (95). These results suggest that urokinase-type plasminogen activator receptor may be important in microglial migration and/or the breakdown in the BBB by acting as an adhesion molecule for parasitized erythrocytes.

Both β-hematin and hematin, which are synthetic products that mimic hemozoins (malarial pigments) normally produced by the malarial parasite, induce a dose-dependent inhibition of murine macrophage production of TNF-α and NO, but not IL-1 (347). These malarial products also trigger the production of ROIs. The production of TNF-α and NO was not altered in murine microglia, however, and β-hematin had less of an oxidative stress (347, 348).

Heme oxygenases function as antioxidants by degrading heme to carbon dioxide, iron, and biliverdin. In human CM, the inducible antioxidant heme oxygenase 1 was isolated to macrophages and ramified microglia located around Dürck's granulomas and petechial hemorrhages induced by *P. falciparum* (314). However, Taramelli et al. (348) found that β-hematin is resistant to heme oxygenase 1 and that heme-iron-mediated oxidative stress may contribute to malaria-induced immunosuppression. In essence, microglia appear less susceptible than macrophages to the immunomodulatory properties of malarial pigments.

Overall, investigation of the pathogenesis of CM largely revolves around understanding the entry of parasitized erythrocytes through the BBB and the subsequent proinflammatory response that occurs. Evidence to date supports the notion that microglia are involved in the neuropathogenesis of CM.

***Trypanosoma brucei*.** Human African trypanosomiasis (HAT) is caused by *Trypanosoma brucei gambiense* or *T. brucei rhodesiense*. Infection with these trypanosomes is associated with severe neurological complications, including sleep disturbances, which are eventually fatal if untreated. Unique factors associated with HAT include a pronounced antigen variation associated with its variable surface glycoprotein, its ability to penetrate into the CNS and take advantage of its immune-privileged status, the toxicity of therapy, and the occurrence of a fatal posttreatment reactive encephalitis. Initial infection is associated with a hematolymphatic first stage, followed by a second stage, which is characterized by CNS invasion.

In the rat model, early infiltration of the brain occurs in areas in which the BBB is not well developed: the sensory ganglia, area postrema, pineal gland, and median eminence (162). Later, the BBB is disrupted more diffusely (288). Astrocyte activation is one of the first signs of neurological involvement (162). Late-stage HAT and the development of PTRE are histologically characterized by perivascular cuffing, nonspecific lymphoplasmacytic meningoencephalitis, microglial hyperplasia, reactive astrocytes, and infrequent demyelination (162).

Although early activation of astrocytes occurs diffusely, marked activation of microglial cells occurs in a discrete distribution in advanced disease (79). Areas of activation include the cerebral cortex, septum, and hypothalamus and are not associated with neuronal damage histologically (79). The onset and progression of microglial cell activation also correlates with the onset and progression of sleep disturbances, leading to speculation about the role of microglia in this prominent clinical manifestation of HAT (79).

Cerebrospinal fluid from patients with African trypanosomiasis induces apoptosis in both human microglial and endothelial cells (128), and cerebrospinal fluid from late-stage disease induces apoptosis at higher levels in microglial cells than does that from early-stage disease. Also, the levels of soluble Fas ligand and anti-Fas antibodies, both potent inducers of the Fas (CD95) apoptotic signaling pathway, are higher than levels found in cerebrospinal fluid from uninfected subjects (128).

Experimental infection with *T. brucei brucei* in rats shows early production of CXCL2/MIP-2, CCL5/RANTES; CCL3/MIP-1α, and, to a lesser extent, CCL2/MCP-1 from both microglia and astrocytes. Production of these chemokines is probably involved in recruitment of T lymphocytes from the circulation into the CNS. Interestingly, *T. brucei brucei* releases a lymphocyte-triggering factor that stimulates $CD8^+$ T cells to secrete IFN-γ, which favors the growth and proliferation of the trypanosomes (270). *T. brucei brucei* also induces iNOS in both astrocytes and microglia in the murine model, and the generation of NO is potentiated by IFN-γ treatment (127).

In essence, microglia appear to be advantageous in combating HAT through their T-lymphocyte-recruiting capabilities, but they are potentially deleterious, as demonstrated in their temporal relationship between activation and progression of clinical disease.

***Acanthamoeba castellani*.** *Acanthamoeba* species are opportunistic parasites typically associated with keratitis. Cerebral acanthamebiasis (granulomatous amebic encephalitis) occurs primarily in immunocompromised patients, including those with AIDS, and is pathologically characterized by focal granulomatous lesions in the CNS as a result of an immunological response by the host to the presence of trophozoites and cysts. Very few studies have actually investigated the role of microglia in this relatively rare clinical disease.

Murine microglia activated with either recombinant prolactin or LPS plus IFN-γ produce synergistic amebastatic activity; infection with *Acanthamoeba castellani* in vitro stimulates TNF-α, IL-6, and IL-1β production (33, 34). More specifically, TNF-α- and IFN-γ-activated microglia have amebicidal activity, whereas those activated by IL-6 and IL-1β with or without

IFN-γ have only amebastatic activity (32). The NO-dependent pathway does not appear to be involved in this amebastatic activity. It appears that activators of microglia such as LPS, prolactin-prolactin receptor complex, and IFN-γ/IFN-γ receptor complex, through the IFN-γ receptor on microglia, lead to induction of inflammatory cytokines, which in turn trigger antimicrobial activity against *A. castellani* infection in the brain.

Prions

The predominant form of human prion disease, Creutzfeldt-Jakob disease (CJD), occurs spontaneously with no known cause, although there are also inherited and iatrogenic forms of CJD (293). Additional human prion diseases include Kuru, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia, as well as scrapie in goats and sheep and bovine spongiform encephalopathy in cattle (299). The recently described variant CJD (374), which is clinically distinct from classic CJD, has similarities to BSE, although a causal link has been elusive (48). Excellent and detailed reviews of prion disease pathogenesis can be found elsewhere (42, 48, 78, 299).

Pathologically, prion disease exhibits spongiform degeneration, prion plaques, astrogliosis, microglial activation, and neuronal apoptosis, which have been linked to clinical disease (360). The pathogenesis of prion diseases largely remains an enigma, with supporters of a protein-only hypothesis and a viral hypothesis continuing to pursue investigative work (78). Despite the controversy, microglia are emerging as a potential mediator of neurodegeneration in prion disease (37, 48).

Prion protein (PrP^{res}), an abnormal derivative of the normal extracellular glycoprotein (PrP^{sen}) with specific conformational changes, is proposed as the infectious agent in prion disease, and specifically the cause of neurodegeneration in prion disease (42). This conformationally abnormal protein has become the most important diagnostic marker in prion disease (55). Normal PrP^{sen} is expressed in the CNS by neurons (182), astrocytes (255), and microglia (49), although it is neuronal expression that appears to be important for accumulation of PrP^{res} in the CNS (48). In the scrapie model, PrP^{res} plaques colocalize with microglia (375). This plaque formation precedes microglial activation, which in turn precedes neurodegeneration (375). At the microscopic level, neuronal apoptosis and neuronal death in general are preceded by microglial activation both in vitro and in vivo (37, 126). Recently, murine microglia demonstrated migration toward PrP^{res} aggregates in vivo in a manner that at least partially relied on neuronal and astrocyte chemokine production (CCL5/RANTES and CCL4/MIP-1β) and the activation of microglial cell chemokine receptor CCR5 (227). Alternatively, in the viral hypothesis, murine models also show that microglia have a high level of infectivity by the so-called CJD agent, which may be a means by which this agent is dispersed and possibly replicated within the CNS (21).

Several experimental studies of PrP^{res} have focused on its neurotoxic portion, called PrP106-126 (113), which is taken up by neurons, astrocytes, and microglia (238). In the mouse model, neurodegeneration by PrP^{res} or PrP106-126 appears to require the presence of specific components: neuronal PrP^{sen}, microglial PrP^{sen}, the presence of activated microglia, and possibly astrocyte PrP^{sen} (42, 52).

Neurons expressing PrP^{sen} become more sensitive to microglial neurotoxins when exposed to PrP106-126 activity (52). PrP106–126 interacts with neuronal PrP^{sen}, which effectively inhibits it and subsequently increases neuronal sensitivity to oxidative stress (48). It has been suggested that PrP^{sen} expression by microglia increases their sensitivity to various activating stimuli and also to proliferation induced by astrocyte-derived cytokines (48). Once activated, microglia are capable of either directly or indirectly affecting neurons (48).

Astrogliosis is a hallmark of prion disease and typically precedes neurodegeneration (48). In fact, it is thought that astrocytes are the cells in which PrP^{res} first replicates in the CNS (98) and contribute to PrP106–126-induced neurotoxicity via decreased glutamate uptake by astrocytes (50, 52). Both microglia (51) and astrocytes (114) proliferate in response to PrP106–126, although astrocyte proliferation is microglia dependent and requires PrP^{sen} (51). PrP106–126 induces microglial production of IL-1 and IL-6 (286), which in turn contributes to the multifactorial process of astrogliosis (140). Another component of PrP^{res}, fibrillar mouse PrP106–132, induces IL-6 and TNF-α, but not IL-1, in adult human microglia (361), suggesting species- and/or age-related differences with regard to cytokine profiles. Thus, one could envision the role of microglia in neuronal damage as occurring indirectly through the proliferation and activation of affected astrocytes (48). In addition to its contribution to astrogliosis, however, a temporal relationship was recently established between activation of microglia, IL-6 production, and microglia-related killing of PrP-treated neurons (28).

Finally, CJD-infected murine microglia display a unique gene expression profile linked to IFN-γ signaling, complement cascade components, lipid and cholesterol metabolism, and several proteases compared to other activating agents (20). This uniqueness held up even compared to expression profiles of microglia exposed to PrP^{res} (20). This provides some insight into what may be considered early microglial changes in CJD.

In summary, activation of microglia by abnormal PrP^{res} may precipitate neuronal damage either directly or indirectly (48). Alternatively, microglia may be a carrier or replicative source of the CJD agent (21, 226). As described previously, evidence for this is drawn predominantly from in vitro models. Evidence of microglial cell involvement in human disease, unfortunately, is limited. Despite this, continued focused research on this cell may elicit more conclusive evidence of its role and may in the end provide a target for therapy.

MICROGLIA IN NEUROINFLAMMATORY AND NEURODEGENERATIVE DISEASES

Although researchers in the early 1900s had a remarkable appreciation of the scavenger and host defense functions of microglia, the concept of activated microglia contributing to brain damage did not emerge until the end of the 20th century (10, 25, 121, 129, 199, 308, 336). As has been mentioned in several sections of this review, substantial support for this concept has come from studies of neurotoxic mediators released from microglia in response to microorganisms or microbial products. A parallel literature has incriminated activated microglia in the neuropathogenesis of inflammatory and degenerative diseases that have been suggested to be triggered

by infectious agents, such as multiple sclerosis (80, 107, 139, 244, 248, 262, 332), Alzheimer disease (22, 35, 57, 104, 142, 236, 248, 252, 262, 271, 304, 318, 346, 367, 380, 381), Parkinson disease (118, 119, 181, 188, 207, 208, 363), amyotrophic lateral sclerosis (181), and Huntington disease (312), as well as in brain injury due to ischemia and trauma (130, 166). In recent studies, activated microglia were demonstrated to manifest pathological effects on neural stem cells (104, 251), the progenitors of neurons both in the developing brain and in the adult brain, where they play an important role in new-memory formation.

Despite considerable evidence that activated microglia can damage or induce apoptotic death of neurons, either directly through the release of toxic mediators such as cytokines and free radicals or indirectly by attracting activated T cells, monocytes, and neutrophils into the CNS, controversy exists over the neurodegenerative versus neuroregenerative roles of microglia (225, 249, 340, 342). The finding of activated microglia in areas of neuronal loss, such as in amyloid plaque deposits seen in the brains of patients with Alzheimer disease, does not necessarily indicate a causal role in the associated neurodegeneration. As pointed out earlier, the facial nerve axotomy model points to a trophic role of activated microglia in neuroregeneration (262, 340). A countervailing concept of how microglia may be involved in Alzheimer disease has also been proposed, i.e., the loss of such a restorative or supportive function by senescent microglia (340). A vaccine trial with amyloid beta-peptide, a putative neurotoxic moiety in Alzheimer disease, has provided conflicting interpretations of the neuroprotective versus neurotoxic roles of microglia (253). In support of the notion that activated microglia contribute to neuronal support, a majority of patients showed clinical improvement, suggesting that microglia were removing amyloid beta-peptide from areas of diseased brain. However, the trial was stopped early after several patients developed severe encephalitis, which hypothetically could be attributable to activation of microglia by amyloid beta-peptide. Thus, the evidence to date suggests that activated microglia function as a "double-edged sword," with neuroprotective features predominating in the healthy nervous system and neurodestructive properties observed in various disease states.

MICROGLIA AS A PHARMACOLOGICAL TARGET

Based on observations that microglia can facilitate the growth of certain intracellular microorganisms such as, HIV-1, *M. tuberculosis*, and *T. gondii*, more attention should be paid to the development of immunotherapeutic and chemotherapeutic strategies that would enhance the intracellular killing of such pathogens. In addition to assessments of the efficacy of conventional antibiotics and cytokines performed in vitro using microglial cell cultures, consideration should be given to the development of drugs that would alter the microglial cell in ways that make it less susceptible to infection or less hospitable for intracellular microbial growth. An example of this approach has been demonstrated in studies of benzodiazepines which suppress HIV-1 replication in microglia by inhibiting NF-κB activation (215).

In disease states in which activated microglia appear to contribute to inflammation-induced injury of the nervous system, anti-inflammatory agents should be investigated. So far, dexamethasone, a glucocorticoid which potently inhibits the generation of many inflammatory mediators by activated microglia, has been demonstrated to be effective as adjunctive therapy for pneumococcal meningitis (359) and tuberculous meningitis (56). Trials of dexamethasone and other anti-inflammatory agents should be considered for other CNS infections where activated microglia appear to contribute to brain damage. Preliminary data suggest that drugs such as minocycline (104, 352), naloxone (60, 206), dextromethorphan (209), and agents that up-regulate glutamate receptors (137, 349) have neuroprotective properties through their effects on microglial cells. Challenges in designing studies to test the therapeutic benefit of agents such as these are substantial and include pharmacological issues (drug penetration into the CNS, optimal dose, and timing of drug administration) and biological considerations (modulating the deleterious aspects of activated microglia without seriously hampering their critical role in host defense and their neuroregenerative properties).

