

THE PREVALENCE OF HEPATITIS C VIRUS INFECTION IN THE UNITED STATES, 1988 THROUGH 1994

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ABSTRACT

Background Because many persons with chronic hepatitis C virus (HCV) infection are asymptomatic, population-based serologic studies are needed to estimate the prevalence of the infection and to develop and evaluate prevention efforts.

Methods We performed tests for antibody to HCV (anti-HCV) on serum samples from 21,241 persons six years old or older who participated in the third National Health and Nutrition Examination Survey, conducted during 1988 through 1994. We determined the prevalence of HCV RNA by means of nucleic acid amplification and the genotype by means of sequencing.

Results The overall prevalence of anti-HCV was 1.8 percent, corresponding to an estimated 3.9 million persons nationwide (95 percent confidence interval, 3.1 million to 4.8 million) with HCV infection. Sixty-five percent of the persons with HCV infection were 30 to 49 years old. Seventy-four percent were positive for HCV RNA, indicating that an estimated 2.7 million persons in the United States (95 percent confidence interval, 2.4 million to 3.0 million) were chronically infected, of whom 73.7 percent were infected with genotype 1 (56.7 percent with genotype 1a, and 17.0 percent with genotype 1b). Among subjects 17 to 59 years of age, the strongest factors independently associated with HCV infection were illegal drug use and high-risk sexual behavior. Other factors independently associated with infection included poverty, having had 12 or fewer years of education, and having been divorced or separated. Neither sex nor racial-ethnic group was independently associated with HCV infection.

Conclusions In the United States, about 2.7 million persons are chronically infected with HCV. People who use illegal drugs or engage in high-risk sexual behavior account for most persons with HCV infection. (N Engl J Med 1999;341:556-62.)

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HEPATITIS C virus (HCV) infection is a leading cause of chronic liver disease in the United States. Before the characterization of HCV,^{1,2} the magnitude of infection could not be reliably determined because assessment of clinical disease (i.e., non-A, non-B hepatitis) underestimated the true extent of infection. After tests to detect antibody to HCV (anti-HCV) became available, studies to determine the prevalence of HCV infection in the general population were

performed, mostly with volunteer blood donors as the subjects.^{3,4} However, the prevalence of HCV among blood donors does not reflect the prevalence in the general population, since even first-time donors are a highly selected group that has been screened for risk factors associated with various infectious diseases. To estimate the true prevalence of HCV infection in the United States, we tested serum samples from participants in the third National Health and Nutrition Examination Survey (NHANES III) for anti-HCV.

METHODS

Survey Design and Collection of Data

The NHANES is conducted periodically by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), to obtain national statistics on the health and nutritional status of the noninstitutionalized civilian population by means of household interviews, standardized physical examinations, and collection and testing of blood samples in special mobile examination centers.⁵ NHANES III, conducted during 1988 through 1994, included a sample of approximately 40,000 persons at least two months of age at 89 randomly selected locations throughout the United States. The study protocol was reviewed and approved by an institutional review board at the CDC. All participants (or their parents, in the case of children) provided written informed consent.

NHANES III was based on a complex, stratified, multistage, probability-sample design.⁵ Persons less than 5 years of age or 60 years of age or older, blacks, and Mexican Americans were sampled at higher frequencies than other persons. After weighting on the basis of age, sex, level of education, and race or ethnic group, the distribution of participants was similar to that of the U.S. population as a whole.

We collected information in interviews on demographic, occupational, and behavioral characteristics. Race or ethnic group was defined by the subjects' choices among the categories non-Hispanic white, non-Hispanic black, and Mexican American. Subjects who did not choose one of these categories were classified as "other" and analyzed with the total population but not in racial-ethnic subgroups. The poverty index was calculated by dividing the total family income by the poverty threshold, as defined by the U.S. Census, with adjustment for family size at the time of the interview. Questions about years of education, marital status, occupation, and military service were asked of participants 17 years of age or older. Questions about sexual behavior and illegal drug use were asked of participants 17 to 59 years old. For illegal

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drug use, questions were limited to the use of cocaine (including "crack" cocaine) and marijuana and did not include the method of administration or history of injection. The questionnaire also asked about some surgical procedures (e.g., hysterectomy) and the frequency of dental visits, but it did not ask whether the subjects had undergone blood transfusion.

