CURRENT CHALLENGES AND MANAGEMENT IN HEPATITIS

EDITED BY

PROF. DR. MANSOOR AHMAD
M. Sc. (Kar.), M.P.P.S., M.P.S.P., M.A.C.S. (USA), M.N.Y.A.S. (USA), D. Sc. (Department of Pharmacy, ETH- Zurich, Switzerland)
Research Institute of Pharmaceutical Sciences,
Department of Pharmacognosy,
Faculty of Pharmacy, University of Karachi

DR. HYDER RAZA, *M.B.B.S.*
Research Institute of Pharmaceutical Sciences,
Department of Pharmacology,
Faculty of Pharmacy, University of Karachi

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This book is dedicated to

Ms. Najma Hashim,
(a school teacher, good friend and strong believer of alternative medicine)

who lost her life in Cancer.

P R E F A C E

Daily hundred of people are either dying or becoming the victim of "Hepatitis" and this is believed to be the most important and unsolved problem of Pakistan. This has many reasons but most understandable thing is unawareness, education, hygiene & hygienic conditions, reuse of disposable syringes, blood selling & transfusion and transfusion of body fluids. The figure of victims in Pakistan is increasing day by day which is an alarming situation. Another reason is non-availability of perfect vaccine or medicine.

Therefore, this book is written with the aim 'how to care hepatitis' with better understanding and knowledge. In this regard material is collected from different sources including INTERNET, research journals, books, personal data and data from hospitals.

Books, there are many, but in this book one will find, simple and systematic explanation of HAV, HBV, HCV, HDV, HEV, HFV, HGV and other hepatitis, laboratory tests, sign & symptoms, transmission, pathogenesis & immunity, treatment, prevention, vaccination, alternative systems and medicine (natural or herbal or homoeopathic medicine).

This book is one of its kind where first time the researched and published data on pharmaceutical products is given for understanding the mechanism/mode of action of drugs, i.e. how are they acting? What are their side effects? How much is their efficacy?

In this a careful attempt has been made to avoid unwanted details and unnecessary explanation. Help from various books and notes of eminent professors of medicine has been taken for the completion of this book for which we are grateful to all of them.

I am very much grateful to all those who in one way or other helped us in bring this book. We are also lucky in receiving financial support and medical literature from M/s Roche Pakistan Ltd. and M/s Macter International Pvt. Ltd. for printing this book. Therefore, our highest gratitude go to them.

We are also thankful to Mrs. Arfa Bano, Miss. Mahjabeen, Miss. Noor Jahan, Mr. Munir Anwar, Mr. Zahid Khan and other colleagues for their help and guidance.

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(Laureate of Presidential Award-2000)
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INTRODUCTION

Liver diseases are emerging as serious world wide problem regardless of their type. Major reports are appearing from hepatitis viruses. In recent years Liver diseases are emerging as serious World Wide problem regardless of their hepatitis and hepatitis viruses gain remarkable attention of scientists due to seriousness of infection and non-availability of medicine, vaccine or other therapeutic agents in any system of medicine in use.

Viral hepatitis is the term reserved for infections of the turn by one or more of the distinct hepatitis viruses. The term hepatitis A and B was first introduced by MacCallum in 1947 in order to categories infection (epidemic) and serum hepatitis. These terms were eventually adopted by World Health Organization (WHO) committee on viral Hepatitis.

Hepatitis foundation international (Hepfi) reports an estimated 80,000 new infections each year in USA for HAV (hepatitis 'A" virus), 400 million people throughout global (HBV) hepatitis 'B' virus) and WHO reports 170 million effected people all over the World. An estimated 8-10 thousand deaths occur annually in USA as a results of HCV (hepatitis 'C' virus) related liver disease, compared to 16,685 IAD deaths in 1997.

These facts and figures are of US and hold Health Organization (WHO) from developed countries or those countries having official record of such kind of diseases, but infect the rate of death is much higher due to lack of awareness, data record maintenance, and resourcefulness of third world countries.

In Pakistan and other neighboring countries like India, Afghanistan, Nepal, Bhutan, Sri Lanka, Thailand, Arab countries, etc, the current mortality figures many triple in the next ten years, as compared to HIV. The disease has latency of 10-30 years and symptom or sign may not appear until cirrhosis is appeared / exist. The hepatic damage is due both to the cystopathic effect of the virus and the inflammatory changes secondary to immune activation.

Ninety percent of infected people of developed and undeveloped countries cannot afford treatment and due to the specific characteristics of the viruses. Hepatitis "C" has been estimated to be the most common cause of chronic liver disease, cirrhosis and liver cancer in Pakistan and India. Different attempts from other part have been made to treat the virus but till to date no success was achieved. Interon alfa". It is an FDA approved drug for the treatment of chronic hepatitis "C". By the use of this drug, six month treatment regimens, some success are achieved with side effects including nausea, headache, fever, myalgias, fatigue, leukopenia, thrombocytopenia, alopecia, irritability, depression, in frequent thyroid abnormalities, pulmonary complications and retained damage).

Those patients having autommune disorders, thyroid dysfunction, decompensated cirrhosis and thrombocytopenia and post-transplant patients are usually rot eligible for treatment with interferon due to this risk of serious side effects.

A combination of interferon with ribavirin (on anti-viral drug) has resulted in significantly improved responses. But the side effects of the combination therapy are there. Usually ribavirin causes hemolytic anemia and leading to teratogenicity.

Another important aspect of the increase of seriousness of disease is the use of alternation medicine, when allopathic medicine fails to provide an answer, more and more distraught patients turns towards alternative medicine, diet supplements and herbal remedies. These remedies fill the selves in supermarkets, pharmacies, health food stoners and clinic of herbal practitioners. Testimonials as well as advertisements in health and nutrition magazines promote the use of herbs without explaining the dangers and side effects. Trust because these are natural preparations from national sources (like plants, animals & minerals).

Herbal remedies are natural but are not regulated by any governmental agency and neither the safety and effectiveness have been tested by any agency of ministry of health.

It has been documented for centuries that some mind / amined / plants, their constituents, part, organs are toxic to the liver or act as toxic agents. Doctor are concerned that many herbal / animal / mineral related liver injuries go unrecognized because patients are not questioned about their use of natural products and diet supplements. A wider variety of herbal remedies contain multiple ingredients and the labeled and actual contents of a product may differ. This make it impossible to identify attack rates for specific herbs.

In a recent article Dr. Raymond S.K off questions the role of herbal product play in undefined hepatitis and fulminant (sudden & severe) disease. In almost 50% of patients, fulminant disease can not be related to any identified hepatitis viruses. Liver injuries directly related to repeated use of herbal products ranges from mild and limited to extensive disease. Dr. Koff believes that unrecognized herbal use may be the cause of unidentified hepatitis and cirrhosis.

It does not mean that all herbs are a threat to the liver, some herbs and numerals given to people can have been found to cause liver damage and some herbs increase liver enzymes and mask the results of conventioned treatment / ongoing disease. Some in only in a small percentage of people, some in all and some may be dose dependent, therefore, it is advised to concern your medical doctor before the use.

TYPES OF HEPATITIS

HEPATITIS A (HAV):

Hepatitis A is a disease of liver and is caused by hepatitis virus, HAV. Hepatitis A virus is one of many hepatitis viruses causing inflammation of the liver. According to USA medical department report each year on estimated 80,000 new infections occur with HAV. A position blood test for HAV is known as IgM hepatitis A antibody test, indicates that the person is suffering with HAV.

HAV is a typical entervirus classified in the picornavirus family. It has a single strand RNA genome and a non-enveloped icosahedral nucleopoid and replicates in the cytoplasm of cell. Also known as enterovirus. It has 1 stereotype and there is no antigenic relationship to HBV or other hepatitis viruses.

SIGNS AND SYMPTOMS:

In HAV infected person fever, anorexia, Roseau, vomiting fatigue and jaundice are typical signs & symptoms. Dark urine, pale face and elevated transaminase level are observed. The incubation period is 30 days (average) but most cases resolve spontaneously the infected person can spread the virus to others after 2 months with 204 weeks. Hepatitis A virus has a short incubation period of 3-4 weeks children with HAV usually have no symptom. Most HAV infections are asymptotic and a detected solely by the presence of IgG antibody. No chronic carries state occur and there is no predisposition to hepatocellular carcinoma. Symptoms will disappear over a 6-12 months period until complete recovery occurs.

TRANSMISSION:

HAV transmission occur person to person by fecal contamination of food & water. Food handlers who are infected can pas the virus on if they do not wash their hands with soap and water after having bowel moment especially when preparing food that are not cooked afterwards. Diaper changing tables, if not cleaned properly or changed after each use, may facilitate the spread of HAV. Fecal residue may remain on the hands of people changing socited diapers anal / oral contact, by putting something in the mouth that had been contamination with infected fees. Eating raw or partially cooked meat, fish, prawns, shellfish contaminated with HAV can spread the disease.

PATHOGENESIS & IMMUNITY:

The pathogenesis of HAV is not completely understood. The virus probably replicates in the GIT and spreads to the liver via blood stream. Hepatocytes are infected but the mechanism by which the cell damage occur is unclear. It is likely that the attack by cytotoxic T-cells causes the damage to the hepatogytes. The infection is cleared, the damage is repaired and no chronic infection ensues. HAV infection can be distinguished pathological among other hepatitis viruses.

Immune response consists equally of IgM antibody, which is detectable at the time jaundice appears, therefore, laboratory diagnosis is important. The appearance of IgM is followed 1-3 weeks later by the period of IgG antibody which provide life protection.

DIAGNOSIS:

The detection of IgM antibody is the most important test. The appearance of IgM is followed by 1-3 weeks later by production of IgG antibody, which provides life long protection.

TREATMENT & PREVENTION:

There is no specific treatment for hepatitis "A" or anti-viral Therapy is available. However, the infection will clear up on its own in a few weeks or months with no serious after effects. Once recovered an individual is there immune. About 1 in 100 with HAV suffer from a sudden and severe infection (fulminant) that may require a liver transplant.

Immune globulin (IG) can provide a temporary immunity to the virus for 2-3 months if given prior to exposure to HAV or given with in 2 weeks after exposure.

Active immunization with a vaccine containing inactivated HAV is available. The virus is grown in human cell culture and inactivated with formation. Two does, an initial dose followed by a booster, 6-12 months later, should be given.

Hepatitis A vaccine (synthetic) obtained from inactive hepatitis A virus, is highly affection in preventing the hepatitis A infection, however, its safety, when given during pregnancy, has not been determined. The vaccine provides protection four weeks after the first infection. A second injection results in long lasting protection, possibly 20 years.

The vaccination is recommended for travelers to developing countries. However, because many people have antibody to HAV, it may be cost effective to determine whether antibodies are present before giving the vaccine passive immunization with immune serum globulin prior to infection or early in the incubation period can prevent or nitrate the disease. Observation of proper hygiene e.g. sewage disposal and hand washing after bowel movements, is of primary important.

VACCINATION:

The vaccine is allowed to persons above 2 years age or older and is recommended for;

Individuals who have chronic liver disease or clotting factor disorders.
Those who have close physical contact with people who live in areas with poor sanitary condition.
Those who travel or work in developing countries (this includes all countries except northern and western Europe, Japan, Australia, New Zealand and north America except Mexico).

- Men who have sex with other man
- User of elite drugs.
- Children in populations that have repeated epidemia of hepatitis A (Alaska natives, American Indiana).
- People who have chronic liver disease should be vaccinated for HAV.

HEPATITIS B (HBV):

This infection is caused by hepatitis B virus (HBV) and this virus alone has infected approximately 400 million people through out the world, making HBV one of the most popular human pathogen. Liver cancer or hepatocellular carcinoma (HCC), over of the most common cancer affecting human body, is primarily related to chromic HBV infection. Recent reports on HBV & HCC incidences relationship showed the well established. But the relationship rate mechanism by HBV transformers Hepatocytes remains nuclear. Before HBV can transform a cell, the virus must first infect it. However, the mechanism through which HBV enter Hepatocytes has not been resolved despite further understanding of the viral proteins involved. Vaccines are available against HBV, but they may not be 100% effective against all variants of HBV. Further more, there is no cure for individuals already infected. Much more research is needed before we fully understand and control the spread of this infectious agent.

HAV is considered predominantly transmitted via the fecal-oral route which HBV is believed to primarily transmitted pareventerally. In 1963, when a research was carried out the search of polymorphic serums proteins, blumberg discovered a previously unknown protein in the blood of an Australian aborigine[1]. This protein was denoted as the Australian (A_4) antigen. It become apparent that this serum protein is related to HBV. It becomes clear in 1968 when other researcher like prince, okochi and Murakani recognized an antigen (now known as HBs Antigen), found only in the serum of HBV infected patient.[2,3] In 1973, Dare reported the presence of virus like particles in the serum of patients suffering from hepatitis B[4]. Lateron these particles were designated as the hepatitis B virus (HBV). The non-related hepatitis viruses were discovered later, but scientists retained the name HBV.

Kaplan (1973) and Robinson (1974) discovered the viral nature and HBV genome[5,6]. HBV has been estimated by WHO to have infected over 2 billion people world wide approximately 500 million are chronic carriers.

PATHOGENESIS OF HBV:

The pathogenesis of both acute and viral hepatitis is slowly being unraveled. Thus far, most data show that members of the hepadraviridae family are not highly cytotoxic perse. It appears that the intense levels of cellular deaths are primarily due to host defence mechanism against HBV infection.[7]

The reports of Kaplan (1973) explains the nature of this viral particles when he detected the endogeneo DNA – dependant DNA polymerize within virus core[5]. On the basis of the discovery of this DNA polymerize Robunson detected and characteristized the HBV genome[6]. The HBV genome is unique in the world of viruses due to its compact

nature, use of overlapping reading frames and dependence on a reverse – transcriptional step, though the vision contains primarily DNA. Therefore, HBV becomes the archetype of hepadravirus family, Hepadnaviridae.

HBsAg (hepatitis B surface antigen) from HBV has already been detected in other primate, human remain its primary host. Recent researches show many related viruses in other species, but each particular virus is specific to its species. The human HBV of archetype, included in Hepadnaviridae family, which consist of duck hepatitis B virus (DHBV), ground squirrel hepatitis virus (GSHV), snow goose hepatitis B virus (SgHBv), wood chuck hepatitis virus (WHO), and woolly monkey hepatitis virus (WmHV).

Transmission of HBV is primarily through blood and / several contact, though other methods of transmission have been suggested. The large reservoir of infected individuals has been sustained a satellite virus known as the hepatitis D virus (HDV). HDV can only replicate in cell already infected with HBV since HDV uses hepatitis B surface proteins to package its own RNA. However, the nature of HDV is quite different from HBV.

SIGN AND SYMPTOMS OF HBV:

Acute HBV infection can be divided into four different stages i.e. a) Incubation period, which is the time between initial viral entry into the cell to first day of symptoms, b) Prec-ieteric or prodromae period, c) Icteric period and d) recovery period. The symptoms of acute HBV infection usually very and depending on individual to individual. Many children and some adults infected with the virus but never show any remarkable symptoms. In general often infected individual experience a certain level of jaundice which leads to develop after the virus can be detected in the blood. Usually jaundice is preceded by mild fevers, fatigue, malaise, loss of appetite and sometimes nausea and vomiting.

During the vitriolic period or blood borne phase, the urine of infected individual become dark, golden-brown. This is after followed by the lightening of the stool as well as the yellowing of the skin, typically seen in jaundice.

There are some common sign and symptoms that suggest the patient (suffer) may have liver problem. But, however, ot all liver problems are related to HBV. Hepatitis A, C, D, E, G viruses as well as alcohol, chemical bacterial and other conditions can damage the liver. The following are the common symptoms of liver damages;

a) Yellow discoloration of skin and / or eyes.
b) Abdominal swelling or severe abdominal pain.
c) Prolonged itching of the skin.
d) Very dark urine.
e) Pale Stool.
f) Passage of bloody or tar – lila stools and
g) Chronic fatigne nausea or loss of appetite.

If somebody suspect he has above same liver from doctor and go far blood in other tests.

TRANSMISSION OF HBV:

HB virus is usually present in the blood of infected individual. However, HB virus has also been detected in other body fluids including urine, saliva, nasopharangeal fluids, serum and menstrual fluids[8,9]. HB virus has not been found in feces, may be due to inactivation and degradation within the intestinal mucasa or by the bacterial flora[10].

Transmission of HB virus is usually occur most effectively through precuaneous introduction that is through the use of infected (HBV) needle, sexual contact, children through mothers, living with an active HBV carrier[11].

High risk groups in HBV infection are;

a) Individuals living in close proximity to a known infected individual.
b) Users of intravenous drugs, particularly those who share their needles.
c) Individuals who have multiple sexual partners.
d) Health care worker (i.e. doctors, dentists, paramedics, nurses etc.).
e) Cleaning staff in health care facilities.
f) Staff of institutions for people with development disabilities.
g) Firefighters.
h) Police Officers.
i) Mortuary attendants.
j) Day care workers.
k) Anyone who may / has come into contact with human body fluid from an unknown or known HBV carrier source.

DIAGNOSIS OF HB VIRUS BY BLOOD TESTS:

Several methods of serological assays are in use for the detection of viral infection as well as the differentiation of chronic and acute HBV infection. But the most sensitive and specific methods used commercially for diagnosis purpose are radioimmunoassay (RIA), and enzyme linked immunosorbent assay (ELISA). In these bioassays specific antibodies are used against various HBV proteins and can be detected as HBs Ag protein (as low as 0.25 mg/ml and anti-HBs antibodies at a level of 1 ml W/mL). PCR has also been used in detecting low level of HBV DNA present in both blood and liver tissue.

BLOOD TEST RESULTS AND THEIR INTERPRETATION:

HBs Ag	Anti-HBs	Anti-HBc	Interpretation
+ve	-ve	-ve	Early acute HBV infection.
+ve	+ve / -ve	+ve	Acute or chronic HBV infection.
-ve	+ve	+ve	Previous HBV infection & current immunity to virus.
-ve	-ve	+ve	Not clear, may be due to previous HBV infection, low level HBV infection or false-position / non-specific reactions if present anti-HBs help validate anti-HBc reactivity.
-ve	-ve	-ve	Liver toxicity due to some other agent than HBV.
-ve	+ve	-ve	Vaccination.

Other biochemical test in support of above mentioned test are;

1. SERUM GLUTAMIC-OXALOCATIC TRANSAMINASE (SGOT) OR ASPARTAME AMINOTRANSFERASE (AST):

This is an enzyme usually present in heart, kidney, liver, muscles and pancreatic tissues. Upon damage the tissue releases it and increases the level in blood. It can be detected with specific test. During pregnancy and deficiency in vit B its actual level decreases in blood. Its normal range in blood is 5-54 U/L.

2. SERUM GLUTANIC – PYRUVIC TRANAMINASE (SGPT) OR ALANINE AMINOTRANSFERASE (ALT):

This enzyme is found mainly in the liver but it has also been detected in heart, muscles and other tissues in negligelde amount. Its increased level in blood indicates liver damage, kidney infection, chemical toxic or even cardiac infraction. Its increased level in blood indicates liver damage, kidney infection, chemical toxics or even cardiac infection. Its range in blood is 0-36 U/L.

3. ALKALINE PHOSPHATES:

This is also an enzyme occur in bone and liver tissues. Its increased level in blood indicates liver & bone marrow damage.

4. GAMMA GLUTAMYTRANSFERASE (GGT):

This enzyme chiefly found in liver cells and is quite sensitive to alcohol consumption. This enzyme level increases in blood when there is liver disease, bile-duet obstruction and / or drug abuse. Its range in blood is 3-59 U/L.

5. LACTOSE DEHYDROGENATES (LDH):

This enzyme is primarily occur in brain, heart, kidney, liver, lungs, and skeletal muscle tissues. Its increased level in blood show cells death and decreased level malnutrition or low tissue organs activity. Its range in blood is 135 – 225 U/L.

6. ALBUMINE:

This is a protein and is synthesized in liver. It is involved in maintaining the blood protein base level. Liver damage or disease may result in decrease of level of albumin in blood. Its range is blood is 35-50 g/L.

When albumin level drops to extremely low levels, fluid from the blood may leaks into surrounding tissues, resulting in swelling /edema.

7. BILIRUBIN (NON-NEONATAL) – TOTAL (CONJUGATED AND UNCONGJUGATED:

Bilirubin is a byproduct of RBCs breakdown. It is actually produced when the hemoglobin ring is opened through other enzyme activities. Bilirubin is typically excreted into the bile, giving bile its pigmentation. Increased levels are associated with liver

chaises, mononucleosis toxicity due to some types of drugs and hemolytic anemia. Its range is 1-17 μ mole/L.

8. BILIRUBIN-DIRECT (NON-NEONATAL-CONJUGATED):

Same as above but its range is 0.00 – 5 mole/L.

9. PROTHROMBIN COAGULATION TIME (PT):

Its usual time is 10-12 seconds, but the changes take place in serological pattern during acute HBV infection are as follows.

TREATMENT AND PREVENTION:

TREATMENT OF ACUTE HBV INFECTION:

Recent treatment of HBV has no specific medicine for the cure of acute viral hepatitis. In most of hepatitis and liver damage cases minimum consumption of alcohol is recommended, if not stopped completely. This helps in the recovery of the liver. In some cases adrenocorticosteroids are recommended, but no effects are recorded for hider HBV infections. It has also been observed that use of steroid in early treatment of HBV infection may development result in the of persistent infection. Therapeutic effectiveness of interferon use on the prognosis and course of acute HBV infection remain unknown.

TREATMENT OF CHRONIC HBV INFECTION:

In this case a number of methods are in use, but the objective of all these treatments are, a) to eliminate infectivity and transmission of HBV to others, b) to arrest the progression of lower disease and improve the clinical prognosis and, c) to prevent the development of hepatocellular carcinoma (HCG). Now a days there are many treatments in use, but the most commonly used treatment is interferon alpha, but most recent is lamivuoline (3TC) being looked at as potential therapeutic agent. The other agents are as followed. They are still in experimental stages.

ANTIVIRAL:

1. Acyclovir (Zovirax, Glaxo-wellcome)
2. Adefovir (GS 840, Gilead Science Inc.)
3. Adeuine Arabinoside (ARA-AMP)
4. Famcidovir (Famvir, Smithkline Beecham)
5. Ganciclovir (Ganciclovir IV, Roche-syntex)
6. Lomivudine (3TC, Epivir, Zeffix, Glaxo, Welcome PLC)
7. Lobucavir (Bristol – Myers – Squibb).
8. N-acetyl - cystenie.

