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Yellow Fever Vaccination

SPECIAL REPORT

The current recommendations for yellow fever vaccination are summarized.

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

After 7 cases of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) were reported to the Advisory Committee on Immunization Practices (ACIP) in June 2001, enhanced surveillance was initiated. Between June 20, 2001, and August 31, 2002, 2 patients with severe adverse events consistent with YEL-AVD and 4 with yellow fever-associated neurotropic disease (YEL-AND) were reported. All were vaccinated in the United States with the 17D-derived yellow fever vaccine, and all recovered, after hospitalization, without sequelae. Of the 12 cases of YEL-AVD reported worldwide since this complication was first recognized in 1996, 5 were persons younger than 50 years of age. The onset of YEL-AVD occurred 1 to 6 days after vaccination.

These and other observations were taken into account in the development of the latest ACIP recommendations for yellow fever vaccination, some of which follow.

General

1. Persons older than 9 months traveling to or living in areas of South America and Africa that lie within the yellow-fever endemic zone should be vaccinated regardless of whether the infection is officially reported or not in those areas and without regard to whether urban or rural areas are being visited.

2. Because of concern of an increased risk of adverse reactions, travelers older than 65 years "should discuss with their physicians the risks and benefits of vaccination in the context of their des-

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tination-specific risk for exposure to yellow fever." However, "yellow fever vaccination . . . should be encouraged as a key prevention strategy."

3. A valid International Certificate of Yellow Fever Vaccination may be required by certain countries if the traveler has been in countries known or thought to have yellow fever—even if the traveler was only in transit.

Infants

1. Travel to infected areas with infants 6 thru 8 months old should be avoided because of an increased risk of YEL-AND (encephalitis); travel to endemic/epidemic zones should be postponed or avoided whenever possible.

2. With infants 6 thru 8 months old with unavoidable exposure to an environment with an increased likelihood of infection, such as active endemic or epidemic transmission, vaccination "might be considered."

3. Because of the risk of YEL-AND, infants younger than 6 months old should in no instance be vaccinated.

Pregnancy and Nursing

1. The safety of yellow fever vaccination during pregnancy has not been established and should only be performed if travel to an endemic area is unavoidable and if an increased risk of exposure exists. Fetal infection with YF17D occurs at a low rate and has not been associated with congenital abnormalities.

2. If international travel requirements, rate than increased risk of infection, is the only reason to vaccinate a pregnant woman, vaccination should be avoided and a waiver letter should be provided. The traveler with a waiver should contact the country's consulate prior to travel.

3. Because postvaccination seroconversion may be reduced in pregnancy, serological tests to evaluate immune response should be considered.

4. Because of a theoretical risk of transmission of the vaccine virus, vaccination of nursing mothers should be avoided, but if travel to high-risk areas cannot be avoided or postponed, vaccination can be performed.

Laboratory Personnel

1. Lab personnel who might be exposed to virulent yellow fever virus or to concentrated preparations of the 17D vaccine strain should be vaccinated.

Altered Immune Status

1. Patients with AIDS, symptomatic HIV infection, leukemia, lymphoma, "generalized malignancy," or who are receiving immunosuppressive therapy including radiotherapy, alkylating drugs, antimetabolites, or high-dose and/or prolonged courses of corticosteroid therapy should not be vaccinated.

2. "Low-dose (ie, 20 mg prednisone or equivalent/day), short-term (ie, less than 2 weeks) systemic corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be sufficiently immunosuppressive to constitute an increased hazard to recipients of yellow fever vaccine."

3. Individuals who have asymptomatic HIV infection, do not have AIDS, have "established laboratory verification of adequate immune system function," and who cannot avoid potential exposure to yellow fever

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virus should be offered the choice of vaccination.

4. If international travel requirements, rate than increased risk of infection, is the only reason to vaccinate an asymptomatic HIV-infected person, vaccination should be avoided and a waiver letter should be provided.

5. Because seroconversion rates after vaccination of asymptomatic HIV-infected persons is reduced, measurement of their neutralizing antibody response to vaccination should be considered prior to travel.

Hypersensitivity

1. Because the vaccine is produced in chick embryos, yellow fever vaccine should not be administered to individuals with hypersensitivity to eggs.

