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INSIDE

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Bites in the Night: A Rabies Immunization Update on People and Animals

CONFERENCE COVERAGE

By Mary Louise Scully, MD

AN EXCELLENT UPDATE ON RABIES WAS PROVIDED BY CHARLES E. RUPprecht, the Rabies Section Chief of the CDC, during the Symposium, *Control of Zoonoses: A Veterinary Perspective* at the recent 51st annual ASTMH meeting in Denver, Colo. The most significant development is that Imovax-ID, the human diploid cell vaccine formulated for pre-exposure *intradermal* rabies vaccination, is no longer available in the United States. This event occurred in April 2001. The WHO position will remain supportive of the intradermal route for pre-exposure vaccination.

This discontinuation occurs in the setting of otherwise continued expansion of the intradermal route for pre-exposure prophylaxis and postexposure treatment, especially in areas of the world where rabies remains a significant health problem and cell-derived vaccines and rabies immune globulin are in short supply. It is thought that the estimated 50,000 rabies deaths reported per year (India alone reports 30,000 deaths per year) is actually an underestimate.[1] For health care providers in the United States, the discontinuation of Imovax-ID eliminates a less-expensive pre-exposure rabies prophylaxis regimen. However, the human diploid cell vaccine Imovax-IM, rabies vaccine adsorbed (RVA), and purified chick embryo cell vaccine (PCEC) remain available in the United States for intramuscular use.

Rabies is an acute, fatal encephalitis caused by neurotropic RNA viruses in the family *Rhabdoviridae*, genus lyssavirus. Classic rabies virus (genotype 1) is the type species of lyssavirus. Only 1 viral species was believed to cause rabies, but more recent investigations have showed at least 7 putative genotypes. Classic rabies virus accounts for most cases of rabies, but all lyssaviruses have shown capacity as human or animal pathogens.

Although many carnivorous mammals can serve as hosts, dogs remain the major reservoir and vector of rabies virus. Worldwide, dogs cause the majority of the human deaths due to rabies. Although domestic and wild cats do *not* seem to act as reservoirs for rabies, cats are effective vectors of transmission; hence, cats should be vaccinated despite the small relative risk of sarcoma.

In the United States, adequate canine and livestock vaccination has largely eliminated rabies from domestic animals, and the majority of animal rabies

occurs in wild terrestrial animals such as raccoons, which accounted for 37.7% of all animal rabies cases in 2000. Skunks, foxes, and other mammals, including mongooses, groundhogs, bobcats, coyotes, badgers, and opossums, accounted for the remainder. Small mammals and rodents such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, rabbits, and hares are not important in the epidemiology of rabies, and bites from these animals rarely require rabies prophylaxis.

Bats account for a relatively small proportion of the animal rabies cases reported in the United States (16.8% in 2000), but in the last 20 years variants of bat rabies have become the most common causes of human death from rabies.[2] Six of the 7 lyssavirus genotypes have been isolated from bats. Of the 39 cases of bat-associated rabies deaths in the United States during the last 50 years, only 9 (23%) reported a definite history of a bite, even though 20 (51%) reported contact with bats.[3] Since bats have small teeth, their bites might have gone unnoticed. Therefore, bat encounters in which a patient awakens to find a bat in the room, finding a bat in the room of an unattended child, or seeing a bat near a mentally impaired or intoxicated person warrant postexposure rabies prophylaxis.[4]

The resurgence of raccoon rabies that began in the Mid-Atlantic states in the late 1970s has spread so that raccoon rabies is now enzootic in all of the eastern coastal states as well as Alabama, Pennsylvania, Vermont, and West Virginia. Oral rabies immunization of free-ranging wildlife using vaccine-laden baits has shown promise in Europe, and similar efforts are under way to limit the expansion of raccoon rabies in the United States. More than 2 million doses of an oral vaccinia-rabies glycoprotein (V-RG) bait vaccine have been distributed in Ohio alone in the last 2 years. Additional states are expected to implement V-RG in the future as well. The hope is to make an immune barrier spanning the country from the shores of Lake Erie in Ohio south to the Gulf of Mexico in Alabama, preventing further westward spread of raccoon rabies.[5] Unfortunately, these types of control measures are less applicable to limiting bat rabies.

A practical question from the audience raised the issue of an allergic reaction in a patient after the third dose of a postexposure series. Rupprecht suggested trying another rabies vaccine formulation. The decision to continue the series should be based on the exposure history. A titer in the midst of the series should not be used to decide if the patient is protected. If a patient has had significant rabies exposure, every effort should be made to complete the recommended postexposure treatment.