IMMUNE SYSTEM MODULATOR:

1. Hepagene (Medeva)
2. Interferon Alpha
3. Thymosin Alpha (Zadaxin, Sciclone Phammuntieal)

MIXED TREATMENT:

1. Interferon Alha + Famcidovir
2. Thynosin Alha (Zadaxin) + Famcidovir
3. Thymosin Alpha (Zadaxin) + Lamivudine

ALTERNATIVE TREATMENTS:

1. Dandelion Roots
2. Liquorice roots.
3. Milk thistle (Silymarin)
4. Selevirm
5. Vitamin E (cod liver oil)

LIVER TRANSPLANTATION:

Liver transplants are recommended when there is an extensive liver damage due to viral or non-viral causes. However, there are many risk factors in liver transplantation for example tansplating a liver into a chronic HBV patient present the likelihood that newly transplanted liver may become reinfected, transplant operators are relatively expensive and every hospital can not perform such operation.

To overcome the transplant problem the scientists are trying to use animal organ or grow new liver cells of the same individual for transplant. However, this technology is still in its initial development stage.

DIET CONTROL TREATMENT:

To minimize any excessive damage a balance and healthy diet is necessary. This helps in fast liver recovery.

1. Nutrictions and balance diet means food from each of the food grapes.
2. No. in take of deep-fried & folly feeds.
3. Minimize or stop alcohol consumption.
4. Minimize consumption of smoked, caused and sated foods, use lemon Gumi, onion, vinegar, garlic, pepper, cloves, etc.
5. Consumption of meat and seafood should be reduced since digesting / processing these forms of food can further tax the liver.
6. The bread & cereals these provide carbohydrates, Rican, thiamin, riboflavin and fiber.
7. Use fruits and vegetable that provide vitamin A, Vitamin C, fiber and flacon.

8. Milk and milk provided calcium, riboflarim, Rican, flacon, vitamin 1, and B12.
9. Increabed intake of high-fiber food (i.e. fresh fruits and vegetables, whole grain, breads, rice and cereals etc).
10. Avoid to take uncooked or half cooked food that have harmful bacteria and other toxic substances.

PREVENTION FROM HBV ATTACK:

a) **UNIVERSAL BLOOD AND BODY FLUID PREVENTION:**

All blood and body fluid should be treated (cleaned) prior to use as if they are infection with HIV, HBV, malaria and other blood borne pathogens. Gloves and other protective materials should be used during the handling of such kind of material. Hands and other open area of body should be washed regularly. Needles and other sharp objects should be handled with care and discard with proper method.

It laboratories, hospitals & home the suspected contaminated surfaces should be disinfected and cleaned with suitable disinfectants, later used material should be discarded according to prescribe methods. Usually 0.5% sodium hypochlorite, 2% aqueonus alkalinized glutaraldehyde, quarterly ammonium or phenolic derivations are used as germicide and disinfectants.

b) **VACCINATION:**

Most recent method to prevent HBV infection is through vaccination. The most common vaccine available in the market is obtained from recombinant technology (recombinant yeast source). The small hepatitis B surface protein (3HBs) is generated by yeast cells. The expression of this protein by yeast results in SHBs particle formation. However, particle are not secreted by the yeast. Disruption of yeast cells is performed in order to liberate the produced spheres into solution. The particles are then purified through clarification, ultrafiltration, chromatography and ultracentrifugation. The purified particles are then absorbed onto aluminum hydroxide to which thimerosal is added to preserve the solution.

Recombinant yeast derived vaccine producing pharmaceutical companies, like Smith Kline Beecham, (Engerix-B), Merck & Co. (Recombirax HB) are usually giving two years shelf life to their products with special instructions (the vaccines should not allow to keep in frozen conditions because it decrease / minimize the immunogencity). Energix-B and Recoribivax HB are chemically similar in structure with 2% yeast remaining insolution. As both are yeast derived, therefore, S-protein is not glyesylated, because yeast does not possess the post-transnational mechanism, but both drugs are quite effective in immunization against various form of HBV.

There are many other form of vaccine of immunization but the most common & effective ones are Engerix-B and Recombivax HB. There are two vaccination schedules 0, 1 & 6 months and 0, 1, 2, & 10 months. It is also recommended that a booster shot be taken after every 5 to 7 years of initial vaccination.

Hepatitis C

INTRODUCTION

The world Health Organization has estimated 170 million people worldwide are infected with hepatitis C. The prevalence in the United States is estimated at 3.9 million. Approximately four time the current number of those infected with the HIV virus. Due to the latent nature of the disease (infection may precede symptoms by an average of 25 years) only one million of these individuals have actually been diagnosed. An estimated 8 -10 thousand deaths occur annually in the United States bas a result of hepatitis C Related liver disease, compared to 16, 685 AIDS deaths in 1997. Hepatitis C mortality figures are expected to triple by the year 2010 giving hepatitis C a resultant mortality that may rival HIV. Ninety percent of those infected internationally cannot afford treatment and due to the specific characteristics of the virus, a vaccine is not expected. Hepatitis , and liver cancer in the Western Hemisphere.

Attempts to treat the virus have been disappointing. Interferon alfa is an FDA approved treatment for chronic hepatitis C. in Six month treatment regimens. Studies have shown an immediate (20-25%) failure rate determined by lack of clearance of the virus.

Those who exhibit viral clearance experience a 30-70 percent relapse rate within the first few months of discontinuing therapy a sustained response lasting at least six months is seen in only 10-15 percent of patients. The side-effect profile of interferon Alfa 2b is high nausea, headache, fever, myalgias, fatigue, leukopenia, thrombocytopenia, alopecia, irritability, depression, infrequent thyroid abnormalities, pulmonary complications, and retinal damage, Patients with autoimmune disorders, thyroid dysfunction, decompensated cirrhosis and thrombocytopenia, and post – transplant patients are usually not eligible for treatment with interferon due to the risk of serious side-effects. Although evidence from multiple studies shows interferon does decrease risk for progression to hepatocellular carcinoma, the risk/ benefit ratio and cost of treatment may render it prohibitive.

The anti-viral drug ribavirin has been used in combination with interferon and has resulted in significantly improved responses: current studies show a 28-66 percent sustained response after 48 weeks of treatment.The side-effects of the combination therapy are, however, " universal, significant, and possibly serious." Ribavirin frequently causes hemolytic anemia leading to necessary dose reductions and is a known teratogen.

As a result of the worldwide need for treatment option, the National Institutes of Health (NIH) will sponsor an international conference on "Complementary and Alternative Medicine in Chronic Liver Disease" August 22-24, 1999 at NIH in Beheads, Maryland.

Hepatitis C is emerging as a serious worldwide problem. In the United States the current mortality figures may triple in the next ten years, rivaling HIV. The disease has a latency of 10-30 years and symptoms or signs may not appear until cirrhosis is evident.

Adequate diagnosis, including liver biopsy, is essential in assessing the current stage of viral infection and the need for treatment. Hepatitis C may manifest as hepatic fibrosis, cirrhosis, hepatocellular carcinoma, lichen planus, glomerulonephritis, mixed cryoglobulinemia, or porphyria. The hepatic damage is due both to the cytopathic effect of the virus and the inflammatory changes secondary to immune activation. The use of the botanical components glycyrrhizin, catechin, Silymarin and phytosterols, and the botanical components glycyrrhizin, catechin, Silymarin and phytosterols, and the antioxidants N-acetylcysteine and vitamin E are reviewed for their efficacy in treating chronic hepatitis and affecting liver damage. (Altern Med Rev 1999:4 (4) : 220-238.)

HISTORY OF HEPATITIS C:

In 1995, when the hepatitis A and B antibody tests became available, it was determined the majority of transfusion-related hepatitis was neither hepatitis A nor B. Hepatitis C was isolated in 1989 with viral genome sequencing that led to the first screening antibody assay in 1990. At that point, incidences in multiple-transfusion recipients were high: 80 percent in more that 1,000 transfusion-dependent thalassemics, and 75 percent of multitransfused patients in remission from leukemia. In 1992, a more sensitive second generation EIA was introduced, which led to a significant reduction in contamination of the blood supply. Today, with more sensitive screening, it is estimated the risk of receiving blood from a donor who is infectious but has not yet seroconverted is 1/100,000.

Current diagnostic antibody assays include the recombinant immunoblot assay (RIBA) which is more affective at excluding false-positive results than previous EIA antibody screening assays. Detection of viral load can be accomplished within days of infection via RT-PCR assays. Viral load assessment is necessary in immuno-comprised individuals who may not produce sufficient antibodies or for those symptomatic individuals who may have false- negative antibody results. It is also necessary as a monitoring tool in antiviral therpay.

THE VIRUS

As a result of host selectivity and hepatitis C viral mutations, the virus now occurs in six different types or genotypes. They appear to wary in virulence and certain genotypes (genotype 1b) may carry a poorer prognosis and be less susceptible to treatment with interferon alfa.

Like other RNA viruses, the hepatitis C virus (HCV) genome is “fluid,” meaning it changes substantially, even within the same infected individual. Because, like other RNA viruses, HCV has an absence of repair mechanisms that operate during DNA replication, it mutates freely. These mutations lead to production of different viral isolates called “quasi-species” that can occur within any given genotype. A person infected with the lb genotype (the most difficult to treat) could therefore have many different quasi-species of that genotype in their body. These mutations have the ability to sidestep the host’s immune surveillance mechanisms because the immune system develops antibodies to only a monitory of the quasi-species. This is believed to be the reason 85 percent of infected individuals do not develop immunity of HCV and go on to develop chronic infections.

Attempts to develop vaccines have been unsuccessful for the same reason; neutralizing antibodies produced against HCV are specific for certain quasi-species and not for others. It would be very difficult to develop a vaccine that would recognize the genetic variants of this diverse virus.

TAXONOMY AND NOMENCLATURE

Hepatitis C virus shares virological and genetic characteristics with the Flaviviridae. Its gnomic organization is similar to that of the flaviviruses and pestiviruses and shares slight sequence identity with these viruses, especially the pestiviruses. Each of these groups of viruses comprises a separate genus within the flavivridae: flavivirus, pestivirus, and hepacivirus.

PROPERTIES OF THE VIRION AND GENOME

Properties of the Vision

Hepatitis C virus is a spherical enveloped virus of approximately 50nm is diameter. Its buoyant density in sucrose is only 1.06 g/cm 3 but much of the virus in chronically infected individuals appears to be bound to antibody, which imparts a higher density of approximately 1.17 g/cm^3.

Properties of the Genome

The genome of HCV is a single-strand linear RNA of positive sense. It is unregimented. A 5' non-coding (NC) region consists of approximately 340 nucleotides and contains an apparent internal ribosomal entry site (IRES). Immediately downstream is a single large open reading frame (ORF) of approximately 9,000 nucleotides, encoding a large polyprote in precursor of approximately 3,000 amino acids that is cotranslationally or posttranslationally cleaved into separate proteins by a combination of host and viral protease's. A capsized protein, two envelope proteins (E1 and E2), and a small protein of unknown function (P7) are encoded in the 5' region of the ORF. At least six nonstructural proteins, including protease, helicase, and RNA polymerize enzymes and regulatory peptides, are arrayed in the 3' portion of the ORF. Finally, there is a 3' NC region that consists of approximately 50 nucleotides, a polypyrimidine track and a highly conserved terminal sequence of approximately 100 nucleotides.

GENETIC HETEROGENEITY: TYPES, SUBTYPES, AND QUASISPECIES:

The genome of HCV is highly heterogeneous. The most highly conserved regions of the genome are parts of the 5' NC region and the terminal 3' NC region. The most highly conserved region of the ORF is the capsized gene. In contrast, the most heterogeneous portions of the genome are the genes encoding the envelope proteins. The 5' end of the E2 gene is the most heterogeneous region of all and has been named the "first hypervariable region" (HVR1). A few strains have a second HVR just 3' of HVR1. The HVR1 consists of approximately 90 nucleotides (30 amino acids) and is believed to be a major neutralization epitope of HCB: its heterogeneity appears to be the result of selective pressures by the host's humoral immune system.

Based on their genetic heterogeneity, HCV strains can be divided into major groups, called types or genotypes (an provisionally classified as separate species) of the virus. Within types, HCV isolates have been grouped into numerous subtypes. Finally, individual isolates consists of heterogeneous populations of the viral genomes that comprise “quasispecies” or “swarms” of closely related but different viruses. Some genotypes of HCV appear to be geographically restricted; others have worldwide distribution. More extensive genetic analysis of HCV has revealed that the hierarchical classification of isolates into types, subtypes, and isolates is somewhat artifactual and the viruses probably exist as a continuum of genetic diversity.

GENETIC COMPLEXITY OF HEPATITIS C. VIRUS

Category	Sequence Identity (%)
Type (Species)	66-69
Subtype	77-80
Isolate	91-95
Quasispecies	>98

IMMUNITY AND RESISTANCE TO INFECTION:

The consequence of the genetic diversity of HCV is a virus that has the ability to escape the immune surveillance of its host, leading to a high rate (more than 80 percent) of chronic infections and lack of immunity to reinfection in repeatedly exposed individuals. Both chronically and lack of solid immunity probably result from the emergence of minor populations of the virus quasispecies that vary in sequence, especially in the HVR1. Data supporting this conclusion came from experimental infections of chimpanzees that develop repeated infections with HCV following up to four sequential inoculations with the virus and from observations of natural reinfections of thalassemic children undergoing repeated transfusions of blood.

Similar conclusions can be drawn form attempts to vaccinate chimpanzees with recombinant HCV envelope antigens expressed in eukaryotic cells: the chimpanzees were protected following challenge with 10 chimpanzee infectiousdoses of the homologous virus but not when rechallenged with 64 chimpanzee infectious doses of a closely related strain of HCV. Attempts to neutralize HCV in vitro reveal that neutralizing antibodies were produced by patients in response to infection with HCV but these neutralizing antibodies were of low titer and specific for individual variants of HCV within the quasispecies infecting the individuals. The sequence-specific neutralization has been localized to one or more epitopes in the HVR1 of the virus. Thus, it will probably be difficult to develop a broadly protective vaccine against HCV.

Despite this pessimism, there may be some reason for hope that HCV can be prevented by immunoprohylaxis. Double-blind placebo-controlled trials of normal immune globulin for the prevention of transfusion-associated non-A non-B hepatitis (most of which was hepatitis C) revealed that, if the globulin was administered prior to transfusion, significant protection against total and Icteric non-A non-B hepatitis, as well as chronic disease, could be achieved. Similarly, when plasma units containing antibody to HCV were screened from pools of plasma destined for fractionation into blood products, the

resultant lots of intravenous immune globulin were associated with a high incidence of hepatitis C in recipients, in contrast to results obtained with most lots of intravenous immune globulin prepared before anti-HCV positive plasma units were removed. Both of these observations strongly suggest that pooled plasma contains a mixture of a antibodies to HCV that is capable of neutralizing diverse HCV strains found in nature. Thus the neutralization epitopes of HCV must be finite in their diversity. If the breadth of this diversity can be mapped it may be possible to construct a polyvalent vaccine that can protect against most if not all HCV variants.

TRANSMISSION

Case-control studies of non-A, non-B hepatitis (hepatitis strains labeled A-G have been identified) have found significant associations between virtual infection and a history of blood transfusions of least six months previously, direct patient care or laboratory works, intravenous (IV) drug use, multiple sexual partners, or sexual or household contact with an infected person. The highest prevalence is among hemophiliacs who received factor concentrate transfusions before 1992. Persons with a history of IV drug use account of possibly 50 percent of chronic infections. Approximately 20 percent of hemodialysis patients worldwide are reported to show anti-HCV antibodies, independent of receiving blood transfusions and positively associated with increasing years on dialysis. Geographical variations of all sources of HCV exist, however, and hemodialysis is not an exception to this rule. In the United States, 35 percent of hemodialysis patients in one study were HCV infected. Sexual transmission and household exposure transmission is a route of infection, but appears to occur infrequently and accounts for possibly 10-15 percent of all cases. In a Japanese study of 154 infected couples, 18 percent of monogamous HCV spouses were co-infected, the risk increasing for each decade of marriage. Alter 19 estimates the likelihood of sexual transmission is approximately five percent, and neither the U.S. Public Health Service nor the NIH recommend barrier precautions in monogamous relationships. Prenatal spread is uncommon and, when it occurs, rarely leads to chronic infection of the child unless the mother is co-infected with HIV.

Current risks for acquiring or having acquired hepatitis C include; illegal intravenous drug use (including short-term use in the previous 20 years), being an organ or transfusion recipient prior to 1992, intranasal cocaine use with shared equipment, tattoo or body piercing with nonsterile instruments, using an infected person’s razor or toothbrush, and engaging in high risk sexual behaviour (having multiple partners or failing to use a condom).

Prior hospitalization is a risk factor (prevalence in hospitalized patients in 2-20 percent). Patient-to-patient transmission has been implicated in outbreaks of HCV in a hematology ward, and surgeon-to-patient transmission has been identified as a cause in a pediatric oncology unit.

CLINICAL COURSE

The current incubation time of HCV is between 2-26 weeks, although 80-90 percent of cases occur within 5-12 weeks post-transfusion.26 Most patients with

acute hepatitis C do not have demonstrable signs or symptoms at the onset of infection. Twelve percent of a cohort of 50 HCV patients had a remembered past history of symptomatic hepatitis: however, due to the high incidence of confection hepatitis, the symptomatic episode may have been simultaneous infection with acute hepatitis A. 27 Only 25 percent of acute non-A non-B hepatitis patients are jaundiced and only 33 percent have significantly elevated alanine aminotransferase (ALT) levels (800 I.U.).

As mentioned previously , the ability of the virus to mutate appears to prevent effective immune eradication, even in the case of a healthy cellular immune response. This is reflected by the high percentage of cases that become chronically infected: studies range from 90 percent for those with genotype Ib, to 75 percent with genotype 2 a or 2b.[29] in the United State, it is generally accepted that at least 85 percent of anti – HCV antibody posit patients will progress to chronic hepatitis.

Chronic hepatitis C is usually characterized by serum ALT levels that have been elevated for 6-12 months after acute onset. Alt levels may normalize within one year, but may again rise and become chronically elevated. Fluctuating transaminses in the absence of alcoholism are accepted to be diagnostic of hepatitis C. 2 However, HCV can and does progress in the absence of signs and symptoms: approximately one-third of those chronically infected with HCV exhibit consistently normal serum ALT levels.

Even in the face of normal liver enzymes and an asymptotic course, thee is a high prevalence of liver disease. In a study of 98 healthy, anti-HCV antibody positive blood donors. 95 percent had histological abnormalities evidenced by liver biopsy and 75 percent were diagnosed with histological evidence of chronic hepatitis.The progression of HCV appears to vary geographically and possibly with gnomic type. In Japan, where the predominant genotype is IB< only two percent of HCV patients appear to recover from acute infections, while the remainder will most commonly progress to chronic hepatitis (30%), cirrhosis (20%), and hepatocellular carcinoma (15%) a mere eight years later. 2 in the United States, progression is slower, with the development of cirrhosis in 20-30 percent of patients in 10-20 years of follow-up.

The most common symptom of HCV is fatigue. In one study of 102 patients referred to a liver unit, fatigue occurred in 35 percent of subjects. the onset of cirrhosis may be relatively asymptotic with only subtle physical changes; palmer erythema, spider angioees (Blanching with pressure) hypertrophy of the parotids, gynecomastia in men (due to decreased clearance of estrogen in the liver), and fibrosis of the palmer tendons of the hand. Once cirrhosis occurs, other symptoms such as muscle weakness, fluid retention, jaundice, bilirubin in the urine, purpura upper intestinal hemorrhage, and pruritis may follow. HCV can also manifest as arthritis, lichen planus, glomerulonephrosis, and essential mixed cryoglobulinemia (arthritis, purpuura, hives, vasculits, glomerulonephritis, and neuropathy) Although cryoglobulins are evident in approximately 33 percent of patients, the clinical syndrome occurs only in 1-2 percent. 34 another potential complication of HCV is porphyria cutanea tarda. It is associated with alcohol abuse, iron overload, and estrogen use, and appears as coetaneous vesicles in sun-exposed areas. The condition, if progressive, leads to skin fragility, bruising and hyperpigmentation.

C0-INFECTION WITH HIV

Among HIV- infected persons, HCV appears to progress more rapidly and lead to increased risk for liver disease. In a population of HCV- infected male hemophiliacs in the United Kingdom, liver-related death rates were approximately 20 times higher than the general population, and 94 times higher in men co-infected with HIV and HCV. Other studies have noted increased replication rates of HCV in HIV positive individuals with a more rapid progression to cirrhosis.

HEPATOCELLULAR CARCINOMA

One of the most concerning aspects of HCV is the risk for hepatocellular carcinoma (HCC). In a cohort of hemophiliacs, an HCV infection of 25 years duration (as compared to those who are HCV-negative) resulted in a 17-fold increase n risk of death from liver disease and a six-fold increased risk of death from liver cancer. In Europe and Japan, 50-75 percent of all patients with HCC have evidence of HCV infection.The incidence of HCC varies with different population studies. in general, 20 percent of patients with chronic HCV develop cirrhosis over a ten-year period. In patients with established cirrhosis due to HCV infection, surveillance studies show 3-4 percent may develop HCC in the first 4-5 years. Progression from cirrhosis to HCC usually takes approximately ten years. Liver Biopsy and the pathology of HCV progression of HCV is determined by liver biopsy and measurement of serum ALT. When serum ALT is consistently above 200 IU/L it is predictive of chronic active hepatitis. The current hisotological classification system for liver biopsies in HCV consists of a grading scale based on necrosis and inflammation, and staging based on fibrosis.This system differentiates mild hepatitis (grade 1-stage 1) from more progressive states of hepatitis (grades 2-4). A biopsy without evidence of fibrosis infrequently progresses to cirrhosis.

EVIDENCE FOR OXIDATIVE STRESS AND CYTOKINE-INDUCED INFLAMMATION IN HCV:

Results of 317 liver biopsy samples from patients with HCV showed evidence of HCV-induced liver damage; lymphoid follicles, large droplet fat, bile duct damage, and Mallory body-like material. Scheur and sherlock sampled 45 HCV patients, 44 percent of whom exhibited developing or established cirrhosis. They concluded the evidence of lymphoid aggregates (lymphocyte clusters) or foolicles in the portal tracts and fatty changes ,along with lobular activity, are the characteristic changes in hepatitis C.Bach and Thung examined 50 biopsy samples from patients with HCV compared to 21 patients with autoimmune chronic hepatitis, and found similar pathologic traits that distinguished the HCV samples; bile duct damage, bile duct loss, steatosis, lymphoid cell aggregation (follicles), and lobular and piecemeal necrosis.

The mechanism involved with liver damage in chronic hepatitis care not completely understood. HCV is thought to be directly cytopathic to hepatic cells, and there is evidence immune mechanisms involved in veridical activity are responsible for the inflammatory infiltrates (lymphoid follicles) that can progress to necrosis. Tumor necrosis factors alpha (TNF-a) is a cytokine secreted by HCV –specific cytotoxic lymphocytes; TNF-a levels are elevated in chronic hepatitis C.Elevated levels of TNF-a have also been correlated with elevated markers of liver damage (serum ALT levels and

alpha –glutathione –s-transferase levels)independent of levels of hepatitis C virus in the blood.TNF- a is one of the cytokines secreted by the specific Th2 humoral defence arm of the proinflammatory lymphokines interleukin 6 (il-6),interleukin 4 (il-4),interleukin 10 (il-a).The other arm of the T lymphocyte system is comprised of TH1 cells, which promote cell-mediated defense, and secrete interleukin 2 (IL-2), interleukin 12 (IL-12), and gamma-interferon (IFN-g).