MICROGLIA: THE KNOWN UNKNOWNS

At the dawn of the 21st century, the physiological role and pathophysiological importance of the mesodermal element of the brain parenchyma—microglial cells—are topics of intense research interest. The field of microglia biology has benefited greatly by the large number of keen minds preoccupied by these cells in the early years of the 20th century and by a dramatic renaissance of interest in microglia at the turn of the century, fostered by technological advances such as the development of reliable techniques for studies of homogenous populations of microglia in culture, monoclonal antibodies for many cell receptors, and assays for a large number of cytokines and chemokines. Although a clearer understanding of the role of microglia in defense against and neuropathogenesis of CNS infections has emerged from this prodigious research effort, much remains unknown about critical aspects of microglia-microbe interactions.

Given the large number of neurotropic pathogens (Table 3), the involvement of microglia in defense and neuropathogenesis has been elucidated for a surprisingly limited number of microorganisms, as has been made evident in this review. Not surprising, however, is the amount of attention paid to HIV-1, but even in this case much remains to be discovered. The tropism of HIV-1 for microglia appears to be shared by some but not all intracellular microorganisms, and many of the neurotoxic mediators produced by HIV-1-infected or viral protein-stimulated microglia have been implicated in the neuropathogenesis of other neurotropic pathogens. Unlike HIV-1, the intracellular replication of some microorganisms is halted in activated microglia. Nevertheless, relatively little is known about the intracellular localization of these infectious agents, and the contribution of oxygen-dependent and oxygen-independent antimicrobial mechanisms of microglia is poorly understood. Studies of the iNOS system of rodent versus human microglia points to the potential importance of animal species differences:

Micronodular lesions, composed of aggregates of microglial cells, are often identified on examination of the CNS at autopsy, as a result of infection from a variety of bacteria, pro-

tozoa, and, especially, viruses. This phenomenon is particularly prominent in patients with AIDS, where microglial nodules are considered one of the histopathological hallmarks of HIV-related brain disease, but may also be seen as a consequence of opportunistic infections by other intracellular pathogens. Fusion of microglia (syncytia) is also observed in vitro following infection with HIV-1 (Fig. 1E). A recent pathologic series of specimens from AIDS patients with microglial nodules found that productive HIV infection was found in 55.1% of microglial nodules, *T. gondii* was found in 34.1%, HCMV was found in 29.1%, and multiple opportunistic agents were found in 9% (261). While the formation of these nodules is often observed, the mechanism behind the formation of these multinucleated giant cells is not completely understood. In our laboratory, CD14, the β2-integrin CD-18, and TNF-α were found to be involved in the formation of multinucleated giant cells by porcine microglia in response to infection with *M. bovis* (277).

The role of microglia in directing T-cell trafficking into the brain is just beginning to be appreciated. The relative importance of activated T cells, as well as other cells of the somatic immune system, in defense of the brain has only recently been considered. Also, the biological and pathophysiological significance of the anatomical heterogeneity of microglia is unknown. While in vitro studies of isolated microglia have contributed many insights into microglia-microbe interactions, these observations need to be interpreted with caution, since in the nervous system microglia are in close proximity to neurons and are surrounded and greatly outnumbered by astrocytes. An area of gaping ignorance is the nature of the complex influence of neurons, astrocytes, and lymphocytes on microglia and vice versa in vivo.

If the escalation of knowledge witnessed in the past decade is any indication of what is to come, we can anticipate answers to many of the questions about the role of microglia in the healthy brain and in disease states. It seems likely that future studies of the roles of microglia in infectious diseases of the CNS will also shed light on the pathogenesis of neuroinflammatory diseases and neurodegenerative disorders which afflict a growing number of elderly individuals. It is also plausible that future studies will yield some surprises regarding the role of microglia and their involvement in pathological processes such as chronic pain (356, 369), drug dependence, and neuropsychiatric disorders.

ACKNOWLEDGMENTS

We are grateful to Cristina Marques and Fred Kravitz for their valuable input and to Miki Olson for help in preparation of the manuscript.

Work in our Neuroimmunology Laboratory cited in this article was supported by NIH grants DA04381, DA09924, T32DA07097, NS038836, and MA066703.

REFERENCES

1. **Adamson, D. C., B. Wildemann, M. Sasaki, J. D. Glass, J. C. McArthur, V. I. Christov, T. M. Dawson, and V. L. Dawson.** 1996. Immunologic NO synthase: elevation in severe AIDS dementia and induction by HIV-1 gp41. Science **274:**1917–1921.
2. **Adle-Biassette, H., F. Chretien, L. Wingertsmann, C. Hery, T. Ereau, F. Scaravilli, M. Tardieu, and F. Gray.** 1999. Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. Neuropathol. Appl. Neurobiol. **25:**123–133.
3. **Aguirre, K., and S. Miller.** 2002. MHC class II-positive perivascular microglial cells mediate resistance to *Cryptococcus neoformans* brain infection. Glia **39:**184–188.
4. **Ajmone-Cat, M. A., A. Nicolini, and L. Minghetti.** 2003. Prolonged exposure of microglia to lipopolysaccharide modifies the intracellular signaling pathways and selectively promotes prostaglandin E2 synthesis. J. Neurochem. **87:**1193–1203.
5. **Albright, A. V., I. Frank, and F. Gonzalez-Scarano.** 1999. Interleukin-2 treatment of microglia has no effect on in vitro HIV infection. AIDS **13:**527–528.
6. **Albright, A. V., J. Martin, M. O'Connor, and F. Gonzalez-Scarano.** 2001. Interactions between HIV-1 gp120, chemokines, and cultured adult microglial cells. J. Neurovirol. **7:**196–207.
7. **Albright, A. V., J. T. Shieh, T. Itoh, B. Lee, D. Pleasure, M. J. O'Connor, R. W. Doms, and F. Gonzalez-Scarano.** 1999. Microglia express CCR5, CXCR4, and CCR3, but of these, CCR5 is the principal coreceptor for human immunodeficiency virus type 1 dementia isolates. J. Virol. **73:**205–213.
8. **Albright, A. V., J. T. Shieh, M. J. O'Connor, and F. Gonzalez-Scarano.** 2000. Characterization of cultured microglia that can be infected by HIV-1. J. Neurovirol. **6**(Suppl. 1)**:**S53–S60.
9. **Albright, A. V., J. Strizki, J. M. Harouse, E. Lavi, M. O'Connor, and F. Gonzalez-Scarano.** 1996. HIV-1 infection of cultured human adult oligodendrocytes. Virology **217:**211–219.
10. **Aloisi, F.** 1999. The role of microglia and astrocytes in CNS immune surveillance and immunopathology, p. 123–133. *In* R. Matsas and M. Tsacopoulos (ed.), Advances in experimental medicine and biology, vol. 468. The functional roles of glial cells in health and disease. Kluwer/Plenum Publishers, New York, N.Y.
11. **Aloisi, F., G. Penna, J. Cerase, B. Menendez Iglesias, and L. Adorini.** 1997. IL-12 production by central nervous system microglia is inhibited by astrocytes. J. Immunol. **159:**1604–1612.
12. **An, S. F., O. Osuntokun, M. Groves, and F. Scaravilli.** 2001. Expression of CCR-5/CXCR-4 in spinal cord of patients with AIDS. Acta Neuropathol. **102:**175–180.
13. **Anders, K. H., W. F. Guerra, U. Tomiyasu, M. A. Verity, and H. V. Vinters.** 1986. The neuropathology of AIDS. UCLA experience and review. Am. J. Pathol. **124:**537–558.
14. **Anthony, D. C., B. Ferguson, M. K. Matyzak, K. M. Miller, M. M. Esiri, and V. H. Perry.** 1997. Differential matrix metalloproteinase expression in cases of multiple sclerosis and stroke. Neuropathol. Appl. Neurobiol. **23:**406–415.
15. **Arribas, J. R., G. A. Storch, D. B. Clifford, and A. C. Tselis.** 1996. Cytomegalovirus encephalitis. Ann. Intern. Med. **125:**577–587.
16. **Aurelius, E., B. Andersson, M. Forsgren, B. Skoldenberg, and O. Strannegard.** 1994. Cytokines and other markers of intrathecal immune response in patients with herpes simplex encephalitis. J Infect Dis **170:**678–681.
17. **Bacon, K. B., and J. K. Harrison.** 2000. Chemokines and their receptors in neurobiology: perspectives in physiology and homeostasis. J. Neuroimmunol. **104:**92–97.
18. **Bagetta, G., M. T. Corasaniti, L. Berliocchi, R. Nistico, A. M. Giammarioli, W. Malorni, L. Aloe, and A. Finazzi-Agro.** 1999. Involvement of interleukin-1beta in the mechanism of human immunodeficiency virus type 1 (HIV-1) recombinant protein gp120-induced apoptosis in the neocortex of rat. Neuroscience **89:**1051–1066.
19. **Bajetto, A., R. Bonavia, S. Barbero, and G. Schettini.** 2002. Characterization of chemokines and their receptors in the central nervous system: physiopathological implications. J. Neurochem. **82:**1311–1329.
20. **Baker, C. A., and L. Manuelidis.** 2003. Unique inflammatory RNA profiles of microglia in Creutzfeldt-Jakob disease. Proc. Natl. Acad. Sci. USA **100:**675–679.
21. **Baker, C. A., D. Martin, and L. Manuelidis.** 2002. Microglia from Creutzfeldt-Jakob disease-infected brains are infectious and show specific mRNA activation profiles. J. Virol. **76:**10905–10913.
22. **Bamberger, M. E., and G. E. Landreth.** 2001. Microglial interaction with beta-amyloid: implications for the pathogenesis of Alzheimer's disease. Microsc. Res. Tech. **54:**59–70.
23. **Banati, R. B.** 2003. Neuropathological imaging: *in vivo* detection of glial activation as a measure of disease and adaptive change in the brain. Br. Med. Bull. **65:**121–131.
24. **Banati, R. B.** 2002. Visualising microglial activation in vivo. Glia **40:**206–217.
25. **Banati, R. B., J. Gehrmann, P. Schubert, and G. W. Kreutzberg.** 1993. Cytotoxicity of microglia. Glia **7:**111–118.
26. **Banisadr, G., F. Queraud-Lesaux, M. C. Boutterin, D. Pelaprat, B. Zalc, W. Rostene, F. Haour, and S. M. Parsadaniantz.** 2002. Distribution, cellular localization and functional role of CCR2 chemokine receptors in adult rat brain. J. Neurochem. **81:**257–269.
27. **Barron, K. D.** 1995. The microglial cell. A historical review. J. Neurol. Sci. **134**(Suppl.)**:**57–68.
28. **Bate, C., R. S. Boshuizen, J. P. Langeveld, and A. Williams.** 2002. Temporal and spatial relationship between the death of PrP-damaged neurones and microglial activation. Neuroreport **13:**1695–1700.
29. **Beaman, B. L.** 1993. Ultrastructural analysis of growth of *Nocardia asteroides* during invasion of the murine brain. Infect. Immun. **61:**274–283.