Two recent companion reviews referenced above deserve special mention as outstanding papers on the past, present, and future of rabies.[2,3] ■

References

1. Rabies vaccines. WHO Weekly Epidemiological Record. 2002;77(14):109-119.
2. Hemachudha T, et al. Human rabies: A disease of complex neuropathogenetic mechanisms and diagnostic challenges. *Lancet Neurol*. 2002;1:101-109.
3. Rupprecht CE, et al. Rabies re-examined. *Lancet Infect Dis*. 2002;2:337-353.
4. CDC. Human rabies prevention-United States, 1999: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 1999;48(No.RR-1).
5. Krebs JW, et al. Rabies surveillance in the United States during 2000. *J Am Vet Med Assoc*. 2001;219: 1687-1699.

Hepatitis A Vaccine—Pushing the Limits

CONFERENCE COVERAGE

By Philip R. Fischer, MD, DTM&H

Synopsis: *New data and consensus discussions provide updated guidance about the use of hepatitis A vaccine for young children, in US residents, and in individuals who are traveling very soon after their pretravel consultations.*

Sources: Mackell S. Immunization Update session, Pediatric Travel Medicine symposium. ASTMH annual meeting, Denver, November 12, 2002; DeSilvestri A, et al. Decline of maternal hepatitis A virus antibody levels in infants. *Acta Paediatr*. 2002;91:882-884; Kanra G, et al. Hepatitis A booster vaccine in children after infant immunization. *Pediatr Infect Dis J*. 2002;21:727-730; CDC. Yellow Book Update. ASTMH annual meeting, Denver, November 13, 2002.

Common US recommendations and licensing suggest that hepatitis A vaccine should not be used before 2 years of age, but European licensing includes 1 year olds, and many American travel medicine providers frequently use the vaccine in even younger children. Similarly, official recommendations call for the use of immune serum globulin (ISG) rather than vaccine to protect travelers who will be leaving

within a few weeks of their pretravel consultation, but many practitioners do not follow this recommendation. New data have recently been published, and new recommendations were discussed at the recent ASTMH meeting in Denver. Awareness of this material can help travel medicine practitioners wisely choose their hepatitis A vaccine at the limits of age and for various itineraries.

Infants

Dr. Sheila Mackell capably reviewed the use of hepatitis A vaccine in children at the November 2002 ASTMH meeting. Various products are widely available and are effective both in stimulating antibody responses and in protecting against clinical hepatitis. Current US recommendations call for the use of hepatitis A vaccine in children 2 years of age and older who are traveling to or residing in a high-risk area. In fact, there are 11 western US states with relatively high risk, and hepatitis A vaccine is recommended for children residing in these states. In Europe, hepatitis A vaccine is used in younger children.

Hepatitis A infection is usually asymptomatic in young children. Some children, however, do become ill. Others can unknowingly transfer infection to peers and adult contacts for weeks after their own infection. This poses potential public health risks, especially for people in contact with returned travelers.

Currently available hepatitis A vaccines are effective in stimulating the development of protective antibody levels for 94-100% of recipients, even when children as young as 1 year of age are included in studies.[1,3] What data can guide our use of hepatitis A vaccine in young children? Seronegative infants (those who did not receive antibodies transplacentally from seropositive mothers) respond well to hepatitis A vaccine.[4,5] Seropositive infants tolerate the vaccine well and do have some priming response.[6] However, seropositive infants usually do not achieve lasting protection from vaccine.[7]

When do infants clear their passively acquired anti-hepatitis A antibody? Earlier in 2002, maternal antibody levels were reported to have "decayed significantly" by 12 months of age, but 39% of tested children were still seropositive at that time.[8] DeSilvestri and colleagues found a surprising 61% of 18 initially seropositive children still to be seropositive at 12 months of age; they did note, however, that some infants in their area became infected during the first year of life. Thus, it could be that some of the seropositive 12 month olds had lost maternal antibody and then acquired a new hepatitis A infection.

In the recent study noted as a source above, Kanra and colleagues followed children they had previously vaccinated as infants, many of whom were seropositive.[7] At age 4 years, 77% of previously vaccinated children were seropositive. The seropositive 4 year olds who were revaccinated boosted their antibody titers, and the seronegative children converted to seropositivity.

Combining all this information, we can conclude that hepatitis A vaccine is probably effective in initially seronegative children of any age. Infants with passively acquired maternal antibody will not always receive full, lasting protection but do not have adverse outcomes related to early vaccination. Thus, potentially seropositive infants going to an area of risk can either receive early vaccine administration or undergo serologic testing to see if vaccination is warranted. If infants have been vaccinated without confirming seronegativity, they should receive subsequent immunization sometime after age 2 to confer long-lasting protection.

