From Schistosomiasis to Hepatitis C: the Spread of HCV in Egypt

A Struthers PhD

University of the Sciences in Philadelphia,
600 South 43rd Street, Philadelphia, Pennsylvania, 19104-4495, USA.

Abstract

Hepatitis C is caused by a virus (HCV) and is transmitted by infected blood. It has no epidemiological relationship with schistosomiasis, which is a parasitic disease that is widespread in Egypt. From the 1950s to the 1980s, Egypt tried to control a schistosomiasis epidemic with a program of mass injections of tartar emetic. Largely because of poor sterilization techniques, this program spread hepatitis C to Egyptians in what is believed to be the largest iatrogenic transmission of blood-borne disease in history.
Struthers A. From Schistosomiasis to Hepatitis C: the Spread of HCV in Egypt Med J Therapeut Africa. 2007;3:213-21.

Keywords: hepatitis C schistosomiasis Egypt public health tragedy review

Schistosomiasis in Egypt

Hepatitis C is a widespread viral disease that is the most common cause of chronic hepatitis, cirrhosis, and hepatocellular cancer.(1,2) The story of the spread of HCV in Egypt in the last several decades begins with schistosomiasis, sometimes known as bilharziasis or bilharzia, an unrelated parasitic infection. Schistosomiasis has existed for millennia and has even been detected in mummies.(3) In Africa and the Middle East, the 2 main schistosome species infecting humans are *Schistosoma mansoni* and *S haematobium*.(4) The parasite schistosome infects humans in contact with fresh water containing specific snails that serve as intermediate hosts, and humans continue the life cycle by eliminating eggs with feces and urine.

Historically, schistosomiasis has been the most important public health problem in Egypt, and S. mansoni has been the principal cause of liver disease in this country.(5) Lower Egypt, with its farming villages along the Nile River delta, has always had high rates of this parasitic infection, but with the spread of irrigation for agriculture, the prevalence in Middle and Upper Egypt increased as well.(6)

The symptoms of the acute form of the disease, known as Katayama's fever, include fever, cough, abdominal pain, diarrhea, hepatosplenomegaly (abnormal enlargement of both the liver and the spleen), and eosinophilia (a large number of eosinophils in the blood).(4) Sometimes central nervous system lesions occur. Granulomatous lesions around ectopic eggs from *S mansoni* in the spinal cord may result in a transverse myelitis (inflammation of a transverse portion of the spinal cord) with severe loss of motor function in the lower extremities and lower portions of the trunk. Continuing infection may cause granulomatous reactions and fibrosis in the affected organs, which in turn may result in polyps in the colon, bloody diarrhea, portal hypertension, vomiting of blood, and enlargement of the spleen (splenomegaly). It can progress to pulmonary hypertension, inflammation of capillaries in the kidneys (glomerulonephritis), and central nervous system lesions.

Parenteral Antischistosomal Therapy

Schistosomiasis was not treatable until 1918.(6) In that year, JB Christopherson discovered that injections with the antimony salt tartar emetic could induce a cure. Because Egypt had the world's greatest schistosomiasis problem, parenteral antischistosomal therapy was extensively adopted starting in the 1920s. The treatment became available in different areas of the country at different times. In rural areas, health centers and traveling clinics practiced parenteral antischistosomal therapy in the form of mass treatment. Although a few antischistosomal drugs could be injected intramuscularly, tartar emetic was injected intravenously, and tartar emetic was the most widely used in Egypt.

Beginning in the 1950s and continuing until the 1980s, the Egyptian Ministry of Health conducted large campaigns using the standard treatment at that time, tartar emetic, as community-wide therapy.(5) Between 1964 and 1982, more than 2 million injections were given annually to an average of 250,000 patients.(6) Thus, in 18 years, approximately 36 million injections were administered, in addition to the numerous injections that had been administered earlier than 1964. Each human under treatment received, or was supposed to receive, a series of injections. In the 1960s, the average number of injections per patient was 9. After 1975, it dropped to 6 or fewer.

The enormous scale of these campaigns is suggested by a 1964 WHO report, describing a clinic. "Patients are grouped according to weight and appropriate dose and are lined up in queues for admission . . . The skilful doctor began injecting at 9:20 am and completed 504 injections of men, women and children by 10:10 am . . . This remarkable performance is being repeated at various tem-

pos all over Egypt . . . The used syringe is placed in an 'out' tray, from which it is taken by the nurse, washed through and boiled for a minute or 2. As soon as the syringe is cold, it is filled with a volume of the drug solution . . . It is then placed in the 'in' tray. . . There are usually 20 to 30 syringes in rotation."(7)

The rapidity of the inoculations, 10 per minute on average, and the small supply of syringes allowed little time for sterilization in boiling water for the recommended 2 minutes. The nurse would have had to wash a syringe, place it boiling water, remove a freshly boiled syringe, allow it to cool, fill it with the drug solution, and bring it to the doctor every 6 seconds, while making sure that each syringe in the queue was boiled for an adequate time.

The evidence that is examined in this paper shows that the syringes were not properly sterilized and thus transferred traces of blood and blood-borne pathogens from human to human. As a result, this massive effort to control one health problem resulted in the creation of another, as HCV was spread through the intravenous injections.(5) Indeed, this is estimated to be the largest known iatrogenic transmission of blood-borne infections in the history of the world.(6)

These mass injections transmitted blood-borne diseases because:

1)Humans received multiple injections over time

2)The injection equipment was insufficiently sterilized

3)Parenteral antischistosomal drugs were injected to humans of all age groups and treatment stages in a mass setting.(6)

Compared with a children's vaccination program, where injection equipment would be reused among a group with a low prevalence of HCV, this program, which treated children and adults, probably treated many more HCV-infected humans.(6) Furthermore, a full course of tartar emetic required several injections. The recommended regimen was 12 to 16 injections, and when the program began, the injections were administered over 2 to 3 weeks, or at the rate of almost one per day. For the comfort of the patients, however, this dosing schedule was changed in the 1960s to once a week over the course of 9 to 16 weeks.

