Conditions as varied as surgery, cancer chemotherapy, peripheral nerve damage, and heart attack can lead to poor memory, depression, fatigue, and exaggerated responses to pain. The common feature of these conditions of the body is that they induce inflammatory responses in the body, outside the central nervous system (the CNS which consists of the brain and spinal cord only). However, the cognitive and emotional effects that inflammatory responses lead to are nevertheless accomplished through the CNS. Memory, mood, activity, and pain are direct products of CNS activity, and not the peripheral immune system.

Until recently the CNS and peripheral immune system were thought to operate independently. Indeed, you cannot find the term “immune system” in the indexes of current major texts in neuroscience nor the terms “CNS” and “brain” in the indexes of major texts in immunology. However, new research has led to important advances in our understanding of how immune-related events in the periphery can influence CNS processes, thereby altering cognition, mood, and behavior, and these advances are suggesting that inflammation may have important long term implications for the brain.

WHAT IS INFLAMMATION?

Since inflammation in the body can lead to inflammation in the brain we first need to understand what inflammation is. Inflammation is part of the immune system’s response to defend you against microbial infections. It is the body’s first line of defense against invasion by microorganisms such as bacteria and viruses, and it is activated rapidly after infection. The microbes are detected as foreign to the body by immune cells such as macrophages (literally “big eater”). When macrophages encounter and recognize a foreign microorganism they engulf the microorganism and, in addition, release a variety of cellular products into the space around them that start and regulate further defenses that include inflammation. Two classes of these products, known as cytokines and chemokines, lead to inflammation. Cytokines are chemical messengers that travel away from the cells that release them so to alter the functioning of other cells. Chemokines also leave the cell and attract other cells into the region. Together, they alter the blood vessels near the site of infection, causing increased blood flow to the area and the entry of immune system cells. These effects account for the swelling, redness, and heat characteristic of inflammation. The chemokines attract immune cells into the infected area, accounting for the pain associated with an inflammatory site. The attracted cells increase the killing of the invader and also wall off the site so that the infection cannot spread.

SICKNESS BEHAVIOR, NEURO-INFLAMMATION, AND IMMUNE-TO-BRAIN COMMUNICATION

Inflammation—swelling, redness, and heat—is part of the immune system’s first response to microbial infections, but this defensive response is not limited to the bodily site of infection. Soon after infection, a pattern develops that includes what is called the “acute phase response (APR)” and “sickness behavior.” Fever is the most prominent feature of the APR and for good reason: many microorganisms reproduce best at humans’ normal core body temperature, and the many of the immune system’s agents for killing them are bolstered by elevated temperature.

Sickness behaviors are well known to anyone who has had the flu. They include reductions in activity, food intake, social interaction, and sexual behavior; mood sags; it is difficult to form new memories; sleep changes; and sensitivity to pain increases (just think of...
how even a light touch hurts when you have the flu). These behaviors are not symptoms of weakness induced by the infection, but rather are an organized set of changes designed by evolution to keep the organism (you) from foraging and thus being subject to predation during a time of weakness.

These changes also reduce the energetic costs of behavior to free available energy stores to fight the infection. Fever, for example, is quite energy intensive, requiring an extra 10 to 12 percent in energy for each degree rise. It is obvious how all the sickness behaviors, with the exception of memory disruption, fit the scheme of keeping us away from our usual activities. Memory disruption serves a different purpose. You can remember (and want to avoid) what you ate before an illness, for example, but the disruption weakens the memory of where you became ill, since it is unlikely that the location caused the illness. Interestingly, during sickness, memory formation that requires the hippocampus is disrupted and the hippocampus is crucial for representing places and contexts.

Most important: we now understand that all of the changes just described are accomplished through the CNS. Fever, for example occurs because the set point of temperature-sensitive cells in the hypothalamus is increased. Of course, behavior, mood, and pain are all products of the CNS. This raises two issues: a) How does the CNS “know” what is going on in the peripheral immune system, and b) What kinds of changes are produced in the CNS that mediate fever and sickness behaviors?

The same cytokines that participate in producing the inflammatory response in the body also initiate the communication process to the CNS. They accumulate in the bloodstream and thereby travel to the brain, where, although they are large proteins and cannot readily cross the blood-brain barrier (cells that make up the blood vessels that go through the brain are organized differently than the cells in other blood vessels and do not allow most substances to leave the blood vessels, thereby helping keep the internal environment in the brain more constant), these chemical signals are carried across the barrier by active transport. They cross into the brain in regions where the barrier is weak, and they bind to receptors on the insides of the cerebral vascular blood vessels, thereby inducing the production of soluble mediators within the epithelial cells that can cross into the brain. In addition, there are neural as well as blood-borne communication routes. For example, there are cytokine receptors on nerves, such as the vagus, that innervate peripheral immune organs, and these nerves communicate to the brain and are activated during infection. (See the Figure.)