2. If international travel requirements, rather than increased risk of infection, is the only reason to vaccinate an individual with egg hypersensitivity, vaccination should be avoided and a waiver letter should be provided.

3. If vaccination is considered essential because of a high risk of exposure and the history of egg allergy is questionable, an intradermal test dose can be administered according to the instructions contained in the package insert.

Simultaneous Administration of Other Vaccines and Chloroquine

1. Available evidence indicates that yellow fever vaccine may be administered simultaneously with the following vaccines: measles, smallpox, BCG, hepatitis A, hepatitis B, Typhim Vi, and Menomune, as well as with immune serum globulin given in the usual IM dose.

2. No data exist regarding possible interference between yellow fever and rabies or Japanese encephalitis vaccines.

3. Chloroquine administration does not interfere with the antibody response to yellow fever vaccine.

Revaccination

1. While evidence indicates that immunity to yellow fever virus induced by vaccination persists for 30-35 years (and probably for life), international health regulations require revaccination at intervals of 10 years.

COMMENT BY STAN DERESINSKI, MD, FACP

It is estimated that approximately 200,000 cases of yellow fever occur throughout the world each year. Illness may range from subclinical to fatal; no specific antiviral therapy is available and the fatality rate of severe yellow fever is approximately 20%.

The live, attenuated vaccine available in the United States is derived from the 17D-204 strain of yellow fever virus. Active solicitation of symptom reports from vaccinees participating in trials yields an incidence of mild adverse events, mostly influenza-like symptoms, in less than 25%, resulting in approximately 1% curtailing their regular activities. Immediate hypersensitivity reactions occur at an estimated incidence of 1 in 130,000 to 1 in 250,000 vaccine recipients; while these predominantly occur in individuals with egg hypersensitivity, it is possible that the gelatin stabilizer in the vaccine preparation may play a role in some cases.

Transient vaccine strain viremia commonly occurs in healthy individuals during the first week after vaccination and ordinarily is not associated with adverse consequences. However, YEL-AND manifesting as encephalitis may occur at an incidence estimated at less than 1 in 8 million vaccine recipients, with much higher rates occurring in infants. 17D virus has been isolated from the brain of at least 1 victim. YEL-AVD has, to date, exclusively occurred after primary vaccination. The estimated incidence in the United States is 1 in 400,000 doses distributed. The most severe forms of the illness are characterized by the development of multiorgan system failure.

The Centers for Disease Control (CDC) requests that they promptly receive reports of patients suspected of having YEL-AND or YEL-AVD. Report forms are available at http://www.vaers.org and can be submitted by fax at 877-721-0366, by mail (PO Box 1100, Rockville, MD 20849-1100), or by phone (800-822-7967). Additional information is available at http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm and at http://www.cdc.gov/travel, as well as at 970-221-6400 and 404-498-1600. The latter 2 numbers for, respectively, the CDC's Divisions of Vector-Borne Infectious Diseases and the Division of Global Migration and Quarantine, can also be called to arrange for serological testing to determine serological responses to yellow fever vaccination in asymptomatic HIV-infected and in pregnant individuals in whom vaccination is indicated.

Editor's Note: *A physician's letter stating the contraindication to vaccination has been acceptable to certain governments outside the United States. Ideally, the letter should be written on letterhead stationary and bear the stamp used by health department and official vaccination centers to validate the International Certifi-*

cate of Vaccination. When planning to use a waiver letter, the traveler should also obtain specific and authoritative advice from the embassy or consulate of the country or countries she or he plans to visit. Waivers of requirements obtained from embassies or consulates should be documented by appropriate letters and retained for presentation with the International Health Certificate. ■

Iron, Lactoferrin, and Biofilms

ABSTRACT & COMMENTARY

Synopsis: *By sequestering iron, lactoferrin enhances twitching motility of P aeruginosa and, as a result, prevents biofilm formation.*

Source: Singh PK, et al. A component of innate immunity prevents bacterial biofilm development. *Nature*. 2002;417: 552-555.