Travelers Soon to Depart

What should be done with travelers who present for consultation just a few days before departure? Currently, the CDC recommends ISG, rather than hepatitis A vaccine, as a means of protecting these travelers. Participants at the ASTMH meeting were told that the CDC is modifying the recommendation to suggest that vaccine be used when departure is within 2 weeks (rather than 1 month) of the pretravel consultation.

The CDC bases this modified recommendation on the knowledge that hepatitis A antibody titers rise to protective levels within 2 weeks of immunization. Others, however, point out that hepatitis A has a month-long incubation period; thus, the vaccine's protective effect would probably overcome this slowly incubating infection if the vaccine were given right up to the time of exposure. In fact, there is some evidence that postexposure hepatitis A vaccination is protective.[9,10] Nonetheless, there is 1 reported case of a healthy adult who was vaccinated 12 days prior to departure and then developed hepatitis A illness after 7 weeks in India.[11] ■

References

1. WHO position paper on hepatitis A vaccines. *Can Commun Dis Rep*. 2000;26-05 (http://www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr/00vol26/dr2605ea.html)
2. Abarca K, et al. Efficacy of hepatitis A vaccination in children aged 12 to 24 months. *Arch Med Res*. 2001;32:468-472.
3. Lopez EL, et al. Safety and immunogenicity of a pediatric formulation of inactivated hepatitis A vaccine in

Argentinean children. *Pediatr Infect Dis J*. 2001;20:48-52.
4. Troisi CL, et al. Immunization of seronegative infants with hepatitis A vaccine (HAVRIX:SKB): A comparative study of two dosing schedules. *Vaccine*. 1997; 15:1613-1617.
5. Piazza M, et al. Safety and immunogenicity of hepatitis A vaccine in infants: A candidate for inclusion in the childhood vaccination programme. *Vaccine*. 1999; 17:585-588.
6. Dagan R, et al. Immunization against hepatitis A in the first year of life: Priming despite the presence of maternal antibody. *Pediatr Infect Dis J*. 2000;19: 1045-1052.
7. Kanra G, et al. Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children. *Turk J Pediatr*. 2000;42:105-108.
8. Lieberman JM, et al. Kinetics of maternal hepatitis A antibody decay in infants: Implicatons for vaccine use. *Pediatr Infect Dis J*. 2002;21:347-348.
9. Sagliocca L, et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: A randomized trial. *Lancet*. 1999;353:1136-1139.
10. Irwin DJ, Millership S. Control of a community hepatitis A outbreak using hepatitis A vaccine. *Commun Dis Public Health*. 1999;2:184-187.
11. Kurup A, et al. Acute hepatitis A in a traveler who had received preexposure inactivated hepatitis A virus vaccine. *Clin Infect Dis*. 1999;28:1324-1325.

Yellow Fever Update

CONFERENCE COVERAGE

By Lin H. Chen, MD

At the 51st meeting of the American Society of Tropical Medicine and Hygiene in Denver, Colo, November 10-14, 2002, a full symposium was devoted to yellow fever (YF). In *Morbidity and Mortality Weekly Report* (November 8, 2002) the CDC published additional adverse events associated with the 17D YF vaccine in the United States as well as the Recommendations of the Advisory Committee on Immunization Practices (ACIP) on Yellow Fever. This timely symposium addressed important issues regarding the assessment of YF fever risks in travelers vs the risks from YF vaccination.

Dr. Tom Monath provided an overview of YF risk in unvaccinated travelers. It is estimated that 9 million travelers visit endemic countries each year. In Africa, travelers can encounter increased mosquito activity in rainy and early dry season (July to October), during rural exposures, in moist savannas, and unfortunately YF risk exists in both cities and towns. During epidemic periods there is *extreme* risk. Surveillance is simply not sensitive; outbreaks occur 1-2 months before recognition and reporting. The ratio of reported vs actual cases is up to 1 in 300. The risk to the traveler spending 1 week in an epidemic region is 1:280. In an endemic region, 1-2% of the local population is infected annually, and the risk to the traveler spending 1 week in an endemic region is estimated to be 1:4200.

There have been 10 reported cases of YF in travelers since 1979. Six cases occurred in the last 5 years, or 0.03/100,000. In comparison, the risk of typhoid fever is 0.03%, and the risk of hepatitis A is 0.3%. South America has reported about 500 cases per year, mostly jungle YF. In 2001, jungle YF occurred in Minas Gerais, near Belo Horizonte.