The TH1 and TH2 systems are mutually inhibitory, serving as a regulatory system in balancing humoral and cell-mediated responses. In the well-studied immune activation of HIV infection, the TH2 system becomes dominant, destroying immune equilibrium and resuming in a progressive reduction of IL-2 and IL-12. In HCV infections, the same dominance of the TH2 system appears to exist: IL-4, IL-6 and IL-10 stimulate humoral immunity and lead to the overproduction of TNF-a, resulting in inflammation and suppressing the production of IL-2 and IFN-g. In a healthy immune system, TH1 cells also support the transformation of CD+8 suppressor cells into active natural killer / cytotoxic cells that directly inactivate virus. Lirussi evaluated natural killer cytotoxic resonse of NK cells in 15 chronic HCV patients and compared them with 23 controls. The NK cell activity in the chronic HCV patients was approximately 50 percent that of the healthy group in three different concentrations of NK cells. The authors suggest an impaired immune response appears to favour chronically of the disease in chronic HCV. Whether impaired activity of the NK cells in chronic HCV infections is due to a dominance of TH2 lymphocytes remains to be seen.[12-22]

HEPATITIS D:

(HDV) is unusual in that it is a RNA defective virus, i.e. it cannot replicate by itself because it does not have the genes for its envelope protein. (HDV) replicate only in cells also infected with HBV, because HDV uses the surface antigen of HBV.

TRANSMISSION:

(HDV) is transmitted by the same means a is HBV, by blood and perinatally. In us most HDV infections occurs in intravenous drug users who share needles. (HDV) infections occurs world wide with a similar distribution to that of HBV infections.

PREVENTION:

A combination of alpha interferon and ribavirin (Rehbetron) is a treatment of choice for chronic hepatitis C. there is no vaccine and hyperimmune globulins are not available. Pooled immune serum globulins are not useful for postexposure prophylaxis.

PATHOGENESIS:

Pathogenesis of hepatitis caused by (HDV) and (HBV) is the same, i.e. the virus infected hypatocytes are damaged by cytotoxic T-cells. It can superinfect those who are already chronic carriers of HBV.

DIAGNOSIS:

The diagnosis of HDV infection in the laboratory is made by decting either delta antigen or IgM antibody to delta antigen in the patient's serum.

PREVENTION:

Alpha interferon can mitigate some of the effects of the chronic hepatitis caused by HDV. There is no vaccine against HDV.

HEPATITIS E:

(HEV) is a major cause of interracially transmitted bacteria. It is an RNA virus which is excreted in the stools. It is a common cause of water-borne epidemics of hepatitis in Asia. Uncommon in United States. (HEV) is non-enveloped single-stranded RNA virus tentatively classified as a member of the calicivirus family.

TRANSMISSION:

(HEV) spreads by fecal oral route it is found in countries where sanitation is poor and cause large epidemics of water borne hepatitis.

PATHOGENESIS:

Clinically the disease resembles hepatitis A, chronic liver disease does not occur and there is no prolonged carrier state.

DIAGNOSIS:

The diagnosis is typically made by excluding HAV and other causes.

PREVENTION:

For prevention there is no-antiviral treatment and no vaccine.

HEPATITIS G:

The most recently discovered virus first isolated from patients with pastrans fusion hepatitis in 1996.

(HGV) is a member of the flavivrus family. It look's a lot like (HCV) that is, it shares about 85% of its genetic sequence with that virus. But so far it does not seem to be infections or to use illness. There are between 900 and 2000 cases of hepatitis G infection each year in US. The role of HGV is yet to be established.

HEPATITIS F:

(HFV) appears to be transmitted by the oral fecal route in a similar manner to hepatitis A and E although the epidemiology of the virus has not yet been fully established. The virus

consist of double stranded DNA currently there is no serological test for diagnosing hepatitis in cause of acute hepatitis.

HEPATITIS X:

Some cases of hepatitis cannot be attributed to the hepatitis A, B, C, D or E viruses. This is called non A, ……E, hepatitis or hepatitis X scientist have identified several candidate viruses, but non have been proven to cause hepatitis. The search of the virus responsible for hepatitis X continues.

OTHER HEPATITIS:

Further such viruses do exist but the hepatitis viruses now account for the number of majority of hepatitis viruses infection.

1. Cytomegalovirus and epstein – Barr virus infection caused abnormal liver function test in most patients and occasionally icteric hepatitis occurs.
2. Herpes simplex is a rare cause of hepatitis in adult most of whom are immunocompromised.
3. Yellow fever virus cause hepatitis in parts of the wold where it is endemie.

UPDATE:

Hepatitis A in 9.1 persons person per 100,000 in US.

Hepatitis B, there are 350 million carriers of HBV world wide about 1 to 1.25 million person in the US are infected.

Hepatitis C, among intravenous drug users 48 to 98% have HCV in the U.A. 4 million people are infected.

Hepatitis D, A total of 15 million people are infected.

Hepatitis E, HeV is rare in the USA.

Hepatitis G, appears to be mino-player in parental hepatitis.

If you have hepatitis C only you are more likely to catch hepatitis A or B tiat could cause more damage to your liver.

Due to liver cancer and cirrhosis 4000 to 5000 deaths each year in US by hepatitis B.

TESTS FOR ACUTE AND CHRONIC VIRAL HEPATITIS

Viral hepatitis continues to be a major cause of morbidity and mortality in North America. The US Centers for Disease Control and Prevention estimates that symptomatic hepatitis infections are diagnosed in about 300,000 patients each year. another estimated 200,000 cases per year are asymptotic and remain undetected.[23]

Although illness is often sub-clinical, viral hepatitis has a substantial impact on society in terms of days lost from work and school, the need for hospitalization, and even loss of life. Hepatotropic viruses also have the potential to cause chronic disease and can be associated with development of liver cirrhosis, hepatocellular carcinoma, and liver failure. Consequently, accurate diagnosis of the specific cause of hepatitis is important for appropriate management.

HEPATITIS A:

Hepatitis A virus (HAV) causes more cases of acute viral hepatitis than all the other hepatototropic viruses combined.[24] Accurate diagnosis is important, not only for the care of the infected patient but also for contacts who may be candidates for immunoglobulin prophylaxis and immunization. Despite several well-recognized risk factors for acute HAV infection, more than 40% of infected persons have no identifiable source of infection.*

Malc homosexuals
Travelers to developing countries
Injecting drug users
Sexual or household contacts
People with multiple sexual partners
Babies born to infected mothers
People of low socioeconomic status
Hemodialysis patients
People who received transfusions before 1992

* Despite well-known risk factors, more than 40% of patients with hepatitis A have no known source of infection.

Diagnosis of acute HAV infection is made by detection of hepatitis A iGM antibody (IgM anti-HAV). Other experimental method of documenting HAV infection, including virus recovery from stool and staining for hepatic HAV antigen, have no routine clinical application. IgM anti-HAV is invariably present at onset of acute HAV infection. Although an IgG antibody response (IgG anti-HAV is also detected in acute HAV infection, IgM anti-HAV must be present for diagnosis

Test	**Detects**
IgM anti-HAV	Acute hepatitis A
HbsAg	Acute or chronic hepatitis B*
Anti-HAV	Acute or chronic hepatitis C

Anti-HAV, hepatitis C antibody; HbsAg, hepatitis B surface antigen; IgM anti-HaV, hepatitis A IgM antibody; IgM anti-HBc, hepatitis B core IgM antibody.*If positive, order test for IgM anti-HBc.

IgM anti-HAV persists for 3 to 6 months after infection. Patients with relapsing HAV infection, in which apparent recovery is associated with further clinical and biochemical flare before eventual recovery, can have IgM anti-HAV for almost 12 months.[25]

IgG anti-HAV develops after natural infection and provides lifelong immunity. Neither reinfection nor chronically occurs with HAV. The presence of IgG anti-HAV in a patient with cirrhosis is indicative of previous HAV infection only. The antibody is also detectable after immunization, making it impossible to differentiate natural infection from immunization. Kinetic studies that measure the waning of antibody levels after HAV vaccination suggest that protection may last for 1 to 2 decades.[26]

HEPATITIS B:

The hepatitis B virus (HBV), a complex DNA virus, produces a number of proteins with corresponding antibodies that enable accurate diagnostic evaluation of the patient with suspected HBV infection.In fact, serologic evidence of acute HBV infection antedates appearance of clinical symptoms by about 1 month. As a result, hepatitis B surface antigen (HbsAg) is almost always detectable when the disease is first seen. HBsAg disappears in acute HBV infection after clearance of the virus.

Test Clinical scenario

Tummunity	**Acute infection**	**Chronic infection**	**Resolution**
HBsAg	+	+	-
Anti-HBc			
IgM	+	-	-
IgG	+	+	+
Anti HBs	-	-	+*
HBV DNA**	+	+/-	-
Hbe Ag**	+	+/-	-
Anti-Hbe**	-	+/-	+

Anti-HBc, antibody to hepatitis B core antigen; anti-Hbe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B DNA; HbeAg, hepatitis B e antigen; +, positive findings; -, negative findings; +/-, inconclusive findings.
* Confers immunity. Hepatitis B immunization results only in anti-HBs production.
**Usually ordered in chronic infections only.

There is a time interval known as the “window period” in which both HBsAg and neutralizing antibodies against. HBsAg (anti-HBs) may be below the level of detection. The sole marker of recent (<6 months) acute HBV infection is an IgM antibody directed against the hepatitis B core antigen (IgM anti-HBc); the presence of anti-HBs indicates immunity. Both HBsAg and anti-HBs may be found simultaneously. The reasons for this include a resolving acute HBV infection or a heterotypic nonneutralizing antibody directed against HBs subdeterminant that is absent from the circulating HBs. The presence of both anti-HBs and hepatitis B core IgG antibody (IgG anti-HBc) suggests immunity was obtained through natural infection. On the other hand, hepatitis B immunization results only in anti-HBs production.

Levels of IgM anti-HBc and IgG anti-HBc rise together really in the course of HBV infection but trail behind HBsAg levels. After reaching a maximal level, titers of IgM

anti-HBc fall, but IgG anti-HBc level remains elevated. IgM anti-HBc is not a neutralizing antibody.

Absence of IgM anti-HBc indicates that HBV infection is not acute. The presence of an "isolated" IgG anti-HBc (i.e. without HBsAg) suggests resolved HBV infection and the decline of IgM anti-HBc to undetectable levels, although immunity to HBV persists. Very young and very old patient and immunocompromised persons, including hemodialysis patients, are less likely to clear acute HBV and are at risk of remaining infected .[27]

Explanation	Recommendation
False-positive and resetting.	Consider cross-reacint antibodies (rheumatoid factor)
Previous infection or community	Anamnestic anti-HBs response to hepatitis B vaccination
Anti-HBs,	antibody to hepatitis B surface antigen.

Chronic HBV infection is suggested by the presence of HbsAg in serum for at least 6 months and is confirmed by the absence of IgM anti-HBc. After it has been determined that HBV is chronic, the level of viral activity or replication is assessed by testing for hepatitis B candidates for antiviral therapy.

Test	Explanation	Comments
HBsAg	Acute or chronic Hepatitis B	Check IgM anti-HBc to differentiate acute from chronic hepatitis; measuring HbeAg to assess viral replication if IgM anti-Hbe is negative.
Anti-HCV	Acute or chronic Hepatitis C	Most cases are chronic

Anti-HCV, Hepatitis C antibody; Hbe Ag, Hepatitis B e antigen; HBsAg, IgM anti-HBC, Hepatitis B core IgM antibody.

HEPATITIS C:

Acute hepatitis C virus (HCV) infection is usually sub-clinical, but the likelihood of chronically is high. Thus, HCV is most typical diagnosed, in the chronic phase. One exception is the healthcare worker who contracts HCV from a needle stick and in whom the onset of HCV infection is detected during occupational health follow-up.

The routine diagnosis of HCV is by antibody testing with an enzyme-linked immunosorbent assay (ELISA).[28] The recombinant immunoblot assay (RIBA) is a supplemental examination and tests for the same antigen as the ELISA. Since hepatitis C antibody (anti-HCV) testing was first introduced a decade ago, it has evolved rapidly. Serologic tests for HCV are now sensitive and specific, and anti-HCV can be detected within a few weeks of acute infection.

The positive predictive value of anti-HCV testing depends heavily on the targeted population. For instance, in populations with low HCV prevalence, the predictive value of a positive second-generation ELISA test is between 50% and 60%. IN contrast, the predictive value of a positive ELISA in populations with high prevalence is about 90%.[28] Thus, in low risk patients, such as blood donors, supplemental RIBA testing is still believed to be necessary, because a positive ELISA may be a false-positive. In high risk group. A positive ELISA is likely to be a true positive, and RIBA is usually not necessary.

A significant advance in HCV research has been molecular testing using the polymerize chain reaction (PCR). This test can detect minute quantities of HCV RNA. HCV RNA is present in blood as early as 1 to 2 weeks after infection.

Tests	**Uses**	**Comments**
Anti-HCV ELISA	Initial diagnosis, Screening test	Can be positive within several weeks of exposure
HCV RIBA	Confirm ELISA result	Useful in low risk patients
HCV by PCR Qualitative	Confirm HCV infection	May be helpful in seronegative patients, confirms virologic response to therapy.
HCV by PCR Quantitative	Assesses viral load less sensitive than qualitative test.	Considered more reproducible
Genotype	Epidemology and research	Mayhave role in predicting treatment response.

PCR – based testing is classified as either qualitative or quantitative. Qualitative assays can detect as few as 100 HCV RNA copiesper milliliter. The results are read as either positive or negative.Quantitative assays, on the pther hand , provide an estimate of viral load. The results state the number of HCV RNA copies, which is quite variable from one assay to another. The lower limit that can be detected ranges from 500 to 2000 copies per milliliter.

Although still not approved by the US food and drug administration , PCR testing for HCV RNA is rapidly becoming integeral part of the evaluation and monitoring of HCV infection. Avoidance of contamination and care ful specimen handling are crucial to obtaining reproducible results.

The genetic hetrogenicity of HCV has lead to the recogination of atleast six distinct, major genotypes of the virus, as well as numerous subtypes. However, homology, among all HCV isolates is about 70%. Sequence homology is about 95% withen each genotype and 80%withen each subtype.[29]

The various genotypes have geographic and epidemiologic differences. Gentypes from 1 through 3 are more prevelant in Western countries and fareast.

Genotype 4 is found predominantly in the Middle East and parts of Central Affrica. Genotypes 5 and 6 are most common in Southeast and South Affrica.

The major clinical correlate of HCV genotypes to date has been as a predictor of responsiveness to interferon. Therapy is less likely to be successful with genotype 1b.

HEPATITIS D:

Heptitis D virus (HDV), an RNA virus, is unable to teplicate on its own and require HBV. Thus, it can cause disease only in patients with HBV infection. In North America, it most often recognized in injecting drugs users. HDV can occur as a super infection in patients with underlying chronic HBV or as a coinfection during acute HBV infection.

The major significance of HDV infection is the propensity to worsen the manifestation of HBV infection. Fulminant hepatitis is more likely to develop in the patients with acute HBV infection who is coinfected with HDV. Also, the patients with chtonic HBV who becomes coinfected with HDV may have an acute worsening of liver disease and a more rapid progression to cirrhosis.[30]

Diagnosis of HDV infection revolves around the identification of antibodies. Antibodies to hepatitis D antigen (anti – HDV) are detectable in only one third of HDV infections. Although antibody tests, can not differentiate between coinfection and superinfection, certain clues can be helpful. Because the production of anti- HDV can be delayed, testng of anti-HDV should be repeated if the clinical picture suggests HDV infection, such as severe hepatits in an injecting drug user with HBV infection. In patients with coinfection high IgM anti-HBc titers and biphasic transaminase elevations may coexist and may represent separate hepatic insults by the two viruses.

VIRAL MARKERS

Heptitis B	**Hepatits D**
Coinfection IgM anti- HBc + Anti-HDV +	HBsAg +
Superinfection IgM anti- HBc- Anti- HDV +	HBsAg+

HEPATITIS E:

Heptitis E virus (HEV) is a very unusual cause of acute hepatitis in the United States. However, because most cases occur in the devolping countries, it should be considered in travelers returning from abroad.31 Dignosis relies on the serologic detection of antibodies against the virus. Both hepatits E IgM antibody

(IgM anti – HEV) and IgG antibody (IgG anti – HEV) are detectable at the onset of illness, although these test are not available for routine diagnostic use. IgM anti- HEV peakes after 5 to 6 weeks of infection and than falls slowly. IgG anti- HEV remains present in less than half of infected paients 14 years after infection.[32]

ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B AND C

Therapy for chronic viral hepatitis that just 10 years ago was considered experimental has now become routine. However, most of the estimated 1 million Americans with chronic hepatitis B virus (HBV) infection and most of the estimated 4 million with chronic hepatitis C virus (HCV) infection have not yet been identified, even though they may benefit from therapy. Worldwide, HBV infection is the leading cause of liver-related deaths (from cirrhoses is and hepatocellular carcinoma). In the United States, chronic HCV infection has emerged as a major contributor to the rising incidence of hepatocellular carcinoma and is now the most common reason for liver transplantation.

As with management of AIDS, the diagnosis, treatment, and follow-up of chronicviral hepatitis are increasingly falling to primary care physicians. For both II BV and II CV, studies in outcome research have clearly demonstrated that successful anti viral therapy can achieve health and quality of life benefits if undertaken early enough in the course of the disease.[33,34,35] It is imperative, therefore, that clinicians learn to identify potential candidates for anti viral therapy and are familiar with the available therapeutic options. A clear understanding of these options requires knowledge of the serologic markers used in diagnosis of viral hepatitis.

HEPATITIS B VIRUS (HBV) INFECTION.

Sero-positivity for hepatitis B surface antigen for longer than 6 months
Seropositivity for hepatitis B e antigen
Measurable HBV DNA in serum

Elevated serum alanine amonotransferase level
Compensated liver disease*

HEPATITIS B VIRUS (HCV) INFECTION

Seroposistivity for HCV RNA antibodies for longer that 6 months
Seropositivity for HCV RNA
Elevated serum alanine aminotransferase level
Compensated liver disease

- if interferon alfa therapy is being considered.

Before antiviral therapy is begun, baseline laboratory studies should be performed, and important contraindication should be considered patients should be monitored regularly and followed closely during therapy for potential adverse effects, including bone marrow suppression.

White blood cell and neutrophil counts
Hemoglobin concentration
Platelet count
Serum Chemistries
Serum creatinine level
Prothrombin time
Thyrotropin (TSH) level
Free thyroxin level

IN HEPATITIS B

No findings of hepatitis B e antigen

IN HEPATITIS C

No findings of hepatitis C virus B E antigen

IN EITHER

-
- Decompensated cirrhosis*
- Psychiatric disorder*
- Severe comorbid condition*
- Normal serum alanine aminotransferase level
-

- If interferon therapy is being considered.

CHRONIC HBV INFECTION

Patients with chronic HBV infection are at increase drink of cirrhosis, hepatocellular carcinoma, and liver failure. In one of the largest prospective studies of hepatocellular carcinoma and HBV, consisting of more than 22,000 men with HBV infection, the relative risk of primary liver cancer in infected patients was 223 times higher than the risk inuninfected controls.[36]

Chronic HBV infection is suggested by persistence of hepatitis B sure antigen (HBs Ag) 6 months after acute infraction. In addition, there may be serologic evidence of ongoing viral replication,. Consisting of detectable hepatitis B E antigen (Hbe Ag) or HBV DNA on quantitative assays or the presence of biochemical markers (e.g., an elevated alanine aminotransferase [ALT] level). Chronic HBs Ag carriers who have active viral reapplication and an elevated ALT value should be evaluated for possible antiviral therapy to prevent the potential consequences of chronic HBV infection.

The goals of antiviral therapy in chronic HBV infection are the following:

- Normalization of ALT level

- Reduction of histologic Necroin flammatory activity
- Sustained loss of Hbe Ag and HBV DNA
- Development of antibody of HB e Ag (anti HBe)

Ultimately, loss of HBs Ag may occur, with complete clearance of viral infection.

Clinicians now have a choice of two agents against HBV infection that have been approved by the US Food and Drug administration (FDA). Interferon alfa – 2b (Intron A) therapy has been shown to be effective but requires subcutaneous or intramuscular administration and has numerous side effects (e.g., flutelike symptoms, malaise, depression). Lamivudine (Epivir), an orally administered antiviral agent, is a major advance in management of HBV infection.[37,38] Therapy should consist of one agent or the other: combining interferon and lamivudine is neither recommended nor approved by the FDA.

INTERFERON ALFA- 2B THERAPY

The FDA-approved regimen of interferon alfa –2b for chronic HBV infection is 5 million IU daily of 10 million 1 U three times a week administered subcutaneously or intramuscularly for 4 months. Treatment is reserved for patients with elevated ALT values, HBe Ag Seropositivity, and detectable serum HBV DNA with compensated liver disease.

The goal of therapy is to eradicate the virus and induce remission of liver disease. Viral eradication is suggested by loss of both HBe Ag and HBV DNA and by seroconversion from HBe. Long-term follow-up of treated patients has found frequent seroconversion from HBs Ag to antibody to HBs Ag, implying complete viralclearance.[39] Cessation of viral replication leads to diminished hepatic necroinflammatory activity and normalization of ALT levels. A meta-analysis of interferon alfa treatment in chronic HBV infection suggested that 30 % to 40 % pf [atoemts ;pst HBV DNA and HBe Ag Subsequently, 5% to 10% of treated patients lost HBs Ag.[40,41]

During interferon alfa therapy, serum ALT levels typically rise precipitously. Such flares suggest enhanced host immunity and may precede loss of HBe Ag, but flares may be poorly tolerated by patients with cirrhosis.

LAMIVUDINE THERAPY

Because of the adverse-effect profile, lack of universal response, and important contraindications to interferon alfa (e.g., decompensated cirrhosis) , release of lamivudine by the FDA in the late 1990s for treatment of chronic HBV infection was eagerly anticipated. This nucleoside analogue directly inhibits replication of HBV by interfering with DNA polymerize. The approved dose is 100 mg in tablet form or 5 mg/ml in oral solution form once daily.

