The purpose of this review was to compare the following 3 coronavirus diseases: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Coronavirus Disease 2019 (COVID-19) with an emphasis on the clinical features, viral characteristics, pathology, immune response, and pathogenesis associated with each. Diagnostics, therapeutics, and vaccines will not be covered in this review, and readers interested in these topics are referred to the ever-expanding literature relating to them. SARS first appeared in Foshan, China in 2002, and by the end of the epidemic in 2003 there had been more than 8000 cases and almost 800 deaths. MERS first appeared in Jeddah, Saudi Arabia in 2012 and, as of March 2021, has had a limited worldwide spread with 2574 infected individuals and almost 900 deaths. COVID-19 first appeared clinically in Wuhan, China, in December 2019 and has since developed into a worldwide pandemic. At time of this writing on June 15, 2021, there have been more than 177 million cases, greater than 3.9 million deaths worldwide, and more than 33.5 million cases in the United States with more than 600 000 deaths. These numbers are certain to increase until this disease is eventually controlled by both public health measures and SARS-CoV-2 vaccination of a majority of the world’s population. Little is known about the pathology associated with Middle East respiratory syndrome coronavirus (MERS-CoV) infection because there is only 1 published complete autopsy report describing the findings in a single decedent.1 In contrast, the pathology associated with SARS-CoV has been well summarized in a review by Gu and Kortweg.2 Although there were relatively few autopsies, we have a good understanding of the pathology associated with this disease.

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affected required ventilatory support. The case fatality rate (ARDS) developed in some patients, and the most seriously of them also developed a dry cough. Pulmonary infiltrates appear until several days after the onset of fever, and some symptoms. In most individuals, the respiratory symptoms did not

8 individuals had laboratory evidence of a SARS-CoV,

and these revealed that the greatest number of positives

occurred during the second week of illness.13

**SEVERE ACUTE RESPIRATORY SYNDROME**

**Clinical Considerations**

SARS is caused by the SARS-CoV virus, a new member of the Coronaviridae, which was declared the etiologic agent of SARS in April 2003 after intensive research and collaboration by a network of international laboratories.9 SARS first appeared in Foshan, China, in November 2002 and spread to more than 24 countries in Asia, Europe, North America, and South America. By the end of the epidemic in July 2003, there had been more than 8000 cases, 774 deaths, and a 9.6% mortality rate,10 with the most cases occurring in China and Hong Kong. In contrast, in the United States only 8 individuals had laboratory evidence of a SARS-CoV infection, and the last case was reported in 2004.11–13

Most patients infected with SARS-CoV were previously healthy adults aged 25 to 70 years, but a few suspected cases of SARS have been reported among children aged less than 15 years. The main mode of transmission was through respiratory secretions. In general, patients typically presented with high fevers (temperatures greater than 100.4°F), chills, rigors, headaches, and generalized body aches. Some patients also presented with only mild respiratory symptoms. In most individuals, the respiratory symptoms did not appear until several days after the onset of fever, and some of them also developed a dry cough. Pulmonary infiltrates consistent with the adult respiratory distress syndrome (ARDS) developed in some patients, and the most seriously affected required ventilatory support.15 The case fatality rate among individuals who were ill and met the current World Health Organization (WHO) case definition for probable and suspected cases of SARS was approximately 3%. Studies have demonstrated that antiviral antibodies usually did not appear until 28 days after onset. Polymerase chain reaction (PCR)-based molecular tests were developed for diagnosis, and these revealed that the greatest number of positives occurred during the second week of illness.13

**Characteristics of SARS-CoV**

Coronaviruses include a number of subfamilies, one of which, Coronaviridae, is subdivided into the following 4 genera: alpha, beta, gamma, and delta. SARS-CoV, MERS-CoV, and SARS-CoV-2 are enveloped, nonsegmented, positive-sense RNA viruses. Viral particles contain 4 main structural proteins designated S for spike, M for membrane, E for envelope, and N for nucleocapsid proteins. These are encoded within the 3' end of the viral genome.14 The most important of these, as far as infection and immunity are concerned, is the S protein, which allows the virus to gain access to the cell via the angiotensin converting enzyme 2 (ACE-2) receptor, a typical zinc metalloproteinase. The receptor binding domain of SARS-CoV is at the C terminus of S1. After binding, the virus gains entry via proteolytic cleavage of the S protein by either a cathepsin or another protease leading to fusion of the viral and cellular membranes. Cleavage of the S protein occurs at 2 sites within the S2 portion of the protein, the first of which separates the receptor binding domain and fusion domains of the S protein. After entry into the cell, the translation of the replicase gene occurs from the viron genomic RNAs. Viral RNA synthesis yields both genomic and subgenomic RNAs. The former serves as mRNA for the structural and accessory genes. The most unusual aspect of coronavirus replication is fusion of the leader and body of the transcription regulating sequences during production of subgenomic RNAs. Despite the marked similarity between SARS-CoV and SARS-CoV-2, the latter has spread much more rapidly that the former, suggesting that this might be due to structural differences in the S proteins of these 2 viruses.16 The S protein of SARS-CoV-2 has a furin-like cleavage site that might facilitate S priming, thereby increasing the spreading efficiency of the latter compared with SARS-CoV.

**Pathology of SARS**

Autopsy findings associated with the SARS infection have been described in several reviews, the most comprehensive of which is that of Kortweg and Gu.2 As expected, the most important organ involved has been the lungs. The localization of SARS-CoV consistently has been identified in pulmonary pneumocytes by means of in situ hybridization and the reverse-transcriptase PCR (RT-PCR). Early on in the SARS epidemic, PCR molecular assays were developed to detect SARS-CoV in lung tissue, and these attained 100% sensitivity and specificity.17 Hadjimichaelou et al13 have developed a molecular-based multiplexed real-time PCR assay for the detection of SARS-CoV. Molecular analysis of tissue samples using PCR revealed SARS-CoV RNA in all of the tissues examined.13 This was confirmed by Farcas et al,12 who detected SARS-CoV RNA in multiple organs such as lungs, gastrointestinal tract, lymph nodes, spleen, liver, and kidneys. However, of note, in 1 patient who died more than 100 days after disease onset, all of the tissues examined by molecular assays were negative for SARS-CoV.12

Grossly, the lungs of SARS decedents were often heavy and congested, and there frequently were pleural effusions. Microscopically, hematoxylin and eosin–stained sections of the lungs revealed prominent hyaline membranes in the alveolar ducts and spaces, diffuse alveolar damage (DAD) with alveolitis, and proliferation of alveolar epithelial cells (Figure 1, A and B). Significant proteinaceous exudates and extensive hyaline membrane formation frequently were seen. Macrophages and rare multinucleated giant cells also were identified in some of the alveolar spaces. Other patients had acute lung injury with a pattern of acute fibrinous and organizing pneumonia, and severe acute respiratory distress syndrome.
membranes (Figure 1, C and D). The other noteworthy pulmonary findings included the presence of thromboemboli in the pulmonary arterial branches, intermingled areas of early DAD, other areas with organizing DAD (Figure 1), and intraalveolar hemorrhage. The inflammatory cell infiltrates were primarily composed of monocytes, lymphocytes, and plasma cells with minimal numbers of neutrophils. The presence of the virus also was demonstrated by electron microscopy (EM) in lung tissues, which showed viral clusters that morphologically were compatible with coronavirus. Viral inclusion bodies also were seen within alveolar epithelial cells. Microscopic examination of other organs, such as the heart, liver, kidneys, and adrenals, revealed inflammatory infiltrates within vessel walls and the stroma of striated muscles. Necrosis in the spleen and lymph nodes also was noted.

**Immune Response to SARS-CoV**

The immune response to SARS-CoV involves both innate and adaptive components of the immune system. Acute phase plasma from patients infected with SARS-CoV has been reported to contain increased quantities of acute phase proteins, such as serum amyloid A and mannose binding lectin, which could bind to the virus and thereby block the S protein. Cytokine storm also may be a part of the acute immune response to SARS infection. Early in the onset of the infection, interleukins (IL)-1β, IL-6, IL-8, IL-12, IL-10, interferon gamma (IFN-γ), and monocyte chemoattractant protein (MCP)-1 can be increased and subsequently decrease with recovery of the patient. However, the exact role of cytokine storm in the pathogenesis of the SARS infection has not been clearly elucidated, and it may be associated with severe lung injury.