30. **Beaman, L., and B. L. Beaman.** 1993. Interactions of *Nocardia asteroides* with murine glia cells in culture. Infect. Immun. **61:**343–347.
31. **Becher, B., V. Dodelet, V. Fedorowicz, and J. Antel.** 1996. Soluble tumor necrosis factor receptor inhibits interleukin 12 production by stimulated human adult microglial cells in vitro. J. Clin. Investig. **98:**1539–1543.
32. **Benedetto, N., and C. Auriault.** 2002. Complex network of cytokines activating murine microglial cell activity against *Acanthamoeba castellani.* Eur. Cytokine Netw. **13:**351–357.
33. **Benedetto, N., and C. Auriault.** 2002. Prolactin-cytokine network in the defence against *Acanthamoeba castellani* in murine microglia. Eur. Cytokine Netw. **13:**447–455.
34. **Benedetto, N., F. Rossano, F. Gorga, A. Folgore, M. Rao, and C. Romano Carratelli.** 2003. Defense mechanisms of IFN-gamma and LPS-primed murine microglia against *Acanthamoeba castellanii* infection. Int. Immunopharmacol. **3:**825–834.
35. **Benveniste, E. N., V. T. Nguyen, and G. M. O'Keefe.** 2001. Immunological aspects of microglia: relevance to Alzheimer's disease: Neurochem. Int. **39:**381–391.
36. **Berman, N. E., J. K. Marcario, C. Yong, R. Raghavan, L. A. Raymond, S. V. Joag, O. Narayan, and P. D. Cheney.** 1999. Microglial activation and neurological symptoms in the SIV model of NeuroAIDS: association of MHC-II and MMP-9 expression with behavioral deficits and evoked potential changes. Neurobiol. Dis. **6:**486–498.
37. **Betmouni, S., V. H. Perry, and J. L. Gordon.** 1996. Evidence for an early inflammatory response in the central nervous system of mice with scrapie. Neuroscience **74:**1–5.
38. **Bezzi, P., M. Domercq, L. Brambilla, R. Galli, D. Schols, E. De Clercq, A. Vescovi, G. Bagetta, G. Kollias, J. Meldolesi, and A. Volterra.** 2001. CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity. Nat. Neurosci. **4:**702–710.
39. **Blasi, E., R. Barluzzi, R. Mazzolla, B. Tancini, S. Saleppico, M. Puliti, L. Pitzurra, and F. Bistoni.** 1995. Role of nitric oxide and melanogenesis in the accomplishment of anticryptococcal activity by the BV-2 microglial cell line. J. Neuroimmunol. **58:**111–116.
40. **Boddeke, E. W., I. Meigel, S. Frentzel, K. Biber, L. Q. Renn, and P. Gebicke-Harter.** 1999. Functional expression of the fractalkine (CX3C) receptor and its regulation by lipopolysaccharide in rat microglia. Eur. J. Pharmacol. **374:**309–313.
41. **Bonwetsch, R., S. Croul, M. W. Richardson, C. Lorenzana, L. D. Valle, A. E. Sverstiuk, S. Amini, S. Morgello, K. Khalili, and J. Rappaport.** 1999. Role of HIV-1 Tat and CC chemokine MIP-1alpha in the pathogenesis of HIV associated central nervous system disorders. J. Neurovirol. **5:**685–694.
42. **Brandner, S.** 2003. CNS pathogenesis of prion diseases. Br. Med. Bull. **66:**131–139.
43. **Braun, J. S., R. Novak, K. H. Herzog, S. M. Bodner, J. L. Cleveland, and E. I. Tuomanen.** 1999. Neuroprotection by a caspase inhibitor in acute bacterial meningitis. Nat. Med. **5:**298–302.
44. **Braun, J. S., R. Novak, P. J. Murray, C. M. Eischen, S. A. Susin, G. Kroemer, A. Halle, J. R. Weber, E. I. Tuomanen, and J. L. Cleveland.** 2001. Apoptosis-inducing factor mediates microglial and neuronal apoptosis caused by pneumococcus. J. Infect. Dis. **184:**1300–1309.
45. **Braun, J. S., J. E. Sublett, D. Freyer, T. J. Mitchell, J. L. Cleveland, E. I. Tuomanen, and J. R. Weber.** 2002. Pneumococcal pneumolysin and H_2O_2 mediate brain cell apoptosis during meningitis. J. Clin. Investig. **109:**19–27.
46. **Brenneman, D. E., G. L. Westbrook, S. P. Fitzgerald, D. L. Ennist, K. L. Elkins, M. R. Ruff, and C. B. Pert.** 1988. Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide. Nature **335:**639–642.
47. **Brosnan, C. F., L. Battistini, C. S. Raine, D. W. Dickson, A. Casadevall, and S. C. Lee.** 1994. Reactive nitrogen intermediates in human neuropathology: an overview. Dev. Neurosci. **16:**152–161.
48. **Brown, D. R.** 2001. Microglia and prion disease. Microsc. Res. Tech. **54:** 71–80.
49. **Brown, D. R., A. Besinger, J. W. Herms, and H. A. Kretzschmar.** 1998. Microglial expression of the prion protein. Neuroreport **9:**1425–1429.
50. **Brown, D. R., and C. M. Mohn.** 1999. Astrocytic glutamate uptake and prion protein expression. Glia **25:**282–292.
51. **Brown, D. R., B. Schmidt, and H. A. Kretzschmar.** 1996. A neurotoxic prion protein fragment enhances proliferation of microglia but not astrocytes in culture. Glia **18:**59–67.
52. **Brown, D. R., B. Schmidt, and H. A. Kretzschmar.** 1996. Role of microglia and host prion protein in neurotoxicity of a prion protein fragment. Nature **380:**345–347.
53. **Brown, H., G. Turner, S. Rogerson, M. Tembo, J. Mwenechanya, M. Molyneux, and T. Taylor.** 1999. Cytokine expression in the brain in human cerebral malaria. J. Infect. Dis. **180:**1742–1746.
54. **Bsibsi, M., R. Ravid, D. Gveric, and J. M. van Noort.** 2002. Broad expression of Toll-like receptors in the human central nervous system. J. Neuropathol. Exp. Neurol. **61:**1013–1021.
55. **Budka, H.** 2003. Neuropathology of prion diseases. Br. Med. Bull. **66:**121–130.
56. **Byrd, T., and P. Zinser.** 2001. Tuberculosis meningitis. Curr. Treat. Options Neurol. **3:**427–432.
57. **Cagnin, A., D. J. Brooks, A. M. Kennedy, R. N. Gunn, R. Myers, F. E. Turkheimer, T. Jones, and R. B. Banati.** 2001. In-vivo measurement of activated microglia in dementia. Lancet **358:**461–467.
58. **Cagnin, A., R. Myers, R. N. Gunn, A. D. Lawrence, T. Stevens, G. W. Kreutzberg, T. Jones, and R. B. Banati.** 2001. In vivo visualization of activated glia by [11C] (R)-PK11195-PET following herpes encephalitis reveals projected neuronal damage beyond the primary focal lesion. Brain **124:**2014–2027.
59. **Cantin, E. M., D. R. Hinton, J. Chen, and H. Openshaw.** 1995. Gamma interferon expression during acute and latent nervous system infection by herpes simplex virus type 1. J. Virol. **69:**4898–4905.
60. **Chang, R. C., C. Rota, R. E. Glover, R. P. Mason, and J. S. Hong.** 2000. A novel effect of an opioid receptor antagonist, naloxone, on the production of reactive oxygen species by microglia: a study by electron paramagnetic resonance spectroscopy. Brain Res. **854:**224–229.
61. **Chao, C., S. Hu, and P. Peterson.** 1997. Glia-mediated neurotoxicity, p. 74–89. *In* P. Peterson and J. S. Remington (ed.), In defense of the brain: current concepts in the immunopathogenesis and clinical aspects of CNS infections. Blackwell Science, Malden, Mass.
62. **Chao, C. C., W. R. Anderson, S. Hu, G. Gekker, A. Martella, and P. K. Peterson.** 1993. Activated microglia inhibit multiplication of *Toxoplasma gondii* via a nitric oxide mechanism. Clin. Immunol. Immunopathol. **67:**178–183.
63. **Chao, C. C., G. Gekker, S. Hu, F. Kravitz, and P. K. Peterson.** 1998. Kappa-opioid potentiation of tumor necrosis factor-alpha-induced anti-HIV-1 activity in acutely infected human brain cell cultures. Biochem. Pharmacol. **56:**397–404.
64. **Chao, C. C., G. Gekker, S. Hu, and P. K. Peterson.** 1994. Human microglial cell defense against *Toxoplasma gondii.* The role of cytokines. J. Immunol. **152:**1246–1252.
65. **Chao, C. C., G. Gekker, S. Hu, W. S. Sheng, K. B. Shark, D. F. Bu, S. Archer, J. M. Bidlack, and P. K. Peterson.** 1996. Kappa opioid receptors in human microglia downregulate human immunodeficiency virus 1 expression. Proc. Natl. Acad. Sci. USA **93:**8051–8056.
66. **Chao, C. C., and S. Hu.** 1994. Tumor necrosis factor-alpha potentiates glutamate neurotoxicity in human fetal brain cell cultures. Dev. Neurosci. **16:**172–179.
67. **Chao, C. C., S. Hu, K. Close, C. S. Choi, T. W. Molitor, W. J. Novick, and P. K. Peterson.** 1992. Cytokine release from microglia: differential inhibition by pentoxifylline and dexamethasone. J. Infect. Dis. **166:**847–853.
68. **Chao, C. C., S. Hu, L. Ehrlich, and P. K. Peterson.** 1995. Interleukin-1 and tumor necrosis factor-alpha synergistically mediate neurotoxicity: involvement of nitric oxide and of *N*-methyl-D-aspartate receptors. Brain Behav. Immun. **9:**355–365.
69. **Chao, C. C., S. Hu, G. Gekker, J. R. Lokensgard, M. P. Heyes, and P. K. Peterson.** 2000. U50,488 protection against HIV-1-related neurotoxicity: involvement of quinolinic acid suppression. Neuropharmacology **39:**150–160.
70. **Chao, C. C., S. Hu, G. Gekker, W. J. Novick, Jr., J. S. Remington, and P. K. Peterson.** 1993. Effects of cytokines on multiplication of *Toxoplasma gondii* in microglial cells. J. Immunol. **150:**3404–3410.
71. **Chao, C. C., S. Hu, T. W. Molitor, E. G. Shaskan, and P. K. Peterson.** 1992. Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. J. Immunol. **149:**2736–2741.
72. **Chao, C. C., S. Hu, K. B. Shark, W. S. Sheng, G. Gekker, and P. K. Peterson.** 1997. Activation of mu opioid receptors inhibits microglial cell chemotaxis. J. Pharmacol. Exp. Ther. **281:**998–1004.
73. **Chauvet, N., K. Palin, D. Verrier, S. Poole, R. Dantzer, and J. Lestage.** 2001. Rat microglial cells secrete predominantly the precursor of interleukin-1beta in response to lipopolysaccharide. Eur. J. Neurosci. **14:**609–617.
74. **Cheeran, M. C., S. Hu, G. Gekker, and J. R. Lokensgard.** 2000. Decreased cytomegalovirus expression following proinflammatory cytokine treatment of primary human astrocytes. J. Immunol. **164:**926–933.
75. **Cheeran, M. C., S. Hu, W. S. Sheng, P. K. Peterson, and J. R. Lokensgard.** 2003. CXCL10 production from cytomegalovirus-stimulated microglia is regulated by both human and viral interleukin-10. J. Virol. **77:**4502–4515.
76. **Cheeran, M. C., S. Hu, S. L. Yager, G. Gekker, P. K. Peterson, and J. R. Lokensgard.** 2001. Cytomegalovirus induces cytokine and chemokine production differentially in microglia and astrocytes: antiviral implications. J. Neurovirol. **7:**135–147.
77. **Chen, S., D. Luo, W. J. Streit, and J. K. Harrison.** 2002. TGF-beta1 upregulates CX3CR1 expression and inhibits fractalkine-stimulated signaling in rat microglia. J. Neuroimmunol. **133:**46–55.
78. **Chesebro, B.** 2003. Introduction to the transmissible spongiform encephalopathies or prion diseases. Br. Med. Bull. **66:**1–20.
79. **Chianella, S., M. Semprevivo, Z. C. Peng, D. Zaccheo, M. Bentivoglio, and G. Grassi-Zucconi.** 1999. Microglia activation in a model of sleep disorder: an immunohistochemical study in the rat brain during *Trypanosoma brucei* infection. Brain Res. **832:**54–62.
80. **Chiang, C. S., H. C. Powell, L. H. Gold, A. Samimi, and I. L. Campbell.**