This seemingly benign change, however, permitted greater transmission of HCV. Those who were already infected with HCV before they started treatment for schistosomiasis were transmitters of the virus. In addition, those who became infected with HCV early in the treatment period who acquired it from their earlier injections became transmitters of HCV in just 2 to 4 weeks. Therefore, at some point in the middle of their therapy, these both previously infected and newly infected individuals were capable of passing the disease to others who chanced to be treated with the same glass syringes or needles. In this way, continuous cycles of infection could have developed within treatment facilities. Such epidemic outbreaks could easily have gone undetected because acute clinical symptoms are not present in about 80% of HCV infections and, in addition, the symptoms could have been confused with schistosomiasis itself or with the side effects of tartar emetic.

Oral drugs for schistosomiasis were developed in the 1970s. The first such drugs, metrifonate and niridazole, were effective against *S haematobium*, but not against *S mansoni*, the largest source of schistosomiasis in Egypt.(6) By the mid-1980s, an effective oral drug for treating *S mansoni*, praziquantel, became available and gradually replaced tartar emetic as the standard treatment throughout Egypt. This not only reduced schistosomiasis; it also stopped the main engine of growth for the hidden HCV epidemic.(5)

High Prevalence of HCV in Egypt

Today, in rural areas where the parenteral antischistosomal therapy program was active, Egypt's population has a high prevalence of hepatitis C.

A cross-sectional study of serum samples from 1,945 Egyptians in 1996 estimated the overall rate of HCV seropositivity (that is, blood that tested positively for HCV RNA) was 15.6% for Egyptians aged 15 to 65.(8) Nationwide, this suggests that in 1996 over 5 million Egyptians were HCV seropositive and that 3.5 million had chronic hepatitis of varying degrees. A more recent estimate is that 8 to 10 million Egyptians have hepatitis C and that 5 to 7 million have active infections.(9)

The prevalence of HCV tends to be highest among humans who live in rural areas and who are old enough to have received parenteral antischistosomal therapy. Children under 5 years old were not treated, and parenteral antischistosomal therapy was stopped between 1982 and 1986, so humans born after 1981 were not injected.(2)

A random sample of 270 rural Egyptians in 1994 found that the prevalence of antibodies to HCV ranged from zero in children between 5 and 10 to 41% in adults over 50 who had the highest likelihood of receiving parenteral antischistosomal therapy.(10) Similarly, a 2001 community-based study of 801 humans who lived in the Nile River delta, an area targeted for antischistosomal therapy, estimated the seroprevalence of HCV among community residents 30 years old or older at 60%.(11) Lower rates have been reported in Upper Egypt. One study of 6,031 participants in this region found that 8.7% had HCV antibodies.(12)

For comparison, in the United States, the National Health and Nutrition Examination Survey, which covered 15,079 participants between 1999 and 2002, found that the prevalence of HCV in this country was 1.6%.(13) For an African comparison, in a maternity hospital in Zimbabwe, antibodies to HCV were

detected in 1.6% of indigent women. This group presumably does not have access to better health care than residents of Egypt, and yet has HCV prevalence similar to those of European and North American women and about 10% of the average prevalence in Egypt.(14) Another comparison comes from the Seychelles Islands off the east coast of Africa. Here, the age-adjusted seroprevalence of anti-HCV was even lower than among the indigent, pregnant women of Zimbabwe, 0.34% in a random sex- and age-adjusted sample of 1,006 humans of 25 to 64 years.(15) In short, the prevalence of HCV in Egypt is 10 to more than 100 times higher than in the industrialized countries in Europe and the Americas or in some other countries in Africa.

A brief look at the progression of hepatitis C and its medical consequences will suggest why the unintentional transmission of HCV was so harmful to Egypt's humans.

Hepatitis C: Background

Hepatitis C has a variable course that may be adversely affected by alcohol consumption and other factors, such as concomitant diseases.(1) HCV was first identified in 1989 by researchers at the Centers for Disease Control and Prevention in the United States, when it was determined to be the primary cause of non-A, non-B hepatitis.(16) It is an RNA virus that has 6 major genotypes and more than 50 subtypes.(1) This extensive genetic variation may explain the difficulties in developing a vaccine and the lack of response to therapy. The HCV RNA genotype that is most common in Egypt is genotype 4a, representing 85% of cases.(17)

HCV is transmitted primarily by exposure to infected blood, which can occur through injection drug use, unsafe medical practices, blood transfusions, and other means.(1,18) After an individual is exposed to HCV, the RNA of the virus can be detected in the blood within 1 to 3 weeks. Within 4 to 12 weeks on average, liver cell injury occurs, manifested by elevation of serum alanine aminotransferase (ALT). The majority of infected humans (60 to 85%) develop chronic infections. By definition, chronic HCV infection indicates that the HCV RNA persists in the blood for at least 6 months, but for most infected individuals it persists for life.

Testing and Treatment

This disease is often a precursor to potentially fatal diseases, such as cirrhosis and hepatocellular carcinoma.(16) Consequently, the United States National Institutes of Health (NIH) recommends testing for hepatitis C in humans with a history of transfusion of blood or blood-products before 1990, on hemodialysis, who have had multiple sexual partners, who are spouses or household members of HCV patients, or who inject drugs or share instruments for intranasal drug administration.(1) Testing is important because humans with hepatitis C are typically asymptomatic or have only minor, non-specific symptoms.