Decreased levels of both CD4(+) and CD8(+) T cells, associated with a lymphopenia early in the infection, reach their nadir on days 5 to 7. These gradually increase during the clinical recovery phase. Immunoglobulin (Ig) G, IgM, and IgA antibodies to SARS-CoV S protein can be detected as early as 4 days after the clinical onset of illness, and most patients have seroconverted by day 14. IgG-neutralizing
antibodies peak at 4 months but by 36 months are greatly diminished. The S and N proteins are the most significant immunogens in SARS-CoV and dominate the antibody response during the course of disease. The S protein, especially the ACE-2 binding region (318-510aa), is capable of evoking the production of neutralizing antibodies to SARS-CoV, while the N protein induces protective and specific cytolytic T cells directed against the virus. These may be important immunogens for the production of an effective, long-lasting immune response against SARS-CoV, as evidenced by the fact that SARS antibodies could be found several years after infection.\textsuperscript{21} Of note, some healthcare workers infected during the 2003 epidemic had detectable IgG antibodies 17 years after infection.\textsuperscript{22} However, currently, there has been no indication that these antibodies provide protection from infection with SARS-CoV-2.\textsuperscript{23}

**Pathogenesis of SARS**

Many of the studies on SARS and its pathogenesis have established that this is a systemic disease that affects many organs. Gu and Korteweg\textsuperscript{2} have reviewed the key findings from a group of autopsies of SARS decedents and have summarized the complex pathology of this disease. The infection begins in the lungs, ultimately activating the host immune system and affecting systemic small vessels. The virus targets epithelial cells of the lungs, thereby leading to severe pulmonary injury. The extensive consolidation of the lungs due to DAD with hyaline membrane formation contributes to the disease progression. The host immune response and its imbalance contribute to the ultimate death of the patient.\textsuperscript{2} The acute phase of DAD usually occurs within 10 days. Hyaline membranes are seen lining the alveolar walls. There are varying degrees of interstitial and airspace edema, interstitial infiltrates of inflammatory cells, and vascular congestion. If the disease progresses, the organizing phase of DAD begins. The most noteworthy findings are the presence of type II pneumocytes and squamous metaplasia with occasional multinucleated giant cells. In addition to the various phases of DAD, other types of lung injury also have been noted, including small airway injury. The latter results in loss of epithelial cilia, denudation, and fibrin deposits.\textsuperscript{2,11} In summary, most studies of the pathology and pathogenesis of SARS have concluded that the lungs, immune system, and small vessels primarily are affected. This leads to consolidation of the lungs with DAD and hyaline membrane formation, which clinically is associated with ARDS and ultimately leads to death. In addition, the decreased immune function and the dysregulation of cytokines, as well as direct viral cytopathic effects, contribute to disease progression and death of the patient.

**MIDDLE EAST RESPIRATORY SYNDROME**

**Clinical Considerations**

The MERS virus first was identified as the causative agent of a viral pneumonia in a 60-year-old Saudi Arabian man who presented in June of 2012 with a 7-day history of fever, cough, expectoration, and shortness of breath.\textsuperscript{24} His clinical status progressively worsened despite treatment with an antiviral agent and multiple antibiotics. These were prescribed to treat a *Staphylococcus aureus* infection, which was detected in a sputum sample taken on his day of admission. *Acinetobacter* was detected in a tracheal aspirate on the day of his death, 11 days after his admission. Identification of the virus was carried out using a variety of molecular techniques, and 90% of the viral genome was identified using the 454-sequencing platform. Real-time polymerase chain reaction (PCR) and cytopathic tissue culture assays excluded a number of different viruses. However, family-wide PCR assays for coronaviruses were positive, establishing that this was a novel RNA beta coronavirus, which subsequently was named MERS-CoV.\textsuperscript{26} Similar to SARS-CoV, it expressed 4 structural proteins, S, E, N, and M, as well as 4 nonstructural proteins.\textsuperscript{27} It was subsequently discovered that this particular virus was endemic to dromedary camels in Saudi Arabia,\textsuperscript{26} and many future patients would link the onset of their symptoms to contact with camels.\textsuperscript{26,28} It was recognized, however, that person-to-person transmission was more common, as was well documented, in the South Korean outbreak.\textsuperscript{29,30} In a relatively short time, many more cases of viral pneumonia attributable to MERS-CoV occurred in Saudi Arabia, and by March 2021 the total number of cases has reached more than 2574 with at least 882 deaths and a worldwide fatality rate of 34.3% (Table 1). Clinically, these patients had succumbed to what was consistent with ARDS. Involvement of other organs, such as the kidneys, was attributed to multigener failure in patients in the terminal stage of their illness.

One of us (RFB) became interested in MERS-CoV during a visit to South Korea in late May of 2015 when several articles appeared in the *Korea Times*\textsuperscript{29,30} describing a rapidly spreading epidemic that had resulted in 35 cases by June 5, 2015, and the quarantining of more than 1600 individuals. The outbreak was traced to a single South Korean male who recently had travelled in the Middle East and may have had contact with dromedary camels. Nine days after returning to South Korea, he presented at an emergency room (ER) with respiratory complaints. He subsequently visited other ERs, and it is believed that, in the process, he infected large numbers of patients in the ER waiting rooms of these hospitals. Of note, this outbreak of MERS in South Korea could be traced to a single individual, the secondary transmission of which suggested a very high R number. Over the remainder of June 2015 and into July 2015, the number of cases in South Korea rapidly increased to a total of 184 with 38 deaths and a fatality rate of almost 20% (Table 1, WHO database). However, South Korean authorities adopted very stringent methods to curtail the outbreak. These included closure of all schools, museums, and other public spaces; quarantining of cities and villages; and strictly

| Country                  | Cases | Deaths | Fatality, % |
|--------------------------|-------|--------|-------------|
| World Health Organization | 2574  | 882    | 34.37       |
| Saudi Arabia             | 2167  | 804    | 37.1        |
| South Korea              | 184   | 38     | 20          |
| United Arab Emirates     | 74    | 10     | 14          |
| Jordan                   | 19    | 6      | 32          |
| Qatar                    | 10    | 4      | 40          |
| Remaining countries      | 44    | 17     | 0–100       |

\textsuperscript{a} Regional Office for the Eastern Mediterranean MERS situation update, December 2020, which was the latest update as of May 2021 at which time there was a total of 2574 cases.

\textsuperscript{b} Instances of 100% were based on only 1 patient who died.
controlling airline flights entering and leaving the country. These measures were highly effective in controlling the epidemic, which officially was declared over in late July 2015. It should be noted that, although forensic autopsies are standard in South Korea, clinical autopsies are rarely performed and were carried out in only 0.03% of all deaths in 2015.33 Furthermore, to the best of our knowledge, no MERS autopsy reports were published in the Korean medical literature (S Kim, written communication, August 13, 2020).

Characteristics of MERS-CoV

MERS-CoV, which is highly endemic in dromedary camels, is a β-coronavirus that belongs to lineage C, while SARS-CoV belongs to lineage B.10,12 It is an enveloped, positive-sense, single-stranded RNA virus with a genome of approximately 30 kB that encodes a large number of proteins. Five unique accessory proteins, at least 2 of which (4A and 4B) can stimulate the production of IFN. Similar to SARS-CoV, MERS-CoV encodes 4 structural proteins, including S, E, M, and N. The S protein is a type 1 transmembrane glycoprotein that has 2 subunits designated S1 and S2. In contrast to SARS-CoV, the cell receptor for MERS-CoV is dipeptidyl peptidase-4 (DPP4), a large, widely expressed ectopeptidase, which is highly expressed on cells of the distal bronchi and type I and II pneumocytes. It also is widely expressed on epithelial cells of other organs and tissues, thus allowing for widespread dissemination. Although there has been extensive genomic recombination of the virus in camels since 2012, none resulted in enhanced receptor binding. In fact, to the contrary, decreased receptor affinity has been reported.

Pathology of MERS

Although there have been at least 804 deaths from MERS in Saudi Arabia (Table 1), there was only 1 complete, published autopsy report from a decedent in the United Arab Emirates and 1 postmortem study in Saudi Arabia in which “blind” needle biopsy specimens were taken from the right lung, heart, liver, kidney, and skeletal muscle.34 The reason for this lack of autopsies is religious in origin. In Islam, disfigurement of the dead, including organ removal, is forbidden unless legally required, as in the case of forensic autopsies.34 Therefore, it is not surprising that, despite the large number of affected individuals and deaths attributable to MERS-CoV in Saudi Arabia, there only has been this 1 published report from the United Arab Emirates. Ng et al1 have reported the autopsy findings of a 45-year-old Filipino male, who was a resident of Abu Dhabi. He presented with a 4-day history of fever, rhinorrhea, and a productive cough, which initially was diagnosed as acute bronchitis. Four days later, he returned to the ER with a persistent cough and shortness of breath. A chest X-ray revealed opacification of the left lung, and he was diagnosed with a pneumonia and placed on levofloxacin, a broad-spectrum, third-generation fluoroquinolone with antibacterial activity. He returned to the ER the same day with worsening shortness of breath and was admitted to the hospital. A nasopharyngeal swab taken 1 day later was positive for MERS-CoV, although bacterial cultures were negative. RT-PCR revealed UpE and ORF1a gene targets. Seven days after his initial presentation, he expired due to his progressively worsening clinical status, and subsequently a complete autopsy was performed.1