1996. Macrophage/microglial-mediated primary demyelination and motor disease induced by the central nervous system production of interleukin-3 in transgenic mice. J. Clin. Investig. **97:**1512–1524.
81. **Colton, C. A., and D. L. Gilberg.** 1987. Production of super-oxide anions by a CNS macrophage, the microglia. Eur. J. Biochem. **223:**284–288.
82. **Cosenza, M. A., M. L. Zhao, Q. Si, and S. C. Lee.** 2002. Human brain parenchymal microglia express CD14 and CD45 and are productively infected by HIV-1 in HIV-1 encephalitis. Brain Pathol. **12:**442–455.
83. **Cotter, R., C. Williams, L. Ryan, D. Erichsen, A. Lopez, H. Peng, and J. Zheng.** 2002. Fractalkine (CX3CL1) and brain inflammation: implications for HIV-1-associated dementia. J. Neurovirol. **8:**585–598.
84. **Cowell, R. M., and F. S. Silverstein.** 2003. Developmental changes in the expression of chemokine receptor CCR1 in the rat cerebellum. J. Comp. Neurol. **457:**7–23.
85. **Cross, A. K., and M. N. Woodroofe.** 1999. Chemokine modulation of matrix metalloproteinase and TIMP production in adult rat brain microglia and a human microglial cell line in vitro. Glia **28:**183–189.
86. **Cross, A. K., and M. N. Woodroofe.** 2001. Immunoregulation of microglial functional properties. Microsc. Res. Tech. **54:**10–17.
87. **Curto, M., C. Reali, G. Palmieri, F. Scintu, M. L. Schivo, V. Sogos, M. A. Marcialis, M. G. Ennas, H. Schwarz, G. Pozzi, and F. Gremo.** 2004. Inhibition of cytokines expression in human microglia infected by virulent and non-virulent mycobacteria. Neurochem. Int. **44:**381–392.
88. **da Cunha, A., J. J. Jefferson, W. R. Tyor, J. D. Glass, F. S. Jannotta, J. R. Cottrell, and J. H. Resau.** 1997. Transforming growth factor-beta1 in adult human microglia and its stimulated production by interleukin-1. J. Interferon Cytokine Res. **17:**655–664.
89. **Dalmau, I., J. M. Vela, B. Gonzalez, B. Finsen, and B. Castellano.** 2003. Dynamics of microglia in the developing rat brain. J. Comp. Neurol. **458:** 144–157.
90. **Davis, L. E., B. L. Hjelle, V. E. Miller, D. L. Palmer, A. L. Llewellyn, T. L. Merlin, S. A. Young, R. G. Mills, W. Wachsman, and C. A. Wiley.** 1992. Early viral brain invasion in iatrogenic human immunodeficiency virus infection. Neurology **42:**1736–1739.
91. **Deckert-Schlüter, M., H. Bluethmann, N. Kaefer, A. Rang, and D. Schluter.** 1999. Interferon-gamma receptor-mediated but not tumor necrosis factor receptor type 1- or type 2-mediated signaling is crucial for the activation of cerebral blood vessel endothelial cells and microglia in murine *Toxoplasma* encephalitis. Am. J. Pathol. **154:**1549–1561.
92. **Deckert-Schlüter, M., H. Bluethmann, A. Rang, H. Hof, and D. Schluter.** 1998. Crucial role of TNF receptor type 1 (p55), but not of TNF receptor type 2 (p75), in murine toxoplasmosis. J. Immunol. **160:**3427–3436.
93. **Deckert-Schlüter, M., C. Buck, D. Weiner, N. Kaefer, A. Rang, H. Hof, O. D. Wiestler, and D. Schluter.** 1997. Interleukin-10 downregulates the intracerebral immune response in chronic *Toxoplasma* encephalitis. J. Neuroimmunol. **76:**167–176.
94. **De Groot, C. J., and M. N. Woodroofe.** 2001. The role of chemokines and chemokine receptors in CNS inflammation. Prog. Brain Res. **132:**533–544.
95. **Deininger, M. H., P. G. Kremsner, R. Meyermann, and H. Schluesener.** 2002. Macrophages/microglial cells in patients with cerebral malaria. Eur. Cytokine Netw. **13:**173–185.
96. **Delgado, M., G. M. Jonakait, and D. Ganea.** 2002. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit chemokine production in activated microglia. Glia **39:**148–161.
97. **del Rio-Hortega, P.** 1932. Microglia, p. 483–534. *In* W. Penfield (ed.), Cytology and cellular pathology of the nervous system. P. B. Hoebaer, New York, N.Y.
98. **Diedrich, J. F., H. Minnigan, R. I. Carp, J. N. Whitaker, R. Race, W. Frey, Jr., and A. T. Haase.** 1991. Neuropathological changes in scrapie and Alzheimer's disease are associated with increased expression of apolipoprotein E and cathepsin D in astrocytes. J. Virol. **65:**4759–4768.
99. **Ding, M., B. A. St. Pierre, J. F. Parkinson, P. Medberry, J. L. Wong, N. E. Rogers, L. J. Ignarro, and J. E. Merrill.** 1997. Inducible nitric-oxide synthase and nitric oxide production in human fetal astrocytes and microglia. J. Biol. Chem. **272:**11327–11335.
100. **Dobbie, M., J. Crawley, C. Waruiru, K. Marsh, and R. Surtees.** 2000. Cerebrospinal fluid studies in children with cerebral malaria: an excitotoxic mechanism? Am. J. Trop. Med. Hyg. **62:**284–290.
101. **Durand, M. L., S. B. Calderwood, D. J. Weber, S. I. Miller, F. S. Southwick, V. S. Caviness, Jr., and M. N. Swartz.** 1993. Acute bacterial meningitis in adults. A review of 493 episodes. N. Engl. J. Med. **328:**21–28.
102. **Ehrlich, L. C., S. Hu, P. K. Peterson, and C. C. Chao.** 1998. IL-10 downregulates human microglial IL-8 by inhibition of NF-kappaB activation. Neuroreport **9:**1723–1726.
103. **Ehrlich, L. C., S. Hu, W. S. Sheng, R. L. Sutton, G. L. Rockswold, P. K. Peterson, and C. C. Chao.** 1998. Cytokine regulation of human microglial cell IL-8 production. J. Immunol. **160:**1944–1948.
104. **Ekdahl, C. T., J.-H. Claasen, S. Bonde, Z. Kokaia, and O. Lindvall.** 2003. Inflammation is detrimental for neurogenesis in adult brain. Proc. Natl. Acad. Sci. USA **100:**13632–13637.
105. **Esiri, M. M., C. W. Drummond, and C. S. Morris.** 1995. Macrophages and microglia in HSV-1 infected mouse brain. J. Neuroimmunol. **62:**201–205.
106. **Fauser, S., M. H. Deininger, P. G. Kremsner, V. Magdolen, T. Luther, R. Meyermann, and H. J. Schluesener.** 2000. Lesion associated expression of urokinase-type plasminogen activator receptor (uPAR, CD87) in human cerebral malaria. J. Neuroimmunol. **111:**234–240.
107. **Filipovic, R., I. Jacovcevski, and N. Zecevic.** 2003. GRO-alpha and CXCR2 in the human fetal brain and multiple sclerosis lesions. Dev. Neurosci. **25:**279–290.
108. **Fischer, H. G., A. K. Bielinsky, B. Nitzgen, W. Daubener, and U. Hadding.** 1993. Functional dichotomy of mouse microglia developed in vitro: differential effects of macrophage and granulocyte/macrophage colony-stimulating factor on cytokine secretion and antitoxoplasmic activity. J. Neuroimmunol. **45:**193–201.
109. **Fischer, H. G., B. Nitzgen, G. Reichmann, U. Gross, and U. Hadding.** 1997. Host cells of *Toxoplasma gondii* encystation in infected primary culture from mouse brain. Parasitol. Res. **83:**637–641.
110. **Fischer, H.-G., and G. Reichmann.** 2001. Brain dendritic cells and macrophages/microglia in central nervous system inflammation. J. Immunol. **166:** 2717–2726.
111. **Fischer-Smith, T., S. Croul, A. E. Sverstiuk, C. Capini, D. L'Heureux, E. G. Regulier, M. W. Richardson, S. Amini, S. Morgello, K. Khalili, and J. Rappaport.** 2001. CNS invasion by $CD14^+/CD16^+$ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection. J. Neurovirol. **7:**528–541.
112. **Flynn, G., S. Maru, J. Loughlin, I. A. Romero, and D. Male.** 2003. Regulation of chemokine receptor expression in human microglia and astrocytes. J. Neuroimmunol. **136:**84–93.
113. **Forloni, G., N. Angeretti, R. Chiesa, E. Monzani, M. Salmona, O. Bugiani, and F. Tagliavini.** 1993. Neurotoxicity of a prion protein fragment. Nature **362:**543–546.
114. **Forloni, G., R. Del Bo, N. Angeretti, R. Chiesa, S. Smiroldo, R. Doni, E. Ghibaudi, M. Salmona, M. Porro, L. Verga, et al.** 1994. A neurotoxic prion protein fragment induces rat astroglial proliferation and hypertrophy. Eur. J. Neurosci. **6:**1415–1422.
115. **Freund, Y. R., N. T. Zaveri, and H. S. Javitz.** 2001. In vitro investigation of host resistance to *Toxoplasma gondii* infection in microglia of BALB/c and CBA/Ca mice. Infect. Immun. **69:**765–772.
116. **Gabuzda, D., J. He, A. Ohagen, and A. V. Vallat.** 1998. Chemokine receptors in HIV-1 infection of the central nervous system. Semin. Immunol. **10:**203–213.
117. **Galea, E., D. J. Reis, E. S. Fox, H. Xu, and D. L. Feinstein.** 1996. CD14 mediate endotoxin induction of nitric oxide synthase in cultured brain glial cells. J. Neuroimmunol. **64:**19–28.
118. **Gao, H. M., J. Jiang, B. Wilson, W. Zhang, J. S. Hong, and B. Liu.** 2002. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. J. Neurochem. **81:**1285–1297.
119. **Gao, H. M., B. Liu, W. Zhang, and J. S. Hong.** 2003. Critical role of microglial NADPH oxidase-derived free radicals in the in vitro MPTP model of Parkinson's disease. FASEB J. **17:**1954–1956.
120. **Gartner, S., and Y. Liu.** 2002. Insights into the role of immune activation in HIV neuropathogenesis. J. Neurovirol. **8:**69–75.
121. **Gehrmann, J., and G. W. Kreutzberg.** 1995. Microglia in experimental neuropathology, p. 883–904. *In* H. Kentenmann and B. R. Ransom (ed.), Neuroglia. Oxford University Press, New York, N.Y.
122. **Gehrmann, J., Y. Matsumoto, and G. W. Kreutzberg.** 1995. Microglia: intrinsic immuneffector cell of the brain. Brain Res. Rev. **20:**269–287.
123. **Gelbard, H. A., H. S. Nottet, S. Swindells, M. Jett, K. A. Dzenko, P. Genis, R. White, L. Wang, Y. B. Choi, D. Zhang, et al.** 1994. Platelet-activating factor: a candidate human immunodeficiency virus type 1-induced neurotoxin. J. Virol. **68:**4628–4635.
124. **Ghorpade, A., R. Persidskaia, R. Suryadevara, M. Che, X. J. Liu, Y. Persidsky, and H. E. Gendelman.** 2001. Mononuclear phagocyte differentiation, activation, and viral infection regulate matrix metalloproteinase expression: implications for human immunodeficiency virus type 1-associated dementia. J. Virol. **75:**6572–6583.
125. **Ghorpade, A., M. Q. Xia, B. T. Hyman, Y. Persidsky, A. Nukuna, P. Bock, M. Che, J. Limoges, H. E. Gendelman, and C. R. Mackay.** 1998. Role of the beta-chemokine receptors CCR3 and CCR5 in human immunodeficiency virus type 1 infection of monocytes and microglia. J. Virol. **72:**3351–3361.
126. **Giese, A., D. R. Brown, M. H. Groschup, C. Feldmann, I. Haist, and H. A. Kretzschmar.** 1998. Role of microglia in neuronal cell death in prion disease. Brain Pathol. **8:**449–457.
127. **Girard, M., Z. Ayed, P. M. Preux, B. Bouteille, J. L. Preud'Homme, M. Dumas, and M. O. Jauberteau.** 2000. In vitro induction of nitric oxide synthase in astrocytes and microglia by *Trypanosoma brucei brucei.* Parasite Immunol. **22:**7–12.
128. **Girard, M., S. Bisser, B. Courtioux, C. Vermot-Desroches, B. Bouteille, J. Wijdenes, J. L. Preud'homme, and M. O. Jauberteau.** 2003. In vitro induction of microglial and endothelial cell apoptosis by cerebrospinal fluids from patients with human African trypanosomiasis. Int. J. Parasitol. **33:** 713–720.
129. **Giulian, D.** 1995. Microglia and neuronal dysfunction, p. 671–684. *In* H.

Kentenmann and B. R. Ransom (ed.), Neuroglia. Oxford University Press, New York, N.Y.
130. **Giulian, D., M. Corpuz, S. Chapman, M. Mansouri, and C. Robertson.** 1993. Reactive mononuclear phagocytes release neurotoxins after ischemic and traumatic injury to the central nervous system. J. Neurosci. Res. **36:** 681–693.
131. **Glass, J. D., H. Fedor, S. L. Wesselingh, and J. C. McArthur.** 1995. Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia. Ann. Neurol. **38:**755–762.
132. **Glass, J. D., and S. L. Wesselingh.** 2001. Microglia in HIV-associated neurological diseases. Microsc. Res. Tech. **54:**95–105.
133. **Goldman, D., X. Song, R. Kitai, A. Casadevall, M. L. Zhao, and S. C. Lee.** 2001. *Cryptococcus neoformans* induces macrophage inflammatory protein 1α (MIP-1α) and MIP-1β in human microglia: role of specific antibody and soluble capsular polysaccharide. Infect. Immun. **69:**1808–1815.
134. **Goldman, D. L., B. C. Fries, S. P. Franzot, L. Montella, and A. Casadevall.** 1998. Phenotypic switching in the human pathogenic fungus *Cryptococcus neoformans* is associated with changes in virulence and pulmonary inflammatory response in rodents. Proc. Natl. Acad. Sci. USA **95:**14967–14972.
135. **Gottschall, P. E., and S. Deb.** 1996. Regulation of matrix metalloproteinase expressions in astrocytes, microglia and neurons. Neuroimmunomodulation **3:**69–75.
136. **Gottschall, P. E., X. Yu, and B. Bing.** 1995. Increased production of gelatinase B (matrix metalloproteinase-9) and interleukin-6 by activated rat microglia in culture. J. Neurosci. Res. **42:**335–342.
137. **Gras, G., F. Chretien, A. V. Vallat-Decouvelaere, G. Le Pavec, F. Porcheray, C. Bossuet, C. Leone, P. Mialocq, N. Dereuddre-Bosquet, P. Clayette, R. Le Grand, C. Creminon, D. Dormont, A. C. Rimaniol, and F. Gray.** 2003. Regulated expression of sodium-dependent glutamate transporters and synthetase: a neuroprotective role for activated microglia and macrophages in HIV infection? Brain Pathol. **13:**211–222.
138. **Grassi, M. P., F. Clerici, C. Perin, A. D'Arminio Monforte, L. Vago, M. Borella, R. Boldorini, and A. Mangoni.** 1998. Microglial nodular encephalitis and ventriculoencephalitis due to cytomegalovirus infection in patients with AIDS: two distinct clinical patterns. Clin. Infect. Dis. **27:**504–508.
139. **Greenlee, J. E., and J. W. Rose.** 2000. Controversies in neurological infectious diseases. Semin. Neurol. **20:**375–386.
140. **Hafiz, F. B., and D. R. Brown.** 2000. A model for the mechanism of astrogliosis in prion disease. Mol. Cell. Neurosci. **16:**221–232.
141. **Halford, W. P., B. M. Gebhardt, and D. J. Carr.** 1996. Persistent cytokine expression in trigeminal ganglion latently infected with herpes simplex virus type 1. J. Immunol. **157:**3542–3549.
142. **Halliday, G., S. R. Robinson, C. Shepherd, and J. Kril.** 2000. Alzheimer's disease and inflammation: a review of cellular and therapeutic mechanisms. Clin. Exp. Pharmacol. Physiol. **27:**1–8.
143. **Hanisch, U. K.** 2002. Microglia as a source and target of cytokines. Glia **40:**140–155.
144. **Hanisch, U. K., M. Prinz, K. Angstwurm, K. G. Hausler, O. Kann, H. Kettenmann, and J. R. Weber.** 2001. The protein tyrosine kinase inhibitor AG126 prevents the massive microglial cytokine induction by pneumococcal cell walls. Eur. J. Immunol. **31:**2104–2115.
145. **Harrison, J. K., Y. Jiang, S. Chen, Y. Xia, D. Maciejewski, R. K. McNamara, W. J. Streit, M. N. Salafranca, S. Adhikari, D. A. Thompson, P. Botti, K. B. Bacon, and L. Feng.** 1998. Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. Proc. Natl. Acad. Sci. USA **95:**10896–10901.
146. **Hausler, K. G., M. Prinz, C. Nolte, J. R. Weber, R. R. Schumann, H. Kettenmann, and U. K. Hanisch.** 2002. Interferon-gamma differentially modulates the release of cytokines and chemokines in lipopolysaccharide- and pneumococcal cell wall-stimulated mouse microglia and macrophages. Eur. J. Neurosci. **16:**2113–2122.
147. **He, J., Y. Chen, M. Farzan, H. Choe, A. Ohagen, S. Gartner, J. Busciglio, X. Yang, W. Hofmann, W. Newman, C. R. Mackay, J. Sodroski, and D. Gabuzda.** 1997. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. Nature **385:**645–649.
148. **Hegg, C. C., S. Hu, P. K. Peterson, and S. A. Thayer.** 2000. Beta-chemokines and human immunodeficiency virus type-1 proteins evoke intracellular calcium increases in human microglia. Neuroscience **98:**191–199.
149. **Hesselgesser, J., and R. Horuk.** 1999. Chemokine and chemokine receptor expression in the central nervous system. J. Neurovirol. **5:**13–26.
150. **Heyes, M. P., B. J. Brew, A. Martin, R. W. Price, A. M. Salazar, J. J. Sidtis, J. A. Yergey, M. M. Mouradian, A. E. Sadler, J. Keilp, et al.** 1991. Quinolinic acid in cerebrospinal fluid and serum in HIV-1 infection: relationship to clinical and neurological status. Ann. Neurol. **29:**202–209.
151. **Hickey, W. F.** 2001. Basic principles of immunological surveillance of the normal central nervous system. Glia **36:**118–124.
152. **Hill, J. O., and K. M. Aguirre.** 1994. $CD4^+$ T cell-dependent acquired state of immunity that protects the brain against *Cryptococcus neoformans.* J. Immunol. **152:**2344–2350.
153. **Ho, W. Z., L. Song, and S. D. Douglas.** 1991. Human cytomegalovirus infection and trans-activation of HIV-1 LTR in human brain-derived cells. J. Acquir. Immune Defic. Syndr. **4:**1098–1106.
154. **Hornig, M., H. Weissenbock, N. Horscroft, and W. I. Lipkin.** 1999. An infection-based model of neurodevelopmental damage. Proc. Natl. Acad. Sci. USA **96:**12102–12107.
155. **Howe, D. K., and L. D. Sibley.** 1995. *Toxoplasma gondii* comprises three clonal lineages: correlation of parasite genotype with human disease. J. Infect. Dis. **172:**1561–1566.
156. **Hu, S., C. C. Chao, L. C. Ehrlich, W. S. Sheng, R. L. Sutton, G. L. Rockswold, and P. K. Peterson.** 1999. Inhibition of microglial cell RANTES production by IL-10 and TGF-beta. J. Leukoc. Biol. **65:**815–821.
157. **Hu, S., C. C. Chao, C. C. Hegg, S. Thayer, and P. K. Peterson.** 2000. Morphine inhibits human microglial cell production of, and migration towards, RANTES. J. Psychopharmacol. **14:**238–243.
158. **Hu, S., C. C. Chao, K. V. Khanna, G. Gekker, P. K. Peterson, and T. W. Molitor.** 1996. Cytokine and free radical production by porcine microglia. Clin. Immunol. Immunopathol. **78:**93–96.
159. **Hu, S., P. K. Peterson, and C. C. Chao.** 1998. Kappa-opioid modulation of human microglial cell superoxide anion generation. Biochem. Pharmacol. **56:**285–288.
160. **Hu, S., W. S. Sheng, J. R. Lokensgard, and P. K. Peterson.** 2002. Morphine induces apoptosis of human microglia and neurons. Neuropharmacology **42:**829–836.
161. **Hu, S., W. S. Sheng, P. K. Peterson, and C. C. Chao.** 1995. Cytokine modulation of murine microglial cell superoxide production. Glia **13:**45–50.
162. **Hunter, C. A., and J. Burke.** 1997. Neuropathogenesis of African sleeping sickness, p. 189–204. *In* P. K. Peterson and J. S. Remington (ed.), In defense of the brain: current concepts in the immunopathogenesis and clinical aspects of CNS infections. Blackwell Science, Malden, Mass.
163. **Husemann, J., J. D. Loike, R. Anankov, M. Febbraio, and S. C. Silverstein.** 2002. Scavenger receptors in neurobiology and neuropathology: their role on microglia and other cells of the nervous system. Glia **40:**195–205.
164. **Ihara, M., H. Tomimoto, M. Kinoshita, J. Oh, M. Noda, H. Wakita, I. Akiguchi, and H. Shibasaki.** 2001. Chronic cerebral hypoperfusion induces MMP-2 but not MMP-9 expression in the microglia and vascular endothelium of white matter. J. Cereb. Blood Flow Metab. **21:**828–834.
165. **Inoue, K.** 2002. Microglial activation by purines and pyrimidines. Glia **40:**156–163.
166. **Ivacko, J. A., R. Sun, and F. S. Silverstein.** 1996. Hypoxic-ischemic brain injury induces an acute microglial reaction in perinatal rats. Pediatr. Res. **39:**39–47.
167. **Jana, M., X. Liu, S. Koka, S. Ghosh, T. M. Petro, and K. Pahan.** 2001. Ligation of CD40 stimulates the induction of nitric-oxide synthase in microglial cells. J. Biol. Chem. **276:**44527–44533.
168. **Janabi, N., S. Chabrier, and M. Tardieu.** 1996. Endogenous nitric oxide activates prostaglandin F_{2alpha} production in human microglial cells but not in astrocytes. J. Immunol. **157:**2129–2135.
169. **Janabi, N., I. Hau, and M. Tardieu.** 1999. Negative feedback between prostaglandin and alpha- and beta-chemokine synthesis in human microglial cells and astrocytes. J. Immunol. **162:**1701–1706.
170. **Jiang, Z. G., C. Piggee, M. P. Heyes, C. Murphy, B. Quearry, M. Bauer, J. Zheng, H. E. Gendelman, and S. P. Markey.** 2001. Glutamate is a mediator of neurotoxicity in secretions of activated HIV-1-infected macrophages. J. Neuroimmunol. **117:**97–107.
171. **John, G. R., S. C. Lee, and C. F. Brosnan.** 2003. Cytokines: powerful regulators of glial cell activation. Neuroscientist **9:**10–22.
172. **Kaur, C., A. J. Hao, C. H. Wu, and E. A. Ling.** 2001. Origin of microglia. Microsc. Res. Tech. **54:**2–9.
173. **Kielian, T.** 2004. Microglia and chemokines in infectious diseases of the nervous system: views and reviews. Front. Biosci. **9:**732–750.
174. **Kielian, T., B. Barry, and W. F. Hickey.** 2001. CXC chemokine receptor-2 ligands are required for neutrophil-mediated host defense in experimental brain abscesses. J. Immunol. **166:**4634–4643.
175. **Kielian, T., P. Mayes, and M. Kielian.** 2002. Characterization of microglial responses to *Staphylococcus aureus:* effects on cytokine, costimulatory molecule, and Toll-like receptor expression. J. Neuroimmunol. **130:**86–99.
176. **Kim, Y. S., and M. G. Tauber.** 1996. Neurotoxicity of glia activated by gram-positive bacterial products depends on nitric oxide production. Infect. Immun. **64:**3148–3153.
177. **Kitai, R., M. L. Zhao, N. Zhang, L. L. Hua, and S. C. Lee.** 2000. Role of MIP-1beta and RANTES in HIV-1 infection of microglia: inhibition of infection and induction by IFNbeta. J. Neuroimmunol. **110:**230–239.
178. **Koenig, S., H. E. Gendelman, J. M. Orenstein, M. C. Dal Canto, G. H. Pezeshkpour, M. Yungbluth, F. Janotta, A. Aksamit, M. A. Martin, and A. S. Fauci.** 1986. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. Science **233:**1089–1093.
179. **Koka, P., K. He, J. A. Zack, S. Kitchen, W. Peacock, I. Fried, T. Tran, S. S. Yashar, and J. E. Merrill.** 1995. Human immunodeficiency virus 1 envelope proteins induce interleukin 1, tumor necrosis factor alpha, and nitric oxide in glial cultures derived from fetal, neonatal, and adult human brain. J. Exp. Med. **182:**941–951.
180. **Kotenko, S. V., S. Saccani, L. S. Izotova, O. V. Mirochnitchenko, and S. Pestka.** 2000. Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10). Proc. Natl. Acad. Sci. USA **97:**1695–1700.