Laboratory Methods

Testing for HCV infection was performed on serum samples collected from subjects at least six years of age who completed the examination component of NHANES III. Serum samples were tested for anti-HCV with use of a second-generation enzyme immunoassay and a supplemental test (EIA 2.0 and HCV MATRIX, Abbott Laboratories, North Chicago, Ill.). Samples that were positive according to HCV MATRIX were considered positive for anti-HCV.

Testing for HCV RNA by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) amplification of the 5' noncoding region on anti-HCV-positive samples as described previously.⁶ Samples found to be negative for HCV RNA were extracted a second time by the same procedure, with an additional incubation at 50°C for 45 minutes with 25 units of reverse transcriptase (Boehringer Mannheim, Indianapolis) and 10 units of RNasin (Boehringer Mannheim).

Nested RT-PCR was used to amplify the 5' noncoding region and the nonstructural coding 5b (NS5b) region with use of previously described primers,^{6,7} except that R1 (5'GCTCTCAGGC-TCGCCGCGTCCTC3') and R2 (5'GCTCTCAGGTCCGCT-GCTCCTC3') were used as internal reverse primers for NS5b amplification. PCR products were separated by electrophoresis on a 2 percent agarose gel, and positive specimens were identified by ethidium bromide staining.⁶ PCR products were purified and cycle-sequenced with use of internal primers with dye-terminator reaction chemistry. Electrophoresis and nucleotide identification were performed with an automated DNA sequencer (ABI 377, Applied Biosystems, Foster City, Calif.).

The genotypes of HCV RNA-positive samples were determined by the sequencing of 300 nucleotides in the NS5b region.⁷ We compared sequences for each genotype with published sequences, using the Wisconsin Genetic Computer Group program, with use of subprograms Gap and Pileup for pairwise alignment.⁸

Serum samples were also tested for serologic markers of hepatitis B virus (HBV) infection⁹ and antibody to herpes simplex virus type 2.^{10,11} Serum alanine aminotransferase activity could not be determined, because the manner in which samples were handled before testing (they were frozen at -20°C and thawed at room temperature) has been shown to result in enzyme degradation.¹²

Statistical Analysis

Estimates of prevalence were weighted so as to represent the total U.S. population and to account for oversampling and for nonparticipation in the household interview and physical examination.¹³ Weights were further ratio-adjusted according to age, sex, and race or ethnic group to match estimates of the distribution of these factors in the civilian noninstitutionalized U.S. population, with adjustment for undercounting.^{13,14} Standard errors were calculated with use of SUDAAN software.¹⁵ For comparisons among subgroups of the NHANES III population, data were adjusted for age by the direct method to match the 1980 U.S. population.¹⁶ Univariate t-statistics were calculated with use of a general linear-contrast procedure in SUDAAN¹⁵ so that we could examine age-adjusted or unadjusted differences in the seroprevalence of HCV between the highest and lowest levels of each variable, with a two-sided P value of less than 0.05 considered to indicate statistical significance.

Backward stepwise logistic regression in SUDAAN was used to determine independent predictors of HCV infection in a multivariate model applied to persons 17 to 59 years old. Variables with a Satterthwaite-adjusted F-statistic at P<0.05 were considered significant and were allowed to remain in the model.¹⁵

RESULTS

Prevalence of Anti-HCV and Social and Demographic Characteristics

Of the approximately 40,000 persons who were selected for inclusion in NHANES III, 30,930 were at least six years old; 25,733 of this group agreed to be interviewed, and 23,527 agreed to be examined. Of these 23,527 subjects, 21,241 (90 percent) were tested for anti-HCV. Rates of participation were lower for subjects 6 to 11 years old (84 percent) and more than 70 years old (82 percent). Rates of participation were no different when we compared persons who reported engaging in high-risk behavior with those who did not. The prevalence of anti-HCV was 1.8 percent (95 percent confidence interval, 1.5 to 2.3 percent), which corresponds to approximately 3.9 million people in the United States (95 percent confidence interval, 3.1 million to 4.8 million) who have been infected with HCV.