Dr. Marty Cetron from the CDC discussed YF vaccine safety. The Asibi YF strain from Nigeria (1927) was the original virus used in the development of the vaccine. The seed lot for 17D YF virus strain has been used for the vaccine since 1942. The 17DD, 17D-204, and 17D-213 are all derived from the 17D strain. Adverse events were initially reported from the United States in 4 recipients aged 63-79 years of age, with an onset between 2-5 days. Additional cases were reported from Brazil in a 5-year-old girl from Goias and a 22-year-old woman from Sao Paolo, and from Australia in a 53-year-old man. Six of the 7 patients died, and vaccine type YF was isolated in 5 of 5 samples obtained.

Since the original reports of YF vaccine-associated viscerotropic disease (YEL-AVD), previously called multiorgan systemic failure, 2 additional cases have been reported from the United States. These patients were a 25-year-old man (April 2001) and a 70-year-old man (March 2002). A third possible case involved a 56-year-old recipient in 1999. Three other cases were described in the letters to *Lancet*; among these are: 45-year-old British male, 50-year-old Swiss male, and 71-year-old German male. Case fatality rates were 54%, and all cases occurred in people receiving their primary vaccinations.

The syndrome has been renamed 17D YEL-AVD. Onset of the syndrome occurs within 2-5 days of vaccination with YF and is associated with fever, myalgia, arthralgia, increased liver enzymes and bilirubin, sometimes with liver failure, thrombocytopenia, DIC, lymphocytopenia.

Through the Vaccine Adverse Event Reporting Sys-

tem (VAERS), increased surveillance has detected 4 cases of neurotropic adverse events following YF vaccination in 2001-2002. These cases presented with meningitis or meningoencephalitis, in which CSF pleocytosis and CSF IgM for YF were detected. Case fatality rates for neurotropic events had been < 5%. Reversion to neurovirulence has an onset from 4-23 days. Previously called postvaccinal encephalitis, the syndrome is called YF vaccine-associated neurotropic disease (YEL-AND) and is associated with a greater risk for children younger than 6 months old.

What is the risk of YEL-AVD? Approximately 200,000 doses of YF vaccines were sold to civilians and 800,000 doses to the military each year; A total of 3-5.5 million doses were distributed to civilians from 1996-2002. Two to 3 cases of YEL-AVD occurred per 1,000,000 doses during this period. Risk by age groups indicated a greater risk in those older than 50.

17D YEL-AVD is a newly recognized syndrome, and 17D YEL-AND is possibly re-emerging. 17D YEL-AVD is *not* caused by the emergence of wild-type YF clone, nor due to vaccine-type virus mutation. It is most likely a result of idiosyncratic host responses, and it appears to be age-related. To date, 17D YEL-AVD has only occurred with primary YF vaccination. Host susceptibility genes may be playing a role, and there can be acquired cofactors or confounders. For example, ISG (ISG) was in much wider use before 1996 and may have played some role. The true incidence of adverse events is unknown but is probably in the range of 3-5 per million for viscerotropic events and 2-3 per million for neurotropic events. Revised guidelines are available via the CDC web site: www.cdc.gov. Enhanced surveillance is done by reporting to www.vaers.org (800-822-7967). Additional information is available from the CDC at www.cdc.gov/ncidod/dvbid/yellowfever/index.htm (970-221-6400 or 404-498-1600).

Dr. Anthony Marfin discussed current research needs to define YF vaccine risks and benefits. He pointed out the rising interest in YF vaccination as a result of growth in general tourism, ecotourism, sports vacations, and lumber/oil development. In addition, the first YF case to be imported to the United States in 72 years occurred in 1996. At the same time, an increased range for the mosquito vector, *Aedes aegypti*, is evident along with increased interest in vector-borne diseases, especially in flaviviruses, since the emergence of West Nile Virus. Future research must focus on the true risk of vaccine, the true risk of YF in travelers to areas, and its pathophysiology.

Dr. Mary Wilson addressed means to raise awareness and risk communication. Specifically, how do we save the greatest number of lives given the current vaccine? Risk of paralytic polio after the first dose of oral polio vaccine is approximately 1:750,000. The risk of death from motor vehicle accident is approximately 1:6700. The risk from YF itself appears to be greater than both, and the risk of adverse events from YF vaccine is smaller than that of death from motor vehicle accident. ■

References

1. CDC. Adverse events associated with 17D-derived yellow fever vaccination—United States, 2001-2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(44):989-993.
2. CDC. Yellow fever vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR Morb Mortal Wkly Rep*. 2002; 51(RR-17):1-12.