181. **Koutsilieri, E., C. Scheller, F. Tribl, and P. Riederer.** 2002. Degeneration of neuronal cells due to oxidative stress—microglial contribution. Parkinsonism Relat. Disord. **8:**401–406.
182. **Kretzschmar, H. A., S. B. Prusiner, L. E. Stowring, and S. J. DeArmond.** 1986. Scrapie prion proteins are synthesized in neurons. Am. J. Pathol. **122:**1–5.
183. **Laflamme, N., H. Echchannaoui, R. Landmann, and S. Rivest.** 2003. Cooperation between toll-like receptor 2 and 4 in the brain of mice challenged with cell wall components derived from gram-negative and gram-positive bacteria. Eur. J. Immunol. **33:**1127–1138.
184. **Laflamme, N., G. Soucy, and S. Rivest.** 2001. Circulating cell wall components derived from gram-negative, not gram-positive, bacteria cause a profound induction of the gene-encoding Toll-like receptor 2 in the CNS. J. Neurochem. **79:**648–657.
185. **Lane, J. H., V. G. Sasseville, M. O. Smith, P. Vogel, D. R. Pauley, M. P. Heyes, and A. A. Lackner.** 1996. Neuroinvasion by simian immunodeficiency virus coincides with increased numbers of perivascular macrophages/microglia and intrathecal immune activation. J. Neurovirol. **2:**423–432.
186. **Lavi, E., J. M. Strizki, A. M. Ulrich, W. Zhang, L. Fu, Q. Wang, M. O'Connor, J. A. Hoxie, and F. Gonzalez-Scarano.** 1997. CXCR-4 (fusin), a coreceptor for the type 1 human immunodeficiency virus (HIV-1), is expressed in the human brain in a variety of cell types, including microglia and neurons. Am. J. Pathol. **151:**1035–1042.
187. **Lazarini, F., T. N. Tham, P. Casanova, F. Arenzana-Seisdedos, and M. Dubois-Dalcq.** 2003. Role of the alpha-chemokine stromal cell-derived factor (SDF-1) in the developing and mature central nervous system. Glia **42:**139–148.
188. **Le, W., D. Rowe, W. Xie, I. Ortiz, Y. He, and S. H. Appel.** 2001. Microglial activation and dopaminergic cell injury: an in vitro model relevant to Parkinson's disease. J. Neurosci. **21:**8447–8455.
189. **Lecointe, D., N. Dugas, P. Leclerc, C. Hery, J. F. Delfraissy, and M. Tardieu.** 2002. Human cytomegalovirus infection reduces surface CCR5 expression in human microglial cells, astrocytes and monocyte-derived macrophages. Microbes Infect. **4:**1401–1408.
190. **Ledeboer, A., J. J. P. Breve, A. Wierinckx, S. van der Jagt, A. F. Bristow, J. E. Leysen, F. J. H. Tilders, and A.-M. van Dam.** 2002. Expression and regulation of interleukin-10 and interleukin-10 receptor in rat astroglial and microglial cells. Eur. J. Neurosci. **16:**1175–1185.
191. **Lee, S. C., D. W. Dickson, and A. Casadevall.** 1996. Pathology of cryptococcal meningoencephalitis: analysis of 27 patients with pathogenetic implications. Hum. Pathol. **27:**839–847.
192. **Lee, S. C., Y. Kress, D. W. Dickson, and A. Casadevall.** 1995. Human microglia mediate anti-*Cryptococcus neoformans* activity in the presence of specific antibody. J. Neuroimmunol. **62:**43–52.
193. **Lee, S. C., Y. Kress, M. L. Zhao, D. W. Dickson, and A. Casadevall.** 1995. *Cryptococcus neoformans* survive and replicate in human microglia. Lab. Investig. **73:**871–879.
194. **Lee, S. C., W. Liu, C. F. Brosnan, and D. W. Dickson.** 1992. Characterization of primary human fetal dissociated central nervous system cultures with an emphasis on microglia. Lab. Investig. **67:**465–476.
195. **Lee, S. C., W. Liu, D. W. Dickson, C. F. Brosnan, and J. W. Berman.** 1993. Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-1 beta. J. Immunol. **150:**2659–2667.
196. **Lee, Y. B., A. Nagai, and S. U. Kim.** 2002. Cytokines, chemokines, and cytokine receptors in human microglia. J. Neurosci. Res. **69:**94–103.
197. **Leonard, J. M., and R. M. Des Prez.** 1990. Tuberculous meningitis. Infect. Dis. Clin. North Am. **4:**769–787.
198. **Li, J., B. Gran, G. X. Zhang, E. S. Ventura, I. Siglienti, A. Rostami, and M. Kamoun.** 2003. Differential expression and regulation of IL-23 and IL-12 subunits and receptors in adult mouse microglia. J. Neurol. Sci. **215:**95–103.
199. **Licinio, J., and M. L. Wong.** 1997. Pathways and mechanisms for cytokine signaling of the central nervous system. J. Clin. Investig. **100:**2941–2947.
200. **Ling, E. A., and W. C. Wong.** 1993. The origin and nature of ramified and amoeboid microglia: a historical review and current concepts. Glia **7:**9–18.
201. **Lipovsky, M. M., G. Gekker, W. R. Anderson, T. W. Molitor, P. K. Peterson, and A. I. Hoepelman.** 1997. Phagocytosis of nonopsonized *Cryptococcus neoformans* by swine microglia involves CD14 receptors. Clin. Immunol. Immunopathol. **84:**208–211.
202. **Lipovsky, M. M., G. Gekker, S. Hu, L. C. Ehrlich, A. I. Hoepelman, and P. K. Peterson.** 1998. Cryptococcal glucuronoxylomannan induces interleukin (IL)-8 production by human microglia but inhibits neutrophil migration toward IL-8. J. Infect. Dis. **177:**260–263.
203. **Lipovsky, M. M., G. Gekker, S. Hu, A. I. Hoepelman, and P. K. Peterson.** 1998. Morphine enhances complement receptor-mediated phagocytosis of *Cryptococcus neoformans* by human microglia. Clin. Immunol. Immunopathol. **87:**163–167.
204. **Lipovsky, M. M., A. E. Juliana, G. Gekker, S. Hu, A. I. Hoepelman, and P. K. Peterson.** 1998. Effect of cytokines on anticryptococcal activity of human microglial cells. Clin. Diagn. Lab. Immunol. **5:**410–411.
205. **Lipton, S. A., and H. E. Gendelman.** 1995. Seminars in medicine of the Beth Israel Hospital, Boston. Dementia associated with the acquired immunodeficiency syndrome. N. Engl. J. Med. **332:**934–940.
206. **Liu, B., L. Du, and J. S. Hong.** 2000. Naloxone protects rat dopaminergic neurons against inflammatory damage through inhibition of microglia activation and superoxide generation. J. Pharmacol. Exp. Ther. **293:**607–617.
207. **Liu, B., H. M. Gao, and J. S. Hong.** 2003. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. Environ. Health Perspect. **111:**1065–1073.
208. **Liu, B., and J. S. Hong.** 2003. Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention. J. Pharmacol. Exp. Ther. **304:**1–7.
209. **Liu, Y., L. Qin, G. Li, W. Zhang, L. An, B. Liu, and J. S. Hong.** 2003. Dextromethorphan protects dopaminergic neurons against inflammation-mediated degeneration through inhibition of microglial activation. J. Pharmacol. Exp. Ther. **305:**212–218.
210. **Liuzzi, G. M., M. P. Santacroce, W. J. Peumans, E. J. Van Damme, B. Dubois, G. Opdenakker, and P. Riccio.** 1999. Regulation of gelatinases in microglia and astrocyte cell cultures by plant lectins. Glia **27:**53–61.
211. **Lodge, P. A., and S. Sriram.** 1996. Regulation of microglial activation by TGB-beta, IL-10, and CSF-1. J. Leukoc. Biol. **60:**502–508.
212. **Lokensgard, J. R., C. C. Chao, G. Gekker, S. Hu, and P. K. Peterson.** 1998. Benzodiazepines, glia, and HIV-1 neuropathogenesis. Mol. Neurobiol. **18:**23–33.
213. **Lokensgard, J. R., M. C. Cheeran, G. Gekker, S. Hu, C. C. Chao, and P. K. Peterson.** 1999. Human cytomegalovirus replication and modulation of apoptosis in astrocytes. J. Hum. Virol. **2:**91–101.
214. **Lokensgard, J. R., M. C. Cheeran, S. Hu, G. Gekker, and P. K. Peterson.** 2002. Glial cell responses to herpesvirus infections: role in defense and immunopathogenesis. J. Infect. Dis. **186(**Suppl. 2**):**S171–S179.
215. **Lokensgard, J. R., G. Gekker, S. Hu, A. F. Arthur, C. C. Chao, and P. K. Peterson.** 1997. Diazepam-mediated inhibition of human immunodeficiency virus type 1 expression in human brain cells. Antimicrob. Agents Chemother. **41:**2566–2569.
216. **Lokensgard, J. R., S. Hu, C. C. Hegg, S. A. Thayer, G. Gekker, and P. K. Peterson.** 2001. Diazepam inhibits HIV-1 Tat-induced migration of human microglia. J. Neurovirol. **7:**481–486.
217. **Lokensgard, J. R., S. Hu, W. Sheng, M. vanOijen, D. Cox, M. C. Cheeran, and P. K. Peterson.** 2001. Robust expression of TNF-alpha, IL-1beta, RANTES, and IP-10 by human microglial cells during nonproductive infection with herpes simplex virus. J. Neurovirol. **7:**208–219.
218. **Lorenzl, S., D. S. Albers, S. Narr, J. Chirichigno, and M. F. Beal.** 2002. Expression of MMP-2, MMP-9, and MMP-1 and their endogenous counterregulators TIMP-1 and TIMP-2 in postmortem brain tissue of Parkinson's disease. Exp. Neurol. **178:**13–20.
219. **Luder, C. G., M. Giraldo-Velasquez, M. Sendtner, and U. Gross.** 1999. *Toxoplasma gondii* in primary rat CNS cells: differential contribution of neurons, astrocytes, and microglial cells for the intracerebral development and stage differentiation. Exp. Parasitol. **93:**23–32.
220. **Luder, C. G., C. Lang, M. Giraldo-Velasquez, M. Algner, J. Gerdes, and U. Gross.** 2003. *Toxoplasma gondii* inhibits MHC class II expression in neural antigen-presenting cells by down-regulating the class II transactivator CIITA. J. Neuroimmunol. **134:**12–24.
221. **Maciejewski-Lenoir, D., S. Chen, L. Feng, R. Maki, and K. B. Bacon.** 1999. Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR-1-expressing microglia. J. Immunol. **163:**1628–1635.
222. **Maeda, A., and R. A. Sobel.** 1996. Matrix metalloproteinases in the normal human central nervous system, microglial nodules, and multiple sclerosis lesions. J. Neuropathol. Exp. Neurol. **55:**300–309.
223. **Mahalingam, S., J. M. Farber, and G. Karupiah.** 1999. The interferon-inducible chemokines MuMig and Crg-2 exhibit antiviral activity in vivo. J. Virol. **73:**1479–1491.
224. **Male, D., and P. Rezaie.** 2001. Colonisation of the human central nervous system by microglia: the roles of chemokines and vascular adhesion molecules. Prog. Brain Res. **132:**81–93.
225. **Mallat, M., and B. Chamak.** 1994. Brain macrophages: neurotoxic or neurotrophic effector cells? J. Leukoc. Biol. **56:**416–422.
226. **Manuelidis, L., W. Fritch, and Y. G. Xi.** 1997. Evolution of a strain of CJD that induces BSE-like plaques. Science **277:**94–98.
227. **Marella, M., and J. Chabry.** 2004. Neurons and astrocytes respond to prion infection by inducing microglia recruitment. J. Neurosci. **24:**620–627.
228. **Marzolo, M. P., R. von Bernhardi, and N. C. Inestrosa.** 1999. Mannose receptor is present in a functional state in rat microglial cells. J. Neurosci. Res. **58:**387–395.
229. **Maschke, M., O. Kastrup, S. Esser, B. Ross, U. Hengge, and A. Hufnagel.** 2000. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). J. Neurol. Neurosurg. Psychiatry **69:**376–380.
230. **Mathisen, G. E., and J. P. Johnson.** 1997. Brain abscess. Clin. Infect. Dis. **25:**763–779; quiz, 780–781.
231. **Mayer, A. M., M. Hall, M. J. Fay, P. Lamar, C. Pearson, W. C. Prozialeck, V. K. Lehmann, P. B. Jacobson, A. M. Romanic, T. Uz, and H. Manev.** 2001. Effect of a short-term in vitro exposure to the marine toxin domoic acid on viability, tumor necrosis factor-alpha, matrix metalloproteinase-9 and superoxide anion release by rat neonatal microglia. BMC Pharmacol. **1:**7.