As reported by Ng et al1, the major gross autopsy findings included massive pleural effusions (5 L), a pericardial effusion (150 mL), edematous consolidated lungs, an abdominal effusion, and widespread congestion of multiple organs.1 Microscopic examination of the lungs revealed DAD in the exudative phase with denudation of the bronchiolar epithelium, prominent hyaline membranes with alveolar fibrin deposits, hyperplasia of type 2 pneumocytes, rare multinucleated syncytial cells, and edematous alveolar septa containing lymphocytes and smaller numbers of macrophages, plasma cells, and neutrophils. Foci of necrotic debris were seen within alveoli and subpleurally. Immuno-histochemical staining with 4 different antibodies revealed multiple foci of MERS-CoV antigen within pneumocytes and syncytial cells. Microscopic examination of hematoxylin and eosin-stained sections of the trachea and bronchi revealed mild to moderate lymphocytic infiltrates localized in the mucosa and submucosa with a scattering of plasma cells and neutrophils. Examination of multiple lymph nodes showed a decrease in lymphoid follicles and a marked interfollicular proliferation of immunoblasts intermixed with reactive lymphocytes. Examination of the spleen revealed immunoblasts and reactive lymphocytes. Changes not specifically related to MERS-CoV were seen in the heart, liver, and kidneys, and MERS-CoV was not detected in these organs. Imaging studies of the lungs of some patients who had recovered from MERS revealed pulmonary fibrosis. Needle biopsy specimens taken after the death of another decedent revealed DAD, a necrotizing pneumonia in the right lung and acute tubular necrosis in the kidneys, and the liver showed mild, chronic, portal lymphocytic infiltrates.33 However, the latter changes should be interpreted with caution because the decedent had a primary cutaneous T-cell lymphoma for which he had received both chemotherapy and radiotherapy. Molecular studies of the virus revealed a genome sequence with 99% homology to other MERS-CoV, and it was closely related to camel-derived strains.

Immune Response to MERS-CoV

The basics relating to immune response to MERS-CoV will be briefly summarized in this section. Readers interested in more detailed information are referred to 2 recent reviews.35,36 Shin et al36 were able to obtain peripheral blood samples from a cohort of 27 Korean patients who were hospitalized in 2015. Plasma cytokines (IL-1β, IL-1RA, IL-6, IL-8, TNFα, and IFN-γ), chemokines (CXCL-10), and antibodies to MERS-CoV were quantified and their levels increased as a function of the severity of disease in individual patients. High numbers of MERS-CoV-reactive CD4+ T cells, as determined by the secretion of IFN-γ, IL-2, or TNF-α on antigen stimulation, were detected in the blood of patients with moderate or severe infections in the acute phase of their disease. In contrast, antibodies and CD8+ T-cell responses were at a low level. Patients in a convalescent stage of their disease had antibodies and elevated levels of both CD4+ and CD8+ cells related to the clinical severity of their disease. CD8+ T cells had increased reactivity against the viral S protein, especially during the acute phase, compared with E/M/N proteins, while somewhat more CD4+ T cells, which were predominant in the convalescent phase, were directed against E/M/N proteins compared with S proteins. The elevated levels of IL-6, IL-10, and MCP-1, which are associated with inflammation, could be reflective of an ongoing inflammatory response in the lungs and...
possibly associated with significant tissue damage. The late increase in the chemokine CCL5 (or RANTES), which is chemotactic for T cells, might be attributable to its secretion by activated virus-reactive T cells. In summary, the study from Shin et al. has provided us with valuable information on the early immune response to MERS-CoV.

Pathogenesis of MERS

Many of the individuals who contracted MERS had known contact with dromedary camels. However, spread also could be driven by person-to-person contact, as was clearly demonstrated in the Korean outbreak of MERS, which was attributable to a single infected individual who presumably had contact with camels while visiting Saudi Arabia. Similar to SARS-CoV and SARS-CoV-2, infection occurred via the respiratory tract, although exactly how this occurred is unclear. Similar to SARS and COVID-19, underlying comorbidities of diabetes, chronic renal disease, obesity, hypertension, chronic cardiac diseases, and lung diseases increased the risk of contracting a MERS-CoV infection. The majority of these patients was male and a subset was highly immunocompromised. DPP4 is highly expressed on type I and II pneumocytes in cells of the distal airways and alveoli as well as in epithelial cells of other organs, such as the thymus, liver, intestine, and kidneys. MERS-CoV antigen was detected by immunohistochemical staining on type I and II pneumocytes of the decedent who had been autopsied. Studies of the pathogenesis of MERS-CoV have been limited by the paucity of autopsy information. However, in vitro studies have revealed significant replication of MERS-CoV in differentiated and undifferentiated primary cultures of primary human epithelial cells. Because the DPP4 receptor is widely expressed on epithelial cells, including those of the kidney, small intestine, liver, prostate, and activated leukocytes, it is entirely possible that, if there had been a sufficient number of autopsies, other organs of involvement might have been identified.

One of the more noteworthy features relating to MERS patients was the much higher fatality rate (Table 1) compared with the rates for SARS and COVID-19 infections. The reasons for these differences remain to be fully elucidated. This is where more information provided by autopsies could have resulted in better treatment strategies for patients who had succumbed to MERS. A large number of these patients were male in older age groups with significant comorbidities, a subset of whom were immunocompromised. All of these same comorbidities also have been observed in patients who have succumbed to COVID-19, and many of the therapeutic advances that have been made in treatment of COVID-19 during 2020 to 2021 might well be applicable to the treatment of patients with MERS. Regarding the treatment of patients who have been severely infected with MERS-CoV, care largely has been supportive. However, a retrospective study by Omrani et al. involving 44 patients provided data suggesting that the administration of ribavirin and alpha interferon, initiated at a median of 3 days after diagnosis, resulted in a modest improvement in survival. This was seen in a group of 20 survivors at 14 days, but not in untreated patients. However, they did not relate the immune responses that they described to the viral genomic load that, at least with COVID-19, has been related to the severity of disease.

Prognosis

Because the overwhelming majority of cases of MERS occurred at a time when there was a limited understanding of the best ways to treat coronavirus diseases and its pathogenesis was not understood, the MERS fatality rate was the highest of the 3 of them. Because we have excluded therapeutics as a topic of this review, it is impossible to say what the prognosis would be today in 2021 compared with what it was when the disease first presented in Saudi Arabia in 2012. However, it is safe to say that, with all that has been learned regarding the treatment of patients who have had COVID-19, the fatality rate of patients who might be infected with MERS probably would be less today than the 34.37% that has been reported by the WHO (Table 1).

CORONAVIRUS DISEASE 2019

Clinical Considerations

COVID-19 is a viral disease caused by infection with the SARS-CoV-2 virus that usually presents as an acute, febrile, respiratory illness with the potential to involve multiple organ systems. In COVID-19, infection is initiated in the lungs by binding of the SARS-CoV-2 virus to a complex of the ACE-2 receptor and accessory proteases, the transmembrane serine protease 2 receptor SS2 and cathepsin L, expressed on respiratory epithelial cells. The distribution of the ACE-2 receptor with the accessory proteases in various cell types in different organs is a determinant of the involvement of these organs in the progression of COVID-19. Although many individuals infected with SARS-CoV-2 may be asymptomatic or have mild flu-like symptoms, acute COVID-19 infections follow a clear pattern. Early infection is followed by pulmonary involvement and severe hyper-inflammation. Prognostic indicators of a more serious and a potentially fatal course include older age, lymphopenia, elevated D-dimer level, elevated troponin levels, and the comorbidities of preexisting cardiovascular disease, hypertension, obesity, diabetes mellitus, and renal disease. Although the lungs and heart primarily are involved, it now has become apparent that many different organs are affected and that the disease can progress rapidly from a pulmonary infection to a systemic disease. One-quarter or more of patients who are hospitalized owing to severe COVID-19 developed macrovascular thrombotic complications, including venous thromboembolism, myocardial injury, or brain infarction and strokes.

COVID-19 pulmonary disease can progress clinically to ARDS. Imaging studies using computed tomography in patients with COVID-19 revealed peripheral and bilateral ground glass opacities that sometimes demonstrate a rounded morphology in the early phase followed by a “crazy paving” pattern. With disease progression, more areas of consolidation are seen, and these can progress to diffuse multifocal airspace disease as seen in patients with advanced ARDS. Although the bilateral peripheral distribution of opacities is characteristic of COVID-19, other viral pneumonias, including those produced by certain strains of influenza, also can show these changes radiologically.

Characteristics of SARS-CoV-2

Shortly after the outbreak of a respiratory illness in Wuhan, China, in December 2019, a causative virus was isolated from airway epithelial cells of affected individuals. Through the application of high-throughput nucleic acid
sequencing, the virus was determined to be a previously unknown beta coronavirus. This novel coronavirus, initially named 2019-nCoV, was identified as a member of the subgenus Sarbecovirus and Orthocoronavirinae subfamily. The WHO designated the illness as COVID-19 and the virus as SARS-CoV-2 because of its close homology with SARS-CoV and partial homology with MERS-CoV viruses. SARS-CoV-2 is the seventh member of the family of coronaviruses that can infect humans.

