The New Yorker

THE SHADLOW EPIDEMIC
Why does the Surgeon General want letters sent to hundreds of thousands of people informing them that they might be dying?

BY JEROME GROOPMAN

May 11, 1998

Last autumn, Dominique Benet called me and asked to be referred to a physician. She is a neighbor and friend who manages a bookstore in downtown Boston. Dominique said that she had no specific worries, but as she was turning thirty-five, she thought that it was time for a checkup. I recommended a young woman internist at our hospital. Four weeks later, Dominique called again: she had just been told that she had hepatitis C.

“You’re sure it’s C?” I asked, trying to contain my concern. “Not A or B?”

Dominique was certain. She was also upset and confused. “It’s hard to believe I’m carrying a potentially fatal virus and yet I don’t feel ill.” She knew nothing about hepatitis C. She had consulted a liver specialist, but he wasn’t able to give her any clear answers about what to expect. She wanted my help.

Because I have a background in oncology and immunology, I have been interested in hepatitis C for some time. In 1991, I chaired a committee that advised the Food and Drug Administration on the risks and benefits of a hepatitis drug, and I’ve been studying how the virus may make liver cells cancerous. I have also cared for many patients in the advanced stages of the disease, unable to prevent their deaths. I asked Dominique for permission to speak with her doctors, and then we’d talk again.

Her internist told me that Dominique seemed perfectly healthy when she was examined, but the routine lab tests conducted on her blood samples revealed a slight abnormality in the liver enzymes. The increases were so minimal that some doctors might have dismissed them as innocuous—signs of someone who had had a few glasses of wine the night before, or was suffering a bad cold. Dominique, however, did not drink alcohol, and hadn’t been ill all autumn. A test to screen for viral hepatitis revealed antibodies to type C. Another test found the virus itself in her blood.

Dominique’s case is typical: Hepatitis C is one of the most clandestine of viruses. It infects healthy people who have no idea that they are being attacked by something they can’t even detect.

Over the past two decades, there has been a hepatitis-C epidemic, but it has been overshadowed by aids: as physicians, public-health officials, and politicians have

focussed on H.I.V., hepatitis C has been silently spreading. Today, it affects four times more people than H.I.V. in the United States. Approximately four million Americans, nine million Europeans, and a hundred and seventy million people worldwide are infected with hepatitis C. In contrast, about a million Americans are thought to be H.I.V. positive. Some four per cent of people between the ages of thirty and fifty are believed to carry the virus; among black American men, it's ten per cent. Each year, there are an estimated thirty thousand new infections and ten thousand deaths. There is no broadly effective treatment, and if none is developed over the next decade, the death rate from hepatitis C could rise to thirty thousand a year—a mortality rate roughly equal to that of aids in 1996.

Hepatitis C is an insidious virus. Most people who come down with hepatitis A or B develop fever, loss of appetite, fatigue, and jaundice: they know they are ill. Most people who contract hepatitis C have no signs or symptoms. What's more, if one contracts hepatitis A—typically by eating contaminated food—the body efficiently purges the virus over a period of weeks or months and establishes lifelong immunity to future exposure. Hepatitis B, transmitted by blood-borne or sexual routes, is also efficiently defeated by the host: about ninety-five per cent of infected adults recover and become immune. But our immune defenses are largely unable to prevent hepatitis C from taking up permanent residence in the liver and the blood. Each time our antibodies and T cells come to recognize and attack the virus, it changes form and escapes. Eighty-five per cent of hepatitis-C infections therefore persist for life— and the infected person often has no symptoms for a decade or more. The onset of symptoms can be devastating: the consequences of a ravaged liver can be hemorrhage, delirium, and death.

Few people are aware that they are carrying hepatitis C until it has severely damaged the liver: In the United States, it's believed that only about a quarter of the cases have been diagnosed. Approximately three million Americans do not know that they are infected with the virus, or that they could be passing it on to others. Hepatitis C is transmitted primarily by infected blood. Before screening for the virus was adopted, about eighty thousand people a year became infected from transfusions with tainted blood. Intravenous drug users in urban areas in America and Europe have an alarmingly high rate of infection: it varies from fifty to nearly ninety per cent in some surveys. Body piercing and tattooing with non-sterile needles have also been implicated in the spread of the virus. Infection can even occur from a nick from a razor blade or the bristle of a toothbrush recently used by an infected person.