BIOFILMS PLAY AN IMPORTANT ROLE IN A VARIETY OF infections, including chronic airway infection caused by Pseudomonas aeruginosa in cystic fibrosis patients. It seems likely that normal mucosal surfaces that are commonly colonized by bacteria have mechanisms that prevent such biofilm formation. Singh and colleagues at the University of Iowa examined the hypothesis that a component of the innate immune system, lactoferrin, that is present in high concentrations at mucosal surfaces, is a component of a defense against the production of biofilms by colonizing bacteria.

In vitro studies using flow cell chambers were continuously perfused with "biofilm medium" in the presence and absence of a concentration of lactoferrin (20 µg/mL) that did not affect the growth of a strain of *Pseudomonas aeruginosa* in a free-swimming state. The typical stages of biofilm development, including attachment, microcolony formation and enlargement, and "towering pillar and mushroom-shaped" biofilm, were observed in the absence of lactoferrin. In contrast, in the presence of lactoferrin, this development pattern was disrupted and differentiated biofilms structures did not develop. There was no effect of lactoferrin, however, upon already mature *P aeruginosa* biofilms.

Observation with time-lapse video microscopy determined that, while lactoferrin caused only a minimal increase in the dividing time of attached bacterial cells, it markedly altered the movement patterns of those bacteria. In particular, lactoferrin markedly decreased the proportion of "squatters" (stationary cells), while markedly increasing the proportion that were "ramblers" (cells that moved away from the site of bacterial division).

Conalbumin, a lactoferrin-like molecule from chicken eggs that, like lactoferrin, binds iron, also impaired biofilm formation, as did deferoxamine. When lactoferrin was saturated with iron, it failed to prevent such formation. Experiments determined that removal of iron from the environment led to an increase in a specialized form of bacterial surface locomotion mediated by type 4 pile called twitching. Lactoferrin was demonstrated to stimulate twitching motility in *P aeruginosa*, an effect that was lost when the organisms resided in established biofilms.

P aeruginosa grown in biofilm was highly resistant to H_2O_2 and to tobramycin, but surface growth in the presence of conalbumin (used in these experiments because of its lesser cost) was associated with a dose-dependent decrease in resistance.

■ COMMENT BY STAN DERESINSKI, MD, FACP

It would seem unlikely that the evolution of host defense mechanisms would ignore such an important aspect of infectious disease as the role of bacterial biofilms. The observations in this remarkable set of experiments demonstrate that this problem has not been ignored—evolution has provided us with at least one innate mechanism of defense against this problem in the form of lactoferrin.

Lactoferrin is present in normal airway secretions at concentrations as high as 1 mg/mL and is also present in high concentrations in tears and breast milk. This cationic protein exerts antibacterial activity by 2 mechanisms: binding to lipopolysaccharides, it disrupts bacterial cell membranes, and sequestration of, making it unavailable to microorganisms.

These experiments demonstrate that lactoferrin impairs *P aeruginosa* biofilm formation by making iron unavailable and consequently stimulating twitching motility of the bacterial cells. Singh et al best summarize the overall conclusions: "Our data indicate that a higher level of iron is required for biofilm formation than is needed for growth. If the iron level is acceptable, *P aeruginosa* is cued to stop moving, form microcolonies, and eventually develop into biofilms. If iron levels are not sufficient, the *P aeruginosa* cells keep moving. This response may protect the bacteria from constructing complex, durable biofilm structures in locations where iron, a critical nutrient, is in short supply." ■

Urban Leishmaniasis

ABSTRACT & COMMENTARY

Synopsis: *Leishmaniasis marches on in parallel with population migrations to urban areas in developing countries.*

Source: Urbanization: An increasing risk factor for leishmaniasis. *WHO Weekly Epidemiological Record*. 2002;77:365-372. http://www.who.int/wer.

It is estimated that 12 million people are infected with *Leishmania* spp., with an annual incidence of 1 to 1.5 million new cases of cutaneous and 500,000 of visceral leishmaniasis. Furthermore, the geographical distribution of this disease is expanding, largely as the result of migration of rural diseases into urban areas in which both human and vector populations are concentrated, allowing increasing numbers of infections.