The prevalence of HCV infection was higher among non-Hispanic blacks than among non-Hispanic whites and higher among male subjects than among female subjects (Table 1). In all racial-ethnic groups, the prevalence of infection was low among subjects in the younger and older age groups (Table 2), although among non-Hispanic blacks prevalence began to increase at an earlier age (12 to 19 years) than in the other groups. The delayed peak in prevalence among Mexican Americans 50 to 59 years old was probably attributable to the small numbers of subjects and may not accurately reflect the true prevalence in this group. Sixty-five percent of all anti-HCV-positive persons were 30 to 49 years old. The highest observed prevalence was 9.8 percent among black men who were 40 to 49 years old. A higher prevalence of HCV infection also was observed among subjects who were below the poverty level, subjects older than 16 years who were divorced or separated, and subjects who had completed 12 or fewer years of education (Table 1). No association was found between the prevalence of HCV infection and residence in a metropolitan area or in a particular geographic region, prior military service, or foreign birth (Table 1).

Risk Factors for HCV Infection

The prevalence of HCV infection was not associated with employment in a health-related occupation (Table 3), surgery that might have included blood transfusion (e.g., hysterectomy), or a higher frequency of dental visits (data not shown). An increased prevalence of infection was associated with a history of cocaine or marijuana use among all racial-ethnic groups, and prevalence increased with an increasing number of times each drug was used (Table 3). Approximately 14 percent of the participants 17 to 59 years old reported ever having used cocaine, with the highest frequency of use (22 percent)

TABLE 1. PREVALENCE OF ANTIBODY TO HCV (ANTI-HCV) ACCORDING TO DEMOGRAPHIC CHARACTERISTICS IN NHANES III.*

CHARACTERISTIC	No. TESTED†	PREVALENCE OF ANTI-HCV (95% CI)	ESTIMATED No. INFECTED NATIONWIDE (95% CI)
		%	thousands
All subjects	21,241	1.8 (1.5–2.3)	3875 (3102–4840)
Race or ethnic group			
Non-Hispanic white	7,965	1.5 (1.1–2.0)	2359 (1774–3137)
Non-Hispanic black	6,119	3.2 (2.6–4.0)‡	762 (609–953)
Mexican American	6,268	2.1 (1.7–2.6)	261 (210–323)
Other	889	2.9 (1.4–5.8)	493 (245–993)
Sex			
Male	10,076	2.5 (2.0–3.2)§	2586 (2012–3323)
Female	11,165	1.2 (0.9–1.6)	1289 (967–1717)
Marital status¶			
Divorced or separated	1,771	5.1 (3.7–7.1)§	921 (668–1270)
Never married, married, or widowed	14,801	1.8 (1.5–2.3)	2855 (2283–3570)
Poverty index			
Below poverty level	5,345	3.2 (2.4–4.3)§	937 (700–1254)
At or above poverty level	13,974	1.6 (1.2–2.0)	2625 (2029–3396)
Education¶			
≤12 yr	11,971	2.8 (2.1–3.6)§	2866 (2216–3706)
>12 yr	4,528	1.3 (0.8–2.0)	898 (583–1384)
Area of residence			
Metropolitan (population, ≥1 million)	10,351	2.2 (1.6–2.8)	2188 (1673–2682)
Nonmetropolitan (population, <1 million)	10,890	1.6 (1.1–2.2)	1686 (1218–2334)
Region of residence			
Northeast	2,718	2.0 (1.4–2.9)	847 (594–1208)
South	9,230	2.0 (1.3–3.1)	1455 (957–2211)
Midwest	4,101	1.3 (0.9–1.8)	642 (443–929)
West	5,192	2.1 (1.3–3.3)	931 (591–1468)
Military-service status¶			
Ever in military	2,399	1.7 (1.2–2.5)	469 (323–680)
Never in military	14,117	2.2 (1.8–2.9)	3290 (2584–4188)
Country of birth			
United States	17,288	1.9 (1.5–2.3)	3390 (2722–4222)
Other	3,895	1.8 (0.9–3.7)	480 (238–966)

*NHANES III denotes the third National Health and Nutrition Examination Survey, and CI confidence interval.

†The totals vary according to the availability of data.

‡P<0.05 for the comparison with non-Hispanic whites.

§P<0.05.

