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## Hidden Danger: The Raw Facts about Hepatitis E Virus

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In 1980, hepatitis E was the last of the 5 recognized types of human hepatitis to be discovered; in 1990, the genome of the etiologic agent of hepatitis E, hepatitis E virus (HEV), was cloned and serological tests were developed [1]. It proved to be the most or second-most important cause of acute clinical hepatitis among adults throughout much of Asia, the Middle East, and Africa [2]. In contrast, HEV was rarely identified in industrialized countries, and the few reported cases of infection were usually in someone who had recently traveled to an endemic region. In the past few years this pattern has changed, as cases of endemic or autochthonous hepatitis E have been diagnosed with increasing frequency in individuals who have not traveled abroad.

HEV exists as at least 4 genotypes. Genotype 1 is the principal cause of disease in much of Asia, the Middle East, and Africa, whereas genotype 2 is associated with outbreaks in Mexico and Central Africa [2]. In 1998, 2 cases of autochthonous hepatitis E were reported in the United States [3]. These appeared not to have been caused by genotypes 1 or 2. At about the same time, HEV was recovered from domestic swine in the United States, and this virus proved to be closely related to the viruses recovered from the 2 humans in the United States with hepatitis E [3,4]. These were the first reports of what became known as genotype 3. Eventually, this genotype was recovered from swine herds throughout the Western Hemisphere and parts of Asia and shown to be highly endemic, infecting >90% of swine in some herds [4,5]. At about the same time, an additional genotype, genotype 4, was recovered from humans in parts of Asia and subsequently from swine in the same regions [6,7]. Both genotypes 3 and 4 continue to be recovered occasionally from humans with hepatitis E, principally from cases in Asia but also from sporadic cases (mostly genotype 3 infections) in North and South America and Europe [8]. However, genotype 1 and, to a lesser extent, genotype 2 have remained the most important causes of epidemics of hepatitis E in developing countries.

Genotypes 1 and 2 may be more virulent than genotypes 3 and 4: clinical hepatitis E caused by genotypes 1 and 2 occurs most frequently in individuals 15–35 years of age, whereas that caused by genotypes 3 and 4 occurs most frequently among immunocompromised individuals (eg, persons >40 years of age, patients infected with human immunodeficiency virus [HIV], and organ transplant recipients) [2,9,10]. Subclinical infections with genotypes 3 and 4 may be responsible for the relatively high prevalence of anti-HEV antibodies in industrialized countries [11].

Shortly after the discovery of genotypes 3 and 4, a zoonotic association between genotypes 3 and 4 and human disease was proposed [4,7]. The prevalence of antibodies to HEV was higher among swine workers than among blood donors in the United States, and epidemiological and

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molecular associations between hepatitis E cases and eating raw or undercooked meat from domestic swine, wild boar, and Sika deer were reported in Japan [12-16].

The increased incidence of reported cases of hepatitis E in Europe has focused attention on a virus that previously had garnered little attention. Cases have been reported with increasing regularity throughout Western Europe, as well as in some Eastern European countries [17, 18]. Most of these have been cases of infection with genotype 3, which is highly endemic among domestic swine and wild boar in the same regions. The consensus is that in most cases of hepatitis E in Europe the disease is zoonotically acquired, but the principal modes of infection (through contaminated food, direct exposure to swine and swine feces, or environmental contamination) are not well understood. Indeed, HEV sequences (and, in 1 case, viable viruses) have been found in raw pork liver purchased from commercial shops in Europe, the United Kingdom, the United States, and Asia. Proper cooking of pork containing HEV would render it safe to eat, but HEV is still viable after heating at 56°C (the temperature of rare to medium-cooked meat) for 1 h [19].

However, much pork is consumed that has not had even that degree of cooking. In this issue of the *Journal*, a case-control study by Colson et al [20] links cases of hepatitis E in 3 separate outbreaks to the consumption of figatellu, a traditional pig liver sausage from Corsica that is widely eaten in southeastern France and commonly consumed raw. Sequences of HEV that closely matched the sequences recovered from the patients were recovered from 7 of 12 figatelli purchased from local supermarkets; the titer of HEV in these sausages was  $10^3$ – $10^6$  genome copies per slice. However, the viability of HEV was not tested. Figatellu is smoked for a few days but not otherwise processed and is usually consumed within 5–25 days. This study has prompted French public health authorities to require that labels on figatellu call for thorough cooking [20].