Examples of newly identified foci or of places where the incidence of zoonotic cutaneous leishmaniasis is increasing include Manaus, Brazil, and several urban areas of Colombia and Saudi Arabia. In Manaus, at the confluence of the Rio Negros and the Rio Solomonos forming the Amazon River in Brazil, there has been progressive intrusion of the urban area into the deforested rain forest. The level of intradomiciliary transmission of *Leishmania* spp. within these "suburbs" is closely correlated with the distance from the remaining remnants of rain forest in which the sylvatic animal reservoirs (opossums, anteaters, and 2-toed sloths) and sandfly vectors naturally reside.

Cities in southwestern Asia are the major foci of anthroponotic cutaneous leishmaniasis, mostly due to *Leishmania tropica*. It is estimated that 270,000 (13.5%) are infected in Kabul, the capital of Afghanistan, a city of 2 million people. The common characteristics of these endemic foci include high population density and poor sanitary conditions. A rapid increase in numbers of cases occurred in the poorest suburbs of Sanliurfa in southern Anatolia where cattle are frequently kept in house basements and the cow dung dried in the streets to be sold as fuel, providing ideal conditions for sandflies to breed and lay eggs.

Zoonotic visceral leishmaniasis is now reported from many areas of Latin America believed to have been previously free of this disease. Prolonged drought in northeastern Brazil has led to migration from rural areas to shanty towns on the outskirts of large cities where the sandfly vector and dogs are present in abundance, sanitary conditions are poor, and malnutrition is prevalent. In southern Europe, this form of leishmaniasis is spreading from rural areas into suburbs where the confluence of dogs and small gardens provide encouragement to the sandfly vectors. The confluence of conditions conducive to propagation of leishmaniasis with the HIV epidemic has led, in southern Europe and elsewhere, to emergence of large numbers of coinfection; these have now been reported from 34 countries around the world. While the availability of highly active antiretroviral therapy is associated with a decreasing incidence of coinfection, even in Europe, where such therapy is widely available, there has been a continuing increase of coinfections in injection drug users. Despite such therapy, a recent PCR examination of used syringes in 2 needle exchange programs in Madrid detected leishmanial DNA in 33% and 52%.

While anthroponotic visceral leishmaniasis primarily remains a rural disease, a link with urbanization has recently been suggested as the result of cases occurring in India in Bombay and in Patna, the capital of Bihar State.

COMMENT BY STAN DERESINSKI, MD, FACP

Poverty and civil strife, both causes of population migrations, crowding, and poor sanitation and hygiene, are the handmaidens of many infectious diseases that afflict untold millions of inhabitants of planet earth. An example, not mentioned above, is the devastating surge of cases of visceral leishmaniasis in Sudan, a site of a seeming never-ending civil war, a condition certain to obliterate any efforts at control of the disease (promed@promed.isid.harvard.edu).

Since no vaccine of proven efficacy is available, methods of leishmaniasis control include control of the sandfly vectors and control of infected animals (in the case of zoonotic forms of the disease) and humans. Rodents and canines comprise most nonhuman animal reservoirs of infection. The sandfly vectors, of the genus *Phlebotomus* in the Old World and both *Lutzomyia* and *Psychdopygus* in the New World, rest and breed in a variety of sites, ranging from cattle sheds to termite hills. These tiny, yet dangerous, pests remain susceptible to standard residual insecticides. Their diminutive size allows them to pass through the mesh of most mosquito netting.

As with so many other diseases that plague the lesser-developed world, public health measures cannot be effectively applied in the absence of massive political, social, and economic changes. ■

TRAPped

ABSTRACT & COMMENTARY

Synopsis: *Recurrent febrile episodes with localized myalgia and an erythematous, tender skin eruption overlying the painful muscle group are among the most common manifestation of the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS).*

Source: Hull KM, et al. The TNF receptor-associated periodic syndrome (TRAPS). *Medicine*. 2002;81:349-368.

HULL AND COLLEAGUES REVIEW THE AVAILABLE DATA from their cohort of more than 50 patients with the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), an autosomal dominantly inherited illness that occurs in individuals of diverse ethnicities. Twenty disease-associated mutations in genes encoding the TNF receptor super family 1A (TNFRSF1A) have been detected in association with this syndrome; nineteen of these are single nucleotide missense mutations, 18 of which account for amino acid substitutions within the first 2 cysteine-rich domains of the extracellular portion of the receptor. Most, but not all, of these mutations are associated with a specific defect in shedding of soluble TNFRSF1A.