The first recommended test is the enzyme immune assay that detects HCV antibodies (anti-HCV).(1) This test is sensitive and specific, is reproducible and inexpensive, and thus is appropriate for screening at-risk populations. HCV RNA assays may be used to confirm the diagnosis. Testing for serum ALT is inexpensive and noninvasive but is less sensitive for determining disease status. A problem is that about 30% of patients with chronic HCV have normal ALT. Repeated ALT testing over time may allow a better assessment of liver injury, but this has not been clearly documented. A liver biopsy cannot serve to diagnose HCV infection, although it can provide useful histologic information on liver injury.

According to the NIH Consensus Statement, treatment for chronic hepatitis C should start when patients have 3 indicators of HCV:

1)Abnormal ALT for over 6 months

2)Positive HCV RNA

3)Liver biopsy has fibrosis and signs of necrosis and inflammation.(1)

The recommended treatment is first, vaccination against hepatitis A and B, and second, pegylated interferon plus the antiviral ribavirin, for 24 to 48 weeks, depending on the genotype of the HCV.(1,18)

A 48-week treatment regimen including a standard dosage of ribavirin was reported most effective against genotype 1, with a sustained viral response of 51% in a single study. A 24-week regimen including a reduced dose of ribavirin is reported sufficient against genotypes 2 and 3, with a sustained viral response of more than 73%. For genotype 4, a 48-week treatment was reported effective, with a 43% sustained viral response rate overall in one retrospective study.(19)

Treatment with pegylated interferon and ribavirin can cause significant side effects, including symptoms similar to influenza, abnormalities in the blood, and neuropsychiatric effects.(1) Depression is common among humans with HCV and also a side effect of interferon. In the registration trials for this combination therapy, side effects resulted in approximately 10 to 14% of the patients. Some of the most common problems were fatigue (up to 64% of patients), headache (up to 62%), myalgia (up to 56%), shaking and fever (up to 48%), and pyrexia (up to 46%).(20)

In Egypt, treatment is costly and not readily available. Interferon therapy, in fact, is unaffordable by the majority of Egyptian HCV patients and by most patients in the developing countries.(21,22) To find more cost-effective medications, other treatments for HCV have been studied in Egypt. In one study, a daily combination of ribavirin (600-800mg) plus amantadine (200mg) and ursodeoxycholic acid

(500mg) was compared with daily silymarin (450mg), an extract of biochemicals from milk thistle.(22) The ribavirin combination outperformed the silymarin treatment on all measures - normalization of ALT, end-of-treatment virologic response, sustained biochemical response (SBR), and sustained virological response (SVR). However, the ribavirin combination produced an SVR of only 2.4%, indicating that both treatments lacked efficacy.

Another study, which tested variations on the dosing regimen of IFN, ribavirin, and amantadine, concluded that the early virologic response to treatment should be used as a predictor for the sustained response in order to avoid unnecessary expenses for nonresponding patients.(23)

With cures and treatments being unpleasant and only sometimes available, affordable, or successful, prevention is critically important in Egypt. Preventative measures to avoid transmission of HCV comprise following standard, universal precautions for protection of medical workers and patients (such as screening the blood supply, screening organ donors, wearing protective gloves, and safely disposing of needles and blood), and avoiding behaviors that could put humans at risk.(1) For HCV-positive individuals, these behaviors include donating blood, tissues, or semen and sharing drug injection equipment. For those in households with an HCV-infected human, risky behaviors include improperly sharing razors or toothbrushes, although close contact with infected family members or even sharing utensils is acceptable.

In short, Egypt is facing huge (but to my knowledge unquantified) costs for the prevention, diagnosis, and treatment of hepatitis C and its sequel diseases, cirrhosis and hepatocellular cancer, in addition to the costs of lost economic activity due to sickness, premature death, or the side effects of treatment. More specifics on these consequences appear later in this paper.

Evidence That Parenteral Antischistosomiasis Transmitted HCV

Several studies have established that the antischistosomal injections, rather than schistosomiasis itself or some other cause, were the probable cause of the hepatitis C epidemic in Egypt.

First, there is evidence that schistosomiasis can exist without leading to HCV. A study in central Sudan, where there is a high prevalence of *S mansoni* infection, found no correlation between the presence of HCV antibodies and S mansoni infection, suggesting that the parasite is not the cause of hepatitis C.(24) A study of 506 residents of an area in Egypt endemic for *S mansoni* also found that there was no association of *S mansoni* infection with the seroprevalence of hepatitis C as indicated by anti-HCV.(25) However, there was a significant association of anti-HCV seropositivity with previous parenteral treatment for schistosomiasis (OR = 7.9).

Second, there is evidence that parenteral antischistosomal therapy is closely associated with the prevalence of HCV in Egypt. A 2001 community-based study of 801 humans over 10 years who lived in the Nile River delta identified no current practices that would contribute to the spread of HCV.(11) It found that the seroprevalence of HCV increased with age - from about 19% in the 10 to 19 year old cohort to about 60% among humans over 30. These findings are consistent with the theory that previous parenteral therapy facilitated HCV transmission.