Dominique and I discussed how she might have contracted the virus. She is from a close, middle-class French-Canadian family in New Hampshire; her mother is a nurse and her father an actuary. (Patients' names and certain identifying details have been changed in this piece.) She could have been infected through sex. Dominique was not promiscuous, but she had had unprotected intercourse with men she didn't really know well. Up to twenty per cent of hepatitis-C cases can be attributed to sexual exposure, although it is not yet clear what kind of exposure poses the greatest risk. Kissing does not appear to pass the virus, for example, but it can be passed during vaginal or anal intercourse: small amounts of blood can be present in semen and vaginal secretions.

We eliminated other forms of transmission: she hadn't been transfused or tattooed and hadn't used intravenous drugs. But she had, it turned out, occasionally used cocaine. "I started in my junior year in college," she told me. "There was more work than I felt confident I could handle. I'd procrastinate, go to movies, watch TV, drop in on friends. I was aiming to go to business school, and wasn't sure I'd make the grades. So I began to snort cocaine, before exams or a big paper, to get a buzz, to stay awake, to take away the fear." She graduated with honors, but by the time she enrolled in business school she could no longer concentrate on her studies and dropped out. Her parents persuaded her to enter a detox program in Vermont. She hadn't used cocaine—or alcohol or any other drug—for more than a decade.

I told her that her earlier cocaine use could have been responsible for her infection. Cocaine powerfully constricts the blood vessels in the nose, and the result is often ulceration of the nasal lining and pinpoint bleeding. When someone infected with hepatitis C inhales cocaine through a straw, microscopic droplets of blood-tinged mucus collect at the upper end of the straw and form a scrim of viral-laden material. Sharing the straw moves the virus around a circle of users, with each subsequent user inhaling the virus, along with the drug, into the vulnerable nasal lining.

There are other ways that the virus can be passed along—during childbirth, for example. But a disturbing fact of the disease is that up to a third of the people who discover they have hepatitis C don't know when, how, or from whom they got it.

The origins of the hepatitis-C epidemic are obscure. Unlike H.I.V., which is the scion of a family of immunodeficiency viruses found in many primates, hepatitis C is not closely related to any animal viruses and stands alone. H.I.V. had been endemic in sub-Saharan Africa, arrived in Europe in the late nineteen-seventies, and was then spread throughout the world by a mobile and sexually active population. By contrast, the hepatitis-C virus is believed to have been in our midst for many decades.

The virus was first clinically recognized in 1975—as a form of hepatitis distinct from types A and B—but it was not identified until 1989. (After efforts to isolate an intact infectious microbe had proved unsuccessful, a group of researchers at the federal Centers for Disease Control and Prevention and a biotechnology company named Chiron successfully pieced together the virus by genetic cloning.) A blood test for hepatitis C was developed in 1990 and had been refined by 1992.

Last year, in March, the National Institutes of Health held a two-day consensus development conference on hepatitis C. The grim finding was that very little is yet known about it. Data on the course of the infection are scant (because many infected people come to medical attention only after several years), so our ability to predict the virus's effect on a patient is poor. Some people will live a normal life span without the virus's significantly damaging the liver; other people develop irreversible scarring and distortion of the organ, resulting in fatal liver failure or cancer. And there are other questions. Why is it that a person can be infected and have no symptoms, even while the virus is destroying the liver? Symptoms that are typical of viral infection—fever, sweats, fatigue, and anorexia—are all healthy indicators of our immune system's doing battle with an

engaged microbial foe. What is happening with hepatitis C? One hypothesis is that it is a master of disguises. When people become infected with it, they actually contract not a single strain but a swarm of viruses, each in a different cloak. And a foe capable of regularly changing its appearance may evade a pitched battle. Another hypothesis is that it carries internal core proteins that can disarm the immune response.