The age of onset of illness in the cohort ranged from 2 weeks to 53 years of age, while the median age at onset was 3 years. The frequency and duration of symptoms were highly variable, but attacks occurred an average of every 5-6 weeks and were present an average of 21 days per month.

Attacks most commonly had a gradual onset, often with a sensation of deep muscle cramping, reaching a maximum intensity over 1-3 days and then persisting at this level for a minimum of an additional 3 days, but most often much longer. Symptoms then gradually resolved. Some patients, rather then suffering from episodic attacks, have continuing symptoms on a daily basis that vary in severity. Fever is invariably present during attacks in adults but sometimes absent in children.

Skin eruption is frequent. While quite varied, the most commonly observed cutaneous manifestation is a centrifugal migratory, erythematous patch that may overlie a localized area of myalgia. The rash is tender, blanchable, and warm to the touch and ranges from 1 to 28 cm in size and is usually single, being present on the limbs or trunk. Some patients have, instead, urticarial-like plaques or generalized erythematous serpiginous patches and plaques.

Myalgia is almost invariably present often, together with fever, heralding the onset of an attack. Only a single area of the body is usually involved but, like the rash, migrates centrifugally. Serum creatine kinase and aldolase concentrations remain normal. MRI shows focal areas of edema. Histological examination of biopsy specimens demonstrates a monocytic fasciitis; myositis is absent.[1] Arthritis, which infrequently occurs, is nonerosive, asymmetric, and monoarticular, primarily involving large joints.

Ninety-two percent of the cohort had abdominal pain during attacks. Testicular or scrotal pain may occur. Eighty-two percent had ocular symptoms including conjunctivitis, periorbital edema, and/or periorbital pain; these may be bilateral or unilateral.

During an acute attack, ESR, CRP, and other markers of acute inflammation are elevated. A polyclonal gammopathy is usually present.

The administration of nonsteroidal anti-inflammatory agents may control fever but usually are not effective in controlling muscle, abdominal, and other pain complaints. Corticosteroids are more effective in reducing the severity of symptoms, but chronic administration does not reduce the frequency of attacks. Etanercept appears to decrease the frequency of attacks. Among agents that do not appear to provide benefit are colchicines, thalidomide, dapsone, methotrexate, and IVIG.

COMMENT BY STAN DERESINSKI, MD, FACP

TRAPS is one of a number of periodic fever syndromes that has been genetically defined in recent years. Three of these, like TRAPS, are inherited in an autosomally dominant fashion: the neonatal onset multisystem inflammatory disorder/chronic infantile neurological cutaneous and articular syndrome, the familial cold autoinflammatory syndrome, and the Muckle-Wells syndrome—each of which is associated with mutations in the gene encoding copyrin. Familial Mediterranean fever, an autosomal recessive disease, is associated with mutations in the gene encoding pyrin, and hyperimmunoglobulinemia D with periodic fever, also autosomal recessive, is associated with altered mevalonate kinase. In children, nonhereditary causes of "autoinflammatory disease" include systemic juvenile idiopathic arthritis and the periodic fever, aphthous stomatis, pharyngitis adenitis (PFAPA) syndrome.[2]

TRAPS was first described among Irish and Scottish individuals and was originally called familial Hibernian fever. While most cases have a family histo-

ry of compatible illness, cases may also occur sporadically. Although the pathogenesis of TRAPS remains undefined, the alteration in TNFRSF1A and the apparent efficacy of etanercept appears to implicate the TNF receptor.

Hull et al point out that the diagnosis of TRAPS should be considered in a patient of any ethnicity, usually with other affected family members, with recurrent febrile episodes lasting more than 5 days, occurring over a period of at least 6 months characterized by the presence of focal myalgia with an overlying erythematous rash, often with abdominal pain and ocular involvement with response to corticosteroids but not colchicine. The diagnosis is confirmed by genetic analysis. ■

References

1. Hull KM, et al. *Arthritis Rheum*. 2002;46:2189-2194.
2. Frenkel J, Kuis W. Overt and occult rheumatic diseases: The child with chronic fever. *Best Pract Clin Rheumatol*. 2002;16:443.