Several controlled trials have demonstrated that 100 mg of lamivudine daily effectively suppresses viral replication and improves liver histologic findings, often with few or no side effects.[42,43] Similar to interferon alfa-2b therapy, lamivudine therapy result in seroconversion(loss of HBe Ag and HBV DNA, with development of anti-HBe) in 16%

to 32% of patients. However, immunologic clearance of viremia is not abrupt, and ALT flares are not common with use of this agent. Unless anti- HBe develops during lamivudine therapy relapse may occur when the drug is stopped, soloing-term suppressive therapy may be necessary.

Lamivudine has several important advantages, including ease of administration, few adverse effects, and safety among patients with advanced live disease. However, optimal duration of therapy is unknown, and seroconversion rates are similar to those of interferon alfa treatment. in addition, escapemutants cause changes in the YMDD (tyrosine, methionine, aspartate, aspartate) region of HBV DNA in15% to 35% of patients undergoing lamivudine monotherapy, resulting in resulting in reduced sensitivity to lamivudine and reappearance of serum HBV DNA.[42,44] The clinical significance of these mutants is unknown, because they may represent a less virulentstrain than the wild type of virus. Whether lamivudine therapy should be continued after development of a mutant HMDD virus is unclear, but patients considering taking the drug should be aware of this potential drawback.

The following table summarizes the relative advantage and disadvantages of interferon alfa-2b andlamivudine treatment of chronic HBV infection.

INTERFERON ALFA –2B	**LAMIVUDINE (EPIVIR)**
ADVANTAGE	
Short – duration (4-month) therapy	Convenient; few adverse effects
Loss of HBeAg in 30% of patients	Loss of HBe Ag in 30% of Patients
Greater response if high Alt level and lower HBV DNA	Histologic response in most patients
Loss of HBsAg in up to 10% of patients	Interferon no better in head-to-head compression
No associated mutations	Effective in patients who fail to respond to Interferon
Long–term follow-up data available	Can be used in patients with liver Decompensation and immunosuppression.
DISADVANTAGES	
Inconvenient (Injection required)	Long-duration therapy (optimal length unknown.

Substantial side effects	Emergence of viral mutation (HMDD).
No batter than lamivudine in head-to-head Comparison.	No loss of HBs Ag.
Limited efficacy in patients with liver Decompensation or immunosu8ppression.	

ALT, alanine aminotransferase; HBV hepatitis B virus; HBe Ag, hepatitis B e antigen; HBs Ag, hepatitis B surface antigen; YMDD, tyrosine, methionine, aspartate, aspartate.

FUTURE THERAPIES

In ongoing clinical trials, adefovir dipivoxil, a nucleotide analogue, has shown potent activity against HBV,[45] and it appears to be effective against YMDD mutants. In the future, patients with chronic HBV infection will probably be treated with a combination of nucleoside and nucleotide analogues, but trials of such combinations are not yet being conducted.

CHRONIC HCV INFECTION

After acute HCV infection, chronic disease develops in 60% to 85% of patients. Development of cirrhosis represents a major hallmark in chronic HCV infection; among patients whose infection progresses to cirrhosis, hepatocellular carcinoma may develop in 1% to 4% per year.[46]

As is HBV infection, the goals of antiviral therapy in chronic HCV infection are to eradicate the virus and halt disease progression. Patients who have anelevated ALT level, Seropositivity for HCV, and consistent inflammation onliver histologic evaluation may be candidates for antiviral therapy.[47] In addition, patients with compensated cirrhosis may achieve histotogic benefit from antiviral therapy.

Patients with chronic HCV infection but normal ALT values are an important group, probably accounting for 15% to 20% of cases of chronic HCV infection. Overall their disease appears to be more indolent than that of patients with HCV infection and elevated ALT levels. Initially, patients with normal ALT values were thought to be less likely to respond to interferon monotherapy than those with elevated levels. However, recent studies suggest that they dorespond to therapy with the newer regimens (discussed later), although what comprises optimal management is unclear.

The original goal of interferon therapy for hepatitis C was normalization of serum ALT values, whereas the current goal is loss of HCV RNA. A number of assays that directly measure HCV RNA, both qualitatively and quantitatively, have been developed. They help direct antiviral therapy, but interpretation of individual values is dependent of proper collection techniques and the reliability of a given laboratory. Serum HCV RNA determination are made on the basis of polymerize chain reaction or branched DNA

signal amplification. It is important to recognize that absolute reported values are not comparable across assays.

Interferon alfa therapy

Initial randomized, placebo-controlled trials of interferon alfa used in chronic non-A non-B hepatitis (even before HCV had been identified) showed that the agent produced results superior to placebo, as defined by improve ALT levels and histologic findings. Three forms of interferon alfa are now available for chronic hepatitis C. The regimen prescribed for interferon alfa-2a (roferon-A)is the same as that for interferon alfa-2b;3 million IU subcutaneously or intramuscularly tree times a week . The third form, consensus interferon (or interferon alfacon-1[Infergen]),has been approved at a dosage of 9 micrograms subcutaneusly three times a week.

Response to antiviral therapy for chronic hepatitis C is categorized as sustained, relapse or no response. Sustained response refers to continued eradication of HCV RNA from scrum at least 6 months after cessation of therapy. Patients have been followed up to 7 years after treatment, and many remain free of virus, both in serum and in liver tissue. Relapse is exemplified in patients who have normalization of ALT levels and elimination of measurable HCV RNA after therapy is discontinued. No response is depicted by patients who never achieve normalization of ALT levels or loss of HCV RNA.

Researchers have identified some predictors of diminished likelihood of sustained response to antiviral therapy for chronic hepatitis C. Among these predicators are a high HCV RNA levels and the presence of HCV genotype 1, which is, unfortunately, the most common genotype in North America. Genotyping is still a research tool, but the clinical significance of a specific to be as a predictor of responsiveness to interferon. Six major HCV genotypes are currently recognized (although genotypes 4,5,and 6 are far less common in the united states than in Europe). Regardless of baseline viral levels, patients infected with genotype 2 or 3 respond better to antiviral therapy an may require a shorter duration of treatment than patients infected with genotype 1.

Ribavirin- and – interferon combination therapy

A significant advance in treatment of chronic HCV infection was the introduction of combination therapy (Robertson) using oral Ribavirin (Rebetol) and interferon alfa – 2b.[48,49] (Previously, orally administered Ribavirin had been shown to improve ALT values, but it had no effect on HCV infection.

Ribavirin combined with interferon was found to be more effective than interferon alfa monotherapy for chronic HCV infection not only in patients with relapse[50] but also in patients using interferon alfa as initial treatment.[51,52] Interferon alfa monotherapy resulted in a sustained- response rate of 5% when used for relapse and 6% to 13% when used as initial therapy. In contrast, combination therapy in a sustained-response rate of 49% when used for relapse during interferon alfa therapy and up to 39% when used as initial therapy.

As was the case with interferon monotherapy, response to combination therapy varied considerably according to HCV genotype. Sustained-response rates of up to 68% were

reported when combination therapy was used as initial treatment for patients with genotype 2 or 3. The optimal regimen for treatment of nonresponders is currently under investigation.

Combination therapy may be associated with numerous side effects, so patients should be closely monitored during treatment. Because irbavirin may cause hemolytic anemia, frequent hemoglobin determinations should be performed. In addition, Ribavirin is abortifacient and teratogenic. Therefore, both men and women should use birth control measures for up to 6 months after cessation of therapy.

Interferon

Flutelike symptoms, anorexia, weight loss
Malaise
Leukopenia, thrombocytopenia
Depression, irritability
Thyroid dysfunction.

Ribavirin

Hemolytic anemia
Teratogenesis and abortifacience
Pruritus, rach
Dyspnea.

Despite its higher cost, Ribavirin and interferon alfa –2b combination therapy is now the treatment of choice in chronic hepatitis C.[53] The recommended regimen is subcutaneous interferon alfa- 2b, 3 million IU three times a week, and daily oral Ribavirin, 400 mg in the morning and 600 mg in the morning and evening in patients weighing more than 165 Ib (75 Kg) or less and 600 mg in the morning and evening in patients weighing more than 165 Ib.

Future therapies

Attachment of interferon to polyethylene glycol (PEG) prolongs the drug's half-life and allows for a sustained-release preparation. Initials have shown that " Pegylated" interferon delivers a significantly higher amount of interferon alfa and that response rates are higher than with the standard three-times-weekly dosing regiment. There is considerable enthusiasm for the prospect of Pegylated interferon in combination with oral Ribavirin, and trials of such a combination are in progress.

Summary

As primary care physicians become increasingly involved in diagnosis and treatment of patients with chronic viral hepatitis, an understanding of the anti-viral options available, their limitations, and their side effects takes on a special importance. For chronic HBV infection, interferon alfa –2b requires only a 4- month course. However, it has adverse effects and contraindications and dose not produce a universal response. Another option for HBV infection is lamivudine, which is administered orally and causes few

side effects. However, relapse may occur when treatment is discontinued, and mutant virus may emerge. For chronic HCV infection, interferon alfa –2b interferon alfa –2b, consensus interferon, and interferon combined with Ribavirin have been used. The combination alternative is emerging as the method of choice in patients who do not have contraindications to oral Ribavirin. Adverse effects are common, and durability of response varies according to HCV RNA level and genotype.

DEVELOPMENT OF PHYTOMEDICINES FOR LIVER DISEASES

Introduction:

Medicinal plants play a key role in the human health care. About 80% of the world population rely on the use of traditional medicine which is predominantly based on plant materials.[54] The traditional medicine refers to a broad range of ancient, natural health care practices including folk/ trible practices as well as ayurveda, Siddha, Amchi and Unani. These medical practices originated from time immemorial and developed gradually, to a large extent, by relying or based on practical experience without signficant6 references to modern scientific principles. These practices incorporated ancient beliefs and were passed on from one generation to another by oral tradition and/ or guarded literature. Although herbal medicines are effective in the treatment of various ailments very often these drugs are unscientifically exploited and / or improperly used. Therefore, these plant drugs deserve detailed studies in the light of modern science.

It is estimated that about 7,500 plants are used in local health traditions in, mostly, rural and tribal villages of India. Out of these, the real medicinal value of over 4,000 plants is either little known or hitherto unknown to the mainstream population.[55] The classical systems of medicine such as Ayurveda, Siddha, Amchi, Unani and Tibetan use about 1,200 plants.[55] A detailed investigation and documentation of plants used in local health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases. Random screening of plants has not proved economically effective.[56]

Ethnopharmacology:

The concept of ethnopharmacology has evolved from the requirement for studies in light of modern science on the drugs use in the traditional medicine. In 1981, Bruhn and Holmstedt defined ethnopharmacology as the interdisciplinary scientific exploration of biologically active agents traditionally observed by man.[57] In its entirety, pharmacology embraces the knowledge of the history source, chemical and physical properties, compounding, biochemical and physiological effects, mechanism of action, absorption, distribution, bio transformation, excretion and therapeutic and other uses of drugs.[58] A drug is broadly defined as any substance (Chemical agent) that affects processes of living. Therefore, briefly, the main component of ethnopharmacology may be defined as pharmacology of drugs used in ethnomedicine.[59]

Many plant derived drugs derived drugs used in modern medicine are developed by ethnomedical leads and subsequent ethnophamacological studies. There are more than 100 drugs of known structure that are extracted from higher plants and used in allopathic medicine.[60,61] A proper ethnopharacological search and follow-up studies can lead to many more useful drugs. Scientific studies available on a good number of medicinal plants, indicate that promising phytochemicals (drugs) can be developed for many health problem.[62] However , phytochemical approach of plant drug discovery empyhsises the devlopement of pure phytochemicals as drugs. This method is expensive and time consuming. It requires, among other things, detailed toxicological studies. In United States of America the development of a drug in this way takes hundreds of millions of dollars and 5-10 years of dedicated work by a team of scientists. Even after that the

probability of success in the clinical trial is very less.63 In India. Central drug Research Center (CDRI), Luck now, screened approximately 2,500 plants, over a period of 20 years for a wide range of pharmacological activities. This did not result in a single successful marketable drug in the pure from, though meanly interesting leads were obtained.64,65 Thr recently launched memory enhancer (Memory plus,Velvette international Pharma products) developed at CDRI is an active fraction from Bacopa monniera containing baccosides. Similarly search for isolated compounds as drugs by CIBA-Geigy Research Center (Mumbai, India) did not prove productive65. However, if a photochemical is developed as a drug and produced by simple chemical synthesis it can be cheaper.

PHYSIOTHERAPEUTIC APPROACH OF DRUG DEVELOPMENT

In physiotherapeutic approach, the emphasis is on the development of a new drug whose extraction and fractionation have emanated on the basis of therapeutic activity. The standard fraction of an active extract or mixture of fractions may prove better therapeutically, less toxic and inexpensive compared to pure isolated compared to pure isolated compound drugs. However, crude plant preparations require modern standards of safety and efficacy. Modern bioassay methods and photochemical profile do provide ways and means of developing quality control as well as determining the expiry date of crude preparations may serve as inexpensive and useful drugs to the masses.

One of the major problems encountered in crude plant drugs is the batch to batch variations in their efficacious. Such variations could arise due to natural genetic variation (Chemotypes), seasonal variation differences in the soil and climatic conditions, nutritional status, etc. of the, medicinal plants. Association of medicinal plants with other in their plants habitant can also influence the medicinal value of them in some cases. This problem can be solved to a large extent by biotechnological intervention such as large-scale in vitro propagation and/or tissue culture. Some of them may be cultivated under controlled ideal conditions, without loss of medicinal value.

Herbal drugs have gained importance in recent years because of their efficacy and cost effectiveness. These drugs are invariably single plant extracts or fractions thereof or fractions thereof or mixtures of fractions / extracts from different plants which have been carefully standardized for their safety and efficacy. Many single plant extracts, which are tested for, at least, their suggested applications are available as prescription drugs in Europe. Some examples of these are Echinaceaspp (Extract of root / aerial part) to stimulate immune system, panax ginseng (root extract) to treat cerebral and peripheral circulatory disturbances and serenoa repens (fruit extract) to treat nonmalignant prostate disease.[65]

In Germany, the Federal Ministry of Health has set up a special commission, which looks after various aspects of herbal medicine[65,66] Many standardized herbal drugs are prepared in China. Medicines if developed properly can remarkably improve our health care.

LIVER DISEASES AND MEDICINAL PLANTS

Liver has a pivotal role in regulation of physiological processes. It is involved in several vital functions such as metabolism, secretion and storage. Furthermore, detoxification of a variety of drugs and xenobiotics occurs in liver. The bile secreted by the liver has, among other things, an important role in digestion. Liver diseases are among the most serious ailment. They may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatitis (Non inflammatory diseases), and cirrhosis (degenerative disorder resulting in fibrosis of the liver).

Liver diseases are mainly caused by toxic chemicals (certain antibiotics, chemotherapeutics, peroxidised, aflatoxin, carbon-tetrachloride, chlorinated Hydrocarbons, etc.) excess consumption of alcohol, infections and autoimmue / disorder. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages in liver.[67,70] Enhanced lipid peroxidation produced during the liver microsomal metabolism of ethanol may result in hepatitis and cirrhosis.[71] It has been estimated that about 90% of the acute hepatitis is due to viruses. The major viral agents involved are Hepatitis B, A, C,D (delta agents). E and G. Of these, Hepatitis B infection often results in chronic liver diseases and cirrhosis of liver. Primary liver cancer has also been shown to be produced by these viruses. It has been estimated that approximately 14-16 million people are infected with this virus in South east Asia region and about 6% of the total population in the region are carriers of this virus.[72] A vaccine has become available for immunization against Hepatitis B virus. Hepatitis C virus. And Hepatitis E infections are also common in countries of South East Asia region.[72]

Plant drugs:

in spite of the tremendous advances made in allopathic medicine, no effective hepato protective medicine is available. Plant drugs are known to play a vital role in the management of liver diseases. There are numerous plants and polyherbal formulations claimed to have hepatoprotective activities. Nearly 150 phytoconsitituents from 101 plants have been claimed to possess liver protecting activity.[73,74] At the same time, surprisingly, we do not.

Most commonly used plants in herbal formulation in India*

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*Andrographis Paniculata (28)**
*Boethaavia diifusa (10) **
*Eclipta alba (10) **
*Picrorhize Lirroa (10)**
Oldenlandia Corymbasa (10)
Asteracantha Longifolia (8)
Apium graveolens (8)
Cassia occidentalis (8)
*Cichorium intybus (8)**
Embelia ribes (8)
*Tinospora cordifolia (8)**
Trachyspermum ammi (8)

(*) Scientifically validated in experimental animals.
Each plant is used in more that the number of formulations giver in bracket.

Have readily available satisfactory plant drugs / formulations to treat severe liver disease. Most of the studies on hepatoprotective plants were carried out using chemical-induced liver damage in rodents as models. A few excellent reviews have appeared on this subject in the recent past.[73,76] This review at tempts to focus on a more practical and systematic approach towards the development of standardized phytomedicine / herbal formulations for liver disorders and to update the literature in the area.

In India.

More than 87 medicinal plants are used in different combinations in the preparation of 33 patented herbal formulations.[74,77] Most commonly used 12 plants in herbal formulations are giver in Table1. Only a small portion of the hepatoprotective plants as well as formulations used in traditional medicine are pharmacologically evaluated for their efficacy. Several plants were reported as hepatoprotective gators during the last decade.[78,103] Some of the polyherbal formulations are verified for their hepatoprotective action against chemical induced liver damage in experimental animals.[73,107,112] In most of these studies, marginal or moderate levels of hepatoprotective activities were observed. The efficacy is not sufficient enough to use as effective drugs.[113] Besides, most of the reported studies describe the beneficial effects of the drugs against a few hepatotoxic chemical – induced subclinical level of hepatotoxicity. It is not known whether or not these.

Plants having liver protective property against toxic chemical induced liver damage experimental animals*

Plants	**Reference number**
Acacia catechu	*25*
Achillea milefoium	*26*
Azadirachta indicia	*27*
Anrographis Paniculata	*28*
Boerhaavia difusa	*29,30*
Capparis Spinosa	*26*
Chelidonium Majus	*20*
Cichorium intybus	*26,31*
Daucus Carota	*32*
Eclipta alba	*33*
Geophilla reniformis	*34*
Glycomis Pentaphylla	*35*
Mikania cordata	*36*
Moringa Oleifera	*37*
Ocimum Sanctum	*38*
Phyllanthus emblica	*39*
Phyllanthus kozhikodianus	*40*
Phyllanthus Maderaspatensis	*41*
Phyllanthus Niruri	*42*
Picrorrhiza Kurroa	*43,45*
Ricinus Communis	*42*
Sida Cordifolia	*46*
Side rhombifolia	*47*
Swertia Chirata	*48*
Tephrosia Purpuria	*49*
Trichopus Zeylanicus	*50*
Verbena officials	*51*
Wedelia Calendulacea	*52*
Withania Somnifera	*53*

- Based on the Publication of Indian authors during 1990-1998

Drugs exhibit any beneficial effects against severe liver damage. Systematic investigations have to be done to separate the good ones from the therapeutically useless plants. Furthermore, in almost all cases the mechanism of their hepatoprotective effects remains to be studied.

The antihepatitis virus activities of the traditional plants are not studied in experimental animals except in a few plants. This is mainly due to the lack of ideal in vivo test systems. *Picrorhizha Kurroa, Glycyrrhiza glabra, Eclipta alba and Andrographis*

paniculata are reported to have activity against jaundice producing Hepatitis B virus.[73,74] *Phyllanthus amorous* also appears to be very effective against hepatitis.[111]

Only a few plants are really very promising hepatoprotective agents based on the available data. These include *P. Kurroa* (Picroliv), *A. Paniculata* (Andrographolide), *Silibum marianum* (Silymarin) [73,115,117] and *Eclipta alba*.[86]

Some of the polyherbal formulations verified for their anti hepatotoxicity against toxic chemical – induced liver damage in experimental animals.

Formulation	References number
Liv. 52	51,52
Liv. 42	21,64
Liver cure	21,64
Livol.	64,
VB.Liv.	21,64
Hepatomed	53
Jigrine	52,54
Tefroli	21,64
Stimuliv	55,
Koflet	56
Icterline	20

Some of the plants shown to have antihepatitaxicity in experimental animals by investigations in foreign countries.

Acacia Catechu
Acuba Japonica
Anacordium Oxidentalis
Aralia Elata
Arnica Montana
Artemisia Capillaries
Atracylodes lanceae
Atracylodes Macrocephata
Baeckea frutescens
Bunium persicum
Bupleurum falcatum
Cucurbita Longa
Cucurbita Pepo
Delphinium denudatum
Dianthus surperbus
Ganoderma Japonicum
Genoderma lucidum
Glycyrrhiza Glabra
Lindera strychinifolia
Linum usitatissimum
Panax ginseng
Peumus boldus
Plantago asiatica
Rauvolfia spp
Schizandra chinensis
Silybum marianum
Thujopsis dolabrata
Withania frutescens
Withania somnifera

Studies carried out in China and Japan resulted in the isolation of a hepatoprotective lignan, gomishin from the fruits of Chinese medicinal plant

Schizandra chinensis. Gomishin is used for the treatment of chronic hepatitis.115,116 Studies carried out at Tropical Botanic Garden and Research Institute (TBGRI) have shown that Trichopus Zeylanicus, Phyllanthus Maderaspatensis, and P. Kozhikodianus are extremely active against paracetamol- indicates liver damage in rat.94,103,108 A recent report indicates that fumaric acid obtained from Sida cordifilia has significant anti –hepatotoxic activity in rats.99 Ursolic acid which occurs in may plants also showed promising hepatoprotection against paracetamol and carbon-tetrachloride induced liver damage in rats.120,121 Some of the plant constituents reported to have antihepatoxic activity are given in. Even these compounds are not subjected to systematic.

Some of the plant constituents possessing hepatoprotective activity [75,76,108,119]

Andrographolide (*Andrographis Paniculata*)
Silybin (*Silybum Marianum)*
Picroside I *(Picrorhiz Kurroa)*
Picrosede II *(Picrorhiza Kurroa)*
Kutkoside *(Picrorhiza Kurroa)*
Gomishins *(Schizandra chinensis)*
Schisandrin A *(Schizandra Chinensis)*
Glycyrrhetinic *(glycyrrhiza glabra)*
Glycyrrhetinic acid *(glycyrrhiza glabra)*
Saikaosaponins *(Bupleurum falcatum)*
Sarmentisins *(sediumsarmentosum)*
Wuweizisu C.*(Schisandra chinensis)*
Catechin *(Anacardium occidentalis)*
Ursolic acid *(Eucalupus spp.etc)*
Curcumin *(Curcuma longa)*
Fumaric acid *(Sida cordifolia)*

Exhaustive studies to demonstrate their efficacy against severe liver damages caused by viruses, hepatotoxic chemicals which damage liver by different mechanisms, etc. Antioxidants can protect experimental animals and human form oxidant mediated liver damages. This effect can be seen even in certain common vitamins, spices vegetables (e.g. vitamin – E and turmeric).