232. **Mazzolla, R., R. Barluzzi, A. Brozzetti, J. R. Boelaert, T. Luna, S. Saleppico, F. Bistoni, and E. Blasi.** 1997. Enhanced resistance to *Cryptococcus neoformans* infection induced by chloroquine in a murine model of meningoencephalitis. Antimicrob. Agents Chemother. **41:**802–807.
233. **McCarthy, M., D. Auger, and S. R. Whittemore.** 2000. Human cytomegalovirus causes productive infection and neuronal injury in differentiating fetal human central nervous system neuroepithelial precursor cells. J. Hum. Virol. **3:**215–228.
234. **McCarthy, M., J. He, and C. Wood.** 1998. HIV-1 strain-associated variability in infection of primary neuroglia. J. Neurovirol. **4:**80–89.
235. **McCarthy, M., C. Wood, L. Fedoseyeva, and S. R. Whittemore.** 1995. Media components influence viral gene expression assays in human fetal astrocyte cultures. J. Neurovirol. **1:**275–285.
236. **McGeer, P. L., and E. G. McGeer.** 1995. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res. Rev. **21:**195–218.
237. **McGrath, N., N. E. Anderson, M. C. Croxson, and K. F. Powell.** 1997. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. J. Neurol. Neurosurg. Psychiatry **63:**321–326.
238. **McHattie, S. J., D. R. Brown, and M. M. Bird.** 1999. Cellular uptake of the prion protein fragment PrP106–126 in vitro. J. Neurocytol. **28:**149–159.
239. **McManus, C. M., C. F. Brosnan, and J. W. Berman.** 1998. Cytokine induction of MIP-1 alpha and MIP-1 beta in human fetal microglia. J. Immunol. **160:**1449–1455.
240. **Meda, L., P. Baron, E. Prat, E. Scarpini, G. Scarlato, M. A. Cassatella, and F. Rossi.** 1999. Proinflammatory profile of cytokine production by human monocytes and murine microglia stimulated with beta-amyloid[25–35]. J. Neuroimmunol. **93:**45–52.
241. **Medana, I. M., T. Chan-Ling, and N. H. Hunt.** 2000. Reactive changes of retinal microglia during fatal murine cerebral malaria: effects of dexamethasone and experimental permeabilization of the blood-brain barrier. Am. J. Pathol. **156:**1055–1065.
242. **Medana, I. M., N. H. Hunt, and T. Chan-Ling.** 1997. Early activation of microglia in the pathogenesis of fatal murine cerebral malaria. Glia **19:**91–103.
243. **Medana, I. M., N. H. Hunt, and G. Chaudhri.** 1997. Tumor necrosis factor-alpha expression in the brain during fatal murine cerebral malaria: evidence for production by microglia and astrocytes. Am. J. Pathol. **150:**1473–1486.
244. **Merrill, J. E.** 1992. Proinflammatory and antiinflammatory cytokines in multiple sclerosis and central nervous system acquired immunodeficiency syndrome. J. Immunother. **12:**167–170.
245. **Messam, C. A., and E. O. Major.** 2000. Stages of restricted HIV-1 infection in astrocyte cultures derived from human fetal brain tissue. J. Neurovirol. **6**(Suppl. 1)**:**S90–S94.
246. **Meucci, O., A. Fatatis, A. A. Simen, and R. J. Miller.** 2000. Expression of CX3CR1 chemokine receptors on neurons and their role in neuronal survival. Proc. Natl. Acad. Sci. USA **97:**8075–8080.
247. **Meyding-Lamade, U., J. Haas, W. Lamade, K. Stingele, R. Kehm, A. Fath, K. Heinrich, B. Storch Hagenlocher, and B. Wildemann.** 1998. Herpes simplex virus encephalitis: long-term comparative study of viral load and the expression of immunologic nitric oxide synthase in mouse brain tissue. Neurosci. Lett. **244:**9–12.
248. **Minagar, A., P. Shapshak, R. Fujimura, R. Ownby, M. Heyes, and C. Eisdorfer.** 2002. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. J. Neurol. Sci. **202:**13–23.
249. **Minton, K.** 2001. Immune mechanisms in neurological disorders: protective or destructive? Trends Immunol. **22:**655–657.
250. **Mittelbronn, M., K. Dietz, H. J. Schluesener, and R. Meyermann.** 2001. Local distribution of microglia in the normal adult human central nervous system differs by up to one order of magniture. Acta Neuropathol. **101:**249–255.
251. **Monje, M. L., H. Toda, and T. D. Palmer.** 2003. Inflammatory blockade restores adult hippocampal neurogenesis. Science **302:**1760–1765.
252. **Monsonego, A., J. Imitola, V. Zota, T. Oida, and H. L. Weiner.** 2003. Microglia-mediated nitric oxide cytotoxicity of T cells following amyloid beta-peptide presentation to Th1 cells. J. Immunol. **171:**2216–2224.
253. **Monsonego, A., and H. L. Weiner.** 2003. Immunotherapeutic approaches to Alzheimer's disease. Science **302:**834–838.
254. **Morner, A., J. A. Thomas, E. Bjorling, P. J. Munson, S. B. Lucas, and A. McKnight.** 2003. Productive HIV-2 infection in the brain is restricted to macrophages/microglia. AIDS **17:**1451–1455.
255. **Moser, M., R. J. Colello, U. Pott, and B. Oesch.** 1995. Developmental expression of the prion protein gene in glial cells. Neuron **14:**509–517.
256. **Moss, D. W., and T. E. Bates.** 2001. Activation of murine microglial cell lines by lipopolysaccharide and interferon-gamma causes NO-mediated decreases in mitochondrial and cellular function. Eur. J. Neurosci. **13:**529–538.
257. **Murphy, G. M., Jr., X. C. Jia, Y. Song, E. Ong, R. Shrivastava, V. Bocchini, Y. L. Lee, and L. F. Eng.** 1995. Macrophage inflammatory protein 1-alpha mRNA expression in an immortalized microglial cell line and cortical astrocyte cultures. J. Neurosci. Res. **40:**755–763.
258. **Murray, H. W., B. Y. Rubin, H. Masur, and R. B. Roberts.** 1984. Impaired production of lymphokines and immune (gamma) interferon in the acquired immunodeficiency syndrome. N. Engl. J. Med. **310:**883–888.
259. **Nagai, A., E. Nakagawa, K. Hatori, H. B. Choi, J. G. McLarnon, M. A. Lee, and S. U. Kim.** 2001. Generation and characterization of immortalized human microglial cell lines: expression of cytokines and chemokines. Neurobiol. Dis. **8:**1057–1068.
260. **Nakamura, Y.** 2002. Regulating factors for microglial activation. Biol. Pharm. Bull. **25:**945–953.
261. **Nebuloni, M., A. Pellegrinelli, A. Ferri, A. Tosoni, S. Bonetto, P. Zerbi, R. Boldorini, L. Vago, and G. Costanzi.** 2000. Etiology of microglial nodules in brains of patients with acquired immunodeficiency syndrome. J. Neurovirol. **6:**46–50.
262. **Nelson, P. T., L. A. Soma, and E. Lavi.** 2002. Microglia in diseases of the central nervous system. Ann. Med. **34:**491–500.
263. **New, D. R., M. Ma, L. G. Epstein, A. Nath, and H. A. Gelbard.** 1997. Human immunodeficiency virus type 1 Tat protein induces death by apoptosis in primary human neuron cultures. J. Neurovirol. **3:**168–173.
264. **Nguyen, M. D., J. P. Julien, and S. Rivest.** 2002. Innate immunity: the missing link in neuroprotection and neurodegeneration? Nat. Rev. Neurosci. **3:**216–227.
265. **Nishiyori, A., M. Minami, Y. Ohtani, S. Takami, J. Yamamoto, N. Kawaguchi, T. Kume, A. Akaike, and M. Satoh.** 1998. Localization of fractalkine and CX3CR1 mRNAs in rat brain: does fractalkine play a role in signaling from neuron to microglia? FEBS Lett. **429:**167–172.
266. **Nottet, H. S., M. Jett, C. R. Flanagan, Q. H. Zhai, Y. Persidsky, A. Rizzino, E. W. Bernton, P. Genis, T. Baldwin, J. Schwartz, et al.** 1995. A regulatory role for astrocytes in HIV-1 encephalitis. An overexpression of eicosanoids, platelet-activating factor, and tumor necrosis factor-alpha by activated HIV-1-infected monocytes is attenuated by primary human astrocytes. J. Immunol. **154:**3567–3581.
267. **Nuovo, G. J., and M. L. Alfieri.** 1996. AIDS dementia is associated with massive, activated HIV-1 infection and concomitant expression of several cytokines. Mol. Med. **2:**358–366.
268. **Ogata, T., M. Chuai, T. Morino, H. Yamamoto, Y. Nakamura, and P. Schubert.** 2003. Adenosine triphosphate inhibits cytokine release from lipopolysaccharide-activated microglia via P2y receptors. Brain Res. **981:**174–183.
269. **O'Keefe, G. M., V. T. Nguyen, and E. N. Benveniste.** 2002. Regulation and function of class II major histocompatibility complex, CD40, and B7 expression in macrophages and microglia: implications in neurological diseases. J. Neurovirol. **8:**496–512.
270. **Olsson, T., M. Bakhiet, B. Hojeberg, A. Ljungdahl, C. Edlund, G. Andersson, H. P. Ekre, W. P. Fung-Leung, T. Mak, H. Wigzell, et al.** 1993. CD8 is critically involved in lymphocyte activation by a *T. brucei brucei*-released molecule. Cell **72:**715–727.
271. **Overmyer, M., S. Helisalmi, H. Soininen, M. Laakso, P. Riekkinen, Sr., and I. Alafuzoff.** 1999. Reactive microglia in aging and dementia: an immunohistochemical study of postmortem human brain tissue. Acta Neuropathol. **97:**383–392.
272. **Park, J. H., and S. H. Shin.** 1996. Induction of IL-12 gene expression in the brain in septic shock. Biochem. Biophys. Res. Commun. **224:**391–396.
273. **Perry, V. H., and L. J. Lawson.** 1992. Macrophages in the central nervous system, p. 393–413. *In* C. Lewis (ed.), The macrophage. Oxford University Press, Oxford, United Kingdom.
274. **Persidsky, Y., and H. E. Gendelman.** 2003. Mononuclear phagocyte immunity and the neuropathogenesis of HIV-1 infection. J. Leukoc. Biol. **74:**691–701.
275. **Persidsky, Y., A. Ghorpade, J. Rasmussen, J. Limoges, X. J. Liu, M. Stins, M. Fiala, D. Way, K. S. Kim, M. H. Witte, M. Weinand, L. Carhart, and H. E. Gendelman.** 1999. Microglial and astrocyte chemokines regulate monocyte migration through the blood-brain barrier in human immunodeficiency virus-1 encephalitis. Am. J. Pathol. **155:**1599–1611.
276. **Peterson, P. K., G. Gekker, M. Bornemann, D. Chatterjee, and C. C. Chao.** 1995. Thalidomide inhibits lipoarabinomannan-induced upregulation of human immunodeficiency virus expression. Antimicrob. Agents Chemother. **39:**2807–2809.
277. **Peterson, P. K., G. Gekker, S. Hu, W. B. Anderson, M. Teichert, C. C. Chao, and T. W. Molitor.** 1996. Multinucleated giant cell formation of swine microglia induced by *Mycobacterium bovis.* J. Infect. Dis. **173:**1194–1201.
278. **Peterson, P. K., G. Gekker, S. Hu, and C. C. Chao.** 1997. Microglia: a "double-edged sword," p. 31–55. *In* P. K. Peterson and J. S. Remington (ed.), In defense of the brain: current concepts in the immunopathogenesis and clinical aspects of CNS infections. Blackwell Science, Malden, Mass.
279. **Peterson, P. K., G. Gekker, S. Hu, J. Lokensgard, P. S. Portoghese, and C. C. Chao.** 1999. Endomorphin-1 potentiates HIV-1 expression in human brain cell cultures: implication of an atypical mu-opioid receptor. Neuropharmacology **38:**273–278.
280. **Peterson, P. K., G. Gekker, S. Hu, W. S. Sheng, W. R. Anderson, R. J. Ulevitch, P. S. Tobias, K. V. Gustafson, T. W. Molitor, and C. C. Chao.** 1995. CD14 receptor-mediated uptake of nonopsonized *Mycobacterium tuberculosis* by human microglia. Infect. Immun. **63:**1598–1602.