CME Questions

25. Which of the following is correct?

a. Leishmaniasis is absent from urban areas.
b. Leishmaniasis is, for inexplicable reasons, disappearing worldwide.
c. Conditions which enhance breeding of sandflys increase the likelihood of transmission of leishmaniasis in endemic areas.
d. Most vectors of leishmaniasis are resistant to existing insecticides.

26. Which of the following is correct?

a. Lactoferrin inhibits biofilm formation by *P aeruginosa*.
b. Lactoferrin is a source of iron for *P aeruginosa*.
c. Lactoferrin is absent from normal airway secretions.
d. The effect of lactoferrin on *P aeruginosa* is to increase the proportion of "squatters."

27. Which of the following is correct regarding yellow fever vaccination?

a. It is absolutely contraindicated in individuals older than 65 years of age.
b. It is absolutely contraindicated in individuals younger than 6 months of age.
c. It is absolutely contraindicated in pregnancy.

In Future Issues:

Corticosteroids and Adult Meningitis

UPDATES

By Carol A. Kemper, MD, FACP

Transfusion-Associated WNV

Source: CDC. *MMWR Morb Mortal Wkly Rep.* 2002;51(43):907.

As of October 2002, 47 cases of possible transfusion-associated West Nile Virus (WNV) infection were reported to the CDC. Further investigation determined that 14 of these persons did not have WNV infection or their infection was unrelated to transfusion. Of the remaining 33 cases (from 17 different states), strong evidence suggests that infection was acquired through receipt of blood components in 6 people. The remaining cases are still being investigated.

Meningoencephalitis occurred in at least 3 of these 6 cases, resulting in 1 death. Most of these patients were immunocompromised and/or received multiple units of blood or fresh frozen plasma. In 3 of the cases, donors of the suspect units became ill 2-5 days after donation. WNV was isolated from an untransfused unit of fresh frozen plasma from 1 of these donors, indicating that the virus can survive in stored, frozen product. A quantitative PCR assay was used to identify virus in several other units, although the units tested negative for WNV-specific IgM antibody.

Any case of WNV infection occurring in patients who have received blood transfusions within the previous 1 month should be reported to the CDC. In addition, potential donors should be counseled to report any signs or symptoms of illness within 2 weeks following donation. This preliminary data suggest that transfusion-related infection may be more severe and may result in greater morbidity, although several of these patients were severely immunosuppressed. The results of quantitative assays of viral load on compromised blood components would be of interest. ■

Patient Privacy Laws—2002

Source: Kulynych J, Korn D. *N Engl J Med*. 2002;347:1133-1134.

The revised federal medical-privacy rule was finally released for public consumption by DHHS in August (Federal Register 67:53182-53273, 2002)—and is a must-read for any clinical researcher. The new 2002 rules have been (somewhat) streamlined and softened compared with the Clinton administration document initially released in December 2000. For example, the older document required appropriate authorization and approval even for a simple chart review with strict time limitations on how and when data could be used; research could not be conducted past a compliance date, even if informed consent had been previously obtained. The time limitations and the number of forms required have now been somewhat lessened. In addition, the earlier document required that all medical data be stripped of 18 identifiers, including birth dates, zip codes, and hospital discharge dates, virtually prohibiting any meaningful epidemiologic investigation. The current document reduces the criteria for performance of a research project, although access is still limited to a specific data set and must be kept to the "minimum necessary."

Despite these improvements, Kulynych and Korn believe the new rules still "pose serious and ill-advised obstacles to clinical studies and other research." In addition, DHHS estimates that it will cost about $450 million to implement these new rules, not to mention the burden it places on hospitals and clinical researchers. Because of the new rules, some researchers have confessed to limiting the number and scope of their projects during the past 2 years. Some brilliant and creative physicians and investigators, without the knack for paperwork, will not survive the shift in policy (or will purposely choose to bow out). The rules and regulations are too stifling, the paperwork overwhelming, and the risk to reputation too great if somehow you don't do everything you're supposed to do. The cost to the public in terms of the loss of meaningful research and valuable epidemiologic investigation cannot be underestimated.