Choleretic and chologague activity

More than 60 medicinal plants have been shown to stimulate secretion of bile fluid (choleric) and salt (chologogue) in experimental animals.[74]

Most of these studies were done on normal anaesthetized rodents. Therefore, these plants do not necessarily show hepatoprotection. However, potent hepatoprotetive plants such as *A. paniculata, P. Kurroa* and *T. Zeylanicus* also stimulate biliary function in normal rats.[96,103,121]

Methods of pharmacological evaluation of hepatoprotective plants

In general, the therapeutic values of drugs are evaluated in animals experimentally made sick. Detailed efficacy and toxicity studies in experimental animals should be followed by clinical trials. Detailed bio-chemical and other *in vitro* assays are required to determine the mechanism of action.

Both *in vivo and in vitro* test systems are used to assess hepatoprotective activity of herbal drugs. However, a single and simple screening method is not available to identify hepatoprotecive drugs with confidence.

In vivo models

Toxic chemicals – induced liver damage

A toxic dose or repeated doses of a known hepatotoxin (Carbon tetrachloride (CCI4), paracetamol, thioacetamide, alcohol, D-galactosamine, allaylalcohol, etc.) is administered, to induce liver damage in experimental animals. The test substance in administered along with, prior to and / or after the toxin treatment. If the hepatotoxicity is prevented or re-duced the test substance is effective.

Liver damage and recovery from damage are assessed by measuring serum marker enzymes, bi-lirubin, histopathological changes in the liver, biochemical changes in liver (e.g. hydroxyproline, lipid, etc.)[122] and bile flow. When liver is damaged liver enzymes such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and alkaline phosphates enter into the circulation. An increase in the levels of these marker enzymes in the serum is an indication of liver damage.[103] Other effects of induced liver damage such as reduction of prothrombin synthesis giving an extended prothrombin time and reduction in clearance of certain substances such as bromsulphthalein can be used in the evaluation of hepatoprotective plants.

The hepatoprotective effect of a drug against different hepatotoxins differs especially when the mechanisms of action of the toxins are deferent.[123] Therefore, the efficacy of each drug has to be tested against hepatotoxins which act by different methods.

Reduction in CCI_4 induced prolongation of hexobarbitione-induced sleeping time.

This method is used to screen anti – CCI_4 toxicity of drugs in animals.[124] Hepatotoxic chemicals like CCI_4 reduce to the levels of drug metabolizing enzymes in liver. Therefore metabolism of hexabarbitone is reduced resulting in prolongation of hexa-barbi like CCI_4 reduce to the levels of drug metabolizing enzymes in liver. Therefore metabolism of hexabarbitone is reduced resulting in prolongation of hexa-barbitone induced sleeping time. If a plant drug reduces this CCI_4 induced prolongation of sleeping time the drug can be considered hepatoprotective against CCI_4 toxicity. (Care has to be taken to see that the drug has no direct effect on drug metabolizing enzymes or narcosis).

Anti- hepatitis virus activity

At present, simple *in vivo* test systems are not available to determine anti hepatitis virus activity in rodent models. However, duck and monkey models have been introduced to test anti hepatitis B activity.[125,127] This area needs to be strengthened.

Choleretic activity

Techniques are available to collect bile by cannulating the bile duct, in anaesthetized as well as conscious animals, to study the effect of drugs on the secretion.[120,122]

Regeneration of hepatocytes

The effect of a drug on hepatocyte regeneration can be tested by surgical removal of a portion of the liver in experimental animals.(Primary culture of hepatocytes may be used to study the effect of the drug on hepatocyte multiplication *in vitro*).

***In vitro* studies**

Fresh hepatocyte preparations and primary cultured hepatocytes are used to study direct antihepatotoxic activity of drugs. Hepatocytes are treated with hepatotoxin and the effect of the plant drug on the same is evaluated. The activities of the transaminases released in to the medium are determined.[124,129] An increase in the activities in the medium indicates liver damage. Parameters such as hepatocyte multiplication morphology, macromolecular synthesis and oxygen consumption are determined. Effective antiviral assays using cell culture and PRC techniques remain to be developed.

Biochemical assays

Since, many toxic chemicals induce liver damage by inducing lipid peroxidation and / or oxidative damage to DNA and reduction in the levels of glutathione, assessment of antioxidant property is using liver homogenates, isolated liver cell membrance, DNA, etc. In the process leading to cirrhosis, accumulations of connective tissue and parenchymal regeneration are competing events. Therefore, the search for agents to prevent liver cirrhosis is, also focused on inhibitors of excessive connective tissue formation in the liver, fibrosuppressive effects by in hibitors of protein hydroxylation can be screened.[130] (The desired organ specificity has to be tested in models of liver cirrhosis and fibrosis *in vivo*).

Dietary prevention of liver damage

Dietary modifications can, to a large extent, prevent toxic environmental chemicals-induced liver damage. Most of the hepatotoxine damages. Antioxidant containing vegetables (e.g. carrot.), spices such as turmeric, vitamin E, etc. when included in the diet, can protect liver from damage, caused by oxidative mechanisms of toxic chemicals. It has been shown that carrot juice can protect mice from CCI 4 induced hepatotoxicity.[85] *In vitro* experiments have demonstrated strong antihepatotxic action of the curcuminoids present in turmeric.[76]

Development of hepatoprotective drugs

Pharmacological validation of each hepatorprotective plant should include efficacy evaluation against liver diseases induced by various agents. Efficacy of the drug against viral hepatitis as well as liver damage induced by hepatotoxic chemicals by oxidative mechanisms or other mechanisms should be determined. Further, the plant drugs have to be evaluated for their evicts on live regeneration and bile section. The same drug is unlikely to be effective against hepatic damage caused by various agents. Therefore, the most effective drugs for each kind of liver disease have to be selected by separate efficacy evaluations. To treat liver disease of unknown causes or multiple causes, a combination of different herbs containing extracts or active fractions (or purified compounds) with activities such as antihepatotoxic anti hepatitis viruses, choleretic and stimulation of hepatocyte regeneration has to be developed. The same treatment may not yield positive results in both severe and mild liver damages. In the case of severe liver damages most of the liver cells would have died and / or fibrotic changes would have occurred. Therefore, the formulation should cantain in addition to the therapeutic agents, potent agents which can regenerate the liver by stimulating the surviving cells to proliferate. As mentioned earlier, may antioxidants can protect liver from oxidative damages. However, these antioxidants, alone can not serve as satisfactory drug to treat severe liver diseases and this has to be included in polyherbal formulations or multidrug therapy. The curative potentiality of polyherabal formulations containing.

Scientifically validated plants / extracts has to be tested again in the formulation form against severe and moderate liver damages caused by diverse agents. The curative as well as preventive potentialities of the drugs have to be evaluated. Special formulations containing immunosuppressive herbs may have to be developed to treat auto-immunity induced liver disorders.

Toxicity determination

If the product of a plant has been raditionally used without any known harmful effects, detailed toxicological studies may not be essential. However, when purified fractions (Polyherbal formulations) are used, toxicity studies are required. Both acute and long-term toxicity studies are to be done in accordance with WHO guidelines.

CONCLUSION

The goal of ethnopharmacological studies on medicinal plants should not be restricted to find new prototype pure compounds as drugs. Active extracts, fractions or mixture of fraction / extracts may prove very effective drugs. Plant drugs (combinations or individual drug) for liver diseases should possess sufficient efficacy to cure severe liver diseases caused by toxic chemicals, viruses (Hepatitis B, Hepatitis C, etc.), excess alcohol intake, etc. a single drug cannot be effective against all types of severe liver diseases. Effective formulations have to be developed using indigenous have to be developed using indigenous medicinal plants, with proper pharmacological experiments and clinical trials. The manufacture of plant products should be governed by standards of safety and efficacy.

Natural Medicine and Hepatitis C

ARTICHOKE (*Cynara scolymus*)

The artichoke has a long folk history in treating many liver diseases. Recent evidence supports this longtime use. The active ingredient in artichoke is cynarin. This compound is found in highest concentrations in the leaves.

Cynara extract has demonstrated liver protecting and regenerating effects, and promotes the outflow of bile from the liver to the gall – bladder. This is very important because if the bile is not being transported adequately to the gallbladder, the liver has an increased risk of being damaged.

ASTRAGALUS (*Astragalus memebranaceus*)

Astragalus is a large genus in the pea family, some species of which are toxic to livestock (Locoweed of the American Southwest is an Astragalus). But the toxins are only in the above- ground parts, and this tonic comes from the root of a now-txic Chinese Species Memaranaceus.

The plant is a perennial with long, fibrous roots, Chinese pharmacies sell bundles of thin root – slices that in both wild and cultivated forms. Chinese pharmacies sell bundles of thin root-slices that resemble tongue depressors and have a sweet taste. These are simmered in medicinal soups, the slices being removed before serving because they are too tough to chew. Chinese pharmacies also sell many preparations of Astragalus, both singly and in combination with other herbs.

Practitioners of traditional Chinese medicine consider astragalus a true tonic that can strengthen debilitated patients and increase resistance to disease in general. In contemporary Chinese medicine, it is also a chief component of zheng fu therapy, a combination herbal treatment designed to restore immune function in cancer patients undergoing chemotherapy and radiation therapy. Research in china has demonstrated increased survival in-patients receiving both herbal and Western therapies, as well as protection from the immunosuppressive effects of the latter. Studies in the West confirm that astragalus enhances immune function by increasing activity of several kings of white blood cells and boosting production of antibodies and interferon, the body’s own antiviral agent.

If you feel you lack energy and vitality, have depressed immunity, nag get too many colds, consider going on a course of astragalus. Follow dosage recommendations on labels.

DANDELION (*Taraxacum officinal*)

The name dandelion is sometimes loosely applied to other milky sapped weeds with fluffy yellow flowers. But true Dandelion is that ubiquitous weed growing prolifically in millions of lawns, backyard ans postures throughout America. This perennial herb has deeply cut leaves forming a basal rosette in the spring and flower heads born on long stalks. All leaves and the hollow flower stems grow directly from the rootstock. The creator of the comic strip "Marvin" once had his adorable diapered hero surveying a clump of dandelions and then thinking to himself, "Dandelions are Nature's way of giving dignity to weeds!"

The late naturopathic physician, john Lust stated in his Herb book that dandelion root is good for all kinds of liver problems, including hepatitis, cirrhosis, jaundice and toxicity in general, as well as getting rid of gallstones. Bring 1 quart of water to a boil, reduce heat to low and add about 20 tbsp. Of fresh dandelion leaves, stems and clean, chopped root. Simmer as long as it takes for the liquid to be reduced you just a pint, then strain. Take 3 tbsp. Six times daily, Dr. lust recommended.

For those desiring something more convenient in capsule form, there is the nick AKN formula from Nature's way, which contains considerable dandelion root and other cleansing herbs. It can be obtained from any local health food store.-

REISHI / SHITAKE MUSHROOMS

In the orient, Reishi is considered a FU ZHEN herb (immune modulation). Presently, Reishi has various applications including lowering or raising blood pressure, stimulating liver actions, blood cleansing, and acting as an adaptogen in helping the body fight the effects of stress.

Chinese herbalists prize it for its abilities to regenerate the liver. In high doses, and to some degree normal doses, Ganoderma maybe classified as a liver detoxicant and protectant. Toxicity studies show no toxic effects on humans. In research, patients are given much higher doses, as high as 10 grams of extract per day, with no ill effect.

The potency of Reishi mushrooms is usually based on its level of triterpenoids. One can determine the level of this by tasting it.

The more bitter it is, the higher the level of triterpenoids.

Because Reishi is a polypore, (a group of hard, woody, bracket –like mushrooms) it is not eaten, but cut into pieces and made into a tea. In China, the average dose is 3 to 5 grams a day. Other popular forms of delivery are the water / alcohol extracts and powders. –

ECHINACEA (*Echinacea Purpurea*)

Knowledge about many of the popular medicinal plants from North America in common use today derives from the Native Americans. Many tribes had thousands of years of direct experience with Herb's. in their culture, and in later early American – European culture, several of these Herb's are of special interest – but especially herbs from the genus indigenous only to North America, Echinacea.

Many Native American tribes had a substantial Pharmacopoeia, and some used herbs and other internal medicines extensively. In the early days of European colonization of the North American continent, native peoples were known to share their considerable skill with the Europeans, who generally were in need of medicines, due to the difficulty of transporting official drugs across the Atlantic. Of all the indigenous medicines introduced by Native Americans, ECHINACEA may be one of the most important.

Echinacea seems to have been used as a remedy for more aliments than any other plant. " Meyer, the German Jay physician who first introduced **ECHINACEA** to the medical profession, learned of its healing virtues from Native Americans (Possibly the Pawnee or Omaha) living in Nebraska at the time. Most of the information's we have on the ethnobotany of Echinacea.

The important constituents, from a pharmacological perspective, of Echinacea can be divided into seven categories: 1) polysaccharides; 2) flavonoids;3) caffeic acid derivatives; 4) essential oils;5 polyacetylenes; 6) alkylamides; and 7) miscellaneous chemicals.

Echinacea both exerts a mild direct cortisone-like effect and enhances the secretion of adrenal cortex hormones. The polysaccharide portion appears to be responsible for the direct anti-inflammatory effects although the alkylamide fraction has also demonstrated some activity.

Echinacea contains a diverse range of active components affecting different aspects of immune function. To fully appreciate Echinacea's effect, it is important to understand some aspects of the immune system.

The immune system is perhaps one of the most complex and fascinating systems of the human body. The immune system's prime functions are protecting the body against infection and the development of cancer. The immune system is composed of the lymphatic vessels and organs (thymus, spleen, and lymph nodes), white blood cells (Lymphocytes, neutrophils, basophils. Eosinophils, monocytes, etc,) specialized cells residing in various tissue (macrophages, mast cells, etc.) and specialized chemical factors, like complement, interferon, and interleukin.

CLINICAL APPLICATIONS

Echinacea has long used clinically for conditions where its pharmacological actions have proven efficacy, especially in infections. Clinical studies have demonstrated effectiveness in a number of infectious conditions. Although many of the studies have utilized injectable preparations, oral preparations are generally thought to yield similar or even better results.

Test tube studies conducted in Germany showed that purified extract from Echinacea stimulate T-cells and macrophages and may have anti-viral properties.[131]

Tthe clinical trial in Germany, fifteen patients with colorectal cancer were injected with 60 mg/square meter of body area of Echinacea (a purified extract of Echinacea) and thymostmulin after initial treatment with cyclophosphamide, an immunosuppressive drug.[132] Tumor regression was not d in two patients after two months of therapy, and disease, stabilized in is x others. (This stabilization was possibly part of the natural course of the disease, however.) Echinacea was also reported to have stimulated macrophages to release chemical messengers such as TNF-a (Tumor Necrosis factor-alpha), IL-1 (Interleukin-1) and interferon beta (IFN-b). This and other studies[133] also noted that Echinacea may have helped increase the number of CD4 cells relative to CD8 cells within three days after cyclophosphamide treatment.

An additional study found that the administration of Echinacea extracts to people stimulated cell mediated immunity after a single dose, but that repeated daily doses suppressed the immune response.[134] injections of purified Echinacea are believed to be relatively non-toxic, even at high doses,[135] although there are reports of skin rashes and insomnia.[136]

Unfortunately, few clinical trials have been performed using either injected polysaccharides or oral, over-the-counter Echinacea supplements which are the most common form of this remedy. Therefore, the effects and ideal dosing of this remedy are unknown.

GARLIC

Garlic is a natural antibiotic. It protects the body from infection detoxifies the body, strengthens blood vessels, and lowers blood vessels. Garlic contains a natural antibiotic, antifungicid, and has many antiviral properties.

Garlic has been used for many medicinal purposes in folk and holistic treatment for heart disease, hypertension, and heavy metal toxicity and is now being looked at for immunotherapy. A review of the literature on garlic appeared in The Journal of the National Medical Association. The clinical and basic studies suggested a broad spectrum of potential uses.[137]

Animal models have demonstrated that garlic may be a non-specific biologi C response modifier.[138] Some researchers have postulated that garlic works as an antioxidant against free –radicals because of its germanium and selenium content.[139]A 1951 study in Science described how mice injected with cancer cells died within sixteen

days, but when mice were treated with garlic extract no deaths occurred in the mice for six months.[140]

Claims of garlic's effectiveness against AIDS- related opportunistic infections are based on test tube studies that showed garlic was an anti- bacterial,[141,142] and anti-fungal agent.[143,144] There have been no studies as yet that have looked at garlic closely for its uses with immunomodulation, but protocols are constantly being written and submitted by community researchers and activists.

Toxicity with garlic usage occurs when too much raw garlic is ingested. The high sulfur content can cause dermatitis; and colitis occurs by an overkill of the normal flora in the gut. In high doses, garlic also may inhibit blood clotting and interfere with proper thyroid function.

HERBA ABROTANI

To stabilize cellular immune functions, one should try to treat with Herba abrotani tea (3 days a week 250 ml containing 10 mg Herba abrotani tea for 60 days).

Herba abrotani is an empiric immunomodifier. The Herba abrotani tea may be considered to be a safe possibility to reduce immunosuppression-induced infectious diseases like in Hepatitis C – Patients.

LICORICE ROOT (*Glycyrrhiza Glabra*)

Studies have shown a component of licorice to be effective in treating viral hepatitis, particularly chronic active hepatitis.

This is probably due to its well-documented antiviral activity. A Glycyrrhizin-containing product is widely used intravenously in Japan for the treatment of hepatitis.

If licorice is used over a long time it is necessary to increase the intake of potassium rich foods.

Glycyrrhizin is a substance isolated from the root of the licorice plant (Glycyrrhiza radix). It is widely used in Japan and is reported to have benefits in the treatment of chronic hepatitis B. Some studies suggest that glycyrrhizin may have anti – HIV properties[145] and may enhance the production of natural killer cells and interferon.[146]

Japanese researchers recently studied the effects of a glycyrrhizin compound called Stronger Neo-Minophagen C (SNMC) in 42 HIV – seropositive hemophiliacs.[147] Participants were randomized to dose regimens of either 100 to 200 ml or 400 to 800 ml administered intravenously daily for the first three weeks and every second day for the following eight weeks. Absolute CD4 counts and CD4/CD8 ratios were unchanged, but " Complete recovery in liver dysfunction," a major problem in HIV-positive hemophiliacs, was reported. The authors conclude that HIV- infected hemophiliacs with impaired immunological ability and liver dysfunction be given prophylactic treatment with SNMC to prevent their conditions from worsening.

At the IX International Conference on AIDS in Berlin, two small, non-randomized studies of glycyrrhizin in asymptotic HIV – positive individuals suggested some benefits to the treatment.[148,149] However, these studies, both of which were conducted in Japan, are difficult to analyze or draw conclusions from, due to the small size and the extremely limited data that were published.

There are reports of glycyrrhizin causing high blood pressure, water retention, and possibly heart complications when taken in very high doses..[150]

BARBERRY (*Berber is vulgaris*)

Known active constituents are Alkaloids – berberine, oxycanthine, palmatine, columbarine, chelidonic acid, tannins

Action are cholagogue, choleretic, bitter, antimalarial, antiemetic, immunostimulant, gut antibiotic.

Medicinal uses are Cholecystitis, cholelithiasis, Biliary infection, constipation, Splenic enlargement, Debilitated condition, marked by poor digestion, e.g., history of alcohol/diet, abuse, or suffered from excessive exposure to drugs, chemicals or industrial pollutants. Inflammatory bowel disease.

Caution: Avoiding pregnancy

Dosage: 1;2 liquid extract 0.5 – 1ml tds 7f

BUPLEURUM (*Bupleurum falcatum*)

Parts used: Root

Known active constituents: Saikosaponins.

Actions: Anti inflammatory, hepatoprotective, hepatic mild sedative, adaptogen, antitussive.

Dosage 1:2 liquid extract 1.5 –3 ml tds

Medicinal uses: Chronic Hepatitis . Hepatomegaly with pain in the upper right quadrant splenomegaly . Chemical liver damage . Liver stasis or liver congestion . Depression . Irregularmenstuation

prostaglandin (PGE2) production. Protects the liver against toxic liver damage. Improves It Increases protein synthesis in the liver .Reduces inflammation by inhibiting liver function after 2-3 months treatment. Clinical trails show it can reduce or remove HBe AG. In 1994 767% of patients with HCV improved in short term on Xiao Chai Hu Tang (Minor Bupleurum and Gan Yan Chong Ji (China).

Caution: It may increase bowel movements and flatulence (wind).

GREATER CELANDINE (*Chelidonium majus*)

Known active constituents: Isoquinoline alkaloids (chelidonine, sanguinarine, chelerythrin, protopine) bitter substances, essential oil.

Actions: Cholagogue, Laxative, diuretic, bitter, spasmolytic to gallbladder and bronchi.

Medicinal uses: Hepatitis (stitch in the liver ,pain radiating to shoulder areas and headaches). Gallstones, conditions involving gall bladder and bile ducts. Intestinal Putrefaction.

It Improves the detoxifying functions of the liver and bowel clearance. Stimulates the secretion of bile and pancreatic juices. Reduces spasms.

Dosage: 1:2 liquid extract 0.35-0.75 mL tds

Cautions: large doses are toxic.

GLOBE ARTICHOKE (*Cynara scoymus*)

Parts used: leaves

Known active constituents: Bitter sesquiterpene lactose – cynaropicrin, flavonoids, coumarins, phenolic acids, cynarin

Actions: Biter tonic, choleretic, cholagogue, diuretic, hepatoprotective, hepatic trophorestroative.

Medicinal uses: liver diseases, jaundice. Liver damage, fatty degeneration of the liver. Chronic constipation. High cholesterol and triglycerides, kidney stones. Sluggish digestion, nausea, anorexia. Chronic constipation. High cholesterol and triglycerides. Arthritis.

It increases bile flow from the liver. Stimulates anti toxic activity of the liver. Lowers plasma cholesterol. Stimulates urine flow.

Dosage: 1:2 liquid extract 0.75-1.5 mL tds

DESMODIUM *(Desmodium ascenders*)

Family: Papillonaceae
Parts used: Non flowering parts, stems and leaves, harvested after flowering.
Found: In Southern Sierra-Leone, North of Liberia in the equatorial forests of Africa.
Actions: hepatoprotective, hepatorestorative, antihepatotoxic, antiallergenic, anti-inflammatory.

Medicinal uses: Viral hepatitis, toxic hepatitis – accidental or due to drug addiction hepatic lesions of alcoholic origin, hepatic lesions due to chemotherapy, autoimmune diseases – asthma, allergies, cirrhosis prevention, nausea, fatigue, loss of appetite, rapid disappearance of ictus and asthenia (between 2 and 7 days).

Desmodium without any toxicity, does not work by antiviral action, but by regenerating and protecting the hepatic cells. It has a protective effect against lysis of the hepatocyte. It can lead to the normalization of transamnases and the prevention of cirrhosis by alleviating anti-inflammatory attacks. Toxic hepatitis generated by carbon tetrachloride is much better tolerated when Desmodium ascenders is administered.