¶Only persons 17 years of age or older are included; values have not been adjusted for age.

among 25-to-29-year-olds and 30-to-39-year-olds. Among those who had ever used cocaine, the prevalence of infection increased with age, reaching 18.8 percent among those 40 to 59 years old, although this age group reported the lowest frequency of use (6 percent). Forty-five percent of participants reported ever having smoked marijuana, and 12 percent reported smoking it 100 or more times. Although the prevalence of HCV infection among those who had smoked marijuana 100 or more times was similar among subjects in all age groups starting at 30 years (12.3 to 12.8 percent), the proportion who reported smoking marijuana 100 or more times was highest among 30-to-39-year-olds (19 percent) and declined after the age of 40 years.

A higher prevalence of HCV infection was also as-

sociated with an early age at first sexual intercourse, a greater number of sexual partners, and infection with herpes simplex virus type 2 (Table 3). Twenty-eight percent of participants 17 to 59 years old reported having had 10 or more sexual partners, and 4 percent reported 50 or more. Although the highest prevalence of HCV infection among participants who reported having 10 or more sexual partners was found among persons 30 to 39 years old (7.4 percent), the proportion that reported having 10 or more partners was similar among persons in all age groups from 25 to 49 years of age (30 to 34 percent).

Among participants of all ages, those with serologic evidence of HBV infection were more than six times as likely to be positive for HCV infection as

TABLE 2. PREVALENCE OF ANTIBODY TO HCV (ANTI-HCV) ACCORDING TO AGE AND RACE OR ETHNIC GROUP IN NHANES III.*

AGE	TOTAL POPULATION		NON-HISPANIC WHITES		NON-HISPANIC BLACKS		MEXICAN AMERICANS	
	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %
6-11 yr	2762	0.2 (0.04-0.6)	732	0.2 (0.02-1.2)	895	0.2 (0.1-0.8)	1014	0.4 (0.1-2.8)
12-19 yr	2905	0.4 (0.2-0.9)	746	0.2 (0.02-1.2)	1017	1.2 (0.4-4.0)	995	0.4 (0.1-1.2)
20-29 yr	3275	1.6 (1.0-2.5)	849	1.6 (0.8-2.9)	1029	1.8 (1.1-2.8)	1255	2.0 (1.4-2.8)
30-39 yr	3121	3.9 (2.8-5.5)	997	3.2 (2.1-5.0)	1041	6.0 (4.6-7.8)	952	3.7 (2.5-5.7)
40-49 yr	2454	3.0 (2.1-4.4)	879	2.6 (1.6-4.4)	751	6.3 (4.2-9.4)	718	3.0 (2.0-4.8)
50-59 yr	1762	1.4 (1.0-2.1)	865	0.4 (0.1-1.0)	447	3.6 (2.2-6.1)	357	6.0 (3.4-10.4)
60-69 yr	2194	0.9 (0.5-1.7)	952	0.7 (0.3-1.9)	527	2.5 (1.8-3.4)	638	1.5 (0.7-3.4)
≥70 yr	2768	1.0 (0.7-1.4)	1945	0.9 (0.6-1.2)	412	2.8 (1.4-5.4)	339	0.2 (0.1-1.0)

*NHANES III denotes the third National Health and Nutrition Examination Survey, and CI confidence interval. Totals include subjects whose race or ethnic group was "other."

TABLE 3. AGE-ADJUSTED PREVALENCE OF ANTIBODIES TO HCV (ANTI-HCV) ACCORDING TO RACE OR ETHNIC GROUP AND POTENTIAL RISK FACTORS FOR INFECTION IN NHANES III.*