In addition, the public should understand that these so-called "privacy" rules will only bring greater intrusion of administrators and bureaucrats into what was previously largely protected information. For example, one research-related hospital administration, in our area, in an attempt to provide adequate "oversight" and to more closely monitor ongoing research activity, now requires that the names and medical record numbers of every person enrolled in a research project be forwarded to administration on a monthly basis—preferably by e-mail. How private is that?

The deadline for implementation of this rule is April 2003. What are you going to do? ■

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

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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. ■

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By Louis Kuritzky, MD

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Daily Vitamin E and Multivitamin-Mineral Supplementation and Acute RTI in Elderly Persons

Source: Graat JM, et al. *JAMA*. 2002;288:715-721.

Vitamin supplementation has been shown to improve cellular immune parameters, but whether vitamin E or multivitamins/minerals (MVIM) have an effect on clinical events has not been clearly elucidated. Since respiratory tract infections (RTI) may become especially consequential for senior citizens, the question of whether vitamin E or MVIM alter the frequency, severity, or duration or such infections is of great clinical relevance.

Graat and associates studied the effect of MVIM, containing traditional RDA levels of multiple vitamins and minerals, including zinc, selenium, iron, magnesium, copper, iodine, calcium, manganese, chromium, molybdenum, and silicium, as well as a separate vitamin E supplement of 200 mg. Study subjects (n = 652) were comprised of noninstitutionalized persons older than age 60 who were followed for 15 months. At baseline, a very small proportion of individuals had suboptimal serum levels of either ascorbic acid (6%) or alpha-tocopherol (1.3%).

MVIM supplementation demonstrated no clinically or statistically significant effect upon RTI incidence, severity, duration, number of symp toms, or restriction of activity. Vitamin E supplementation demonstrated worse outcomes than placebo in reference to illness severity, duration, symptoms, fever, and restriction of activity. Graat et al caution that not only do their data discourage employment of MVIM due to lack of efficacy, but also due to a deleterious effect of vitamin E. ■

B-Type Natriuretic Peptide Levels and Outcome in Patients with Heart Failure

Source: Bettencourt P, et al. *Am J Med*. 2002;113:215-219.

Brain natriuretic peptide (BNP) levels reflect the degree of cardiac ventricular wall stress and are useful to diagnose chronic heart failure (CHF), as well as differentiate other dyspnea syndromes (in which BNP levels are not elevated) from CHF. BNP levels correlate with severity of CHF, hence, in any one episode of CHF, their degree of elevation might provide prognostic information. Bettencourt and colleagues examined the relationship between hospital BNP levels (on admission and discharge) in persons with acute decompensation of CHF, and subsequent hospital CHF readmission or death.

All subjects (n = 43) received "standard" CHF treatment, including diuretics (furosemide, and in some cases, spironolactone) and ACE inhibitors. Subjects were followed for 6 months.

When patients were hospitalized for CHF, BNP levels typically decreased with treatment. After hospital discharge, in the group that remained event free during follow-up, the decline in BNP during hospitalization (47%) was much more substantial than the decline in persons who required readmission (17%). Patients whose BNP increased during the index admission were more than 3 times more likely to require readmission or die during follow-up. BNP, and its response to treatment, provides important prognostic information in persons with CHF. ■

Companion Influence During Primary Care Medical Encounters

Source: Schilling LM, et al. *J Fam Pract*. 2002;51:685-690.

It is commonplace in primary care settings for patients to be accompanied by family, friends, or caretakers in the examining room during some portion or all of the clinician-patient interaction. The effect of the "third person" (3P) has received little literature scrutiny. Schilling and colleagues studied 226 adult medical encounters, approximately half of which included another accompanying adult who spent any portion of the visit in the examining room. Patients, companions, and clinicians rated the influence of the companion upon the visit. Aspects of the clinical encounter that were monitored included physician understanding, patient understanding, counseling time, length of visit, treatment, referrals, and number of tests ordered.