Direction for use: Acute hepatitis. All varieties of viral hepatitis. Boil 8-10 grams of the dried = plant (without roots) for approximately 15 minutes in 1.5 liters of water. Filter. Drink decoction within 24 hours. If treated early in the disease, a normalization of transaminases can occur in 1-6 weeks, disappearance of ictus, and a return to the general state of health. Toxic hepatitis, Accidental or de to drug addiction. Same preparation and dosage as above. Prevention of hepato – digestive side effects of chemotherapy ……..> 2 days prior and 5 days after chemotherapy, 7-8 grams of the plant in decoction as above every day.

ST.JOHN,S WART (*Hypericum perforatum*)

Parts used: Above ground parts

Known active constituents: Hyericin, pseudo – hypericin, flavonoid, tannins, resin, essential oil, zanthones

Actions: Antidepressant, antiviral/ antirectroviral, diuretic, antineoplastic

Medicinal uses: HIV, Hepatitis B and C, herpes, depression, anxiety, stress, diarrhoea, gastroenteritis, sciatica, headaches.

Scientific research demonstrates a potent activity against retroviruses (HIV, human immuno deficiency virus) and enveloped viruses (Hepatitis B, C not A), herpes family of viruses, influenza, togaviruses. Inactivates human retroviruses (HIV). Interferes with the assembly or processing of viral components by an infected cell thereby reducing the production of mature viral particles. Reduces fluid retention and hastens the elimination of toxins in the urine. Zanthones inhibit Mono-amine oxidease (MAO) enzyme systems.

Dosage: 1 : 2 High Grade liquid extract 0.75 –2 mL tds

CHAPARRAL (Larrea mexicana)

Parts used: Leaves

Known active constituents: 8% LIGNAN NDGA – nor-dihydroguaretic acid (one of the best natural antioxidants known)

Actions: antioxidant, anticancer, anti-inflammatory 7F

Medicinal uses: cancer, chemotherapy (Synergistically). It is 5 lipoxygenase inhibitor. Inhibtor of anaerbic glycolysis which the cancer cell relies on for energy.

Dosage: 1:2 liquid extract 0.5-1 .25 mL tds

Caution: May cause hepatitis. May stimulate tumour growth. Five cases of acute or subacute hepatitis following the ingestion of chaparral (Larrea tridenta) capsules or tablets have been reported. (Herbal Gram No. 28, 38,1993) No compounds thus far discovered in chaparral are noted for their hepatotoxicity.

PICORRHIZA (*Picrorrhiza kurroa*)

Parts used: Root

Known active constituent:s Iridoid glycosider (Picrosider I, II, III and Kutkoside) Cucurbitacin glycosides (Bitterness of root)

Actions: Hepatoprotecive, anti-inflammatory, anti allergic, immunostimulant, bitter tonic, choleretic.
Medicinal uses: Viral liver disease especially Hepatitis B Virus. Toxic liver infections. Acute and chronic infections weakened immunity. Auto-immune disease. Asthma, Vitligo. Fevers.

It mops up free radicals (antioxidant). Boosts all aspects of immunity (T lymphocytes, B Lymphocytes) and phagocytes. Causes a rapid fall in bilirubin levels and quicker recovery in infective hepatitis. Increases protein synthesis in the liver. Has marked anti-Hepatitis B surface antigen activity.

Dosage: 1:2 liquid extract 0.3-1.4 mL tds

Cautions: Large doses can cause diarrhoea, flatulence, flatulence, griping, skin rash.

PHYLLANTHUS (*Phyllanthus amorous*)

Parts used: Leaves or herb

Known active constituents: Lignans – Phyllanthin and hypo-phyllanthin, flavonoids, alkaloids and invitro antiviral agent geraniin (tannin).

Actions: antiviral, hepatoprotective, hypoglycaemic.

Medicinal uses; Viral liver diseases including acute hepatitis and chronic persistent hepatitis. Jaundice. Diabetes.

It Inhibits DNA polymerize (the enzyme that Hepatitis B- like viruses need for replication of the virus). Lancet 1988 –59% days. Up to 9 months later HBs Ag had not returned. Inhibits HIV reverse transcrptase in vitro.

Dosage: 1:2 liquid extract 0.75-2 mL tds higher end of dose for acute states

SCHISANDRA (Schisandra chinesis)

Parts used: Berries

Known active constituents: Lignans – schizandrins

Action: bacteriostatic, hepatoprotective, cardiotonic, sedative.

Medicinal uses: chronic hepatitis with elevated serum transaminase. Liver damage. Fatigue. Night sweats. Insomnia. Excessive stress. Forgetfulness. Heart palpitations. Chronic diarrhoea.

It improves protein synthesis in the liver. Elevates liver microsmes which increases the liver's ability to detoxify foreign substances in the body. Stimulates central nervous system. Accelerates repair of liver function.

Dosage: Decoction 3-9 gram/ day 1:2 liquid extract 1.25-3 mL tds.

MILK THISTLE (*Silymarin*)

Milk Thistle (Silymarin) is reported to be an anti –inflammatory and mast cell stabilizer that helps protect the liver against toxin, drugs, and the affects of alcohol (Better Nutrition for today's Living, March 1993). It would be interesting to find out if any has tried Milk Thistle and noticed any improvement.

FAMILY: Composite (Composite)
GENUS: Silybum
SPECIES: Marianum

COMMON NAMES: Marian Thistle, St. Mary's Thistle, Our Lady's Thistle

IDENTIFICATION:

An annual or biennial herb growing up to 6 feet tall, milk thistle has coarse, lobed, prickly-edged leaves streaked with conspicuous white veins. Crimson to reddishviolet flowers (May-June) are borne in solitary heads, 2 inches across, surrounded by prominent, spiny bracts.

USES:

The seeds, fruit, and leaves of milk thistle (Silybum marianum), a plant native to Europe, have used since the Roman times as a live tonic. Also known as Marian, is now widely used for liver disorders. In numerous clinical studies, silymarin has been shown to have therapeutic effects in treating several types of liver ailments such as cirrhosis, chronic hepatitis, chronic hepatitis, and fatty infiltration of the liver.

Biopsies and laboratory studies have demonstrated that silymarin protects the liver from the damaging effects of alcohol and toxic chemicals and stimulates the production of jew liver cells to replace damaged ones. Silymarin may also help prevent or treat gallstones by increasing the solubility of the bile, and provides an antidote to the death cap mushroom (Amanita phalloides), which kills its victims by destroying liver cells. The standard dosage of milk thistle extract based on 70-80 percent silymarin content is from 70-210 milligrams three times daily. Milk thistle extracts have shown very low toxicity, even taken over a long time.

- Protects liver cells from solvent damage (alcohol & carbon tetrachloride)
- Protects liver cells from liver poisoning
- Acts as an antidote to death cap (A.Phalloides) mushrooms
- Stimulates production of new liver cells.
- Helps skin conditions related to poor live function.
- Fights pollutants and inhibits free- radical damage.
- Slows the advancement of liver Cirrhosis
- Perhaps helpful in treating Hepatitis B

CONTAINS:

Several flavonolignans, including silybin, isosilybin, dehydrosilybin, silydianin and silychristin.

Brief Report on Chinese Herbal Medicine

Trial for Hepatitis C

And a Chinese Herbal Formula

The John Hunter hospital has now completed its trial of herbal medicine therapy for Hepatitis C. This was a placebo controlled trial of a tablet form of herbal extract for patients presenting with hepatitis C. there were 16 herbs in the tablet preparation and the proportions of the herbs used will not be here, some of the herbs include Salvia, Paeonia and Ginseng root.

We took into the trial, patients who had not been treated with Interferon or patients who had relapsed following treatment with Interferon, There were no other strict entry criteria apart from them having a definitive hepatitis C antibody and abnormal liver function test on at least 3 occasions.

Patients were treated with 5 tablets 3 times daily with either the active tablet or the placebo and a small number of patients who, at the end of six months of treatment on placebo, requested it, and they too received active tablets for a further 6 months. Our analysis, therefore, includes all patients treated blind plus a small number who were treated, knowing that they were receiving the active tablet after their initial placebo treatment.

None of the patients had any severe adverse side-effects although two patients withdrew from the trial because of side-effect symptoms one of whom complained of palpitations which stopped on ceasing the tablets and one of whom had significant bowel symptomatology in the form of diarrhea and bloating.

Overall, we found that compliance with the tablets was good.

Our results to date show there were no effects of the medication on haemtoloical parameters and that there was a fall in ALT in patients on active treatment. Six patients normalized their ALT during the treatment period but we have no evidence that nay patient has been cured by the herbs.

At this stage of our analysis, it would appear that the medication has certainly done no harm and may well be offering some opportunity of minimizing inflammation in the liver of patients with hepatitis C. We need to do more detailed analysis or the results or the results at this stage and I could certainly not recommend the present combination of herbs as the ultimate management for hepatitis C.

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CHINESE HERBAL FORMULA

NOTE:

Most of these herbals have some known anti-viral properties, but these are huge doses. Please research this and check with your Dr and practitioner before trying this, as they may be harmful to some. Herbal doesn't mean non-toxic. Also, I believe 'cure' means the same thing as ' responder' with IFN, i.e.; there are normal left's or pcr, but no decrease in disease progression. I have not seen one case or heard of one case of ' cure' but suspected long term remission has been achieved by some methods.

In a report in the Chinese Journal of integrated Traditional and Western medicine (1994), a claimed rate of cure of 56% with most other patients showing improvements, was obtained when the following formula was administered to treat hepatitis C:

Astragalus:	30 grams
Salvia:	30 grams
Forsythia:	30 grams
Red peony:	30 grams
Ho-shou-wu:	15 grams
Crataegus:	15 grams
Crataegus:	15 grams
Moutan:	15 grams
Gardenia:	15 grams
Dandelion:	15 grams
Bupleurum:	10 grams

The herbs are decocted and the amount indicated here is taken in two divided doses each day, for three months. The formula can be modified to address specific symptoms by adding additional herbs (e.g. for pain in the liver area, loss of appetite, or abdominal distention). As with treatments for hepatitis B, the formula contains herbs for treating damp-heat (forsythia, gardenia, dandelion, and bupleurum), blood stagnation (salvia, red peony, crategus, moutain), and deficiency of qi and blood (astragalus and ho-shou-wu).

Due to the long course of therapy, one may wish to subsitutrate dried extracts: a dose of three teaspoons (9grams), three times daily of this formulation should produce similar response [about 27 grams per day of dried extracts is roughly equivalent to a decoction of 160 grams of crude herbs, somewhat less than is recommended in the above clinical trial; the patient cost of this treatment is about $500 per three months course]. Some patients may experience loose stool or diarrhea in response to this therapy (e.g. ho shou wu, gardenia, and dandelion can act as laxatives), thus one may nee to adjust the formulation somewhat if this reaction occurs and persists. It is not known if good results can be obtained by substituting powdered herbs for the extracts. If one wished to substitute tablets (which are comprised mainly of powdered crude herbs), Salvia Shgou Wu contains the salvia (extract), astragalus, Crataegus, ho-shou-wu and red peony, while Nuphar 14 contains the moutan, bupleurum, and gardenia, as well as additional salvia, and Red Peony Tablets contains the dandelion and forsythia, as well as some additional red peony (extract),. The use of these tablets will result in less relative dosage of the

herbs than in the decoction formula, but there are additional herbs that would be expected to support their actions. One might consume three tablets of each formula each time, three time daily [total: 27 tablets per day; patient cost is about$300 per three month course]. Using the tablets, one would expect to need a somewhat longer therapy than the higher dose decoctions or granules. The dose of one or more of the formulas could be increased (e.g. to four tablets each time), if desired.

Until clinical work with hep;C and Chinese herbs is carried out in the United States with available materials that are in a form suitable for administration, it may be difficult to convince medical practitioners and patients to try this method. Because the herbs are non-toxic, some patients may wish to utilize this therapy in place of, or in addition to, treatment by interferon. It is reasonable to begin collecting information from such patients to provide case histories in an effort to eventually develop a clinical trial.

OTHER CHINESE HERB THERAPIES FOR HEPATITIS C

Chinese medical treatment is often based on the model of treating hepatitis B.

Even though the viruses are quite different, the fact that the diseases are caused by viruses that ultimately damage the liver remains the same, and the herb therapies are thus similar in nature at least until further diagnostic information is available. Hepatitis B is treated by herbs for the traditional categories of pathological disturbance labeled as damp-heat, qi and blood stasis, and for qi, blood, and yin deficiency.

Herbs are also given according to specific manifestation of the disease and underlying constitutional factors. Chinese tonic herbs have been shown to enhance interferon production and thus may substitute for interferon therapy (six months of alpha interferon infections is the standard procedure). Use of exogenous alpha interferon is often unsuccessful and, sometimes, there is a rebound of hepatitis C viremia after apparently successful treatment with this drug.

Herb therapy provides its effects through more mechanisms of antiviral action than simply increasing interferon, and it can be pursued for a longer time, due to absence of substantial side-effects. Cures for hepatitis B have been repeatedly reported in the Chinese literature and are accomplished by administering non-toxic herbs and vitamins.

ITM is currently involved in evaluating a formulation for treatment of hepatitis B in China. A related protocol, being used in the U.S., is to consume 9 tablets of the Seven Forests Eclipta Tablets (or 4 of the larger tablets of White Tiger Baicalcumin) and 1 tablet of the White Tiger Quercenol each time, three times daily for 12 weeks; favorable responses for hepatitis B have been informally reported to ITM from both the American cases and the initial Chinese research with 40 patients).

Other studies reported in the Chinese medical literature.

The details of the treatment were not specified. Patients were given different formulas according to presentation of constitution and symptoms; typical herbs used included smilax, scute, dictamnus, salvia, epimedium, loranthus, and lycium fruit. Inosine and vitamins were also given orally. It was claimed that 20 of the 33 patients (60.6%) so-treated were cured.[151]

The patient selected for treatment were suffering from aplastic anemia and had probably become infected by hepatitis C as the result of blood transfusions. The patients were treated according to different diagnosis, with high-dosage herb combinations. As an example, for patients with symptoms such as pallor, lassitude, anorexia, nausea, abdominal fullness, and thins stools, the prescription included.[152]

25 grams pseudostellaria,
25 grams astragalus,
10 grams citrus, 10 grams tang-kuei,
12 grams cardamon,
20 gams peony,
20 grams bupleurum,
25 grams polygonatum,
20 grams coix,
20 grams plantago seed.

Patients also received intravenous vitamins and other nutrient factors.

Among 21 patients with hepatitis C, 17 were reprotedly improved by the treatment, but only 3 were said to be cured.Patients who had a history of blood transfusion and who tested positive for hepatitis C were divided into two groups; the control group received alpha-interferon and the herb group received herbal decoction (depending on presenting symptoms and signs). As an example, for those classified as presenting liver qi stagnation and spleen deficiency, the formula was,[153]

15 grams bupleurum,
12 grams hoelen,
10 grams atractylodes,
10 grams codonopsis,
10 grams peony,
6 grams chih-ko,
6 grams gardenia,
6 grams curcuma,
5 grams licorice.

For those classified as having accumulated heat toxin, the formula was:

15 grams lithospermum,
15 grams hu-chang,
15 grams forsythia,
12 grams scrophularia,

12 grams gardenia,
10 grams raw rehmannia,
10 grams mountan,
10 gams red epony,
6 grams curcuma,
5 grams licorice.

Other herbs might be added to these base formulas for treating specific symptoms. Among the 32 persons treated by herbs, 4 were cured and 25 others were improved. With the alpha interferon, 2 of 32 patients were cured, and 19 others were improved.

CHINESE HERBAL MEDICINE IMPLICATED IN LIVER FAILURE

Another case of acute hepatitis and liver failure linked to consumption of the Chinese herbal medication, ma-huang, has been reported by clinicians at the University of California at San Francisco (UCSF).

A 63- year-old Chinese woman developed fulminant liver failure requiring transplantation following the use of the mixture of 12 plant species. She was one of three people who presented to UCSF with acute hepatitis associated with Chinese herbal medications during a two month period.

"The patient transplanted did not have a history of chronic liver disease nor alcohol consumption, "Eric M. Yoshida and colleagues from UCSF wrote[154] "Viral studies, however, revealed seropositivtiy for hepatitis B surface antigen and hepatitis B core antibody (HbcAb) IgG: serum hepatitis B virus DNA was 511."

Lake et al. Noted that serology for HbcAb IgM was negative. Serologies for hepatitis C, hepatitis A IgM, and hepatitis D, likewise, were negative.

When first admitted to the hospital, the woman was notably jaundiced and encephalopathic with no stigmata of chronic liver disease, and initial clinical impression was a fulminant viral hepatitis. A history was taken and the woman acknowledged taking the Chinese herbal medication mahang for a one-week period four weeks before admission.

Coagulopathy, jaundice, and encephalopathy progressively worsened requiring endotracheal incubation. Liver transplantation was performed and gross inspection of the explained liver revealed marked collapse and very small regenerative nodules. Histologic examination of the explant revealed massive centrilobular necrosis with periportal bile ductular proliferation and inflammation.

The UCSF cases are not the first to implicate ma-huang in the development of acute hepatitis and liver failure. In 1996, Nadir et al. Also reported such a case.[155]

"Our transplanted patient would have had a fatal outcome, which is infrequently reported, had an allograft not been available," Yoshida et al. Wrote.

"The recent experience at UCSF demonstrates that liver injury from traditional Chinese medicines does not always resolve, and urgent transplantation may be required. It remains to be seen whether or not the recent cluster of cases at UCSF represents a trend that grows with the increasing use of 'alternative' medicines."

OTHER OPTIONS FOR TREATMENT OF HEPATITIS C

The continuing search for more effective modes of therapy for hepatitis C viral (HCV) infection bears witness to the imperfection of current therapy. Although the ultimate therapeutic goal continues to be eradication of all detectable virus, there is a grudging, growing realization that in many patients, this goal is difficult or impossible to achieve. Accordingly, other important and useful goals are being perused, including, (1) diminution of virus levels in the blood and risk of infectivity, (2) diminution in the activity of hepatic inflammation, (3) diminution of the rate of progression of hepatitis fibrosis, and prevention or delay in the development of cirrhosis and hepatocellular carcinoma.

Several approaches to management of chronic hepatitis C, beyond interferons or Ribavirin, have been tested, and the current status of the major approaches is summarized below.

Iron Reduction

It has been known for many years that iron is an element required for replication of virtually all organisms, including virulent microorganisms. Patients with infections or other inflammatory conditions have decreases in serum iron concentrations, due largely to the effects of inteerleukin-1, an important mediator of the inflammatory response.This hyperemia is a host defense mechanism that helps to limit infection. Although the effects of iron and limitation of its availability have been studied mainlyin bacterial and fungal infections, there is evidence for similar effects in viral infections as well. A role for iron influencing the natural history of viral hepatitis was emphasized by Blumberg and colleagues more than 15 years ago. They observed that patients with hepatitis B viral infection with higher serum iron or ferritin levels had greater likelihood of development of chronic infections than those with lower levels, who more often resolved their infections spontaneously. Several other groups have reported that larger stores of hepatic iron are positively associated with progression of hepatic fibrosis/ cirrhosis and hapatocellular carcinoma in patients with chronic hepatitis B.

Increases in levels of serum ferritin, iron, and transferring saturation also have been noted with high frequencies in patients with chronic hepatitis C 2 and the higher levels, in general, been associated with lesser likelihood of response to interferon (IFN) therapy. For example, in nine different studies involving 434 patients, the levels of serum ferritin have been lower in complete responders to IFN than in non complete responders. Elevations of serum ferritin or transferring saturation in such patients is not usually associated with hepatic iron overload. Nonetheless, complete responders to IFN have on average, lower hepatic iron concentrations than do noncomplete responders. In addition, lack of stainable iron in nonparenchymal cells (especially endothelial cells in portal tracts) has been associated with greater likelihood of complete response of chronic hepatitis C to therapy with IFN. (2) Indeed, the presence of portal iron deposits was as strong a discriminator of response as viral genotype or the level of viral RNA in serum..

Hayashi and colleagues reported that iron reduction alone, by repeated venesection, led to significant improvement in serum alanine aminotransferase (ALT) levels in chronic hepatitis C.

Indeed, the levels became normal in 5 of 10 subjects studied. This was confirmed in 12 additional studies involving a total of 306 patients. In addition, in some, iron reduction alone led to a modest, albeit usually not statistically significant, decrease in serum levels of HCV RNA. Addition of IFN after iron reduction led to further and larger decreases in serum HCV RNA levels and to significant improvement in biochemical and virological responses. Of particular interest is a recent study in which previously untreated patients received IFN alone or IFN after iron reduction. A total of 29 percent (6/21) of the former but 59 percent (10/17) of the latter had a complete biochemical response, and this was sustained in 29 percent (5/17) versus 5 percent (1/21) for more than 6 months after therapy was discontinued. Clearly, these results need confirmation in a large multicenter trial. Although the mechanisms underlying a beneficial effect of iron on chronic hepatitis C remain unclear, there is experimental evidence for the following. (1) nonspecific effects of iron to increase oxidative stress enhance peroxidation of lipids and oxidative damage of other cellular components, perhaps with depletion of thiols or other antioxidant protective factors; (2) adverse effects of iron on host immunity, including impairment of function of antigen-presenting cells, impairment of cloning efficiency of T helper – 1 and cytotoxic T Iymphocyte subsets, impairment of T Iymphocyte proliferation and maturation, impairment of proinflammatory T cell responses, and impairment of natural killer cell-dependent Iysis of infected cells; and (3) impairment of humoral immunity.

Antioxidants and Anti-inflammatory Agents.

Other approaches to treatment, such as the use of N-acetyl cysteine (NAC), or other – SH donors, are based upon the knowledge that, in chronic hepatitis C (as in other liver diseases), oxidative stress increases and plasma and liver GSH concentrations decrease. Oral NAC (1800 mg/d), although having little effect alone, enhanced the response to IFN. (6) Favorable effects of vitamin E alpha-tocopherol) on oxidative stress and activation of the cascade of fibrogenesis were reported recently. In a few small studies, similar effects have been reported for aspirin, other nonsteroidal anti-inflammatory drugs, pentoxyfylline, and colchicine. Similar nonspecific effects probably account for the improvements in serum ALT levels reported in chronic hepatitis C patients treated with many other concoctions, including traditional Chinese remedies and extract of snap cucumber. Whether such improvements in blood tests will be associated with diminution in the rate of progression to birding fibrosis, cirrhosis, or hepatocellular carcinoma is currently unknown but is clearly an important issue.