VARIABLE	TOTAL POPULATION		NON-HISPANIC WHITES		NON-HISPANIC BLACKS		MEXICAN AMERICANS	
	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %	NO. TESTED	PREVALENCE OF ANTI-HCV (95% CI) %
Worked in health-related occupation†								
Never	15,625	2.0 (1.6-2.5)	6405	1.6 (1.1-2.1)	4154	3.7 (3.0-4.6)	4419	2.7 (2.1-3.4)
Ever	769	1.4 (0.7-3.1)	313	1.4 (0.5-3.5)	337	2.1 (1.2-3.7)‡	106	0.6 (0.1-3.2)‡
Lifetime cocaine use§								
Never	10,050	1.1 (0.8-1.4)	3374	0.8 (0.5-1.3)	3056	2.1 (1.6-2.8)	3178	2.1 (1.4-3.2)
1-10 times	732	9.3 (5.3-16.3)	260	12.3 (5.1-29.9)	216	12.1 (6.9-21.0)	235	12.4 (7.1-21.7)
>10 times	519	17.8 (12.3-25.8)‡	167	11.6 (7.6-17.8)‡	219	25.3 (18.5-34.7)‡	111	26.0 (18.2-37.2)‡
Lifetime marijuana use§								
Never	6,997	0.8 (0.6-1.2)	2210	0.6 (0.3-1.1)	1949	1.9 (1.3-2.6)	2458	1.6 (1.0-2.6)
1-99 times	3,276	1.9 (1.4-2.7)	1184	1.3 (0.8-2.2)	1169	5.1 (3.4-7.6)	850	4.1 (2.2-7.6)
≥100 times	1,025	9.5 (7.4-12.2)‡	405	6.6 (4.6-9.4)‡	373	15.3 (9.9-23.6)‡	215	23.4 (17.0-32.2)‡
Age at first sexual intercourse§								
≥18 yr	4,126	0.7 (0.4-1.4)	1704	0.3 (0.1-0.8)	880	3.0 (1.4-6.4)	1332	1.5 (0.8-2.6)
<18 yr	6,337	3.2 (2.4-4.1)‡	1897	2.8 (2.0-4.0)‡	2285	4.4 (3.4-5.7)	1933	4.5 (3.4-5.9)‡
No. of lifetime sexual partners§								
0-1	2,808	0.6 (0.3-1.0)	1007	0.3 (0.1-1.2)	459	2.4 (1.6-3.8)	1171	0.9 (0.5-1.5)
2-9	5,545	1.6 (1.1-2.2)	1800	1.2 (0.7-2.0)	1895	3.0 (2.2-4.1)	1646	3.3 (2.2-5.2)
10-49	2,299	3.3 (2.6-4.3)	824	2.9 (2.0-4.2)	839	4.7 (3.1-7.2)	544	6.0 (3.8-9.5)
≥50	454	9.4 (5.6-15.8)‡	140	11.8 (6.0-23.0)‡	225	9.1 (5.6-14.7)‡	74	6.1 (2.5-15.1)‡
Herpes simplex virus type 2 infection†								
No	8,107	1.3 (1.0-1.7)	3555	1.1 (0.8-1.6)	1719	2.1 (1.3-3.3)	2529	1.7 (1.3-2.3)
Yes	3,453	3.4 (2.4-4.9)‡	803	2.8 (1.6-4.9)‡	1635	5.0 (3.7-6.9)‡	899	3.6 (2.2-5.9)‡

*NHANES III denotes the third National Health and Nutrition Examination Survey, and CI confidence interval. Totals include subjects whose race or ethnic group was "other."

†Only persons 17 years of age or older are included. Totals vary according to the availability of data.

‡P<0.05 for the comparison between the lowest and the highest categories (or between the two categories) for the variable in question.

§Only persons 17 to 59 years old are included. Totals vary according to the availability of data.

participants without evidence of HBV infection (10.2 percent vs. 1.6 percent [$P<0.001$], after adjustment for age). Similarly, participants who were positive for HCV infection were nearly six times as likely to be positive for HBV infection as those who were negative for HCV infection (25.7 percent vs. 4.5 percent [$P<0.001$], after adjustment for age). The age-adjusted prevalence of coinfection with HBV and HCV increased with an increasing number of times cocaine or marijuana was used and with an increasing number of lifetime sexual partners.

Using multivariate analysis, we found that the factors with the strongest independent associations with HCV infection among persons 17 to 59 years old were illegal drug use (ever having used cocaine or having smoked marijuana 100 or more times) and high-risk sexual behavior (an early age at first intercourse or 50 or more lifetime sexual partners) in the absence of illegal drug use (Table 4). Marital status, income (above or below the poverty level), and the number of years of education also remained independently associated with infection, whereas race or ethnic group did not. No significant interactions were found between age and sex, race or ethnic group and sex, or illegal drug use and high-risk sexual behavior. Including an interaction term for age and race or ethnic group in the model had no effect on the adjusted odds ratios.