Another study in this issue of the *Journal*, by Legrand-Abrevanel et al [21], also addresses the issue of autochthonous hepatitis E but from the standpoint of the characteristics and epidemiology of the disease among solid-organ transplant recipients who had incidentally contracted hepatitis E. The authors studied 38 patients in southwestern France with HEV genotype 3 infection, 58% of which progressed to chronicity. The patients were compared with matched control participants in southwestern France who had no evidence of HEV infection. According to the results of a questionnaire, consumption of game meat (hunted animals such as wild boar, deer, and hares), consumption of processed pork (pate, sausages, etc), and consumption of mussels were all statistically significantly more common among case patients than among control participants (68% of case patients vs 47% of control participants consumed game meat, 97% of case patients vs 84% of control participants consumed processed pork, and 100% of case patients vs 78% of control participants consumed mussels). The association between hepatitis E and consumption of game meat remained statistically significant after logistic regression analysis.

Eating undercooked pork and pork products appears to be quite common in Europe. Although the study by Legrand-Abrevanel et al [21] did not address the consumption of undercooked meat, other studies have explored its association with hepatitis E. A case-control study by Wich-mann et al [22] in Germany, where hepatitis E is a reportable disease, found that consumption of raw or undercooked beef, wild boar meat, and offal (liver, kidney, and intestine) was statistically significantly associated with autochthonous HEV infection after bivariate analysis, but only consumption of offal and consumption of wild boar meat were independently associated with hepatitis E after conditional logistic regression. What is noteworthy is that 79% of case patients and 66% of control participants had consumed raw or undercooked pork products during the previous 2 months.

What is not clear is how effective the usual processing procedures for uncooked meat and offal and their products are in inactivating pathogens such as HEV. Processes such as salting, air-drying, and smoking are ancient traditions of human-kind that are now perpetuated for taste rather than the necessity of preserving food. HEV can be found in the liver, blood, and intestinal tract, which are all consumed in one form or another and often together, such as in sausages. How safe are these products? The question is difficult to answer because HEV grows poorly in cell culture, and in vivo testing of viability requires nonstandard laboratory animals—nonhuman primates or pigs for genotypes 3 and 4.

Is the frequency of hepatitis E increasing in industrialized countries or is this only a perception? Probably the latter is correct. There has been a rapid rise in pork consumption in some developing countries, but this may not be true in Western countries. Although the per capita consumption of pork in Europe is already the highest in the world [23], pork consumption has remained relatively stable in recent years, for example, in Hungary, as has identification of hepatitis cases in at least 1 medical center where HEV has also been identified in the livers of 3 suspect meat sources: swine, wild boar, and roe deer [24,25]. Similarly, the frequency of HEV infection of swine in Spain has been relatively constant, at least since 1985 [26]. Thus, a doubling of reported hepatitis E cases in European countries from 2004 through 2005 does not likely reflect increased pork consumption or increased infection of swine [27]. More likely, it could simply reflect increased testing for hepatitis E. Commercial tests for antibodies to HEV have been notoriously unreliable, and a hepatitis E test has never been licensed in the United States. This lack of interest in hepatitis E tests by the industry most likely reflects their calculation that such tests will not be very profitable. Consequently, testing for hepatitis E in the West has been sporadic at best. However, the industry is beginning to take notice of the growing interest in hepatitis E in industrialized countries. Most commercial tests remain suspect, as comparisons reveal different results with different tests [28]. Several years ago, most of the anti-HEV tests available at the time were compared, using a panel of coded samples [29]. The study revealed wide discrepancies in sensitivity and specificity. A comparison of currently available diagnostic tests for hepatitis E could provide the medical community with the information needed to choose tests that accurately reflect the extent of hepatitis E, which in turn should aid in better understanding the sources of infection.

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