Additional Notes from the ASTMH Meeting

CONFERENCE COVERAGE

By Lin H. Chen, MD

Emerging Infections and Outbreaks

Abstract #274. Marcos LA, et al. A case-control study of human fascioliasis in the province of Azangaro, Puno (Peru). Marcos et al evaluated epidemiological and clinical indicators, laboratory results (including hematocrit, eosinophil counts, Fas2-ELISA, and *Fasciola hepatica* egg counts in feces), animal feces, and relationship of fascioliasis to other intestinal parasites. Compared to controls, subjects with *F hepatica* had a greater degree of eosinophilia. The main risk associated with *F hepatica* infection appeared to be drinking alfalfa juice. Patients frequently presented with periods of jaundice. *Ascaris lumbricoides* was the only intestinal parasite associated with fascioliasis. The diagnosis of fascioliasis should be considered in assessing eosinophilia in returned travelers, especially if specific epidemiologic risks exist.

Abstract #359. McLaughlin JB, et al. Outbreak of echovirus 18 meningitis in a summer camp—Prince William Sound, Alaska, 2001 (national implications). McLaughlin et al conducted telephone interviews with attendees of a summer camp and ill contacts to determine the causes of a viral meningitis outbreak. A total of 79

case patients were identified, and echovirus 18 was identified from 11 case patients. Water sources for the camp were found to be untreated and contained high fecal coliform counts. State regulations may be needed to protect the health of camp attendees.

Abstract #527. Miller RS, et al. Serologic evidence of unusual JE complex flaviviruses along the Thai-Myanmar border. Miller et al studied unspecified febrile illnesses in the Thai-Myanmar border in Sangkhlaburi, Thailand. Screening of villagers has shown very high antibody titers against West Nile Virus (WNV) and lower titers against Japanese Encephalitis. Sentinel surveillance in animals during 2001 showed seroconversion to flavivirus in 50% of ducks and most pigs, most of which occurred following 21 days in the field. Some samples showed high titers to WNV, and further identification is being conducted. This report indicates the possible presence of WNV in Thailand.

Malaria

Abstract #51. Maguire JD, et al. Therapeutic efficacy of chloroquine or mefloquine for uncomplicated *Plasmodium falciparum* and *P vivax* malaria in Javanese migrants to Papua, Indonesia. Between November 1996 and July 1999, 698 *P falciparum* and 723 *P vivax* infections in migrants were studied. Chloroquine failed in 80% of *P falciparum* infections and in 60% of *P vivax* infections. Maguire et al found no mefloquine treatment failures; thus, mefloquine is effective against chloroquine-resistant *P falciparum* and *P vivax*.

Abstract #199. Dev V. Emergence of multidrug-resistant malaria in the northeastern India. *P falciparum* causes roughly 60% of malaria cases (and *P vivax* causes the rest) in northeastern India. Chloroquine and sulfadoxine-pyrimethamine (SP) were evaluated for treatment efficacy against *P falciparum*. Dev et al reported chloroquine sensitivity in 57% of cases, whereas 35% showed late treatment failure, and 8% showed early treatment failure. Among the cases that received SP, 79% responded and 21% failed. Failures to chloroquine and SP were treated with quinine and all responded. Multidrug-resistant strains of *P falciparum* appears to have been introduced in India at the border with Myanmar and can spread further with migration of people.

Abstract #567. Miller RS, et al. Azithromycin-quinine combination therapy for the treatment of uncomplicated falciparum malaria in Thailand. Combinations of azithromycin (500 mg b.i.d. for 3 days, 500 mg b.i.d. for 5 days, or 500 mg t.i.d. for 3 days) and oral quinine (30 mg/kg/d divided q8 hours) were evaluated for treatment efficacy against *P falciparum* on the Thai-Myanmar border, using quinine-doxycycline for 7 days as control. Azithromycin 500 mg b.i.d. for 5 days or 500 mg t.i.d. for 3 days in combination with oral quinine led to 100% cure. However, there was 10% recrudescence at 28 days following the regimen with azithromycin 500 mg b.i.d. for 3 days. This combination has potential uses in falciparum malaria patients for whom doxycycline is contraindicated, such as young children and pregnant women.

Schistosomiasis

Abstract #263. Jackson F, et al. Schistosomiasis prophylaxis using DEET. Fifteen subjects applied 50% DEET during an expedition to Lake Malawi, an area known to have schistosomiasis. The group's average contact with water was 48 hours. The subjects were followed up 3 months later with urine microscopy, eosinophil count, and schistosomal egg antigen ELISA. Thirteen subjects were found to be free of schistosomiasis. Two subjects whose tests showed schistosomiasis were found to have positive tests on blood samples taken before their exposure in Lake Malawi. This report suggests that application of DEET 8-12 hours after exposure may prevent schistosomiasis.

