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National Consensus of Hepatitis C

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Special Report

National Consensus of Hepatitis C

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Medical Associations invited:
Infectology
Pediatrics
Internal Medicine
Gastroenterology

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Introduction

The global impact of infection with hepatitis C virus (HCV) is huge. It is estimated that nearly 170 million people are infected with HCV around the world and that it is one of the most common causes of morbidity and mortality. The condition progresses in 80% of the cases despite significant cellular and antibody mediated immune responses, and evolves into a chronic disease. The natural course of the disease leads to liver cirrhosis and hepatocellular carcinoma after an asymptomatic period that can last as long as two or three decades.

Michael Houghton's group discovered HCV 10 years ago; since then there have been some very important advances in the knowledge of its biological characteristics, diagnostic laboratory tests, its natural course and treatment. The first consensus took place in the United States in 1997, organized by the *Institutos Nacionales de Salud*. The goal was to divulge and discuss the most significant advances in the understanding of HCV infection. Five years later, the Second Consensus was held (June 10th–12th, 2002) in that country. The European Association for the Study of Liver Diseases organized its First Consensus for the Management of Hepatitis C in 1999. In Mexico, the first National Consensus of Hepatitis C was held in 1997. Nevertheless, considerable new and important information on the subject has been reported since then. It is worthwhile to analyze the new data because the complex characteristics of the HCV molecule vary greatly in natural course, epidemiology, clinical and therapeutic behavior of the disease.

The purpose of this consensus was to make known the most significant new data about HCV in order to establish new therapeutic guidelines for our country.

This document presents the conclusions on each subject related to HCV infection. The debate was organized according to the guidelines for evidence-based medicine and tried to answer the following questions:

- What is the natural course of hepatitis C?
- What are the best tests to diagnose hepatitis C?
- Which patients should receive treatment?
- What is the most effective medical treatment?
- What are the recommendations to prevent the disease?

Nahum Méndez-Sánchez, M.D., PhD
National Consensus of Hepatitis C
Coordinator
Mexican Association of Hepatology

I. Epidemiology

In Mexico, the prevalence of HCV among blood donors is 0.5–1.5%. In our country, until 1994 the main transmission mechanism was blood transfusion (official regulation NOM003-SSA2-1993, issued on July 18th, 1994). However, there are other risk factors in Mexican hospitals that need to be assessed; for example, endoscopes, surgical procedures and injection of drugs from multidose vials. The most prevalent genotype in Mexican patients is 1b (> 60%). The blood banks must use third-generation ELISA assays or others with the same or better sensitivity and specificity to detect contaminated products. It is imperative that positive cases are reported, and the reports should be in accordance with the Secretaría de Salud regulations. Electronic mail has been suggested as an easier way to report positive cases. Although occupational transmission is low (1–2%) among health workers, there are some guidelines to follow in cases of needle-stick or penetration injury:

1. Antibodies for HCV detection through ELISA 3 assay of the worker and the patient; if positive, then,

2. Perform qualitative polymerase chain reaction (PCR); if positive, then,
3. Perform hepatic function tests (HFT); if positive, then,
4. Perform quantitative PCR and refer the subject for a complete study and for treatment, if necessary.
5. If the result is negative, repeat the antibodies for HCV measurement two months later. The study ends if the new result is negative.

The most important transmission route in couples is percutaneous transfer (sharing syringes), not through sexual contact. Sexual transmission is probable when a person has more than six partners (promiscuity). In these cases, the use of some kind of protection is recommended. Clinical study of the couple's antibody levels should be measured using ELISA 3 assays.

Mother-fetus transmission is also a possibility when a HIV positive mother also carries HCV and the viral load is high, or continues to use intravenous drugs.

Breast-feeding is not contraindicated in HCV positive mothers; however, it must be avoided if there are skin lesions. It is obligatory to inform the mother about the possible transmission.