Antioxidants in the Treatment of Hepatitis C

Recent evidence has shown oxidative stress and lipid peroxidation play a major role in the fatty liver accumulation (steatosis) that leads to necroinflammation and necrosis of hepatic cell.72,73 Necrosis, both the piecemeal and bridging types, are associated with a poor prognosis in chronic hepatitis.74 Fatty tissue accumulation in the liver increase the potential for oxidative stress to trigger lipid peroxiation, leading to cytotoxic intermediates that induce inflammation and fibrosis via immunological pathways.75 Both in alcoholic and nonalcoholic hepatitis, steatosis (fatty tissue accumulation) and the lipid peroxidation that

follows can lead to activation of stellate cells, the principal cells in the liver responsible for fibrogenesis and, ultimately, cirrhosis."

Understanding the role of lipid peroxiation in liver disease has lead to studies using antioxidant therapy in a variety of hepatic disease states. Alcohol-induced hepatitis has a free radical related pathogenesis. Wenzel studied a group of 56 patients with acute alcohol-induced toxic hepatitis. Half of them (n=31) were given 600mg d-alpha tocopherol, 200 mcg selenium, and 12 mg zinc. This protocol lowered the levels of bilirubin, ammonia, and malondialdehyde (a marker of hepatic free radical production) significantly when compared to the control group. The hospital stay of the supplemented group was reduced by six days and the mortality was reduced to 6.5 percent (2 of 31 patients) compared to 40 percent (10 of 25 patients) in the control group.

Antioxidants have also been used in combination with interferon alfa2 in children with acute hepatitis B. One study looked at 73 children with acute hepatitis B given tocopherol and interferon alfa2 simultaneously, and found significantly shorter recovery times, higher levels of endogenous alpha-interferon, and a significant increase in the elimination of Hbe antigen with the addition of vitamin E.

Studies using antioxidants in hepatitis C have focused on the effect of a variety of antioxidants, both nutrients and botanicals. Beloqui treated 24 patients with chronic hepatitis C, 14 who had shown no response to interferon after four months. The group was given 600mg N-acetylcysteine three times daily for 5-6 months in addition to interferon. Serum ALT values steadily declined in all 14 subjects over the 5-6 months period and normalized in 41 percent of the group on combination therapy. The group previously receiving no treatment had no effect from the N-acetylcysteine after one month.

Hoglum treated six patients who had failed interferon therapy and had evidence of fibrosis in liver biopsy. Stellate cell activation in the liver was subsequently measured by the presence of malondialdehyde protein adducts in the biopsy. Treatment with d – alpha tocophrol at the dosage of 1200 I.U.daily for eight weeks was found to stop the fibrogenesis initiated by stellate cell activation. The treatment did not, however, decrease ALT levels, viral titers , or the degree of hepatocellular inflammation.

Glycyrrhizin

Phytopharmacology

In Japan ,glycyrrhizin has been an accepted treatment of chronic hepatitis for over 20 years. Glycyrrhizin is a conjugate of glycyrrhetinic acid and glucuronic acid. Orally administered glycyrrhizin is metabolized in the intestine to glycyrrhetinic acid, while intravenous glycyrrhizin cannot be metabolized to glycyrrhetinic acid until it is excreted through the bile into the intestines (Figure 4). Both glycyrrhizin and glycyrrhetinic acid have been found to possess antiviral activity. In vitro studies Nose found smaller doses of glycyrrhizin (1000 micrograms / mL) in lowering transaminase levels. On the other hand, in other studies, using murine IFN-g production as a measure of immune modulation, glycyrrhizin was more effective than glycyrrhetinic acid.

The first evidence of glycyrrhizin's antiviral effect was found in 1977 in culture studies with herpes simplex virus type 1. In 1990, Crance found complete inhibition of hepatitis A virus antigen expression at concentrations of 1000 and 2000 meg / mL. The mechanism of glycyrrhizin's antiviral effect was later discovered not to be direct viral inhibition, as previously thought, but inhibition of the virus's ability penetrate the human hepatocyte. The hepatitis A virus enters cells by the process of endocytosis, a process that glycyrrhizin interrupts by altering cell membrane penetrability. Glycyrrhizin also appears to work as a free radical scavenger: studies with ischemia-reprerfusion damage in rat liver (using pre-treatment with subcutaneous glycyrrhizin) significantly decreased lipid peroxides and transaminase levels. As mentioned earlier, glycyrrhizin also acts via immune modulation: intravenous injections in mice induced IFN-g peaks and subcutaneous glycyrrhizin activated murine hepatic T-cells.

CLINICAL TRAILS

The first randomized trial using intravenous glycyrrhizin was run in 1977 when Suzuki looked at its effect in 133 cases of chronic hepatitis B. The glycyrrhizin was given as Stronger Neo Minophagen C (SNMC) N a solution of 2 mg glycyrrhizin, 1 mg cystenine, and 20 mg glycine per mL. Glycine was added to prevent pseudoaldosteronism, and cysteine was added to assist cysteine-related conjugation reactions in liver detoxification pathways. SNMC (40mL) was administered intravenously daily for four weeks. Significant improvements were found in transaminase values and no side-effects were observed.

Later studies found improvements in liver histology: 29 of 45 hospitalized patients had histologically significant improvements in liver biopsy after eight week of SNMC at 100mL daily. Withdrawal of the SNMC caused a rebound of the transaminases which could be reduced with a step-wise withdrawal of the daily eight-week doze of 100mL. A similar phenomenon of transaminase rebound is found after elimination of long-term therapy with ribavirin.

A long-term trial with SNMC in patients with chronic hepatitis C included 84 patients who were given the medication between January 1979 and April 1984. These patients were given 100mL of SNMC intravenously daily for eight week and 2-7 times weekly for 2-16 years (median 10.1 years). They were compared to a control group of 109 patients who, due to a lack of home health-care services, received only oral botanical and nutritional supplements. On follow-up the serum ALT levels fell to normal in 30 (35.7%) of the group receiving SNMC and in seven (6.4%) of the control group. The 15-years incidence of cirrhosis was 21 percent in the SNMC group and 37 percent in the control group. The incident of HCC after 15 years of treatment was 12 percent in the SNMC group and 25 percent in the control group. In this study, patients treated with SNMC for 10 years had incidences of HCC comparable to Japanese interferon-treated patients. The incidence of HCC in lymphoblastoid interferon-treated hepatitis C patients in the same Japanese hospital was 0.1%, 0.6% and 1.5% per year (for the histologic stages I, II, and III, respectively). The incidence in the SNMC patients was 0.3% for Stage I and II, and 1.3% for stage III. 104 Side-effects related to hypokalemia (10.7%) and hypertension (3.6%) necessitated the use of spironolactone. No one in the study discontinued medication as a result of side-effects. Several questions arise as a result of data on

SNMC; for example, it is not clear to what extent the cysteine and glycine contributed to the positive effects of the glycyrrhizin.

While the metabolism of oral glycyrrhizin is mediated by intestinal bacteria and results in enzymatic conversion to glycyrrhetinic acid (Figure 4), both oral and intravenous routes of administration appear to have hepatoprotective properties. Eighty subjects with acute or chronic hepatitis B were given either oral doses of 7.5 g crude glycyrrhiza root, concentrated to contain 750 mg glycyrrhizin, (30days for the acute group and 90 days for chronic group; n=20 in each group),and compared to identical group receiving conventional treatment of Inosine plus ploy I:C. Results showed significantly more marked improvement in indices of liver function and negative conversion of HbsAG and HbeAG in the glycyrrhizingroup than in the control group. In fact, none of the patients in either control group seroconverted. In the glycyrrhizin groups, indicators of liver function returned to normal in 85 percent of subjects with acute hepatitis and 75 percent of those with chronic hepatitis, compared to 35 percent and 10 percent, respectively, in the control groups.

Catechins

Catechins are a class of flavonoids with hepato protective activity. Early research in animals has shown their ability to decrease the hepatotoxicity of ethanol,carbon tetrachloride, phalloidins and other toxic compounds in rat hepatic tissue. Numerous animal studies have also demonstrated catechins' antioxidant effect (including the inhibition of lipid peroxidation) and ability to stimulate cell – mediated immunity.

(+) – Cyanidanol 1-3 is pure catechin (trade names Catergen, Kanebo, Zyma) derived from Uncaria gambir (Figure5). In the early 1980s it was the subject of extensive study in the United kingdom and other parts of Europe as a potential treatment for alcoholic hepatitis . Results were disappointing ; evidence for alternation in the course of alcohol related liver disease was not evidence, even at dosage of 2-3 grams daily for six months. The research on its use in viral hepatitis has been more promising. A double – blind trial compared 3 gm catechin daily (n=58) with placebo (n=66) for 50 days in 124 patients with acute viral hepatitis of various types . Serum AST,ALT, and serum bilirubin were tested every five days. There was a significant difference in effectiveness depending on the type of hepatitis being treated. For patients with hepatitis C the serum AST and ALT levels were significantly lower in the catechin group than the placebo group from the fortieth day on. There were moderate but significant differences in the hepatitis B group in a favor of catechin ,and no significant difference in the hepatitis A group.

In other clinical trails of acute hepatitis B, catechin was shown to lower serum biririubin and transaminase levels, and accelerate the disappearance of Hbs Ag. Trials using catechin in chronic hepatitis showed improvements in liver histologies.And inhibition of liver lipid peroxidation. In a study with 338 chronic hepatitis B patients, Suzuki.showed catechin increased the rates of disappearance of Hbe Ag in chronic hepatitis. In this trial,174 patients received catechin ata dose of 1.5 grams saily for two weeks, Followed by 2.25 grams daily for 14 weeks. The Hbe Ag titer decreased by at least 50 percent in 44/144 patients, and the HbeAg disappeared in 16/144 catechin patients compared to 4/140 placebo patients. The nutrient was well tolerated with the only appreciable side-effect being a transient febrile reaction in 13 patients.

There have been reports of six patients with catechin-related hemolytic anemia, all with demonstrable red blood cell (RBC) antibodies. The hemolysis resolved after discontinuation of the dr4ug and did not return even though autoantibodies to RBCs were still detectable in the blood. Other researchers have reported incidents of hemolysis in patients on catechin but the symptoms remit when the drug is withdrawn and no sequelae or fatalities have been documented. this data, however, was collected from patients who were taking a highly purified pharmaceutical form of catechin (AK cyanidonol) at a dose of 1-2 grams per day, duplicating the average dose used in treating hepatitis. In the United States, whole botanical sources of catechins, from Uncaria gambir for example, are typically used. Catechin consent of gambir ranges from 2-10 percent. While these doses are unlikely to result in side-effects, it remains to be seen whether lower concentrations of catechin will afford the same effectiveness as the purified form.

Hydrophilic Bile Salts

Supplemental (tauro-) ursodeoxycholic acid has led to improvements in serum ALT levels, in both the absence and the presence of IFN. (7) These effects seem to be related to the beneficent effect of hydrophilic bile salts on many chronic inflammatory conditions involving the liver.

Cytokines and Other Immunomodulating Agents

Cytokines and other Immunomodulating agents have also undergone limited trials in chronic hepatitis C. Effects of granulocyte/monocyte colony stimulating factor (GM-CSF) have generally been disappointing; it is expensive, poorly tolerated, and without beneficial effect except perhaps in a rare patient who develops severe neutropenia due to IFN, in whom GM-CSF may permit continuation of higher doses of IFN. In one reasonablylarge (110 patients), doubly masked, randomized trial, thymosin alpha- I Plus IFN was compared with placebo and IFN alone. (8) A complete serum ALT response was reported in 42 percent of those treated with the combination, compared with 3 percent in those treated with placebos and 17 percent in those treated with IFN alone. The reason for the unusually low latter percentage was not clear, nor were long-term follow-up data available.

Ribavirin: Mechanisms of Action.

Ribavirin is a guanosine analogue with antiviral activity against RNA and DNA viruses. In combination trials with interferon, sustained virological responses have been as higher as 47 percent after 27 weeks of treatement. Although repeated studies have shown significant reduction of ALT levels after six months of treatment with Ribavirin alone, multiple studies have failed to detect any significant antiviral activity. The benefit of ribavrin in post-liver transplant patients with hepatitis C is a result of decreased lobular inflammation and normalization of ALT levels, and not a reduction of viral load.

There is evidence Ribavirin specifically inhibits cytokin production by macrophages, Ning assessed the effect of ribavrin in an experimental model of fulminant murine hepatitis (MHV-3). Even though Ribavirin had minimal antiviral activity, it significantly reduced macrophage activation and decreased production of IL-4, but did not effect the

production of IL-2 or IFN-g. The authors concluded the beneficial effect of Ribavirin in this situation was the specific preservation of TH1 cytokines and the inhibition of TH2 cytokines.

OVERVIEW ON HEPATITIS

Definition

An inflammation of the liver

Causes, incidences, and risk factors

Hepatitis can be caused by bacterial or viral infections, infestation with parasites, chemicals (alcohol or drugs), toxins, or immune diseases. It can be short-term (acute), long-term (Chronic), or life-threatening (fulminant). Hepatitis can cause permanent liver damage.

The incidence, severity, and means of contagion vary with different forms of hepatitis. Some forms of infectious hepatitis are transmitted through blood products, some through eating contaminated food, some through sexual contact, and some through unknown means.

Specific types of hepatitis include:

- hepatitis A
- hepatitis B
- hepatitis C
- hepatitis D
- chronic active hepatitis
- chronic persistent hepatitis
- autoimmune hepatitis
- drug-induced hepatitis
- alcoholic hepatitis
- non-alcoholic hepatitis

Prevention

Prevention of hepatitis varies with each type of infection. Some general precautions to reduce the change of contracting hepatitis or other infections include:

1. Avoid contact with blood or blood products.
2. Avoid sexual contact with a person infected with hepatitis or person with unknown health history. Practice safer sex behaviors.
3. Avoid contact with blood or blood products whenever possible.
   (Note: Blood donors are screened for the virus, but this is not 100% accurate)
4. Wash hands thoroughly or clean up extensively after using the restroom if there is contact with anyone's blood, feces, or body fluids.
5. Hepatitis B vaccine is available for people in high-risk groups.
6. Hepatitis A vaccine is available for people in high risk professions like nursery attendants, institutional care workers, nurses, physicians, and people traveling to undeveloped countries.
7. Avoid IV drug use.

Symptoms

- dark urine
- loss of appetite
- fatigue
- general discomfort, uneasiness, or ill feeling (malaise)
- abdominal distention
- generalized itching
- jaundice
- fatigue
- loss of appetite
- nausea and vomiting
- low grade fever
- pale or clay colored stools
- generalized itching
- abnormal urine color, ark urine
- abnormal taste
- abdominal pain
- abdominal indigestion
- point tendemess

additional symptoms that may be associated with this disease:

- yellow skin, jaundice
- breast development in males
- abdominal fullness, gaseous
- nosebleed – symptom
- depression

Signs and tests

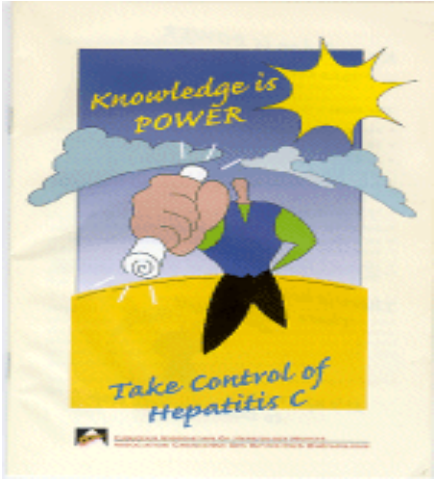
Physical examination of the abdomen shows an enlarged and tender liver.
Tests include:

- hepatitis virus serology
- liver function tests

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
What is it?	HAV is a virus That causes inflammation of the liver. It does not lead to chronic disease.	HBV is a virus That causes inflammation of the liver. It can cause liver cell damage, leading to cirrhosis and cancer.	HCV is a virus That causes inflammation of the liver. It can cause liver cell damage, leading to cirrhosis and cancer.	HDV is a virus That causes inflammation of the liver. It only infects those persons with HBV.	HEV is a virus. That causes inflammation of the liver. It is rare in the U.S. there is no chronic state.
Incubation Period	2 to 7 weeks. Average 4 weeks	6 to 23 weeks. Average 17 weeks.	2 to 25 weeks. Average 7to9 wks.	2 to 8 weeks.	2 to 9 weeks. Average 40 days.
How is it Spread?	Transmitted by fecal/oral route, through close person to person contact or ingestion of contaminated food and water	Contact with infected blood, seminal fluid, vaginal secretions, contaminated needles, including tattoo and body-piercing tools. Infected mother to newborn. Human bite. Sexual contact.	Contact with infected blood, contaminated IV needles, razors, and tattoo or body-piercing tools, infected mother to newborn. NOT easily spread through sex.	Contact with infected blood, contaminated needles. Sexual contact with HDV infected person.	Transmitted through fecal/oral route. Outbreaks associated with contaminated water supply in other countries.
Symptoms	May have none. Others may have light stools, dark urine, fatigue, fever, nausea, vomiting, abdominal pain, and jaundice.	May have none. Some persons have mild flu-like symptoms, dark urine, light stools, jaundice, fatigue and fever.	Same as HBV	Same as HBV	Same HBV
Treatment of Chronic Disease	Not applicable.	Interferon and Lamivudine with varying success.	Inferon and combination therapies with varying success.	Inferon with varying success.	Not applicable
Vaccine	Two doses of vaccine to any one over 2 yrs of age or older.	Three doses may be given to persons of any age.	None	HBV vaccine prevents HDV infection.	None
What is at Risk?	House hold or sexual contact with an infected person or living in an area with HAV outbreak Travelers to developing countries, persons engaging in anal/oral sex and injection drug users.	Infants born to infected mother, having sex with an infected person or multiple partners, infection drug users, emergency responders, healthcare workers, persons engaging in anal/oral sex, and hemodialysis patients.	Blood transfusion recipients before 1992, healthcare workers, injection drug users, hemodialysis patients, infants born to infected mother, multiple sex partners.	Injection drug users, persons engaging in anal/oral sex and those having sex with an HDV infected person.	Travelers to developing counties specially pregnant women.
Prevention	Immune globulin within 2 week of exposure. Vaccination. Washing hands with soap and water after going the toilet. Use household bleach (10 parts water to 1 part bleach) to clean surfaces contaminated with feces, such as changing tables. Safe sex.	Immune globulin within 2 weeks of exposure. Vaccination provides protection for 18 years. Clean up infected blood with house hold bleach and wear protective gloves. Do not share razors, toothbrushes, or needles. Safe sex.	Clean up spilled blood with household bleach. Wear gloves when touching blood. Do not share razors toothbrushes, or needles with any one. Safe sex.	Hepatitis B vaccine to prevent HBV infection. Safe sex.	Avoiding drinking or using potentially contaminated water.

ARTICLE FOR PARAMEDICAL AND NURSES

Knowledge is POWER



Take Control of Hepatitis C

The Facts

Hepatitis C virus (HCV) is an infection that affects the liver

* HCV is contracted through blood-to-blood contact
* As many as 300,000 Canadians are infected with the hepatitis C virus
* Only 25% of these Canadians are aware they carry the hepatitis C virus
* HCV affects each person differently
* Sometimes there are no symptoms; sometimes there are
* HCV can progress slowly, or become a serious threat to your health in as little as five years
* Hepatitis C patients should not use alcohol or recreational drugs

There is hope. There is treatment. It's up to you to take the first step!

If you've just been diagnosed with the hepatitis C virus (HCV), you probably have a lot of questions. You may be confused, perhaps scared, and certainly concerned about what having hepatitis C means to you, your family, and your future. It is important to know you are not alone - you have the support of your health care professionals - and effective treatment exists than may be right for you.

This pamphlet, "Knowledge is Power - Taking Control of Hepatitis C" will give you a better understanding of HCV so you can choose your treatment with confidence and base your decisions on the facts, not the fear. A glossary of the terms, which are

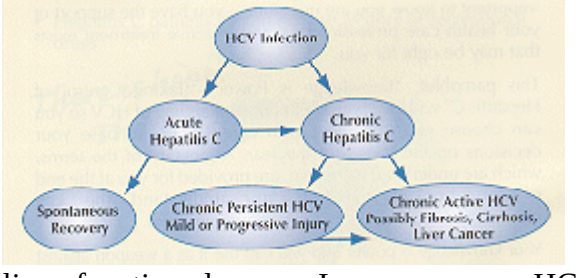
underlined in the text, are provided for you at the end of this booklet to help you understand the key medical/technical terms that are commonly used.

Your knowledge is power and you can use it as a weapon against hepatitis C.

What is Hepatitis C?

Quite simply, hepatitis C is a disease caused by the hepatitis C virus (HCV) which has infected your liver. A virus is a very small organism that attaches itself to your healthy cells and forces them to make more of the virus. Your body tries to fight viruses with antibodies, but the hepatitis C virus is particularly strong; it will change to fight back against your body's defenses. Unfortunately, antibiotics, which kill bacteria are not at all effective against viruses.

Experts have identified two types of hepatitis C: acute hepatitis C (short-term infection) and chronic hepatitis C , (long-term, progressive infection). These are broken into sub categories.



Chronic hepatitis C can occur on its own and is generally the more serious of the two types. In about 80% of cases, however, acute hepatitis C develops into chronic hepatitis C over time. Both chronic hepatitis C and acute hepatitis C can cause very different degrees of symptoms and liver function damage. In many cases, HCV infection can be treated effectively with medication.

How you may have become infected?

Hepatitis C is contracted from blood-to-blood contact. This means that you probably became infected by blood tainted with the virus entering your bloodstream. You may never discover how you contracted hepatitis C, but now that you are aware of your infection, it is up to you to take precautions to protect your family, friends, co-workers, or anyone else who may come in contact with your blood. If you use common sense and educate your loved ones with the facts about hepatitis C, you and they can live risk free.

Important facts to know

- The risk of spreading hepatitis C through normal household contacts is very low
- Oral transmission of HCV has not been proven, so you can hug and kiss your family and friends
- Breast milk, semen, urine, saliva, and tears may contain the hepatitis C virus
- **Do not** share razors, toothbrushes or any other personal hygiene instrument that could contain blood particles and infect another. You can share bathroom facilities
- There is a 2% to 3% chance that HCV can be transmitted through sexual intercourse. The presence of sexually transmitted diseases (STD's) increase the risk of transmitting hepatitis C. Inform your partner of your infection and if you are sexually active with multiple partners, you should always use a condom
- Menstrual blood is known to carry HCV - women should avoid sex during this time
- You must not give blood or donate organs

- There is a chance that the virus can be passed to your newborn during childbirth

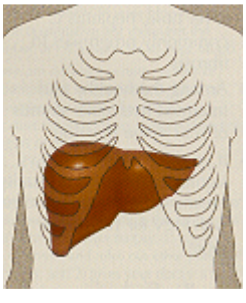
Your liver and HCV

Your liver works 24 hours a day, performing over 500 vital functions for your body. Almost all the blood returning from your intestinal tract to your heart passes through your liver. It is absolutely necessary to your body's healthy function and you cannot live without it.