The electrical and chemical activity of the CNS changes soon after infection. During this period, resident immune cells of the brain, called microglial cells (one of the non-neuronal cell types that live in the brain), become activated and produce cytokines, leading to a neuroinflammatory response. That is, cytokines from the body induce the CNS to make cytokines; in other words, peripheral inflammation induces neuroinflammation—inflammation in the brain. Furthermore, this microglial activation and resulting cytokine production in the brain is critical in producing the APR and sickness behaviors. We know this from research showing that if we block microglial activation, CNS cytokine production, or CNS cytokine receptors, we can block these behaviors.

**WHAT HAPPENS IF THESE PROCESSES BECOME EXAGGERATED OR PROLONGED?**

Often, a set of mechanisms that evolved to handle acute emergencies lead to outcomes that nature
did not intend if they are engaged too long. During a normal infection, neuroinflammation and the resulting adaptive sickness behaviors persist only for several days. However, if these responses become exaggerated or prolonged, the outcomes may well become established, leading to cognitive impairment instead of brief memory disruption, depression instead of reduced mood, fatigue instead of inactivity, and chronic pain instead of acute pain. That is, physiology can become pathology when a set of processes designed to be relatively brief becomes prolonged.

The next challenge is to determine what is able to produce a prolonged or exaggerated neuroinflammatory response. Since peripheral inflammatory events initiate the process that leads to neuroinflammation, the most obvious culprit would be the occurrence of prolonged or repeated peripheral inflammatory challenges that produce continuous immune-to-CNS signaling. Consider the classic examples—surgery, cancer chemotherapy, peripheral nerve damage, and myocardial infarction. These conditions all produce very large and prolonged peripheral inflammation. Thus, many of the pathological changes that result from these conditions may reflect persistent neuroinflammation-produced sickness behaviors. If this is correct, one might wonder why anti-inflammatory drugs are not more effective than they have proved to be. However, peripheral inflammation is highly complex and involves many immune cells and their products. Existing anti-inflammatory drugs often target only one of these. For example, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, inhibit only a hormone, prostaglandins, leaving other actors in inflammation (cytokines, chemokines, etc.) untouched. The development of more effective anti-inflammatories is a very active area.

A second way that central neuroinflammation could be prolonged is less obvious. The CNS may come to over-respond to the same signal from the peripheral immune system. As noted above, microglia and the cytokines they produce when activated are at the core of the neuroinflammatory response that produces sickness behaviors. If microglia were to become “sensitized,” which means they respond in exaggerated or prolonged fashion, then sickness behaviors would become intensified and prolonged—pathology instead of physiology.

The sensitization scenario is compelling. A number of conditions have been shown to sensitize microglia. Prolonged peripheral inflammation not only involves increased signaling to the CNS, but it also often sensitizes microglia. For example, peripheral nerve damage sensitizes spinal cord microglia, generating a “double whammy” in producing chronic pain. Most encouragingly, studies in numerous animal models show that the development and expression of chronic pain can be blocked with drugs that inhibit either microglial activation within the spinal cord, or the inflammatory cytokines that microglia produce.

In addition, microglia also can become sensitized without a prolonged peripheral inflammation. For example, aging appears to sensitize microglia so that microglia, particularly in the hippocampus, respond in exaggerated fashion to input. Thus, neuroinflammation produced by surgery, peripheral infection, and the like, is greatly exaggerated in aged subjects. Correspondingly, aging also augments the chances of depressive behaviors, cognitive impairments, and pain produced by peripheral inflammatory events. Encouragingly, however, some human studies show that inhibition of microglia and cytokines in the brain blunts such pathological outcomes.

**FINAL THOUGHTS**

Often, pathology results from mechanisms that evolution designed to operate temporarily, but are now, in modern times, driven in prolonged or repeated fashion. For example, the stress response evolved to help organisms deal with acute fight/flight emergencies. However, when the stress response is activated in prolonged fashion by situations that did not exist in evolutionary time (e.g., providing care to a loved one with Alzheimer’s), pathological outcomes can result. Because of our ability to change our environment, we are exposed to new conditions much more rapidly than new evolution can occur. Cancer chemotherapies, surgeries, old age, heart disease, etc., were not much present in evolutionary time, and the cognitive impairments, depression, fatigue, and chronic pain that often result can be understood as the products of prolonged or excessive activation of the immune-to-CNS circuitry designed to combat infection, but not designed to operate in chronic fashion. Importantly, this perspective suggests new targets for drug development to combat these disorders. Blockade of inflammation in the periphery and microglial activation/cytokine action in the CNS, may well become important therapies for a range of disorders not often thought of as mediated by these factors.
Further Reading:
Maier, S. F. (2003). Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. Brain, Behavior, and Immunity, 17, 69-86. (Abstract only.) (Full text; payment required.)