II. Natural course of hepatitis C

Less than 25% of the patients present with jaundice, nausea, anorexia and malaise. These symptoms usually appear seven to eight weeks after exposure to the virus (range, 2–26 weeks). Most patients show mild hepatitis symptoms; fulminating hepatitis is very rare at this stage. Viral RNA appears in the blood in the two weeks following contact, and aminotransferases (ALT) rise several weeks later. In nearly 15% of the cases, the infection is self-limited, viral RNA is undetectable and ALT returns to normal. There is chronic viremia in 85–90% of infected persons, 70% of whom develop some chronic liver damage with risk of progression to cirrhosis and hepatocellular carcinoma (4%). During chronic hepatitis there can be unspecific symptoms, such as fatigue. It is impossible to predict exactly which patients will suffer cirrhosis or cancer, although several factors seem to affect the course of the disease. Viral genotypes, subtypes 1a and 1b, are related to more rapid progression, more extended liver damage and poor therapeutic response. Alcohol abuse (> 50 g per day) hastens the course to chronic hepatitis. Studies show that the viral load is higher in those with alcohol induced liver disease than in patients who do not consume alcohol.

III. Physiopathological aspects in HCV infection

Hepatitis C virus is considered as a separate type, *Hepacivirus*, in the *Flaviviridae* family. It is a cytopathic virus characterized by its great genomic variability. It replicates both inside and outside the liver through the use of an RNA polymerase; there are often errors in transcription and these have been implicated in the generation of the subtypes. HCV pathogenic activity interferes with cellular immunity. Viral particle half-life *in vivo* is purported to be very short. Viral damage to the liver depends on viral and genetic factors, such as immune response, which determine the outcome of the disease. Some specific HLA alleles (DRB1, DQB1 and DR13) confer protection against progression of this condition.

IV. Mechanisms and cofactors of fibrosis

Knowledge of the natural course of liver fibrosis was stimulated by the development of quantitative methods (Knodell and Metavir indexes) to measure the magnitude of necrotic inflammation and fibrosis through hepatic biopsies. It has been shown that there are three types of individuals, according to the progress of their fibrotic response: those called quick responders, who show a response about 10 years after viral contact; intermediate cases that show fibrosis after 20–30 years, and slow responders who develop fibrosis 30 years or longer after contamination. Six independent factors relate to the absence of significant fibrosis after treatment: basal fibrosis magnitude; sustained response to virus; age; corporal mass index; absence of basal activity, and viral load below 3.5 million copies per milliliter.

V. The role of liver biopsy with regard to hepatic damage

1. Biopsy still stands as the best method to precisely assess the activity and progress of lesions.
2. Biopsy is indicated in patients younger than 65 years to determine the severity of the non-inflammatory lesion and fibrosis, and sometimes to determine the outcome. It is also indicated in confirmed HCV positive patients with high levels of aminotransferase, no medical contraindications for the biopsy and who will receive medical treatment.
3. The use of the Metavir index is suggested for various reasons. It is the only index that has been validated, it uses the least number of variables to define the level of viral activity, it expresses precisely the class of every variable, and it has a better correlation with ALT levels than any other index.

VI. HCV infection diagnosis

Diagnostic tests are classified as either serological or molecular biological. Among the serological tests, 3rd generation ELISAs are sensitive and specific enough to diagnose HCV infection. RIBA techniques should be avoided because they do not clarify the questionable cases after ELISA and their cost is high.

The tests based on molecular biology are qualitative or quantitative; they confirm the active infection and are use-

ful to monitor antiviral treatment. Qualitative tests can confirm or eliminate viremia, whereas quantitative techniques are used to determine the viral load. Moreover, the use of the WHO international standard expressed in IU/mL is now recommended. Titers above 800 000 IU/mL are considered abnormally high. The most sensitive qualitative confirmatory test is the Cobas Amplicor HCV, which detects levels as low as 50 IU/mL. Finally, another molecular biology based test, genetic typification, is useful to recommend treatment duration and to determine the outcome.

