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Some Uncommon Facts About the Common Cold

ABSTRACT & COMMENTARY

Synopsis: *Paranasal sinus involvement in the common cold may be explained by the finding that nose blowing is associated with the passage of nasal secretions into the paranasal sinuses.*

Source: Gwaltney JM Jr, et al. Nose blowing propels nasal fluid into the paranasal sinuses. *Clin Infect Dis* 2000;30:387-391.

The common cold is frequently associated with symptoms suggestive of the presence of paranasal sinusitis and evidence indicates that fluid may frequently be present in the sinuses of patients with colds. Gwaltney and colleagues set out to determine a potential mechanism for this finding.

Intranasal pressures were measured in healthy adult volunteers during nose blowing, sneezing, and coughing, and paranasal sinus CTs were performed after each of these maneuvers with instillation of radiopaque contrast medium into the nasopharynx. While mean intranasal pressure transiently increased to only 6.6 mm Hg and 4.6 mm Hg after, respectively, coughing and sneezing, it increased to 66.2 mm Hg after nose blowing. The mean pressure during quiet respiration was only 0.9 mm Hg. Sneezing with the mouth closed was associated with peak intranasal pressures of 88-76 mm Hg.

Mathematical modeling indicated that only trivial amounts of nasal fluid would flow into the maxillary sinus after sneezing or coughing. In contrast, 1 mL flowed into this cavity after nose blowing. Consistent with this prediction, CT scans demonstrated contrast intrusion into the osteomeatal complex and ethmoid and sphenoid sinuses of all four volunteers and in the maxillary and frontal sinuses of two of the four. Air bubbles were seen in the maxillary and sphenoid sinuses of one of the volunteers.

COMMENT BY STAN DERESINSKI, MD, FACP

This same investigative group has previously demonstrated that the overwhelming majority of patients with symptoms of the com-

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INSIDE

mon cold have CT evidence of paranasal sinus abnormalities.[1] The proposed means by which these abnormalities occur have included direct viral infection of the sinus mucosa and secondary bacterial infection. The observations described above provide another, more direct mechanism—the propulsion of nasal secretions into the sinuses as a result of nose blowing, something that occurs an average of 45 times during the first three days of an experimental cold.[2] This phenomenon had previously been suggested to Gwaltney et al by the detection of air bubbles in the sinuses of patients with colds.

One potential consequence of this hydrodynamic effect is secondary bacterial infection of the paranasal sinuses, a complication said to occur in approximately 2% of common colds.[3] Making a clinical distinction between the patient with bacterial sinusitis from that with uncomplicated but symptomatic nonbacterial sinusitis ("viral sinusitis") is quite difficult. No single finding is diagnostic. A biphasic illness may occur and the presence of several of the following is suggestive: maxillary toothache, poor response to decongestants, history or observation of colored or purulent nasal discharge, and abnormal transillumination.[4,5]

The treatment of the uncomplicated common cold has been the subject of a series of meta-analyses by the Cochrane group. Their conclusions include the following:

- A single dose of nasal decongestant is associated with a mean 13% decrease in subjective symptoms relative to placebo.[6] No evidence supports their repeated use over several days.
- The use of heated, humidified air is associated with subjective, but not objective improvement.[7]
- The benefit of zinc lozenges is uncertain.[8]
- Vitamin C does not prevent the common cold, but high doses may have a modest (8-9%) reduction in duration of symptoms.[9]
- The role of Echinacea preparations is unclear.[10]
- Antibiotic therapy was associated with increased incidence of adverse events, but no improvement in symptoms.[11]

Unfortunately, the question of antibiotic therapy remains a complicated one. A recent study attempted to determine if the putative anti-inflammatory effects of macrolide antibiotics might improve the symptoms of the common cold, independently of their antimicrobial effects.[1] In this study, patients were randomized to receive either clarithromycin or trimethoprim-sulfamethoxazole; there was no difference in outcomes.[12] Unfortunately, no placebo group was included.