Prevalence of Viremia and Distribution of Genotypes

The prevalence of positivity for HCV RNA among anti-HCV-positive participants was 73.9 percent (95 percent confidence interval, 65.8 to 83.0 percent). This prevalence corresponds to an estimated 2.7 million persons (95 percent confidence interval, 2.4 million to 3.0 million) with chronic HCV infection nationwide. Non-Hispanic blacks were more likely to be HCV RNA-positive (86.2 percent; 95 percent confidence interval, 78.0 to 95.2 percent) than non-Hispanic whites (67.6 percent; 95 percent confidence interval, 56.1 to 81.6 percent) or Mexican Americans (73.6 percent; 95 percent confidence interval, 66.8 to 81.2 percent) ($P=0.02$ for both comparisons).

Among subjects who were anti-HCV-positive, there was little variation in the prevalence of HCV RNA according to age among those who were at least 20 years old (weighted average, 75.6 percent; 95 percent confidence interval, 67.3 to 84.9 percent). Although this prevalence was 2.5 times as high as that among younger persons (weighted average, 30.1 percent; 95 percent confidence interval, 9.8 to 92.8 percent), the validity of this difference is questionable because of the small number of HCV RNA-positive persons less than 20 years old (four subjects), and the wide, unstable confidence interval. The only significant difference according to sex was among non-Hispanic blacks, of whom male subjects were more likely to be positive for HCV RNA

TABLE 4. RELATIVE ODDS OF POSITIVITY FOR ANTIBODIES TO HCV AMONG SUBJECTS 17 TO 59 YEARS OLD, ACCORDING TO SELECTED VARIABLES IN NHANES III.*

VARIABLE	ADJUSTED ODDS RATIO (95% CI)
Race or ethnic group	
Mexican American	1.60 (0.92–2.79)
Non-Hispanic black	1.44 (0.90–2.30)
Non-Hispanic white†	1.00
Sex	
Male	1.22 (0.75–1.98)
Female†	1.00
Marital status	
Divorced or separated	1.70 (1.08–2.66)
Never married, married, or widowed†	1.00
Education	
≤12 yr	1.92 (1.01–3.67)
>12 yr†	1.00
Poverty index	
Below poverty level	2.37 (1.50–3.75)
At or above poverty level†	1.00
Marijuana use	
≥100 times	2.99 (1.69–5.27)
1–99 times	1.15 (0.61–2.16)
Never†	1.00
Cocaine use	
Ever	4.70 (2.49–8.87)
Never†	1.00
No. of sexual partners	
≥50	5.16 (1.80–14.73)
2–49	2.54 (1.14–5.66)
0–1†	1.00
Age at first sexual intercourse	
<18 yr	2.94 (1.50–5.78)
≥18 yr†	1.00

*The values were derived from the logistic-regression model, with control for age. NHANES III denotes the third National Health and Nutrition Examination Survey, and CI confidence interval.

†Subjects in this category served as the reference group.

than female subjects (97.8 percent vs. 70.2 percent, $P=0.002$). Genotype was determined for 250 of the 283 HCV RNA-positive samples (88.3 percent); 56.7 percent of the 250 samples were classified as 1a, 17.0 percent as 1b, 3.5 percent as 2a, 11.4 percent as 2b, 7.4 percent as 3a, 0.9 percent as 4, and 3.2 percent as 6.

DISCUSSION

The data from our national seroprevalence survey indicate that HCV infection is the most common chronic blood-borne infection in the United States. Our estimates of prevalence might be considered conservative. The NHANES III excluded incarcerated and homeless persons, groups that have high rates of HCV infection, and although the proportion of anti-HCV-positive persons found to have viremia was consistent with that observed in other studies,¹⁷⁻¹⁹ we tested only a single sample for each

subject. Some HCV-infected persons are intermittently positive for HCV RNA,²⁰ and a single negative result does not exclude the possibility of chronic infection. The predominance of genotype 1a among HCV-infected persons in our study may reflect the unselected nature of the population, as compared with populations of patients referred for evaluation and treatment in other studies.²¹

In most cases, transmission of HCV had occurred in the recent past, primarily among young adults as a result of drug use and high-risk sexual behavior. The low prevalence of anti-HCV among older persons is most likely due to a cohort effect, with the risk of acquiring HCV infection lower in the distant past than in the recent past. The rates of antibody loss and death from liver disease among HCV-infected persons are reportedly low.^{17,20} The low prevalence of anti-HCV among persons less than 20 years old also reflects a low risk of infection, since the sensitivity of second-generation anti-HCV assays for detecting HCV infections is the same in infants, children, and adults.^{22,23}

