

be cured (13). Most HCV infections persist, but some spontaneously resolve during the first year of infection. In about 80% of infected people, the virus is able to avoid clearance by the immune system, and the result is chronic HCV infection (14,15). In a study of 251 HCV patients, Huang et al. (16) reported that 34% spontaneously cleared the HCV infection, while 66% had a chronic HCV infection. The Huang study implicated differences in the human genome as responsible for the patient's ability to clear the infection, or to suffer from a chronic infection. This difference took the form of a polymorphism in the DNA sequence of the human interferon (IFN)-gamma gene. This polymorphism occurred in one of the promoters of this gene. Patients resolving the infection, and patients with chronic infection, had different DNA sequences in this promoter.

The fact that some people infected with HCV spontaneously recover, while others progress and suffer from chronic HCV, has further bases in the immune system. Most people infected with HCV mount CD8<sup>+</sup> T-cell responses. However, what distinguishes people who recover from acute HCV and those who progress to chronic HCV, is that those who quickly recover also mount an effective CD4<sup>+</sup> T-cell response (in addition to the CD8<sup>+</sup> T-cell response), while those who progress to chronic HCV mount only CD8<sup>+</sup> T-cell

responses, but fail to mount a CD4<sup>+</sup> T-cell response (17). In other words, although increased numbers of viral antigen-specific CD8<sup>+</sup> T cells are present in most patients, these cells are not maximally activated, where inadequate inactivation occurs because of lack of CD4<sup>+</sup> T-cell response. CD4<sup>+</sup> T cells serve as Mother Nature's adjuvant.

Smyk-Pearson et al. (18) characterized CD8<sup>+</sup> T cells that specifically recognize and kill HCV infections, but that have not been helped by CD4<sup>+</sup> T cells. These CD8<sup>+</sup> T cells are helpless, impaired in the ability to generate a secondary response upon rechallenge, where the unhelped memory cytotoxic T lymphocytes divided less and were unable to provide complete protection against HCV.

#### IV. DRUGS AGAINST HCV

Traditionally, the most commonly used anti-HCV drugs are IFN-alfa2 and ribavirin. Ribavirin, which is a guanosine analog, is effective against a variety of viruses, that is, viruses with a DNA genome and viruses with a ribonucleic acid (RNA) genome. With HCV, ribavirin's effect is transient, but when combined with IFN-alpha, the combination can permanently eradicate that particular HCV

<sup>13</sup>Weigand K, Stremmel W, Encke J. Treatment of hepatitis C virus infection. *World J. Gastroenterol.* 2007;13:1897–905.

<sup>14</sup>Wöfl M, Rutebemberwa A, Mosbrugger T, et al. Hepatitis C virus immune escape via exploitation of a hole in the T cell repertoire. *J. Immunol.* 2008;181:6435–46.

<sup>15</sup>Blackard JT, Shata MT, Shire NJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. *Hepatology* 2008;47:321–31.

<sup>16</sup>Huang Y, Yang H, Borg BB, et al. A functional SNP of interferon-gamma gene is important for interferon-alpha-induced and spontaneous recovery from hepatitis C virus infection. *Proc. Natl Acad. Sci. USA* 2007;104:985–90.

<sup>17</sup>Smyk-Pearson S, Tester IA, Klarquist J, et al. Spontaneous recovery in acute human hepatitis C virus infection: functional T-cell thresholds and relative importance of CD4 help. *J. Virol.* 2008;82:1827–37.

<sup>18</sup>Smyk-Pearson S, Tester IA, Klarquist J, et al. Spontaneous recovery in acute human hepatitis C virus infection: functional T-cell thresholds and relative importance of CD4 help. *J. Virol.* 2008;82:1827–37.