A subset of patients may, however, benefit from antibiotic therapy. Kaiser and colleagues randomized patients to receive either co-amoxiclav or placebo. While no improvement was associated with antibiotic therapy in the entire group of patients, in the subset (approximately 20%) whose entry cultures yielded either *S. pneumoniae*, *M. catarrhalis*, or *H. influenzae*, co-amoxiclav administration was associated with significantly less severe and prolonged illness. Unfortunately, this subset could not be identified by clinical criteria.[13] Thus, the findings have no current practical significance since waiting for culture results would likely obviate the benefit in the subset with evidence of bacterial respiratory pathogens. Withholding antibiotics is often difficult and time-consuming for the clinician, given the fact that 44% of adults believed that antibiotic therapy is effective in the treatment of the common cold.[14]

Another intervention that has been evaluated is the use of nasal corticosteroids. Unfortunately, the use of intranasal fluticasone propionate did not improve the symptoms of the common cold and its use was associat-

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ed with increased viral shedding, a finding also reported with aspirin administration.[15,16]

On the other hand, two other interventions have each been demonstrated to reduce nasal secretions: oral administration of antihistamines (brompheniramine, clemastine fumarate) and the intranasal administration of ipatropium bromide.[2,17,18] The reduction of rhinorrhea may potentially decrease the amount of fluid expelled into the paranasal sinuses during nose blowing and thereby diminish the risk of bacterial sinusitis. ❖

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Epidemic Transmission of HIV in Renal Dialysis Centers in Egypt

ABSTRACT & COMMENTARY

Synopsis: *Practicing clinicians need to inquire in some detail about the dialysis history of patients coming from countries where dialysis practices for control of blood-borne pathogens are inadequate.*

Source: El Sayed NM, et al. Epidemic transmission of human immunodeficiency virus in renal dialysis centers in Egypt. *J Infect Dis* 2000;181:91-97.

This epidemic of hiv in dialysis centers in egypt was detected in 1993 and occurred on the heels of a larger outbreak reported in part by Hassan and associates in 1994.[1] The outbreak occurred even though after the 1990 outbreak the Egyptian Ministry of Health had instituted an effective plan for control of HIV in dialysis units. The WHO, the CDC, and other agencies got more involved after 1993 in this most unfortunate outbreak.

In the current article, two dialysis centers, a private dialysis center (PDC), and a university dialysis center (UDC), are involved. At the time of the investigation, a total of 39 patients were identified, but subsequent to the analysis, a total of 64 patients were identified, representing 32% of all known HIV-infected Egyptians.

Of the original 39 patients identified, 21 were from

the UDC and 11 of these had been previously dialyzed at the PDC. Ten of these 11 had been dialyzed from 1 to 48 times at the PDC. Transfusion history was positive in 20 of the 39 patients, with all but one transfusion having occurred in Egypt.

The PDC was located in a "poorly maintained private apartment" where there was a staff with no formally trained dialysis nurses. A single syringe, admittedly unlabeled at times, was probably used for more than one patient. Nurses also reported carrying in their pockets a syringe with heparinized saline.

The UDC resided in the university hospital, but its medical director was the same as that for the PDC. There were three shifts a day for dialysis patients using six dialysis machines. As in the PDC, nurses admitted to using a single syringe for more than one patient. Prefilled heparinized saline syringes were refrigerated overnight. Nurses carried these syringes in their pockets or placed them on a wheeled tray shared by patients in all shifts.

A control center that used more careful procedures had no HIV infection among 75 patients who received dialysis. In this center there were no reprocessing dialyzers.

The V3 loop of the HIV glycoprotein 120 was sequenced in 14 samples from 13 patients related to the outbreak. All sequences from the outbreak belonged to HIV-1 serogroup B and were 96% homologous. Individual variations in the V3 amino acid further supported that the outbreak strains were the same.

The PDC was closed from July to October of 1993 and the UDC was limited in the number of dialysis shifts. Educational programs emphasized national guidelines.

COMMENT BY JOSEPH F. JOHN, MD

Surely this epidemic caused a stir, evidenced by the lateness of this report—seven years later—and the nonemotive language used in this report. Much credit goes to the Joint UN Program on HIV/AIDS, the WHO, the CDC, and certainly valiant Egyptian physicians and scientists who finally brought this report to light.

The report is important since it shows that HIV may be relatively easily transmissible in a dialysis unit where there is a break in technique or repeat exposure to blood products. Further, it is important since it uncovered a mode of transmission for HIV that may be underappreciated throughout the world.

How many unrecognized reservoirs of HIV are there worldwide? A recent unrecognized epidemic reported in the *New York Times* of HIV among young heroin users in Siberia highlights another example of reservoirs of unrecognized HIV-infected individuals.[2] Patients exposed to practices in certain dialysis centers may be another global reservoir. Patients from dialysis centers that use ineffective infection measures may end up at other medical facilities throughout the world. Practicing clinicians need to inquire in some detail about the dialysis history of patients coming from countries where dialysis practices for control of bloodborne pathogens are inadequate. ❖

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Fatal Yellow Fever in a U.S. Traveler to Venezuela

ABSTRACT & COMMENTARY

Synopsis: *An unvaccinated traveler acquired fatal yellow fever in the Venezuelan Amazon region.*

Source: CDC. Fatal yellow fever in a traveler returning from Venezuela, 1999. *MMWR Morb Mortal Wkly Rep* 1999;49: 303-305.