Coronaviruses are RNA viruses with a single-stranded, 5'-capped, positive strand RNA molecule ranging from 26 to 32 kb, including at least 6 open reading frames (ORF). The first ORF (ORF1a/b) represents approximately two thirds of the genome and encodes replicate proteins. The other ORFs mainly encode 4 structural proteins, namely S, M, E, and N proteins. The major differences between SARS-CoV-2, SARS-CoV, and MERS-CoV are in open reading frame 3b (ORF3b), S and open reading frame-8 (ORF8), especially in S1 and ORF8. The S protein mediates coronavirus entry into host cells. Like SARS-CoV, ACE-2 is the host cell receptor for SARS-CoV-2. The N protein is important for the virus capsid and modulates the initial innate immune response by inhibiting type I IFN production. The M protein and E proteins are involved in viral morphogenesis, assembly, and budding. Emergence of genomic diversity and recurrent mutations in SARS-CoV-2 virus has been documented, likely reflecting adaptation to the human host. Currently, more variants have been found, some of which, excepting the South African mutant 501Y.V2, may increase infectivity without necessarily increasing virulence or resistance to currently available vaccines. However, there is ongoing concern that some of the vaccines currently in use may not confer effective immunity against some of these variants. These recently have been reclassified by the WHO and given Greek letters beginning with alpha (α) for the variant (B.1.1.7) that first was identified in the United Kingdom and delta (Δ) for the especially contagious variant (B.1.617.2) first identified in India.

Pathology

Pulmonary Pathology.—From an analysis of the autopsy findings of decedents who have succumbed to COVID-19, the most common pathologic finding seen early in the course of the disease is a distinctive interstitial pneumonia with features of DAD (Figure 2, A through C). This COVID-19 interstitial pneumonitis can be accompanied by small vessel thrombi with associated hemorrhages in the lung periphery. The interstitial pneumonitis also may be complicated and masked by multiple pulmonary thromboemboli. Polak et al recognized 3 patterns within the spectrum of COVID-19 pulmonary disease, namely, epithelial, vascular, and fibrotic. The epithelial pattern is that of the exudative phase of DAD and is characterized by hyaline membranes, detachment and atypia of type II pneumocytes, and an interstitial inflammatory response. The vascular pattern exhibits microvascular damage, microthrombi, and AFOP. The dominant feature of AFOP is intraalveolar fibrin “balls” or aggregates with loose fibroblastic tissue surrounding the fibrin, typically in a patchy distribution; however, hyaline membranes are absent. A lymphocytic interstitial pneumonitis with intraalveolar fibrin deposition may represent a transition from the DAD to the AFOP pattern, and the vascular pattern may represent a variant within the spectrum of DAD. Cases of early COVID-19 pneumonitis frequently exhibit increased intravascular megakaryocytes and fibrin deposits as well as microthrombi indicative of a prothrombotic state. The fibrotic pattern corresponds to the proliferative and fibrotic phases of DAD.

Correlation has been made between the histologic patterns and those seen radiographically, as follows. The early exudative phase is associated with ground glass opacities, proliferative lesions with crazy paving, and a late fibrous phase with a consolidative pattern, more frequently seen in the lower and middle lobes. Correlation has been made between the histologic patterns and those seen radiographically, as follows. The early exudative phase is associated with ground glass opacities, proliferative lesions with crazy paving, and a late fibrous phase with a consolidative pattern, more frequently seen in the lower and middle lobes. Correlation with pathophysiologic findings indicates that early DAD is related to a type L pattern of low pulmonary elastance, whereas the AFOP pattern is seen with a more prolonged illness and is associated with a type H pattern of high pulmonary elastance. Intertitial pneumonitis with classic DAD and AFOP patterns has been described originally in cases of SARS. Finally, Borczuk et al recently have reviewed the pulmonary pathology of 68 autopsies from 3 particularly hard hit areas, 2 in the United States and 1 in Italy. Unsurprisingly, 60% of the decedents had at least 3 comorbidities. DAD was seen in 87% of the decedents’ lungs, and tracheobronchitis also was frequently seen. In 42% of the decedents’ lungs, there were large vessel thrombi and focal microthrombi, especially with platelets, which were seen in 84% of the lungs. In a smaller cohort of these decedents, virus particles were identified by a variety of methods. These were noted in some cases in hyaline membranes and in areas where there was actively evolving...
Coronary artery disease. Another manifestation of on electrocardiograms in the absence of obstructive arrhythmias, and ST segment elevations, and/or depression dial injury as manifested by elevated serum troponin levels, disease. Clinical features are consistent with acute myocardial frequently is involved in many patients with COVID-19.

**Cardiovascular Pathology.**—The cardiovascular system frequently is involved in many patients with COVID-19 disease. Clinical features are consistent with acute myocardial injury as manifested by elevated serum troponin levels, arrhythmias, and ST segment elevations, and/or depression on electrocardiograms in the absence of obstructive coronary artery disease. Another manifestation of cardiac involvement is Takotsubo stress cardiomyopathy or, as it is commonly known, the “broken heart syndrome.” The troponin elevations, especially when accompanied by elevations of brain natriuretic peptide, carry increased risk for adverse outcomes. Although myocardial injury could reflect a COVID-19–related coronary event, angiographic studies in such patients usually do not show obstructive coronary artery disease. Myocarditis has been suspected clinically, and magnetic resonance imaging studies have provided some evidence of myocarditis in many of these patients. However, autopsy findings have revealed that a more classical myocarditis, which is characterized by lymphocytic infiltrates with associated myocyte damage, is uncommon.

In a comprehensive study of the hearts of 21 autopsied patients, 80% of the decedents had widespread myocardial macrophase infiltration consistent with a generalized inflammatory state. In contrast, only 3 (14%) hearts had changes consistent with lymphocytic myocarditis as defined by lymphocytic infiltrates associated with myocyte necrosis. In another study of 13 decedents, elevated troponin levels were associated with focal cardiomyocyte degeneration but no evidence of myocarditis. A third study from the Mayo Clinic compared decedents of COVID-19 (n = 15; 12 active, 3 cleared), influenza A/B (n = 6), and nonvirologically mediated deaths (n = 6). An ACE-2 immunohistochemical H-score was compared across cases. Viral detection encompassed SARS-CoV-2 immunohistochemistry, ultrastructural examination, and droplet digital PCR. Nonocclusive fibrin microthrombi, without ischemic injury, were identified in 16 decedents (12 COVID-19, 2 influenzaAs, and 2 controls) and were more common in the active COVID-19 cohort (P = .006). Four decedents with active COVID-19 had focal myocarditis, while 1 decedent with cleared COVID-19 had extensive disease. Arteriolar ACE-2 endothelial expression was lower in COVID-19 decedents versus controls (P = .004). ACE-2 myocardial expression did not differ by disease category, sex, age, or number of patient comorbidities (P = .69, P > .99, P = .46, P = .65, respectively). Immunostaining for SARS-CoV-2 was nonspecific, while EM and droplet digital PCRs studies were negative for virus. Four of 15 (26.7%) COVID-19 patients had underlying cardiac amyloidosis. These detailed histopathologic, immunohistochemical, ultrastructural, and molecular cardiac studies showed no definitive evidence of direct myocardial infection. COVID-19 decedents frequently had cardiac fibrin microthrombi without universal acute ischemic injury. While myocarditis was present in 33.3% of active and cleared COVID-19 decedents, it usually was limited in extent. Kawakami et al and Pelligrini et al also have reported microthrombi as a frequent finding in the hearts of COVID-19 decedents without evidence of myocarditis. In another literature review with a large sample size of 277 autopsy cases, myocarditis was reported in only 20 hearts (7.2%). Most of these, more likely than not, were not functionally significant, making the true prevalence of myocarditis much lower (<2%). In another literature review, Kawakami et al also found a similarly low prevalence of myocarditis. However, it is noteworthy that at least 1 acute, potentially COVID-19–related cardiovascular histopathologic finding, such as focal cardiomyocyte necrosis (Figure 3, A and B), macrovascular or microvascular thrombi (Figure 3, C), inflammation, or intraluminal megakaryocytes, was reported in 47.8% of the autopsy cases. Thus, pathologic studies have documented that COVID-19–related cardiac histopathologic findings are common, while myocarditis is infrequent.

The hypothesis has been advanced that vascular pericytes may be infected by the SARS-CoV-2 virus and produce capillary endothelial cell and microvascular dysfunction resulting in individual cardiomyocyte necrosis. EM studies have revealed particles consistent with SARS-CoV-2 virus involving myocardial endothelial cells and interstitial cells but not cardiac myocytes. It is noteworthy that Fox et al have found changes, in some cases, evidence of endotheliitis and vasculitis involving small cardiac vessels without lymphocytic infiltrates involving the myocardium proper. Conversely, Pelligrini et al, using a viral detection probe, found no detectable virus in myocardial endothelium.
The microthrombi in the vessels had high fibrin and complement content suggesting that hyperinflammation with elevated cytokines was responsible. Collectively, these recent studies have provided an objective assessment of cardiac involvement.