Bacterial Infections

Abstract #36. Mohamed MA, et al. Rapid diagnosis of typhoid fever by enzyme immunoassay (EIA) detection of Salmonella serotype *typhi* antigens from urine. Investigators developed an EIA using monoclonal antibodies to detect somatic antigen 9, flagellar antigen d, and Vi capsular polysaccharide antigen from urine. The test detected Vi antigen from 73% of 44 patients with typhoid fever. The sensitivity increased to 100% when testing was done during the first week of fevers. False-positive results occurred in patients with brucellosis, but the test can be useful in the diagnosis of typhoid fever.

Abstract #414. Dualan ARA, et al. Bacteriology of drinking water in the greater Manila area of the Philippines. Coliform and bacteriological tests performed at the University of the Philippines College of Public Health in 1998 were analyzed retrospectively. Analysis of drinking water from Metro Manila and surrounding provincial areas showed that provincial water was more likely to have higher coliform and total bacteriological counts (TBC). Filteration of water improved the coliform content and TBC. Surprisingly, bottled water was more likely to have coliforms and higher TBC than public water. Boiling the water may be advised! ■

'Mad Deer Disease'—Another Reason to Become a Vegetarian?

ABSTRACTS & COMMENTARY

Synopsis: *The emergence of chronic wasting disease, a transmissible spongiform encephalopathy in North American cervids, raises concern about potential transmission to humans, as has occurred elsewhere with bovine spongiform encephalopathy and vCJD.*

Sources: Wisconsin deaths may be first instance of 'mad deer' disease transmission to humans. Reuters Medical News. July 31, 2002; Regalado A. Spreading 'mad deer' plague leaves US scientists baffled. *The New York Times*. May 2002; http://www.maddeer.org/plague.html; http://www.madison.com/captimes/opinion/column/guest/23628.php; McCombie B. Who is to blame for mad deer? *The Progressive*. August 2002; www.progressive.org/August%202002/mcco0802.html; Mad deer disease spreads across the USA—Hunters are starting to worry. *Outdoor Life*. Oct 1999; http://www.organicconsumers.org/Meat/maddeerusa.cfm; McCombie B. Stop the madness. Malady threatens Wisconsin's elk, deer and, ultimately, people. *Isthmus Newspaper*. Madison, WI, July 2000. http://www.madison.com/captimes/opinion/column/guest/23628.php.

THREE DEER HUNTERS, AGED 30 AND YOUNGER FROM Utah, Oklahoma, and Maine died of Creutzfeldt-Jakob disease (CJD) during the period of 1997-2000. This raised an alarm since the national occurrence of CJD is approximately 1 per million, and the disease generally affects older people. Because of the common variable of consuming deer meat, autopsies were performed to confirm the diagnoses. The results of the autopsies demonstrated that the 3 had died of sporadic CJD and not the more "virulent" form of variant CJD (vCJD). More recently, the Centers for Disease Control and Prevention (CDC) is helping the Wisconsin health department review the cases of 3 hunting partners who died in the 1990s (2 in 1993 and 1 in 1999) of rare brain disorders.

vCJD, also known as "mad cow disease," is responsible for somewhere between 43 and more than 100 deaths in Europe; numbers vary depending on the source of information that is reviewed. Concern over vCJD is that it has a shorter incubation period and affects people at an earlier age.

Chronic wasting disease (CWD) is a variant of the mad cow disease that has been reported in deer and elk. CJD and CWD are classified as transmissible spongiform encephalopathy (TSE). The "infectious" agent associated with TSE is a small, relatively stable protein known as a prion. Prions are normally folded in a loopy pattern resembling a corkscrew, but when they unfold, they can cause other prions to change shape. This triggers the chain reaction that ultimately results in destruction of tissue, typically in the brain.

CWD was first noticed in a Colorado research facility in 1967 and slowly spread among wild deer and elk in Nebraska and Wyoming. It has also been found in captive elk in Colorado, Kansas, Montana, Nebraska, Oklahoma, Saskatchewan, and South Dakota. In Colorado at least 15% of some wild herds are affected. Because it has also been found in animals imported into Wisconsin, authorities there recommend following the lead of Montana, which placed a moratorium on the importation of all game farm animals. Testing of animals in Wisconsin was negative in 1999, but in 2001, 3 animals tested positive for CWD.

The Food and Drug Administration (FDA) has gone on record saying that mad deer disease is not a threat in the United States. Dr. Ermias Belay of the CDC told a panel investigating this that the cases "suggest a possible relationship with CWD," but investigations found "no strong evidence of a causal link" with the patients' illnesses. The FDA has now suggested, however, that significant efforts be undertaken to remove the CWD from the US deer and elk populations.

COMMENT BY THOMAS G. SCHLEIS, MS, RPH

Tom Thorn, a Wyoming state veterinarian, when discussing CWD, stated, "You cannot say with 100 percent certainty that it won't transmit to people, but there is no evidence that it will transmit to people." That essentially sums up the wealth of knowledge we have about mad deer disease—maybe it's a threat, maybe it's not.