On sept. 26, 1999, a man returned to marin County, Calif., after a 10-day trip to the rainforests of the Amazon region of Venezuela. He presented to a local emergency room on Sept. 28 with a two-day history of fever, chills, headache, photophobia, myalgias and arthralgias, nausea, vomiting, and upper abdominal discomfort. He was found to be icteric (bilirubin 5.9 mg/dL) and to have upper abdominal tenderness. His ALT was more than 5000 U/L, WBC 3400/mm^3, platelet count 77,000/mm^3, and creatinine 5.9 mg/dL. He worsened and died on Oct. 4. Postmortem examination revealed hepatic necrosis with numerous Councilman bodies, as well as disseminated aspergillosis. Yellow fever viral antigen was detected in the liver by immunohistochemistry and yellow fever genome by PCR. His serum IgG antibody titer to this flavivirus increased from undetectable on presentation to 1:128 subsequently.

The patient had received multiple vaccinations, but not against yellow fever, prior to travel. Five of six travel companions had received yellow fever vaccine; all were healthy on follow-up.

COMMENT BY STAN DERESINSKI, MD, FACP

This was only the second case of imported infection with this flavivirus in the United States since 1924. A fatal case in an unvaccinated American traveler to the jungles of Brazil along the Rio Negro and Amazon rivers occurred in 1996.[1] The current case occurs in the face of a resurgence of yellow fever over the last two decades.[2] Yellow fever is currently endemic in sub-Saharan Africa and tropical South America, with transmission occurring in Bolivia, Brazil, Colombia, Ecuador, French Guiana, Peru, and Venezuela. There has been a recent increase in yellow fever activity in Brazil, as well as Bolivia, where it is occurring in urban areas.[3,4] On May 2, 2000, the 26th fatality among 51 cases in the previous 12 months in Goias State occurred. The patient had been offered vaccination 10 days earlier during a door-to-door program designed to arrest yellow fever activity, but refused.

Sylvatic yellow fever is the result of a transmission cycle involving non-human primates, mosquitoes, and humans, while the urban cycle involves only humans and mosquitoes. The latter, *Aedes aegypti*, breed in man-made containers. After an incubation period of 3-6 days, the onset of illness is abrupt, with fever, chills, headache, and myalgia. Conjunctival injection is common, as is relative bradycardia and leukopenia. Illness may progess, with the development of vomiting, abdominal pain, jaundice, renal dysfunction, and bleeding. Management is supportive.

Administration of yellow fever 17D vaccine is recommended, but not required, for travelers to Venezuela coming directly from the United States.[5] This live attenuated viral vaccine is safe, with a low rate of significant adverse reactions, although the incidence of anaphylaxis has been estimated to be approximately one in 131,000.[6] A single dose provides protective long-lasting immunity in more than 95% of recipients. As with other live viral vaccines, its administration is contraindicated in significantly immunocompromised individuals and best avoided in pregnancy. Its use may, however, be considered (and is recommended by the CDC) in pregnant individuals traveling to highly endemic areas. The vaccine is also contraindicated in infants younger than 4 months of age and in individuals with severe egg allergy. ❖

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RSV Protects Itself From Programmed Cell Death

ABSTRACT & COMMENTARY

Synopsis: *Some viruses are cleared through apoptosis, but there are viral-induced mechanisms to thwart the programmed cell death.*

Source: Krilov LR, et al. Alterations in apoptosis of cord and adult peripheral blood mononuclear cells induced by in vitro infection with respiratory syncytial virus. *J Infect Dis* 2000; 181:349-353.

The understanding of apoptosis is gaining importance in many fields of medicine, particularly infectious diseases. Journals are now dedicated to the process that features programmed cell death related to normal tissue turnover and to immune-induced factors. It is usually hard to determine if apoptosis in a given disease is good or bad for humans. In general, apoptosis is a protective process, then in viral illnesses the process could be viewed as a way to remove, for example, virus-infected cells. Certain viruses, conversely, have evolved mechanisms for blocking apoptosis.