Rao et al, however, noted in 2002 that all the previous studies were cross-sectional surveys, making it impossible to know whether the HCV infections existed before the antischistosomal campaigns.(2) These investigators also identified a limitation in most of the published studies: the unstated assumption that all individuals in the survey are independent of each other and that rates of infection are uniformly distributed. However, if parenteral antischistosomal therapy caused the transmission of HCV, these assumptions would not be valid because HCV infections would tend to be clustered in the households that decided to receive the therapy. Their study, therefore, tested the hypotheses that members of a household were more likely to participate in an antischistosomal campaign if another member participated and that HCV should thus be found more often in the participating households. Their analysis identified a significant clustering of HCV infections within particular households. The infections were not distributed uniformly across the village and were more likely to occur in houses whose occupants were injected. This provides additional evidence that the parenteral antischistosomal therapycampaigns are associated with the transmission of HCV infections in Egypt. After Rao's study, investigators still concluded that the campaign was the seminal event in the spread of HCV in Egypt. A 2004 study of hepatitis C risk factors concluded that prior antischistosomal injections significantly predict of HCV (OR = 4.3).(26)

Because HCV was not identified until 1989 and blood screening was not introduced until 1995, other means of HCV transmission could also have occurred in the last half of the twentieth century.(27) Among these are surgery, blood transfusion, organ transplantation, dental procedures, abortion, long-term hospitalization, hemodialysis, intravenous drug abuse, sexual contact, manicures, pedicures, tattooing, acupuncture, and circumcision.(28) Egyptian children who have HCV-infected mothers are at a high risk of being infected with HCV themselves, according to one study.(29)

Even today, because HCV is so common in Egypt, blood transfusion remains a major risk of HCV transmission among the country's children, according to a single-center study.(30) Supporting this, a 1995

study found that HCV seroprevalence was 70% in hemodialysis patients and 76% in thalassemic children (who receive frequent transfusions).(31) This study also noted that schistosomiasis did not appear to affect the seroprevalence of this disease.

The transmission of blood-borne pathogens can also be fostered by certain traditions. In the villages, many Egyptians rely on informal medical providers (mostly men who are "injectionists," barbers, and staff members at drug stores) for injections, dental work, wound treatment, and male circumcision.(32) In fact, these informal providers were preferred, even when primary health care facilities were accessible. In 2 villages studied, more than half of all newborns were delivered by traditional birth attendants. The informal health care providers knew little about HCV, and their practices could be contributing to HCV transmission.

Although other means of transmission may have contributed to the spread of HCV in Egypt and, indeed, may still be contributing to it, the current medical literature is unanimous that the antischistosomiasis injections are the primary cause of this country's hepatitis C epidemic.

High Prevalence of Schistosomiasis in Egypt

Unfortunately, Egypt's antischistosomiasis campaigns succeeded in spreading HCV, but not in controlling schistosomiasis. A recent study of over 89,000 individuals in 251 rural communities in Egypt determined that the prevalence of *S haematobium* infection in 4 governorates where it is endemic averaged 7.8% and ranged from 4.8 to 13.7%.(33) In areas where *S mansoni* is endemic, the prevalence of *S mansoni* infection in 5 governorates averaged 36.4% and ranged from 17.5 to 42.9%. This is not to say that the therapy failed to work on the individuals treated. But it does indicate that the fundamental causes of the infections, such as infested canal water and poor sanitation, still exist, at least in rural areas, exposing humans to the parasite.

Coinfection

With high prevalence rates for both HCV and schistosomiasis, it is inevitable that Egypt has a large number of humans with both diseases. Having both is more damaging to the liver and is associated with higher mortality rates than having just one. A prospective, long-term study of 126 Egyptian patients with schistosomiasis, HCV, or both followed these 3 groups for 40 to 85 months.(34) Of the group with both diseases, 48% had liver cirrhosis, compared with only 15% in the group with HCV alone, and none in the group with schistosomiasis. Hepatocellular cancerwas found only in the group with concomitant HCV and schistosomiasis. In addition, this group had more advanced liver disease, higher measures of HCV RNA, higher incidence of cirrhosis, and by far the highest mortality rate during follow-up, 48%.

Two other coinfection states need to be considered: HCV with HIV and HCV with hepatitis B virus (HBV). Although in the United States, HCV often appears as a coinfection with HIV/AIDS, in Egypt, the prevalence of HIV/AIDS in 2001 was <0.1% for adults.(35) Thus, the comorbidity of HCV and HIV is not a critical health issue for this country.

In contrast, hepatitis B virus (HBV) has a high prevalence in Egypt. Seroprevalence rates for HBV in one Nile delta village, reported in a 1996 study, were 24% in the general population and 66% in the group aged 40 to 67 years.(36) Although a full examination of the effects of HBV is beyond the scope of this paper, coinfection of HCV with HBV may lead to aggravated symptoms and a faster progression to hepatocellular carcinoma.(37) In addition, the combination of HCV and HBV has a significant additive effect on the risk of developing hepatocellular carcinoma (OR = 42.9).(36)

Egypt initiated a universal hepatitis B virus immunization of infants in 1991.(39) A study of acute viral hepatitis at a major urban referral center in Egypt determined that HBV decreased as a cause of symptomatic hepatitis between 1982 and 2002, dropping from 43.3 to 28.5% ($P < 0.01$).(39) To clarify, this is not the general prevalence of hepatitis B in Egypt, but the prevalence in a symptomatic population that was referred to a specialty hospital. Its significance is that it shows a dramatic drop in patients with HBV.