The list of TSEs is becoming extensive. We have scrapie in sheep, mad cow, mad deer, mad elk, CWD, CJD, and vCJD.

Having grown up in Wisconsin where the 4 favorite pastimes are eating, drinking, watching television, and hunting, I can only imagine the effect this information has had in that state. Wisconsin has approximately 100 deer and elk farms, and it is big business, with elk calves selling for around $1500 and bull breeding garnering as much as $20,000. Farms sell venison, and the velvet that peels from new elk antlers are considered an aphrodisiac in Asia, selling for $17 an ounce. Hunting guides can also package tours that cost from $1000 to $10,000 depending on the ultimate "prize." This is a billion-dollar

industry with hunters killing close to half a million deer annually. With no mandatory reporting required for animals suspected of CWD, the disease could go unchecked for years.

What is important here is that this phenomenon be thoroughly investigated. Lab studies have suggested that CWD could theoretically infect humans by converting human prion proteins into their deadly form in a lab dish after exposure to CWD prions. If we have learned anything from mad cow disease, it is that denial can be deadly. With mad cow disease, it was years before British officials were convinced that there was a causal link and appropriate action was taken. It is vital that we do not allow the same mistake to happen here. ■

CME Questions

18. Which one of the following statements regarding YF is correct?

a. More people are infected with YF in South America than Africa annually.
b. Young adult recipients are more susceptible to develop YF vaccine adverse neurotropic disease (YEL-AND).
c. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) occurs in 1:4200 vaccine recipients.
d. YEL-AVD is associated with fever, myalgia, arthralgia, increased liver enzymes and bilirubin, some with liver failure, thrombocytopenia, DIC, and lymphocytopenia.

19. All of the following are true concerning rabies *except*:

a. In the last decade, human rabies deaths in the United States were increasingly due to bat variant rabies.
b. Cats are effective vectors of rabies and should be vaccinated.
c. Oral rabies bait vaccines are being used in the control of raccoon rabies in the United States.
d. Worldwide, raccoons are the main reservoir and vector of rabies virus.
e. Intradermal human diploid cell vaccine is no longer available on the US market.

20. Which of the following is *not* true about hepatitis A vaccination?

a. Vaccination is now recommended for healthy, nontraveling children in some urban areas of the United States.
b. Vaccination causes serious adverse outcomes in young infants.
c. The hepatitis A vaccine is licensed for use prior to 2 years of age in Europe.
d. Postexposure vaccination is often protective against hepatitis A infection/disease.

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

PHARMACOLOGY WATCH

FDA Approves Generic Version of AstraZeneca's Prilosec

The FDA has approved the first generic version of AstraZeneca plc's blockbuster drug, omeprazole (Prilosec). KUDCO, a subsidiary of Germany's Schwartz Pharma was granted the approval in a court ruling in mid-October. The FDA has cleared a number of other generic versions of the drug; however, this is the first, in the eyes of the courts, that does not infringe on patents held by AstraZeneca. In a complicated set of deals, KUDCO is partnering with Andrix Pharmaceuticals and Genpharm Inc to bring the drug to market by early 2003. Prilosec, with worldwide sales of more than $4 billion a year, has been the focus of intense legal wrangling as AstraZeneca has pulled all the stops to prevent marketing of generic forms of the drug. Meanwhile, consumer groups hoping to bring down the cost of prescription medications have been urging the Bush administration to speed generics, such as omeprazole, to market. The FDA has approved omeprazole for over-the-counter use but is still working with AstraZeneca on labeling language. Consumers can expect OTC Prilosec in the second quarter of next year.

Pegasys Approved To Treat Hepatitis C

A second pegylated interferon has been approved for the treatment of chronic hepatitis C infection. F. Hoffmann-La Roche Ltd's peginterferon alfa-2a (Pegasys) will compete with Schering-Plough's peginterferon alfa 2-b (PegIntron) for this indication. It is estimated that nearly 4 million Americans have evidence of infection with hepatitis C, of which nearly 3 million have chronic hepatitis C infection. In the last few years, standard treatment has become interferon either standard or pegylated, alone or in combination with ribavirin. Standard interferon must be given 3 times a week. Adding polyethylene glycol (PEG) to the interferon molecule increases the elimination half-life, allowing for less-frequent dosing, generally once a week. Pegasys is approved only as monotherapy; however, Schering-Plough has applied for approval of combination therapy with Pegasys and ribavirin. The FDA has fast-tracked the application, with final approval expected before the end of year.