Respiratory syncytial virus (RSV) is gaining importance in adult as well as pediatric infections. In this report, workers at North Shore University Hospital and NYU School of Medicine took peripheral blood mononuclear cells (PBMCs), either cord blood PBMCs from infants or adults, and exposed them to RSV. Apoptosis was blunted in PBMCs, including specific lymphocyte populations (B, T, and NK cells), and macrophages. The effect was more pronounced in adult blood than in cord blood.

COMMENT BY JOSEPH F. JOHN, MD

It is thought that the pathogenesis of RSV relates to host responses increasing reactivity of airways. RSV is known to infect macrophages and monocytes in vitro, so impairment of apoptosis in these cells' lines was predictable. The decrease of apoptosis in lymphocytes may

be less related to direct infection than to cytokine-mediated processes.

The industry is working hard to develop molecules that interact with apoptosis mechanisms. It will not be surprising to see imminent development of a compound that could promote normal apoptosis in non-immunosuppressed patients infected with RSV. On the other hand, this study raises the issue of an additional mechanism by which RSV affects neutropenic patients such as those in bone marrow units, who have a catastrophic response to this virus. Perhaps direct infection of non-PBMC cells plays a larger role in neutropenic patients. ❖

New Blood Markers Related to Chronic Fatigue Syndrome

ABSTRACT & COMMENTARY

Synopsis: *De Meirleir and colleagues, through a series of intensely conducted studies, show that chronic fatigue syndrome patients often form an abnormal R-binding protein that likely is associated with dysregulation of 2-5A binding.*

Source: De Meirleir K, et al. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 2000;108:99-105.

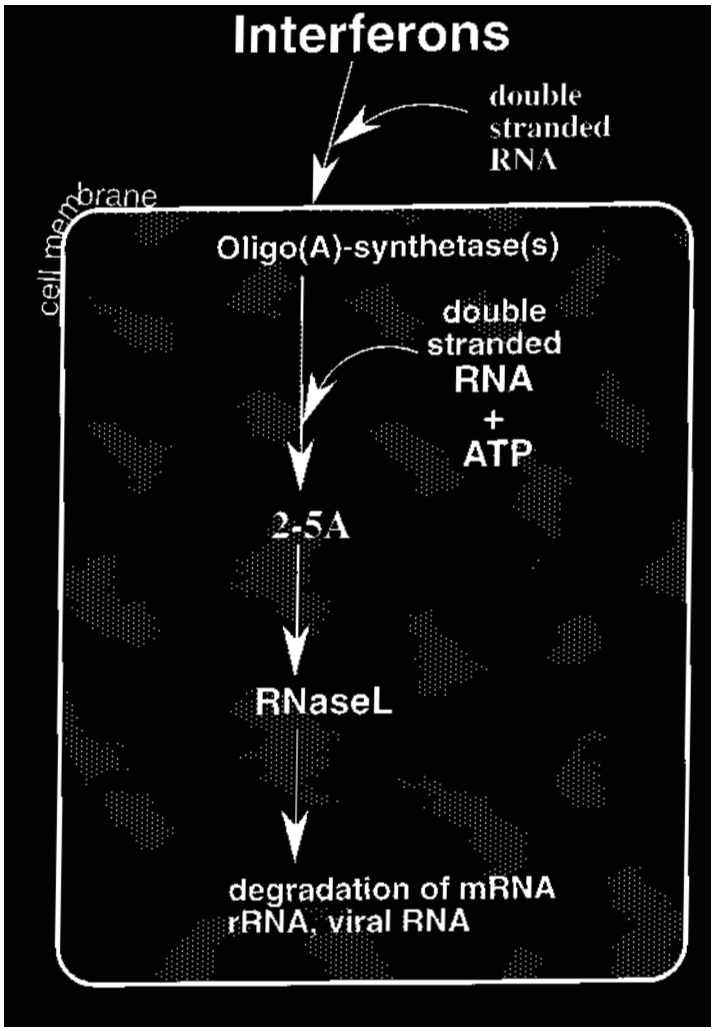
Physicians are taught little about a cellular system designed to degrade residual single-stranded RNA. One such system uses the activation of an enzyme called RNase L. When this enzyme is activated through binding of a polynucleotide called 2-5-oligoadenylate (2-5A) it acts to degrade single-stranded RNA. The generation of 2-5A oligonucleotides begins with the priming of the cell by circulating interferons. Interferon signals the production of intracellular 2-5 synthetase. Next comes a crucial though poorly understood step. 2-5 synthetase requires the action of double-stranded RNA to become activated. Once activated and exposed to ATP, 2-5A is formed and then binds to RNase L, which then leads to the degradation of single-stranded RNA.