Another study also suggests that HBV is not nearly the problem that HCV is. It involved 20,000 Egyptian rural villagers, of whom 1,715 subjects were symptomatic for hepatitis and screened for ATL.(40) Of this group, 47 who had ALT at least twice normal level were tested for various forms of hepatitis. None of the tested individuals had serological evidence of either acute HBV or HCV. However, 33 had active HCV infection, as indicated by both anti-HCV and HCV RNA. Only 2 subjects were positive for hepatitis B surface antigen and had chronic HCV infection. As in the other study, the infection rate was much lower for HCB than for HCV. Concomitant HBV and HCV infections are less common than either infection alone, and they seem to be associated with more severe liver disease. (41)

Long-term Consequences of HCV

Up to 85% of HCV infections persist for life, leading to chronic hepatitis.(42) Only an estimated 15% to 20% of humans with HCV infections have symptomatic acute viral hepatitis, but the majority of this population in Egypt develops chronic hepatitis that is frequently asymptomatic and thus undetected for years.(9) Chronic hepatitis, once established, can slowly progress to fibrosis and cirrhosis and can eventually lead to hepatocellular carcinoma.(37) Over the course of 20 to 40 years, roughly 20% of those with HCV-induced chronic hepatitis develop

cirrhosis.(9) Possibly 10% of this group (that is, 2 to 3% of those with HCV-induced chronic hepatitis and cirrhosis) die each year as a result of complications of cirrhosis or hepatocellular carcinoma. In addition, in the United States, Europe, and Japan, infection with HCV is the most common indication for liver transplantation.(37)

Hepatocellular Cancer in Egypt

Hepatocellular cancer is the fifth most common malignancy in the world,(43) and HCV is one of the major risk factors contributing to the development of this cancer.(39) Of the deaths in Egypt in 2002, 8.1% were from cancer of all types. Liver cancer (not necessarily hepatocellular cancer) was the third leading cause of cancer deaths in Egypt for males (8 per 100,000, projected for 2005) and the fifth leading cause for females (4 per 100,000 population).(44)

There is convincing evidence that widespread HCV in Egypt has been a cause of hepatocellular carcinoma. A study published in 1999 found that seropositivity for HCV was significantly ($P < 0.001$) more frequent in patients with hepatocellular carcinoma (76%) than in patients with bladder cancer (47%).(37) This study found that HCV were strongly correlated with hepatocellular cancer in Egypt. It also found that comorbid HCV and HBV were also strongly correlated with hepatocellular carcinoma, but that HBV alone was not. A Chinese study affirmed that HCV is a significant risk factor. The mechanism by which HCV causes or promotes hepatocellular carcinomais poorly understood.(45)

Because HCV damages the liver in ways that lead to or creates conditions that increase the likelihood of hepatocellular carcinoma, over time its prevalence in Egypt should be increasing. This hypothesis has been tested. In a study of patients with chronic liver disease at the Cairo Liver Center, the proportion of humans with hepatocellular carcinoma attributable to HBV and HCV rose significantly over a 10-year period. Of the 22,450 total patients, an average of 5.9% had hepatocellular carcinoma, but over the 10 years of the study the proportion of patients with it rose significantly, nearly doubling from 4.0% in 1993 to 7.2% in 2002 ($P>0.001$).(46)

A second long-term study found a similar pattern. At the Mansoura University Gastroenterology Center in lower Egypt, a 13-year study of patients with hepatocellular carcinoma determined that the number of newly diagnosed cases of hepatocellular carcinoma was increasing annually and that its prevalence of was high in HCV patients.(47)

Other types of cancer may also be facilitated by HCV. For instance, a study of 227 Egyptian patients with non-Hodgkin's lymphoma (NHL) and 227 matched controls found that NHL can be an outcome of chronic HCV infection.(48)

It is possible that the role of HCV in causing hepatocellular carcinoma has been overestimated. A study of 30 newly diagnosed patients with hepatocellular carcinoma who also had anti-HCV tried to find undetected HBV infections.(49) None of the patients had hepatitis B surface antigen (HBsAg) in their blood, but 73% had HBV DNA in the cancerous liver tissues or adjacent nontumorous liver tissues. Many of these patients (10 of 22) had more than one HBV gene. In serological surveys, such patients would have been classified as having HCV-associated hepatocellular carcinoma, although the data suggest that HBV could have played a role in the progression of their disease.

The Ongoing Burden of HCV in Egypt

Chronic hepatitis C in Egypt is associated with a number of other diseases in addition to cancer and cirrhosis, many of them potentially life-threatening. These diseases include neutropenia, thrombocytopenia, hepatic fibrosis, diabetes mellitus, and necrolytic acral erythema.

"A study of 2 groups of 100 randomly selected Egyptians, one group with chronic active hepatitis C with positive HCV RNA and one group of healthy humans, concluded that anti-HCV was independently associated with both neutropenia and thrombocytopenia.(50)

"Cairo University Children's Hospital performed a liver biopsy on 43 children, with a mean age of 8.7, who had been diagnosed with HCV.(22) Hepatic fibrosis was present in 72% of these children.

"In a 1998 study of HCV-seropositive patients with chronic liver disease, 25% (150 of 591) had associated diabetes mellitus, while only 11% (25 of 223) of the seronegative control group had diabetes.(51) Patients with chronic hepatitis C in Egypt are 3 times more likely to develop diabetes mellitus than patients who are HCV seronegative.

"A rare skin lesion affecting the toes and feet, necrolytic acral erythema, which mostly has been reported in Egypt, has been identified as a cutaneous marker for HCV infection.(52)

Such diseases, along with cirrhosis, hepatocellular carcinoma, and schistosomiasis, indicate that Egypt will continue to face serious liver health problems in the future. As an example, one study predicted that around the year 2016, 350,000 to 700,000 new humans would develop liver cirrhosis as a result of HCV.(8)

Lessons from the Egyptian HCV Epidemic

Could the spread of HCV in Egypt by parenteral antischistosomiasis therapy have been avoided? Perhaps, because the need for proper sterilization of needles to prevent the transmission of blood-borne pathogens was understood before the 1960s.(53)

The central problem with the parenteral antischistosomal therapyprogram was not in the basic concept of inoculating humans against a serious disease, but in the execution of the program, specifically in the inadequate sterilization of needles and the timing of the injections starting in the 1960s.