HRT Reduces Alzheimer's Risk, Study Says

Yet another study has weighed in on the issue of hormone replacement therapy and the risk of Alzheimer's disease (AD). This study of a population of older adults in Cache County, Utah showed that 10 years or more of HRT significantly reduced the risk of Alzheimer's disease. Importantly, the study also showed that once women are in the early stages of Alzheimer's disease, it is too late for HRT to have any benefit. The rate of AD was evaluated in 1357 men (median age, 73.2 years) and 1889 women (mean age, 74.5 years). After a 3-year follow-up, women who formerly used HRT or women who are currently using HRT for longer than 10 years had a statistically significant reduction in the rate of AD (HRT users represented 26 cases/1066 women, non

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

HRT users represented 58 cases/800 women [adjusted HR, 0.59; 95% CI, 0.36-0.96]). Almost all the HRT-related reduction in the incidence of AD was among women who had formerly used HRT. A related editorial suggests that there may be a critical period soon after menopause, which is characterized by rapid estrogen depletion, where HRT may provide the most neuroprotective benefit for women (*JAMA*. 2002;288:2123-2129, 2170-2173). In mid-October officials from the National Institutes of Health announced that they would continue to study the effects of HRT or conditions such as osteoporosis and AD. This announcement was important in light of the early termination of the Women's Health Initiative study on hormone replacement in July. Currently, the National Institute on Aging is funding 3 studies that will compare how well HRT combination therapy or estrogen alone helps prevent memory loss and loss of cognitive function in women older than 65.

Heparin Plus Alteplase More Effective

Patients with submassive pulmonary emboli (PE) will fare better treated with heparin plus alteplase compared to heparin alone, according to a new study. Alteplase, a thrombolytic agent, is commonly used in the treatment of massive PE. This study seeks to define the drug's role in submassive PE in hemodynamically stable patients. Two hundred fifty-six patients with PE and pulmonary hypertension or RV dysfunction but without arterial hypertension or shock were evaluated. One hundred thirty-eight received heparin plus alteplase 100 mg and 118 received heparin plus placebo. The primary end point was in-hospital death or treatment escalation (pressors, repeat thrombolysis, intubation, CPR, or emergency embolectomy). The primary end point occurred nearly 3 times as often in the heparin plus placebo group, all due to treatment escalation. In-hospital death was nonsignificantly higher in the heparin group, 3.4%, vs 2.2% for the alteplase group ($P = .71$). However, 30-day event-free survival was higher with heparin vs alteplase ($P = .005$). The authors conclude that thrombolytic therapy with alteplase plus heparin should be considered in patients with submassive PE (*N Engl J Med*. 2002;347:1143-1150).

Digoxin Effects Differ By Sex

Digoxin should be used with caution in women with heart failure and may even be associated with an increase in mortality, according to a new study. The Digitalis Investigation Group looked at 6800 patients on digoxin therapy with the primary end point being mortality from any cause. While there was no increased mortality in men on digoxin, women on the drug had a higher rate of death compared to the placebo group (33.1% vs 28.9%, respectively; 95% CI,-0.5-8.8). The authors conclude that the effect of digoxin therapy differs between men and women. Women with congestive heart failure of a higher mortality rate associated with use of the drug, while the same is not seen with men (*N Engl J Med*. 2002;347:1403-1411).

McClellan Named FDA Commissioner

The Food and Drug Administration finally has a commissioner, after 2 years of vacancy in the position. The new commissioner, Mark McClellan, MD, was approved quickly and unanamously. He has a background in both medicine and economics, and has been an advisor to both Presidents Clinton and Bush. He has most recently been a professor of medicine and economics at Stanford University. Dr. McClellan joins the FDA at a time of unprecedented change and turmoil. There is high turnover at the agency, and criticism from consumer groups that drug approvals take too long on the one hand, and are too cursory on the other. President Bush has recently backed removing legal obstacles to the approval of generic drugs, a move meant to reduce prices for consumers, and a move that is not popular with Pharma.

FDA Actions

The FDA has approved 2 formulations of buprenorphine, a new schedule III narcotic for treatment of patients with narcotic addiction. Buprenorphine will be marketed as Subutrex by Reckitt Benckiser pharmaceuticals, while the second preparation, which combines buprenorphine with naloxone, will be marketed by the same company as Suboxone. The combination with naloxone is intended for maintenance therapy since naloxone will safeguard against intravenous abuse. The FDA took the unusual step of putting buprenorphine into the schedule III category rather than schedule II to allow easier prescribing in compliance with recent congressional legislation making maintenance narcotics more available to patients.

Bristol-Myers has received approval to market Metaglip, a new combination drug for treatment type 2 diabetes. Metaglip combines gliptizide and metformin in a single tablet for initial therapy of type 2 diabetes. ■