VII. Hepatocarcinoma and viral hepatitis C

Hepatocellular carcinoma ranks fourth among gastrointestinal malignant neoplasias and is the eighth most common cause of death by cancer in the world. Although it has geographical variations, HCV is considered a risk factor for this type of tumor. HCV itself does not have carcinogenic potential, but the common denominator is hepatic cirrhosis. People with chronic hepatitis C evolving to cirrhosis are at a 1–4% annual risk for developing liver carcinoma. Ultrasound monitoring and alpha-fetoprotein measurements are recommended at least every six months.

VIII. First time treatment for Hepatitis C

The therapeutic goals in hepatitis C are virus elimination and relief of symptoms, and the prevention of cirrhosis, complications, hepatic descompensation, and hepatic carcinoma.

The minimal requirements that the patient with hepatitis C must meet to be a suitable candidate for treatment are:

1. Persistent ALT elevation for six months or more.
2. HCV-RNA detectable in the blood.
3. Compensated liver disease.
4. High patient motivation.
5. Findings in the liver biopsy compatible with diagnosis.
6. Absence of contraindications to antivirals.

The following factors are considered contraindications for antiviral treatment with interferon: descompensated liver disease, severe neuropsychiatric disorder, concomitant descompensated diseased, autoimmune condition, pregnancy and the inability to use effective birth control methods. Contraindications for the use of ribavirin include anemia (Hb <11.0 g/dL), pregnancy, renal failure and other causes of hemolytic anemia.

There are different types of responses to antiviral treatment. There is no correlation between the biochemical response (ALT normalization) and viral response (negative HCV-RNA). Nevertheless, ALT and HCV-RNA determinations are suggested as monitoring tools.

The best indicator of an effective treatment is a sustained viral response (negative results for HCV-RNA in qualitative RT-PCR for six months after finishing the therapeutic program). An early viral response (negative result for HCV-RNA or a 2 $\log_{10}$ decrease by weeks 12 and 24 in the program) predicts a sustained viral response. It is unlikely that patients without an early viral response will achieve a sustained viral response even after continued treatment for 12 months.

Subjects with persistent HCV-RNA levels during treatment are considered nonresponders; people with negative results at the end of the treatment who later become positive by HCV–RNA again are considered recurrent.

Interferon (IFN) is the therapeutic mainstay in chronic viral hepatitis C. Combination therapy with pegylated alpha-interferon plus ribavirin substantially improves the viral elimination index, with responses being above 50% (range, 54–56%); at present, it is considered the first choice in therapeutic schemes. The possibility of viral elimination is better in genotype 1 and 2 carriers (response, 76–82%) than in those with genotype 1 (response, 42–46%). The recommended treatment time is 12 months for genotype 1. Some recent studies suggest that six-month programs could be sufficient for patients with genotypes 2 and 3.

Combination therapy, with pegylated alpha-interferon and ribavirin, correlates with adverse events (pseudogrippal syndrome, anemia, leukopenia, thrombocytopenia, depression, renal failure, thyroid dysfunction, etc.) that lead to dose reduction or treatment suspension in 10–20% of patients. Close monitoring by laboratory examinations and periodic clinical evaluations are imperative.

Some treatments and experimental programs from research protocols, which are not available for clinical use and whose usefulness are still to be confirmed, include new drugs and therapeutic combinations.

IX. Hepatitis C treatment in patients who are nonresponders to previous treatment

Selection of a candidate for a new treatment after a poor response to previous antiviral therapy requires the consideration of several factors such as: the failing scheme, genotype, response in previous therapy, drug tolerance, adherence to the therapeutic scheme and liver lesion severity. These patients should be evaluated and treated by a specialist in gastroenterology, hepatology, or both.

It is very unlikely that people with poor viral response to an initial program with alpha–IFN plus ribavirin would achieve a better result with a second scheme using the same drugs.

Recent therapeutic studies with a combination of pegylated IFN (PEG–IFN) plus ribavirin in patients who did not respond to the administration of IFN plus ribavirin show a sustained viral response in 10–20% of the cases; the odds are better in genotype 2 and 3 carriers. These results suggest that this scheme could be beneficial to this group of patients.

One of the main goals in multiple clinical studies is the effective treatment of patients who did not respond to IFN plus ribavirin. These studies assess the efficacy and safety of new drugs, several combination schemes with two or more drugs and the application of more prolonged periods of treatment. Conclusions will be available in the next few years.