In answering these questions, physicians and scientists face a fundamental problem. If we are to understand how a virus attacks cells and reproduces, it must be cultured in a test tube. Hepatitis C cannot yet be grown outside the body. This means that it is extremely difficult to devise a means of blocking or poisoning it. The polio vaccine was made possible only by the discovery of how to grow polio virus in cells in the laboratory. The same basic step underlies all the remarkable advances made against H.I.V., a virus similar in size and complexity to hepatitis C. Researchers are currently studying hepatitis-C genes and proteins, but only as bits and pieces, outside the dynamic environment of an infected cell. Many scientists, including several in my laboratory, have tried and failed to devise a culture system. Key H.I.V. enzymes have been analyzed within the culture system, and, as a result, a diversity of drugs have been developed to contain the virus. These drugs, used in combination, have had a profound impact. This year, a study showed more than a forty-per-cent reduction in aids deaths. For many, H.I.V. is being transmuted from a sure death sentence to a chronic controlled condition.

In 1997, the N.I.H. budget for H.I.V. research totalled a billion and a half dollars, or about sixteen hundred dollars per infected person in the country. In contrast, the N.I.H. spent twenty-five million on hepatitis-C research the same year. That is about six dollars per infected person.

In 1983, a forty-six-year-old teacher named Donald Brady required urgent coronary-artery bypass surgery for unrelenting angina. During the operation, he received scores of blood products. The operation was successful: the blood flow to Donald’s heart was restored. He returned to an active life as a prep-school Latin teacher and the head of a growing family. But in 1993 he came back to the hospital, complaining of fatigue. After he underwent various tests, his condition was diagnosed as advanced cirrhosis—an irreversible scarring and distortion of the liver. Over the next months, the globes of his eyes turned a ghoulish mango color, and his skin became pocked with spidery capillaries. The blood that had helped to save his life in 1983 now threatened to end it.

Donald’s abdomen began to swell from retained fluid, or ascites. “What should I call the baby?” he joked grimly. He then developed bleeding, first from the nose and then into the skin and the stomach.

As a hematologist, I was asked to assist in managing the bleeding. There was little that could be done. The liver was so badly damaged that it could no longer produce the proteins that mesh into the fabric of a clot. Donald’s platelets, the tiny cells that are also essential to clot formation, were dangerously low as well, a common consequence of cirrhosis. A cirrhotic liver blocks the normal flow of blood in the abdomen and the blockage causes the adjoining spleen to balloon. As the spleen increases in size from a fist to a football, it sequesters the body’s platelets. What’s more, with the normal flow of

blood blocked, the veins that line the stomach and the esophagus also start to balloon. These veins, or varices, are particularly fragile, and, expanded, they readily rupture.

Donald bled repeatedly from ruptured varices over the months I cared for him. Sometimes the blood gushed into his stomach, and he vomited it out. He would then be rushed to the hospital, an expandable tube would be thrust down his esophagus, the bleeding varices would be compressed, and ligatures would be placed around them to try to prevent another such episode. At other times, the blood slowly trickled down his intestines. The blood would then be digested and absorbed into his circulation, but his failing liver could not detoxify the released substances: the toxic detritus eventually passed into Donald's brain, subtly at first, so that he was just inattentive, but it would then build up so that he was at the point of delirium. Again, he would be brought to the hospital, and his stomach would be lavaged, his bowels purged, and a tube inserted to search for the sources of the blood.

We all knew it was just a matter of time before he would die, so desperate measures were considered. There is no effective treatment for patients with advanced cirrhosis. Their only real hope is a liver transplant. This can buy some years before the transplanted liver, too, becomes infected from the virus-laden blood and fails. But no donor was found in time for Don Brady. He ultimately succumbed to an uncontrolled hemorrhage. Donald's death was not unusual. Within five years of diagnosis, half the patients with advanced cirrhosis caused by hepatitis C will be dead.

In 1991, the F.D.A. considered contacting people, like Don Brady, who had received tainted blood. The newly developed blood-screening tests were starting to identify donors infected with hepatitis C. While my committee was evaluating a possible drug therapy, the F.D.A. sought counsel from another advisory committee—this one on blood products—which included physicians, blood-bank officials, and hemophiliacs.