281. **Peterson, P. K., G. Gekker, S. Hu, W. S. Sheng, T. W. Molitor, and C. C. Chao.** 1995. Morphine stimulates phagocytosis of *Mycobacterium tuberculosis* by human microglial cells: involvement of a G protein-coupled opiate receptor. Adv. Neuroimmunol. **5:**299–309.
282. **Peterson, P. K., S. Hu, W. R. Anderson, and C. C. Chao.** 1994. Nitric oxide production and neurotoxicity mediated by activated microglia from human versus mouse brain. J. Infect. Dis. **170:**457–460.
283. **Peterson, P. K., S. Hu, J. Salak-Johnson, T. W. Molitor, and C. C. Chao.** 1997. Differential production of and migratory response to beta chemokines by human microglia and astrocytes. J. Infect. Dis. **175:**478–481.
284. **Peterson, P. K., S. Hu, W. S. Sheng, F. H. Kravitz, T. W. Molitor, D. Chatterjee, and C. C. Chao.** 1995. Thalidomide inhibits tumor necrosis factor-alpha production by lipopolysaccharide- and lipoarabinomannan-stimulated human microglial cells. J. Infect. Dis. **172:**1137–1140.
285. **Peudenier, S., C. Hery, L. Montagnier, and M. Tardieu.** 1991. Human microglial cells: characterization in cerebral tissue and in primary culture, and study of their susceptibility to HIV-1 infection. Ann. Neurol. **29:**152–161.
286. **Peyrin, J. M., C. I. Lasmezas, S. Haik, F. Tagliavini, M. Salmona, A. Williams, D. Richie, J. P. Deslys, and D. Dormont.** 1999. Microglial cells respond to amyloidogenic PrP peptide by the production of inflammatory cytokines. Neuroreport **10:**723–729.
287. **Pfister, H. W., W. Feiden, and K. M. Einhaupl.** 1993. Spectrum of complications during bacterial meningitis in adults. Results of a prospective clinical study. Arch. Neurol. **50:**575–581.
288. **Philip, K. A., M. J. Dascombe, P. A. Fraser, and V. W. Pentreath.** 1994. Blood-brain barrier damage in experimental African trypanosomiasis. Ann. Trop. Med. Parasitol. **88:**607–616.
289. **Poland, S. D., L. L. Bambrick, G. A. Dekaban, and G. P. Rice.** 1994. The extent of human cytomegalovirus replication in primary neurons is dependent on host cell differentiation. J. Infect. Dis. **170:**1267–1271.
290. **Polfliet, M. M. J., F. van de Veerdonk, E. A. Dopp, E. M. L. van Kesteren-Hendrikx, N. van Rooijen, C. D. Dijkstra, and T. K. van den Berg.** 2002. The role of perivascular and meningeal macrophages in experimental allergic encephalomyelitis. J. Neuroimmunol. **122:**1–8.
291. **Polfliet, M. M. J., P. J. G. Zwijnenburg, A. M. van Furth, T. van der Poll, E. A. Dopp, C. R. de Lavalette, E. M. L. van Kesteren-Hendrikx, N. van Rooijen, C. D. Dijkstra, and T. K. van den Berg.** 2001. Meningeal and perivascular macrophages of the central nervous system play a progective role during bacterial meningitis. J. Immunol. **167:**4644–4650.
292. **Pratt, B. M., and J. M. McPherson.** 1997. TGF-beta in the central nervous system: potential roles in ischemic injoury and neurodegenerative diseases. Cytokine Growth Factor Rev. **8:**267–292.
293. **Prusiner, S. B.** 1991. Molecular biology of prion diseases. Science **252:**1515–1522.
294. **Pulliam, L., J. A. Clarke, D. McGuire, and M. S. McGrath.** 1994. Investigation of HIV-infected macrophage neurotoxin production from patients with AIDS dementia. Adv. Neuroimmunol. **4:**195–198.
295. **Pulliam, L., D. Moore, and D. C. West.** 1995. Human cytomegalovirus induces IL-6 and TNF alpha from macrophages and microglial cells: possible role in neurotoxicity. J. Neurovirol. **1:**219–227.
296. **Rasley, A., J. Anguita, and I. Marriott.** 2002. *Borrelia burgdorferi* induces inflammatory mediator production by murine microglia. J. Neuroimmunol. **130:**22–31.
297. **Reddehase, M. J.** 2000. The immunogenicity of human and murine cytomegaloviruses. Curr. Opin. Immunol. **12:**738.
298. **Ren, L. Q., N. Gourmala, H. W. Boddeke, and P. J. Gebicke-Haerter.** 1998. Lipopolysaccharide-induced expression of IP-10 mRNA in rat brain and in cultured rat astrocytes and microglia. Brain. Res. Mol. Brain. Res. **59:**256–263.
299. **Rezaie, P., and P. L. Lantos.** 2001. Microglia and the pathogenesis of spongiform encephalopathies. Brain Res. Rev. **35:**55–72.
300. **Rezaie, P., G. Trillo-Pazos, I. P. Everall, and D. K. Male.** 2002. Expression of beta-chemokines and chemokine receptors in human fetal astrocyte and microglial co-cultures: potential role of chemokines in the developing CNS. Glia **37:**64–75.
301. **Rezaie, P., G. Trillo-Pazos, J. Greenwood, I. P. Everall, and D. K. Male.** 2002. Motility and ramification of human fetal microglia in culture: an investigation using time-lapse video microscopy and image analysis. Exp. Cell Res. **274:**68–82.
302. **Rietschel, E. T., and H. Brade.** 1992. Bacterial endotoxins. Sci. Am. **267:**54–61.
303. **Ring, A., J. N. Weiser, and E. I. Tuomanen.** 1998. Pneumococcal trafficking across the blood-brain barrier. Molecular analysis of a novel bidirectional pathway. J. Clin. Investig. **102:**347–360.
304. **Rogers, J., and L. F. Lue.** 2001. Microglial chemotaxis, activation, and phagocytosis of amyloid beta-peptide as linked phenomena in Alzheimer's disease. Neurochem. Int. **39:**333–340.
305. **Rosenberg, G. A., L. A. Cunningham, J. Wallace, S. Alexander, E. Y. Estrada, M. Grossetete, A. Razhagi, K. Miller, and A. Gearing.** 2001. Immunohistochemistry of matrix metalloproteinases in reperfusion injury to rat brain: activation of MMP-9 linked to stromelysin-1 and microglia in cell cultures. Brain Res. **893:**104–112.
306. **Rosenberg, G. A., N. Sullivan, and M. M. Esiri.** 2001. White matter damage is associated with matrix metalloproteinases in vascular dementia. Stroke **32:**1162–1168.
307. **Rosenstiel, P., R. Lucius, G. Deuschl, J. Sievers, and H. Wilms.** 2001. From theory to therapy: implication from an in vitro model of ramified microglia. Microsc. Res. Tech. **54:**18–25.
308. **Rothwell, N. J.** 1998. Interleukin-1 and neurodegeneration. Neuroscientist **4:**195–201.
309. **Rozenfeld, C., R. Martinez, R. T. Figueiredo, M. T. Bozza, F. R. Lima, A. L. Pires, P. M. Silva, A. Bonomo, J. Lannes-Vieira, W. De Souza, and V. Moura-Neto.** 2003. Soluble factors released by *Toxoplasma gondii*-infected astrocytes down-modulate nitric oxide production by gamma interferon-activated microglia and prevent neuronal degeneration. Infect. Immun. **71:**2047–2057.
310. **Saito, Y., L. R. Sharer, L. G. Epstein, J. Michaels, M. Mintz, M. Louder, K. Golding, T. A. Cvetkovich, and B. M. Blumberg.** 1994. Overexpression of nef as a marker for restricted HIV-1 infection of astrocytes in postmortem pediatric central nervous tissues. Neurology **44:**474–481.
311. **Samson, M., F. Libert, B. J. Doranz, J. Rucker, C. Liesnard, C. M. Farber, S. Saragosti, C. Lapoumeroulie, J. Cognaux, C. Forceille, G. Muyldermans, C. Verhofstede, G. Burtonboy, M. Georges, T. Imai, S. Rana, Y. Yi, R. J. Smyth, R. G. Collman, R. W. Doms, G. Vassart, and M. Parmentier.** 1996. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature **382:**722–725.
312. **Sapp, E., K. B. Kegel, N. Aronin, T. Hashikawa, Y. Uchiyama, K. Tohyama, P. G. Bhide, J. P. Vonsattel, and M. DiFiglia.** 2001. Early and progressive accumulation of reactive microglia in the Huntington disease brain. J. Neuropathol. Exp. Neurol. **60:**161–172.
313. **Scheld, W. M., U. Koedel, B. Nathan, and H. W. Pfister.** 2002. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J. Infect. Dis. **186**(Suppl. 2)**:**S225–S233.
314. **Schluesener, H. J., P. G. Kremsner, and R. Meyermann.** 2001. Heme oxygenase-1 in lesions of human cerebral malaria. Acta Neuropathol. **101:**65–68.
315. **Schluesener, H. J., P. G. Kremsner, and R. Meyermann.** 1998. Widespread expression of MRP8 and MRP14 in human cerebral malaria by microglial cells. Acta Neuropathol. **96:**575–580.
316. **Schluter, D., N. Kaefer, H. Hof, O. D. Wiestler, and M. Deckert-Schluter.** 1997. Expression pattern and cellular origin of cytokines in the normal and *Toxoplasma gondii*-infected murine brain. Am. J. Pathol. **150:**1021–1035.
317. **Schluter, D., L. Y. Kwok, S. Lutjen, S. Soltek, S. Hoffmann, H. Korner, and M. Deckert.** 2003. Both lymphotoxin-alpha and TNF are crucial for control of *Toxoplasma gondii* in the central nervous system. J. Immunol. **170:**6172–6182.
318. **Schubert, P., T. Ogata, C. Marchini, and S. Ferroni.** 2001. Glia-related pathomechanisms in Alzheimer's disease: a therapeutic target? Mech. Ageing Dev. **123:**47–57.
319. **Schut, R. L., G. Gekker, S. Hu, C. C. Chao, C. Pomeroy, M. C. Jordan, and P. K. Peterson.** 1994. Cytomegalovirus replication in murine microglial cell cultures: suppression of permissive infection by interferon-gamma. J. Infect. Dis. **169:**1092–1096.
320. **Schwab, J. M., H. J. Schluesener, K. Seid, and R. Meyermann.** 2001. IL-16 is differentially expressed in the developing human fetal brain by microglial cells in zones of neuropoesis. Int. J. Dev. Neurosci. **19:**93–100.
321. **Shams, H., B. Wizel, D. L. Lakey, B. Samten, R. Vankayalapati, R. H. Valdivia, R. L. Kitchens, D. E. Griffith, and P. F. Barnes.** 2003. The CD14 receptor does not mediate entry of *Mycobacterium tuberculosis* into human mononuclear phagocytes. FEMS Immunol. Med. Microbiol. **36:**63–69.
322. **Sheng, W. S., S. Hu, C. C. Hegg, S. A. Thayer, and P. K. Peterson.** 2000. Activation of human microglial cells by HIV-1 gp41 and Tat proteins. Clin. Immunol. **96:**243–251.
323. **Shieh, J. T., A. V. Albright, M. Sharron, S. Gartner, J. Strizki, R. W. Doms, and F. Gonzalez-Scarano.** 1998. Chemokine receptor utilization by human immunodeficiency virus type 1 isolates that replicate in microglia. J. Virol. **72:**4243–4249.
324. **Shimeld, C., J. L. Whiteland, S. M. Nicholls, E. Grinfeld, D. L. Easty, H. Gao, and T. J. Hill.** 1995. Immune cell infiltration and persistence in the mouse trigeminal ganglion after infection of the cornea with herpes simplex virus type 1. J. Neuroimmunol. **61:**7–16.
325. **Shimeld, C., J. L. Whiteland, N. A. Williams, D. L. Easty, and T. J. Hill.** 1997. Cytokine production in the nervous system of mice during acute and latent infection with herpes simplex virus type 1. J. Gen. Virol. **78:**3317–3325.
326. **Shrikant, P., and N. Benveniste.** 1996. The central nervous system as an immunocompetent organ. J. Immunol. **157:**1819–1822.
327. **Si, Q., M. Cosenza, M. L. Zhao, H. Goldstein, and S. C. Lee.** 2002. GM-CSF and M-CSF modulate beta-chemokine and HIV-1 expression in microglia. Glia **39:**174–183.
328. **Si, Q., M. O. Kim, M. L. Zhao, N. R. Landau, H. Goldstein, and S. Lee.**