Assertions regarding the cell types infected by the SARS-CoV-2 virus based solely on EM findings are suspect. Analysis of 4 cases of COVID-19 myocarditis using molecular biologic methodology found that SARS-CoV-2 directly infects cardiomyocytes and does not infect cardiac macrophages, fibroblasts, or endothelial cells. Infection of cardiomyocytes occurs through an ACE-2 and endosomal cysteine protease dependent pathway. Infection of human pluripotent stem cell–derived cardiomyocytes and engineered heart tissues showed that cytokine production, sarcomere disassembly, and cell death were a direct consequence of cardiomyocyte infection. However, overt myocarditis in COVID-19 is infrequent. The most plausible explanation for multifocal myocyte injury in most cases is hyperinflammation–induced endothelial dysfunction. Troponin elevation also can develop with right ventricular strain caused by the COVID-19 pneumonitis and hypoxemia.

Liver and Gastrointestinal Tract Involvement.—Abnormal increases in the levels of alanine amino transferase and aspartate amino transferase have been reported, but these primarily have been in patients with severe cases of COVID-19. However, the prognostic significance of these abnormalities remains to be determined, and it is unclear whether these might be attributable to underlying hepatic disease or secondary to drugs that may have been administered during the course of treatment. Currently, there is a paucity of histopathologic evidence, other than a brief summary by Eketunde et al, which can be correlated with the elevated alanine amino transferase/aspartate amino transferase enzyme levels that were reported by Xu et al and Polak et al. Histopathologic findings included hepatic steatosis, portal fibrosis, lobular cholestasis, acute necrosis, central vein thrombosis, lymphatic infiltrates, and ductal and Kupffer cell proliferation. Some of these may have antedated COVID-19 infection and may represent unrelated pathologic changes. Nevertheless, abnormal liver function test results suggest that there may be as yet unrecognized COVID–19–related hepatic pathology. To date, no pathologic changes have been reported in the gastrointestinal tract, except for vascular thrombosis and resultant intestinal ischemic enteritis that are probably unrelated to COVID–19 infection.

Lymphoreticular, Hematopoietic, and Endocrine Systems.—It has been suggested that hemophagocytic lymphohistiocytosis may be associated with cytokine storm in patients with severe COVID–19 disease. However, so far morphologic evidence of prominent erythrophagocytosis has been found in only a few cases. Lymphoid depletion in lymph nodes and spleen has been reported with a reduction of white pulp with loss of peripheral cuff lymphocytes. This is consistent with a viral attack on immunocytes and the lymphopenia that may be seen at the time of presentation.

Iuga et al have reported adrenal vascular changes consisting of fibrinoid necrosis of small vessels, mainly arterioles in adrenal parenchyma, capsule, and adjacent periadrenal adipose tissue. However, there is no indication of how many of the 5 decedents’ adrenal glands showed these changes.

Integumentary System.—Magro et al were the first to describe purpuric skin lesions associated with COVID–19 infection in 3 of 5 patients, all of whom succumbed to the disease. One of these patients developed retiform purpura with extensive inflammation on the buttocks. Microscopic examination of the skin biopsy specimen revealed a thrombogenic vasculopathy associated with extensive necrosis of the epidermis and adnexa. Severe interstitial and perivascular neutrophilia and prominent destruction of neutrophils also were noted. A second patient developed superficial vascular ectasia and an occlusive arterial thrombus within the deeper reticular dermis, and a third developed purpuric eruptions on various parts of her body. Microscopic examination of a biopsy specimen revealed perivascular lymphocytic infiltrates in the superficial dermis and small thrombi within venules of the deeper dermis. A number of these lesions were associated with complement activation.

In a larger series, Gianotti et al described a wide spectrum of dermatologic findings in adults and children with COVID–19, including urticarial lesions, chilblains, targetoid lesions (erythema multiforme–like lesions), exanthema, maculo–hemorrhagic rash, or chickenpox–like lesions. Histopathologic analysis of these cases showed a wide spectrum of morphologic patterns. A constant in all skin biopsy specimens was the presence of prominent dilated blood vessels with a swollen endothelial layer, vessels engorged with red blood cells, and perivascular infiltrates, consisting mainly of CD8+ lymphocytes and eosinophils. In 2 cases, there was a diffuse coagulopathy in the cutaneous vascular plexus. In the early phases of the disease, after activation by the virus, numerous collections of Langerhans cells were found in the epidermis. These dermatologic findings associated with the corresponding histopathologic features have led to a recommendation that dermatologists should suspect the possibility of COVID–19 infection, especially in patients with skin lesions accompanied by fever and cough.

Kidneys.—The pathologic basis for severe acute renal failure in some patients requires further evaluation. Some decedents had prominent thrombi in glomerular capillaries, although glomerular involvement was limited in many cases. It is likely that the acute renal failure is a secondary form of acute tubular necrosis. Santoriello et al have reported detailed renal pathologic findings in a cohort of 42 decedents with a median age of 71.5 years who had been hospitalized at Columbia University Medical Center. Histopathologic changes associated with a clinical history of hypertension and/or diabetes were seen in a high percentage of the kidneys. Changes more specifically related to COVID–19 infection included focal renal blilirubin thrombi. None of the decedents had significant tubulitis or other findings consistent with interstitial nephritis, nor were viral inclusions identified in any of the kidneys. Kudose et al have reported on the kidney biopsy findings of 17 patients with COVID–19. These revealed a broad spectrum of glomular and tubular disease and provided strong evidence for cytokine–mediated effects and enhanced adaptive immune responses rather than direct viral infections of the kidneys. The most noteworthy clinical finding was a marked elevation of serum creatinine–associated mild acute tubular injury. Su et al have reported on renal histopathologic findings in a cohort of 26 Chinese decedents who succumbed to COVID–19. The mean age was 69 years, and the cause of death for all of these patients was...
respiratory failure associated with multiorgan dysfunction. Nine of 26 showed signs of renal injury, as evidenced by increased serum creatinine values and/or new-onset proteinuria. Histopathologic examination of the kidneys of these decedents revealed diffuse proximal acute tubular injury, vascular degeneration, and aggregates of erythrocytes obstruction of glomerular capillaries. In addition to the direct effects relating to SARS-CoV-2, there were other unrelated factors contributing to acute tubular injury.

**Brain and Peripheral Nervous System.**—The common presenting clinical symptoms of anosmia, dysgeusia, or ageusia early on suggested the possibility that COVID-19 might infect the peripheral nervous system and the brain via entry through the olfactory tracts and bulbs.

Recently however, it has been reported by Rhea et al.\(^98\) that the S1 protein of SARS-CoV-2 crossed the blood–brain barrier in mice injected intravenously with radio-iodinated S1 protein. If we can extrapolate from this study, it is entirely possible that this process might also occur in humans. In one of the first reports relating to brain involvement, Politi et al.\(^99\) described magnetic resonance imaging alterations consisting of cortical hyperintensity in the right rectus gyrus and the olfactory bulbs, although viral RNA was difficult to detect in them at autopsy. However, nonneuronal expression of ACE-2 receptors on support and stem cells in human olfactory epithelium may be a possible mode of entry.\(^100\) This was followed-up by a number of reports describing neurologic features of COVID-19 infection. Mao et al.\(^101\) reported on a cohort of 214 patients, 78 of whom had neurologic symptoms. The most serious of these in a cohort of 6 patients were impaired consciousness and acute cerebrovascular disease.\(^100,102–105\)

**Neuropathologic Findings.**—Despite all of these reports, until recently there has been a paucity of articles focusing specifically on neuropathologic findings associated with COVID-19 infection. However, in the most recent and most comprehensive of these, Matschke et al.\(^106\) reported on the neuropathologic findings in a cohort of 43 decedents who had succumbed to COVID-19 infections. Thirteen of these had preexisting neurologic conditions such as neurodegenerative diseases or epilepsy. Death primarily was due to pulmonary complications associated with their infections. The brains of 13 decedents showed gross evidence of either fresh or older territorial ischemic infarcts without any evidence of cerebral bleeding or small vessel thrombosis. A highly variable degree of reactive astrogliosis was found in various regions of the brains of all of the decedents. SARS-CoV-2 RNA was detected by a real-time quantitative PCR in frontal lobe tissue of 23 decedents, and SARS-CoV-2 protein could be detected in 8 of 13 decedents who were positive for SARS-CoV-2 by real-time quantitative PCR. Cytotoxic CD8\(^+\) lymphocytes were seen in the frontal cortex, basal ganglia, and brain stem. Larger numbers were seen in perivascular regions and brainstem and only small numbers in the meninges and olfactory bulbs. However, the latter showed a high degree of astrogliosis and microgliosis.