The possible benefit of "maintenance" treatment with low doses of PEG–IFN in nonresponders to PEG–IFN plus ribavirin is yet to be proven.

X. Treatment for hepatitis C in children

1. The causal agent (HCV) has the same genotypes in children as those described for the adult population (genotype 1b predominates).
2. The natural course in the pediatric population has a liver tissue damage range similar to that described in adults (minimal, light, moderate or intense damage). There are even some cases with fast progression and fibrosis.
3. There does not seem to be a higher risk of infection in children born to HCV positive mothers through vaginal or cesarean delivery.
4. HCV has been found in colostrum from infected mothers, especially those with a high viral load (>800 000 IU/mL). The risk of infection to the child in these circumstances is low (2–3%) and breast-feeding is not contraindicated. However, it is imperative to inform the mother so that she may decide to feed her child with formula.
5. Extrahepatic findings of HCV infection are infrequent.
6. Liver biopsy is recommended before starting treatment to evaluate the severity of liver damage and determine an outcome.
7. Diagnostic tests are the same as in adults. Diagnostic HCV tests must be performed on every newborn from mothers with HCV infection. IFN is contraindicated during the first two years of life.
8. Treatment response to standard IFN seems a better choice than that reported in the adult population. PEG–IFN is not yet authorized for pediatric administration.
9. IFN toxicity is similar to that described in adults.
10. The use of ribavirin is not recommended in children. Some reports of its use in combination with IFN, using small subject groups, indicate that it could be useful in adolescents.
11. Complete immunization schemes against hepatitis virus A and B are recommended in every patient infected with HCV. Immunosuppressed patients should receive a double-dose of the vaccine.
12. It is imperative to recommend birth control methods to every patient treated with IFN and ribavirin because of the risk of congenital malformations.

XI. Patients with normal transaminase levels

1. The definition of a patient with normal transaminase levels includes these criteria: normal ALT and AST serum levels on three or more occasions (within a six-month period), positive test to antibodies against HCV and positive HCV–RNA. It is also necessary to perform an ultrasound examination to eliminate cirrhosis in the presence of normal transaminase levels, and a full blood count to assess thrombocytopenia, an indicative factor of cirrhosis.
2. Prevalence of normal transaminase levels in patients with HCV infection approaches 25%.
3. It is important to differentiate between patients with normal transaminase levels and those with "near normal levels", who suffer more severe hepatic tissue damage.
4. Alcohol avoidance is recommended, as well as obesity and vitamin complements with iron, because these factors could favor viral replication.
5. Hepatic biopsy is not recommended in this group, if subjects are not participating in study protocols or there is no doubt about the diagnosis.
6. Reported studies that included a liver biopsy show that hepatic damage tends to be slight, but sometimes it can be significant (even with cirrhosis).
7. The accumulated risk of variable fibrosis is 0.05 points Metavir a year in patients with normal transaminase levels, compared with 0.13 in patients with high transaminase serum levels.
8. Treatment should not be initiated in people with normal transaminase levels. The patient is the right person to make the decision based on quality of life, anxiety, depression, motivation to receive treatment and findings in the basal hepatic biopsy.
9. The reported series with antiviral therapy show that a sustained viral response is similar to that in patients with high transaminase levels (54–57% with a combination of PEG–IFN plus ribavirin).
10. Every patient with normal transaminase levels should be under observation by measuring transaminase levels every six months. The risk of an elevation in transaminase serum levels in the first five years is 40%, and after that period it is almost zero.