Some on the blood-products committee felt that not enough was known about the virus or how to treat it. Why, then, should people be told? The information could cause profound anxiety and might not be beneficial. Moreover, there was the expense of tracing recipients. Many transfused people die from the medical illness that prompted their need for blood, and the money could be better spent in educating the public about the virus. Other members of the committee—the hemophiliacs in particular—argued vigorously that recipients of tainted blood had the right to know that they might be infected. In the end, the committee failed to reach a consensus. In the early nineties, the American Association of Blood Banks, the umbrella organization that includes the Red Cross and other major providers of blood products, could not reach an agreement, either, and looked to the government for guidance. But without a clear decision from its advisory committee the F.D.A. did not take action. As a result, there was also no effective campaign to educate the public. The consequence? Those who had received transfusions before 1992 were never contacted, and no systematic attempt was made to reach other high-risk groups.

"I'm supposed to have a liver biopsy," Dominique told me. She was concerned about the procedure. "With all the sophisticated tests that I've had already—ultrasounds and

enzymes and virus levels—why can't they figure out what is going on in my liver without stabbing me?"

Because, I explained, it was the only way of determining the extent of the damage. Liver enzymes can be perfectly normal, even though the liver itself is being damaged. And measurements of virus in the blood will not necessarily reflect the degree to which the liver is inflamed. The fact that there is no accurate test to show the extent of disease is one more indication of its covert nature. An invasive biopsy was the only way of assessing Dominique's status, and deciding on treatment. If the biopsy showed widespread cirrhosis, the disease was irreversible, and there was little chance of its responding to interferon, the only proven treatment for the virus.

I accompanied Dominique to her biopsy, and stood off to the side as the gastroenterologist wiped the last traces of iodine from her tense abdomen. He then thrust a long thin trocar into an area just below Dominique's lower right ribs, and in a swift single movement passed skin, muscle, and the tight capsule of the liver, and penetrated deep into the pliant organ. In a similarly deft movement, the instrument was withdrawn, a long sliver of meaty tissue held firmly in its bore.

Later that week, I sat beside the pathologist peering into a microscope. Before us were the labyrinthine caverns of the liver. Distorting its fine mosaic of cuboidal cells were sharp bands of early scarring. Voracious white blood cells studded the field, like vultures feeding on carrion; the usually spacious nuclei of the liver cells were condensed and black, like droplets of crude oil. "Chronic active hepatitis, with some necrosis and fibrosis, but no evidence yet of cirrhosis," the pathologist said. The diagnosis meant that Dominique had a chance.

Interferon is a naturally occurring protein that was discovered forty-one years ago, and was so named because of its ability to interfere with virus reproduction. It is believed to obstruct the viral machinery while also boosting the immune response against the infectious microbe. In some fifty per cent of patients being treated with interferon, liver enzymes return to normal, and for as many as half of these patients the virus in their blood falls to undetectable levels. But interferon's effect is limited: the responses to treatment are transient, and the vast majority of patients relapse after the drug is stopped. Interferon is also difficult to tolerate in the amounts needed for treatment. It regularly causes flulike symptoms—fever, malaise, anorexia, and muscle aches—or even thyroid dysfunction and arthritis. Many patients become significantly depressed; a few become suicidal. Back in 1991, when our advisory committee to the F.D.A. voted to approve the drug, we had to acknowledge that there was no evidence that interferon treatment would save lives, but we were aware of the lack of any alternative, and of the desperate need of hepatitis-C patients for relief. The drug could provide a respite from the virus for several months, and might, so we hoped, slow the march to cirrhosis and death. Seven years later, the options for treatment have barely changed.

With the biopsy results in hand, I advised Dominique that she should be treated with interferon. She had probably been carrying the virus for more than a decade, and, with hepatitis C, the longer one lives, the greater the risk for disease. After two decades, up to

a third of those infected were predicted to develop cirrhosis. As Dominique enters her forties and fifties, the risk of fatal cirrhosis will probably rise. But with interferon she might be able to slow the infection.

