and/or IL-6; individually or in combination, these cytokines trigger the hypothalamus to raise the set point to febrile levels.

ELEVATION OF THE HYPOTHALAMIC SET POINT BY CYTOKINES

During fever, levels of prostaglandin E_2 (PGE_2) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE_2 are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous pyrogens and pyrogenic cytokines interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

The key events in the production of fever are illustrated in Fig. 23-1. Myeloid and endothelial cells are the primary cell types that produce pyrogenic cytokines. Pyrogenic cytokines such as IL-1, IL-6, and TNF are released from these cells and enter the systemic circulation. Although these circulating cytokines lead to fever by inducing the synthesis of PGE_2, they also induce PGE_2 in peripheral tissues. The increase in PGE_2 in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some systemic PGE_2 escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE_2 in the brain that starts the process of raising the hypothalamic set point for core temperature.

There are four receptors for PGE_2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever: when the gene for this receptor is deleted in mice, no fever follows the injection of IL-1 or endotoxin. Deletion of the other PGE_2 receptor genes leaves the fever mechanism intact. Although PGE_2 is essential for fever, it is not a neurotransmitter. Rather, the release of PGE_2 from the brain side of the hypothalamic endothelium triggers the PGE_2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine 5′-monophosphate (cAMP), which is a neurotransmitter. As shown in Fig. 23-1, the release of cAMP from glial cells activates neuronal endings from the thermoregulatory center that extend into the area. The elevation of cAMP is thought to account for changes in the hypothalamic set point either directly or indirectly (by inducing the release of neurotransmitters). Distinct receptors for microbial products are located on the hypothalamic endothelium. These receptors are called *Toll-like receptors* and are similar in many ways to IL-1 receptors. IL-1 receptors and Toll-like receptors share the same signal-transducing mechanism. Thus, the direct activation of Toll-like receptors or IL-1 receptors results in PGE_2 production and fever.

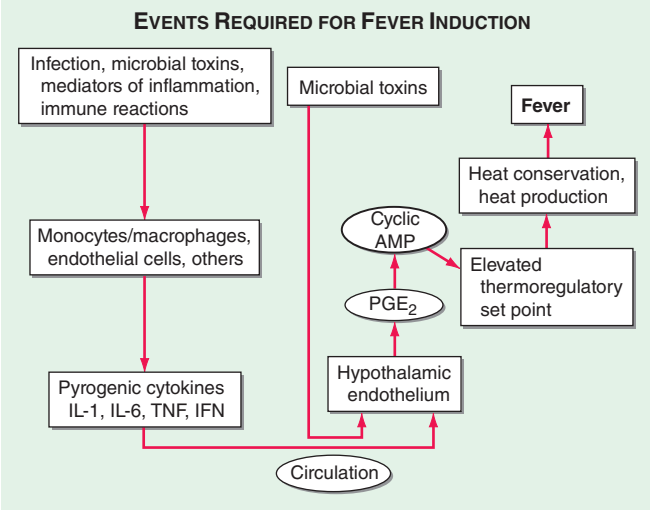

FIGURE 23-1 Chronology of events required for the induction of fever. AMP, adenosine 5′-monophosphate; IFN, interferon; IL, interleukin; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.

PRODUCTION OF CYTOKINES IN THE CNS

Cytokines produced in the brain may account for the hyperpyrexia of CNS hemorrhage, trauma, or infection. Viral infections of the CNS induce microglial and possibly neuronal production of IL-1, TNF, and IL-6. In experimental animals, the concentration of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain substance or brain ventricles than with systemic injection. Therefore, cytokines produced in the CNS can raise the hypothalamic set point, bypassing the circumventricular organs. CNS cytokines likely account for the hyperpyrexia of CNS hemorrhage, trauma, or infection.

APPROACH TO THE PATIENT: Fever

PHYSICAL EXAMINATION

The chronology of events preceding fever, including exposure to other infected individuals or to vectors of disease, should be ascertained. Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease. Moreover, physicians should be aware that newborns, elderly patients, patients with chronic liver or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active infection in the absence of fever due to a blunted febrile response.

LABORATORY TESTS

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections.

Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or possible disease, the most valuable measurements are the C-reactive protein level and the erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting occult disease. Measurement of circulating IL-6 is useful because IL-6 induces C-reactive protein. Acute-phase reactants are discussed in Chap. 325.

FEVER IN PATIENTS RECEIVING ANTICYTOKINE THERAPY

Patients receiving long-term treatment with anticytokine-based regimens are at a disadvantage because of lowered host defense against infection. Even when the results of tests for latent *Mycobacterium tuberculosis* infection are negative, active tuberculosis can develop in patients receiving anti-TNF therapy. With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12, or TNF in patients with Crohn's disease, rheumatoid arthritis, or psoriasis, the possibility that these therapies blunt the febrile response must be kept in mind.

The blocking of cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections. The opportunistic infections reported in patients treated with agents that neutralize TNF-α are similar to those reported in the HIV-1-infected population (e.g., a new infection with or reactivation of *Mycobacterium tuberculosis*, with dissemination).

In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. A similar situation is seen in patients receiving high-dose glucocorticoid therapy or anti-inflammatory agents such as ibuprofen. Therefore, low-grade fever is of considerable concern in patients receiving anticytokine therapies. The physician should conduct an early and rigorous diagnostic evaluation in these patients.