2002. Vpr- and Nef-dependent induction of RANTES/CCL5 in microglial cells. Virology **301:**342–353.
329. **Simpson, J. E., J. Newcombe, M. L. Cuzner, and M. N. Woodroofe.** 1998. Expression of monocyte chemoattractant protein-1 and other beta-chemokines by resident glia and inflammatory cells in multiple sclerosis lesions. J. Neuroimmunol. **84:**238–249.
330. **Skiest, D. J.** 2002. Focal neurological disease in patients with acquired immunodeficiency syndrome. Clin. Infect. Dis. **34:**103–115.
331. **Skoldenberg, B.** 1996. Herpes simplex encephalitis. Scand. J. Infect. Dis. Suppl. **100:**8–13.
332. **Smith, M. E.** 2001. Phagocytic properties of microglia in vitro: implications for a role in multiple sclerosis and EAE. Microsc. Res. Tech. **54:**81–94.
333. **Song, X., S. Shapiro, D. L. Goldman, A. Casadevall, M. Scharff, and S. C. Lee.** 2002. Fc gamma receptor I- and III-mediated macrophage inflammatory protein 1α induction in primary human and murine microglia. Infect. Immun. **70:**5177–5184.
334. **Sorensen, T. L., M. Tani, J. Jensen, V. Pierce, C. Lucchinetti, V. A. Folcik, S. Qin, J. Rottman, F. Sellebjerg, R. M. Strieter, J. L. Frederiksen, and R. M. Ransohoff.** 1999. Expression of specific chemokines and chemokine receptors in the central nervous system of multiple sclerosis patients. J. Clin. Investig. **103:**807–815.
335. **Sowa, G., G. Gekker, M. M. Lipovsky, S. Hu, C. C. Chao, T. W. Molitor, and P. K. Peterson.** 1997. Inhibition of swine microglial cell phagocytosis of *Cryptococcus neoformans* by femtomolar concentrations of morphine. Biochem. Pharmacol. **53:**823–828.
336. **Spranger, M., and A. Fontana.** 1996. Activation of microglia: a dangerous interlude in immune function in the brain. Neuroscientist. **2:**293–299.
337. **Stalder, A. K., A. Pagenstecher, N. C. Yu, C. Kincaid, C.-S. Chiang, M. V. Hobbs, F. E. Bloom, and I. L. Campbell.** 1997. Lipopolysaccharide-induced IL-12 expression in the central nervous system and cultured astrocytes and microglia. J. Immunol. **159:**1344–1351.
338. **Stoll, G., S. Jander, and M. Schroeter.** 2002. Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system. Adv. Exp. Med. Biol. **513:**87–113.
339. **Strack, A., V. C. Asensio, I. L. Campbell, D. Schluter, and M. Deckert.** 2002. Chemokines are differentially expressed by astrocytes, microglia and inflammatory leukocytes in *Toxoplasma* encephalitis and critically regulated by interferon-gamma. Acta Neuropathol. **103:**458–468.
340. **Streit, W. J.** 2002. Microglia as neuroprotective, immunocompetent cells of the CNS. Glia **40:**133–139.
341. **Streit, W. J.** 1995. Microglial cells, p. 85–96. *In* H. Kettenmann and B. R. Ransom (ed.), Neuroglia. Oxford University Press, New York, N.Y.
342. **Streit, W. J.** 1993. Microglial-neuronal interactions. J. Chem. Neuroanat. **6:**261–266.
343. **Streit, W. J., M. B. Graeber, and G. W. Kreutzberg.** 1988. Functional plasticity of microglia: a review. Glia **1:**301–307.
344. **Suzuki, Y.** 2002. Host resistance in the brain against *Toxoplasma gondii.* J. Infect. Dis. **185**(Suppl. 1)**:**S58–S65.
345. **Suzuki, Y., and K. Joh.** 1994. Effect of the strain of *Toxoplasma gondii* on the development of toxoplasmic encephalitis in mice treated with antibody to interferon-gamma. Parasitol. Res. **80:**125–130.
346. **Szczepanik, A. M., S. Funes, W. Petko, and G. E. Ringheim.** 2001. IL-4, IL-10 and IL-13 modulate A beta(1–42)-induced cytokine and chemokine production in primary murine microglia and a human monocyte cell line. J. Neuroimmunol. **113:**49–62.
347. **Taramelli, D., N. Basilico, E. Pagani, R. Grande, D. Monti, M. Ghione, and P. Olliaro.** 1995. The heme moiety of malaria pigment (beta-hematin) mediates the inhibition of nitric oxide and tumor necrosis factor-alpha production by lipopolysaccharide-stimulated macrophages. Exp. Parasitol. **81:**501–511.
348. **Taramelli, D., S. Recalcati, N. Basilico, P. Olliaro, and G. Cairo.** 2000. Macrophage preconditioning with synthetic malaria pigment reduces cytokine production via heme iron-dependent oxidative stress. Lab. Investig. **80:**1781–1788.
349. **Taylor, D. L., L. T. Diemel, and J. M. Pocock.** 2003. Activation of microglial group III metabotropic glutamate receptors protects neurons against microglial neurotoxicity. J. Neurosci. **23:**2150–2160.
350. **Thomas, E. W.** 1992. Brain macrophages: evaluation of microglia and their functions. Brain Res. Rev. **17:**61–74.
351. **Thomas, E. W.** 1999. Brain macrophages: on the role of pericytes and perivascular cells. Brain Res. Rev. **31:**42–57.
352. **Tikka, T. M., and J. E. Koistinaho.** 2001. Minocycline provides neuroprotection against *N*-methyl-D-aspartate neurotoxicity by inhibiting microglia. J. Immunol. **166:**7527–7533.
353. **Tornatore, C., A. Nath, K. Amemiya, and E. O. Major.** 1991. Persistent human immunodeficiency virus type 1 infection in human fetal glial cells reactivated by T-cell factor(s) or by the cytokines tumor necrosis factor alpha and interleukin-1 beta. J. Virol. **65:**6094–6100.
354. **Townsend, G. C., and W. M. Scheld.** 1998. Infections of the central nervous system. Adv. Intern. Med. **43:**403–447.
355. **Trillo-Pazos, G., A. Diamanturos, L. Rislove, T. Menza, W. Chao, P. Belem, S. Sadiq, S. Morgello, L. Sharer, and D. J. Volsky.** 2003. Detection of HIV-1 DNA in microglia/macrophages, astrocytes and neurons isolated from brain tissue with HIV-1 encephalitis by laser capture microdissection. Brain Pathol. **13:**144–154.
356. **Tsuda, M., A. Mizokoshi, Y. Shigemoto-Mogami, S. Koizumi, and K. Inoue.** 2004. Activation of p38 mitogen-activated protein kinase in spinal hyperactive microglia contributes to pain hypersensitivity following peripheral nerve injury. Glia **45:**89–95.
357. **Ulvestad, E., K. Williams, S. Mork, J. Antel, and H. Nyland.** 1994. Phenotypic differences between human monocytes/macrophages and microglial cells studied in situ and in vitro. J. Neuropathol. Exp. Neurol. **53:**492–501.
358. **Vallat-Decouvelaere, A. V., F. Chretien, G. Gras, G. Le Pavec, D. Dormont, and F. Gray.** 2003. Expression of excitatory amino acid transporter-1 in brain macrophages and microglia of HIV-infected patients. A neuroprotective role for activated microglia? J. Neuropathol. Exp. Neurol. **62:**475–485.
359. **van de Beek, D., J. de Gans, P. McIntyre, and K. Prasad.** 2003. Corticosteroids in acute bacterial meningitis. Cochrane Database Syst. Rev. **2003:** CD004305.
360. **Van Everbroeck, B., E. Dewulf, P. Pals, U. Lubke, J. J. Martin, and P. Cras.** 2002. The role of cytokines, astrocytes, microglia and apoptosis in Creutzfeldt-Jakob disease. Neurobiol. Aging **23:**59–64.
361. **Veerhuis, R., J. J. Hoozemans, I. Janssen, R. S. Boshuizen, J. P. Langeveld, and P. Eikelenboom.** 2002. Adult human microglia secrete cytokines when exposed to neurotoxic prion protein peptide: no intermediary role for prostaglandin E2. Brain Res. **925:**195–203.
362. **Verderio, C., and M. Matteoli.** 2001. ATP mediates calcium signaling between astrocytes and microglial cells: modulation by IFN-gamma. J. Immunol. **166:**6383–6391.
363. **Vila, M., V. Jackson-Lewis, C. Guegan, D. C. Wu, P. Teismann, D. K. Choi, K. Tieu, and S. Przedborski.** 2001. The role of glial cells in Parkinson's disease. Curr. Opin. Neurol. **14:**483–489.
364. **Voyvodic, J. T.** 1996. Cell death in cortical development: how much? Why? So what? Neuron **16:**81–90.
365. **Waksman, Y., J. M. Olson, S. J. Carlisle, and G. A. Cabral.** 1999. The central cannabinoid receptor (CBI) mediates inhibition of nitric oxide production by rat microglial cells. J. Pharmacol. Exp. Ther. **288:**1357–1366.
366. **Walker, D. G., S. Itagaki, K. Berry, and P. L. McGeer.** 1989. Examination of brains of AIDS cases for human immunodeficiency virus and human cytomegalovirus nucleic acids. J. Neurol. Neurosurg. Psychiatry **52:**583–590.
367. **Walker, D. G., L. F. Lue, and T. G. Beach.** 2001. Gene expression profiling of amyloid beta peptide-stimulated human post-mortem brain microglia. Neurobiol. Aging **22:**957–966.
368. **Wang, J., K. Crawford, M. Yuan, H. Wang, P. R. Gorry, and D. Gabuzda.** 2002. Regulation of CC chemokine receptor 5 and CD4 expression and human immunodeficiency virus type 1 replication in human macrophages and microglia by T helper type 2 cytokines. J. Infect. Dis. **185:**885–897.
369. **Watkins, L. R., E. D. Milligan, and S. F. Maier.** 2003. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. Adv. Exp. Med. Biol. **521:**1–21.
370. **Weinstein, D. L., D. G. Walker, H. Akiyama, and P. L. McGeer.** 1990. Herpes simplex virus type I infection of the CNS induces major histocompatibility complex antigen expression on rat microglia. J. Neurosci. Res. **26:**55–65.
371. **Wierzba-Bobrowicz, T., E. Gwiazda, E. Kosno-Kruszewska, E. Lewandowska, W. Lechowicz, E. Bertrand, G. M. Szpak, and B. Schmidt-Sidor.** 2002. Morphological analysis of active microglia-rod and ramified microglia in human brains affected by some neurological diseases (SSPE, Alzheimer's disease and Wilson's disease). Folia Neuropathol. **40:**125–131.
372. **Wildemann, B., K. Ehrhart, B. Storch-Hagenlocher, U. Meyding-Lamade, S. Steinvorth, W. Hacke, and J. Haas.** 1997. Quantitation of herpes simplex virus type 1 DNA in cells of cerebrospinal fluid of patients with herpes simplex virus encephalitis. Neurology **48:**1341–1346.
373. **Wiley, C. A., R. D. Schrier, J. A. Nelson, P. W. Lampert, and M. B. Oldstone.** 1986. Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. Proc. Natl. Acad. Sci. USA **83:**7089–7093.
374. **Will, R. G., J. W. Ironside, M. Zeidler, S. N. Cousens, K. Estibeiro, A. Alperovitch, S. Poser, M. Pocchiari, A. Hofman, and P. G. Smith.** 1996. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet **347:**921–925.
375. **Williams, A., P. J. Lucassen, D. Ritchie, and M. Bruce.** 1997. PrP deposition, microglial activation, and neuronal apoptosis in murine scrapie. Exp. Neurol. **144:**433–438.
376. **Williams, E., X. Alvarez, and A. A. Lackner.** 2001. Central nervous system perivascular cells are immunoregulatory cells that connect the CNS with the peripheral immune system. Glia **36:**156–164.
377. **Williams, K., N. Dooley, E. Ulvestad, B. Becher, and J. P. Antel.** 1996. IL-10 production by adult human derived microglial cells. Neurochem. Int. **29:** 55–64.
378. **Williams, K. C., S. Corey, S. V. Westmoreland, D. Pauley, H. Knight, C. deBakker, X. Alvarez, and A. A. Lackner.** 2001. Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency

virus in the brains of macaques: implications for the neuropathogenesis of AIDS. J. Exp. Med. **193:**905–915.
379. **Williams, K. C., and W. F. Hickey.** 2002. Central nervous system damage, monocytes and macrophages, and neurological disorders in AIDS. Annu. Rev. Neurosci. **25:**537–562.
380. **Xia, M. Q., and B. T. Hyman.** 1999. Chemokines/chemokine receptors in the central nervous system and Alzheimer's disease. J. Neurovirol. **5:**32–41.
381. **Xia, M. Q., S. X. Qin, L. J. Wu, C. R. Mackay, and B. T. Hyman.** 1998. Immunohistochemical study of the beta-chemokine receptors CCR3 and CCR5 and their ligands in normal and Alzheimer's disease brains. Am. J. Pathol. **153:**31–37.
382. **Xiong, H., J. Boyle, M. Winkelbauer, S. Gorantla, J. Zheng, A. Ghorpade, Y. Persidsky, K. A. Carlson, and H. E. Gendelman.** 2003. Inhibition of long-term potentiation by interleukin-8: implications for human immunodeficiency virus-1-associated dementia. J. Neurosci. Res. **71:**600–607.
383. **Ying Wang, J., F. Peruzzi, A. Lassak, L. Del Valle, S. Radhakrishnan, J. Rappaport, K. Khalili, S. Amini, and K. Reiss.** 2003. Neuroprotective effects of IGF-I against TNFalpha-induced neuronal damage in HIV-associated dementia. Virology **305:**66–76.
384. **Yoshiyama, Y., H. Sato, M. Seiki, A. Shinagawa, M. Takahashi, and T. Yamada.** 1998. Expression of the membrane-type 3 matrix metalloproteinase (MT3-MMP) in human brain tissues. Acta Neuropathol. **96:**347–350.
385. **Zehntner, S. P., M. Brisebois, E. Tran, T. Owens, and S. Fournier.** 2003. Constitutive expression of a costimulatory ligand on antigen-presenting cells in the nervous system drives demyelinating disease. FASEB J. **17:**1910–1912.
386. **Zysk, G., W. Bruck, J. Gerber, Y. Bruck, H. W. Prange, and R. Nau.** 1996. Anti-inflammatory treatment influences neuronal apoptotic cell death in the dentate gyrus in experimental pneumococcal meningitis. J. Neuropathol. Exp. Neurol. **55:**722–728.