XII. Treatment for patients with cirrhosis

1. Compensated cirrhosis is not an exclusion criterion to receive treatment against hepatitis C virus.
2. Definition of compensated cirrhosis must include the following parameters: total bilirubin below 2 mg/dL, serum albumin above 3.5 g/dL, prothrombin time above 50% or prolongation less than three seconds, absence of significant esophageal varices, ascites or encephalopathy.
3. Compensated cirrhotic patients who receive standard IFN show a lesser response than those without cirrhosis.
4. PEG–IFN is more effective than standard interferon.
5. Interferon toxicity in cirrhotic patients is greater than in non-cirrhotic subjects. It is necessary to suspend therapy in up to 14% (*versus* 10%) and reduce the doses in up to

42% of cases. In a recent study, PEG–IFN showed lesser toxicity than did standard interferon.
6. Evidence shows a reduction in the extension of fibrosis with IFN therapy, although the observation period was short (12–18 months).
7. There are reports with five years of follow-up whose objective is to evaluate the PEG–IFN effect on prophylaxis to cirrhosis complications (portal hypertension, ascites and encephalopathy).
8. Given that the average survival rate in people with advanced cirrhosis (Child C) is less than five years, and given the high toxicity, administration of IFN in this group of patients is not recommended.

XIII. Treatment for acute hepatitis

1. Hepatitis C virus seems more vulnerable to treatment in the early stages of disease.
2. Most of the cases of acute hepatitis reported in other countries are the result of blood transfusions.
3. Up to one third of the subjects present with acute symptoms (jaundice, asthenia and adynamia), and a high percentage of them eliminate the virus spontaneously.
4. Up to two thirds of patients are asymptomatic and can evolve to chronic disease.
5. According to some studies, persons with high viral loads (> 800 000 IU/mL) are at significant risk of progressing to the chronic stage.
6. Current evidence suggests that patients with acute viral C hepatitis can receive conventional drug schemes.
7. Some therapeutic randomized case control studies show that it is possible to achieve a sustained viral response at the end of the treatment in nearly 40% of cases, with the usual doses of standard IFN over six months.
8. There is as yet no defined optimal moment to initiate treatment (before or after eight weeks). More studies are needed.
9. Two recent non-controlled studies on early treatment (one and eight weeks) with standard IFN in high doses (5–10 million IU) three times a week or on a daily basis for one month, and then on alternate days for 20 weeks, found viral responses in more than 90–98% of cases. Nevertheless, more information is needed.
10. Because in Mexico detection of acute hepatitis cases is very low, every subject with risk factors (transfusions, health workers who suffered penetration injuries and drug addicts, among others) should be submitted as soon as possible for detection tests, i.e., antibodies to HCV.

XIV. Hepatitis C and liver transplant

1. Hepatitis C is the most common indication for a liver transplant.
2. Every patient has recurrent viral infection, but with diverse activity grades.
3. Medium survival times among patients transplanted for hepatitis C is similar to those transplanted for other reasons.
4. Prophylactic antiviral therapy is recommended in study protocols only.
5. Medical treatment in patients with recurrence and proved biochemical and histological activity should include standard combination therapy.
6. Treatment with PEG–IFN plus ribavirin is promising, but there is not enough data to recommend it.
7. Immunosuppression to prevent rejection should be used carefully; low doses of steroids or induction therapy are suggested.

XV. Hepatitis C and HIV

1. Patients with chronic HCV hepatitis and also infected with HIV have a greater risk of liver disease progression than do subjects infected with hepatitis C virus only.
2. Liver disease progression is directly related to viral load of HIV and hepatitis C virus.
3. Highly active antiretroviral treatment (HAART) increases survival among patients with AIDS; terminal liver disease in persons infected with both viruses is an important cause of death.
4. Candidates for treatment are those with CD4 counts >200 cells/mL, viral load <10 000 IU/mL after HAART (viral load is not very important without HAART), positive HCV–RNA and an absence of cirrhosis.

XVI. Hepatitis C and hemophilia

1. Lyophilized factor VIII from Mexican plasma is recommended to reduce the risk of infection with HCV. The blood product must be very pure, inactivated or recombinant.
2. Cryoprecipitate administration may increase the risk of infection with hepatitis C virus.
3. Liver disease progress in hemophiliacs is similar to that for those without hemophilia.
4. There is no need for a liver biopsy at the start of treatment, but transjugular liver biopsy is suggested in case of diagnostic doubt.
5. Disease course in hemophiliac patients infected with HCV and HIV is the same as for people infected with both viruses without hemophilia.
6. Response to combination therapy is similar to that in the general population.
7. Liver transplantation is not only the first therapeutic choice for terminal liver disease in patients with hepatitis C and hemophilia, it is also the treatment for hemophilia.