Mukerji and Solomon\(^107\) very recently have reviewed the gross brain autopsy findings of 142 decedents. There was a high incidence of preexistent brain disease, most frequently consisting of neurodegeneration, prior strokes, and atherosclerosis. A total of 92 (65%) of the decedents’ brains had no significant findings. The remaining 50 decedents’ brains had significant neuropathologic findings of which hemorrhage was the most frequent, and these included petechial hemorrhages (n = 9), large cerebral hemorrhages (n = 4), large acute and/or subacute infarcts (n = 11), and lacunar and watershed infarcts. They also found severe edema resulting from brain herniation (n = 5) and, most frequently, mild to moderate edema without herniation (n = 34). It was concluded that acute hypoxic injury and mild to moderate nonspecific inflammation were the most common, and they suggested that their frequency is unlikely to change. Correlating with these findings, Oxley et al.\(^108\) reported large vessel strokes as presenting symptoms in 5 patients aged younger than 50 years, all of whom survived. Finally, Dixon et al.\(^109\) have carried out a retrospective case study of reports describing 10 COVID-19 patients with cerebral microhemorrhages that were detected by magnetic resonance imaging. These microhemorrhages had a predilection for several sites in the brain, but they were similar to those seen in critically ill non–COVID-19 patients. Histopathologic evidence of neurovascular injury in several patients who had other significant COVID-related brain pathology has been provided by Jaunmuktane et al.\(^110\) and Lee et al.\(^111\) This raises the question as to whether these microhemorrhages were COVID-19 specific or secondary to the critical illness and accompanying hypoxia of COVID-19 patients.

Finally, and most recently, Thakur et al.\(^112\) have reported on the neuropathologic findings of 41 consecutive decedents who had succumbed to SARS-CoV-2 infections. Neuropathologic examination revealed both local and focal hypoxic/ischemic changes in all of the brains and microglial nodules accompanied by neuronophagia, especially in the brain stem. RT-PCR revealed detectable but low or very low levels of viral RNA in the majority of brains, but these were much lower than those found in the nasal epithelia. It was concluded that the microglial activation nodules and neuronophagia most likely were the result of systemic inflammation.

**Neuropsychiatric and Cognitive Sequelae.**—Of major concern are the long-term neurologic, neuropsychiatric, and cognitive sequelae associated with COVID-19 infection that recently have been described in a subset of patients.\(^113–116\) Graham et al.\(^117\) have reported on a group of 50 SARS-CoV-2 patients who were seen in the Neuro–COVID-19 Clinic at Northwestern University who were “long haulers.” The main neurologic symptoms were “brain fog,” headache, numbness/tingling, dysgeusia, anosmia, myalgias, dizziness, pain, blurred vision, tinnitus, and dysgeusia in frequencies ranging from 81% for “brain fog” to 29% for tinnitus. Dysgeusia or ageusia, which are especially common, appear to be attributable to the expression of ACE-2 receptors on type II taste receptor cells in the fungiform papillae of the tongue.\(^118\) This potentially also could provide another portal of entry for SARS-CoV-2 into the body via the oral cavity. Frequent comorbidities were depression/anxiety and autoimmune diseases, and the latter was seen more frequently in females. The authors speculated that the high frequency of fatigue and “brain fog” might represent a mild form of postinfection encephalopathy. However, to the best of our knowledge, no specific neuroradiologic or neuropathologic findings have yet been described that could explain these disturbances. Only time will tell how important these will be in the future.\(^116\) Ending on a positive note, there are anecdotal reports that vaccination against SARS-CoV-2 can result in a return to normality in some individuals. All of the clinical and pathologic manifestations of severe COVID-19 are summarized in Table 2.
Immune Response in COVID-19

Multiple lines of evidence indicate that innate immune responses are intimately tied to the severity of COVID-19 disease progression. Coronaviruses, including SARS-CoV-2, use multiple mechanisms to influence innate immune responses, starting with suppression of IFN activation in the infected host cell. After viral fusion with the host cell membrane, these viruses transmit their single-stranded (sense) sRNA genome into the cytoplasm for rapid translation of nonstructural proteins as well as replication. Like other coronaviruses, SARS-CoV-2 RNA polymerase (nsp12) has an associated proofreading subunit for RNA editing that suppresses mutation rates compared with other, smaller RNA viruses. This editing function is related to the relatively low but significant mutation rates for SARS-CoV-2 compared with other RNA viruses, such as the HIV. Although double-stranded RNA replication intermediates are potent activators of host IFNs, the virus evades host cell antiviral sensors by confining RNA replication to double-membrane vesicles, thus shielding double-stranded RNA from detection. In addition, nonstructural viral proteins act to suppress translation of host cell mRNAs including that of IFN. Consistent with this, genome-wide association studies indicate that polymorphisms of toll-like receptor-3, a component of the host cell pathway for detection of RNA-DNA hybrids during viral genome replication, are associated with higher risk for severe disease.

Cytokines.—An imbalance in IFN responses, specifically in the viral-mediated suppression of IFN-1 activation, may increase viral load early in infection in SARS-CoV. In roughly 15% of COVID-19 patients, the worsening of symptoms, as the virus was cleared approximately 7 days after the onset of symptoms, has been associated with a dysregulated immune response. Lymphocytopenia with specific reductions in natural killer and CD8+ T cells and delayed production of IFN-1 have been associated with more severe disease in human and animal models of coronavirus disease. Later in the infection, individuals with severe disease showed significant increases in IL-6, IL-10, IL-2, and IFN-γ compared with those seen in milder cases. Elevated levels of proinflammatory cytokines in plasma are linked to a significant migration of reactive cells, mainly neutrophils and monocytes, into the lungs resulting in tissue damage. This phenomenon, known as “cytokine storm,” has not been well-defined. Induction of proinflammatory cytokines is shared with SARS-CoV and MERS, and it has been suggested that cytokine inhibition may be effective in reducing lung damage and the inflammatory state. Of note, although mortality is associated with sustained increases in IL-1 and IL-6, clinically, IL-6 blockade has not had a significant effect in reducing worsening of disease or overall mortality rates. Genome-wide association studies have revealed that variants of genes in immune pathways related to type I IFNs are linked to more severe disease, indicating that this arm of the innate immune system plays a critical role in determining the course of disease. However, clinical approaches to modulate IFNs for both SARS-CoV and MERS-CoV, in addition to SARS-CoV-2, have yielded conflicting results, either worsening or rapidly ameliorating symptoms.

Adaptive Immune Responses.—SARS-CoV-2 has diverse effects on the adaptive immune responses. Autoantibodies against type 1 IFNs are found in 10% of patients with severe disease, and the virus appears to be able to suppress antigen presentation of MHC class I and class II molecules, further impairing the adaptive immune response. Neutralizing antibody responses, mainly to the S and N proteins, arise in the acute phase of disease and can be observed as early as 1 day after the onset of symptoms. Median times for IgG responses were at 14 days after symptom onset, compared with 5 days for IgA and IgM responses. Seropositivity for recovered individuals may be greater than 90%. However, the longevity of the humoral response is an open question. Some studies indicate that it can last for more than 4 months and others suggest that antibodies may disappear after a few weeks. Unfortunately, individuals with asymptomatic or mild infections, which could be up to 75% of the total, may not develop high levels of antibody-mediated immunity. The possibility of short-lived humoral immunity for SARS-CoV-2 may be common to other coronaviruses, as suggested by the significantly decreasing efficacy of coronavirus vaccines over a period of months in farm animals.

Cellular Immune Responses.—There is increasing evidence that cellular immune responses also may be an important determinant of longstanding immunity to SARS-CoV-2. A recently published Centers for Disease Control and Prevention bulletin reported that T-cell responses were detectable using enzyme-linked immunospot assays in a group of blood donors who previously had PCR-confirmed SARS, MERS, and COVID-19 Viral Diseases—Barth et al
SARS-CoV-2 infections, even when antibodies were not detected. Nearly 20% of these individuals had undetectable IgG responses 60 days after infection, but the vast majority of these IgG-negative patients showed T-cell-mediated immunity. Both T-cell and B-cell immunity was detectable until a median of 75 days (range = 24 to 154 days) after the onset of symptoms. Thus, multiple studies indicate that the immune response to SARS-CoV-2 may result in the generation of a pool of long-lasting memory T cells.

Finally, Dan et al. analyzed the long-term immune responses in a study of 185 individuals who had been infected with COVID-19. This group of patients included 42 individuals who were 6 months or more after infection. Circulating antibodies, memory B cells, and SARS-CoV-2-specific CD4+ and CD8+ T cells were quantified. Although the initial responses were heterogeneous, S-specific IgG and neutralizing antibodies persisted with only modest declines in half-lives at 6 to 8 months, and their half-lives were comparable to those seen with other viral infections. Based on these observations, it was concluded that humoral and cellular immunity was measurable in approximately 90% of the infected individuals at 5 months or more. This finding suggested that a more durable immunity might be possible, and this is supported by the relatively small number of cases of reinfection that have been reported to date.