To help prevent such tragedies in the future, one observer, Goldstein, believes that public health authorities should apply the "precautionary principle."(53) In the field of public health, the precautionary principle means that when a public health action is proposed, all risks and consequences must be taken into account. An action should not be taken if there is uncertainty about its impact. Goldstein suggests 3 rules to avoid harm. First, create multidisciplinary and multi-organizational approaches to problems; second, consider all potential risks as well as benefits; and third, install surveillance to detect incipient adverse consequences as soon as possible.

Nonetheless, it is not clear that Egyptian health authorities would have acted differently even if they followed the above rules. The mass parenteral parenteral antischistosomiasis therapy campaigns were arguably multidisciplinary and multi-organizational, as stipulated by the first rule, at least to the extent of marshalling Egypt's resources and allowing WHO inspections. Perhaps the health authorities could have consulted experts on sterilization techniques or patient safety, but they could not have found an expert on the infectious life cycle of the hepatitis C virus, for the disease was unknown.

Weighing risks and benefits, as stipulated by the second rule, is certainly a reasonable practice in public policy, and in retrospect (and only in retrospect) the Egyptian health authorities did not perform a sufficient examination of risks and benefits. However, they were facing a substantial known risk, in the form of schistosomiasis, and a substantial known benefit, in the form of a treatment that had been shown to be effective. Would the health experts possibly have considered that they might be spreading a yet-to-be-discovered virus? Or that the consequences would have been so damaging? It seems doubtful.

Moreover, there is a major difference between weighing risks and benefits, on the one hand, and seeking near certainty, on the other. Most actions in public health as well as other fields have some uncertainty about their impact, and a decision to proceed can rarely if ever be made with certainty. In fact, the fundamental scientific principal is that a theory cannot be proved true, but only false. Those theories that have not been disproved, the theory of relativity, the theory of evolution, are theories, however much science may rely on them. Thus, all scientific decisions involve some uncertainty. Although the history of the parenteral antischistosomal therapy campaign can be usefully read as a warning to be cautious about starting a program that could potentially affect the country's future health and economic well-being, as an admonition to decision makers to be humble about their ability to foresee the full consequences of their actions, or as an object lesson on the need to consider the worst possible case, it cannot logically mean that near certainty is required before action is taken.

Finally, Goldstein's third rule suggests that a surveillance system might have detected problems with the PAT program (side effects, inadequate sterilization, etc.) and stopped it before it did excessive damage. A good surveillance system, indeed, would have been an appropriate addition to a health initiative that was, in some respects, like a large, weakly monitored clinical study. Such a system might have stopped the injection program before it created the hepatitis C epidemic, if the health authorities had understood the circumstances and acted cautiously. But is it possible that Egyptian health authorities would have created the type of surveillance that could have detected a largely asymptomatic disease that had not been previously identified? This is unanswerable. Nevertheless, surveillance would not have caused harm and might have prevented a disaster. Thus, one lesson from the Egyptian HCV experience is that a good surveillance system should accompany a public health program.

In contrast to the worldwide HIV/AIDS epidemic, no social movement developed around the spread of hepatitis C in Egypt. It was reported by the press as a scandal and managed by the politicians without any involvement of infected humans.(54)

References

1.National Institutes of Health Consensus Statement. Management of Hepatitis C: 2002. At http://consensus.nih.gov/2002/2002HepatitisC2002116html.htm. Accessed 08Jul2007.

2.Rao MR, Naficy AB, Darwish MA, Darwish NM, Schisterman E, Clemens JD, Edelman R. Further evidence for association of hepatitis C infection with parenteral schistosomiasis treatment in Egypt. BMC Infect Dis. 2002;2:29, Epub 04Dec2002.

3.Deelder AM, Miller RL, deJonge N, Krijger N. Detection of schistosome antigen in mummies. Lancet. 1990. 335:724-725.

4.Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Parasitic Diseases. Schistosomiasis public information fact sheet. Laboratory Identification of Parasites of Public Health Concern Web site. At www.dpd.cdc.gov, accessed 14Jun2007.

5.Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. Hepatology. 2006;43:915-22.

6.Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, El Khoby T, Abdel-Wahab Y, Aly Ohn ES, Anwar W, Sallam I. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000;355:887-91.

7.Maegraith BG. Treatment of bilharziasis in Egypt, UAR. Geneva. 1964. Cited by: Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, El Khoby T, Abdel-Wahab Y, Aly Ohn ES, Anwar W, Sallam I. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000;355:887-91.

8.Mohamed MK, Rakhaa M, Shoeir S, Saber M. Viral hepatitis C infection among Egyptians the magnitude of the problem: epidemiological and laboratory approach. J Egypt Public Health Assoc. 1996;71:79-111.

9.Strickland GT, Elhefni H, Salman T, Waked I, Abdel-Hamid M, Mikhail NN, Esmat G, Fix A. Role of hepatitis C infection in chronic liver disease in Egypt. Am J Trop Med Hyg. 2002;67:436-42.

10.Abdel-Wahab MF, Zakaria S, Kamel M, Abdel-Khaliq MK, Mabrouk MA, Salama H, Esmat G, Thomas DL, Strickland GT. High seroprevalence of hepatitis C infection among risk groups in Egypt. Am J Trop Med Hyg. 1994;51:563-7.

11.Darwish MA, Faris R, Darwish N, Shouman A, Gadallah M, El-Sharkawy MS, Edelman R, Grumbach K, Rao MR, Clemens JD. Hepatitis c and cirrhotic liver disease in the Nile delta of Egypt: a community-based study. Am J Trop Med Hyg. 2001;64:147-53.

12.Nafeh MA, Medhat A, Shehata M, Mikhail NN, Swifee Y, Abdel-Hamid M, Watts S, Fix AD, Strickland GT, Anwar W, Sallam I. Hepatitis C in a community in Upper Egypt: I. Cross-sectional survey. Am J Trop Med Hyg. 2000;63:236-41.