XVII. Hepatitis C and alcohol

1. Alcohol consumption increases the progress of hepatitis C.
2. The risk is even higher when the subject ingests 30 to 50 g of alcohol per day.
3. The risk of liver cancer in people with hepatitis C and cirrhosis is higher when they consume alcohol.
4. Infected patients should be advised to avoid alcohol.
5. Antiviral therapy is not recommended in patients who consume alcohol.

XVIII. Hepatitis C and addictions

1. Risk factors for HCV infection changed in Mexico after 1994; transfusion-related transmission decreased and transmission related to other factors, especially drug abuse, increased.
2. Drug abuse, including intravenous and inhaled drugs, is constantly increasing in Mexico.
3. The risk correlated with drug use is even higher when several drugs are consumed simultaneously, along with alcohol consumption and risky sexual practices.
4. The risk of infection with HCV in intravenous drug users is 88% a year, and liver disease progression is faster. Infection treatment is only indicated in those individuals who stop drug use, ...
5. In addition, worsening of the infection and depression are more common in those who still use drugs.
6. Response to therapy is similar to those who do not use drugs, as long as drug use is stopped.
7. In cases of continued drug use, it is advised to not share needles, and the application of HAV and HBV vaccines is recommended.

XIX. HCV infection and renal disease

1. Prevalence of HCV infection is decreasing in chronic renal failure patients.
2. Risk of contamination is 10% each year during hemodialysis.
3. Risk factors in patients submitted to chronic dialysis are:
   a. Blood transfusion before July 1994 (date of regulation on routine detection in blood donors).
   b. Nosocomial transmission after contamination in hemodialysis units and HCV positive organ reception.
4. Given the possibility of false-positive results with ELISA in patients on hemodialysis, a PCR qualitative test followed by ELISA should be ordered every three months for every patient on hemodialysis.
5. Patients on hemodialysis must be managed as being potentially infected, and routine and standard precautionary measures must be in place in hemodialysis units.
6. Almost 75% of the patients on hemodialysis have normal transaminase levels, even those with viral replication and tissue damage.
7. Treatment with IFN is indicated for those with viral replication and liver biopsy without cirrhosis.
8. Interferon is contraindicated for those with a renal transplant, because it increases the risk of rejection.
9. Renal and liver transplants are not recommended in patients with HCV cirrhosis.
10. Contamination with HCV in renal transplant recipients used to occur before or during the transplant procedure, because the donor organ was HCV positive.
11. HCV positive subjects long-term survival (~10 years) decreases for the patient and for the organ.
12. The concomitant infection with HBV, use of immunosuppressive agents and alcohol consumption are risk factors for liver disease progression secondary to HCV in patients with renal transplant.
13. Immunization with double-dose vaccine to HBV and HAV is advised in cases of renal failure, regardless of the serological result for hepatitis C virus.

XX. Extrahepatic symptoms in infection with HCV

1. Extrahepatic findings in HCV infection are cryoglobulinemia, porphyria cutanea tarda, vitiligo and membranoproliferative glomerulonephritis.
2. Diabetes and non-Hodgkin's lymphoma are extrahepatic manifestations that may be related to HCV infection, but also to the immunomodulators used.

XXI. Adverse reactions and quality of life

1. Hepatitis C has a negative impact on the quality of life.
2. Drug therapy improves life quality (compared with the basal state).
3. Treatment with PEG–IFN has collateral effects similar to those after standard IFN, except for the decrease in platelets and lymphopenia.
4. Interferon is not indicated in patients with non-compensated cirrhosis.
5. Life quality is better during PEG–IFN administration than during standard IFN use.
6. The adverse effects of IFN lead to suspension in 10–20% cases, according to the type of IFN used.
7. Pregnancy must be avoided with at least two birth control methods being used during antiviral drug administration and for at least six months after finishing the scheme.
8. Complete and detailed information about adverse effects of antiviral drugs must be provided.
9. There must be some form of education for the candidates of HCV treatment.