**Antibody Responses.** In contrast to the immune responses that have been described in adults, there are distinctly different antibody responses to SARS-CoV-2 in children. As reported by Weisberg et al., adult patients had anti-S IgG, IgM, and IgA antibodies and IgG anti-N antibodies. On the other hand, children either with or without the multisystem inflammatory syndrome had restricted classes of antibodies and these primarily were anti-S, but not anti-N antibodies. Furthermore, children with or without multisystem inflammatory syndrome had decreased neutralizing antibodies compared with both COVID-19 groups, indicating a diminished protective response. As the authors have suggested, this has implications for the development of age-related targeted strategies for both testing and protection of different segments of the population.

Finally, Ng et al. used a variety of assays to detect antibodies reactive with SARS-CoV-2 proteins and preexisting cross-reactive IgG antibodies directed against the S protein of seasonally spreading human coronaviruses. Such antibodies were detected in the sera of 21 of 48 uninfected healthy children, whose ages ranged from 1 to 16 years. In contrast, only 1 of 43 young adults, whose ages ranged from 17 to 25 years, had such antibodies. Based on this observation, one possible reason that children may have milder symptoms or be asymptomatic for SARS-CoV-2 is the presence of these preexisting, cross-reactive antibodies. In conclusion, although great progress has been made in understanding the immune response evoked by SARS-CoV-2, much still remains to be learned.

**Pathogenesis of COVID-19 Infection**

In severe acute COVID-19 respiratory syndrome, the SARS-CoV-2 virus primarily infects type II pneumocytes expressing the ACE-2 receptor in alveoli. Active replication of the SARS-CoV-2 virus causes the host cells to undergo a highly inflammatory form of lytic programmed cell death (pyroptosis) and the release of viral nucleic acids and proinflammatory cytokines. The cytokines are recognized by pattern-recognition receptors on adjacent pulmonary monocytes and resident alveolar macrophages, which trigger the production of more proinflammatory cytokines and chemokines, including IL-1β, IL-6, IL-8, GM-CSF, TNF-α, IFN-γ, IP-10/CXCL10, MCP-1/CC12, MIP-1α/CCL3, and MIP-1β/CCL4. Inflammatory monocytes, CD4+ and CD8+ T cells, neutrophils, and natural killer cells are then recruited to the lung parenchyma and interstitium. The monocytederived classic M1 macrophages and CD4+ T cells exacerbate inflammation by producing additional cytokines. A profibrotic subset of alternative M2 macrophages also are recruited to the lung, and, in this milieu, a prothrombotic state is induced in the pulmonary microvasculature.

A proinflammatory feedback loop is established that triggers a circulating cytokine storm and leads to ARDS, septic shock, and hemophagocytic macropathies in the reticuloendothelial system throughout the body. Thus, the hyperinflammation associated with COVID-19 disease results from a dysregulated host innate immune response.

Severe COVID-19 disease manifests itself as a severe form of DAD in the acute, exudative phase. COVID-19–induced DAD is characterized by damage to alveolar capillary endothelium and type II pneumocytes leading to alveolar septal edema and the formation of hyaline membranes, accumulation of numerous megakaryocytes, platelets, and neutrophils in alveolar capillaries, and precipitation of fibrin inside and outside of the alveolar capillaries with a relatively mild accumulation of lymphocytes and macrophages within alveoli. The AFOP pattern appears to be a variant without hyaline membranes. The fibrin deposits provide evidence for a pulmonary thrombotic microangiopathy, which often results in fibrin-platelet thrombi in alveolar capillaries and small pulmonary arteries. Similar changes have been identified in DAD of other etiologies, including influenza and SARS-CoV. However, the changes in full-blown COVID-19 DAD are more extensive and severe and collectively constitute a distinct and characteristic type of COVID-19 DAD. In some patients, the pulmonary thrombotic microangiopathy progresses to a diffuse hypercoagulable state that can lead to deep vein thrombosis and large pulmonary thromboemboli. A clinical marker for patients at risk for this coagulopathy is elevated plasma D-dimer at the time of presentation. A postulated underlying mechanism for severe COVID-19–associated pneumonia is a state of virally induced hyperinflammation that has been variously designated as macrophage activation syndrome, cytokine storm, and secondary hemophagocytic lymphohistocytosis. This hyperinflammatory response most likely involves activation of the innate and acquired immune responses. Hence, the initial pulmonary pathology is a florid DAD with an immunothrombotic microangiopathy. Patients who succumb after a more prolonged clinical course are likely to show late-stage DAD and/or organizing pneumonia.

The multisystem microthrombi and macrothrombi confirmed that COVID-19 was a systemic vascular disease. Initially, the pathogenesis of COVID-19 was thought to involve an endothelitis due to the uptake and proliferation of the virus in endothelial cells, first in the lungs followed by infection of endothelium in multiple vascular beds. However, there is conflicting evidence for endothelitis due to SARS-CoV-2 infection. The role of endothelitis was supported by EM detection of virus-like particles, as well as by reports of ACE-2 receptor expression on endothelial cells. However, molecular biological studies have failed to confirm viral infection of endothelial cells. Other in vitro
studies revealed that human endothelial cells are moderately permissive for SARS-CoV-2 infection. Nevertheless, abundant evidence indicates that endothelial dysfunction with a prothrombotic phenotype has a major role in the pulmonary and systemic manifestations associated with COVID-19 disease.

Endothelial damage and dysfunction likely is initiated by attachment of SARS-CoV-2 to ACE-2 molecules followed by cellular ACE-2 downregulation. Subsequent endothelial injury is an underlying mechanism that likely links inflammation and thrombosis in severe COVID-19. The hypothesis has been advanced that exposure to SARS-CoV-2 triggers a unique endothelial exocytotic response that simultaneously activates 2 pathways, microvascular inflammation and thrombosis, leading to hyperinflammation and diffuse thrombosis that is characteristic of severe COVID-19. Exocytosis that is a rapid response to injury in which multiple agonists, such as P-selectin and von Willebrand factor, are secreted from injured endothelial cells, leads to high circulating levels of these molecules in patients with COVID-19. The cellular mechanisms for this phenomenon of virally triggered endothelial exocytosis are under active investigation, but at this time it can be concluded that COVID-19 is a microvascular disease due to direct or indirect induction of widespread endothelial dysfunction.

**Prognosis**

The outcome for infected patients is strongly influenced by the severity of presenting symptoms and the viral load at the time of presentation, as well as the presence or absence of predisposing risk factors and comorbidities. Fortunately, patients with mild symptoms, no comorbidities, and a low viral load will recover within a short time. Patients with severe respiratory symptoms who have been exposed to a large viral load, especially those with preexisting comorbidities, such as diabetes, hypertension, obesity, and preexistent cardiac, pulmonary, and renal diseases, have a more guarded prognosis. However, this has improved as therapeutic approaches have been targeted to deal with the different organ systems involved. Nevertheless, a significant mortality rate continues for all 3 coronavirus diseases. As recently reported by Goshua et al, mortality due to COVID-19 infection and the endotheliopathy and associated coagulopathy were significantly correlated with increased levels of von Willebrand factor antigen and soluble thrombomodulin in critically ill patients with severe infections.

Furthermore, there is increasing recognition that COVID-19 can result in prolonged illness even in patients with mild acute symptoms, including young adults. A chronic postinfectious COVID-19 condition has been identified in patients with initial mild as well as severe acute illness. Persistent symptoms include myalgia, intense fatigue, ageusia and anosmia, sensation of fever, shortness of breath, chest tightness, tachycardia, headaches, and anxiety. The condition has been designated as long-COVID or “long-haul” COVID, or most recently as “post-acute sequelae SARS-CoV-2 infection,” and the affected individuals are designated as COVID “long haulers.” These persistent symptoms represent a prototype of chronic fatigue syndrome and are compatible with a neurologic disorder linked to dysautonomia. They might be related to endothelial injury and microangiopathy that resemble the late-stage Kawasaki-like syndrome seen after COVID-19 infection in children.

**Comparison of SARS and MERS With COVID-19**

As summarized in Table 3, a comparative analysis of the SARS, MERS, and COVID-19 pandemics reveals commonalities and unique features of each disease. SARS and MERS affected thousands of individuals in a few countries; whereas, as of June 15, 2021, COVID-19 has affected more than 177 million individuals worldwide (Table 3). The vastly greater magnitude of the COVID-19 pandemic is related to a combination of factors including a high rate of infectivity (\(R > 2.5\)) and a longer incubation time with a negative serial interval during which asymptomatic individuals shed virus and can infect others, thereby making the spread of COVID-19 more difficult to contain than SARS and MERS.