13.Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705-14.

14.Madzime S, William MA, Mohamed K, October T, Adem M, Mudzamiri S, Woelk GB. Seroprevalence of hepatitis C virus infection among indigent urban pregnant women in Zimbabwe. Cent Afr J Med. 2000;46:1-4.

15.Bovet P, Yersin C, Herminie P, Lavanchy D, Frei PC. Decrease in the prevalence of hepatitis B and a low prevalence of hepatitis C virus infections in the general population of the Seychelles. Bull World Health Organ. 1999;77:923-8.

16.Ballester JM, Rivero RA, Villaescusa R, Merlín JC, Arce AA, Castillo D, Lam RM, Ballester A, Almaguer M, Melians SM, Aparicio JL. Hepatitis C virus antibodies and other markers of blood-transfusion-transmitted infection in multi-transfused Cuban patients. J Clin Virol. 2005;34 Suppl 2:S39-46.

17.Madwar M, Talkhan H, el-Salam A, Gabal HA, Zikery A, Gharieb H. Study of the significance of percentage of peripheral CD4+ & CD8+ T cells and the hepatitis C virus genotypes in Egyptian patients with chronic hepatitis C. J Egypt Public Health Assoc. 1998;73:41-55.

18.National Center for Complementary and Alternative Medicine. Hepatitis C and Complementary and Alternative Medicine: 2003 Update. National Center for Complementary and Alternative Medicine Web site. At http://nccam.nih.gov/ health/hepatitisc, accessed 01Jul2007.

19.Roulot D, Bourcier V, Grando V, Deny P, Baazia Y, Fontaine H, Bailly F, Castera L, De Ledinghen V, Marcellin P, Poupon R, Bourlière M, Zarski JP, Roudot-Thoraval F; Observational VHC4 Study Group. Epidemiological characteristics and response to peginterferon plus ribavirin treatment of hepatitis C virus genotype 4 infection. J Viral Hepat. 2007;14:460-7.

20.Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006;55:1350-9.

21.El-Zayadi AR, Attia M, Badran HM, El-Tawil A, Zalata K, Barakat E, Selim O, El-Nakeeb A, Saied A. Non-interferon-based therapy: an option for amelioration of necro-inflammation in hepatitis C patients who cannot afford interferon therapy. Liver Int. 2005;25:746-51.

22.El-Hawary MA, El-Raziky MS, Esmat G, Soliman H, Abouzied A, El-Raziky M, El-Akel W, El-Sayed R, Shebl F, Shaheen AA, El-Karaksy H. Assessment of hepatic fibrosis in pediatric cases with hepatitis C virus in Egypt. World J Gastroenterol. 2007;13:2846-51.

23.El-Zayadi AR, Attia M, Barakat EM, Badran HM, Hamdy H, El-Tawil A, El-Nakeeb A, Selim O, Saied A. Response of hepatitis C genotype-4 naïve patients to 24 weeks of Peg-interferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: a non-randomized controlled study. Am J Gastroenterol. 2005;100:2447-52.

24.Mudawi HM, Smith HM, Rahoud SA, Fletcher IA, Babikir AM, Saeed OK, Fedail SS. Epidemiology of HCV infection in Gezira state of central Sudan. J Med Virol. 2007;79:383-5.

25.el-Sayed HF, Abaza SM, Mehanna S, Winch PJ. The prevalence of hepatitis B and C infections among immigrants to a newly reclaimed area endemic for *Schistosoma mansoni* in Sinai, Egypt. Acta Trop. 1997;68:229-37.

26.el-Sadawy M, Ragab H, el-Toukhy H, el-Mor Ael-L, Mangoud AM, Eissa MH, Afefy AF, el-Shorbagy E, Ibrahem IA, Mahrous S, Abdel-Monem A, Sabee EI, Ismail A, Morsy TA, Etewa S, Nor Edin E, Mostafa Y, Abouel-Magd Y, Hassan MI, Lakouz K, Abdel-Aziz K, el-Hady G, Saber M.Hepatitis C virus infection at Sharkia Governorate, Egypt: seroprevalence and associated risk factors. J Egypt Soc Parasitol. 2004;34(1 Suppl):367-84.

27.Ahmetagi S, Muminhodzi K, Cickusi E, Stoji V, Petrovi J, Tihi N. Hepatitis C infection in risk groups. Bosn J Basic Med Sci. 2006;6:13-7.

28.Karaca C, Cakaloglu Y, Demir K, Ozdil S, Kaymakoglu S, Badur S, Okten A.Risk factors for the transmission of hepatitis C virus infection in the Turkish population. Dig Dis Sci. 2006;51:365-9.

29.Mohamed MK, Magder LS, Abdel-Hamid M, El-Daly M, Mikhail NN, Abdel-Aziz F, Medhat A, Thiers V, Strickland GT. Transmission of hepatitis C virus between parents and children. Am J Trop Med Hyg. 2006;75:16-20.

30.El-Raziky MS, El-Hawary M, El-Koofy N, Okasha S, Kotb M, Salama K, Esmat G, El-Raziky M, Abouzied AM, El-Karaksy H. Hepatitis C virus infection in Egyptian children: single centre experience. J Viral Hepat. 2004;11:471-6.

31.El Gohary A, Hassan A, Nooman Z, Lavanchy D, Mayerat C, el Ayat A, Fawaz N, Gobran F, Ahmed M, Kawano F, et al. High prevalence of hepatitis C virus among urban and rural population groups in Egypt. Acta Trop. 1995;59:155-61.

32.el Katsha S, Labeeb S, Watts S, Younis A. Informal health providers and the transmission of hepatitis C virus: pilot study in 2 Egyptian villages. East Mediterr Health J. 2006;12:758-67.