Profesores

Dr. Juan Ramón Aguilar Ramírez
Jefe del Departamento de Gastroenterología
Hospital Central Militar
México, D. F.
Dr. Jesús Aguirre García
Departamento de Anatomía Patológica
Hospital General SSA y Facultad de Medicina, UNAM
México, D. F.
Dr. Héctor Baptista González
Jefe del Banco de Sangre
Fundación Clínica Médica Sur
México, D.F.
Dr. Francisco Javier Bosques Padilla
Secretario del Area de Investigación
Hospital Universitario José E. González
Monterrey, N. L.
Dr. Octavio Campollo Rivas
Unidad de Hepatología
Hospital Civil de Guadalajara
Guadalajara, Jal.
Dra. Ana María Contreras
Departamento de Investigación y Nefrología
Centro Médico Nacional de Occidente
Guadalajara, Jal.
Dra. Margarita Dehesa Violante
Jefe del Departamento de Gastroenterología
Hospital de Especialidades del Centro
Médico Nacional Siglo XXI, IMSS
México, D. F.
Dr. Diego García Compeán
Departamento de Gastroenterología
Hospital Universitario de Monterrey
Monterrey, N. L.
Dra. Solange Heller Rouassant
Jefa del Departamento de Gastroenterología Pediátrica
Hospital General del Centro Médico Nacional La Raza, IMSS
México, D. F.
Dr. Jesús Alberto Juárez Navarro
Departamento de Gastroenterología
Hospital de Especialidades del Centro
Médico Nacional Siglo XXI, IMSS
México, D. F.
Dr. David Kershenobich Stalnokowik
Jefe del Departamento de Gastroenterología
Instituto Nacional de Ciencias Médicas
y Nutrición "Salvador Zubirán"
México, D. F.
Dr. René Malé Velázquez
Jefe del Departamento de Gastroenterología
Hospital del Carmen
Guadalajara, Jal.
Dr. Antonio Marín López
Director General
Centro Nacional de la Transfusión Sanguínea
México, D. F.
Dr. Nahum Méndez-Sánchez
Presidente
Asociación Mexicana de Hepatología
Director del Departamento de
Investigación Biomédica
Fundación Clínica Médica Sur
México, D. F.
Dra. Linda Elsa Muñoz Espinoza
Jefa de la Unidad de Hígado
Hospital Universitario de Monterrey
Monterrey, N. L.
Dr. Marco Antonio Olivera Martínez
Departamento de Gastroenterología
Instituto Nacional de Ciencias Médicas
y Nutrición "Salvador Zubirán"
México, D. F.
Dr. Raúl Pichardo Bahena
Director
Departamento de Anatomía Patológica
Fundación Clínica Médica Sur
México, D.F.
Dr. Jorge Luis Poo Ramírez
Director
Centro de Investigación Farmacológica y Biotecnológica
Fundación Clínica Médica Sur
México, D. F.
Dra. Mayra Virginia Ramos Gómez
Jefa del Departamento de Gastroenterología
Centro Médico "20 de Noviembre" ISSSTE
México, D. F.
Dr. Francisco Sánchez Avila
Centro de Investigación Farmacológica y Biotecnológica
Fundación Clínica Médica Sur
México, D. F.
Dr. Luis Enrique Soto Ramírez
Departamento de Infectología
Instituto Nacional de Ciencias Médicas
y Nutrición "Salvador Zubirán"
México, D. F.
Dr. Rafael Ignacio Trejo Estrada
Departamento de Gastroenterología
Hospital de Especialidades del Centro
Médico Nacional Siglo XXI, IMSS
México, D. F.
Dr. Misael Uribe Esquivel
Coordinación General de los
Institutos Nacionales de Salud
Secretaría de Salud
México, D. F.
Dra. Florencia Vargas Vorackova
Departamento de Gastroenterología
Instituto Nacional de Ciencias Médicas
y Nutrición "Salvador Zubirán"
México, D. F.