Many of the clinical features of SARS and MERS resemble those that have been described for COVID-19. However, based on the paucity of autopsy information for these 2 diseases, they seem to be more limited in terms of multiorgan involvement compared with that seen in SARS-CoV-2. Similarly, until early March of 2020, there was only a single, published COVID-19 autopsy report describing the multiorgan pathology associated with SARS-CoV-2 infection. However, within a very short time an increasing number of reports has been published describing in detail the complex pathology associated with COVID-19, including a meta-analysis of 135 decedents carried out at multiple institutions in the United States and 1 institution in Brazil. This report provides a compilation of data, including preexistent conditions that contributed to adverse clinical courses, weights of target organs such as the lungs, heart, and kidneys, and a summary of the major pathologic findings in various organs. Almost all of the decedents had more than 1 pathologic condition and the most frequent of these involved the lungs, heart, and vascular systems. Autopsy reports have been crucial in increasing our understanding of this infection and in developing improved treatment strategies. The autopsy report by Ng et al of a MERS decedent provided invaluable information relating to the pathology associated with this disease and revealed that the pulmonary pathology was similar to that seen in decedents who had succumbed to either COVID-19 or SARS. In contrast to SARS-CoV and SARS-CoV-2, which bind to the ACE-2 receptor, the MERS S protein binds to DPP4 receptors. Accompanying the report from Ng et al was a commentary by Walker emphasizing the importance of this autopsy to better understand the pathogenesis of MERS-CoV, which has been the subject of a number of publications between 2012 and 2019.

**CONCLUSIONS AND QUESTIONS**

Although SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses are structurally similar and rely on the S protein to attach to the target cellular receptors, there are significant differences in the pathology associated with each of these diseases. In contrast to SARS and MERS, there now are many autopsy reports involving more than 300 decedents that have established that COVID-19 is a multisystem disease with major involvement of the lungs and secondarily of the heart, brain, and, less frequently, the gastrointestinal tract, kidneys, integumentary, and endocrine systems. This
is associated with major activation of the inflammatory and immune systems. For all 3 of these diseases, the mainstay of therapy for patients with life-threatening respiratory failure is supportive with the provision of supplemental oxygen, artificial ventilation, and use of the extracorporeal membrane oxygenator when necessary, together with other therapeutic interventions. However, autopsy studies have made it abundantly clear that COVID-19 patients have a systemic viral illness with the expected accompaniment of major activation of the inflammatory and immune systems. These studies also provide evidence that SARS-CoV-2 patients have a baseline hypercoagulable state and are at increased risk for a pulmonary thrombotic microangiopathy, as well as the development of deep venous thromboses and major pulmonary thromboembolisms, indicating that COVID-19 is a vascular disease.49,153

Although therapeutic interventions have not been a subject of this review, a brief comment relating to this topic seems appropriate. The autopsy findings support evaluation and management for coagulopathy early in the course of disease and judicious use of prophylactic anticoagulants while the patients are hospitalized. There also is evidence that the use of ACE-2 inhibitors, statins, and possibly IL-6 antagonists might be beneficial, especially in the setting of cytokine storm in patients with COVID-19.174 Treatment guidelines now have been issued by the National Institutes of Health to reduce the viral load and antithrombotic therapy for thrombotic and thromboembolic disease in COVID-19 patients and the administration of dexamethasone to dampen the hyperimmune inflammatory response (COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 [COVID-19] Treatment Guidelines. National Institutes of Health [Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed December 2020]). Other therapeutic approaches, including the administration of genetically engineered monoclonal antibodies directed against SARS-CoV-2 to patients, are also in clinical use. We now have entered a new phase in the battle to control COVID-19 and that is to ensure the availability of a number of vaccines, some of which are RNA-based and can be up to 95% effective in preventing SARS-CoV-2 infections compared with placebo controls. The primary major concern at this point in time is that recurrent mutations in the S glycoprotein have been identified and can drive antibody escape of the virus.176 This development notwithstanding, hopefully vaccines will have a major impact on controlling COVID-19 infections and ultimately will bring this pandemic to an end.177

| Table 3. Comparison of Biologic, Clinical, and Epidemiologic Features of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19a |
|-----------------------------------------------|
| **SARS-CoV-2** | **SARS-CoV** | **MERS-CoV** |
| Homology with SARS-CoV-2 | - | 79.5% | 40% |
| Possible natural reservoir | Bats | Bats | Bats |
| Possible intermediate host | Pangolins179 and turtles | Palm civets | Dromedary camels |
| Betacoronavirus lineage | B | B | C |
| Predominant cellular receptor | ACE-2 | ACE-2 | DPP4 (also known as CD26) |
| Clinical symptoms | SARS | SARS | SARS |
| Mortality rate | 4.2% | 11% | 42% |
| Outbreak dateb | December 2019 | November 2002 | September 2012 |
| Confirmed cases (date of data) | 177 million (June 15, 2021) | 8096 (July 31, 2003) | 2566 (December 2020) |
| Total deaths (date of data) | 3.9 million (June 15, 2021) | 774 (July 31, 2003) | 866 (January 31, 2020) |
| Case fatality rate | 8.6% | 9.6% | 34.4% |
| Countries, areas or territories with cases (date of data) | 219 (January 20, 2021) | 29 (July 31, 2003) | 27 (January 31, 2020) |
| Incubation period, days (range) | 3.0 (0–24.0) | 6.4 (2–10) | 7 (2–17) |
| Major routes of transmission | Respiratory aspires, droplets, contacts, and feces | Respiratory aspires, droplets and contacts (WHO, 2003) | Unprotected contact with infected dromedary camels or infected people |
| Age, mean in yearsb (range in yearsc) | In Wuhan, China: 56 (22–92) | In an ICU in the Lombardy region of Italy: 63 (56–70) | In New York City: 63 (0–107) |
| | 39.9 (1–91) | 39.5 (15–86) | 39.9 (1–91) |
| Proportion of health workers affected | 3.8% | 23.1% | 19.1% |
| Male:female ratio | 1.06:1 | 1:1.25 | 1:2.52 |
| Risk areas | Europe, Americas | China | Saudi Arabia |
| Risk factors | Male, older ages, and preexistent comorbidities | Cw*0801 HLA | Age >30 yr, Saudi nationality, comorbidities, the interval time from onset to hospital admission >14 d |

Abbreviations: ACE-2, angiotensin converting enzyme-2; CD 26, cluster determinant-26; COVID-19, coronavirus disease 2019; DPP4, dipeptidyl peptidase-4; HLA, human leukocyte associated antigen; ICU, intensive care unit; WHO, World Health Organization.

a Data derived from a report by Hu et al14 (open access publication). Much of the data in this table are taken from reports of the WHO and are cited in Hu et al.54

b Dates for determination of outbreak date, confirmed cases, and case fatality rate are based on WHO determinations of start and end of the SARS, MERS, epidemics as well as the ongoing COVID-19 pandemic. The SARS epidemic encompassed 2002 to 2003 and the MERS epidemic occurred during 2012 to 2020. Also see da Costa et al.162

c The age range and mean age of diagnosed cases in the 3 epidemics are from data cited in Hu et al.54
Although much has been learned about COVID-19 during the past 20 months since its outbreak in December 2019, much is still to be learned about this devastating disease. To that end, we would like to conclude our review by raising the following questions relating to COVID-19 that hopefully will be answered in the future:

1. Given the close structural homology of the human coronaviruses, why has the COVID-19 pandemic involved more than 177 million people worldwide compared with the very localized SARS and MERS epidemics involving only thousands of people and why do some SARS-CoV-2 infected individuals become “super spreaders”?

2. Why is there such a broad spectrum of responses of individuals infected with SARS-CoV-2 virus ranging from either none or mild symptoms in 80%, major respiratory illness in 15%, and life-threatening or fatal systemic disease in 5%? Is it only preexisting comorbidity or are there other unknown factors?

3. What are the mechanisms responsible for the systemic microvascular involvement and thrombotic state in COVID-19? Is direct viral infection of endothelial cells or hyperinflammation-induced endothelial dysfunction responsible?

4. What are the long-term clinical, pathologic, and neurologic sequelae of individuals who have recovered from their SARS-CoV-2 infections?

5. What are the neuropsychiatric, neurophysiologic correlations, if any, associated with the so-called “long haulers” syndrome seen in some individuals who have recovered from acute infections?

6. What lessons can we learn from COVID-19 about the molecular pathology and evolution of coronaviruses, especially in the context of their emergence during the past 20 years?

7. How critical is it to continue molecular surveillance of COVID-19 variants and how could this affect our ability to treat future patients who become infected with these variants?

8. Why are some of the variants of SARS-CoV-2 more transmissible than others? Is it because they have a better ability to evade the antiviral response or greater infectivity, is it both of these, or something that has yet to be identified?

Hopefully, answers to these questions will provide us with a better understanding of the viral, immunologic, and pathologic features of COVID-19 and will result in better treatment strategies, and ultimately lead to the control of this devastating pandemic.

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