33.El-Khoby T, Galal N, Fenwick A, Barakat R, El-Hawey A, Nooman Z, Habib M, Abdel-Wahab F, Gabr NS, Hammam HM, Hussein MH, Mikhail NN, Cline BL, Strickland GT. The epidemiology of schistosomiasis in Egypt: summary findings in nine governorates. Am J Trop Med Hyg. 2000;62(2 Suppl):88-99.

34.Kamal S, Madwar M, Bianchi L, Tawil AE, Fawzy R, Peters T, Rasenack JW. Clinical, virological and histopathological features: long-term follow-up in patients with chronic hepatitis C co-infected with S. mansoni. Liver. 2000;20:281-9.

35.Central Intelligence Agency. The World Factbook Web site. Egypt. At: https://www.cia.gov/library/publications/the-world-factbook/index.html. Updated 19Jun2007, accessed 07Jul2007.

36.Darwish MA, Faris R, Clemens JD, Rao MR, Edelman R. High seroprevalence of hepatitis A, B, C, and E viruses in residents in an Egyptian village in The Nile Delta: a pilot study. Am J Trop Med Hyg. 1996;54:554-8.

37.Yates SC, Hafez M, Beld M, Lukashov VV, Hassan Z, Carboni G, Khaled H, McMorrow M, Attia M, Goudsmit J. Hepatocellular carcinoma in Egyptians with and without a history of hepatitis B virus infection: association with hepatitis C virus (HCV) infection but not with (HCV) RNA level. Am J Trop Med Hyg. 1999;60:714-20.

38.Zhang JY, Wang X, Han SG, Zhuang H. A case-control study of risk factors for hepatocellular carcinoma in Henan, China. Am J Trop Med Hyg. 1998;59:947-51.

39.Zakaria S, Fouad R, Shaker O, Zaki S, Hashem A, El-Kamary SS, Esmat G, Zakaria S. Changing patterns of acute viral hepatitis at a major urban referral center in Egypt Clin Infect Dis. 2007;44:e30-6, Epub 17Jan2007.

40.Meky FA, Stoszek SK, Abdel-Hamid M, Selim S, Abdel-Wahab A, Mikhail N, El-Kafrawy S, El-Daly M, Abdel-Aziz F, Sharaf S, Mohamed MK, Engle RE, Emerson SU, Purcell RH, Fix AD, Strickland GT. Active surveillance for acute viral hepatitis in rural villages in the Nile Delta. Clin Infect Dis. 2006;42:628-33, Epub 25Jan2006.

41.Crespo J, Lozano JL, Carte B, de las Heras B, de la Cruz F, Pons-Romero F. Viral replication in patients with concomitant hepatitis B and C virus infections. Eur J Clin Microbiol Infect Dis. 1997;16:445-51.

42.Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. Hepatology. 1997;26(3 Suppl 1):15S-20S.

43.el-Zayadi AR, Badran HM, Barakat EM, Attia Mel-D, Shawky S, Mohamed MK, Selim O, Saeid A. Hepatocellular carcinoma in Egypt: a single center study over a decade. World J Gastroenterol. 2005;11:5193-8 .

44.World Health Organization. WHO Global InfoBase Online Web site. Reports: The Impact of Cancer. At www.who.int/ncd_surveillance, accessed 28Jun2007.

45.Nada O, Abdel-Hamid M, Ismail A, El Shabrawy L, Sidhom KF, El Badawy NM, Ghazal FA, El Daly M, El Kafrawy S, Esmat G, Loffredo CA. The role of the tumor necrosis factor (TNF)--Fas L and HCV in the development of hepatocellular carcinoma. J Clin Virol. 2005;34:140-6.

46.el-Zayadi AR, Badran HM, Barakat EM, Attia Mel-D, Shawky S, Mohamed MK, Selim O, Saeid A. Hepatocellular carcinoma in Egypt: a single center study over a decade. World J Gastroenterol. 2005 Sep 7;11(33):5193-8.

47.Abdel-Wahab M, El-Ghawalby N, Mostafa M, Sultan A, El-Sadany M, Fathy O, Salah T, Ezzat F. Epidemiology of hepatocellular carcinoma in lower Egypt, Mansoura Gastroenterology Center. Hepatogastroenterology. 2007;54:157-62.

48.Cowgill KD, Loffredo CA, Eissa SA, Mokhtar N, Abdel-Hamid M, Fahmy A, Strickland GT.Case-control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. Int J Epidemiol. 2004;33:1034-9. Epub 2004 May 20.

49.Momosaki S, Nakashima Y, Kojiro M, Tabor E. HBsAg-negative hepatitis B virus infections in hepatitis C virus-associated hepatocellular carcinoma. J Viral Hepat. 2005;12:325-9.

50.Farrag KA, Elkemary TA, Saleh SA, Mangoud H. Blood count profile in chronic active hepatitis (C) Egyptian patients. J Egypt Public Health Assoc. 2004;79:83-94.

51.el-Zayadi AR, Selim OE, Hamdy H, Dabbous H, Ahdy A, Moniem SA. Association of chronic hepatitis C infection and diabetes mellitus. Trop Gastroenterol. 1998;19:141-4.

52.El-Ghandour TM, Sakr MA, El-Sebai H, El-Gammal TF, El-Sayed MH. Necrolytic acral erythema in Egyptian patients with hepatitis C virus infection. J Gastroenterol Hepatol. 2006;21:1200-6.

53.Goldstein BD. The precautionary principle also applies to public health actions. Am J Public Health. 2001;91:1358-61.

54.Radi S. [Press debates, scandals, and implementation of a prevention policy: on hepatitis C in Egypt]. [Article in French]. Rev Epidemiol Sante Publique. 2006;54 Spec No 1:1S45-52.