The hepatitis C virus lives in your liver. When it invades healthy liver cells, it causes those cells to become inflamed. Over time, this will affect the way your liver functions. How hepatitis C affects you, and if or when you will experience decreased liver function, is different for everyone. There is no way to predict how you will react to HCV. However, there are some things we do know:

- You can live with HCV for many years without experiencing any major symptoms, or you might experience minor symptoms such as fatigue. Symptoms can come and go over time, and the presence or absence of symptoms do not relate to the degree of liver damage that may be occurring.
- Chronic, long-term inflammation of the liver can cause liver cell damage and result in fibrosis (liver scarring), or even cirrhosis. These changes can happen in as little as 5 years, or can take as long as 30 years. About 20% of chronic hepatitis patients develop cirrhosis within 10 to 20 years.
- Use of recreational drugs or alcohol affect how fast inflammation develops into fibrosis or cirrhosis.
- There is an increased risk of liver cancer in people with cirrhosis proper nutrition, plenty of rest, avoiding recreational drugs or alcohol, and a responsible approach to treatment can make all the difference in managing hepatitis C. Taking control of your HCV won't be easy; it will take commitment. Your knowledge of hepatitis C can give you the power to take control of your health and your future.

How your liver works for you?



Your liver:

- Cleans alcohol, drugs, harmful by-products, and other toxins from your blood
- Converts most medicines, like allergy medications, into forms your body can use
- Removes old red blood cells

Your liver makes essential proteins:

- That transport nutrients and other substances through the blood to other organs and tissues
- To clot your blood
- That provide resistance to infection and bacteria

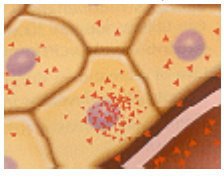
Your liver maintains a healthy balance in your body of:

- Hormones
- Cholesterol - your liver produces it, excretes it, converts it
- Essential vitamins and minerals
- Glucose (simple sugars), by producing, storing and supplying it to the rest of your body
- Fat, by producing and supplying it to the rest of your body

Phases of Hepatitis C

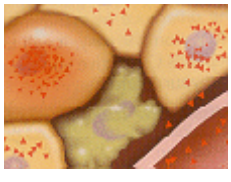
Phase I: Infection

* HCV virus enters the blood stream, attaches to liver cells, and begins to reproduce
* New virus, made in infected liver cells, invades more liver cells and infects them



Phase II: Inflammation

- Infected liver cells become inflamed
- The inflammation causes liver cells to die



Phase III: Fibrosis

- Over time, hepatitis C commonly progresses to fibrosis
- Among the healthy and inflamed liver cells strands of scar tissue develop
- If your liver biopsy shows significant fibrosis, it usually means you've been infected with HCV for 10 years or more

Phase IV: Cirrhosis

- When fibrosis increases, cirrhosis begins to appear
- Cirrhosis affects how blood flows in and out of the liver. This impairs normal liver functions

Tests often used for Hepatitis C patients

The following chart will help you understand the tests and procedures commonly used to diagnose HCV and to monitor its progress in your liver.

Test Definition and Comments

Hepatitis C antibody (Anti-HCV)

HCV antibodies_are produced by your body to fight HCV, and then remain in your system for life. This test measures the presence of HCV antibodies in your blood.

Alanine aminotransferase (ALT)

When liver cells are injured or destroyed enzymes_from those cells escape into your blood. This test measures the level of the enzyme ALT in your blood and is a general indicator of inflammation.

Hepatitis C RNA (HCV RNA) or Polymerase Chain Reaction (PCR)

This blood test can be done for two different reasons:

a) the qualitative test tells whether or not there is HCV in your blood; and
b) the quantitative test measures the number of HCV particles in your blood.

Genotyping

There are different genetic strains of hepatitis C. It is extremely helpful to know the genotype of your virus because different types require different lengths of treatment.

Liver biopsy

A liver biopsy involves removal of a small piece of liver tissue through a needle. The specimen is analyzed under a microscope to determine the amount of liver damage. A liver biopsy: 1) confirms the diagnosis and rules out other potential disorders; and 2) gives your doctor a true picture of the stage and degree of activity of hepatitis C in your liver.

Ultrasound

An ultrasound uses sound waves to create a picture of the liver. It reveals the size and texture of your liver, and the size of bile ducts and blood vessels. It is a safe and painless way to investigate your liver and the supply of blood to it.

What's next?

You now have a good idea of what hepatitis C is, how it affects your liver, and what you can do to safeguard yourself and others. Now it's time to make some important decisions - to use the knowledge you've gained about HCV to take charge of your future health.

Your options

Let's be clear - there is no treatment that will work for every single patient with HCV infection. This is not to say that there isn't hope, but treatment of hepatitis C is a big decision - a commitment on your part. Talk to your doctor or nurse discuss realistic treatment goals based on your diagnosis. Do you want;

*more energy to feel less tired or fatigued?

* to reduce your chances of developing cirrhosis or liver cancer?

* to help your liver recover normal functioning?

Outlined below are treatment alternatives you should be aware of. Do some research and talk to your doctor or nurse about which choice is best for you.

Herbal remedies

Generally, there are less scientific proof to support claims made on behalf of herbal medicines. Alternative medicines are not rigorously controlled, so, proof of safety, possible side effects,_exact ingredients, potency, purity, directions for use, and the effectiveness of the herb, may be difficult to determine. Some herbs may cause serious problems to your liver, and your general health, if not taken properly. It is very important that you inform your nurse or doctor about any herbal remedy you are taking or are thinking of taking.

Interferon therapy

Alpha interferon is approved for the treatment of HCV infection. Interferon treatment is injected three times per week and is effective for approximately 50% off patients - meaning that these patients had an undetectable amount of the HCV in their bloodstream immediately following the end of the treatment. However, when thee same patients were tested for the hepatitis C virus six months later, more than half had relapsed.

Interferon seems to work best for chronic hepatitis C patients the sooner it is used after infection. The treatment course is twelve months. The side effects include flu-like symptoms, muscle cramping, headaches, fever, fatigue, or depression. As well, some patients may show a reduction in disease-fighting white blood cells, or a decrease in the number of platelets in their blood.

Combination therapy

According to recent Canadian guidelines, the recommended treatment for HCV infection is with a combination of interferon alfa-2b and ribavirin. Rebetron* is the combination of these two therapies which together have produced better results than either treatment used alone. Rebetron* combines ribavirin capsules (taken orally twice daily) and interferon alfa-2b (injected 3 times weekly).
Interferon is a biological response modifier. This drug helps your body's immune system to fight infection. Ribavirin, on the other hand, is an antiviral agent, which fights HCV.

The success of any treatment is not measured by how effective it is while you are taking it, but whether the results can be maintained for at least six months after treatment. Studies, where combination therapy was the only treatment ever used by a patient, showed that 41% had undetectable levels of HCV-RNA in their blood six months following treatment, and 62% showed improvement in their liver tissue. As well, the use

of combination therapy in patients who were previously treated with interferon and then relapsed, showed that 49% had undetectable levels of HCV-RNA in their blood.

The side effects of combination therapy will vary from patient to patient. In addition to the side effects of interferon therapy, ribavirin can also cause shortness of breath, coughing, and anemia. If you suffer from any form of heart disease, please notify your healthcare professional.

It is very important that both you and your partner use effective birth control methods while taking combination therapy, and for six months following the end of your treatment. Failure to do so may result in serious birth defects. Consult your doctor or nurse about the best form of birth control for you and your partner.

Combination therapy has been researched, tested, and approved for treatment of hepatitis C. No, it's not for everyone - but it may be for you. How well Rebetron* works for you will depend on a number of factors, but you should discuss Rebetron* with your doctor or nurse, and ask if this option is right for you.

HOMEOPATHY

The history of homeopathy

Samul Hahnemann, a German physician, began to develop the major principles of homeopathy some 200 years ago, although there is some suggestion that the concept of "like cures like" may well have been an observation made by the father of medicine, Hippocrates. The oft quoted and classical beginning of homeopathy is Hahnemann's observations in relation to quinine.

Quinine given on its own appeared to produce symptoms similar to tertian fever; every three days while taking quinine, the individual experienced a pyrexia; similar to that experienced by those suffering from malaria, an endemic disease in both southern and central Europe some 200 years ago. Giving malaria suffers quinine in low (infinitesimal) doses seemed to have a positive therapeutic effect on the illness.

It was through this observation that two Hahnemann's major principles of homeopathic prescribing were established. The first is that a remedy given to a healthy patient "proves". This effectively means that an individual can write down "a remedy picture" while taking it in homeopathic potency and then recording the symptoms in some detail for the ensuing two or three weeks. Thus, proving a remedy on a number of healthy individuals allowed a remedy picture to be established which could then be matched with a patient's symptoms when they presented with an illness. Hahnemann's second major concept, "like cures like" was then employed to treat the patient by utilizing the illness picture that matched the proving.

The political debate

As Hahnemann was establishing the principles of homeopathic prescribing some 200 years ago, two schools of thought in relation to the manufacture and prescribing of homeopathic medicine began to emerge. The first was the classical Kentian approach in which only a single remedy was used at any one time. Kent was an American homeopath and the use of Kent's material medical revolved solely around the prescription of single remedies, often in very high potencies (that is very dilute remedies) largely prescribed on the basis of the individual's constitutional type. Simultaneously, in both the German and French speaking countries of central Europe, there were those among Hahnemann's disciples who began to use homeopathic mixtures or complexes to treat illnesses in situations where they were unsure about exactly which remedy would be best, or indeed in situations where perhaps two or more remedies might be indicated based on the providing. Some of Hahnemann's original manuscripts also suggest that the use of mixed homeopathic remedies was a perfectly valid and frequently clinically indicated mechanism through which to approach illness.

To some extent an artificial division has emerged within the homeopathic world. Those who appear to support the use of a Kentian approached based exclusive on single remedies and those who prescribe homeopathic complexes or mixtures of more than two remedies in order to treat a specific problem. In effect, many homeopaths in both continental Europe and North America will tend to use both singles and complexes depending on the specific indication and presenting symptoms. In England the vast

majority of homeopaths adhere to the Kentian school of prescribing singles, largely directed at the individual's constitutional type. In essence, complex homeopathy is defined as the use of two or more homeopathic remedies in a single preparation, frequently with varying potencies.

Homeopathic prescribing

Homeopathic prescribing can be divided into three main areas. Remedies are prescribed for acute conditions; 200 years ago most illnesses tended to be acute, frequently involving acute infections. The prescription of homeopathic remedies in these situations centers around the use of relatively low potencies given frequently, the usual potencies involved those which can be bought in most health food stores such as a C6 dilution. The second major area of homeopathic prescription involves single remedies prescribed for a particular constitutional type. For instance, dark harried females who frequently suffer from menstrual problems, headaches and are drawn to tears easily will fit the picture of a "Sepia constitution". Therefore the prescription of Sepia can be used to treat the constitution and thereby hopefully improve any illness by dealing with the person's constitutional weaknesses through the use of a high potency remedy given infrequently C200 or 1M may be used. Inspite of this a Sepia constitutional type who may develop an acute urinary infection would be given Cantharis in a C6 potency every hour or two in order to deal with the acute illness. It is, however, in the treatment of chronic illness that the third system, the use of complex remedies comes to the fore. Frequently individuals with multiple symptoms will develop complicated and, in homeopathic terms, frequently confusing remedy pictures. As a sequence the prescription of complexes or mixtures gained many disciples in the early days of homeopathy and is still practiced largely by both French and German homeopaths.

Modern homeopathy

As the pattern of illness has changed over the last 2 centuries, many homeopaths have adapted their prescribing in order to respond to the challenge of chronic illness and pollution that is unfortunately part of our modern western society. The first change is the use of nosodes, an approach unknown and unrecognized in Hahnemann's time. One of the first individuals to utilize nosodes coherently was Dr. Edward Bach, who also developed the Bach Flower Remedies. He noted that many individuals with persistent digestive problems appeared to be experiencing low grade chronic infection of the intestine. As a consequence he developed the bowel nosodes which are in themselves complexes. These involve mixtures of bacterial preparations and bowel tissue given in potency in order to treat underlying digestive complaints. Abnormal digestive fermentation, or dysbiosis, has been recognized as the basis of much pathology by naturopaths, homeopaths and those practicing within the field of nutritional medicine. A modern Western diet, high in refined foods and sugar, has only served to exacerbate this problem and the epidemic of "candida" is just one such example of the problems that may occur when an abnormal fermentation process is present in either the large or small intestine. Complex remedies such as the bowel nosodes can frequently be used to approach these problems as part of an appropriate treatment regime involving diet, and frequently combined with some herbal remedies and nutritional supplements in order to normalize gut fermentation.

Exposure to chemicals, such as pesticides, herbicides and organophosphates can also be treated by the use of appropriate nosodes. These remedies contain homeopathic does of toxins which, when given to patients who have been chemically poisoned, appear to trigger an acute reaction which in turn seems to mimic the original poisoning episode. Therefore, by employing the simple principle of "like cures like", chemical mixtures in homeopathic potency can be given to those suffering from chemical exposure in order to detoxify their tissues and treat their symptoms.

The use of isopathy or homeopathic immunotherpy (HIT) has received much publicity recently, particularly in relation to David Reilly's work in this field 1. It is clear from this work that if an individual is suffering from hay fever, a potency of pollens may prove to be effective in their treatment. If an individual suffers from asthma, triggered possibly by house dust mite, house dust, cat hair, dog hair and feathers, then those who utilized the principles of homeopathic immunotherpy will frequently prescribed mixtures involving potencies of each of these items. They will therefore be prescribing a complex remedy in order to treat an individual's allergic symptoms. It is interesting to note that this "modern approach to homeopathy" does not involve a classical symptoms pictures, but utilizes remedies based solely on conventional medical knowledge and the individual's allergic profile.

Many of the complex remedies currently used in Germany have, to some extent, moved away completely from classical homeopathic prescribing and their indications are based solely on the patient's presenting symptoms and diagnosis. An excellent recent review published in the British Medical Journal by Linde et al2 indicated that there were a lare number of clinical trials looking at the use of Hypericum (St John's Wort) in the treatment of depression. Hypericum was frequently used in material amounts as a herbal remedy, and the studies indicated that good arguments are beginning to emerge for the use of Hypericum in mild depressive states. Not only do the preliminary clinical trials suggest quite a defined effect on mood, but they also imply that there are far fewer side effects from the use of Hypericum than there would be from the regular use of conventional anti-depressant remedies.

Hypercium is frequently prescribed as part of a complex remedy. For instance, neurapas, a product produced by Pascoe, one of the German pharmaceutical houses, contains not only hypericum but also other remedies such as Passiflora and Valerian. It is registered and licensed in Germany under its trade name, Neuropas (Extr. Herb. Hyperi (aquos. Sicc. 6:1} 80.0 mg, Extr. Rad. Valeriannae [spir. Sicc. 4:1] 40.0 mg, Extr. Herb. Passiflorae [spir. Sicc. 6:1] 40.0 mg, Rhiz. Corydalidis cavae 40.0 mg, Herb. Eschscholtziae californ. 40.0 mg, Cicuta virosa D2 0.1 mg) Neurapas represents a typical example of a modern complex remedy involving mixtures of a variety of homeopathic products balanced within one product and targeted at a specific symptom. Valerian is prescribed to help the sleep disturbance often associated with depression and the Pasiflora to help symptoms of anxiety, again frequently associated with depressive illness. Not only is Neurapas as a complex remedy specifically targeted at depressive illness, but modern homeopathy is also beginning to establish itself by increasingly exposing its treatments to properly controlled clinical trials. Such studies suggest that Neuropas is at least as good as conventional antidepressants in mild depression, and furthermore appears to cause fewer adverse reactions and seems to be far less addictive than some of the powerful chemical agents used to treat this conditions.

Echinaceae, a well-known immune stimulant, is also a major component of many complex remedies designed to treat viral and bacterial infections. Pascotox contains not only a herbal extract of Echinaceae, but also many accompanying homeopathic remedies frequently utilized in acute viral and bacterial infections such as Bryonia and Ferrum Phos (Extr. Rad. Echinaceae nag. Sicc. 90 mg, Baptisia D4 16 mg, Bryonia D1 16mg, Eupator. Perfol. D2 16mg, Arnica D3 16 mg, Ferrum phosphoric D8 16 mg, thuja D4 16 mg, China D3 16 mg, Lachesis D8 16 mg, Lachesis D15 16 mg, Cuprum sulfuric D4 16 mg). Again, this remedy has been exposed to appropriate clinical trials and shown to be effective in the treatment of acute viral infections.

Conclusion.

Complex remedies are not new but have their foundations firmly rooted in the origins of homeopathic prescribing. While in the past there have been many vitriolic battles between those who adhere only to the single homeopathic approach and those who espoused complexes, the reality is that many modern homeopaths use combinations of both singles and mixed homeopathic remedies. These are particularly valuable in the treatment of chronic illness. The use of modern homeopathic complexes has evolved so that they can be simply and effectively applied in the treatment of common, often chronic, conditions. Their indications, as we have implied with the evidence provided for two such remedies, are much simpler and more direct than the process involved in taking a prolonged classical homeopathic history. It is quite clear that there is an important place for both homeopathic complexes and the prescription of classical single remedies in the treatment of a whole variety of different complaints. The detailed prescription will inevitably depend on the patient’s presenting symptoms and response to treatment, as well as the homeopath’s experience. It is also apparent that homeopathy, like any branch of medicine, must continue to develop and evolve, and it is gratifying to see areas that involve complexes, such as homeopathic immunotherpy, developing into an essential part of homeopathic prescribing while being firmly grounded in the principles of conventional allergy.

Seeking the chance for a cure in Chronic Hepatitis

38 Annual Meeting of the European Association for the study of the Liver (EASL)
Geneva, Switzerland, 3-6 july 2003

The Annual Meeting of the European Association for the Study of the Liver (EASL) is a prestigious international congress. This year it attracted over 2500 delegates from around the world. The outstanding scientific program reflected many of the most recent developments in the field of hepatology. These includes, but were not restricted to advances in the management of viral hepatitis.

Several oral and poster presentations dealt with the treatment of hepatitis C and hepatitis B using peginterferon alfa-2a(40KD) (Pegasys®) with or without ribavirin. The recent introduction of pegylated interferons such as Pegasys, in the fight against Hepatitis C represented a major step forward in the treatment of this disease. Pegylated interferons in combination with ribavirin are rapidly becoming the accepted new gold standard in the treatment of HCV. As a main sponsor of the 38th Annual Meeting of ESLA, F. Hoffmann-La Roche Ltd. organized a satellite symposium that provided further insight in to the successful use of Pegasys in patients with hepatitis C, and the future role of Pegasys in the treatment of patients chronically infected with hepatitis B.

Pegasys plus ribavirin is highly effective in most patients with HCV genotype 2/3 infection.

M. Shiffman, Liver Transplant Program, Medical College of Virginia, Richmond, Virginia USA *et al.*

An analysis of pooled data from two large multicenter studies (NV 15942) investigated the virological response in 632 patients with HCV genotypes 2/3. Patients had received treatment with Pegasys (180 µg/week) plus ribavirin (800 or 1000/1200mg/day) for 24 or 48 weeks.

Of the 626 patients with post baseline HCV RNA assessment 97.9% achieved at least a temporary virological response at some time during treatment. A sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after the end of treatment was achieved by 80.6% of patients HCV RNA was assessed Using the Roche Cobas Amplicor^{R} HCV test v 2.0 which has a detection limit of 100 copies/ml (or 501U/ml).

Only 5.6% of patients experienced a breakthrough or relapse (defined as detectable HCV RNA during or following treatment after previously documented virological response) and just 1.1% failed to respond to therapy (defined as continual viramemia throught treatment and follow-up.)

SVR rates were generally similar across all treatment arms in the two studies, ranging from 77.8% (with Pegasys 180 µg/week plus Ribavirin 1000/1200 mg/day for 48 weeks in NV 158012) to 82.3% (with Pegasys 180 µg/week plus ribavirin 800mg/day for 24 weeks in NV15942). SVR rates were not compromised when ribavirin was given at a low dosage (800mg/day) or when the combination was administered for 24 weeks rather than 48 weeks. The results show that regardless of baseline viral load, patients with HCV

genotype 2/3 can be treated for 24 weeks with out sacrificing efficacy, thereby limiting side effects and the cost of treatment.

The study also showed that adherence played an important role in achieving optimal response to treatment. Among patients treated with Peagsys plus 800mg ribavirin daily over 24 weeks, SVR was achieved in 91% of patients with 280% adherence. Among those with = 80% adherence, 75% achieved a SVR, while only 33% of those who withdrew prematurely did so.

The author concluded that the majority of patients with HCV genotype 2/3 infection, treated with the combination of Pegasys and ribavirin can now be cured, especially if measures are taken to ensure adherence.

Long-term virological response – 4 year virus free

M. Swain, Division of Hepatology, University of Calgary, Calgary, Alberta, Canada, *et al*

Patients with chronic Hepatitis C who had achieved a SVR, define as undetectable HCV RNA (<501U/ml) six months after the end of treatment with Pegasys, with or without ribavirin, entered a follow up study to investigate the durability of the SVR. These were patients participating in five Pegasys pivotal trials and none of them had received any anti-HCV therapy after their original study treatment.

To date, 463 patients have been enrolled in the long term follow-up 131 (28%) have received Pegasys monotherapy and 332 (72%) have received combined Pegasys plus ribavirin.

After up to four years of follow-up, >99% of patients who achieved a SVR following treatment with pegasys, with or without ribavirin in pivotal clinical trials remained HCV RNA negative.

Quantifiable HCV RNA levels have been detected in only 4 (<1%) patients, two patients had received Pegasys (180 µg/week) plus ribavirin (1000/1200 mg/day) for 24 weeks in their original protocols.

The authors concluded that treatment with Pegasys alone or in combination with ribavirin results in durable SVR in patients with chronic hepatitis.

Non-responders to conventional interferon and ribavirin combination therapy

Pegasys plus ribavirin show promise in patients in whom previous conventional interferon and ribavirin combination therapy has failed.

An ongoing, prospective Mexican/Brazilian study to evaluate the efficacy and safety to evaluate the efficacy and safety of Pegasys and combination therapy, for the treatment of CHC, in patients who either did not respond to or relapsed after previous treatment with conventional interferon and ribavirin.

Patient in this trial are receiving Pegasys (180µg/week) plus (800mg/day) for 48 weeks. A total of 131 (96 non-responders, 35 relapsed) have now completed 24 weeks and 107 have completed 48 weeks on study.

Among the non-responders 67% (64/96) and 58% (45/77) had undetectable HCV RNA levels after 24 and 48 weeks of therapy respectively. Among the patients with virological relapse 89% (31/35) and 80% (24/30) had an undetectable HCV RNA at 24 and 48 weeks respectively.

The authors concluded that these preliminary findings reveal encouraging results for the antiviral efficacy of Pegasys and in patients who have relapsed or not responded to previous conventional interferon and ribavirin combination therapy.

SUBJECT INDEX

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