Physicians reported that having a companion present generally was either neutral to or increased physician and patient understanding. Almost universally, physicians perceived no effect upon treatments, referrals, or number of tests ordered whether a companion was present. On the other hand, 25-32% of physicians felt that the 3P caused an increase

in the length of visit or time spent counseling. Although overall the presence of an adult companion may enhance physician and patient understanding, it appears to be potentially at the expense of greater time required for counseling and the visit itself. ■

Efficacy of Handrubbing with Alcohol-Based Solution vs. Standard Handwashing with Antiseptic Soap: Randomized Clinical Trial

Source: Girou E, et al. *BMJ*. 2002; 325:362-365.

Handwashing (HWS) is generally recognized as the single most influential factor to reduce transmission of nosocomial infections. Unfortunately, studies indicate that half or less of clinicians comply with appropriate HWS recommendations. Despite interventions to increase adherence with handwashing (eg, more sinks, educational programs), results have been disappointing. Although handrubbing with alcohol (HRA) is suggested as an alternative to HWS, its acceptance has been impeded by lack of clinician confidence that an alcohol based, waterless hand antiseptic is sufficiently effective in reducing bacterial contamination.

Girou and associates performed a prospective, randomized, blinded trial in 3 intensive care units. Subjects (health professionals) were randomly assigned to chlorhexidine 4% (Hibiscrub) or handrubbing with an alcohol- based solution. Hand cultures were performed immediately before, and 1 minute after cleansing.

Both maneuvers were effective in reducing bacterial contamination, but HRA was substantially more effective (83% vs 58% reduction in contaminating bacteria). HWS and HRA occupied essentially the same mean amount of time (about 30 seconds). Previous in-vitro studies have shown that HRA is more effective than soap. Incorporation of HRA may enhance control of nosocomially transmitted infections but may require enhanced clinician education for endorsement. ■

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A Program To Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home

Source: Gill TM, et al. *N Engl J Med*. 2002;347:1068-1074.

Most literature that addresses restoration of function in elders focuses upon rehabilitation of persons who have recently suffered a morbid event, such as a stroke or hip fracture. Whether other frail elders might benefit from 'prehabilitation' strategies is little studied. To that end, Gill and colleagues recruited a population (n = 188) of seniors (> age 75) who were defined as "frail" by means of a rapid-gait test and a mobility test (ability to rise from a chair with arms folded).

The intervention program included instructions in safe techniques for moving in bed and outdoors, gait training, removal of environmental hazards (eg, loose rugs, cords, clutter) and installation of adaptive equipment in bathrooms. Interventions were monitored for 16 visits over 6 months, with last follow-up at 12 months.

The recipients of the home intervention had significantly less disability and less admission to a nursing home. Interventions included the service of a physical therapist, but the entire mean cost of intervention, including equipment and supplies, was $1998 per participant. The subjects who suffered severe disability at baseline continued to experience deterioration over time, despite receiving the same interventions. Gill et al comment that though the frequency of physical therapy visits is in excess of that allowed for reimbursement by Medicare, the overall cost-per-patient is comparatively moderate. ■

Treatment of Chronic Painful Diabetic Neuropathy with Isosorbide Dinitrate Spray

Source: Yuen KCJ, et al. *Diabetes Care*. 2002;25(210):1699-1703.

Painful diabetic neuropathy (PDN) is a troublesome and often refractory clinical dilemma. Nitric oxide (NO) production is impaired in PDN and is suspected of playing a pathogenetic role in producing pain and burning. All clinical formulations of nitrates are NO donors. Based upon anecdotal observations that individual PDN patients reported a favorable effect of isosorbide dinitrate (ISDN) spray on pain symptoms, Yuen and colleagues initiated a formal clinical trial.

Patients (n = 22) had all suffered chronic PDN and had failed traditional treatments, such as acetaminophen, amitriptyline, or gabapentin, either due to lack of efficacy, intolerance, or both. The trial was structured such that patients received either 40% propylene glycol (placebo) or 30 mg isosorbide dinitrate (1 spray) QHS in a double-blind crossover fashion for 2 sessions of 4 weeks each, punctuated by a 2-week washout period.

Use of ISDN spray produced a statistically significant reduction in pain and burning. Side effects (transient headache) were mild. ISDN may be of value in treatment of PDN, perhaps through a mechanism of increased delivery of NO. ■