I was cautious about asserting that anyone had actually been cured. The recent data were mostly from Europe, where genetic strains of hepatitis C differ from those in the United States and seem to be more sensitive to interferon. Very recent studies, I continued, suggested that a small number of patients, perhaps five to ten per cent, have shown no evidence of the virus for several years after stopping interferon therapy. There was also a study in which an experimental antiviral agent, ribavirin, was being added to interferon in an attempt to improve the slim rate of potential cures. I told Dominique that this was the clinical trial that I would enter if I were her, and she agreed to participate in it. She said that she was determined to do what she could to combat the virus.

On a Sunday afternoon some four weeks later, I dropped in on Dominique at the bookstore. She was pale, and her movements were slow. She was suffering the side effects of interferon. Although she took the injection, as she had been instructed, at night and with Tylenol (in order to sleep through its immediate toxicity), she told me that her days were marked by migraines, profuse sweating, muscle cramps, and fever. She was unable to exercise; she was losing weight, because she had no appetite; and she was finding it hard to concentrate at work. Her internist had recently given her the antidepressant Zoloft, but it was too soon to tell if it would help.

I tried to be encouraging. Some of the worst side effects waned after a month or two, and her first set of test results suggested that she was responding to the combined treatment.

Over the following weeks, there were several positive signs. The level of hepatitis C in her blood dropped, and her liver enzymes became normal. With each favorable result, the prospect of a cure appeared more possible. And, short of a cure, the hope that she would have a prolonged respite from active infection and that her inflamed liver might recover seemed even more likely.

The Surgeon General of the United States, Dr. David Satcher, recently testified in Congress that blood banks and hospitals have been instructed to send out letters over the next eighteen months to those most at risk of having received a tainted blood transfusion before 1992. The recipients will be notified that they may been given blood from someone who later tested positive for hepatitis C, and they will be advised to have themselves tested for the virus. Dr. Satcher, who was just appointed Surgeon General this February, has had to overcome resistance to the decision. As in 1991, some still argue that not enough is known about the natural course of the infection to justify the anxiety that these letters will provoke. A number of the intended recipients will have died, some—as happened with Donald Brady—from the virus itself. Hundreds of thousands of letters are supposed to go out. It is believed that most of the recipients will prove to be hepatitis-C carriers.

Dr. Satcher’s decision represents an important change in government policy, and indicates how seriously the new Surgeon General views the looming epidemic. He also

intends to act on recommendations concerning the need for greater public education and the importance of testing for all groups at risk. Yet it is still unclear how the massive program of tracing recipients and having them tested, counselled, and referred for medical evaluation can be put into effect. No government funds have been appropriated for it.

The majority of people now identified as having hepatitis C are poor, are black or Hispanic, and are in contact with intravenous drugs; their plight has frequently been overlooked by the larger society. But middle- and upper-class Americans who received blood transfusions before 1992 or who flirted with cocaine or unknowingly slept with an infected person may soon learn that they carry the virus. It is unlikely that they will accept the discovery quietly. They will make demands, both of science and of the government. Hepatitis C is already the leading cause for liver transplant in America. Each transplant can cost an average of three hundred thousand dollars. It is estimated that, short of transplant, standard yearly care for a person with advanced cirrhosis or liver cancer costs twenty thousand dollars. Counting loss of productivity, this will add more than six hundred million dollars to health-care costs each year, well into the next millennium.

I thought I was so brave, that I was so determined and strong," Dominique began, her gaze unsteady. "It was all empty bravado."

She had just returned from seeing the liver specialist, where she learned that after three debilitating months of interferon and ribavirin therapy she had relapsed. Her liver enzymes were elevated again, and the virus in her blood had abruptly raced up to a high level. The data from studies of interferon alone indicate that a patient whose virus breaks through within three months is unlikely to respond to further treatment.

Dominique was asked by the specialist to stay in the research study for the sake of obtaining complete data, but she was also told that, given the persistence and severity of her side effects, it would be understandable if she opted to drop out. She had decided to stop treatment.

We sat for a long while in silence, and agreed that there was only one choice: to wait, and hope that medical science will move more quickly than the course of her infection.