Other studies have demonstrated that injection-drug use is the single most important risk factor for HCV infection.²⁴⁻²⁶ Because history of injection-drug use was not ascertained in the NHANES III, and because there is no biologically plausible mechanism to explain transmission through marijuana use, it has to be presumed that marijuana use serves as a surrogate for other methods of transmission (such as injection-drug use and high-risk sexual practices). In contrast, among persons who use cocaine, transmission could occur through sharing of blood-contaminated straws or other devices.¹⁸ However, intranasal cocaine use in the absence of injection-drug use has been very uncommon among patients with acute hepatitis C²⁶; among injection-drug users with acute hepatitis C, most report also having used cocaine and marijuana (unpublished data). Although intranasal cocaine use could have contributed to the transmission of HCV, it is unlikely to explain the large number of infections associated with drug use in our study.

The lack of a biologically plausible mechanism of transmission through marijuana use, the relation among age, seroprevalence, and patterns of cocaine use, and the direct correlation between coinfection with HBV and HCV and the frequency of drug use suggest that a substantial proportion of HCV-infected persons who reported the use of illegal drugs as defined in our study also had a history of injection-drug use. However, other risk factors, such as high-risk sexual activity or blood transfusion during treatment for traumatic injuries, might be associated with the use of drugs that are not injected and might account for an unidentified proportion of infections in this risk group.

The proportion of HCV infections associated

with high-risk sexual behavior was similar to that found for persons with acute hepatitis C.²⁶ The dose-response relation between the prevalence of infection and increasing numbers of sexual partners, even after adjustment for illegal drug use, is consistent with the results of other studies.^{24,27-29} Although the spread of HCV through sexual activity might be inefficient, as demonstrated by the low infection rates among the spouses of persons with hepatitis C,³⁰ the large number of chronically infected persons in the population provides numerous opportunities for exposure among persons who have multiple sexual partners.

The NHANES III did not obtain information on transfusion history, and we cannot directly estimate the proportion of infections acquired by this route. The incidence of transfusion-associated hepatitis C was relatively high during the two or more decades before the NHANES III, and older persons were disproportionately affected.³¹⁻³³ On the basis of the age-specific incidence of post-transfusion hepatitis during the 20 years before this study, the CDC estimates that transfusions might have been the source of infection for about 7 percent of the 3.9 million living persons who have been infected with HCV (unpublished data). This proportion is consistent with the low prevalence of HCV infection currently observed among older persons and with the results of studies of acute community-acquired non-A, non-B hepatitis, which indicated that less than 20 percent of cases were acquired through transfusions.^{20,24,25,34} Since 1990, HCV has rarely been transmitted by blood transfusion in the United States.

Although occupational exposure, such as unintentional needle-stick injuries, can result in infection,^{30,35} health care workers in general appear not to be at increased risk for HCV infection,³⁶⁻³⁸ and they do not make up a substantial part of the HCV-infected population. The extent to which perinatal exposure contributes to HCV infection in the general population could not be measured by the NHANES III, but it is likely to be relatively low.

Neither sex nor racial-ethnic group was associated with HCV infection independently of the socio-demographic and behavioral risk factors we studied. Low socioeconomic status might represent unidentified factors that enhance the opportunity for exposure to infected persons.

In the United States, there is a large reservoir of HCV-infected persons who can transmit the infection to others and who are at risk for HCV-related chronic diseases. To prevent new infections, public health programs should focus on preventing the initiation of high-risk drug-related and sexual behavior and on providing risk-reduction counseling and services to those engaged in high-risk activities.³⁰ In addition, we need to develop more effective therapies for persons with infection,^{39,40} particularly for those

with genotype 1 — the most common genotype in the United States and the most difficult to treat — as well as approaches to the treatment of current or former injection-drug users. Most HCV-infected persons are younger than 50 years of age. As a result, the burden of disease associated with HCV infection is likely to increase during the next 10 to 20 years as this cohort reaches the age at which complications of chronic liver disease typically occur. The frequency of such complications might be reduced if infected persons were identified and provided with counseling and appropriate medical care.^{30,41}

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