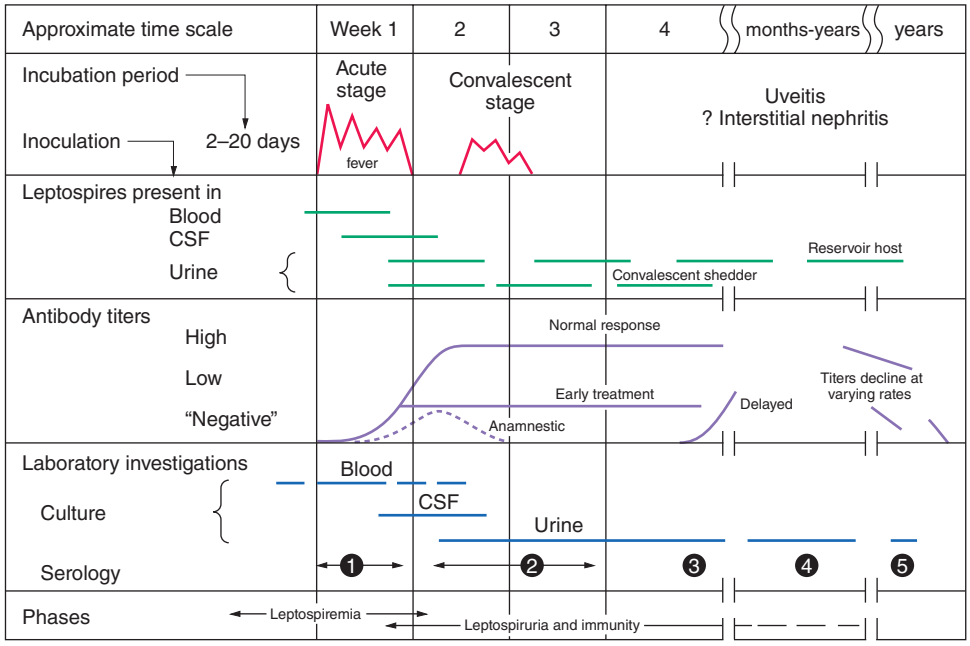

FIGURE 208-3 **Biphasic nature of leptospirosis and relevant investigations at different stages of disease.** *Note that an incubation period of up to 1 month has now been documented.* Specimens 1 and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup. CSF, cerebrospinal fluid. *(Reprinted as adapted by PN Levett: Clin Microbiol Rev 14:296, 2001 [from LH Turner: Leptospirosis. BMJ 1:231, 1969] with permission from the American Society for Microbiology and the BMJ Publishing Group.)*

von Willebrand factor in patients with leptospirosis reflect endothelial cell activation. Experimental models show that pathogenic leptospires or leptospiral proteins are able to activate endothelial cells in vitro and to disrupt endothelial-cell barrier function, promoting dissemination. Platelets have been shown to aggregate on activated endothelium in the human lung, whereas histology reveals swelling of activated endothelial cells but no evident vasculitis or necrosis. Immunoglobulin and complement deposition have been demonstrated in lung tissue involved in pulmonary hemorrhage.

Leptospira species have a typical double-membrane cell wall structure harboring a variety of membrane-associated proteins, including an unusually high number of lipoproteins. The peptidoglycan layer is located close to the cytoplasmic membrane. The lipopolysaccharide (LPS) in the outer membrane has an unusual structure with a relatively low endotoxic potency. Pathogenic leptospires contain a variety of genes coding for proteins involved in motility and in cell and tissue adhesion and invasion that represent potential virulence factors. Many of these are surface-exposed outer-membrane proteins (OMPs). To date, the only leptospiral virulence factor shown to satisfy Koch's molecular postulates is *loa22* encoding a surface-exposed protein with an unknown function. However, the gene is not confined to pathogenic *Leptospira* species.

Immunity to *Leptospira* depends on the production of circulating antibodies to serovar-specific LPS. It is unclear whether other antigens play a significant role in protective humoral immunity. Moreover, immunity may not be confined to antibody responses; involvement of the innate-immune Toll-like receptor 2 (TLR2) and TLR4 activation pathways in controlling infection has been demonstrated, whereas in vaccinated cattle a cell-mediated immune response is correlated with protection.

It is likely that several surface-exposed proteins mediate leptospire–host cell interactions, and these proteins may represent candidate vaccine components. Although animal-model studies have shown various degrees of vaccine efficacy for various putative virulence-associated OMPs, it is not yet clear whether such proteins elicit acceptable levels of sterilizing immunity.

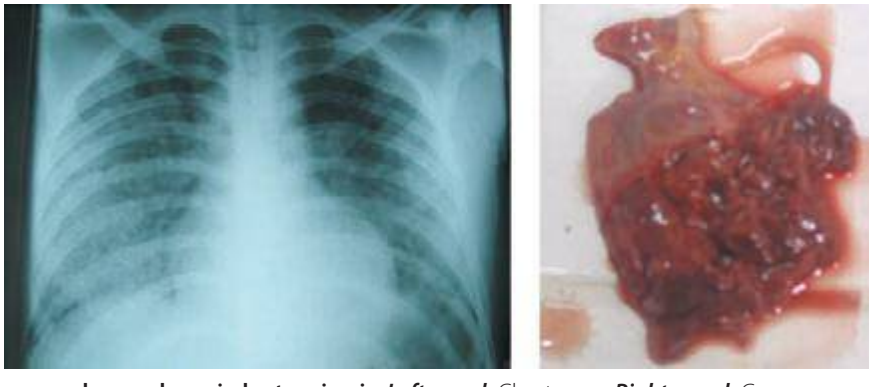

FIGURE 208-4 **Severe pulmonary hemorrhage in leptospirosis.** ***Left panel:*** Chest x-ray. ***Right panel:*** Gross appearance of right lower lobes of lung at autopsy. This patient, a 15-year-old from the Peruvian Amazonian city of Iqitos, died several days after presentation with acute illness, jaundice, and hemoptysis. Blood culture yielded *Leptospira interrogans* serovar Copenhageni/Icterohaemorrhagiae. *(Adapted with permission from E Segura et al: Clin Infect Dis 40:343, 2005. © 2005 by the Infectious Diseases Society of America.)*