You might ask what is the true significance of this highly regulated system to degrade single-stranded RNA? The answer involves observations made primarily in in vitro analysis. Picornavirus, for example, clearly induces this system in vitro that regulates the replication of the virus. Blocks in the RNase L system can lead to increased viral replication. HIV, with all its intricacies, has a way of thwarting the RNase L system. In January 1999, Martinand and colleagues, including a coauthor in the current offering, showed that HIV induced an RNase L inhibitor that leads to upregulation of HIV replication.[1] Other such inhibitors likely exist that allow unbridled replicaton of certain viruses.

Now enter chronic fatigue syndrome (CFS), for several years believed to be associated with a broad-based immune dysregulation. Even though CFS patients frequently have elevated antibody to various proteins of EB virus and human herpes virus 6 (HHV-6), these viruses play a causal role in CFS. In the current article, De Meirleir and colleagues, through a series of intensely conducted studies, show that CFS patients often form an abnormal R-binding protein that likely is associated with dysregulation of 2-5A binding.

Figure

Pathway of Single-Stranded RNA Degradation in Mammalian Cells



De Meirleir has the largest CFS clinic in Europe, so he and his colleagues can study large numbers of patients. In the present study, they studied 57 patients who satisfied the CDC criteria for CFS. Controls were healthy subjects with fibromyalgia or depression. Another control group was 28 healthy "noncontact" controls recruited from the hospital and university staff. In this group were two persons who had "frequent contact with either CFS patients or their blood samples."

Identification of 2-5 binding activity used production of radiolabeled 2-5A that was incubated with protein extracts from peripheral blood mononuclear cells (PBMCs) and separated on an SDS gel using denaturing conditions. The proteins by size that were bound to 2-5A were visualized by autoradiography.

Both healthy subjects and CFS patients make normal 80 kDa and 40 kDa RNase L proteins. In 50 (88%) of CFS patients, however, there is a third protein band on SDS-PAGE seen around 37 kDa. It is present in only 28% of healthy controls and 38% of fibromyalgia patients, respectively. Two contact controls had elevated 37 kDa levels.

Each of the proteins suspected to be RNase Ls were shown to bind 2-5A, a necessary but not sufficient requirement of RNase Ls.

Analyzed another way, the ratio of the 37 kDa to the 80 kDa was equal to 0.5 in 72% of CFS patients, compared to only 1% of the healthy controls. These data emerge suggesting the potential for a sensitive, fairly specific, blood-based biochemical test.

COMMENT BY JOSEPH F. JOHN, MD

Those of us who care for CFS patients have known for several years of an abnormal R ding protein suggested from the work of Suhadolnik and colleagues.[2] This new article from De Meirleir et al in Brussels (with basic science help from French workers) adds credence to the observation of defective RNase L proteins as applied to a larger group of CFS patients.

What does all this mean clinically? For starters, the credibility of CFS as a syndromic entity with cellular abnormalities certainly increases. Komaroff, a long-time CFS therapist and observer, in an accompanying editorial states clearly that there has been growing evidence for the immunological dysfunction in CFS.[3] Now there is no doubt about some biochemical dysregulation.

So how should clinicians proceed with securing these data for patients suspected of having CFS? Few labs perform the assay for the low-molecular-weight RNase L. A lab known as RED provided the laboratory support for this study. The RNase L assay requires a pellet consisting of peripheral blood mononuclear cells that is well preserved in the cold. RED will process well-preserved PBMCs for RNase L proteins. Up to 88% of CFS patients will have PBMCs that produce the low-molecular-weight RNase L (DeMeirleir, personal communication) and the low-molecular-weight protein is expressed in few normal PBMCs.

Another lab here in the United States, known as ImmunoScience, also performs a set of tests for CFS using a slightly different method. Elevated levels of the 80 kDa RNase L are supposed to reflect the abnormality in CFS cells that not only produce a low-molecular-weight RNase L but also overproduce the 80 kDa protein.

There may be several reasons to monitor the 37 kDa protein in CFS patients. Therapies that decrease the level of the abnormal protein may be associated with clinical improvement. Insurance companies, which for years have balked at providing disability for CFS patients, may welcome a biochemical marker for the disease. Finally, patients themselves will gain peace of mind knowing that their multisystem symptomatology is associated with some cellular abnormality.

The biology of CFS now suggests that a cellular abnormality in RNA metabolism may be associated with the disease.[3] Work in vitro with picornavirus and reovirus has found that an intact R system as stimulated by interferon results in effective degradation of single-stranded viral RNA. Interestingly, HIV RNA degradation is defective in HIV-infected patients due to an inhibitor of R that serves to allow upregulation of HIV and increased viral replication. Other viral systems have not been well studied.

What is far from clear is whether the R system functions to degrade host cell RNA. If the differential effect of R on host vs. viral RNA can be demonstrated, we will have a better appreciation for the R defect in CFS patients. If the R system serves primarily to degrade viral RNA, we must continue to search for a viral cause of CFS.

In process is a clinical trial of an interferon inducer known as polyI:polyC (Ampligen) that has enrolled more than 125 patients. The Ampligen 516 trial is a double-blinded, placebo-controlled format that includes analysis of the RNase L system in CFS patients treated with Ampligen or placebo. We all eagerly await the results of that trial. ❖

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Long-Term Outcomes of Persons with Lyme Disease

ABSTRACT & COMMENTARY

Synopsis: *These data support clinicians who chose to advise their Lyme disease patients that adverse post-disease outcomes are the clear exception.*

Source: Seltzer EG, et al. Long-term outcomes of persons with Lyme disease. *JAMA* 2000;283:609-616.

A variety of anecdotal reports suggest that Lyme disease may be associated with long-term sequelae of diverse nature. Connecticut, which requires all Lyme disease to be reported, was the setting for the evaluation of 672 persons identified as having Lyme disease, compared with a matched group of persons without the disease. Follow-up was up to 11 years in duration (mean 51 months), and mean patient age was 36.

Most people (71%) identified no long-term sequelae; 9% felt they were still not cured; and 20% were uncertain if they were cured. Persons who felt they were not cured were more likely to suffer impairments in activities of daily living in years following treated Lyme disease. However, the data comparing the control cohort to the post-Lyme disease group indicated that there were similar frequencies of complaints among controls as among Lyme disease subjects. Additionally, persons who met the most stringent criteria for confirmed Lyme disease actually had a lower frequency of difficulties with daily activities than those whose fulfillment of diagnostic criteria was less complete, a percentage of whom must surely have been incorrectly diagnosed as having Lyme disease.

There were rare instances of Lyme disease sufferers who experienced significant complications such as (recurrent) arthritis in persons who did not receive prompt treatment and are genetically disposed to autoimmune-mediated arthritis. On the other hand, these data support clinicians who chose to advise their Lyme disease patients that adverse post-disease outcomes are the clear exception. (*Dr. Kuritzky is Clinical Assistant Professor, University of Florida, Gainesville, FL.*) ❖

CME Questions

30. In outbreaks of HIV involving dialysis units, what likely mode of transmission has been uncovered?
a. Unsuspected sexual exposure
b. Lack of glove use in initiating dialysis
c. Contaminated dialysis tubing
d. Reuse of heparinized tubing

31. What is the role of apoptosis in RSV infected macrophages?
a. RSV induces apoptosis
b. RSV has no effect on apoptosis
c. RSV inhibits apoptosis
d. RSV stimulates cytokine production by macrophages that reduce macrophage viability

32. The R system provides for metabolism of what product?
a. DNA
b. Single-stranded RNA
c. Double-stranded RNA
d. 2'5' oligoadenylate (2-5A)

33. Which of the following is correct?
a. Sneezing, but not coughing or nose blowing is associated with the propulsion of nasal secretions into the paranasal sinuses.
b. The presence of air bubbles in a paranasal sinus is unequivocal evidence of anaerobic infection.
c. The administration of antihistamines, nasal decongestants, and intranasal ipatropium bromide are each associated with decreased nasal secretions in patients with the common cold.
d. Intranasal flucitasone decreases viral shedding in patients with the common cold.

34. Which of the following is correct?
a. The yellow fever virus is a retrovirus.
b. *Aedes aegypti* is a competent vector of yellow fever virus.
c. Relative tachycardia is a common clinical finding in patients with yellow fever.
d. The yellow fever vaccine in common use in the United States is a killed whole virus vaccine.

Readers are Invited...

Readers are invited to submit questions or comments on material seen in or relevant to *Infectious Disease Alert.* Send your questions to: Neill Larmore—Reader Questions, *Infectious Disease Alert,* c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Infectious Disease Alert* via the Internet by sending e-mail to neill.larmore@medec.com. We look forward to hearing from you. ❖

In Future Issues:

Changing Carriage Rate of *Neisseria meningitis* Among University Students